Serum sodium alterations in SARS CoV-2 (COVID-19) infection: impact on patient outcome

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Abstract

Objective: Hyponatremia is the most common electrolyte disorder in hospitalized patients and occurs in about 30% of patients with pneumonia. Hyponatremia has been associated with a worse outcome in several pathologic conditions The main objective of this study was to determine whether serum sodium alterations may be independent predictors of the outcome of hospitalized COVID-19 patients.
Design and methods: In this observational study, data from 441 laboratory-confirmed COVID-19 patients admitted to a University Hospital were collected. After excluding 61 patients (no serum sodium at admission available, saline solution infusion before sodium assessment, transfer from another hospital), data from 380 patients were analyzed.
Results: 274 (72.1%) patients had normonatremia at admission, 87 (22.9%) patients had hyponatremia and 19 (5%) patients had hypernatremia. We found an inverse correlation between serum sodium and IL-6, whereas a direct correlation between serum sodium and PaO_2/FiO_2 ratio was observed. Patients with hyponatremia had a higher prevalence of non-invasive ventilation and ICU transfer than those with normonatremia or hypernatremia. Hyponatremia was an independent predictor of in-hospital mortality (2.7-fold increase vs normonatremia) and each mEq/L of serum sodium reduction was associated with a 14.4% increased risk of death.
Conclusions: These results suggest that serum sodium at admission may be considered as an early prognostic marker of disease severity in hospitalized COVID-19 patients.

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Introduction

Hyponatremia, defineed as a serum sodium concentration [Na^+] <135 mEq/L, is the most common electrolyte disorder in hospitalized patients (up to 30%) (1, 2). The syndrome of inappropriate antidiuresis (SIAD) is the cause of hyponatremia in 40–50% of cases. However, the prevalence may be even higher in some pathological conditions, including, for instance, pneumonia, subarachnoid hemorrhage and traumatic brain injury (3).

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Noteworthy, infectious diseases and inflammatory conditions are effective triggers for non-osmotic induction of vasopressin secretion. In these situations, vasopressin secretion is mainly due to interleukin-6 (IL-6), which is released by monocytes and macrophages. IL-6 can cross the blood-brain barrier and activates the circumventricular organs by binding to IL-6 receptors. This, in turn, induces vasopressin release by the supraoptic (SON) and the paraventricular nuclei (PVN) (4). In addition, IL-6 can directly induce vasopressin secretion by binding to IL-6 receptors expressed by the cells of the SON and the PVN (5). Therefore, IL-6 appears to play an important role in the pathogenesis of hyponatremia secondary to SIAD.

The COVID-19 infection is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). It originated in Wuhan (China) and it spread throughout the world with more than 62 000 000 affected patients by the end of November 2020 (COVID-19 Dashboard by the Center for System Science and Engineering (CSSE) at John Hopkins University (6). In its severe form, COVID-19 infection can cause interstitial pneumonia, multiple organ failure and death. More than 1 400 000 patients died because of COVID-19 infection by the end of November 2020.

Hyponatremia occurs in about 30% of patients with pneumonia (7) and it has been previously reported in 30–60% of SARS CoV-1 patients (8, 9, 10). The prevalence of hyponatremia in COVID-19 patients has not been clearly defined, so far (11, 12). Analyses from series of patients in China reported a median serum [Na^+] of 138 mEq/L (13). However, natremia was significantly lower in patients with pulmonary involvement (14). Although SIAD appears in principle as the main determinant of hyponatremia in COVID-19 infection, other etiologies may be present. Hypovolemic hyponatremia may occur, for instance, as a consequence of diuretic therapy to treat pulmonary edema (11).

It is known that hyponatremia, even when mild, is associated with a worse outcome and an increased risk of death in different pathological conditions, including pneumonia (15), heart failure (16), acute myocardial infarction (17), cirrhosis (18), cancer (19, 20), elderly patients (21), and intensive care patients (22). These data have been confirmed by an extensive meta-analysis, which included 82 publications for a total of more than 850 000 patients (23). Noteworthy, we have recently demonstrated that human cancer cell lines cultured in reduced extracellular [Na^+] show a significant increase in their proliferation rate and invasive potential (24).

In SARS CoV-1 patients hyponatremia was associated with a worse outcome (ICU transfer, death) (9). As per SARS CoV-2 patients, early observations reported that hyponatremia was associated with progression to a more severe disease (14, 25, 26).

Interestingly, an hyperinflammation syndrome characterized by a massive release of cytokines may contribute to a fatal outcome in SARS CoV-2 infection, determining multiple organ failure (27). IL-6 appears to be one of the most important cytokines involved in COVID-19-induced pathology. Based on these data, tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, has demonstrated clinical efficacy in the treatment of seriously ill patients (28). Interestingly, SIAD resolution after treatment with tocilizumab in a 6-years old girl with juvenile idiopathic arthritis has been reported (29). A subgroup of patients from our previous study, who had abnormal IL-6 levels, hyponatremia and rapid deterioration of respiratory function, received tocilizumab infusion and serum [Na^+] normalization was observed (14).

In order to evaluate the clinical impact of serum [Na^+] alterations and their correlation with IL-6 levels, we retrospectively evaluated data from all COVID-19 patients admitted to the Units (Internal Medicine, Infectious Diseases, Respiratory Diseases, Intensive Care) at the Careggi University Hospital in Florence that had been transformed into COVID-19 Units during the first wave of the pandemic in Spring 2020.

Subjects and methods

Patients

This observational study named 'Natremia, syndrome of inappropriate antidiuresis and pro-inflammatory cytokines' was revised and approved by the Ethical Committee of the Careggi University Hospital. Data from 441 laboratory-confirmed COVID-19 patients admitted from February 28 to May 28, 2020, at Internal Medicine, Infective Disease, Respiratory Disease and Intensive Care Units of the Careggi University Hospital in Florence, Italy, completely transformed into COVID-19 Units were examined. All the biochemistry measurements were performed at the central lab of the Careggi University Hospital. Of the 441 patients, those for whom serum [Na^+] and/or hemogasanalysis were not available ($n=39$), or those who were transferred from other hospitals and/or had received an infusion of saline solution ($n=22$) were excluded from the analysis, which finally included 380 patients.

Statistical analysis

Data were expressed as mean ± s.d. when normally distributed, and as median (quartiles) for parameters with non-normal distribution, unless otherwise specified. Serum [Na^+] was adjusted for serum glucose concentration by the formula: serum [Na^+] (mEq/L)+0.016 × (serum [glucose] (mg/dL) − 100). We compared age, gender, total days of hospitalization, and serum [Na^+], PaO_2/FiO_2 (P/F) ratio and IL-6 level at admission. For those with low $PaCO_2$ (i.e. <35 mmHg), PaO_2 was corrected by the formula: $PaCO_2 \times 1.66 + PaO_2 - 66.4$.

In order to verify the possible relationship between serum (Na^+), IL-6 levels and P/F ratio, we applied the fitting model analysis. Kaplan–Meier analysis of survival was performed with the definition of hazard ratios (HR) and 95% confidence intervals, and a stepwise Cox regression was carried out for multivariate analysis adjusting all data for age and sex. All analyses were carried out with SPSS 22.0.1 statistical package and a $P < 0.05$ was considered statistically significant.

Results

Serum [Na^+], IL-6 and P/F ratio

The patients ($n=380$), which were finally included in the study, were divided into three groups according to serum [Na^+] at admission: patients with low serum [Na^+] (i.e. <135 mEq/L) (hypoNa group, $n=87$, 22.9%), patients with high serum [Na^+] (i.e. >145 mEq/L) (hyperNa group, $n=19$, 5%) and patients with normal serum [Na^+] (i.e. 135–145 mEq/L) (normoNa group, $n=274$, 72.1%). The distribution in the three groups was defined after correcting serum [Na^+] for serum glucose. In particular, 10 patients were relocated from the hypoNa group into the normoNa group, whereas 1 patient was relocated from the normoNa to the hyperNa group after correction.

In the hypoNa group, the lowest serum [Na^+] was 116 mEq/L (range: 116–134 mEq/L). In the hyperNa group, the highest serum [Na^+] was 170 mEq/L (range: 146–170 mEq/L). HyperNa patients were older compared to normoNa and hypoNa patients (Table 1).

In order to identify acute hypoxemic respiratory failure, we analyzed the ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the inspired oxygen fraction (FiO_2), known as P/F. This is a widely used index of pulmonary gas exchange function, which allows to classify patients' respiratory impairment in defining acute lung injury (P/F ≤ 300 mmHg) and adult respiratory distress syndrome (P/F ≤ 200 mmHg) (30). HypoNa patients showed lower P/F ratio values compared to normoNa patients and higher IL-6 levels compared to normoNa and hyperNa patients. Males and females were equally distributed within the three groups and the mean duration of hospitalization was similar. Serum creatinine and blood urea nitrogen (BUN) are also reported in Table 1. Of the 87 hypoNa patients, values of serum creatinine above the upper limit of normal were found in 20 cases. BUN was available for 28 hypoNa patients and in 7 of

Table 1 Demographic and clinical characteristics of the patients.

	Hyponatremia, (n = 87)	**Normonatremia,** (n = 274)	**Hypernatremia,** (n = 19)	***P* value**
Age (years)	69.5 ± 12.8	65.9 ± 16.5	82.2 ± 13.1†,*	<0.0001
Males, *n* (%)	59 (68)	167 (61)	8 (42)	0.104
Hospitalization (days)	19.6 ± 16.0	16.0 ± 13.5	19.0 ± 11.1	0.090
Serum [Na^+] (mEq/L)	132.0 ± 2.9***,††	139.0 ± 2.4	154.1 ± 7.8***	<0.0001
Serum glucose (mg/dL)	121.8 ± 43.3	127.7 ± 49.0	119.4 ± 52.5	0.504
Serum creatinine (mg/dL)	1.0 (0.8–1.2)	0.9 (0.8–1.1)	1.1 (0.9–1.6)	0.784
Serum creatinine > 1.2 mg/dL, *n* (%)	20 (23)	56 (20)	8 (42)	0.086
BUN (mg/dL)	18.7 (14.0–25.7)	18.7 (14.0–26.6)	51.4 (18.7–56.1)	0.768
n	28	82	11	
BUN > 23.4 mg/dL, *n* (%)	7 (25)‡	21 (26)‡	8 (73)	0.005
BUN/creatinine	16.1 (14.2–20.2)	18.0 (15.1–21.9)	20.6 (17.8–27.1)	0.086
n	28	82	11	
BUN/creatinine >20, *n* (%)	7 (25)	29 (35)	6 (55)	0.213
P/F (mmHg)	250.2 ± 87.0*	291.1 ± 84.1	268.4 ± 100	0.001
IL-6 (pg/mL)	20.5 (13.5–44.1)*,‡	9.5 (5.1–22.3)	7.1 (3.6–18.3)	<0.0001
NIV, *n* (%)	34 (39)‡,**	62 (22)‡	1 (5)	0.001
ICU transfer, *n* (%)	30 (34)‡,**	59 (22)‡	1 (5)	0.007

Serum creatinine normal values: 0.7–1.2 mg/dL; BUN normal values: 4.7–23.4 mg/dL.
†$P < 0.001$ vs hyponatremia; *$P < 0.001$ vs normonatremia; ‡$P < 0.05$ vs hypernatremia; **$P < 0.05$ vs normonatremia; ***$P < 0.0001$ vs normonatremia; ††$P < 0.0001$ vs hypernatremia.

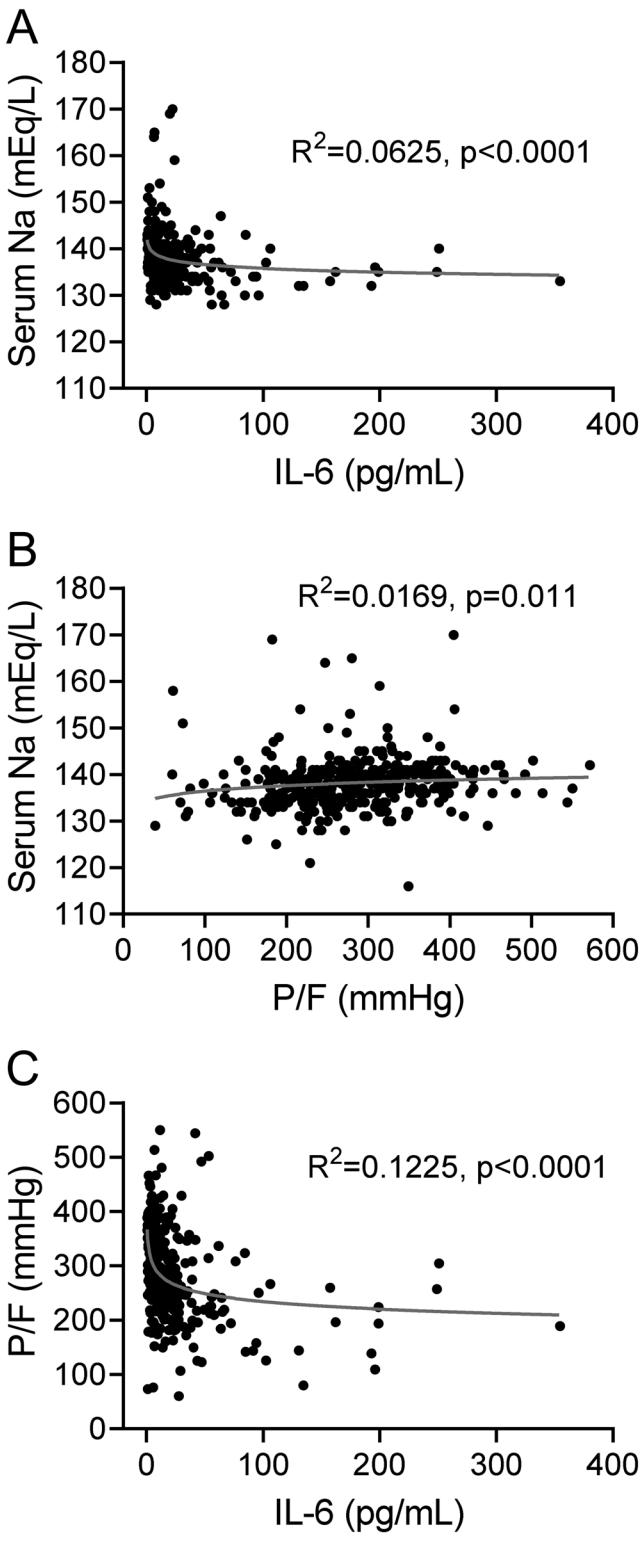

Figure 1

(A) Best-fitting model for serum [Na^+] variation as a function of IL-6 levels. (B) Best-fitting model for serum [Na^+] variation as a function of P/F ratio. (C) Best-fitting model for P/F ratio as a function IL-6 levels variation.

them values above the upper limit of normal occurred. In these patients, a BUN/creatinine ratio > 20, which suggests a reduced extracellular fluid (ECF) volume, was also found (Table 1).

When the whole population was considered, a tight association among serum [Na^+], IL-6 and P/F ratio was observed. Figure 1 shows the best-fitting model for variation in serum [Na^+] as a function of IL-6 levels (Fig. 1A) and P/F ratio (Fig. 1B). In particular, serum [Na^+] was inversely correlated with IL-6 levels, whereas a direct correlation was observed between serum [Na^+] and P/F ratio. Figure 1C shows the best-fitting model for P/F ratio as a function of IL-6 levels variation and indicates that IL-6 levels were inversely correlated with the P/F ratio.

Patients' outcome

The hypoNa group showed a higher prevalence of non-invasive ventilation (NIV) (39%) and ICU transfer (34%) compared to normoNa (22% for both, P= 0.001 and P= 0.007, respectively). Only a small percentage of patients with hypernatremia required non-invasive ventilation or ICU admission (i.e. 5% for both), despite an older age of the patients in this group compared to the other ones (82.2 ± 13.1, P=0.001 vs hypoNa and vs normoNa groups).

After a mean follow-up of 17 ± 14 (mean ± s.d.) days, 45 in-hospital deaths were observed. Of those cases, 23 occurred in normoNa patients, and 19 and 3 in hypoNa and in hyperNa subjects, respectively. Kaplan–Meier curves showed that hypoNa patients had an increased risk of death when compared to normoNa subjects (P < 0.001). Conversely, no difference between hyperNa and normoNa patients was observed (P=0.224) (Fig. 2). Hence, hyperNa patients were excluded from the following analyses.

When serum [Na^+], IL-6 and P/F ratio were considered in the same Cox regression model, after adjusting for age and gender, serum [Na^+] and IL-6 maintained a significant association with increased in-hospital mortality (HR=1.144 (1.006;1.301) for each mEq/L reduction of serum [Na^+] and HR=1.008 (1.003;1.013) for each pg/mL increase of serum IL-6, respectively; both P < 0.05). Conversely no association between the P/F ratio and mortality was observed (not shown).

Accordingly, when hyponatremia and elevated IL-6 (>10 pg/mL) were considered in the same Cox regression model, they resulted in association with 2.7-fold and 10.7-fold increased risk of mortality, respectively (HR=2.705 (1.134;6.454), P=0.025 and HR=10.717 (1.409;81.517), P=0.022 for hyponatremia and elevated IL-6 respectively).

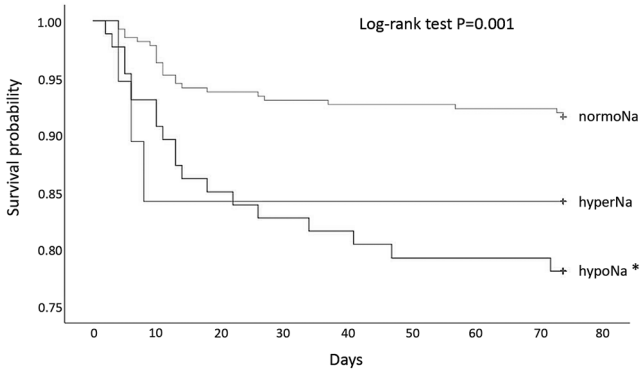

Figure 2

Kaplan–Meier curves in patients with hyponatremia (hypoNa), normonatremia (normoNa) or hypernatremia (hyperNa) at admission. *$P < 0.001$ *vs* normoNa.

Discussion

COVID-19 infection has represented a new and unexpected clinical challenge worldwide. Thus, the overall management and pharmacological treatment of affected patients have been somewhat empirical during the first wave of the pandemic earlier in Spring 2020. In such a situation, the observation of clinical signs and laboratory parameters has been an important issue, in order to find possible guidance to identify the most appropriate intervention strategies and early markers of patients' outcome.

Among laboratory indexes, in principle hyponatremia should not be an unexpected finding in COVID-19 patients. Pneumonia, cytokine release, diuretic administration are very well-known etiologies of hyponatremia. In our series of 380 patients, hyponatremia was found in 87 patients (22.9%) at the time of hospital admission. Hypernatremia was found in 19 patients (5%) and was associated with more advanced age. This is not surprising if we consider the rather frequent occurrence of dehydration in the elderly (31).

In agreement with our preliminary data on a limited series of patients (12), we confirmed the presence of an inverse correlation between serum [Na^+] and IL-6, whereas a direct correlation between serum [Na^+] and P/F ratio was observed. Therefore, hyponatremia appears to be associated with a worse respiratory performance and higher IL-6 levels.

Pro-inflammatory cytokines released by monocytes and macrophages, and particularly IL-6, are able to induce vasopressin secretion via two mechanisms: by a direct non-osmotic stimulation and by damaging alveolar basement membrane, which induces hypoxia, pulmonary vasoconstriction and vasopressin release (32, 33, 34, 35). Hence, in COVID-19, IL-6 could be viewed as the common pathogenic denominator of lung injury and acute respiratory insufficiency on one hand and SIAD-related hyponatremia on the other hand.

Several demographic, clinical and laboratory parameters correlate with prognosis and severity of COVID-19 infection (36, 37). Among biochemical markers, lower lymphocyte and platelet counts, increased IL-6 and IL-10 levels, abnormalities in coagulation parameters and in the indexes of liver and kidney function were found to be related to severe disease and unfavorable outcomes (38). More recently, hyponatremia has been suggested as an independent variable for COVID-19 progression to severe disease and death (25, 26, 39, 40, 41).

Following our previous brief report (12), we confirmed here in a much larger cohort that hyponatremic COVID-19 patients presented a higher risk of ICU transfer, NIV and in-hospital mortality than normonatremic and hypernatremic patients. These findings are also in agreement with data from a recently published multicenter, observational cohort study performed in patients with COVID-19 infection in New York City (42).

Noteworthy, in the present study, we also demonstrated by multivariate analysis that both serum [Na^+] and IL-6 are significantly associated with increased in-hospital mortality independently of age and gender, whereas we did not observe any correlation between P/F and the number of deaths. Other studies reported a correlation between P/F and mortality in COVID-19 patients, yet when a cut-off of 200 mmHg was considered (43, 44). In addition, we can hypothesize that respiratory failure and lung involvement in COVID-19 patients are just a part of a multiple organ failure. In such a scenario, it is then conceivable that serum [Na^+] and IL-6 levels, as markers of the cytokine storm induced by SARS-CoV-2 infection, rather than P/F, may predict a higher risk of in-hospital death. In particular, a 14.4% (0.6%–30.1%) increased risk of death was observed for each mEq/L decrease of serum [Na^+], whereas a 0.8% (0.3%–1.3) increased risk of death was observed for each pg/mL increase of serum IL-6. Furthermore, hyponatremia and elevated IL-6 (i.e. >10 pg/mL) resulted in a 2.7- and 10.7-fold increased risk of death compared to their normal counterparts, respectively. Of the pro-inflammatory cytokines, IL-6 exerts a crucial role in the cytokine storm, and it has been described that high levels are a predictor of COVID-19 severity (45, 46). However, admittedly serum [Na^+] has the advantage to be readily available by using point-of-care tests. Furthermore,

it is worth noting that the association between low serum [Na^+] and increased mortality was maintained even after adjustment for IL-6 levels. To our knowledge, this is the first study in which IL-6 was included among possible confounders.

This finding suggests interesting clinical considerations and it could be explained by the fact that SIAD, which is defined as a form of hyponatremia with normal ECF volume, is not the only cause of hyponatremia in COVID-19 patients. Although SIAD has been reported as the most frequent etiology of hyponatremia in COVID-19 (11, 47, 48), other conditions can contribute to this electrolyte imbalance, such as vomiting and diarrhea that induce hyponatremia associated with reduced ECF volume (49), or an inadequate dietary intake of sodium. Based on the values of creatinine, BUN and BUN/creatinine that we found in hypoNa patients, we can hypothesize that a subset of these patients were likely to have a reduced ECF volume. On the other hand, the massive release of IL-6 may not be the only determinant of SIAD in SARS-CoV-2 affected patients. Human coronaviruses can present neuroinvasive properties, which may lead to inappropriate vasopressin secretion (50). Furthermore, it has been demonstrated that the expression and activity of angiotensin-converting enzyme type 2 (ACE2), which represents the receptor for SARS-CoV-2 on the cell surface, are induced by dietary sodium restriction in rat kidney (51). Since ACE2 is highly expressed also in human proximal tubules, we can hypothesize a role of virus-induced tubular injury in disrupting the function of ion channels, thus contributing to serum [Na^+] alterations.

The strength of our data is reinforced by the fact that in our database serum (Na^+) was corrected for serum glucose, in order to exclude pseudohyponatremia conditions in not well-controlled diabetic patients. This correction is important because it allows a correct definition of different groups (normonatremia, hyponatremia, hypernatremia) and avoids the introduction of errors in the subsequent analyses. In our study, after correcting serum [Na^+] for serum glucose, ten patients were relocated from the hyponatremic into the normonatremic group, whereas one patient was relocated from the normonatremic to the hypernatremic group. Similarly, the correction of PaO_2 values for $PaCO_2$ allows not to overestimate the efficiency of pulmonary gas exchange in conditions of hyperventilation. To our knowledge, no other study that addressed serum [Na^+] alterations in COVID-19 patients has considered these potential interfering factors on statistical analyses.

Some limitations should be recognized. Admittedly, in our study, we included only hospitalized individuals, and therefore, our data did not represent all COVID-19 patients. Nevertheless, patients who require hospitalization are in principle those with an increased risk of a more negative outcome. Despite that, serum [Na^+] and IL-6 significantly and independently predicted a worse outcome. In addition, it should be recognized that some correlations between serum [Na^+] and other parameters were relatively weak, although statistically significant. Hence, whether these correlations are clinically meaningful need to be confirmed in larger multicenter studies. With regard to this point, the above mentioned multicenter study performed in patients with COVID-19 infection in New York City supports our findings (42).

In summary, currently available data suggest that the identification of early prognostic markers such as IL-6 and the more readily available serum [Na^+] may be of help in order to timely identify COVID-19 patients with a potential progression to a more severe clinical picture and, consequently, to initiate appropriate therapeutic strategies without any delay. Unfortunately, the COVID-19 pandemic is not at the end yet and additional studies should further clarify this issue.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Patients' consent
Written consent has been obtained from each patient/subject or legal representative after a full explanation of the purpose and the nature of all procedures used.

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