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Vitamin D Deficiency and Low Serum Calcium as Predictors of Poor Prognosis in Patients with Severe COVID-19

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ABSTRACT

Background: The severity of Coronavirus Disease 2019 (COVID-19) is a multifactorial condition. An increasing body of evidence argues for a direct implication of vitamin D deficiency, low serum calcium on poor outcomes in COVID-19 patients. This study was designed to investigate the relationship between these two factors and COVID-19 in-hospital mortality.

Materials: This is a prospective study, including 120 severe cases of COVID-19, admitted at the department of Reanimation-Anesthesia. Vitamin D was assessed by an immuno-fluoroassay method. Total serum calcium by a colorimetric method, then, corrected for serum albumin levels. The association with in-hospital mortality was assessed using the Kaplan-Meier survival curve, proportional Cox regression analyses and the receiver operating characteristic curve.

Results: Hypovitaminosis D and hypocalcemia were very common, occurring in 75% and 35.8% of patients. When analyzing survival, both were significantly associated with in-hospital mortality in a dose-effect manner ($p_{Log\text{-}Rank} = 0.009$ and 0.001 respectively). A cutoff value of 39 nmol/l for vitamin D and 2.05 mmol/l for corrected calcemia could predict poor prognosis with a sensitivity of 76% and 84%, and a specificity of 69% and 60% respectively. Hazard ratios were (HR = 6.9, 95% CI [2.0–24.1], p = 0.002 and HR = 6.2, 95% CI [2.1–18.3], p = 0.001) respectively.

Conclusion: This study demonstrates the high frequency of hypocalcemia and hypovitaminosis D in severe COVID-19 patients and provides further evidence of their potential link to poor short-term prognosis. It is, therefore, possible that the correction of hypocalcemia, as well as supplementation with vitamin D, may improve the vital prognosis.

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Introduction

It has already been more than eleven months now since the declaration of the first confirmed case of Coronavirus Disease 2019 (COVID-19) in Wuhan Province, China, and eight months since its official designation as a pandemic by the World Health Organization (WHO). In the course of its propagation, the outbreak has reached more than two hundred countries around the six world continents. Intriguingly, however, is the very widely heterogeneous rate of reported contaminations, severe cases and related mortality, not only across countries, but also across different areas within the same country (1, 2).

In fact, it is widely recognized that COVID-19 severity is a multifactorial condition; several risk factors have been identified, including advanced age, ethnicity, type 2 diabetes, hypertension, obesity, renal dysfunction, and cardiovascular diseases (3–7). Interestingly, each of these factors is also known to be related to vitamin D deficiency in some way (1, 7, 8). This has led to raising the issue of whether inadequate vitamin D levels can affect the progression or even the prognosis of COVID-19.

Vitamin D is a secosteroid with a hormonal function; its synthesis, from cholesterol, starts in the epidermis under the effect of the sun's ultraviolet B (UVB) rays (7). In reality, the link between vitamin D and respiratory infections of all kinds - bacterial, viral, and fungal - has been raised far earlier than the COVID-19 era (8–10). The first assumptions date back to the early part of the previous century, when it has been noted that there was an inverse correlation between the amount of UVB solar irradiation and the mortality rate during the 1918–1919 influenza pandemic (4). On the basis of the above mentioned arguments, several studies have been designed with the aim to explore that association. Although the findings are very heterogeneous and inconsistent, most of the observational studies agreed on a strong and significant association between vitamin D deficiency and the risk of both upper and lower respiratory tract infections (3, 9). There is even some research demonstrating that adequate vitamin D levels correlate with a better prognosis in a number of respiratory infections such as those caused by Mycobacterium tuberculosis and the common influenza virus (9).

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In the ongoing pandemic, a substantial body of evidence, particularly from observational and ecological surveys, involving countries from all over the world, suggests an inverse relationship between vitamin D status and the likelihood of infection, progression toward severity, and even fatality from COVID-19 (3,9). However, no definitive conclusions have yet been pronounced.

On the other side, hypocalcemia is a common in-hospital complication, which occurs concurrently with other bio-clinical disorders such as an unbalanced status of vitamin D and parathyroid hormone (PTH) release, hypoproteinemia, and even chronic kidney disease. It is tightly linked to a poor prognosis, especially in critical patients; however, its association with the progression of COVID-19 has not been well investigated (11, 12).

In light of the above-cited data, this study was carried out to assess both vitamin D and serum calcium status among COVID-19 severely affected patients, and to test the hypothesis of a possible link between their serum levels and short-term prognosis of this affection.

Materials and methods

Patients and study design

This is a cohort, prospective, single-center study conducted at the Reanimation-Anesthesia Department of the Frantz Fanon University Hospital (CHU) Blida. Algeria. This department was converted, since the onset of the pandemic, into a COVID-19 center, set up to receive severe to critical cases of this infection. Patients admitted between July the 6th and August the 15th, 2020, for a confirmed COVID-19 severe and critical form, and who had been tested on admission for vitamin D and serum calcium levels were included in this study. Ineligibility criteria were: age $<$ 18 years, patients deceased or transferred within 48 hours of admission, pregnancy, and ongoing malignancy. This study was conducted in accordance with the Declaration of Helsinki; it was approved by the institution's ethics committee. The requirement for written informed consent was waived given the context of the fast spread of this disease.

Confirmatory diagnosis and end-point criteria

The COVID-19 diagnostic and severity definition was performed according to WHO criteria. Details are provided elsewhere (13, 14). In this study, all patients were followed for a period of 3 to 28 days depending on patient state, length of hospital stay and survival. The final endpoint was in-hospital mortality within 28 days of admission.

Laboratory parameters and definitions

For all included patients, a venipuncture blood sample was drawn upon admission; the same blood sample was used to assess all the biochemical parameters. All tests were performed in the same laboratory.

Vitamin D status was assessed by measuring the serum level of total 25-hydroxy-vitamin D (25 (OH) D total), using a sequential competitive immuno-fluoroassay method on VIDAS®. According to the Endocrine Society 2011 recommendations (15); subjects were assigned into one of the following categories based on their total 25 (OH) D levels: optimal: ($>$78 nmol/l or $>$30 μg/l), insufficiency (52–75 nmol/l or 20–29 μg/l), deficiency (26–52 nmol/l or 10–20 μg/l) and severe deficiency ($<$26 nmol/l or $<$10 μg/l).

Total serum calcium was determined by a colorimetric method and then corrected for albumin levels using the following formula:

$$\text{Corrected serum calcium} = \text{measured serum calcium} - 0.025 * (\text{serum albumin} - 40).$$

Following our laboratory's norms, hypocalcemia was defined as a corrected serum calcium level of less than 2.20 mmol/l. In further statistical analysis, the study population was divided into three groups based on the tertiles of the corrected serum calcium.

In addition to 25 (OH) D and total serum calcium, all patients were tested upon admission for the following laboratory parameters: hypersensitive troponin (hsTrp), inflammatory markers: C-reactive protein (CRP), white blood cells (WBC), neutrophils, lymphocytes, neutrophil to lymphocyte ratio (NLR) and platelets; blood glucose and renal markers: blood urea nitrogen (BUN), serum creatinine (Scr); nutritional markers: serum albumin, total protein, and total cholesterol (TC); liver enzymes: lactate dehydrogenase (LDH), glutamo-oxaloacetic transaminase (GOT) glutamo-pyruvic transaminase (GPT), γ-glutamyl-transpeptidase (GGT), and alkaline phosphatases (ALP).

Acute kidney injury (AKI) was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines (16) by an increase in serum creatinine of 26.5 μmol/l (03 mg/l) within 48 hours or at least a 50% increase in serum creatinine over 7 days. Cardiac injury was defined based on the hsTrp Kit by an hsTrp $>$100 ng/l or an increase of more than 30% of the baseline value.

Statistical analysis

For continuous variables, the normality of the distribution was examined using the Shapiro-Wilk test. Then, they were presented as Means ± Standard Deviations or medians (interquartile) and compared by the Student t-test or Mann-Whitney U-test according to their distribution normality. Qualitative variables were described as percentages and compared with the Pearson χ2 test.

Survival and cumulative in-hospital mortality rates were compared between the 25 (OH) D classes and the serum calcium tertiles, separately, using the Kaplan-Meier method. The curves were then compared using the Log Rank test. The association between these two variables and in-hospital mortality was assessed by uni-variate and multi-variate proportional Cox regression analysis. The variables included in

Table 1. Biological Characteristics and Outcomes of Severe COVID-19 Patients.

	Total n = 120	Non-survivors n = 37 (30.8)	Survivors n = 83 (69.2)	p
Male gender n (%)[a]	83 (69.2)	23 (62.2)	60 (72.3)	0.26
Age (years)	62.3 ± 17.6	68.6 ± 18.4	59.5 ± 16.6	**0.008**
25(OH)D (μg/l)	20.9 ± 14.1	14.1 ± 9.8	23.9 ± 14.7	**<0.0001**
Calcium (mmol/l)	2.14 ± 0.17	2.02 ± 0.15	2.2 ± 0.16	**<0.0001**
Albumin (g/l)[b]	39.0 (09)	37.0 (09)	39.0 (10)	**0.007**
Total Protein (g/l)	69.5 ± 8.9	66.6 ± 9.9	70.8 ± 8.1	**0.015**
TC (mmol/l)	3.4 ± 1.11	2.76 ± 0.77	3.64 ± 1.13	**<0.0001**
WBC (10^9 e/l)	11.9 ± 6.0	13.0 ± 6.2	11.5 ± 5.9	0.19
Lym count (10^9 e/l)	1.23 ± 0.66	0.72 ± 0.32	1.46 ± 0.65	**<0.0001**
Neut count (10^9e/l)	9.94 ± 5.8	11.6 ± 5.8	9.2 ± 5.7	**0.035**
NLR	12.6 ± 9.5	18.7 ± 9.8	9.9 ± 7.9	**<0.0001**
Platelet (10^9 e/l)	293 ± 119	249 ± 111	313 ± 117	**0.007**
CRP (mg/l)	43.2 ± 40.6	74.8 ± 33.8	26.3 ± 33.5	**<0.0001**
Glucose (mmol/l)	11.8 ± 7.4	14.5 ± 8.9	10.7 ± 6.4	**0.013**
BUN (mmol/l)	12.5 ± 8.6	16.3 ± 10.6	10.8 ± 7.0	**0.001**
SCr (μmol/l)	184 ± 165	238 ± 187	160 ± 150	**0.016**
hsTrp (ng/l)	34.1 ± 74.1	63.6 ± 115	21.0 ± 39.8	**0.003**
LDH (IU/l)	365 ± 203	464 ± 205	322 ± 188	**<0.0001**
GOT (IU/l)	59.7 ± 45	66 ± 39.6	56.9 ± 47	0.27
GPT (IU/l)	51.0 ± 40.1	51.1 ± 39	51.0 ± 40.7	0.98
γ-GT (IU/l)	54.9 ± 50.3	56.8 ± 44.9	54.0 ± 52.7	0.78
ALP (IU/l)	174 ± 103	199 ± 117	162 ± 94.7	0.07
AKI n (%)[a]	30 (25)	15 (40.5)	15 (18.1)	**0.009**
Cardiac injury n(%)[a]	23 (19.2)	12 (32.4)	11 (13.3)	**0.014**
Serum Calcium tertiles (T) (%)[a] <0.0001				
T1 [2.21–2.48] mmol/l	43 (35.8)	5 (13.5)	38 (45.8)	
T2 [2.06–2.20] mmol/l	30 (25)	10 (27)	20 (24.1)	
T3 [1.49–2.05] mmol/l	47 (39.2)	22 (59.5)	25 (30.7)	
25(OH) D levels (%)[a] 0.001				
>30μg/l	30 (25)	4 (10.8)	26 (31.3)	
20–29 μg/l	23 (19.2)	4 (10.8)	19 (22.9)	
10–19 μg/l	35 (29.2)	14 (37.8)	21 (25.3)	
<10 μg/l	32 (26.7)	15 (40.5)	17 (20.5)	
Survival duration (Days) [min–max]		7.7 ± 4.7 [03–28]	–	–

25(OH) D: 25-hydroxy vitamin D, AKI: acute kidney injury, ALP: alkaline phosphatases, BUN: blood urea nitrogen, CRP: C-reactive protein, GOT: glutamo-oxaloacetic transaminase, GPT: glutamo-pyruvic transaminase, γ-GT: gamma-Glutamyl-Trans-peptidase, hsTrp: high sensitive troponin, LDH: lactate dehydrogenase, Lym count: lymphocyte count, Neut count: neutrophils count, NLR: neutrophils to lymphocyte ratio, SCr: serum creatinine, TC: total cholesterol, WBC: white blood cells.
Continuous variables presented as Means ± Standard Deviations and compared by the Student t-test.
[a]Qualitative variables are described as number (percentages) and compared with the Pearson χ^2 test.
[b]Continuous variables presented as medians (interquartile) and compared by Mann-Whitney U-test.
Bold values indicate a statically significant association $p < 0.05$.

the fitted model were those associated with in-hospital mortality in the uni-variate model ($p < 0.1$).

The area under the receiver operating characteristic (AUC) curve (ROC curve) with its 95% confidence interval was calculated in order to evaluate the prognostic performance of 25(OH) D and corrected serum calcium. Cutoff values were determined using the Youden index; the maximum value reflects the best balance between sensitivity and specificity.

For all statistical tests, a p value of less than 0.05 was considered statistically significant. The statistical analysis was performed using SPSS software version 25.0.

Results

Baseline characteristics of the study population

As shown in Table 1; a total of 120 severe COVID-19 patients were included in this study, predominantly males (69.2%). The mean age was 62.3 ± 17.6 years. Approximately three-quarters of enrolled patients had an inadequate 25 (OH) D level, distributed as follows: vitamin D insufficiency (19.2%), vitamin D deficiency (29.2%), and severe vitamin D deficiency (26.7%). Hypocalcemia on admission was also very common as only 35.8% of patients admitted had adequate levels of corrected serum calcium. During their follow-up, about 25% of the patients developed an AKI, 19.2% developed a cardiac injury and 30.8% of them did not survive. The mean duration between intensive care unit (ICU) admission and death was 7.7 ± 4.7 days, range [03–28] days.

A comparison of the bio-clinical characteristics between deceased and survived patients is provided in Table 1. Deceased patients were significantly older (68.6 ± 18.4 vs 59.5 ± 16.6, $p = 0.008$). As expected, there was a significant difference in baseline laboratory parameters and onset of vital organ injury between the two groups. In particular, there were significantly higher incidences of acute renal and cardiac complications among patients who did not survive (40.5% vs 18.1%, $p = 0.009$ and 32.4% vs 13.3%, $p = 0.014$ respectively). In addition, the deceased patients were admitted with higher blood glucose levels and inflammatory markers (CRP, neutrophils and NLR) as well as with lower levels of corrected serum calcium, 25(OH) D, albumin, total protein, TC, platelets and lymphocytes. Moreover, among the deceased patients, only 10.8% and 13.5% were admitted with adequate levels of 25(OH) D and corrected serum calcium, respectively (Table 1).

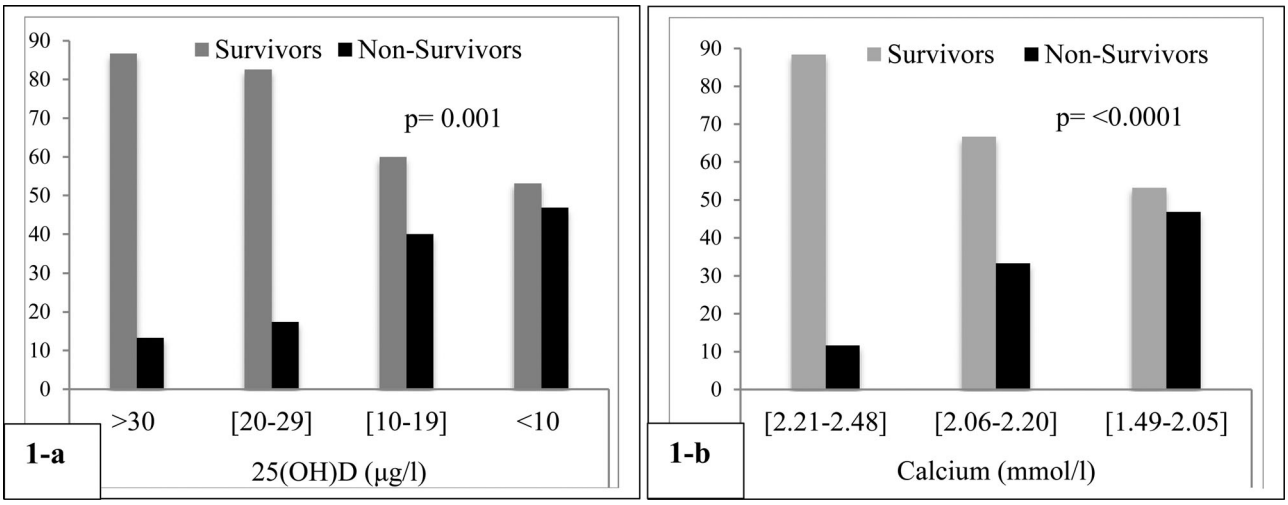

Figure 1. Mortality rates according to 25 (OH) D levels (a) and serum calcium tertiles, (b) in severe COVID-19 patients.

Hypovitaminosis D, hypocalcemia and COVID-19 in-hospital mortality rates

The mortality rates, according to vitamin D status and corrected serum calcium tertiles are presented in Figure 1(a,b) respectively. In both cases, a highly significant linear-by-linear association was found, indicating a dose-effect relationship between these two parameters and short-term mortality (p for trend =0.001 and 0.0001 respectively).

The lowest mortality rate was observed among the group with adequate 25(OH) D levels (>78 nmol/l or 30 µg/l) (13.3%); the rate increases gradually and inversely across the 25(OH) D classes; the highest mortality rate was recorded in the group with severe vitamin D deficiency (46.9%). Similarly, an inverse relationship was also noted between the mortality rate and corrected serum calcium tertiles, as assessed on admission; the highest mortality rate was recorded among patients who were admitted with serum calcium in the third tertile (< 2.05 mmol/l) (46.8%).

The relevance of this association was further demonstrated by the Kaplan-Meier survival curve analysis for crude cumulative in-hospital mortality as shown in Figure 2. Indeed, the remarkably divergent curves for severe vitamin D deficiency and the third tertile of corrected serum calcium ($p_{Log\text{-}Rank}$ =0.009 and 0.001 respectively), indicates a significantly reduced survival likelihood in these two groups (Figure 2(a,b), respectively).

Hypovitaminosis D, hypocalcemia and short-term mortality risk

The proportional Cox regression analysis was used to assess the hazard ratio (HR) of short-term mortality in relation to both hypovitaminosis D and hypocalcemia. One crude model and two adjusted ones were performed for this purpose. Results are provided in Table 2.

In the unadjusted analysis, and when taking the sufficient vitamin D group (>78 nmol/l or 30 µg/l) as a reference, patients who were admitted with vitamin D deficiency and severe deficiency had a relative risk of in-hospital mortality of 3.23 and 4.33 respectively (HR = 3.23, 95% CI [1.06–9.8], p = 0.039 and HR = 4.33, 95% CI [1.43–13.1], p = 0.009). Adjustment for age and gender in the second model did not affect the quality of this association. However, when further adjustment was made for Model 3 (AKI, cardiac injury, FBG, TC, Albumin, LDH, CRP, and NLR), only severe vitamin D deficiency remained significantly associated with an increased risk of in-hospital mortality (HR = 6.9, 95% CI [2.0–24.1], p = 0.002).

Similarly, hypocalcemia was significantly related to a higher risk of in-hospital mortality. Indeed, when taking the first tertile of the corrected serum calcium as a reference, subjects who were admitted with serum calcium levels within the second and the third tertiles had a 3.3 and 5.1 fold higher risks. Further adjustment to the final model did not influence the significance of this risk for both tertiles (HR = 3.34, 95% CI [1.03–10.8], p = 0.045 and HR= 6.2, 95% CI [2.1–18.3], p = 0.001) respectively.

Predictive performance of hypovitaminosis D and hypocalcemia for in-hospital mortality

The ROC curve was performed in order to test the prognostic effectiveness of vitamin D status and corrected serum calcium in the early prediction of survival probability in severely COVID-19-affected patients. The characteristics of the ROC curve, the cutoff values, and their predictive performance are presented in Figure 3 and Table 3 respectively.

Both parameters showed satisfying and comparable predictive abilities (AUC= 0.73 and 0.77, p < 0.0001 respectively, for 25 (OH) D and corrected serum calcium). For a value of less than 15 µg/l (<39 nmol/l), 25 (OH) D could predict a poor prognosis with a sensitivity of 76% and a specificity of 69%. Similarly, a serum calcium level of less than 2.05 mmol/l could predict short-term mortality with a sensitivity of 84% and a specificity of 60%.

Discussion

This prospective, single-center, cohort study was designed with the aim to assess vitamin D and serum calcium status

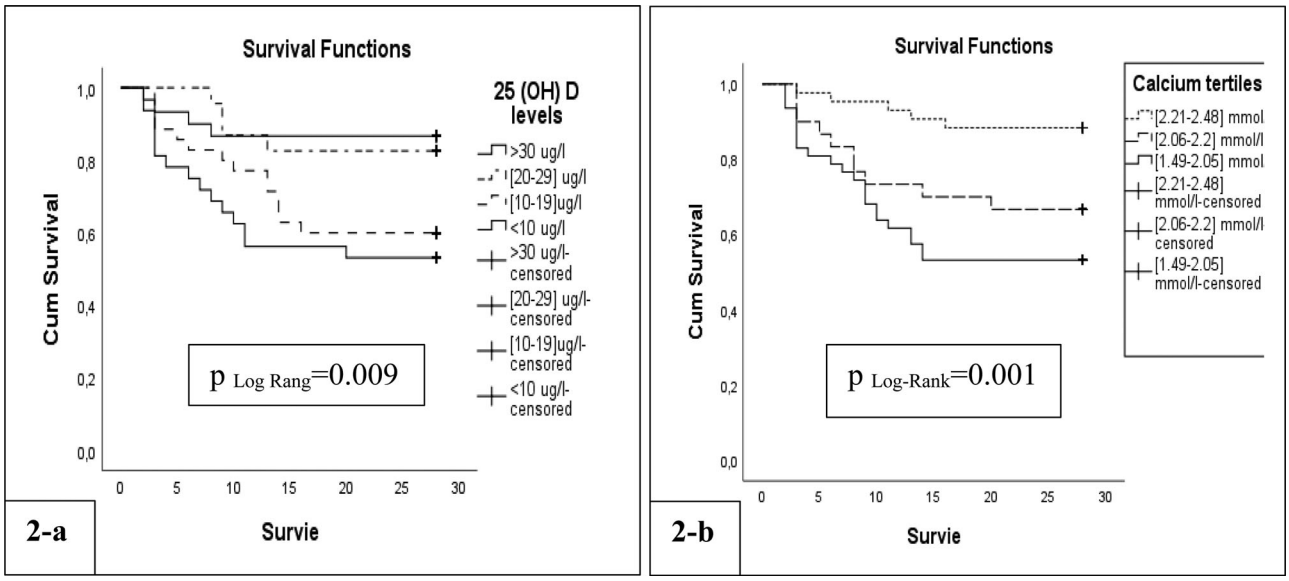

Figure 2. Kaplan-Meier curve for crude cumulative in-hospital mortality by 25(OH) D levels (a) and serum calcium tertiles (b) in severe COVID-19 patients.

Table 2. Univariate and Multivariate Cox Regression Analysis of 25(OH) D Levels, Serum Calcium Tertiles and In-Hospital Mortality in Severe COVID-19 Patients.

		Model 1		Model 2		Model 3	
		HR 95% CI	p	HR 95% CI	p	HR 95% CI	p
25 (OH) D	>30 μg/l	1	–	1	–	1	–
	20–29 μg/l	1.26 [0.32–5.04]	0.74	1.41[0.35–, 5.6]	0.62	1.3 [0.3–5.7]	0.73
	10–19 μg/l	3.23 [1.06–9.8]	**0.039**	3.41 [1.11–10.4]	**0.031**	2.7 [0.8–9.4]	0.1
	<10 μg/l	4.33 [1.43–13.1]	**0.009**	5.9 [1.77–19.5]	**0.004**	6.9 [2.0–24.1]	**0.002**
Serum CaT	T1 [2.21–2.48] mmol/l	1	–	1	–	1	–
	T2 [2.06–2.20]mmol/l	3.3 [1.12–9.6]	**0.03**	3.95 [1.34–11.7]	**0.013**	3.34 [1.03–10.8]	**0.045**
	T3 [1.49–2.05] mmol/l	5.1 [1.9–13.5]	**0.001**	5.7 [2.12–15.0]	**0.001**	6.2 [2.1–18.3]	**0.001**

25(OH) D: 25-hydroxy vitamin D, Serum CaT: Serum calcium tertiles. Model 1: unadjusted model, Model 2: adjusted for age and sex, Model 3: adjusted for model 2, acute kidney injury, cardiac injury, blood glucose, CRP, NLR, LDH, albumin and total cholesterol. HR: Hazard ratio, 95% CI: 95 % confidence interval.
Bold values are statistically significant at $p < 0.05$.

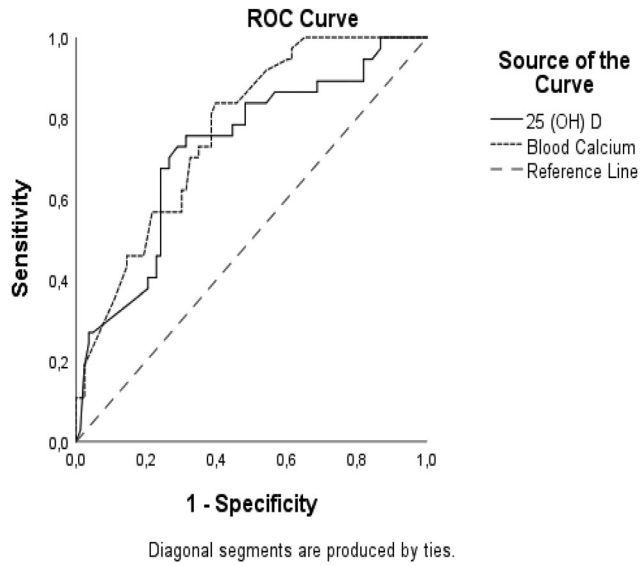

Figure 3. Receiver operating characteristic curve of 25(OH) D and serum calcium in predicting in-hospital mortality of severe COVID-19 patients.

in COVID-19 severely affected patients, but also to test the assumption of a possible link between these two parameters and the short-term prognosis of the disease. The most relevant finding of this study was the revelation of a significant association between severe vitamin D deficiency as well as hypocalcemia with short-term COVID-19 mortality in ICU. This association was independent of other confounding factors with already proven prognostic value such as inflammatory markers (CRP, NLR and neutrophils), AKI, cardiac injury, gender, and age.

Globally, our observations are consistent with most previous studies that have investigated the link between vitamin D status and COVID-19. For example, in two retrospective observational studies conducted, one in Switzerland (17) and the other in the Middle East (18), involving respectively 107 and 7807 suspected COVID-19 subjects. The authors have reported a positive association between vitamin D deficiency, and the likelihood of infection but also of hospitalization for COVID-19. Another retrospective observational study conducted in Italy and involving critical COVID-19 patients (19) had found that patients who were admitted with severe vitamin D deficiency were at significantly higher risk of short-term mortality. Similarly, a recent large meta-analysis including 1368 confirmed COVID-19 cases reported that vitamin D deficiency was associated with poor prognosis (20).

In the course of this pandemic, the hypothesis of a possible link between vitamin D status and COVID-19 severity first arose from the observation of an extremely

Table 3. Cutoff and Performances of 25(OH) D and Serum Calcium in Predicting In-Hospital Mortality of Severe COVID-19 Patients.

	AUC	95% CI	p	Cutoff	Se (%)	Sp (%)	YI
25 (OH)D (μg/l)	0.73	[0.63–0.82]	<0.0001	15.3	76	69	0.44
Serum Calcium (mmol/l)	0.77	[0.68–0.85]	<0.0001	2.03	84	60	0.44

25 (OH) D: 25-hydroxy vitamin D, AUC: area under the curve, YI: Youden index, Se: sensitivity. Sp: specificity, 95% CI: 95% confidence interval.

heterogeneous "geographical" distribution of reported contamination and mortality rates, not only across countries and continents, but also across regions within the same country. Over the past few months, several ecological studies had attempted to test the accuracy of this assumption (8,10). From this context, a study involving 88 countries worldwide provided the first evidence of a significant correlation between latitude, sunshine level and mortality by COVID-19 (21). Another, large-scale study, including 117 countries around the world, had reported that the mortality rate per million inhabitants was significantly lower in the countries below 35° latitude (22). In the same context, several authors have extended the analysis by incorporating vitamin D levels in addition to latitude and sunshine. Ilie et al (10), for example, in a study involving 20 European countries, had observed a significant negative correlation between average vitamin D levels and the number of declared cases as well as the number of deaths per million inhabitants.

Together with geographical disparity, numerous additional shreds of clinical evidence have contributed to the basis of the "vitamin D hypothesis". From the physiological perspective, the possible protective role of vitamin D against viral infections such as COVID-19 may be attributed to its modulating effects on the innate and adaptive immune system (5, 6). These immunomodulatory effects are well characterized since the detection of vitamin D receptors on a wide range of immune cells, such as macrophages, monocytes, dendritic cells as well as T and B lymphocytes (1, 23). On one side, vitamin D boosts innate immunity through the stimulation of gene expression of numerous peptides such as cathelicidins, IL-37 and defensins. Besides their antimicrobial activities, these peptides may also contribute to endotoxin neutralization, thus minimizing inflammatory extension (2, 4, 7). On the other side, and through its anti-inflammatory actions, vitamin D acts as a key factor in the regulation of the adaptive immunity as it can suppress the responses induced by the T helper cell type 1 (Th1) and thus contributes to the attenuation of the cytokine storm particularly that of interleukin 6 (IL6). The latter is considered as the trigger of the systemic extension of inflammatory response, and of numerous acute complications, particularly pulmonary ones, observed in severely affected COVID-19 patients (3, 9).

Another important finding derived from this study is the revelation of an inverse association between corrected hypocalcemia, as assessed on admission, and short-term mortality in severe COVID-19 patients. Among our study patients, hypocalcemia was very common and could be partly explained by impaired intestinal absorption, hypovitaminosis D, but mostly by hypoalbuminemia and hypoproteinemia; conditions that are particularly prevalent in intensive care, including severe cases of COVID-19 (11, 12, 14).

Although the prognostic value of hypocalcemia is well known in hospital settings, particularly in intensive care (12, 24), its association with COVID-19 severity was mentioned only anecdotally. For example, in a retrospective study, including 241 confirmed COVID-19 cases, of whom 80% were severe to critical cases, the incidence of hypocalcemia was estimated to be as high as 74%, the authors found that patients with a serum calcium level of less than 2.0 mmol/l had also a higher incidence of multi-organ failure, septic shock, and a higher 28-day mortality rate. However, the authors did not correct serum calcium for serum albumin levels (11).

The results of our study should be interpreted taking into account several limits; in particular with regard to the sample size and its single-center design, as these may affect the strength or generalizability of the reported findings. Further prospective studies with a larger sample size are therefore needed. In addition, the serum calcium values were those of total calcium rather than ionized calcium, the latter representing the active fraction and better reflecting true hypocalcemia. However, we believe that the correction for albumin levels can, at least partially, overcome this limitation. Further studies integrating a more extended phosphocalcic profile with PTH, ionized calcium, magnesium, and phosphorus are also desirable to better clarify the link with COVID-19 severity.

Conclusion

Our study demonstrates the high frequency of hypocalcemia and hypovitaminosis D in severe COVID-19 patients and provides further evidence of their potential link to poor short-term prognosis. It is, therefore, possible that correction of albuminemia, hypocalcemia as well as supplementation with vitamin D may attenuate the severity and improve the vital prognosis. Randomized controlled trials should be conducted to evaluate the effects of this supplementation and to confirm preliminary hypotheses drawn from observational studies.

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