



Hypochloremia associated with a greater incidence of pneumonia in chronic hemodialysis patients with COVID-19: a center's experience

Hipocloremia asociada a una mayor incidencia de neumonía en pacientes en hemodialisis crónica con COVID-19: experiencia de un centro

Dear Editor,

Serum chloride has recently gained importance in the assessment of patients with heart failure and sepsis.^{1,2} In some studies, hypochloreaemia has been associated with higher mortality rates.² At the same time, the COVID-19 pandemic continues to be, to this day, a significant threat to health services worldwide. It is widely accepted that patients with cardiovascular comorbidity or chronic kidney disease are vulnerable to more severe forms of this disease.³

We carried out a retrospective cohort study. We analysed the serum chloride, C-reactive protein (CRP), procalcitonin, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) of the 11 patients on our long-term haemodialysis programme who developed SARS-CoV-2 infection diagnosed by PCR/TMA during the second wave of the pandemic at our hospital (August-December 2020). We collected demographic data, length of hospital stay, diagnosis of pneumonia (yes/no) and the final outcome of the infection (cure or death). The median chloride level was taken into consideration as a cut-off point to divide the patients into two groups (1: ≤ 97 mEq/l; 2: >97 mEq/l).

The median age was 60 years (q25-q75: 56–63); 36.36% (n=4) were female. All patients required hospital admission. The mean length of hospital stay was 19.81 ± 13 days. Nine patients had COVID-19 pneumonia and three (27.3%) died. The median serum chloride level was 97 mEq/l (q25-q75: 94–99). The rest of the variables are shown in Table 1.

When these variables were compared based on chloride levels, significant differences were found only in the anion gap value ($p=0.045$). There were no significant differences in terms of inflammation parameters, pH, sodium, potassium and bicarbonate.

Group 1 (serum chloride ≤ 97 mEq/l) had a higher incidence of pneumonia ($p=0.049$) (Fig. 1) and a greater tendency to be admitted to the intensive care unit ($p=0.029$). Moreover, despite not reaching statistical significance, a higher mortality rate was evident in the group with lower chloride levels.

Patients on long-term haemodialysis have been particularly affected in this pandemic.³ To our knowledge, this is

the first study that focuses entirely on patients on long-term haemodialysis and the possible utility of serum chloride levels at hospital admission for COVID-19. There are currently a number of studies showing a tendency in patients positive for SARS-CoV-2 to have lower serum chloride levels.⁴ Additionally, a recent cohort of patients hospitalised for COVID-19 shows that a 26% of patients had hypochloreaemia, with this being more common in patients on haemodialysis.⁵ In addition other cohorts show that median serum chloride was significantly lower in patients with severe disease.^{6,7}

Hypochloreaemia is a prognostic marker of heart failure, even more powerful than sodium levels, due to its influence on neurohormonal activation and resistance to diuretics.¹ However, this would not fully explain its role in the pathophysiology of COVID-19.

The possible influence of endothelial dysfunction within the pathophysiology of COVID-19 has been documented,^{8,9} and in some recent studies chloride has been linked to endothelial dysfunction through some ion channels.¹⁰ In our study, the median NLR, an emerging marker of inflammation, endothelial dysfunction and prognosis in COVID-19,³ was higher in patients with hypochloreaemia. However, these

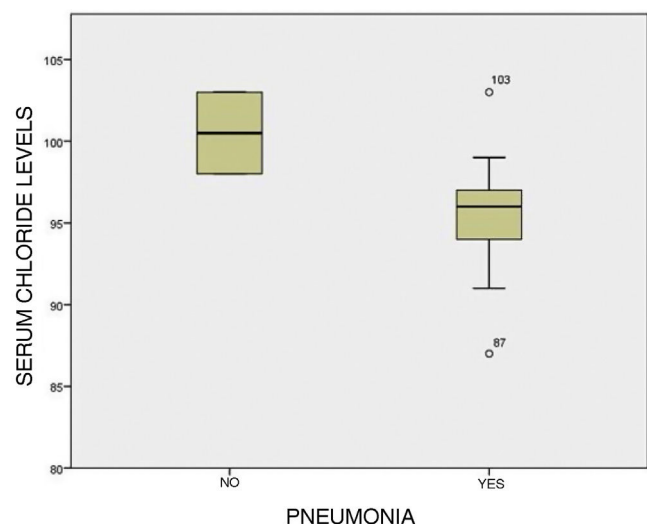


Fig. 1 – Serum chloride levels and diagnosis of SARS-CoV-2 pneumonia in patients on long-term haemodialysis.

Table 1 – Baseline characteristics and blood test of the patients based on serum chloride levels at hospital admission.

	Total sample (n = 11)	Group 1 (Cl <97 mEq/l) (n = 7)	Group 2 (Cl >97 mEq/l) (n = 4)	p
Age (years), median (q25-q75)	60 (56–63)	60 (36–67)	59 (58–62)	0.924
Female, n (%)	4 (36.4)	3 (42.9)	1 (25)	0.554
ICU admission, n (%)	5 (45.5)	5 (71.1)	0 (0)	0.029
Pneumonia, n (%)	9 (81.8)	7 (100)	2 (50)	0.049
Death, n (%)	3 (27.3)	3 (42.9)	0 (0)	0.143
C-reactive protein (mg/l), mean ± SD	42.41 ± 13.67	50.59 ± 42.03	28.09 ± 27.78	0.368
Procalcitonin (ng/mL), median (q25-q75)	0.54 (0.17–1.35)	1.12 (0.18–1.47)	0.34 (0.11–64.61)	0.571
NLR, mean ± SD	6.01 ± 4.08	7.13 ± 4.63	4.07 ± 2.2	0.252
PLR, mean ± SD	284.45 ± 136.64	279.02 ± 151.83	293.97 ± 126.26	0.872
Admission time (days), mean ± SD	19.81 ± 13.47	20.57 ± 15.78	18.5 ± 10.15	0.821
Sodium (mEq/l), mean ± SD	135.27 ± 3.52	133.86 ± 3.24	137.75 ± 2.75	0.075
Anion gap (mEq/l), mean ± SD	18.88 ± 4.29	20.77 ± 3.99	15.57 ± 2.53	0.045
pH, mean ± SD	7.43 ± 0.04	7.43 ± 0.03	7.43 ± 0.05	0.845
Potassium (mEq/l), median (q25-q75)	4.2 (3.71–4.6)	4.2 (4.2–4.5)	4.05 (3.18–6.35)	1.000
Bicarbonate (mEq/l), mean ± SD	24.37 ± 3.11	23.47 ± 2.69	25.95 ± 3.54	0.220

ICU: intensive care unit; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SD: standard deviation.

results were not statistically significant due to the small size of the population studied.

It would be reasonable to think that the anion gap influences the results. However, in our analysis all the other variables involved in the anion gap formula (sodium, potassium and bicarbonate) did not show significant differences between groups, and this finding is therefore attributable to serum chloride itself.

In conclusion, in the absence of further studies, long-term haemodialysis patients with SARS-CoV-2 infection and lower serum chloride levels at hospital admission could have a greater tendency to develop pneumonia and require admission to the intensive care unit.

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Including KDIGO cardiovascular risk stratification into SCORE scale could improve the accuracy to better stratify cardiovascular risk

Incluir la estratificación de riesgo KDIGO en la escala SCORE podría mejorar la exactitud para estratificar mejor el riesgo cardiovascular

Dear Editor,

Chronic kidney disease (CKD) is a common condition worldwide;¹ however, it is vastly underdiagnosed as it frequently remains asymptomatic until reaching advanced

stages.² Thus, a recent database study performed in Spain has shown that in adults, the prevalence of identified CKD reaches only 5% of the population, which is far from previous nation-wide, population-based studies.³ The CKD prevalence is expected to increase in the next future, as people will be

Table 1 – Cardiovascular risk stratification according to 2019 ESC and KDIGO guidelines.

	2019 ESC	KDIGO
Very high risk	<ul style="list-style-type: none"> • Documented ASCVD • T2DM with TOD^a or ≥3 major risk factors, or T1DM of long duration (>20 years) • Severe CKD (eGFR < 30 mL/min/1.73 m²) • SCORE ≥ 10% • FH with ASCVD or another major risk factor 	<ul style="list-style-type: none"> • eGFR < 30 mL/min/1.73 m² or eGFR 30–44 mL/min/1.73 m² with UACR ≥ 30 mg/g or eGFR 45–59 mL/min/1.73 m² with UACR > 300 mg/g
High risk	<ul style="list-style-type: none"> • Markedly elevated single risk factors (TC > 310 mg/dL, LDL-C > 190 mg/dL, or BP ≥ 180/110 mmHg) • Patients with FH without other major risk factors • Patients with DM without TOD^a, with DM duration ≥ 10 years or another additional risk factor • Moderate CKD (eGFR 30–59 mL/min/1.73 m²) • SCORE ≥ 5% and < 10% 	<ul style="list-style-type: none"> • eGFR 30–59 mL/min/1.73 m² with UACR < 30 mg/g or eGFR 45–59 mL/min/1.73 m² with UACR 30–300 mg/g or eGFR ≥ 60 with UACR > 300 mg/g
Moderate risk	<ul style="list-style-type: none"> • SCORE ≥ 1% and < 5% • Young patients (T1DM < 35 years; T2DM < 50 years) with DM duration < 10 years, without other risk factors 	<ul style="list-style-type: none"> • eGFR ≥ 60 mL/min/1.73 m² with UACR 30–300 mg/g^b
Low risk	<ul style="list-style-type: none"> • SCORE < 1% 	<ul style="list-style-type: none"> • eGFR > 60 mL/min/1.73 m² with UACR < 30 mg/g

^a Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

^b Modified from original KDIGO as ESC includes 45–59 GFR as high risk category.

ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; ESC: European Society of Cardiology; FH: familial hypercholesterolemia; KDIGO: Kidney Disease: Improving Global Outcomes; LDL-C: low-density lipoprotein cholesterol; SCORE: Systematic Coronary Risk Estimation; T1DM: type 1 DM; T2DM: type 2 DM; TC: total cholesterol; TOD: target organ damage.