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ORIGINAL RESEARCH

Impact of Hyponatraemia at Clinical Stable-State on Survival in Patients with Chronic Obstructive Pulmonary Disease

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Introduction: Hyponatraemia has been suggested to be associated with morbidity and mortality among various medical disorders. Evidence on the association between stable-state hyponatraemia and prognosis in patients with chronic obstructive pulmonary disease (COPD) is lacking.

Methods: All COPD patients followed up in a regional hospital in year 2015 were included, with their clinical outcomes reviewed in the subsequent eight years. Association between stable-state hyponatraemia and mortality was evaluated. Stable-state hyponatraemia is defined as baseline serum sodium levels, at least 90 days away from the last AECOPD <135 mmol/L.

Results: There were 271 COPD patients included. Hyponatraemia was associated with shorter overall survival with adjusted hazard ratio (aHR) 1.74 (95% CI = 1.07–2.65, p = 0.026). The median overall survival was 3.05 years (95% CI = 2.65–3.46) for patients in the hyponatraemia group, in contrast to 3.35 years (95% CI = 2.86–3.83) for those without hyponatraemia. The highest baseline serum sodium levels were significantly negatively associated with annual acute exacerbation of COPD (AECOPD) and annual hospitalized AECOPD frequency in the follow-up period, with Pearson correlation coefficient of −0.16 (p = 0.011) and – 0.14 (p = 0.027), respectively.

Conclusion: Stable-state hyponatraemia was associated with increased mortality and probably AECOPD frequency among patients with COPD.

Keywords: chronic obstructive pulmonary disease, acute exacerbation of chronic obstructive pulmonary disease, hyponatraemia, sodium, electrolyte

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease that is associated with significant morbidity and mortality. It is estimated that COPD causes three million deaths annually globally.[1] The reported poor prognostic factors in COPD include low forced expiratory volume in one second (FEV_1),[2] low body-mass index,[3] male sex[4] and history of acute exacerbation of COPD (AECOPD).[5] A multidimensional index, the BODE index, was also developed to assess individual risk of death from COPD.[6,7]

Hyponatraemia has been postulated to have prognostic value in patients with various diseases. The reported negative outcomes associated with hyponatraemia include higher hospital readmission rates,[8] as well as increased mortality in both hospitalized[9] and non-hospitalized patients.[10] The prognostic influence of hyponatraemia in patients with COPD has also been studied, but mainly on the sodium level at the time of AECOPD, and its relationship with the outcome. In non-hospitalized AECOPD, hyponatraemia was present in 22% of the patients and was found to be correlated with higher

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Charlson comorbidity index (CCI), higher leucocytes, lower hemoglobin, lower platelet, higher neutrophil-to-lymphocyte ratio, lower eosinophilia, higher aspartate aminotransferase and C-reactive protein values ($P < 0.001$, for all), and higher frequency of 1-month revisit.[11] Hyponatraemia among hospitalized patients with AECOPD was also found to be associated with poor outcomes.[12–14] A sodium threshold lower than 129.7 mmol/L was demonstrated in one study to exhibit better discriminatory power for death prediction.[15] However, controversies occurred in the prognostic value of this common electrolyte disturbance among patients with AECOPD as negative results were shown in other studies.[16,17]

While the evidence of the prognostic role of hyponatraemia in AECOPD has been demonstrated in some studies, the role of stable-state hyponatraemia among patients with COPD has not been studied. In view of the knowledge gap, this study was set forth to investigate the impact of stable-state hyponatraemia in patients with COPD on the survival and future exacerbation frequency.

Methods

We included all COPD patients seen in the respiratory outpatient clinic at Queen Mary Hospital, Hong Kong in year 2015 who had baseline spirometry performed and follow-up progress available in the subsequent eight years. The patients were followed up until 31st December 2022. Patients with co-existing asthma, any history of malignancies, those who did not have spirometry to confirm the diagnosis of COPD and patients with alternative causes of hyponatraemia (drug-induced hyponatraemia, heart failure, hypothyroidism and adrenal insufficiency) were excluded. Clinical and laboratory data were retrieved from the electronic patient records (ePR) of the Hospital Authority. The study was approved by the Institutional Review Board (IRB number: UW 23–356). Patient informed consent was waived as it was a retrospective study without active patient recruitment, and all retrieved clinical data were de-identified. Regular use of inhaled corticosteroid (ICS), long-acting beta-agonists (LABA) and long-acting anti-muscarinic (LAMA) for at least 12 months was defined as continuous use within the study period.

The baseline serum sodium levels, at least 90 days away from the last AECOPD, were retrieved from electronic patient record (ePR). Normonatraemia, hyponatraemia and hypernatraemia were defined as serum sodium levels of 135–145 mmol/L, <135 mmol/L and >145 mmol/L on at least 2 measurements in year 2014 to 2015. Clinical stable state was defined as exacerbation- and systemic corticosteroid-free for at least 90 days, and without any clinical evidence of acute or subacute symptomatic deterioration.

Severity of hyponatraemia was further stratified into mild (130–134 mmol/L), moderate (121–129 mmol/L) and severe (<120 mmol/L).[18]

AECOPD was defined as an event characterized by dyspnea and/or cough and sputum that worsened over ≤14 days.[19,20] Mild exacerbation was defined in patients treated with short-acting bronchodilators (SABD) only. Moderate exacerbation was defined in patients who were treated with SABDs and oral corticosteroid ± antibiotics. Severe exacerbation was defined in patients that required hospitalization or a visit to the emergency room.[19]

The primary outcome was overall survival. The secondary outcomes included the association between highest and lowest blood sodium levels with annual frequency of AECOPD and hospitalized AECOPD in the follow-up period among the normonatraemia and hyponatraemia groups, as well as the association with the highest and lowest blood sodium levels. The results were also compared among patients with hyponatraemia corrected, hyponatraemia uncorrected and patients with normonatraemia.

Statistical Analysis

Categorical variables were expressed as frequency and percentage and compared using Chi-square tests or Fisher's Exact tests. Continuous variables were expressed as mean (± standard deviation [S.D.]) or median (Interquartile range [IQR]) and compared using Student's t-tests or Mann Whitney *U*-tests between groups. Cox regression analysis was used to assess overall survival. Kaplan–Meier analysis was used to estimate the cumulative death rates with stratified log-rank statistics to assess the effects of hyponatraemia with respect to the composite end point. The relationship between hyponatraemia and annual frequency of AECOPD and hospitalized AECOPD in the follow-up period was assessed by using the Pearson's correlation coefficient metrics. Multi-variate analysis was adjusted for potential confounders

including age, gender, baseline FEV_1, baseline CCI, AECOPD frequency in the past 3 years before recruitment and other factors that were significantly different at baseline.

The statistical significance was determined at the level of $p<0.05$ with two-sided test. All the statistical analyses were done using the 28th version of the SPSS statistical package.

Results

Patient Characteristics

A total of 371 patients with COPD were identified with 27 excluded as they did not have baseline serum sodium level available, 47 excluded due to history of malignancies and 26 excluded due to history of heart failure (Figure 1). A total of 271 patients were included in the final analysis (Table 1).

A total of 228 (84.1%) were males, with a mean age of 80.0 ± 9.0 years. Forty-four (16.2%) patients had hyponatraemia, and 227 (83.8%) never had hyponatraemia at clinically stable-state. Seven patients had moderate hyponatraemia and 37 with mild hyponatraemia. The mean duration of the follow-up was 4.31 ± 2.12 years. Among the patients with hyponatraemia, 37 had syndrome of inappropriate secretion of antidiuretic hormone (SIADH) confirmed by urine and serum osmolality, urine serum concentration as well as hydration status. Baseline serum sodium level was not significantly associated with baseline lung function parameters, mMRC dyspnoea scale and past AECOPD numbers, with a p-value of >0.05 in Pearson correlation.

Hyponatraemia and Overall Survival

All patients died during the 8 years of follow-up. The causes of death included pneumonia (41.7%), AECOPD (20.7%), cardiovascular or cerebrovascular events (11.1%), malignancies that were newly developed in the follow-up period (10.0%), gastrointestinal diseases (6.3%), renal failure (2.6%), and miscellaneous causes (7.7%). Patients in the hyponatraemia group had shorter overall survival with a hazard ratio of 1.45 (95% confidence interval [CI] = 1.04–2.01, p = 0.029). The median overall survival was 3.05 years (95% CI = 2.65–3.46) for patients in the hyponatraemia group, in contrast to 3.35 years (95% CI = 2.86–3.83) for those without hyponatraemia. The adjusted HR (aHR) after adjusting for age, gender, baseline FEV_1,

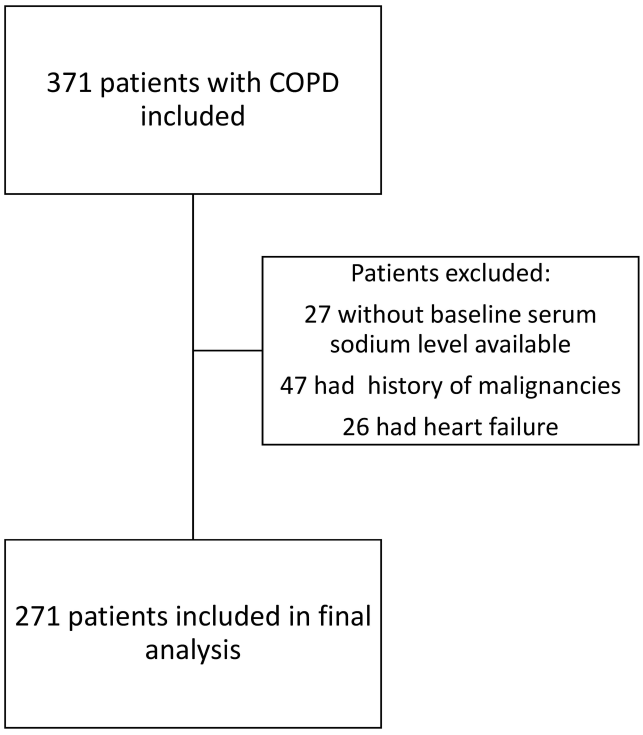

Figure 1 Patient selection flow chart.

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Table 1 Baseline Clinical Characteristics of Patients with Chronic Obstructive Pulmonary Disease with or Without Hospitalized Exacerbation in the Past 1 Year

	Hyponatraemia Group (n = 44)	Normonatraemia Group (n = 227)	Whole Cohort (n = 271)	p-values^
Age (years)	81.2 ± 8.5	79.8 ± 9.1	81.0 ±9.0	0.33
Gender				0.36
Male	35 (79.5%)	193 (85.0%)	228 (84.1%)	
Female	9 (20.5%)	34 (15.0%)	43 (15.9%)	
Smoking status				0.44
Current smoker	17 (38.6%)	74 (32.6%)	91 (33.6%)	
Former smoker	27 (61.4%)	153 (67.4%)	180 (66.4%)	
Medication				
LABA	33 (75.0%)	162 (71.4%)	195 (72.0%)	0.62
LAMA	30 (68.2%)	142 (62.6%)	172 (63.5%)	0.27
ICS	44 (100%)	217 (95.6%)	261 (96.3%)	0.16
Baseline lung function parameters at recruitment				
FEV_1 (L)	0.91 ±0.38	1.02 ±0.44	1.02 ±0.45	0.21
Baseline FEV_1 (% predicted)	39.7 ±14.7	49.1 ±19.8	48.9±20.0	0.014*
Baseline FVC (L)	2.14 ±0.73	2.23 ±0.73	2.15 ±0.76	0.62
Baseline FVC (% predicted)	72.3 ±19.5	78.4 ±25.1	74.8 ±24.9	0.29
Baseline FEV_1/FVC ratio	43.7 ±17.0	49.4 ±15.8	48.0 ±14.7	0.32
Bronchodilator reversibility (mL)	163 ±151	99 ±97	101 ±100	0.22
Bronchodilator reversibility (%)	17.0 ±14.4	11.8 ±13.4	12.0 ±13.2	0.28
Baseline laboratory parameters				
Eosinophil count (x cells/μL)	217 ±209	255 ±248	253 ±247	0.35
Eosinophil %	3.09 ±2.44	3.49 ±3.31	3.47 ±3.30	0.43
Lowest sodium level (mmol/L)	132 ± 2	139 ± 2	138 ± 4	<0.001*
Highest sodium level (mmol/L)	140 ± 4	143 ± 3	142 ± 3	<0.001*
eGFR (mL/min/1.73m^2)	109 ±52	99.8 ±52.3	105 ±57	0.62
Charlson co-morbidity index	5.25 ± 1.73	4.59 ± 1.72	4.90 ± 1.83	0.024*
Influenza vaccination	26 (59.1%)	126 (55.5%)	152 (56.1%)	0.66
Pneumococcal conjugate vaccine	2 (4.5%)	25 (11.0%)	27 (10.0%)	0.19
Pneumococcal polysaccharide vaccine	2 (4.5%)	36 (15.9%)	38 (14.0%)	0.082

Notes: Data expressed as mean ± S.D. ^Compared between hyponatraemia and non-hyponatraemia groups. *Statistically significant.
Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; eGFR, estimated glomerular filtration rates; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LAMA, long acting anti-muscarinic.

baseline CCI, AECOPD frequency in the past 3 years before recruitment, influenza and pneumococcal vaccination status was 1.74 (95% CI = 1.07–2.65, p = 0.026) (Figure 2). After excluding the patients who died of malignancies, the OS was still significantly different in the hyponatraemia group and normonatraemia subgroups. The aHR was 1.74 (95% CI = 1.06–2.84, p = 0.027), while the median OS was 3.09 years (95% CI = 2.72–3.45) and 3.24 years (2.69–3.79) in hyponatraemia group and normonatraemia subgroups, respectively.

Hyponatraemia and Annual AECOPD Frequency in the Follow-Up Period

The association between the highest and lowest blood sodium levels in the whole cohort with the annual AECOPD and hospitalized AECOPD frequency in the follow-up period for the whole cohort. The highest baseline serum sodium level was significantly negatively correlated with the annual AECOPD frequency in the follow-up period with Pearson correlation coefficient (r) of – 0.16 (p = 0.011). The lowest baseline sodium level was negatively correlated with the annual AECOPD frequency in the follow-up period with r of −0.11 (p = 0.071) which did not reach statistical significance. The highest baseline sodium level was significantly negatively correlated with the

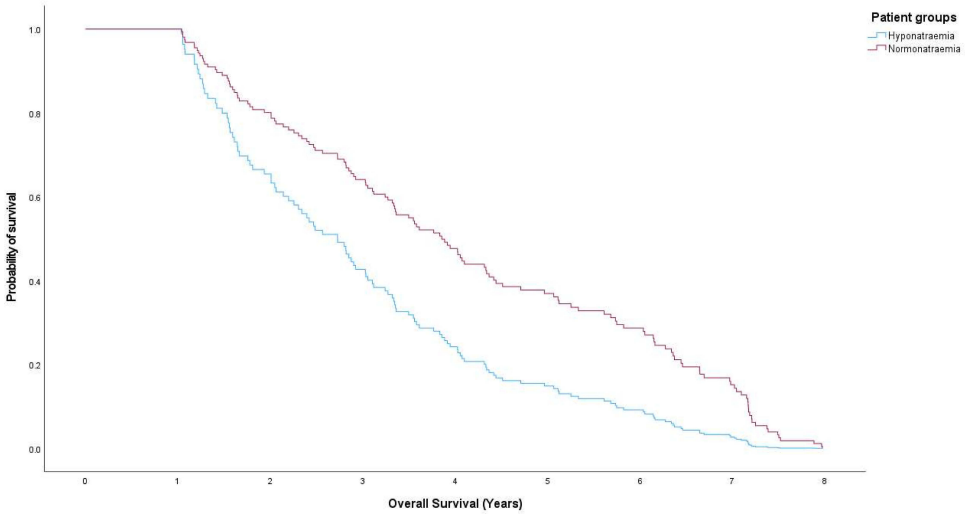

Figure 2 Kaplan–Meier curve of on the overall survival among patients with or without hyponatraemia at stable state.

annual hospitalized AECOPD frequency with r of −0.14 (p = 0.027). The lowest baseline sodium level did not significantly correlate with the annual hospitalized AECOPD frequency with r of −0.09 (p = 0.14). The annual AECOPD frequency in the follow-up period was numerically higher in the hyponatraemia group than in the normonatraemia group, with median of 1.71 [IQR 0.84–3.66] versus 1.13 [IQR = 0.41–2.79], respectively (p = 0.06). The annual hospitalized AECOPD frequency in the follow-up period was numerically higher in the hyponatraemia group with a median of 1.46 [IQR 0.67–3.05] compared to those without hyponatraemia with a median of 1.00 [IQR = 0.34–2.25] (p = 0.18).

Analysis was performed to compare patients with hyponatraemia corrected, hyponatraemia uncorrected and patients with normonatraemia. There were 8 patients with hyponatraemia uncorrected and 36 patients with hyponatraemia corrected. Patients with hyponatraemia uncorrected had statistically shorter OS than those with normonatraemia, with HR of 2.37 (95% CI = 1.16–4.83, p = 0.018), but not for those with hyponatraemia corrected, with HR of 1.27 (95% CI = 0.86–1.88, p = 0.24). The median OS was 1.76 years (95% CI = 1.04–2.48) in the uncorrected hyponatraemia group, 3.16 years (95% CI = 2.42–4.70) in the corrected hyponatraemia group and 3.35 years (95% CI = 2.86–3.83 years) in the normonatraemia group. The aHR was 1.6 (95% CI = 1.01–3.82, p = 0.047) for the uncorrected hyponatraemia group and 2.08 (95% CI = 0.81–5.32, p = 0.13) in the corrected hyponatraemia group (Figure 3). The median annual AECOPD

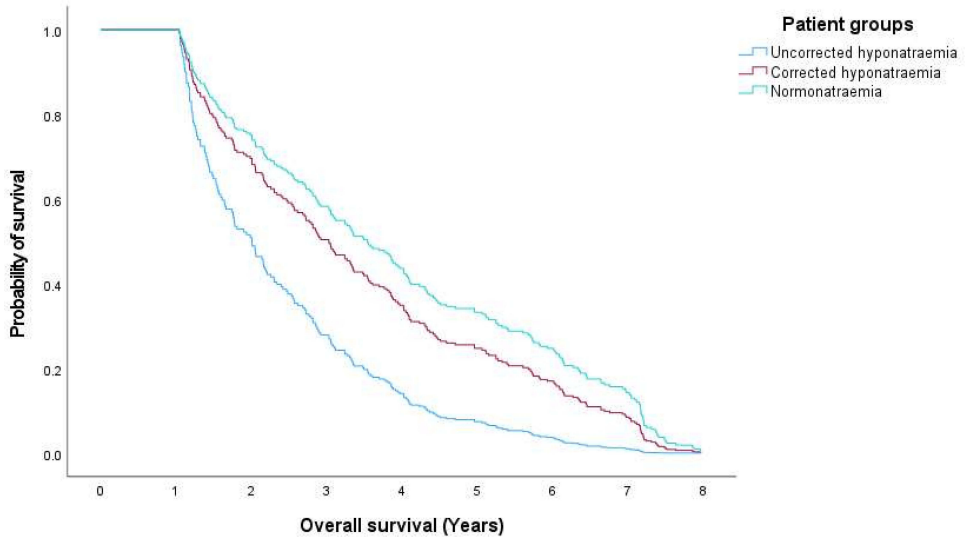

Figure 3 Kaplan–Meier curve of on the overall survival among patients with or without corrected hyponatraemia and normonatraemia at stable state.

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frequency was 4.26 [IQR = 0.28–9.19] in the uncorrected hyponatraemia group, 1.29 [0.70–2.48] in the corrected hyponatraemia group and 1.06 [0.38–2.84] in the normonatraemia group, p = 0.002. The median annual hospitalized AECOPD frequency was 3.85 [IQR = 0.25–6.31] in the uncorrected hyponatraemia group, 1.00 [0.50–2.00] in the corrected hyponatraemia group and 1.00 [0.33–2.27] in the normonatraemia group, p = 0.017.

Degree of Hyponatraemia and Clinical Outcomes

There were 37 and 7 patients with mild and moderate hyponatraemia, respectively. The mild hyponatraemia subgroup had a significantly shorter OS with HR of 1.58 (95% CI = 1.09–2.28, p = 0.016), while the HR was 1.06 (0.55–2.08, p = 0.86) in the moderate hyponatraemia subgroup. The aHR was 2.11 (95% CI = 1.25–3.58, p = 0.005) and 1.48 (95% CI = 0.62–3.50, p = 0.44) in mild and moderate hyponatraemia subgroups, respectively. The annual AECOPD frequency in the follow-up period was higher in the moderate hyponatraemia group than in the mild hyponatraemia group, with median of 2.78 [IQR 0.98–4.74] versus 1.60 [IQR = 0.74–2.78], respectively (p = 0.08). The annual hospitalized AECOPD frequency in the follow-up period was higher in the moderate hyponatraemia group with a median of 2.00 [IQR 0.88–4.50] compared to those mild hyponatraemia with a median of 1.25 [IQR = 0.50–2.33] (p = 0.24).

Discussion

Our study suggested a negative impact of baseline hyponatraemia among patients with COPD, which was associated with shorter overall survival and probably increased AECOPD frequency. This concurred with previous findings of the adverse effects from hyponatraemia in both COPD and other medical disorders.

It has been reported that water retention and hyponatraemia were observed in advanced stage of COPD.[21] The association between hyponatraemia, morbidity[22–25] and mortality has been demonstrated in the literature across different medical conditions.[25–28] Improvement of hyponatraemia was also observed to be associated with a reduced risk of overall mortality.[29,30] The negative impact of this electrolyte disturbance, even a mild one at stable state, should not be neglected as there are numerous reports on its adverse outcomes.

In our study, the same phenomenon is observed again. To our best knowledge, this is the first report on the impact of stable-state hyponatraemia as an independent predictor of mortality. The highest stable-state serum sodium level was also shown to be correlated with subsequent AECOPD and hospitalized AECOPD frequency.

The findings of our study call for the attention to monitor electrolytes among patients with COPD. Indeed, it is not uncommon to observe hyponatraemia in patients with COPD. Stable-state hyponatraemia was observed among 16.2% of patients, and the majority of them were due to SIADH. The degree of hyponatraemia can be mild, in which some physicians might have overlooked. In the hyponatraemia group, the mean lowest baseline serum sodium level was 132 ± 2 mmol/L, which might be taken as lowish level only in real-world clinical settings without the need of intervention. It is not surprising that some clinicians may decide not to take further actions when the serum sodium level is just marginally low. However, the presence of such a low serum sodium level already suggests ongoing physiological disturbances that lead to electrolyte disturbance, mostly through SIADH. It is crucial to be alerted to even trivial hyponatraemia among patients with COPD at stable-state, as it is definitely an abnormality that is associated with poor prognosis. Timely investigations and management of hyponatraemia is important as previous studies have demonstrated the beneficial effect of correcting hyponatraemia. The possible alternative causes should not be overlooked as our study also suggested that 7.7% of the patients without a documented history of malignancies eventually died of a newly developed malignancies in the follow-up period. The possibility of an occult malignancy, in particular lung cancer, should be aggressively investigated in this group of patients. Alternatively, smoldering and low-grade infections or infestations could also be contributing to hyponatraemia in these patients. This is supported by the fact that the majority of patients in this cohort died of pneumonia. Vaccination against various pathogens and evidence-based withdrawals of ICS cannot be over-emphasized. Last but not least, monitoring of cardiac function, both left and right ventricular function should be advised as these patients are prone to develop cardiovascular diseases including left heart failure as well as cor pulmonale from advanced COPD, which could also be linked to the development of hyponatraemia.

Our study concurs with the literature that correction of hyponatraemia is beneficial, in terms of OS and AECOPD frequency. While identifying the cause of hyponatraemia is important, correction of hyponatraemia by fluid restriction in

SIADH, replacement with sodium chloride or other means depending on the underlying cause could be a simple and cost-effective mean to prevent the adverse outcomes among patients with COPD.

We attempted to investigate the association between the degree of hyponatraemia and various clinical outcomes. However, as there were no patients in the severe hyponatraemia group and only 7 in the moderate hyponatraemia group, we could not draw a definite conclusion due to a small sample size, though the numbers point towards the possible role of more severe hyponatraemia might be linked to increases in the number of subsequent AECOPD.

The limitations of this study include the single-centre retrospective nature and the relatively small number of patients. Being retrospective in nature, the number of blood tests for serum sodium level and the timing of the tests were not unified. Ideally, a protocolized regular monitoring of renal function in a prospective study could avoid this potential selection bias. The relatively small sample size also limits the ability of this study to draw a definite conclusion and having a study with larger scale shall be able to overcome this limitation. The cause of hyponatraemia was undetermined in 6 out of the 44 patients. This might limit the assessment of the association between hyponatraemia and prognosis in COPD. Patients included in this study were followed up in the respiratory specialty clinic, who represent mainly more severe COPD. Lack of those patients with mild COPD who were managed in the primary care setting may lead to selection bias. However, both hyponatraemia and mortality are expected to be seen in more severe COPD, thus unlikely to have a major impact on the study findings even without including milder COPD patients.

Taken together, our present findings provide further evidence on the adverse outcomes from stable-state hyponatraemia. Hyponatraemia is associated with both higher mortality and probably subsequent AECOPD frequency. This calls for the regular monitoring of serum sodium level among patients with COPD. Aggressive management of hyponatraemia is warranted in COPD.

Conclusions

Stable-state hyponatraemia is a common electrolyte disturbance in COPD, occurring in 16.2% of the patients. It is associated with increased mortality and probably AECOPD frequency among patients with COPD. Monitoring of serum sodium level with prompt correction would be beneficial in terms of mortality and exacerbation reduction.

Clinical Trials Details

This study is not a clinical trial, and no registration detail will be provided.

Data Sharing Statement

All available data are presented in the manuscript, and no additional data will be provided. Data are not available to be shared.

Ethics Approval and Consent to Participate

This study and the waiver of informed consents were approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (UW 23-356). The study was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest in this work.

References

1. Mortality GBD. Causes of death C. global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the global burden of disease study 2013. *Lancet*. 2015;385:117–171.
2. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. A 15-year follow-up study. *Am Rev Respir Dis*. 1979;119:895–902. doi:10.1164/arrd.1979.119.6.895
3. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary disease. The national institutes of health intermittent positive-pressure breathing trial. *Am Rev Respir Dis*. 1989;139:1435–1438. doi:10.1164/ajrccm/139.6.1435
4. de Torres JP, Cote CG, Lopez MV, et al. Sex differences in mortality in patients with COPD. *Eur Respir J*. 2009;33:528–535. doi:10.1183/09031936.00096108
5. Lenoir A, Whittaker H, Gayle A, Jarvis D, Quint JK. Mortality in non-exacerbating COPD: a longitudinal analysis of UK primary care data. *Thorax*. 2023;78:904–911. doi:10.1136/thorax-2022-218724
6. Ong KC, Earnest A, Lu SJ. A multidimensional grading system (BODE index) as predictor of hospitalization for COPD. *Chest*. 2005;128:3810–3816. doi:10.1378/chest.128.6.3810
7. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:1005–1012. doi:10.1056/NEJMoa021322
8. Corona G, Giuliani C, Parenti G, et al. The economic burden of hyponatremia: systematic review and meta-analysis. *Am J Med*. 2016;129:823–35e4. doi:10.1016/j.amjmed.2016.03.007
9. Corona G, Giuliani C, Parenti G, et al. Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. *PLoS One*. 2013;8:e80451. doi:10.1371/journal.pone.0080451
10. Selmer C, Madsen JC, Torp-Pedersen C, Gislason GH, Hyponatremia FJ. all-cause mortality, and risk of cancer diagnoses in the primary care setting: a large population study. *Eur J Intern Med*. 2016;36:36–43. doi:10.1016/j.ejim.2016.07.028
11. Tokgoz Akyil F, Tural Onur S, Abali H, et al. Hyponatremia is an independent predictor of emergency department revisits in acute exacerbation of COPD. *Clin Respir J*. 2021;15:1063–1072. doi:10.1111/crj.13409
12. Garcia-Sanz MT, Martinez-Gestoso S, Calvo-Alvarez U, et al. Impact of hyponatremia on COPD exacerbation prognosis. *J Clin Med*. 2020;9:503. doi:10.3390/jcm9020503
13. Deep A, Behera PR, Subhankar S, Rajendran A, Rao CM. Serum electrolytes in patients presenting with acute exacerbation of chronic obstructive pulmonary disease (COPD) and their comparison with stable COPD patients. *Cureus*. 2023;15:e38080. doi:10.7759/cureus.38080
14. Fan L, Sun D, Yang J, et al. Association between serum sodium and long-term mortality in critically Ill Patients with comorbid chronic obstructive pulmonary disease: analysis from the MIMIC-IV database. *Int J Chron Obstruct Pulmon Dis*. 2022;17:1143–1155. doi:10.2147/COPD.S353741
15. Chalela R, Gonzalez-Garcia JG, Chillaron JJ, et al. Impact of hyponatremia on mortality and morbidity in patients with COPD exacerbations. *Respir Med*. 2016;117:237–242. doi:10.1016/j.rmed.2016.05.003
16. Lindner G, Herschmann S, Funk GC, Exadaktylos AK, Gygli R, Ravioli S. Sodium and potassium disorders in patients with COPD exacerbation presenting to the emergency department. *BMC Emerg Med*. 2022;22:49. doi:10.1186/s12873-022-00607-7
17. Winther JA, Brynildsen J, Hoiseth AD, et al. Prevalence and prognostic significance of hyponatremia in patients with acute exacerbation of chronic obstructive pulmonary disease: data from the Akershus cardiac examination (ACE) 2 study. *PLoS One*. 2016;11:e0161232. doi:10.1371/journal.pone.0161232
18. Castello LM, Gavelli F, Baldrighi M, et al. Hypernatremia and moderate-to-severe hyponatremia are independent predictors of mortality in septic patients at emergency department presentation: a sub-group analysis of the need-speed trial. *Eur J Intern Med*. 2021;83:21–27. doi:10.1016/j.ejim.2020.10.003
19. (GOLD) GIfCOLD. Global initiative for chronic obstructive lung disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: 2023 Report. 2023.
20. Celli BR, Fabbri LM, Aaron SD, et al. An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the Rome proposal. *Am J Respir Crit Care Med*. 2021;204:1251–1258. doi:10.1164/rccm.202108-1819PP
21. Valli G, Fedeli A, Antonucci R, Paoletti P, Palange P. Water and sodium imbalance in COPD patients. *Monaldi Arch Chest Dis*. 2004;61:112–116. doi:10.4081/monaldi.2004.708
22. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med*. 2006;119:71e1–8. doi:10.1016/j.amjmed.2005.09.026
23. Renneboog B, Sattar L, Decaux G. Attention and postural balance are much more affected in older than in younger adults with mild or moderate chronic hyponatremia. *Eur J Intern Med*. 2017;41:e25–e6. doi:10.1016/j.ejim.2017.02.008
24. Kuo SCH, Kuo PJ, Rau CS, Wu SC, Hsu SY, Hsieh CH. Hyponatremia is associated with worse outcomes from fall injuries in the elderly. *Int J Environ Res Public Health*. 2017;14:460. doi:10.3390/ijerph14050460
25. Peri A. Morbidity and mortality of hyponatremia. *Front Horm Res*. 2019;52:36–48.
26. Choi JS, Kim CS, Bae EH, et al. Prognostic impact of hyponatremia occurring at various time points during hospitalization on mortality in patients with acute myocardial infarction. *Medicine*. 2017;96:e7023. doi:10.1097/MD.0000000000007023
27. Madan VD, Novak E, Rich MW. Impact of change in serum sodium concentration on mortality in patients hospitalized with heart failure and hyponatremia. *Circ Heart Fail*. 2011;4:637–643. doi:10.1161/CIRCHEARTFAILURE.111.961011
28. Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med*. 2010;170:294–302. doi:10.1001/archinternmed.2009.513
29. Corona G, Giuliani C, Verbalis JG, Forti G, Maggi M, Peri A. Hyponatremia improvement is associated with a reduced risk of mortality: evidence from a meta-analysis. *PLoS One*. 2015;10:e0124105. doi:10.1371/journal.pone.0124105
30. Yoshioka K, Matsue Y, Kagiyama N, et al. Recovery from hyponatremia in acute phase is associated with better in-hospital mortality rate in acute heart failure syndrome. *J Cardiol*. 2016;67:406–411. doi:10.1016/j.jjcc.2015.12.004