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Original Article

Hypocalcemia: A key biomarker in hospitalized COVID-19 patients

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ABSTRACT

Background: At the end of 2019 a new respiratory syndrome emerged in China named Coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 infection. Considering the severity of the disease in adult subjects with one or more chronic pathologies, it was mandatory to find simple and effective biomarkers for negative prognosis of the disease easily available at the admission to the hospital.

Methods: To identify possible parameters showing association with the outcome in COVID-19 patients with pre-existing chronic diseases, blood biochemical profiles of 511 patients, enrolled from March to June 2020, were retrospectively evaluated. The pathological conditions taken into consideration were diabetes, arterial hypertension, chronic kidney disease, cardiovascular diseases, chronic obstructive pulmonary disease, obesity, and cancer. All the data were collected upon admission to the emergency room (ER) during the indicated period.

Results: We observed that serum and ionized calcium were prevalently altered in our cohort. We determined that hypocalcemia was a major parameter associated with mechanical ventilation and poor prognosis, correlating also with the presence of comorbidities such as cardiovascular diseases, chronic kidney disease, and cancer. In addition, we found a positive correlation between hypocalcemia and clinical complications during hospitalizations.

Conclusions: Our results strengthen the relevance of serum calcium concentration as a useful prognostic biomarker in hospitalized COVID-19 patients.

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome CoronaVirus 2.

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At a glance commentary

Scientific background on the subject

A new infectious syndrome has recently emerged in China named Coronavirus disease 2019 (COVID-19). COVID-19 is particularly severe in adult subjects affected by one or more chronic pathologies. Thus, it is critical to identify simple and effective biomarkers for negative prognosis of the infection, easily accessible at the hospital admission.

What this study adds to the field

We report that hypocalcemia is a major parameter associated with poor prognosis of hospitalised COVID-19 patients, also correlating with the presence of comorbidities like chronic kidney disease, cardiovascular diseases, and cancer. Hypocalcemia also correlates with clinical complications during patient hospitalization, strengthening the value of calcemia as prognostic biomarker in COVID-19 patients.

The global pandemic caused by the novel coronavirus SARS-CoV-2 has put a strain on hospital systems. Even though most of the cases were usually asymptomatic or mild symptomatic, a substantial percentage required hospitalization and, in specific clinical conditions, intensive care [1–3]. The presence of comorbidities has undoubtedly been unfavourable for the prognosis, especially in patients of advanced age [4–8]. Thus, the need to find a biomarker capable of identifying patients at higher risk for severe outcomes, that could require intensive care, represents a primary goal.

Several biochemical parameters have been evaluated and particular attention has been focused on calcemia, also considering the primary role of calcium for viral infection and replication [9]. Particularly, it has been reported that a high percentage of COVID-19 hospitalized patients showed hypocalcemia [10–19], a condition that can be critical, especially for patients with pre-existing chronic pathologies [20–23]. Our retrospective analysis also confirms that serum calcium concentration is one of the most altered parameters among hospitalized COVID-19 patients, especially in those with the most critical conditions. Since hypocalcemia has been recognized as a significant risk factor for hospitalization, here we evaluated the predictive and prognostic value of this biomarker, mostly focusing on high risk COVID-19 patients. These include, in particular, those presenting comorbidities such as diabetes, obesity, arterial hypertension, Chronic Kidney Disease (CKD), Cardiovascular Diseases (CVD), Chronic Obstructive Pulmonary Disease (COPD), and cancer.

Materials and methods

We studied 712 patients admitted to the ER of the Hospital Universitario Principe de Asturias (HUPA) in Alcalá de Henares (Madrid–Spain) from March to June 2020. The only inclusion criterion was the RT-qPCR positive test for SARS-CoV-2. Thus, 36 patients were excluded from the study for testing negative. 165 subjects were also excluded for lack of clinical data due to the non-hospitalization. In summary, a total of 511 patients whose clinical information was available in the database of the hospital were included in our study. Among the comorbidities reported by the patients on admission, the presence of diabetes, arterial hypertension, obesity, CKD, CVD, COPD, and cancer was evaluated. A patient with at least one pre-existing chronic disease has been classified as a patient with comorbidities. The admission to the intensive care was recorded as an index of severe COVID-19. The presence of complications during the hospitalization was assessed, such as superinfection, thrombotic complications, and the onset of hyponatremia with sodium <130 mEq/L. All the biochemical data have been obtained from venous blood samples upon admission to the ER. Baseline serum calcium (reference range 8.5–10.5 mg/dL) has been measured by the analyzer Siemens Dimension EXL 200 and integrated with RAPIDPoint 500 for ionized calcium (reference range 1.1–1.3 mmol/L). Inflammatory parameters like Lactate Dehydrogenase (LDH - reference range 80–300 mU/mL), reactive C Protein (rCP - reference range <5 mg/L) and ferritin (reference range, men 30–400 ng/mL, women 15–150 ng/mL) were evaluated by using Siemens Dimension EXL 200.

Calculation

Statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS) software, version 25 (SPSS Inc., Chicago, IL, USA). All the findings were considered statistically significant with a p-value < 0.05.

Hypocalcemia has been defined as serum calcium concentration <8.5 mg/dL and ionized calcium as <1.18 mmol/L. We performed Kolmogorov–Smirnov test to determine the distribution in our cohort. Subsequently, we used Mann–Whitney U test, Kruskal–Wallis test, $\chi 2$, and Fisher test. To calculate odds ratio, we divided the population in two groups: hypocalcemic and non-hypocalcemic, defined as above. To be noted, the non-hypocalcemic group can be considered as a normocalcemic subpopulation, since we did not observe any hypercalcemic condition. The Mann–Whitney U test was used to calculate the p-values of our non-parametric distributions. Kuskal–Wallis test was employed to evaluate if the presence of 2 complications per patient might influence the developing of hypocalcemia. All the recorded comorbidities were analysed using the Pearson's chi-squared test to highlight statistical differences in the hypocalcemic and/or normocalcemic subpopulations.

Results

The clinical records of 511 patients with the diagnosis of COVID-19 enrolled in this study were analysed. The cohort baseline personal and biochemical characteristics are summarized in Table 1. In brief, age, sex, comorbidities, and relevant laboratory results obtained at the time of admission to the ER have been reported. It should be noted that 99.2% (N = 507/511) of patients presented a pulmonary infiltrate,

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Table 1 Baseline characteristics of the COVID-19 patients included in the study.

Patient Baseline Characteristics	No. (%)
Total No.	511
Age median [IQR]	67.8 [55–79]
Gender	
Female	217 (42.5%)
Male	294 (57.5%)
Obesity (>30 kg/m^2)	
Yes	96 (18.8%)
No	415 (81.2%)
Pulmonary infiltrate	507 (99.2%)
Comorbidities	
Total No.	390 (76.3%)
Hypertension	297 (58.1%)
Diabetes	192 (29.7%)
Cancer[a]	93 (18.2%)
COPD	39 (7.6%)
CKD	53 (10.4%)
CVD	124 (24.3%)
Mechanical ventilation	
Yes	66 (12.9%)
No	445 (87.1%)
Exitus	
Yes	159 (31.1%)
No	352 (68.9%)
Total deaths with comorbidities	150 (94.3%)
Pre – admission mean time in days [IQR]	4.74 [2–7]
Serum Calcium mg/dL [IQR][b]	8.58 [8.3–9]
Ionized Calcium mmol/L [IQR]	1.09 [1.05–1.16]
rCP mg/L [IQR]	93.6 [23.9–138.45]
LDH mU/mL [IQR]	366.38 [240.75–428.25]
Ferritin ng/mL [IQR]	1013.96 [2–6402]

[a] All types of cancers have been considered.
[b] Serum Calcium has been corrected for serum albumin. IQR: Inter Quartile Range.

defining our cohort of patients as affected by severe COVID-19 [Table 1].

Among the biochemical parameters analyzed, alterations of calcium level were evident, either serum and/or ionized, supporting calcium relevance in COVID-19 disease. Indeed, we observed median value of 8.58 mg/dL, with values ranging from 8.3 to 9 mg/dL, for serum calcium (reference range 8.5–10.5 mg/dL) and of 1.09 mmol/L for ionized calcium (reference range 1.1–1.3 mmol/L), defining an overall picture of hypocalcemia. Conversely, rCP, LDH, and ferritin resulted notably increased. Thus, we analyzed the correlation between inflammatory factors and hypocalcemia. The analysis revealed that LDH and rCP positively correlate with hypocalcemia ($p = 0.001$ and $p = 0.002$, respectively), as shown in Fig. 1. No significant correlation was observed with ferritin ($p = 0.362$).

Considering that 64.6% (N = 42/65) of intubated patients were hypocalcemic and 55% (N = 82/149) of dead patients presented onset of hypocalcemia [Table 2], we decided to verify whether hypocalcemia might influence the prognosis of hospitalized COVID-19 patients.

We firstly verified the existence of a correlation between hypocalcemia and outcome in our monocentric population. Particularly, we observed that hypocalcemia positively correlates with intubation/mechanical ventilation ($p = <0.001$) and with poor prognosis ($p = 0.003$) [Table 3]. Thus, our findings strongly suggest that hypocalcemia can be considered a predictive biomarker of poor outcome for COVID-19 hospitalized patients.

Since 76.3% of patients presented chronic diseases [Table 1], we evaluated if the presence of comorbidities associated to hypocalcemia might play a role in the course of the disease. To this purpose, we first assessed the diseases mainly associated with poor prognosis in our COVID-19 cohort, correlating each recorded disease with each condition, mechanical ventilation and exitus [Table 4]. Secondly, we analysed the correlation of the specific comorbidities with serum and ionized calcium and we evaluated if they might represent an additional risk of hypocalcemia occurrence in case of SARS-CoV-2 infection [Table 5].

As shown in Table 4, almost all the comorbidities presented a strong association with exitus, but only CVD positively correlated with both mechanical ventilation and exitus.

Interestingly, the only associated condition that did not correlate with exitus was obesity (defined as BMI>30 kg/m^2), although strongly correlated with intubation. As a matter of facts, the number of obese patients is 96/511 (18.8%) and 33.3% of the intubated population was obese. This result might indicate that a BMI> 30 kg/m^2 is a predictive factor for the severity of the disease, but not for its outcome.

As shown in Table 5, the presence of comorbidities correlated with hypocalcemia (serum calcium $p = 0.03$ and ionized calcium $p = 0.008$), independently of the number of comorbidities for patient.

However, considering them separately, only CKD showed a correlation with both serum and ionized hypocalcemia (serum calcium $p = 0.02$ and ionized calcium $p = 0.007$). In addition, a positive correlation, even though only with serum calcium, was found for CVD (serum calcium $p = 0.03$ and ionized calcium $p = 0.703$) and cancer (serum calcium $p = 0.035$ and ionized calcium $p = 0.691$). Interestingly, as reported in the previous paragraph, CVD resulted as the main comorbidity associated to both intubation and exitus in our patient cohort and, in addition, it positively correlated with serum hypocalcemia. Finally, we verified if clinical complications during hospitalization, such as superinfection, thrombosis, and hyponatremia, might correlate with hypocalcemia. Interestingly, 184 COVID-19 patients presented one or more complications and the 54.3% of these (N = 100/184) presented hypocalcemia. As shown in Table 6, hypocalcemia positively correlated ($p < 0.01$) with the presence of complications. Finally, no statistically significant variations in serum and ionized calcium level have been observed depending on gender differences (Odds Ratio 0.813, confidence interval 0.55–1.18, $p = 0.61$).

Discussion

In this monocentric retrospective study, we evaluated the prognostic value of hypocalcemia in hospitalized patients with COVID-19. Despite the fact that there are several options for the prevention, diagnosis and treatment of COVID-19

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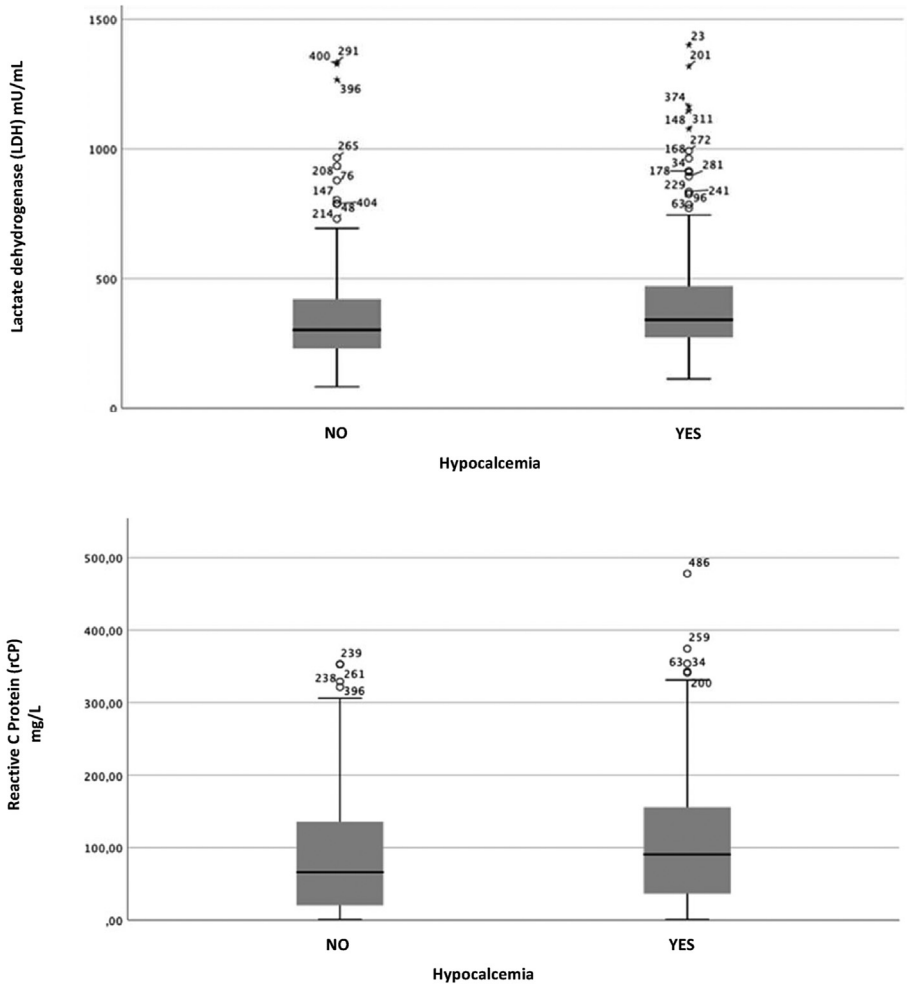

Fig. 1 **Inflammatory parameters LDH (up) and rCP (bottom) in patients with (YES) or without (NO) hypocalcemia.** Statistical significance p = 0.001 for LDH and p = 0.002 for rCP.

disease, the high rate of respiratory complications and mortality caused by the pandemic brought out the need to find and confirm early markers of disease [1,2,24]. Several authors reported the prevalence of the decreased serum calcium level in COVID-19 patients, independent of the disease severity, which is not surprising given that it was common in patients with Sars and Ebola infections [9,25,26]. However, the number of studies related to the association between hypocalcemia and COVID-19 is still limited, even presenting some caveats, to allow a proper meta-regression analysis [27,28]. In addition, other authors pointed attention to the relevance of

Table 2 Overview of hypocalcemia recurrence in COVID-19 patients included in the study.

Patient Classification	No (%)
Total patients with recorded calcemia	464
Total hypocalcemic patients	208 (44.8%)
Total intubated patients	65[a]
Total hypocalcemics among intubated	42 (64,6%)
Total hypocalcemics with comorbidities among intubated	33 (50.7%)
Total deaths	149[b]
Total hypocalcemics among deaths	82 (55%)
Total hypocalcemics with comorbidities among deaths	78 (52.3%)
Total patients with recorded ionized calcemia	426

[a] Calcium levels were available only for 65/66 intubated patients.
[b] Calcium levels were available only for 149/159 dead patients.

Table 3 Analysis of the association between hypocalcemia and mechanical ventilation or exitus.

Outcome	Odds Ratio [confidence interval]	Serum Calcium p value
Mechanical ventilation	2.563 [1.48–4.42]	**<0.001**
Exitus	1.83 [1.23–2.72]	**0.003**

Odds ratio and Mann–Whitney U test have been employed. Statistical significance at $p < 0.05$.

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Table 4 Analysis of the association between comorbidities and mechanical ventilation and exitus.

Comorbidities (N)	Mechanical Ventilation (N = 66)	p value	Exitus (N = 159)	p value
Diabetes (152)	15	0.181	65	**0.0001**
Hypertension (297)	34	0.244	122	**0.0001**
COPD (39)	2	0.131	23	**0.0001**
CVD (124)	9	**0.031**	68	**0.0001**
CKD (53)	4	0.218	30	**0.0001**
Obesity (96)	22	**0.002**	31	0.782
Cancer (93)	15	0.307	41	**0.004**

Pearson's chi-squared test has been employed. Statistical significance at $p < 0.05$.

Table 5 Association between hypocalcemia and comorbidities presented by COVID-19 patients.

	Odds Ratio [confidence interval]	Serum Calcium p value	Ionized Calcium p value
Comorbidities	1.60 [1.004–2.55]	**0.030**	**0.008**
Diabetes	1.08 [0.73–1.60]	0.340	0.18
Hypertension	1.18 [0.81–1.72]	0.130	0.053
CKD	1.57 [0.87–2.82]	**0.020**	**0.007**
Obesity	1.19 [0.75–1.88]	0.141	0.071
COPD	1.41 [0.715–2.79]	0.351	0.748
CVD	1.66 [1.092–2.53]	**0.030**	0.703
Cancer	1.53 [0.71–2.79]	**0.035**	0.691

Odds ratio and Mann–Whitney U test have been employed. Statistical significance at $p < 0.05$.

hypercalcemia in severe COVID-19, making the prognostic significance of hypocalcemia questionable [29].

In our monocentric study, first we observed that 44.8% of our hospitalized COVID-19 patients had low serum and ionized calcium levels, corrected to the concentration of albumin. This percentage is not as high as those reported in other studies [10–19], but the results are nonetheless relevant considering that the recorded calcium value interquartile range is from 8.3 to 9 mg/dL for serum calcium (reference range 8.5–10.5 mg/dL) and from 1.05 to 1.16 mmol/L for ionized calcium (reference range 1.1–1.3 mmol/L), shifting the population curve towards the lower limit and without any case of hypercalcemia. Indeed, the average value of both parameters highlights the prevalent condition of hypocalcemia (calcium level especially ≤8.5 mg/dL). In addition, 64.6% of intubated patients were hypocalcemic and hypocalcemia was recorded in 55% of deaths. Interestingly, we found a correlation between hypocalcemia and both mechanical ventilation and exitus, suggesting the relevance of hypocalcemia in influencing the prognosis of COVID-19 patients. In addition, we found a positive correlation between hypocalcemia and inflammatory markers such as LDH and rCP, as reported by other authors [10,11,19], while ferritin did not show statistically significative correlation. The finding argues for a possible involvement of calcium in the pathophysiology of the disease in association with the cytopathic effect of SARS-CoV-2 infection [30]. In this context, it should be considered that 99.2% of the enrolled patients had pulmonary infiltration. We also evaluated if hypovitaminosis D might be a factor influencing calcium concentration, but we did not observe any correlation between hypocalcemia and vitamin D serum values, most likely due to the few records of vitamin D (N = 71/511; $p = 0.066$ $\chi 2$ test), as well as of PTH values (N = 90/511; $p = 1$ Fisher test), which did not allow proper statistical analyses. However, at least for PTH, it is possible to make a consideration. Particularly, only 3/90 recorded PTH values were <20 pg/mL and only 1/3 of the patients were hypocalcemic too. Thus, it is more likely that the hypocalcemia observed in our cohort was PTH-independent.

Table 6 Analysis of the association between hypocalcemia and clinical complications during hospitalization.

	Odds Ratio [confidence interval]	Serum Calcium p value
Complications	1.88 [1.29–2.75]	**<0.01**
2 complications[a]		**0.002**

Odds ratio and Kruskal Wallis test have been employed. Statistical significance at $p < 0.05$.

[a] It is not possible to calculate the odds ratio for more than one clinical complication per patient.

Since 76.3% of our patients presented pre-admission comorbidities, a condition that exposed them to a higher risk of poor prognosis in the case of SARS-CoV-2 infection, we verified if hypocalcemia could be a useful tool to recognize COVID-19 patients mainly prone to critical illness. This is useful to rapidly identify subjects who require increased attention during hospitalization, being at a higher risk of intubation and poor prognosis. Indeed, 94.3% of the deaths had previous chronic diseases and 52.3% of them presented hypocalcemia. To this purpose, we not only found the existence of a correlation between the presence of comorbidities and hypocalcemia, but we recognized in CKD, CVDs, and cancer, three pathologies in which the concomitant SARS-CoV-2 infection determined the lowering of serum calcium level. Furthermore, we also found a significant reduction of ionized calcium in CKD patients, recognizing CKD as a pathology critical for hypocalcemia occurrence in case of SARS-CoV-2 infection. However, CKD is a condition that can cause hypocalcemia,and our finding is in line with authors who associated it with poor prognosis in COVID-19 patients [6]. Also, some types of cancer present hypocalcemia [31] and it is important to monitor calcium levels especially when bone-modifying therapies are administered [32]. This aspect becomes even more important in the case of concomitant SARS-CoV-2 infection based on the latest evidence that acute hypocalcemia is an emerging characteristic of the osteometabolic phenotype in COVID-19 patients [33]. One additional aspect has been evidenced by our analysis of comorbidities. Particularly, CVD appears the only disease associated not only with hypocalcemia but also with both mechanical ventilation and exitus, suggesting that it is the major condition in which, in the course of Sars-CoV2 infection, hypocalcemia plays a role in the worsening of clinical conditions, shifting them from severe to critical, at least in our cohort.

Finally, we demonstrated the association between hypocalcemia and the occurrence of complications during

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hospitalizations, such as superinfection, thrombotic complications, and hyponatremia onset, strengthening the role of hypocalcemia as a biochemical marker to predict the outcome of COVID-19 patients.

Conclusions

n this study, we demonstrated that hypocalcemia appears a useful biomarker of poor outcome in patients with COVID-19, finding a correlation with both mechanical ventilation and exitus. Interestingly, hypocalcemia positively correlated with the occurrence of clinical complications during hospitalization, beyond the positive correlation also with inflammatory parameters such as LDH and rCP. In addition, the presence of comorbidities should always be considered in association with hypocalcemia in the risk of poor prognosis, with particular attention to patients with CKD, cancer, and CVD. Especially for CVD, hypocalcemia is associated with both intubation and death. Further investigations are necessary on ionized calcium in larger cohorts. Finally, whether calcium supplementation can be a useful therapeutic strategy remains to be investigated.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of the Universitary Hospital "Príncipe de Asturias", Madrid, España (protocol number ANA-COVID-LIB 17/2021; released on 11/04/2021).

Author contributions

ES, MJR-A, FDR and AB have conceptualized this work. MJR-A, YFV, GG, MBG and BBC collected the data and contributed to create the dataset. MJR-A, ES, YFV, GG, DB, FDR and AB have analyzed the data. ES, MJR-A, FDR and AB have written, reviewed and edited the manuscript. All the authors approved the final version of the manuscript.

Data availability statement

The database used for the analysis reported in this work will be made available by the authors, without any reservation.

Conflict of interest

The authors declare that the research was conducted in the absence of any conflict of interest.

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