



Electrolyte imbalance in COVID-19 patients admitted to the Emergency Department: a case–control study

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Abstract

In patients visiting the emergency department (ED), a potential association between electrolytes disturbance and coronavirus disease 2019 (COVID-19) has not been well studied. We aim to describe electrolyte disturbance and explore risk factors for COVID-19 infection in patients visiting the ED. We carried out a case–control study in three hospitals in France, including adult ED inpatients (≥ 18 years old). A total of 594 ED case patients in whom infection with COVID-19 was confirmed, were matched to 594 non-COVID-19 ED patients (controls) from the same period, according to sex and age. Hyponatremia was defined by a sodium of less than 135 mmol/L (reference range 135–145 mmol/L), hypokalemia by a potassium of less than 3.5 mmol/L (reference range 3.5–5.0 mmol/L), and hypochloremia by a chloride of less than 95 mmol/L (reference range 98–108 mmol/L). Among both case patients and controls, the median (IQR) age was 65 years (IQR 51–76), and 44% were women. Hyponatremia was more common among case patients than among controls, as was hypokalemia and hypochloremia. Based on the results of the multivariate logistic regression, hyponatremia, and hypokalemia were associated with COVID-19 among case patients overall, with an adjusted odds ratio of 1.89 [95% CI 1.24–2.89] for hyponatremia and 1.76 [95% CI 1.20–2.60] for hypokalemia. Hyponatremia and hypokalemia are independently associated with COVID-19 infection in adults visiting the ED, and could act as surrogate biomarkers for the emergency physician in suspected COVID-19 patients.

Keywords COVID-19 · Electrolyte imbalance · Hyponatremia · Hypokalemia

Abbreviations

ACE inhibitors	Angiotensin-converting enzyme inhibitors
ACE2	Angiotensin-converting enzyme 2
ADH	Antidiuretic hormone
ARBs	Angiotensin receptor blockers
ED	Emergency Department
RAS	Renin–angiotensin system

Introduction

Since reported in late December 2019 from the Hubei province in China, coronavirus disease 2019 (COVID-19) has spread worldwide [1]. The World Health Organization (WHO) declared COVID-19 a pandemic in mid-March 2020. Clinical presentation of COVID-19 infection is wide, from asymptomatic infection to severe viral pneumonia with acute respiratory distress syndrome (ARDS) [2–4].

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Animal studies found that COVID-19 uses angiotensin-converting enzyme 2 (ACE2) as a cellular entry receptor [5]. ACE2, one of the key enzymes in the renin–angiotensin system (RAS), plays a significant role in regulating fluid and electrolyte balance [6]. Thus, hypokalemia has been described in COVID-19 patients in China. In a study including one hundred seventy-five COVID-19 patients, 18% were classified as having severe hypokalemia, 37% had hypokalemia, and 46% had normokalemia [7]. Water excretion may also be disturbed in Coronavirus infection [8], and hyponatremia has been reported in COVID-19 patients in a clinical case and in a small study in the United States [9, 10]. Hyponatremia and hypokalemia were reported in a series of 12 patients in China [11]. Moreno-P et al. described 306 COVID-19 patients in Spain with potassium measured in the first 72 h of admission. They found that hypokalemia was independently associated with requiring invasive mechanical ventilation, but mortality was not influenced by low potassium [12].

Despite these known electrolyte imbalances, no previous study has evaluated the association between COVID-19 and these imbalances in a large multicentric cohort. We recommend screening patients presenting to the emergency department (ED) with electrolyte imbalances for COVID-19. Here, we carried out a case–control study to explore electrolytes disturbance and the risk of COVID-19 in adult patients presenting to the ED in three designated hospitals in France.

Methods

Study design and participants

This case–control study included adult ED inpatients (≥ 18 years old) from three ED in France: Nantes University Hospital, la Pitié Salpêtrière University Hospital and Nancy University Hospital. All patients who were admitted to the ED between March 15 and March 31, 2020, and who had a measurement of electrolytes by indirect potentiometry were included in our study. COVID-19 diagnosis was confirmed by a positive reverse transcription-PCR (RT-PCR) targeting different genes of COVID-19 on nasopharyngeal swab [13]. All of the COVID-19 PCR swabs were performed in ED. Patients admitted to the Intensive Care Unit (ICU) after ED were classified as having a critical infection, the remaining patients were regarded as having relatively mild to-moderate presentation of the infection. For each case patient, a control was randomly selected from the target population, that is adult patients presenting to the ED during the same period without COVID-19 infection and with biological data, and matched for sex and age, using a custom script with the R software (version 3.6.0).

Data collection

Demographic, drug exposures, presenting signs and symptoms, clinical, laboratory, and outcome data were extracted from electronic medical records using a standardized data collection form. The data extracted from included patients were checked by two physicians (EM and QLB).

Definition

Hyponatremia was defined by a sodium of less than 135 mmol/L, hypokalemia by a potassium of less than 3.5 mmol/L, and hypochloremia by a chloride of less than 95 mmol/L.

Statistical analysis

Continuous and categorical variables were presented as median (IQR) and n (%), respectively. The between-group relative difference in clinical features, drug exposures, and electrolytes was used to compare case patients and controls. Logistic regression models were fitted for estimating the odds ratio and corresponding 95% confidence interval for the risk of COVID-19 associated with variables of interest. Models separately included clinical features, drug exposures, and electrolytes (univariate logistic regression, unadjusted models), as well as all baseline covariates together (multivariate logistic regression, adjusted model). We then performed a subgroup analysis, based on the severity of the presentation of COVID-19 infection in the ED, separating patients admitted or not in the ICU, and comparing them to non-COVID-19 ED patients.

A two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were done using the R software (version 3.6.0), including the package `finalfit` from the calculation of the adjusted odds ratios.

Ethics

The study was approved by the Research Ethics Commission of Nantes University Hospital (GNEDS-13-04-2020). The sponsor of the study is CHU de Nantes (Nantes University Hospital), Delegation for Clinical Research and Innovation. Owing to its retrospective nature on de-identified data, an informed consent was waived. In France, the study is excluded from the legal requirements applicable to research involving humans within the provisions of the French Public Health Code.

Results

1801 adult patients visited the ED and had a measurement of electrolytes in the three specified hospitals during the study period. 1:1 matching was unsuccessful for one case patient. Overall, we included 594 cases and 594 controls in the analysis. Among both case patients and controls, the median (IQR) age was 65 years (IQR 51.5–76), ranging from 19 to 99 years, and 44.2% were women (Table 1). Major comorbidities and drugs associated with electrolyte imbalance were retrospectively screened. Hypertension was the most common comorbidity ($n=470$, 39.6%), followed by diabetes ($n=222$, 18.7%), and congestive heart failure ($n=168$; 14.1%, Table 1). 249 (41.9%) patients received diuretic therapy, 159 (13.4%) angiotensin-converting enzyme (ACE) inhibitors, and 142 (12.0%) angiotensin-receptor blockers (ARB). Table 1 showed that the percentage of patients who received diuretic therapy was

20.5% among case patients and 21.4% among controls (relative difference, 4.1%); the percentage of patients who received ACE inhibitors was 11.8% among case patients and 15.0% among controls (relative difference, 21.3%); the percentage of patients who received ARBs was 14.0% and 10.0%, respectively (relative difference, 28.9%).

On initial measurement of electrolytes in the ED, 194 (16.3%) had hyponatremia, 148 (12.5%) had hypokalemia, and 141 (11.9%) had hypochloremia (Table 1). We found that hyponatremia, hypokalemia, and hypochloremia were more frequent in case patients than in controls. The percentage of patients with hyponatremia was 20.4% among case patients and 12.3% among controls (relative difference, 39.7%), the percentage of patients with hypokalemia was 15.1% and 9.8%, respectively (relative difference, 35.6%), and the percentage of patients with hypochloremia was 14.1% and 9.6%, respectively (relative difference, 32.1%). Table 2 reports unadjusted estimates of the risk of COVID-19 according to electrolytes disturbance showing potential

Table 1 Demographic, clinical, and laboratory findings of patients with COVID-19 (Case patients) and matched controls

	All adults ($N=1188$)	Case patients ($n=594$)	Controls ($n=594$)
Age, median (IQR), year	65 (51.5–76)	65 (52–76)	65 (51–76)
Sex, n (%), 95% CI			
Male	663 (55.8, 52.9–58.6)	333 (56.0, 51.9–60.0)	330 (55.6, 51.4–59.6)
Female	524 (44.2, 41.3–47.0)	261 (44.0, 39.9–48.0)	263 (44.3, 40.2–48.4)
Comorbidities, n (%), 95% CI			
Hypertension	470 (39.6, 36.8–42.4)	242 (40.7, 36.7–44.8)	228 (38.4, 34.4–42.4)
Diabetes	222 (18.7, 16.5–21.0)	120 (20.2, 17.0–23.6)	102 (17.1, 14.2–20.5)
Chronic kidney disease	110 (9.3, 7.7–11.0)	51 (8.6, 6.5–11.1)	59 (9.9, 7.6–12.6)
Congestive heart failure	168 (14.1, 12.2–16.2)	84 (14.1, 11.4–17.2)	170 (14.3, 25.0–32.4)
Liver cirrhosis	19 (1.6, 0.1–2.4)	8 (1.3, 0.1–2.6)	11 (1.9, 1.0–3.2)
Medication, n (%), 95% CI			
Potassium-sparing diuretics	46 (3.9, 2.8–5.1)	27 (4.5, 3.0–6.5)	19 (3.2, 1.9–4.9)
Other diuretics	203 (17.1, 14.9–19.3)	95 (16.0, 13.1–19.1)	108 (18.2, 15.1–21.5)
Angiotensin-converting enzyme inhibitors	159 (13.4, 11.5–15.4)	70 (11.8, 9.3–14.6)	89 (15.0, 12.2–18.1)
Angiotensin receptor blockers	142 (12.0, 10.2–13.9)	83 (14.0, 11.3–17.0)	59 (10.0, 7.6–12.6)
Corticosteroids	62 (5.2, 4.0–6.6)	31 (5.2, 3.6–7.3)	31 (5.2, 3.6–7.3)
Initial clinical findings, n (%), 95% CI			
Diarrhea	202 (17.0, 14.9–19.2)	156 (26.3, 22.8–30.0)	46 (7.7, 5.7–10.2)
Vomiting	137 (10.6, 9.8–13.5)	52 (8.7, 6.6–11.3)	85 (14.3, 11.6–17.4)
Initial laboratory tests			
Sodium, mmol/l; median (IQR)	139 (136–141)	138 (135–141)	139 (137–141)
Hyponatremia, n (%), 95% CI	194 (16.3, 14.3–18.6)	121 (20.4, 17.2–23.8)	73 (12.3, 9.7–15.2)
Potassium, mmol/l; median (IQR)	4.0 (3.7–4.3)	3.9 (3.6–4.3)	4.0 (3.75–4.3)
Hypokalemia, n (%), 95% CI	148 (12.5, 10.6–14.5)	90 (15.1, 12.4–18.3)	58 (9.8, 7.4–12.4)
Chloride, mmol/l; median (IQR)	101 (98–104)	100 (97–104)	102 (99–105)
Hypochloremia, n (%), 95% CI	141 (11.9, 10.0–13.8)	84 (14.1, 11.4–17.2)	57 (9.6, 6.9–11.7)
Urea, mmol/l; median (IQR)	5.6 (4.2–8.1)	5.6 (4.0–8.1)	5.6 (4.3–8.0)
Creatinine, μ mol/l; median (IQR)	78.2 (64–101)	79 (65–102)	78 (64–99.5)

95% CI 95% interval confidence, IQR interquartile

Table 2 Results of the logistic regression analysis comparing ED patients with COVID-19 and ED patients without COVID-19. Odds ratios for COVID-19 associated with drugs and electrolyte disturbance, unadjusted odds ratios (univariate logistic regression) and adjusted odds ratios (multivariate logistic regression)

	Unadjusted OR for COVID-19 OR (95% CI)	<i>P</i> value	Adjusted OR for COVID-19, OR (95% CI)	<i>P</i> value
Comorbidities				
Hypertension	1.10 (0.87–1.39)	0.43	1.01 (0.73–1.39)	0.957
Diabetes	1.22 (0.91–1.63)	0.19	1.25 (0.89–1.76)	0.195
Chronic kidney disease	0.85 (0.57–1.26)	0.41	0.85 (0.52–1.37)	0.497
Congestive heart failure	1.00 (0.72–1.38)	0.98	1.21 (0.80–1.84)	0.370
Liver cirrhosis	0.72 (0.28–1.79)	0.49	0.50 (0.17–1.39)	0.194
Medication				
Potassium-sparing diuretics	1.35 (0.81–2.20)	0.24	1.30 (0.75–2.23)	0.34
Other diuretics	1.45 (0.80–2.68)	0.22	1.71 (0.89–3.34)	0.11
Angiotensin-converting enzyme inhibitors	0.76 (0.54–1.07)	0.12	0.78 (0.53–1.16)	0.22
Angiotensin receptor blockers	1.49 (1.04–2.13)	0.03	1.50 (0.97–2.31)	0.07
Corticosteroids	1.01 (0.60–1.69)	0.97	1.32 (0.75–2.35)	0.34
Initial clinical findings				
Diarrhea	4.19 (2.97–6.02)	<0.001	5.04 (3.47–7.46)	<0.001
Vomiting	0.57 (0.39–0.81)	0.002	0.34 (0.22–0.51)	<0.001
Initial laboratory tests				
Hyponatremia	1.82 (1.33–2.51)	<0.001	1.89 (1.24–2.89)	0.003
Hypokalemia	1.65 (1.16–2.35)	0.005	1.76 (1.20–2.60)	0.004
Hypochloremia	1.55 (1.09–2.22)	0.016	1.09 (0.68–1.75)	0.73

OR odds ratios, 95% CI 95% confidence interval

association. After multivariable adjustment, an association with COVID-19 was maintained by hyponatremia (adjusted odds ratio, 1.89 [95% CI 1.24–2.89]) and for hypokalemia (adjusted odds ratio, 1.76 [95% CI 1.20–2.60]). Moreover, when comparing models including electrolytes to models not including them, the likelihood ratio test was very significant (Log Likelihood ratio = -808.90, $p < 0.001$). Furthermore, when we stratified by sodium levels, we found that middle hyponatremia (Na = 130 to 135 mmol/l) was significant ($n = 162$, odds ratio, 1.88 [95% CI, 1.22–2.91], $p = 0.004$) but not severe hyponatremia (Na < 130 mmol/l, $n = 32$, odds ratio, 1.90 [95% CI 0.81–4.60], $p = 0.144$). When we stratified by potassium levels, we found that middle hypokalemia ($K = 3–3.5$ mmol/l) was significant ($n = 127$, odds ratio, 1.85 [95% CI 1.23–2.82], $p = 0.004$), but not severe hypokalemia ($K < 3$ mmol/l, $n = 21$, odds ratio, 1.27 [95% CI 0.48–3.29], $p = 0.622$). Importantly, after multivariable adjustment, neither ARBs (1.50 [95% CI 0.97–2.31]) nor ACE inhibitors (0.78 [95% CI 0.53–1.16]) were significantly associated with the risk of COVID-19.

We then performed a subgroup analysis, based on the severity of the presentation of COVID-19 infection in the ED, separating patients admitted or not in the ICU, to test if the association was maintained in the most severe patients. Among the 594 patients with COVID-19 diagnosed in the ED, 96 (16.2%) patients admitted to the Intensive Care Unit (ICU) after ED were classified as having a critical infection,

the remaining patients were regarded as having relatively mild to-moderate presentation of the infection. Hyponatremia maintained association with COVID-19 among patients who were admitted to the ICU (adjusted odds ratio, 2.80 [95% CI 1.39–5.58]) but not hypokalemia 1.97 [95% CI 0.96–3.88], Table 3).

Discussion

In this case-control study, we found that hyponatremia and hypokalemia were independently associated with COVID-19 in adults visiting the ED. Hyponatremia and hypokalemia were more frequent among patients who were infected with COVID-19 than among the controls who were matched for age and sex and after multivariable adjustment. Hyponatremia was also associated with COVID-19 and the most severe presentation of the disease; that is, requiring ICU admission. Importantly, we confirmed that there is no association between ARBs or ACE inhibitors and the risk of COVID-19 among patients visiting the ED.

Recent literature has shown an association between COVID-19 and hyponatremia. In a limited series of 12 patients with COVID-19 admitted in a tertiary hospital in Guangdong, China, Hong et al. reported 50% of the patients had hypokalemia, and 50% had hyponatremia, correlating with the degree of renal injury [11]. They concluded that

Table 3 Results of the multivariate logistic regression analysis comparing ED patients without COVID-19 ($n=594$), patients with mild to moderate presentation of COVID-19 ($n=498$), and patients with critical presentation ($n=96$)

	Multivariate logistic regression, controls versus cases with mild to moderate presentation, Adjusted OR, (95% CI)	<i>P</i> value	Multivariate logistic regression, controls versus cases with critical presentation, adjusted OR, (95% CI)	<i>P</i> value
Comorbidities				
Hypertension	1.17 (0.87–1.58)	0.297	1.06 (0.57–1.94)	0.85
Diabetes	1.15 (0.84–1.56)	0.392	1.61 (0.87–2.90)	0.12
Chronic kidney disease	1.01 (0.65–1.55)	0.978	0.64 (0.22–1.64)	0.37
Congestive heart failure	0.95 (0.66–1.36)	0.767	0.71 (0.26–1.80)	0.49
Liver cirrhosis	0.53 (0.20–1.20)	0.152	0.00 (0.00–4213.52)	0.98
Medication				
Potassium-sparing diuretics	1.19 (0.66–2.10)	0.560	2.03 (0.68–5.23)	0.168
Other diuretics	0.78 (0.55–1.11)	0.165	2.98 (0.91–8.71)	0.054
Angiotensin-converting enzyme inhibitors	0.89 (0.46–1.61)	0.705	1.03 (0.48–2.12)	0.933
Angiotensin receptor blockers	1.18 (0.79–1.74)	0.418	2.23 (1.04–4.73)	0.037
Corticosteroids	1.12 (0.67–1.84)	0.659	1.29 (0.42–3.47)	0.64
Initial clinical findings				
Diarrhea	3.31 (2.48–4.43)	<0.001	5.08 (2.68–9.59)	<0.001
Vomiting	0.43 (0.28–0.63)	<0.001	0.30 (0.13–0.64)	0.003
Initial laboratory tests				
Hyponatremia	1.63 (1.10–2.39)	0.014	2.80 (1.39–5.58)	0.004
Hypokalemia	1.67 (1.18–2.34)	0.003	1.97 (0.96–3.88)	0.056
Hypochloremia	0.96 (0.61–1.51)	0.875	1.70 (0.77–3.66)	0.180

OR odds ratios, 95% CI 95% confidence interval

in severe patients, the early renal injury in COVID-19 can often cause hypokalemia and hyponatremia. Inciardia et al. reported the case of a healthy 53-year-old patient in Italy who developed acute myopericarditis with systolic dysfunction a week after onset of fever and dry cough due to COVID-19. Blood sample tests revealed hyponatremia and hypochloremia [9]. In the US, Aggarwal et al. reported that among 19 patients with COVID-19 infection admitted to the ED, 50% presented with hyponatremia [10]. Thus, our multicenter study confirmed that hyponatremia is frequent in COVID-19 adults, found in 20.4% of the patients. In our study, we did not find significant association between COVID-19 severity and hypokalemia ($p=0.056$), contrary to the previous study [12]. Moreno-P et al. found that hypokalemia (potassium ≤ 3.5 mmol/l) was independently associated with requiring invasive mechanical ventilation (odds ratio: 8.98, 95% CI 2.54–31.74). However, our findings are limited by the reduced number of patients with COVID-19 hospitalized in intensive care unit ($n=96$), compared to the number cases with middle to moderate COVID-19 ($n=498$) and to controls ($n=594$).

In COVID-19 adults, hyponatremia may be linked to the increased release of antidiuretic hormone (ADH) in response to a volume depletion following gastrointestinal fluid losses. In our cohort, 26.3% of the patients had diarrhea

and 8.7% presented with vomiting, significantly more than non-COVID-19 patients. Thus, these symptoms are common in patients with COVID-19, and can trigger the increased ADH release due to extracellular dehydration state. On the other hand, a syndrome of antidiuresis (SIAD) can occur in response to COVID-19 complications like pneumonia or acute respiratory distress syndrome. In the present study, among 594 cases, 498 (83.8%) had symptoms of pneumonia.

As not much is known about the prevalence of hypokalemia in patients with COVID-19. Chen et al. reported that among 175 patients with COVID-19 (92 women and 83 men; median age, 46 [IQR, 34–54] years), 39 (22%) had severe hypokalemia (under 3 mmol/L), and 69 (40%) hypokalemia (3–3.5 mmol/L). They found that urine potassium loss was the primary cause of hypokalemia, consistent with the pathogenesis of COVID-19 [7], which stimulates RAS.

Our study has some limitations. First, due to the retrospective study design, not all known prognostic factors were available in all patients. For instance, bicarbonate measurement was not available in our case–control study. Second, we did not analyze COVID-19 treatments (i.e., antivirals and antibiotics) received by the patients before ED admission. Therefore, their role might be underestimated in ICU admission or invasive ventilation, especially in patients admitted

to the ED late in their illness. Third, since COVID-19 PCR swabs were only performed in patients with a suspicious presentation at ED presentation, some control patients could be COVID-19 patients. However, we checked the medical wards of the controls and none of them received a diagnosis of COVID-19 during their hospital stay. Fourth, severity of the disease was only evaluated by ICU admission, and we did not collect data on in-hospital mortality. This may limit our assertion that hyponatremia was associated with the most severe presentation of the disease.

Conclusions

To the best of our knowledge, this is the largest case–control cohort study that analyze electrolytes disturbance among patients presenting to the ED during the COVID-19 pandemic. We found that hyponatremia and hypokalemia at ED admission were independently associated with COVID-19, and that the association was maintained for hyponatremia in a subgroup analysis of the most severe patients. Thus, hyponatremia and hypokalemia could act as surrogate biomarkers for the emergency physician in suspected COVID-19 patients to rapidly screen at-risk patients.

Author contributions EM, HDC, LF, and NG conceived the study. EM, QLB, and LF developed the analysis plan. YF, TC, MCR AK, AB, and DM collected the data. EM and QLB undertook the main analysis. EM wrote the first draft of the paper, with all other authors making important critical revisions. All authors have read and approved the final version of the manuscript.

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Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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Informed consent Owing to its retrospective nature on de-identified data, an informed consent was waived. In France, the study is excluded

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