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Original article

The impact of the correction of hyponatremia during hospital admission on the prognosis of SARS-CoV-2 infection☆

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ABSTRACT

Background: SARS-CoV-2 infection is frequently associated with hyponatremia (plasma sodium <135 mmol/L), being associated with a worse prognosis. The incidence of hyponatremia is estimated to be 20–37% according to the series, but there are no data on the prognosis after correction of hyponatremia. Therefore, our objectives were: to analyse the incidence and severity of hyponatremia at hospital admission, and to determine the association of this hyponatremia with the prognosis of COVID-19.
Methods: Observational and retrospective cohort study. Patients who were admitted with a diagnosis of COVID-19 infection and hyponatremia, in the period March-May 2020, were included. We recorded epidemiological, demographic, clinical, biochemical, and radiological variables of SARS-CoV-2 infection and hyponatremia at the time of diagnosis and during hospitalization. The clinical follow-up ranged from admission to death or discharge.
Results: 91 patients (21.8%) of the 414 admitted for SARS-CoV-2 infection presented hyponatremia (81.32% mild hyponatremia, 9.89% moderate and 8.79% severe). The absence of correction of hyponatremia 72–96 h after hospital admission was associated with higher mortality in patients with COVID-19 (Odds Ratio 0.165; 95% confidence interval: 0.018–0.686; $p = 0.011$). 19 patients (20.9%) died. An increase in mortality was observed in patients with severe hyponatremia compared with moderate and mild hyponatremia during hospital admission (37.5% versus 11.1% versus 8.1%, $p = 0.041$).
Conclusion: We conclude that persistence of hyponatremia at 72–96 h of hospital admission was associated with higher mortality in patients with SARS-Cov-2.

Impacto de la corrección temprana de la hiponatremia en el pronóstico de la infección del síndrome respiratorio agudo grave del coronavirus 2 (SARS-CoV-2)

Palabras clave:
Síndrome respiratorio agudo grave del coronavirus 2
Enfermedad del coronavirus 2019
Hiponatremia y mortalidad

RESUMEN

Introduccion: La infección por SARS-CoV-2 se asocia con frecuencia con hiponatremia (sodio plasmático <135 mmol/l), relacionándose con peor pronóstico. La incidencia de la hiponatremia se estima en 20–37% según las series, pero no existen datos sobre el pronóstico tras la corrección de la hiponatremia. Por ello, nuestros objetivos fueron: analizar la incidencia y gravedad de la hiponatremia al ingreso hospitalario, y determinar la asociación de dicha hiponatremia con el pronóstico del COVID-19.

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Material y método: Estudio de cohorte observacional y retrospectivo. Se incluyeron pacientes que ingresaron con diagnóstico de infección por COVID-19 e hiponatremia, en el periodo marzo-mayo 2020. Registramos variables epidemiológicas, demográficas, clínicas, analíticas y radiológicas de la infección por SARS-CoV-2 e hiponatremia al momento del diagnóstico y durante la hospitalización. El seguimiento clínico comprendió desde el ingreso hasta el exitus o el alta.
Resultados: 91 pacientes (21,8%) de los 414 ingresados por infección del SARS-CoV-2 presentaron hiponatremia (81,32% hiponatremia leve, 9,89% moderada y 8,79% grave). La ausencia de corrección de la hiponatremia a las 72–96 horas del ingreso hospitalario estuvo asociado a mayor mortalidad en los pacientes con COVID-19 (OR 0,165; 95% intervalo de confianza: 0,018–0,686; p = 0,011). Fallecieron 19 pacientes (20,9%). Se observó un aumento de la mortalidad en pacientes con hiponatremia grave en comparación con hiponatremia moderada y leve durante el ingreso (37,5% versus 11,1% versus 8,1%, respectivamente, p = 0,041).
Conclusiones: La persistencia de la hiponatremia tras las primeras 72–96 horas del ingreso hospitalario fue asociada a mayor mortalidad+- en los pacientes con SARS-Cov-2.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has a variable clinical spectrum, ranging from an asymptomatic carrier state, anosmia, ageusia or mild upper respiratory tract disease to severe pneumonia that can lead to acute respiratory distress syndrome, severe respiratory failure accompanied by various extrapulmonary manifestations including multi-organ failure with cardiovascular, neurological, renal involvement and even death[1,2]. In addition, renal injury may be associated with abnormalities in the mechanisms involved in regulating sodium and water balance.

Hyponatraemia defined as plasma sodium levels Na^+ <135 mmol/l is the most common electrolyte abnormality in hospitalised patients[3]. The risk of death during hospital admission is increased by more than 50% compared to patients with normal sodium levels[4]. A prevalence of hyponatraemia of up to 28–30% has been described in patients admitted with community-acquired pneumonia (CAP), increasing the risk of mortality and admission to intensive care units (ICU) and prolonging hospital stay, in addition to generating a significant economic burden for the health system[5,6]. The risk of hyponatraemia occurrence in patients with CAP varies according to the causative pathogen in up to 46% of patients with *Legionella pneumophila* infection compared to 14% of patients with CAP caused by other pathogens[7], while the incidence of hyponatraemia in patients with coronavirus disease of 2019 (COVID-19) described in recent cohorts ranges from 20% to 37%[8–10]. In addition, an association of hyponatraemia with higher mortality from COVID-19 has been described in American and Chinese cohorts. That is why recent studies have attempted to associate hyponatraemia as a marker of poor prognosis in these patients[11,12].

It should be noted that up to 60% of SARS-CoV-1 patients had watery diarrhoea associated with mild hyponatraemia, secondary to virus replication within intestinal epithelial cells[13]. Initially, several case reports described the association between syndrome of inappropriate antidiuretic hormone secretion (SIADH) and sodium loss in stool as the most common etiological agents of COVID-19[14–16]. To date, the possible underlying pathophysiological mechanisms are unknown, and it is unclear whether hyponatraemia is caused by a specific involvement of COVID-19 or secondary to the respiratory complication of the infectious condition.

However, at present there is no information available regarding the impact on mortality risk and poor prognosis in patients with COVID-19 after correction of hyponatraemia. Furthermore, it is important to correctly manage hyponatraemia caused by easily reversible mechanisms, as effective intervention can result in over-correction (hypernatraemia) and associated sequelae, including haemorrhage, arrhythmia and osmotic demyelination syndrome[17]. Therefore, our objectives were: to analyse the incidence and severity of hyponatraemia on admission for COVID-19 in our hospital and to determine the association of hyponatraemia with prognosis.

Material and methods

Study design

Single-center, retrospective, observational cohort study. All consecutive patients over 18 years of age who were admitted to our hospital with a diagnosis of SARS-CoV-2 infection from 15 March to 15 May 2020, who also had a diagnosis of hyponatraemia, were included. The diagnosis of COVID-19 was defined by a positive quantitative real-time polymerase chain reaction (RT-PCR) in a nasopharyngeal swab for SARS-CoV-2 virus, according to the criteria proposed by the Spanish Ministry of Health technical document[18] and using the Seegene COVID-19 kit.

Ethical principles

The study complied with the principles set forth in the Declaration of Helsinki and was approved by the Drug Research Ethics Committee of our hospital. The application for a waiver of informed consent was approved, providing a detailed justification, while protecting the patients' right to privacy at all times. Data on hospitalization, clinical and demographic characteristics were obtained from hospital records and electronic medical records of the included patients. All data were collected anonymously and none of the authors were the patients' attending physicians.

Definition of variables

The following variables were recorded for the study: the patients' pre-admission comorbidities, clinical, laboratory and radiological data on SARS-CoV-2 infection at the time of diagnosis and during hospitalisation and, finally, data related to hyponatraemia.

The comorbidities recorded were hypertension (HTN), type 2 diabetes mellitus (DM2), obesity (defined as body mass index > 30 kg/m^2), dyslipidaemia, smoking, obstructive sleep apnoea syndrome (OSAS), chronic obstructive pulmonary disease, asthma, obstructive uropathy and cancer. Chronic kidney disease (CKD) was classified based on the estimated glomerular filtration rate (eGFR) using the *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI) equation, as recommended by the *Kidney Improving Global Outcomes* international group. CKD was considered when eGFR < 60 $mL/min/m^2$ (stages G3-G5). History of antihypertensive

Table 1
Epidemiological characteristics, comorbidities and antihypertensive treatment of patients stratified by 3 different serum sodium levels.

Variable		Total (n = 91)	Sodium concentration			
			130–135 mmol/l (n = 74)	126–129 mmol/l (n = 9)	<125 mmol/l (n = 8)	P-value
Sex, n (%)	Males	64 (70.3)	54 (72)	6 (66.7)	4 (50)	–
Age (mean ± SD)	68.9 ± 15.1	67.9 ± 15.1	72.6 ± 17.6	74.3 ± 12.8	0.399	
Comorbidities, n (%)	CKD	11 (12.1)	7 (9.5)	3 (33.3)	1 (12.5)	0.116
	3a	2 (2.2)	1 (1.35)	0 (0)	1 (12.5)	0.029
	3b	7 (7.7)	4 (5.4)	3 (33.3)	0 (0)	
	4	2 (2.2)	2 (2.7)	0 (0)	0 (0)	
	HTN	50 (55)	38 (51.35)	6 (66.7)	6 (75)	0.335
	Obesity	10 (11)	10 (16.2)	0 (0)	0 (0)	0.275
	DM 2	27 (29.67)	25 (33.8)	0 (0)	2 (25)	0.106
	Dyslipidemia	30 (33)	25 (33.8)	2 (22.2)	3 (37.5)	0.753
	Cancer	20 (22)	17 (23)	1 (11.1)	2 (25)	0.703
	Asthma	1 (1.1)	1 (1.4)	0 (0)	0 (0)	0.890
	COPD	4 (4.4)	2 (2.7)	1 (11.1)	1 (12.5)	0.257
	Smoking	16 (17.58)	13 (17.6)	1 (11.1)	2 (25)	0.756
	OSAHS	3 (3.3)	3 (4.1)	0 (0)	0 (0)	0.700
	Obstructive uropathy	2 (2.2)	2 (2.7)	0 (0)	0 (0)	0.791
Previous treatment, n (%)	ACEI	20 (22)	13 (17.6)	2 (22.2)	5 (62.5)	0.014
	ARB	13 (14.3)	11 (14.9)	1 (11.1)	1 (12.5)	0.944

ARB: angiotensinII receptor blocker; SD: standard deviation; DM 2: diabetes mellitus type 2; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease according to the *Kidney Improving Global Outcomes* (KIDGO) classification; HTN: arterial hypertension; ACEI: angiotensin converting enzyme inhibitor; n: number of patients; %: percentage.

treatment with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) was recorded.

Regarding variables related to SARS-CoV-2 infection, in cases where the initial RT-PCR was negative and the clinical suspicion remained high, a second RT-PCR and/or chest computed tomography (CT) scan was performed. The radiological diagnosis of pneumonia, the treatment used, and the presence of diarrhoea were included. In addition, severity of infection was defined according to the technical document of the Spanish Ministry of Health[18], with COVID-19 critical status being the need for mechanical ventilation or other criteria for ICU care (respiratory failure, septic shock and/or multi-organ failure). COVID-19 outcome was also recorded as death from hospital admission to discharge or post-hospitalisation control 3 months after hospital discharge.

Regarding the variables related to hyponatraemia, at least one measurement of plasma sodium concentration was obtained at hospital admission. Hyponatraemia values were corrected with glycaemia, for every 100 mg/dl increase in glucose we used a correction factor of 1.7 mmol/l in plasma sodium[19]. Patients were classified into 3 groups according to the severity levels of hyponatraemia at hospital admission: mild hyponatraemia was defined as natraemia between 130 and 135 mmol/l, moderate between 125 and 129 mmol/l and severe if Na^+ values were less than 125 mmol/l. The correction of hyponatraemia was performed according to the recommendations of the current clinical guidelines[20]. There was no regularity in the natraemia controls; they were carried out according to the criteria of the attending physicians. Serum sodium was collected longitudinally on the day of admission, 24–48 h and 72–96 h after hospital admission.

Statistical analysis

Descriptive statistics were used for the presentation of variables. Non-parametric quantitative variables were expressed as medians and interquartile ranges, while parametric quantitative variables were expressed as means and standard deviations. The Kolmogorov-Smirnov test was used to assess the distribution of the variables. The single-factor analysis of variance (ANOVA test) was used for continuous variables when normality and homogeneity of variance were met. Otherwise, the nonparametric Mann-Whitney U or Kruskal-Wallis test was used. In addition, cross-tabulations were generated, using the Chi-square test and Fisher's exact test in the analysis of categorical variables. In order to analyse the association between correction of hyponatraemia and in-hospital mortality from COVID-19, the Chi-square and Student's t tests were used, and a multivariable model was subsequently generated using Cox regression. All statistical tests were considered bilateral and significant values were those with a bilateral $p < 0.05$. The data were analysed with the statistical software SPSS-IBM (version 21.0).

Results

A total of 414 patients were admitted to our hospital between 15th March and 15th May 2020 with a diagnosis of COVID-19, with a positive RT-PCR test for SARS-CoV-2. The incidence of hyponatraemia < 135 mmol/l was 21.98% (n = 91), with a mean age of 68.9 ± 15.1 years, increasing according to the severity of hyponatraemia. 70.3% of our sample were male. The mean hospital stay was 13 days (IQR: 7–38). The most common comorbidities were: HTN (55%), dyslipidaemia (30.3%) and DM2 (29.7%), while CKD (eGFR < 60 ml/min) was observed in 11 patients (12.1%). 22% and 13% of the patients had received prior antihypertensive treatment with ACEIs and ARBs, respectively. The rest of the baseline characteristics are described in Table 1.

The patients were classified into 3 groups according to the degree of hyponatraemia at hospital admission: 74 patients (81.32%) had mild hyponatraemia, 9 patients (9.89%) moderate hyponatraemia, and 8 patients (8.79%) severe hyponatraemia (Table 1). A statistically significant relationship was found (p = 0.029) between the severity of hyponatraemia and the stage of CKD, with stage 3 b being the most common in 7 (7.7%); distributed in 4 (5.4%) and 3 (33.3%) in mild and moderate hyponatraemia, respectively, as well as with treatment with ACEIs: 13 (17.6%), 2 (22.2%) and 5 (62.5%) in the mild, moderate and severe hyponatraemia group, respectively (p = 0.014) (Table 1).

There were no statistically significant differences between hyponatraemia groups in terms of serum glucose, urea, creatinine, uric acid, troponin, creatine phosphokinase, calcium, phosphorus, potassium, thyroid hormones and fibrinogen. Procalcitonin (1.8 ± 2 ng/mL), C-reactive protein (6.5 ± 3.1 mg/dl), lactate

Table 2
Laboratory results of patients stratified by 3 serum sodium levels.

Variable		Overall ($n=91$)	Sodium concentration			p-value
			130–135 mmol/l ($n=74$)	125–129 mmol/l ($n=9$)	<125 mmol/l ($n=8$)	
Laboratory values (mean ± SD)	Na^+ (mmol/l)	131.11 ± 3.8	132.68 ± 1.3	127.11 ± 1.4	121.13 ± 3	–
	Na^+ adjusted to glucose (mmol/l)	131.6 ± 4	133.2 ± 1.4	127.3 ± 1.3	121.3 ± 1.2	–
	Glucose (mg/dl)	154.9 ± 91.9	162.2 ± 97.9	130.6 ± 57.1	114.9 ± 42	0.265
	Urea (mg/dl)	55.7 ± 40.2	55.2 ± 38.9	70.3 ± 48.4	43.9 ± 43.7	0.392
	Creatinine (mg/dl)	1.2 ± 1.2	1.1 ± 1.1	1.7 ± 1.9	1 ± 0.7	0.348
	Uric acid (mg/dl)	5.3 ± 2.6	5.2 ± 2	7.4 ± 6.2	4.2 ± 2.1	0.106
	LDH (IU/l)	362.5 ± 252.5	347.2 ± 158	351.2 ± 124	513 ± 708.7	0.211
	Troponin (ng/mL)	29.6 ± 24.3	26.7 ± 21.2	22.3 ± 23.6	51.3 ± 36.7	0.246
	CPK (µmol/l)	223 ± 815.2	224.3 ± 887.7	238 ± 256.1	197.71 ± 211.5	0.996
	Ca^{+2} (mmol/l)	8.2 ± 1.4	8.3 ± 1.4	7.4 ± 2.2	7.9 ± 0.73	0.280
	P^{+3} (mg/dl)	3.3 ± 0.8	3.3 ± 0.8	3.7 ± 0.9	3.2 ± 0.6	0.327
	K^+ (mmol/l)	5.9 ± 12.6	6.2 ± 14	4.8 ± 0.5	4.5 ± 0.8	0.902
	Cl– (mmol/l)	93.7 ± 10.3	94.7 ± 10.7	93 ± 5.6	84.7 ± 6	0.032
	Plasma osmolarity	280.1 ± 12	283.6 ± 9.1	273.2 ± 9.2	255.9 ± 9	–
	Procalcitonin (ng/mL)	0.8 ± 2.8	0.8 ± 3	0.3 ± 0.3	1.8 ± 2	0.639
	CRP (mg/dl)	19 ± 56.5	21.7 ± 62.3	8.1 ± 6.7	6.5 ± 3.1	0.664
	Ferritin (ng/mL)	1446.9 ± 3494.7	1056.2 ± 820.3	1219.3 ± 715.2	5825.7 ± 12313	0.05
	TSH (µunits/mL)	2.1 ± 2.8	1.7 ± 1.5	1.4 ± 1.2	5.1 ± 6.5	0.066
	T_4 (ng/dl)	1.3 ± 0.35	1.4 ± 0.4	1.4 ± 0.4	1.1 ± 0.3	0.534
	Fibrinogen (mg/dl)	638.3 ± 198.3	644.5 ± 195.4	674.7 ± 209.7	543.5 ± 210.2	0.337
	D-dimer (ng/mL)	2076.6 ± 2973.3	2056.6 ± 2747.6	1017.9 ± 712.5	3297.8 ± 5341.9	0.310

Ca^{+2}: serum calcium; Cl-: serum chloride; CPK: creatinine phosphokinase; SD: standard deviation; K^+: serum potassium; LDH: lactate dehydrogenase; n: number of patients; Na^+: plasmatic sodium; P^{+3}: Serum phosphate; CRP: C-reactive protein; T_4: free thyroxine; TSH: thyroid stimulating hormone.

Table 3
Clinical characteristics and degrees of severity of the 2019 coronavirus disease in patients stratified by 3 different serum sodium levels.

Variable		Total $n=91$ (100%)	Sodium concentration			P-value
			130–135 mmol/l $n=74$ (81.3%)	125–129 mmol/l $n=9$ (9.9%)	<125 mmol/l $n=8$ (8.8%)	
COVID diagnosis	RT-PCR SARS-CoV-2	66 (72.5)	56 (75.7)	5 (55.6)	5 (62.5)	0.355
	Clinical signs and symptoms	25 (27.5)	18 (24.3)	4 (44.4)	3 (37.5)	
COVID-19 severity, *n* (%)	Mild	12 (13.2)	10 (13.5)	1 (11.1)	1 (12.5)	0.012
	Moderate	14 (15.4)	14 (18.9)	0 (0)	0 (0)	
	Severe	54 (59.3)	43 (58.1)	8 (88.9)	3 (37.5)	
	Critical	11 (12.1)	7 (9.5)	0 (0)	4 (50)	
Clinical, *n* (%)	Pneumonia	87 (95.6)	74 (100)	8 (88.9)	5 (62.5)	0
	Unilateral infiltrates	7 (7.7)	5 (6.8)	1 (11.1)	1 (12.5)	0
	Bilateral infiltrates	80 (87.9)	69 (93.24)	7 (77.8)	4 (50)	
	Diarrhoea	23 (25.3)	19 (25.7)	1 (11.1)	3 (37.5)	0.450
Readmissions	0	77 (84.6)	63 (85.1)	7 (77.8)	7 (87.5)	0.274
	1	10 (11)	8 (10.8)	1 (11.1)	1 (12.5)	
	2	1 (1.1)	1 (1.4)	0 (0)	0 (0)	
	3	2 (2.2)	2 (2.7)	0 (0)	0 (0)	
	4	1 (1.1)	0 (0)	1 (11.1)	0 (0)	

n: number of patients; RT-PCR: quantitative real-time polymerase chain reaction; SARS-CoV-2:*severe acute respiratory syndrome coronavirus 2%*: percentage.

dehydrogenase (513 ± 708.7 IUI/l), thyroid stimulating hormone (5.1 ± 6.5 U/mL) and D-dimer (3. 297.8 ± 5,341.9 ng/mL) showed higher values in patients with severe hyponatraemia compared to the rest of the groups, without being statistically significant (Table 2). Mean serum chloride values were significantly lower (84.7 ± 6 mEq/l, $p=0.032$) and significantly higher ferritin (5825.7 ± 1231.3, $p=0.05$) in the severe hyponatraemia group (Table 2).

95.6% of the patients developed pneumonia, of these 80 (87.9%) patients developed pneumonia with bilateral infiltrates. Twenty-three (25.3%) suffered from diarrhoea, with this being more frequent in patients with severe hyponatraemia (37.5%). COVID-19 critical status was observed in 11 patients (12.1%); 7 of them had mild hyponatraemia (9.5%) and the remaining 4 had severe hyponatraemia (50%) ($p=0.012$) (Table 3).

Regarding the treatment of SARS-Cov-2 infection, hydroxychloroquine was the most used drug during hospital admission in 89% of cases, maintaining this prevalence in the 3 hyponatraemia groups, followed by azithromycin (67%), dexamethasone (65.9%), interferon (41.8%) and lopinavir-ritonavir (37.4%). 58.2% of the patients were treated with low molecular weight heparin (LMWH) (Table 4).

Nineteen patients (20.9%) died, 10 of them during admission and the remaining 9 after hospital discharge. An increased mortality was observed in patients with severe hyponatraemia compared to the moderate and mild hyponatraemia group (50% versus 22.2% versus 17.6%, respectively, $p=0.10$). This result was statistically significant with respect to in-hospital mortality (37.5% versus 11.1% versus 8.1%, respectively; $p=0.041$). Of the 19 patients who died, the mean survival was 19.5 days (Table 5).

Table 4
Treatment received by patients with coronavirus disease 2019 stratified by 3 serum sodium levels.

Variable		Total $n = 91$ (100%)	Sodium concentration			P-value
			130–135 mmol/l $n = 74$ (81.3%)	125–129 mmol/l $n = 9$ (9.9%)	<125 mmol/l $n = 8$ (8.8%)	
Treatment received, *n* (%)	Hydroxychloroquine	81 (89)	66 (89.2)	8 (88.9)	7 (87.5)	0.989
	Azithromycin	61 (67)	51 (68.9)	6 (66.7)	4 (50)	0.557
	Ritonavir/lopinavir	34 (37.4)	31 (41.9)	3 (33.3)	0 (0)	0.064
	Steroids	60 (65.9)	51 (68.9)	6 (66.7)	3 (37.5)	0.204
	Cyclosporine	9 (9.9)	8 (9.8)	0 (0)	1 (12.5)	0.571
	Interferon	38 (41.8)	36 (48.6)	2 (22.2)	0 (0)	0.014
	Heparin	53 (58.2)	42 (56.8)	5 (55.6)	6 (75)	0.601
	Co-trimoxazole	1 (1.1)	1 (1.2)	0 (0)	0 (0)	0.890
	Ceftriaxone	38 (41.76)	29 (39.2)	4 (44.4)	5 (62.5)	0.440

n: number of patients; %: percentage.

Table 5
Mortality of patients with coronavirus 2019 disease stratified by 3 serum sodium levels.

Variable		Total $n = 91$ (100%)	Sodium concentration			P-value
			130–135 mmol/l $n = 74$ (81.3%)	125–129 mmol/l $n = 9$ (9.9%)	< 125 mmol/l $n = 8$ (8.8%)	
Death, *n* (%)	Totals	19 (20.9)	13 (17.6)	2 (22.2)	4 (50)	0.100
	At admission	10 (11)	6 (8.1)	1 (11.1)	3 (37.5)	0.041
	After admission	9 (9.9)	7 (9.5)	1 (11.1)	1 (12.5)	0.955
Survival in days (mean ± SD)		19.5 ± 18	16.8 ± 14.4	15 ± 9.9	30.5 ± 29.6	0.405

SD: standard deviation; n: number of patients; %: percentage.

Table 6
Multivariate Cox regression adjustment model of natraemia correction at 72–96 h adjusted for age, sex, baseline creatinine and D-dimer.

	P-value	HR	95.0% CI for HR	
			Lower	Higher
Na+ correction at 72–96 h	0.019	0.149	0.030	0.735
Sex	0.728	1.335	0.262	6.798
Age at admission	0.903	0.997	0.948	1.048
Serum creatinine; mg/dl	0.233	1.258	0.863	1.833
D-dimer; ng/mL	0.010	1.000	1.000	1.000

HR: *hazard ratio*; CI: confidence interval; Na^+: plasma sodium.

Hyponatraemia correction at 24–48 h had no significant relationship with survival on univariate analysis (*odds ratio* [OR]: 0.425 [0.096–1.777]; 95% confidence interval [CI]; $p = 0.206$), while correction at 72–96 h had a statistically significant association with survival (OR: 0.185 [0.042–0.812]; 95% CI; $p = 0.024$). This relationship was maintained in a Cox regression model that included variables related in other studies to mortality in COVID-19 disease such as age, sex and D-dimer. In addition, baseline creatinine was included as it also had a statistically significant association with mortality and potentially with sodium levels (Table 6).

Discussion

This longitudinal retrospective cohort of 414 hospitalised patients with a diagnosis of COVID-19 demonstrates a high incidence of hyponatraemia < 135 mmol/l at hospital admission of 21.98%, with mild hyponatraemia being the most frequent in 81% of cases, which coincides with data published by other cohorts[8,9,21–23], such as the *Health Outcome Predictive Evaluation for COVID-19*(HOPE-COVID-19) study, a multicentre study of 37 hospitals in 7 countries, with Spanish collaboration, where 25% of patients hospitalised for COVID-19 had hyponatraemia[10]. Tzoulis et al.[23] recently published a retrospective study of 488 hospitalised COVID-19 patients, mean age 68 years, from 2 London hospitals between February and May 2020; hyponatraemia at admission was 24.6%, coinciding with our data.

Various mechanisms have been postulated as leading to an increased prevalence of hyponatraemia in non-COVID-19 CAP patients, such as SIADH, some drugs such as diuretics and certain pathogens such as *Legionella pneumoniae*[24]. According to previously published results in case reports and descriptive studies, SIADH appears to be the main cause of COVID-19-associated hyponatraemia[25], according to the diagnostic criteria proposed by Bartter and Schwartz[20]. The pathophysiological explanation for this event occurs as in other infectious diseases, where some alteration of the host immune system is involved[26]. This can lead to the development of a poor response in the mechanisms involved in regulating water balance, which leads in severe cases to an overproduction of antidiuretic hormone (ADH) of non-osmotic cause. This problem is mainly due to an excess of water and not to a deficit of salt, which accumulates in the nervous system, worsening its functioning.

On the other hand, numerous studies have shown a significant increase in serum levels of interleukin 1 and 6 (IL-1, IL-6) in patients with severe COVID-19[27]. IL-6 is presumed to play a role in sodium homeostasis by non-osmotic release of vasopressin/arginine[14]. In support of this hypothesis Berni et al.[28] observed an improvement in hyponatraemia in a small cohort of 29 patients with COVID-

19 after anti-IL-6 therapy. Coinciding with these data, our study found SIADH and hypovolaemic hyponatraemia due to gastrointestinal losses as the main aetiologies in the group of patients with severe hyponatraemia in those cases where a correct assessment of volume status, urinary and serum osmolarity could be obtained for a reliable diagnosis, but IL-6 measurement was not routinely performed.

On the other hand, this electrolyte balance disturbance produced by unknown factors may be accentuated or triggered in those patients with serious underlying diseases such as heart failure, cancer or respiratory problems. In addition, direct disruption of the renin angiotensin-aldosterone system through binding of SARS-CoV-2 to angiotensin-converting enzyme 2 has also been involved in the pathogenesis of COVID-19 and related electrolyte disturbances[12].

As in other infectious diseases, hyponatraemia in COVID-19 has been shown to be a marker of poor prognosis. Our study showed that severe hyponatraemia and the absence of hyponatraemia correction at 72–96 h after hospital admission was associated with increased risk of mortality and severity of COVID-19. More patients with severe hyponatraemia at hospital admission died compared with moderate and mild hyponatraemia cases. Atila et al.[22] studied the prevalence and impact of dysnatraemias on mortality 30 days after hospital admission in COVID-19 patients with positive SARS-CoV-2 PCRs compared to patients with suspected COVID-19 but negative SARS-CoV-2 PCRs. Of 172 cases and 849 controls, hyponatraemia was present in 29% versus 17.6% respectively, the risk of mortality attributable to hyponatraemia in the cases was statistically significant (*hazard ratio* [HR]: 1.4; 95% CI: 1.1–16.6; $p = 0.05$). Therefore, the authors conclude that hyponatraemia should be considered a poor prognostic marker associated with mortality from COVID-19 and worse adverse events (need for mechanical ventilation, admission to intensive care units, and longer hospital stays). Another study of a multicentre retrospective cohort of 1254 patients diagnosed with COVID-19 observed a 9.9% prevalence of hyponatraemia and 2.4% of hypernatraemia in 3 hospitals in Hubei, China. Patients with hyponatraemia were older, had a greater number of comorbidities, and developed severe hyponatraemia. They required increased oxygen supply, antibiotic therapy, and corticosteroids. Hyponatraemia was the most common electrolyte disorder in this population and was associated with an increased risk of severe disease and increased hospital mortality[12]. Another very similar study was published by the De-Carvalho et al. group[8], who described the impact of hyponatraemia on the poor prognosis of COVID-19. From a retrospective longitudinal cohort in Nantes, of 296 patients, 2 groups were compared: patients with hyponatraemia < 135 mmol/l ($n = 92$; 31%) versus normonatremic patients ($n = 198$; 67%). Hyponatraemia was an independent predictor of adverse outcomes (adjusted OR: 2.77 [1.26–6.15]; $p = 0.011$). Severity of COVID-19, length of hospital stays for surviving patients, and mortality were higher among patients with hyponatraemia compared with those with normonatraemia. Finally, Tzoluis et al.[23] found very similar data to those discussed above. The authors recommend the use of natraemia on admission as well as other systematic biomarkers already studied (white blood cell count, lymphocytes and C-reactive protein) in order to provide a tool for dynamic risk stratification during the clinical course of COVID-19 and to assist in clinical decision making. However, one of the limitations of this study was the absence of data on the use of diuretics and fluid administration, making it difficult to confirm whether serum sodium is a predictor of poor prognosis or whether it is a side effect of other undocumented problems.

There are currently no consensus or clinical guidelines for the management of hyponatraemia in COVID-19. The therapeutic approach will depend on its aetiology, tonicity, volume status and patient comorbidities, in accordance with the recommendations of the current hyponatraemia clinical guidelines[20]. As previously mentioned, it is very likely that the cause of hyponatraemia in COVID-19 is multifactorial, including SIADH and gastrointestinal loss of sodium due to diarrhoea or vomiting. It is important to emphasise the need for early clinical assessment of volume status in order to decide between 2 therapeutic strategies: fluid replacement therapy, in cases of hypovolaemic hyponatraemia secondary to gastrointestinal losses; reduced fluid intake or the use of diuretics in cases of hyponatraemia secondary to SIADH can be associated with the administration of urea, selective vasopressin V2 antagonist (tolvaptan) and hypertonic saline, depending on the severity of neurological symptoms, these patients should be monitored in critical care units, as treating hyponatraemia is as important as its correction time. This therapeutic approach is relevant in COVID-19 patients, who require cautious and conservative fluid resuscitation to avoid iatrogenic complications, such as acute lung oedema and exacerbation of lung damage secondary to SARS-CoV-2 infection, while preventing hypernatraemia, which is induced by negative fluid balance. This is why the use of serum osmolality, urinary osmolality and urinary sodium levels is crucial to establish a correct diagnosis of vascular tonicity and blood volume status in cases of hyponatraemia.

Although correction of hyponatraemia decreases the increased risk of mortality associated with hyponatraemia in non-COVID-19 patients, this fact has not yet been clearly established. However, a sub-analysis of the EVEREST study population of patients with hyponatraemia < 130 mmol/l showed a significant reduction in cardiovascular morbidity and mortality after discharge in patients treated with tolvaptan[29]. On the other hand, Corona et al.[30] performed a meta-analysis based on 15 published studies of 13,816 hyponatraemic patients with a mean follow-up of 33.6 months, including data on the effect of Na^+ correction on mortality. The overall mortality rate in those patients who corrected hyponatraemia was reduced by up to 60% compared to patients who did not correct hyponatraemia. However, the association was stronger and persisted at 12 months, with up to a 70% reduction in mortality rate when a sensitivity analysis was performed based on those studies in which the threshold for correction of hyponatraemia went up to 130 mmol/l. Although a cause-effect relationship cannot be established from our data, our study showed that the absence of hyponatraemia correction 72–96 h after hospital admission was an independent risk factor for increased mortality in patients with COVID-19.

Our study had the following limitations: given the excessive burden of care generated by the need for management and hospital admission of patients with COVID-19, coinciding with the first wave of the pandemic, data could only be obtained to determine the aetiology of hyponatraemia in severe cases. In the remaining patients it was not possible to obtain additional clinical and laboratory data to make a reliable diagnosis of hyponatraemia. Secondly, because of its retrospective and observational design, the results only reflect the association of severe hyponatraemia with in-hospital death in COVID-19, but no causal relationship is inferred. Although attempts were made to adjust for different covariates at hospital admission, such as dynamic changes in hyponatraemia throughout hospitalisation, the chronicity or aetiology of hyponatraemia in mild and moderate cases could not be determined.

Our main strength was to compare the correction of hyponatraemia at 72–96 h after admission between the surviving and deceased groups. To our knowledge this is the first study to evaluate sustained hyponatraemia as a poor prognostic factor in patients diagnosed with COVID-19 and therefore adds valuable information to the literature.

Conclusions

We conclude that sustained hyponatraemia during the first 72–96 h of hospital admission was associated with increased mortality in patients with COVID-19. We believe that the results of our retrospective review will help to raise the clinical awareness of professionals involved in the management of patients with COVID-19 on a sometimes not well managed aspect, especially now that the world is in the midst of an ongoing pandemic.

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Conflict of interests

The authors declare no conflict of interest.

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