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Inverse relationship between IL-6 and sodium levels in patients with COVID-19 and other respiratory tract infections: data from the COVIVA study

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Abstract

Objective: Hyponatremia in COVID-19 is often due to the syndrome of inadequate antidiuresis (SIAD), possibly mediated by interleukin-6 (IL-6)-induced non-osmotic arginine vasopressin (AVP) secretion. We hypothesized an inverse association between IL-6 and plasma sodium concentration, stronger in COVID-19 compared to other respiratory infections.

Design: Secondary analysis of a prospective cohort study including patients with COVID-19 suspicion admitted to the Emergency Department, University Hospital of Basel, Switzerland, between March and July 2020.

Methods: We included patients with PCR-confirmed COVID-19 and patients with similar symptoms, further subclassified into bacterial and other viral respiratory infections. The primary objective was to investigate the association between plasma sodium and IL-6 levels.

Results: A total of 500 patients were included, 184 (37%) with COVID-19, 92 (18%) with bacterial respiratory infections, and 224 (45%) with other viral respiratory infections. In all groups, median (IQR) IL-6 levels were significantly higher in hyponatremic compared to normonatremic patients (COVID-19: 43.4 (28.4, 59.8) vs 9.2 (2.8, 32.7) pg/mL, $P < 0.001$; bacterial: 122.1 (63.0, 282.0) vs 67.1 (24.9, 252.0) pg/mL, $P < 0.05$; viral: 14.1 (6.9, 84.7) vs 4.3 (2.1, 14.4) pg/mL, $P < 0.05$). IL-6 levels were negatively correlated with plasma sodium levels in COVID-19, whereas the correlation in bacterial and other viral infections was weaker (COVID-19: R = −0.48, $P < 0.001$; bacterial: R = −0.25, $P = 0.05$, viral: R = −0.27, $P < 0.001$).

Key Words

▶ COVID-19
▶ CRP
▶ PCT
▶ interleukin-6
▶ hyponatremia

Conclusions: IL-6 levels were inversely correlated with plasma sodium levels, with a stronger correlation in COVID-19 compared to bacterial and other viral infections. IL-6 might stimulate AVP secretion and lead to higher rates of hyponatremia due to the SIAD in these patients.

Background

Hyponatremia, defined as a plasma sodium concentration < 135 mmol/L, is the most common electrolyte disorder in both in- and outpatient settings (1). It is indicative of disturbed water homeostasis that can occur secondary to a broad spectrum of diseases (e.g. heart failure, liver insufficiency, CNS disorders) (1), medications (e.g. diuretics, antiepileptics) (2), or in stress situation such as in the postoperative period (3) or after extreme sport performances (4). The awareness by physicians tends to be low (5) although hyponatremia is associated with increased mortality and morbidity (6) such as gait instability (7, 8), falls (7), osteoporosis (9, 10), fractures (9, 10), and attention deficit (7, 8, 11). More specifically, hyponatremia is highly relevant in patients with respiratory tract infections because of its high prevalence (8.1–44.4%) and its prognostic significance (12, 13, 14, 15, 16, 17), especially in patients with COVID-19 (18).

We recently showed a higher prevalence of hyponatremia in patients with COVID-19 in comparison to patients with clinical COVID-19 suspicion but negative PCR testing (29% vs 17%; vs 19.5% in the whole cohort) on hospital admission (19). Hyponatremia on admission was associated with higher 30-day overall mortality and 30-day rehospitalization rates. In both community-acquired pneumonia and COVID-19, one of the main etiologies for hyponatremia is the syndrome of inadequate antidiuresis (SIAD) (18, 20, 21, 22) being characterized by an imbalanced arginine vasopressin (AVP) secretion (23). The exact pathophysiological mechanism leading to SIAD in these patients remains elusive, although the contribution of interleukin-6 (IL-6) is gaining credibility (18, 21, 24).

IL-6 is a key component of the 'cytokine storm' and subsequent multiorgan failure in patients with COVID-19 (25). IL-6 is also involved in the 'immunoendocrine interface', where it stimulates the secretion of adrenocorticotropic hormone from the anterior pituitary (26, 27) and AVP from the posterior pituitary (27, 28). Exogenous IL-6 administration in rats and humans leads to an acute increase of AVP (27, 28). Recently, previous works showed an inverse relationship between IL-6 and plasma sodium levels in patients with COVID-19 (21, 24, 29, 30); interestingly, an increase in sodium levels was observed in

eight patients whose IL-6 levels decreased after treatment with the anti-IL-6 antibody tocilizumab (24). However, this was only demonstrated in patients with COVID-19 without a control group, i.e. bacterial pneumonia or other viral respiratory infections for which the relationship between IL-6 and sodium levels has never been investigated, and without comparison to other inflammatory markers.

This study aimed to investigate the relation between the pro-inflammatory cytokine IL-6 and plasma sodium levels in patients with confirmed COVID-19 in direct comparison to patients with other acute viral respiratory infections and bacterial respiratory infections. We hypothesized a negative association between IL-6 levels and sodium levels on admission with a stronger association in COVID-19 compared to other viral and bacterial respiratory infections.

Methods

Study design and participants

This prospective, observational cohort study included consecutively enrolled patients aged 18 years and older presenting with clinically suspected or confirmed SARS-CoV-2 infection to the Emergency Department (ED) of the University Hospital in Basel, Switzerland, during the first wave of the COVID-19 pandemic between March and July 2020. A detailed description of the study has been published elsewhere (19). All patients underwent nasopharyngeal SARS-CoV-2 PCR swab tests. Patients were considered COVID-19 positive if at least one SARS-CoV-2 PCR swab test performed on the day of ED presentation or within 14 days prior to or post-ED presentation was positive in combination with clinical signs and symptoms of COVID-19 infection, even in case of bacterial superinfection. The diagnosis of patients with negative SARS-CoV-2 PCR swab test was retrospectively chosen out of a predefined diagnoses list by a pool of five trained physicians after reviewing all the available medical data (e.g. clinical examination and radiological findings), including 30-day post-discharge follow-up information. For this current analysis, we included patients with other viral respiratory infections

and bacterial respiratory infections. All participating patients or their legally authorized representatives consented by signing a local general consent form. The study was registered on ClinicalTrials.gov (NCT04366765), conducted according to the principles of the Declaration of Helsinki, and approved by the Ethical Committee Northwest and Central Switzerland. The authors designed the studies, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to submit it for publication.

The full data set included 1081 patients. Twenty-two patients were excluded due to missing sodium levels and 559 patients were excluded due to another diagnosis than acute respiratory tract infections, i.e. cardiovascular disease (e.g. pulmonary embolism) or other pulmonary noninfectious diseases (e.g. bronchial asthma) (Fig. 1). According to sodium levels on admission, patients were subclassified into normonatremic (135–145 mmol/L), hyponatremic (<135 mmol/L), and hypernatremic (>145 mmol/L).

Blood sampling

Blood samples were routinely drawn from every patient at the time of ED presentation. Routine laboratory parameters, e.g. plasma sodium and C-reactive protein (CRP), were determined in every patient as part of the local standard operating procedure by COVID-19 suspicion. Timing and type of subsequent laboratory measurements

during hospital stay were left to the discretion of the treating physicians and were not part of this study protocol. In addition to the routine laboratory measurements, serum samples were collected at the time of ED presentation and stored at –80°C. IL-6 and procalcitonin (PCT) were measured in frozen serum samples in a dedicated external laboratory (Roche Diagnostics) on an Elecsys® analyzer. Treating physicians were blinded for IL-6 and PCT but not the remaining investigational inflammatory biomarkers such as leucocytes or CRP.

Study outcomes

The primary outcome was the association between admission plasma sodium levels with serum IL-6 levels in patients with COVID-19, bacterial, and other viral respiratory infections on hospital admission.

Secondary outcomes were the associations between admission plasma sodium levels and other inflammatory markers (i.e. CRP and PCT) in patients with COVID-19, other viral respiratory infections, and bacterial respiratory infections, as well as the determination of inflammatory markers cut-offs for increased likelihood of hyponatremia and the association between each inflammatory marker and hyponatremia with a composite unfavorable outcome (30-day all-cause mortality or intensive care unit (ICU) admission).
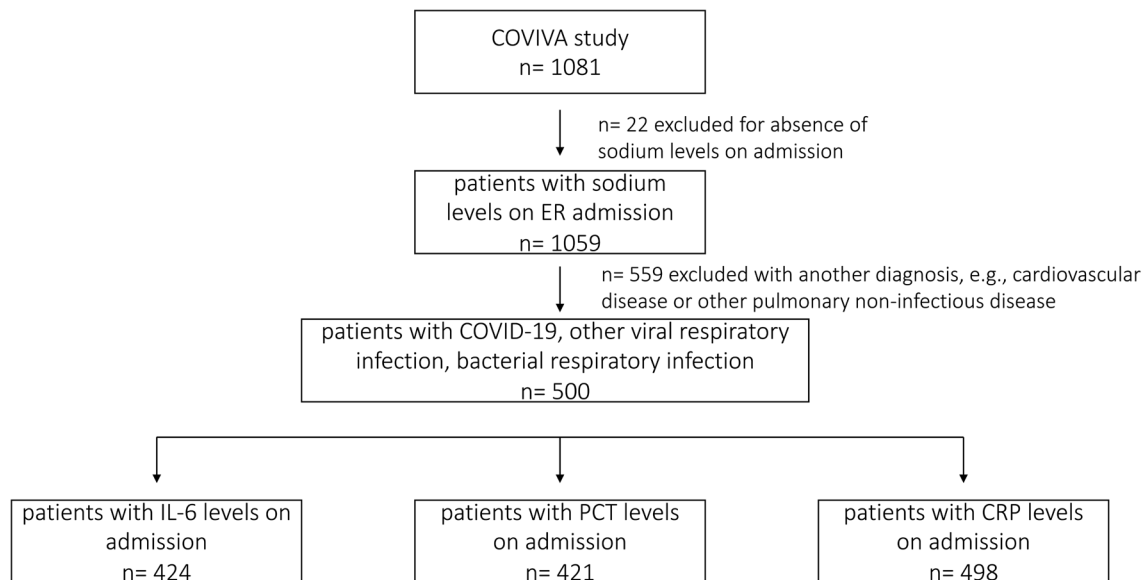
Figure 1
Study flowchart. Flowchart showing patient enrolment. The total data set included 1081 patients; 22 patients were excluded for the absence of sodium levels measured, and 559 patients were subclassified with another diagnosis than respiratory tract infections, e.g. cardiovascular or other pulmonary noninfectious diseases. In total, 500 patients with COVID-19, other viral respiratory infections, and bacterial respiratory infections were analyzed. COVIVA, coronavirus survival study; ER, emergency room; IL-6, interleukin-6; PCT, procalcitonin; CRP, C-reactive protein.

Statistical analysis

Baseline characteristics are summarized using descriptive statistics. Discrete variables are expressed as frequencies (percentage (%) and number of patients (n)). Continuous variables are expressed as median and interquartile range (IQR, 25th to 75th percentiles).

The primary endpoint was the association of plasma sodium levels (mmol/L) and serum IL-6 levels (pg/mL) by fitting a univariable and a multivariable linear regression model with the assumption of direct influence of IL-6 levels on sodium levels – the predictor variable was log-transformed to achieve a near normal distribution. Adjusting covariates included age, sex, severity of disease measured with the National Early Warning Score 2 (NEWS2) ([31]) on admission, and the total number of comorbidities. The sum in numbers of predefined comorbidities per patient was used for adjustment, ranging from 0 to 12. Model selection was based on the smallest Akaike's information criterion (AIC). The associations are visualized with scatterplots.

Secondary endpoints included the association between plasma sodium levels (mmol/L) and other inflammatory markers, i.e. CRP (mg/L) and PCT (ng/mL), using a similar method as for IL-6 levels. Assuming pure correlation and in order to compare our results to the available literature, we also calculated Pearson correlation coefficients between inflammatory parameters and sodium levels for the respective groups. Furthermore, IL-6, CRP, and PCT levels between hyponatremic and normonatremic patients of each etiology were assessed using a Mann–Whitney *U* test and presented visually by boxplots. The best cut-off for IL-6, CRP, and PCT for predicting first, hyponatremia, and second an unfavorable outcome (composite outcome of admission to the ICU and 30-day all-cause mortality) was determined using the Youden index ([32]); the optimal cut-point being defined as the point closest to the upper left corner, i.e. 100% sensitivity and 100% specificity, on the receiver-operating characteristic area under the curve (AUC). The AUCs were compared using the DeLong test ([33]). Patients were classified according to the best cut-off in below-threshold and above-threshold for each inflammatory marker. Both groups (below- vs above-threshold) were compared for hyponatremia risk or unfavorable outcome, respectively, using a univariable and a multivariable (adjusted for age, sex, severity of disease measured with the NEWS2 on admission, and the total number of comorbidities) logistic regression models. Statistical models for each inflammatory marker were compared based on AIC.

We investigated the association between both IL-6 (as continuous predictor) and hyponatremia on mortality in a multivariable logistic regression model. All analyses were performed using the statistical program R (version 4.0.5 or higher). A two-sided significance level of 0.05 was used for every analysis.

Results

Baseline characteristics

Overall, 500 patients were included, of whom 184 (37%) were diagnosed with COVID-19, 224 (45%) with other viral respiratory infections, and 92 (18%) with bacterial respiratory infections. The median (IQR) age was 57 years (43, 70), and 280 (56%) were female. Hyponatremia prevalence was 21% in the pooled group, 28% in patients with COVID-19, 12% in other viral respiratory infections, and 30% in bacterial respiratory infections. Detailed baseline characteristics can be found in Table 1.

IL-6 and sodium levels on admission

IL-6 levels on admission were available in 424 of 500 patients. In the pooled data set, the median (IQR) IL-6 level was significantly higher in hyponatremic compared to normonatremic patients on admission (48.9 (21.6, 90.1) vs 8.3 (2.5, 36.3) pg/mL; $P < 0.001$) (Fig. 2 and Table 2). This was also true for hyponatremic compared to normonatremic patients in all three individual groups (COVID-19: 43.4 (28.4, 59.8) vs 9.2 (2.8, 32.7) pg/mL, $P < 0.001$; other viral respiratory infections: 14.1 (6.9, 84.7) vs 4.3 (2.1, 14.4) pg/mL, $P < 0.05$; bacterial respiratory infections: 122.1 (63.0, 282.0) vs 67.1 (24.9, 252.0) pg/mL, $P < 0.05$) (Fig. 2 and Table 2). IL-6 levels were negatively correlated with plasma sodium levels in all three groups, whereas the correlation in bacterial and other viral infections was weaker than in COVID-19 (COVID-19: R = −0.48, $P < 0.001$; viral: R = −0.27, $P < 0.001$; bacterial: R = −0.25, $P = 0.05$) (Fig. 3). In the multivariable regression models, a doubling (i.e. 100% increase) in IL-6 levels leads to a decrease in sodium levels by −0.62 mmol/L (95% CI (−0.83, −0.42); $P < 0.01$) in the pooled data; more specifically, a decrease of −0.97 mmol/L (95% CI (−1.46, −0.49); $P < 0.01$) in patients with COVID-19, −0.35 mmol/L (95% CI (−0.69, −0.07); $P < 0.05$) in other viral respiratory infections, and −0.69 mmol/L (95% CI (−1.32, −0.07); $P < 0.05$) in bacterial respiratory infections (Supplementary Table 6, see section on supplementary materials given at the end of this article).

Table 1 Baseline characteristics. Data from 500 patients; 184 patients with COVID-19, 224 patients with other viral respiratory infections, and 92 patients with bacterial respiratory infections. Data are presented as numbers (%) and median (IQR: 25th–75th).

	Overall	COVID-19	Viral controls	Bacterial controls
Number of patients	500	184	224	92
Age (years)	57 (43, 70)	57 (44, 69)	52 (36, 64)	72 (57, 79)
Sex female, *n* (%)	220 (44)	81 (44)	104 (46)	35 (38)
Length of hospital stay (days) (IQR)	0 (0, 6)	3 (0, 8)	0 (0, 1)	5 (0, 10)
Number of comorbidities, *n* (%)	2 (0, 3)	1 (0, 3)	1 (0, 3)	3 (2, 4)
NEWS total, *n* (IQR)	2 (0, 4)	3 (1, 5)	1 (0, 3)	5 (3, 7)
Respiratory rate (/min) (IQR)	20 (16, 23)	20 (16, 24)	18 (15, 21)	22 (19, 27)
Temperature (°C) (IQR)	37.0 (36.6, 37.7)	37.1 (36.8, 38.0)	36.9 (36.5, 37.3)	37.3 (37.0, 38.2)
Blood pressure systolic (mmHg) (IQR)	137 (122, 154)	135 (122, 149)	142 (125, 156)	133 (120, 153)
Blood pressure diastolic (mmHg) (IQR)	82 (72, 89)	82 (72, 90)	82 (74, 89)	80 (70, 86)
Heart rate (/min) (IQR)	90 (78, 103)	89 (80, 103)	88 (76, 101)	96 (82, 110)
IL-6 admission (pg/mL) (IQR)	13.1 (2.9, 51.2)	20.6 (4.5, 45.5)	4.6 (2.1, 17.0)	80.7 (33.2, 282.0)
CRP admission (mg/L) (IQR)	11.6 (1.6, 58.3)	28.9 (2.7, 72.8)	3.3 (0.9, 14.9)	73.3 (14.8, 133.8)
PCT admission (ng/mL) (IQR)	0.04 (0.02, 0.10)	0.05 (0.02, 0.11)	0.03 (0.01, 0.06)	0.14 (0.05, 0.48)
Sodium admission (mmol/L) (IQR)	138 (135, 141)	137 (134, 140)	139 (137, 141)	137 (134, 140)
Normonatremia, *n* (%)	382 (76)	127 (69)	193 (86)	62 (67)
Hyponatremia, *n* (%)	106 (21)	52 (28)	26 (12)	28 (30)
Hypernatremia, *n* (%)	12 (2)	5 (3)	5 (2)	2 (2)

CRP, C-reactive protein; IL-6, interleukin-6; IQR, interquartile range; mmHg, millimeters of mercury; NEWS, National Early Warning Score; *n*, number; PCT, procalcitonin.

CRP and sodium levels on admission

CRP levels on admission were available in 498 of 500 patients. In the pooled data set, the median (IQR) CRP level was significantly higher in hyponatremic compared to normonatremic patients on admission (60.2 (23.9, 125.0) vs 6.6 (1.2, 34.9) mg/L; $P < 0.001$) (Table 2 and Supplementary Fig. 1). This was also true for hyponatremic compared to normonatremic patients in all three groups (COVID-19: 49.4 (26.0, 103.3) vs 11.2 (1.4, 50.7) mg/L, $P < 0.001$; other viral respiratory infections: 36.3 (7.0, 77.2) vs 2.8 (0.9, 12.2) mg/L, $P < 0.001$; bacterial respiratory infections: 110.4 (58.3, 185.5) vs 49.1 (10.3, 113.8) mg/L, $P < 0.01$) (Table 2 and Supplementary Fig. 1). CRP levels were negatively correlated with plasma sodium levels in all three groups, whereas the correlation in bacterial and other viral infections was slightly weaker than in COVID-19 (COVID-19: R = −0.36, $P < 0.001$; viral: R = −0.37, $P < 0.001$; bacterial: R = −0.27, $P = 0.01$) (Supplementary Fig. 2). In the multivariable regression models, a doubling (i.e. 100% increase) in CRP levels leads to a decrease in sodium levels by −0.69 mmol/L (95% CI (−0.83, −0.49); $P < 0.01$) in the pooled data; more specifically, a decrease of −0.55 mmol/L (95% CI (−0.90, 0.07); $P < 0.05$) in patients with COVID-19, −0.55 mmol/L (95% CI (−0.83, −0.35); $P < 0.01$) in other viral respiratory infections, and −0.76 mmol/L (95% CI (−1.32, −0.21); $P < 0.01$) in bacterial respiratory infections (Supplementary Table 7).

PCT and sodium levels on admission

PCT levels on admission were available in 421 of 500 patients. In the pooled data set, the median (IQR) PCT level was significantly higher in hyponatremic compared to normonatremic patients on admission (0.14 (0.05, 0.26) vs 0.04 (0.02, 0.07) ng/mL; $P < 0.001$) (Table 2 and Supplementary Fig. 3). This was also true for hyponatremic compared to normonatremic patients in all three groups (COVID-19: 0.13 (0.06, 0.23) vs 0.04 (0.02, 0.06) ng/mL, $P < 0.001$; other viral respiratory infections: 0.06 (0.02, 0.15) vs 0.03 (0.01, 0.05) ng/mL, $P < 0.05$; bacterial respiratory infections: 0.23 (0.14, 0.69) vs 0.09 (0.04, 0.30) ng/mL, $P < 0.05$) (Table 2 and Supplementary Fig. 3). PCT levels were negatively correlated with plasma sodium levels in all three groups, whereas the correlation in bacterial and other viral infections was weaker than in COVID-19 (COVID-19: R = −0.36, $P < 0.001$; viral: R = −0.27, $P < 0.001$; bacterial: R = −0.14, $P = 0.248$) (Supplementary Fig. 4). In the multivariable regression models, a doubling (i.e. 100% increase) in PCT levels leads to a decrease in sodium levels by −2.1 mmol/L (95% CI (−3.33, −0.69); $P < 0.01$) in the pooled data; more specifically, a decrease of −4.51 mmol/L (95% CI (−6.52, −2.5); $P < 0.01$) in patients with COVID-19, −7.35 mmol/L (95% CI (−12.48, −2.23); $P < 0.01$) in other viral respiratory infections, and −1.52 mmol/L (95% CI (−4.02, −0.9); $P = 0.21$) in bacterial respiratory infections (Supplementary Table 8).
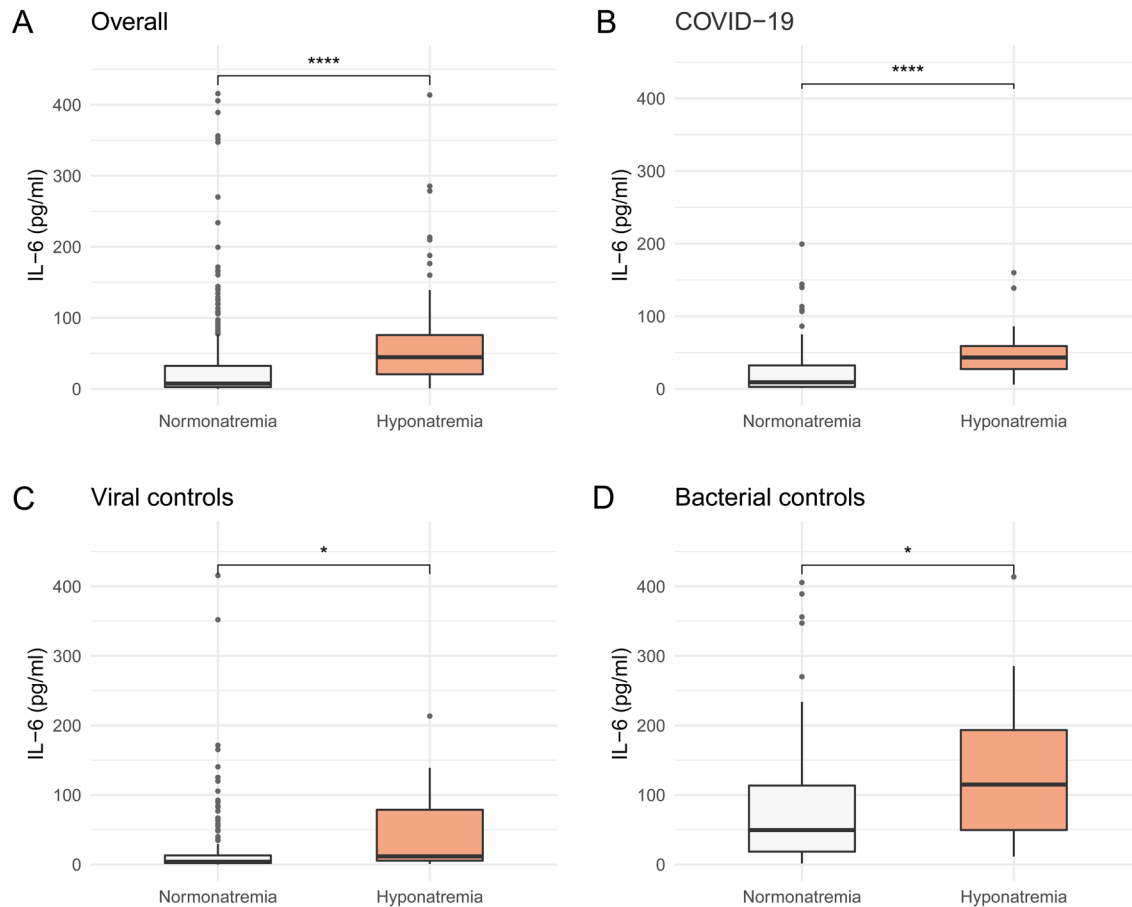
Figure 2
Interleukin-6 levels on admission. Interleukin-6 levels were visualized in boxplots for the pooled data set (A), patients with COVID-19 (B), patients with other viral respiratory infections (C), and patients with bacterial respiratory infections (D) subgrouped in plasma sodium level category on admission. The Mann–Whitney *U* test was applied to assess differences between the subgroups. In the pooled group and in each etiology, hyponatremic patients showed significant higher IL-6 levels in comparison to normonatremic patients.

Prediction of hyponatremia with inflammatory markers

For IL-6, the AUC was 75% (95% CI (69, 81)) with the best cut-off at 11.0 pg/mL (specificity 58.0%, sensitivity 86.5%) (Fig. 4). For CRP, the AUC was 79% (95% CI (74, 84)) with the best cut-off at 15.3 mg/L (specificity 66.7%, sensitivity 83.8%). For PCT, the AUC was 77% (95% CI (71, 83)) with the best cut-off at 0.1 ng/mL (specificity 81.2%, sensitivity 64.9%) The AUCs between CRP and IL-6 ($P=0.03$) were significantly different, while no difference between CRP and PCT ($P=0.49$) or IL-6 and PCT ($P=0.49$) could be seen. For IL-6, patients above-threshold showed a higher risk

for hyponatremia compared to those below-threshold (unadjusted OR: 8.8; 95% CI (4.6, 18.9); $P<0.01$ and adjusted OR 7.4; 95% CI (3.5, 17.4); $P<0.01$). For CRP, patients above-threshold showed a higher risk for hyponatremia compared to those below-threshold (unadjusted OR: 10.3; 95% CI (5.5, 20.9); $P<0.01$ and adjusted OR: 8.0; 95% CI (4.0, 17.1); $P<0.01$). For PCT, patients above-threshold showed a higher risk for hyponatremia compared to those below-threshold (unadjusted OR: 7.3; 95% CI (4.2, 12.8); $P<0.01$ and adjusted OR: 6.4; 95% CI (3.4, 12.3); $P<0.01$). According to Akaike's information, the adjusted CRP model provided the best fit (Supplementary Table 9).

Table 2 Inflammatory parameters. Data are presented for normonatremic and hyponatremic patients with COVID-19, other viral respiratory infections, and bacterial respiratory infections on admission. Hypernatremic patients are not displayed in the subgroups. Data are presented as median (IQR), *n* = number.

	Overall		COVID-19		Viral controls		Bacterial controls	
	Normonatremia (*n* = 382)	Hyponatremia (*n* = 106)	Normonatremia (*n* = 127)	Hyponatremia (*n* = 52)	Normonatremia (*n* = 193)	Hyponatremia (*n* = 26)	Normonatremia (*n* = 62)	Hyponatremia (*n* = 28)
IL-6 (pg/mL) Median (IQR)	8.3 (2.5, 36.3)	48.9 (21.6, 90.1)	9.2 (2.8, 32.7)	43.4 (28.4, 59.8)	4.3 (2.1, 14.4)	14.1 (6.9, 84.7)	67.1 (24.9, 252.0)	122.1 (63.0, 282.0)
CRP (mg/L) Median (IQR)	6.6 (1.2, 34.9)	60.2 (23.9, 125.0)	11.2 (1.4, 50.7)	49.4 (26.0, 103.3)	2.8 (0.9, 12.2)	36.3 (7.0, 77.2)	49.1 (10.3, 113.8)	110.4 (58.3, 185.5)
PCT (ng/mL) Median (IQR)	0.04 (0.02, 0.07)	0.14 (0.05, 0.26)	0.04 (0.02, 0.06)	0.13 (0.06, 0.23)	0.03 (0.01, 0.05)	0.06 (0.02, 0.15)	0.09 (0.04, 0.30)	0.23 (0.14, 0.69)

IL, interleukin; CRP, C-reactive protein; PCT, procalcitonin; IQR, interquartile range.

## Prediction of worse outcome with inflammatory markers and hyponatremia

The outcome was defined as the composite of ICU admission or 30-day all-cause mortality. For IL-6, the AUC was 80% (95% CI (73, 86)) with the best cut-off at 14.6 pg/mL (specificity 57.4%, sensitivity 90.9%) (Fig. 4). For CRP, the AUC was 82% (95% CI (76, 87)) with the best cut-off at 28.6 mg/L (specificity 69.5%, sensitivity 87.9%). For PCT, the AUC was 75% (95% CI (67, 84%)) with the best cut-off at 0.1 ng/mL (specificity 70.4%, sensitivity 75.8%). The AUCs compared with the DeLong test (33) showed no significant difference between CRP, IL-6, and PCT. For IL-6, patients above-threshold showed a higher risk for the composite outcome compared to those below-threshold (unadjusted OR: 13.5; 95% CI (4.7, 57.0); $P < 0.01$ and adjusted OR: 3.5; 95% CI (1.0, 16.4); $P = 0.06$). For CRP, patients above-threshold showed a higher risk for the composite outcome compared to those below-threshold (unadjusted OR: 9.9; 95% CI (4.2, 27.1); $P < 0.01$ and adjusted OR: 4.1; 95% CI (1.6, 12.2); $P < 0.01$). For PCT, patients above-threshold showed a higher risk for the composite outcome compared to those below-threshold (unadjusted OR 4.5; 95% CI (2.2, 9.4); $P < 0.01$ and adjusted OR: 1.9; 95% CI (0.7, 4.6); $P = 0.18$). According to Akaike's information, the adjusted CRP model was considered significantly better compared to the other models (Supplementary Table 10).

In a bivariable logistic regression model, IL-6 levels above-threshold was independently associated with the composite outcome (OR 16.2; 95% CI (5.6, 69.2), $P < 0.001$), whereas the presence of hyponatremia was not (OR 1.3; 95% CI (0.6, 2.7), $P = 0.46$). After adjusting for further covariables, IL-6 levels above-threshold remained significant (OR 3.9; 95% CI (1.1, 18.2); $P = 0.05$; Supplementary Table 11).

Discussion

Our study has three main findings. First, inflammatory parameters are significantly higher in hyponatremic compared to normonatremic patients with respiratory tract infections on hospital admission; second, plasma sodium levels were inversely associated with inflammatory markers; and finally, IL-6 is independently associated with an unfavorable outcome. To our knowledge, we provide, for the first time, data on the relationship between sodium and IL-6 in patients with respiratory tract infections other than COVID-19.

We hereby confirm the previously described inverse relationship between plasma sodium levels and IL-6 levels in patients with COVID-19 and, in addition, show a

## Interleukin−6 and sodium on admission
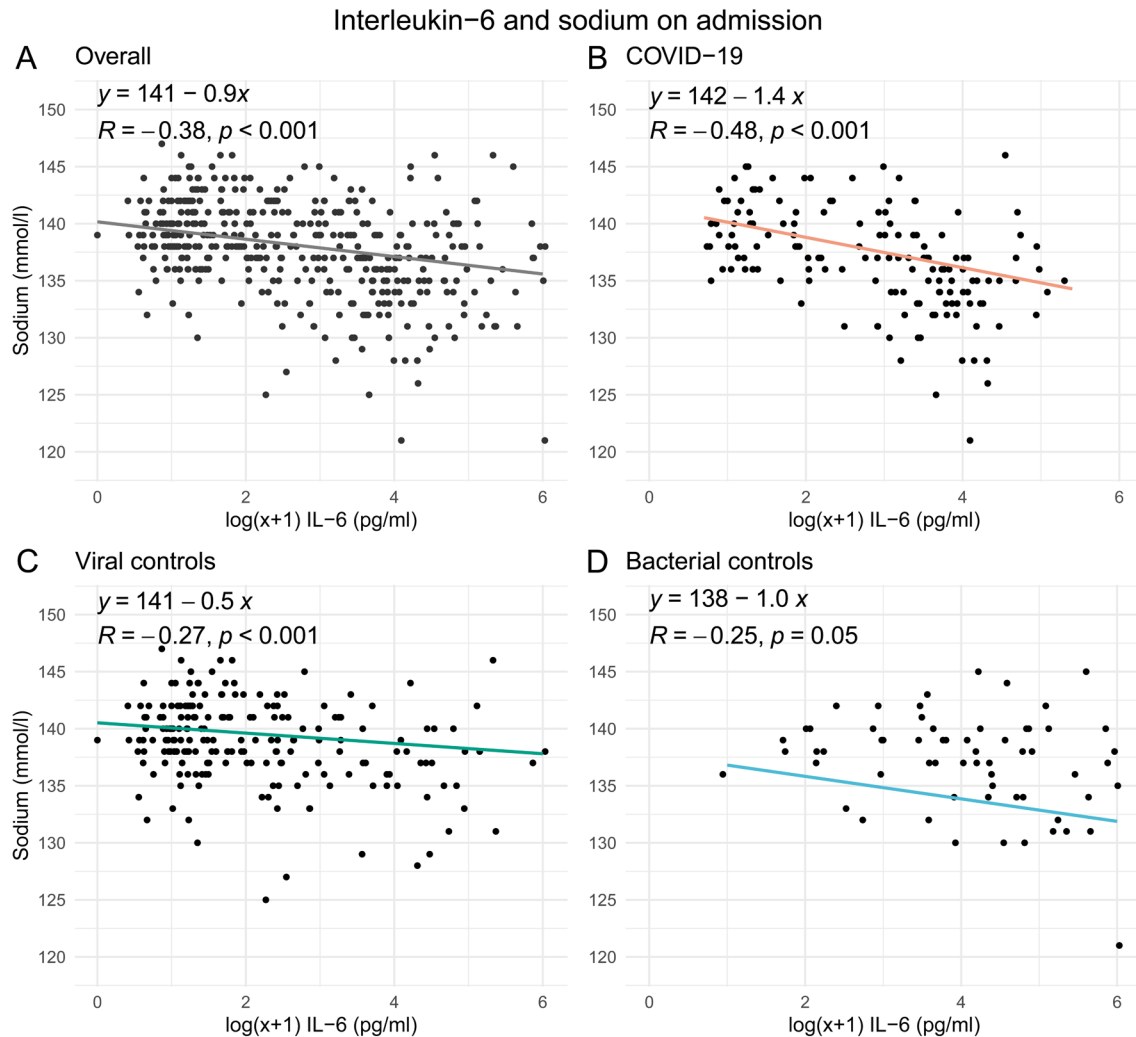
Figure 3

Relation between sodium and interleukin-6 levels. The relation between sodium and interleukin-6 levels is visualized in scatterplots for the pooled dataset (A), patients with COVID-19 (B), other viral respiratory infections (C), and bacterial respiratory infections (D). The linear regression equation and Pearson correlation coefficient are given for the pooled data set and all three groups individually. In the pooled group and in each etiology, a significant negative relation between sodium and interleukin-6 levels was observed. The predictor variable was logarithmically ($\log(x+1)$) transformed.

stronger association in patients with COVID-19 compared to other viral or bacterial respiratory infections. Berni *et al*. recently showed a negative association (29) and a strong negative correlation between plasma sodium levels and IL-6 levels, with a correlation coefficient ($R = -0.60$, $P = 0.0006$) similar to ours ($R = -0.48$, $P < 0.001$) (24). Furthermore, we were able to define a cut-off at 11.0 pg/mL above which the risk for hyponatremia increases by 7.4-fold when adjusted for confounders. In addition, IL-6 values above 14.6 pg/mL were associated with increased odds for an unfavorable composite, i.e. 30-day all-cause mortality or ICU admission. Berni *et al*. used a similar cut-off at 10 pg/mL and showed a lower mean sodium concentration at higher IL-6 levels as well as a lower

mean index of respiratory performance (PaO_2/FiO_2 ratio) (24). Using this cut-off, they further showed an increased risk for death (IL-6 > 10 pg/mL: HR 10.7) (24) comparable to the odds for the composite unfavorable outcome in this study.

We observed the highest IL-6 levels in bacterial respiratory infections but with a similar hyponatremia prevalence as in COVID-19. Reasons for this finding can only be speculated. There might be a higher central sensitivity to IL-6 in COVID-19 or, in parallel to IL-6, other molecules such as angiotensin II, which is upregulated in COVID-19 (34) and increases central osmosensitivity (35), that could stimulate AVP release as well. Angiotensin-converting enzyme 2 downregulation in COVID-19
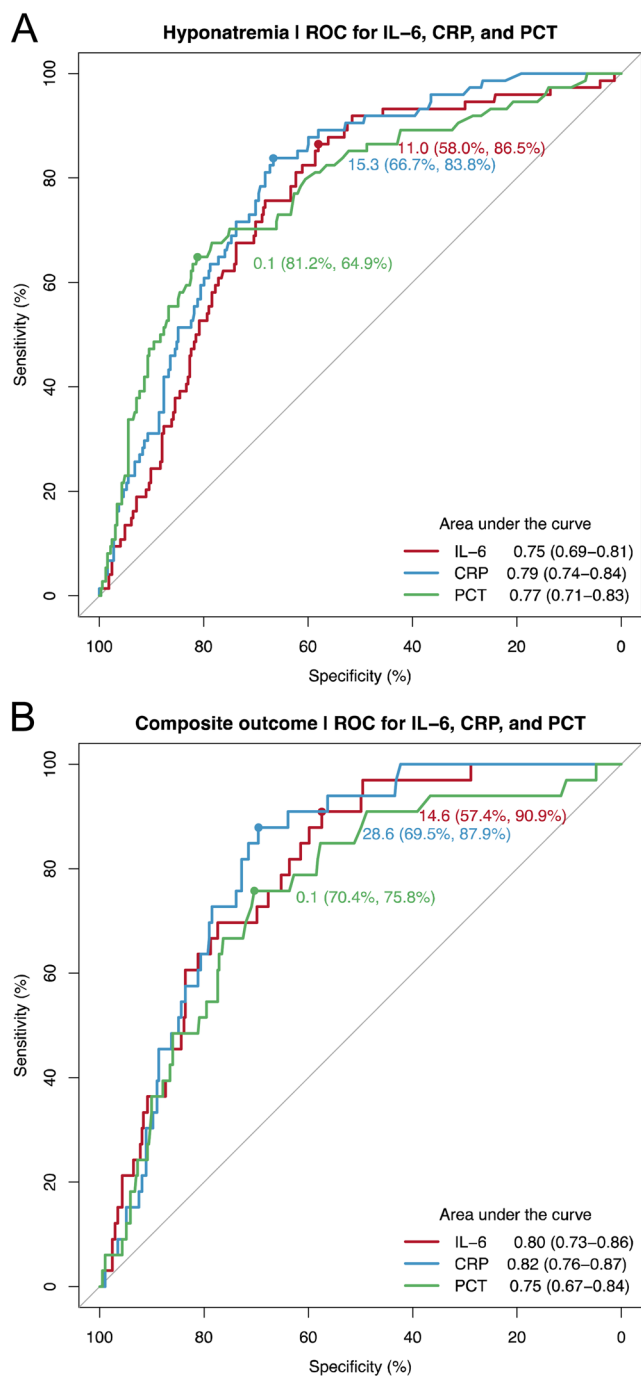
Figure 4

Predictive performance of inflammatory biomarkers regarding hyponatremia and the composite outcome. Receiver-operating characteristic areas under the curve (ROC) and best cut-offs for inflammatory markers for the risk of hyponatremia (A) and the risk of the composite outcome (B). The points and text indicate the optimal cut-off (specificity, sensitivity). Areas under the curve are displayed with 95% CIs.

might lead to higher angiotensin II levels and acute respiratory distress syndrome (36). Alternatively, patients with bacterial infections might partially compensate hyponatremia development with free water loss through perspiratio insensibilis due to tachypnoea and high fever. This hypothesis is supported by the vital signs in our cohort (Table 1).

IL-6 antagonism could represent an unexploited treatment strategy for SIAD secondary to inflammatory disorders. This is supported by data from Berni *et al.*, who showed that sodium levels increased in patients with COVID-19 treated with the IL-6 receptor antagonist tocilizumab (24) and a case report of a child with systemic juvenile idiopathic arthritis (37). For this purpose, further research should first better identify the IL-6-dependent hyponatremia subtypes and then investigate the targeted use of IL-6 blockers in these patients. Alternatively, IL-6 might just represent the strength of the inflammatory reaction, leading to a proportional increase in the capillary leak and to a relative hypovolemia that would trigger a non-osmotic AVP secretion.

IL-6 stimulates CRP synthesis in the liver. Although CRP increase might be delayed, we showed a negative relation with plasma sodium levels that was similar throughout all three subgroups. These findings agree with another prospective (38) an another retrospective study (42), which also reported higher CRP levels in hyponatremic patients. Of note, one of them found no correlation with IL-6 (39). One possible explanation could be that they used different time points of CRP and sodium values (at admission) and IL-6 values (highest levels during hospitalization). In our analysis, CRP stood out as the best marker to predict hyponatremia (AUC 79%) and the unfavorable outcome (AUC 82%). Based on our analyses and its broad availability, we propose CRP as the best of the three inflammatory markers to predict the likelihood of hyponatremia; however, our results only show a slight superiority of CRP compared to IL-6. We tend to believe that IL-6 causes both CRP synthesis in the liver and AVP release from the posterior pituitary and that CRP is to be considered as a surrogate marker of IL-6. The reason why CRP performs better might be a delay between IL-6 exposure and the subsequent CRP and AVP increases that would then better coincide with each other than with IL-6 itself.

PCT helps distinguishing viral from bacterial respiratory infections (40) and guides antibiotics in patients with lower respiratory tract infections (41). As expected, PCT was, therefore, lower in patients with COVID-19 and other viral respiratory infections as

compared to patients with bacterial infections. There was a negative correlation between PCT and plasma sodium levels in patients with COVID-19 and other viral respiratory infections. However, the range of values observed in our cohort corresponded to a decrease in plasma sodium levels of less than 1 mmol/L, and the negative association only reached statistical significance for COVID-19. Furthermore, PCT production depends on endotoxins and diverse cytokines such as TNF, IL-1, IL-2, and IL-6 (42). However, PCT does not decrease after administration of tocilizumab (43); therefore, IL-6 is probably not the main cytokine triggering PCT synthesis. PCT reflects a more pronounced global inflammatory response (44) and might not be a causative trigger for hyponatremia. This is supported by the fact that hyponatremia prevalence is not higher in patients with bacterial respiratory infections in comparison with patients with COVID-19 despite much higher PCT levels. We do not recommend the use of PCT to predict hyponatremia because the calculated cut-off is very low (0.1 ng/mL), and its determination is quite costly.

Our study has limitations. First, we were not able to differentiate between hyponatremia subtypes. It would have been interesting to compare IL-6 levels in patients with SIAD and hypovolemic hyponatremia. Second, we did not examine the course of plasma sodium and inflammatory markers during hospitalization. Plasma sodium levels of hyponatremic patients often increase during hospitalization (39). This can be explained by the resolution of the SIAD by clinical improvement. Third, this is a cohort study and causality can therefore not be proven. The role of anti-IL-6 as a treatment of SIAD or of hyponatremia in guiding anti-IL-6 treatment should be investigated in further studies.

Conclusion

IL-6 levels were inversely associated with plasma sodium levels, with a stronger relationship in patients with COVID-19 compared to patients with bacterial and other viral infections. This further supports the importance of IL-6 as a non-osmotic stimulus for AVP secretion and subsequent SIAD.

References

1 Burst V. *Etiology and Epidemiology of Hyponatremia*, pp. 24–35. S. Karger AG, 2019. (https://doi.org/10.1159/000493234)

2 Liamis G, Megapanou E, Elisaf M & Milionis H. *Hyponatremia-Inducing Drugs*, pp. 167–177. S. Karger AG, 2019. (https://doi.org/10.1159/000493246)

3 Ayus JC, Wheeler JM & Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Annals of Internal Medicine* 1992 **117** 891–897. (https://doi.org/10.7326/0003-4819-117-11-891)

4 Ayus JC, Varon J & Arieff AI. Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. *Annals of Internal Medicine* 2000 **132** 711–714. (https://doi.org/10.7326/0003-4819-132-9-200005020-00005)

5 Greenberg A, Verbalis JG, Amin AN, Burst VR, Chiodo Iii JA, Chiong JR, Dasta JF, Friend KE, Hauptman PJ, Peri A, *et al.* Current treatment practice and outcomes. Report of the hyponatremia registry. *Kidney International* 2015 **88** 167–177. (https://doi.org/10.1038/ki.2015.4)

6 Peri A. *Morbidity and Mortality of Hyponatremia*, pp. 36–48. S. Karger AG, 2019. (https://doi.org/10.1159/000493235)

7 Renneboog B, Musch W, Vandemergel X, Manto MU & Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *American Journal of Medicine* 2006 **119** 71.e1–71.e8. (https://doi.org/10.1016/j.amjmed.2005.09.026)

8 Suárez V, Norello D, Sen E, Todorova P, Hackl MJ, Hüser C, Grundmann F, Kubacki T, Becker I, Peri A, *et al.* Impairment of neurocognitive functioning, motor performance, and mood stability in hospitalized patients with euvolemic moderate and profound hyponatremia. *American Journal of Medicine* 2020 **133** 986.e5–993.e5. (https://doi.org/10.1016/j.amjmed.2019.12.056)

9 Barsony J, Kleess L & Verbalis JG. *Hyponatremia is Linked to Bone Loss, Osteoporosis, Fragility and Bone Fractures*. Karger, 2019. (https://doi.org/10.1159/000493237)

10 Corona G, Norello D, Parenti G, Sforza A, Maggi M & Peri A. Hyponatremia, falls and bone fractures: a systematic review and meta-analysis. *Clinical Endocrinology* 2018 **89** 505–513. (https://doi.org/10.1111/cen.13790)

11 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. *European Journal of Internal Medicine* 2017 **41** e25–e26. (https://doi.org/10.1016/j.ejim.2017.02.008)

12 Potasso L, Sailer CO, Blum CA, Cesana-Nigro N, Schuetz P, Mueller B & Christ-Crain M. Mild to moderate hyponatremia at discharge is associated with increased risk of recurrence in patients with community-acquired pneumonia. *European Journal of Internal Medicine* 2020 **75** 44–49. (https://doi.org/10.1016/j.ejim.2019.12.009)

13 Krüger S, Ewig S, Giersdorf S, Hartmann O, Frechen D, Rohde G, Suttorp N, Welte T & CAPNETZ study group. Dysnatremia, vasopressin, atrial natriuretic peptide and mortality in patients with community-acquired pneumonia: results from the German competence network CAPNETZ. *Respiratory Medicine* 2014 **108** 1696–1705. (https://doi.org/10.1016/j.rmed.2014.09.014)

14 Nair V, Niederman MS, Masani N & Fishbane S. Hyponatremia in community-acquired pneumonia. *American Journal of Nephrology* 2007 **27** 184–190. (https://doi.org/10.1159/000100866)

15 Zilberberg MD, Exuzides A, Spalding J, Foreman A, Jones AG, Colby C & Shorr AF. Hyponatremia and hospital outcomes among patients with pneumonia: a retrospective cohort study. *BMC Pulmonary Medicine* 2008 **8** 16. (https://doi.org/10.1186/1471-2466-8-16)

16 Schuetz P, Haubitz S, Christ-Crain M, Albrich WC, Zimmerli W, Mueller B & ProHOSP Study Group. Hyponatremia and anti-diuretic hormone in Legionnaires' disease. *BMC Infectious Diseases* 2013 **13** 585. (https://doi.org/10.1186/1471-2334-13-585)

17 Miyashita J, Shimada T, Hunter AJ & Kamiya T. Impact of hyponatremia and the syndrome of inappropriate antidiuresis on mortality in elderly patients with aspiration pneumonia. *Journal of Hospital Medicine* 2012 **7** 464–469. (https://doi.org/10.1002/jhm.1936)

18 Tzoulis P, Grossman AB, Baldeweg SE, Bouloux P & Kaltsas G. Management of endocrine disease: dysnatraemia in COVID-19: prevalence, prognostic impact, pathophysiology and management. *European Journal of Endocrinology* 2021 **185** R103–R111. (https://doi.org/10.1530/EJE-21-0281)

19 Atila C, Sailer CO, Bassetti S, Tschudin-Sutter S, Bingisser R, Siegemund M, Osswald S, Rentsch K, Rueegg M, Schaerli S, *et al.* Prevalence and outcome of dysnatremia in patients with COVID-19 compared to controls. *European Journal of Endocrinology* 2021 **184** 409–418. (https://doi.org/10.1530/EJE-20-1374)

20 Cuesta M, Slattery D, Goulden EL, Gupta S, Tatro E, Sherlock M, Tormey W, O'Neill S & Thompson CJ. Hyponatraemia in patients with community-acquired pneumonia; prevalence and aetiology, and natural history of SIAD. *Clinical Endocrinology* 2019 **90** 744–752. (https://doi.org/10.1111/cen.13937)

21 Frontera JA, Valdes E, Huang J, Lewis A, Lord AS, Zhou T, Kahn DE, Melmed K, Czeisler BM, Yaghi S, *et al.* Prevalence and impact of hyponatremia in patients with coronavirus disease 2019 in New York City. *Critical Care Medicine* 2020 **48** e1211–e1217. (https://doi.org/10.1097/CCM.0000000000004605)

22 Tzoulis P, Waung JA, Bagkeris E, Hussein Z, Biddanda A, Cousins J, Dewsnip A, Falayi K, McCaughran W, Mullins C, *et al.* Dysnatremia is a predictor for morbidity and mortality in hospitalized patients with COVID-19. *Journal of Clinical Endocrinology and Metabolism* 2021 **106** 1637–1648. (https://doi.org/10.1210/clinem/dgab107)

23 Robertson GL. Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. *American Journal of Medicine* 2006 **119** (Supplement 1) S36–S42. (https://doi.org/10.1016/j.amjmed.2006.05.006)

24 Berni A, Malandrino D, Parenti G, Maggi M, Poggesi L & Peri A. Hyponatremia, IL-6, and SARS-CoV-2 (COVID-19) infection: may all fit together? *Journal of Endocrinological Investigation* 2020 **43** 1137–1139. (https://doi.org/10.1007/s40618-020-01301-w)

25 Fajgenbaum DC & June CH. Cytokine storm. *New England Journal of Medicine* 2020 **383** 2255–2273. (https://doi.org/10.1056/NEJMra2026131)

26 Bethin KE, Vogt SK & Muglia LJ. Interleukin-6 is an essential, corticotropin-releasing hormone-independent stimulator of the adrenal axis during immune system activation. *PNAS* 2000 **97** 9317–9322. (https://doi.org/10.1073/pnas.97.16.9317)

27 Mastorakos G, Weber JS, Magiakou MA, Gunn H & Chrousos GP. Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: potential implications for the syndrome of inappropriate vasopressin secretion. *Journal of Clinical Endocrinology and Metabolism* 1994 **79** 934–939. (https://doi.org/10.1210/jcem.79.4.7962300)

28 Palin K, Moreau ML, Sauvant J, Orcel H, Nadjar A, Duvoid-Guillou A, Dudit J, Rabié A & Moos F. Interleukin-6 activates arginine vasopressin neurons in the supraoptic nucleus during immune challenge in rats. *American Journal of Physiology: Endocrinology and Metabolism* 2009 **296** E1289–E1299. (https://doi.org/10.1152/ajpendo.90489.2008)

29 Berni A, Malandrino D, Corona G, Maggi M, Parenti G, Fibbi B, Poggesi L, Bartoloni A, Lavorini F, Fanelli A, *et al.* Serum sodium alterations in SARS CoV-2 (COVID-19) infection: impact on patient outcome. *European Journal of Endocrinology* 2021 **185** 137–144. (https://doi.org/10.1530/EJE-20-1447)

30 Machiraju PK, Alex NM, Safinaaz & Vadamalai V. Hyponatremia in coronavirus disease-19 patients: a retrospective analysis. *Canadian Journal of Kidney Health and Disease* 2021 **8** 20543581211067069. (https://doi.org/10.1177/20543581211067069)

31 Royal College of Physicians. *National Early Warning Score (News) 2: Standardising the Assessment of Acute-Illness Severity in the NHS. Updated Report of a Working Party*. London: Royal College of Physicians, 2017.

32 Youden WJ. Index for rating diagnostic tests. *Cancer* 1950 **3** 32–35. (https://doi.org/10.1002/1097-0142(1950)3:1<32::aid-cncr2820030106>3.0.co;2-3)

33 DeLong ER, DeLong DM & Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988 **44** 837–845. (https://doi.org/10.2307/2531595)

34 Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, *et al.* Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China: Life Sciences* 2020 **63** 364–374. (https://doi.org/10.1007/s11427-020-1643-8)

35 Zhang Z & Bourque CW. Amplification of transducer gain by angiotensin II-mediated enhancement of cortical actin density in osmosensory neurons. *Journal of Neuroscience* 2008 **28** 9536–9544. (https://doi.org/10.1523/JNEUROSCI.1495-08.2008)

36 Kuba K, Yamaguchi T & Penninger JM. Angiotensin-converting enzyme 2 (ACE2) in the pathogenesis of ARDS in COVID-19. *Frontiers in Immunology* 2021 **12** 732690. (https://doi.org/10.3389/fimmu.2021.732690)

37 Hodax JK, Bialo SR & Yalcindag A. SIADH in systemic JIA resolving after treatment with an IL-6 inhibitor. *Pediatrics* 2018 **141** e20164174. (https://doi.org/10.1542/peds.2016-4174)

38 Ayus JC, Negri AL, Moritz ML, Lee KM, Caputo D, Borda ME, Go AS & Eghi C. Hyponatremia, inflammation at admission, and mortality in hospitalized COVID-19 patients: a prospective cohort study. *Frontiers in Medicine* 2021 **8** 748364. (https://doi.org/10.3389/fmed.2021.748364)

39 Martino M, Falcioni P, Giancola G, Ciarloni A, Salvio G, Silvetti F, Taccaliti A & Arnaldi G. Sodium alterations impair the prognosis of hospitalized patients with COVID-19 pneumonia. *Endocrine Connections* 2021 **10** 1344–1351. (https://doi.org/10.1530/EC-21-0411)

40 Self WH, Balk RA, Grijalva CG, Williams DJ, Zhu Y, Anderson EJ, Waterer GW, Courtney DM, Bramley AM, Trabue C, *et al.* Procalcitonin as a marker of etiology in adults hospitalized with community-acquired pneumonia. *Clinical Infectious Diseases* 2017 **65** 183–190. (https://doi.org/10.1093/cid/cix317)

41 Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, *et al.* Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections.

Cochrane Database of Systematic Reviews 2017 **10** CD007498. (https://doi.org/10.1002/14651858.CD007498.pub3)

42 Maruna P, Nedelníková K & Gürlich R. Physiology and genetics of procalcitonin. *Physiological Research* 2000 **49** (Supplement 1) S57–S61.

43 Li P, Lu Z, Li Q, Wang Z, Guo Y, Cai C, Wang S, Liu P, Su X, Huang Y, *et al.* Administration timing and efficacy of tocilizumab in patients with COVID-19 and elevated IL-6. *Frontiers in Molecular Biosciences* 2021 **8** 651662. (https://doi.org/10.3389/fmolb.2021.651662)

44 Becker KL, Nylén ES, White JC, Müller B & Snider Jr RH. Clinical review 167: procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 1512–1525. (https://doi.org/10.1210/jc.2002-021444)