

# Diagnosis of vitamin D deficiency in patients admitted in ICU with COVID 19 disease

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## Abstract

Vitamin D deficiency is common in critically ill patients, and the role of this vitamin D in COVID-19 patients could be important. Vitamin D is crucial in immunomodulation and infection control. Moreover, its deficiency has been associated with respiratory distress syndrome, pulmonary fibrosis (through activation of the renin-angiotensin system), increased levels of IL-6, and cardiovascular adverse events. Various scientific societies recommend the screening of vitamin D in individuals at risk for deficiency. Despite that, the demographics of Vitamin D levels amongst critically ill patients with a confirmed diagnosis of COVID-19 are currently unknown. We propose a study to determine if vitamin D deficiency in hospitalized patients diagnosed with COVID 19 is considered an important factor in the development of the disease.

During the period from March 16 - April 26, 2020, 226 patients were admitted in ICU, and the value of 25-hydroxy-vitamin D was observed in only 17 patients (7.5%).

Besides that, we obtained relevant data: all patients with serum determinations of 25-hydroxyvitamin D presented a level lower than 20 ng/ml and thirteen patients (76,5%) levels < 12,5 ng/ml. We conclude that vitamin D deficiency is common in critically ill COVID-19 patients, and it continues being undiagnosed, even of the collective knowledge of its immunological role.

**Keywords:** Vitamin D, Immunomodulation, Intensive care, Critical care, COVID-19, SARS-COV2.

## Introduction

The novel coronavirus infection (COVID-19), first identified in December 2019 in Wuhan, China, has contributed to significant mortality in several countries with the number of infected cases increasing exponentially worldwide. Therefore, the search for possible strategies that allow reducing the number of infected or influencing the main immunological mechanisms of the virus, is one of the main therapeutic approaches.

Vitamin D deficiency in critically ill patients has been reported for years in different diseases and patient populations, and it's been associated with worse clinical outcomes. Critical COVID-19 patients, have common risk factors (comorbidities, inadequate intake, absence of sun exposure and immobilization), frequently received antiretrovirals therapy, that increase the catabolism of this vitamin [1].

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Interest in the role of vitamin D in COVID-19 has increased in the last months because vitamin D is essential in several mechanisms to reduce infections (physical barrier, innate and adaptive immunity) and to modulate excessive inflammation [2]. Moreover, its deficiency has been associated with respiratory distress syndrome, pulmonary fibrosis through activation of the renin-angiotensin system (RAS), and increased levels of IL-2. In critically ill patients it is also important to mention the role of vitamin D in the cardiovascular system and its association with myopathy, and both situations increase the likelihood of complications during intensive care unit (ICU) stay [3]. The prevalence of vitamin D deficiency in intensive care units ranges typically between 40 and 70% [4].

Various scientific societies recommend the screening of vitamin D in individual at risk for deficiency and although there is no global consensus, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends to supplement vitamin D in critically ill patients if plasma measured levels are low (25-hydroxy-vitamin D < 12.5 ng/ml, or 50 nmol/l) [5].

Despite that, to our knowledge, the demographics of Vitamin D levels amongst critically ill patients with a confirmed diagnosis of COVID-19 are currently unknown.

The aim of our study was to evaluate the prevalence of measurement of vitamin D levels in a consecutive population of COVID-19 patients admitted to intensive care units of a single centre and to evaluate its relationship with clinical outcomes.

## Material and Methods

We performed a retrospective transversal study, adults patients diagnosed with COVID-19 infection according to World Health Organization criteria, consecutively admitted to the ICU from Hospital Clinic Barcelona (HCB), Spain, between March 16 and April 26, 2020.

The study was approved by the Ethics Committee of HCB with approval number HCB/2020/0580 in accordance with the Helsinki Declaration of 1975.

Through electronic medical record, we collected the level of serum 25-Hydroxyvitamin D, parathormone (PTH), total serum proteins, calcium, and phosphate during ICU stay with central core laboratory head assessment, requested by ICU doctors during admission to the units.

The measurement method used for the assessment of 25-Hydroxyvitamin D was by an automated chemiluminescence immunoassay with a Liaison analyzer™ (Diasorin, Saluggia, Italy).

Vitamin D deficiency was defined as a 25-hydroxyvitamin D level < 20 ng/ml. According to ESPEN guidelines a 25-hydroxyvitamin D < 12.5 ng/ml was cut-off to considerate that vitamin D has to be supplemented [5].

Hypocalcemia and hypercalcemia were defined as serum calcium levels less than 8.5 mg/dL and more than 10.6 mg/dL respectively. Corrected calcium was calculated by measured total calcium / (0,6 + (total proteins/18,5)).

Hypophosphatemia and hypophosphatemia were defined as serum phosphate levels less than 3.5 mg/dL and more than 4.5 mg/dL, respectively. Elevated PTH level was defined as a serum PTH level more than 65 pg/mL [6].

All critically ill patients were characterized by sex, race, chronic renal failure, and Charlson index. APACHE II and SOFA were registered at admission. Requirements of mechanical ventilation and days of therapy, use of corticosteroids, antiretroviral therapy, hospital-acquired infections, ICU length of stay, mortality, and vitamin D and calcium metabolism analysis were collected.

## Statistical Analysis

A descriptive analysis was performed using Statistical Package for Social Sciences version 22.0 (SPSS, Chicago, IL). Data are presented in number and proportions (%) for categorical variables and mean and standard deviation (SD) for continuous variables.

## Results

We evaluated 226 adult patients diagnosed with COVID-19 infection. Basal demographical data and ICU outcomes of these patients are shown in table 1.

Fifty-eight percent of patients were men, and median age was 64 years. Median SOFA was 10 (3,28), mainly at the expense of respiratory failure. Seventy-six percent of patients presented a nosocomial infection during the stay at ICU. Seventeen patients (7,5%) had at least one Vitamin D

**Table 1:** Baseline patient characteristics and ICU outcomes of patients with 250h measurement.

	n=17
Age (years)	64.94(10.69)
Sex	Female: 7(41.2%) Male: 10(58.8%)
Smoke History	4(23.5%)
BMI (kg/m <sup>2</sup> )	29.11(3.93)
Charlson Index score	2.8 (1.81)
Chronic Kidney Disease	2(11.8%)
APACHE II	16.59 (7.81)
SOFA score	10.53(3.28)
Mechanical ventilation	15 (88.2%)
Mechanical ventilation (days)	18 (12.4)
ICU acquired weakness	16 (94.1%)
Length of ICU stay	27.88(10.39)
Altered liver function	8(47.1%)
xAnti-Retroviral Drugs	17(100%)
High-dose Steroid	16(94.1%)
Nosocomial infection	13(76.5%)
Pneumonia	4(23.5%)
Urinary Tract Infection	2(11.8%)
Catheter-related Bloodstream Infection	7(41.2%)
Septic Shock	6(35.3%)
Mortality	1(5.9%)

Data are in number and proportions (%) for categorical variables and in mean and standard deviation (SD) for continuous variables.

Abbreviations: BMI: Body Mass Index; Charlson Index score: Charlson Combined Comorbidity Index score; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Care Unit.

serum determination, all of them with 25-hydroxyvitamin D serum value lower than 20 ng/ml.

Thirteen patients (76.5%) had 25-hydroxyvitamin D levels < 12.5 ng/ml, with 3 patients with values lower than 5 ng/ml. Hypocalcemia and hypophosphatemia were observed in 6 (35.2%) and 11 (64.7%) patients, respectively. All patients had elevated PTH levels (Table 2). Table 3 shows the serum values of each of the evaluated patients.

## Discussion

Despite significant and recent scientific evidence of the vitamin D role on critical illness, only 7.5 % of patients admitted to the ICU had at least one measurement of vitamin D levels during the stay at ICU. Vitamin D measurements have not been adequately included as a part of the routine tests to be evaluated in patients admitted at ICU an even less so in patients diagnosed with COVID -19. These findings could suggest that, if the prevalence of vitamin D deficiency in patients diagnosed with COVID-19 is similar to other critical care patients, there could be a large number of patients that would not be diagnosed.

We propose a different hypothesis to explain the low request of vitamin D, lack of knowledge, skepticism of physicians, and the absence of a global consensus regarding the importance of treatment vitamin D deficiency in critical care illness.

**Table 2:** Vitamin D and mineral metabolism related variables.

	n=17
Total Serum Calcium(mg/dL)	7.9(0.76)
Corrected total serum Calcium (mg/dL)	8.8(0.75)
Serum Posphate (mg/dL)	3.723(1.04)
Total serum Proteins(g/L)	54.76(4.94)
Serum creatinine(mg/dL)	0.89(0.59)
25-Hydrovitamin D (ng/mL)	9.98(4)
25-Hydrovitamin D < 20ng/mL	17 (100 %)
25-Hydrovitamin D < 12,5 ng/ml	13 (76,5%)
Parathormone(pg/mL)	116(97.63)

Data are in number and proportions (%) for categorical variables and in mean and standard deviation (SD) for continuous variables.

**Table 3:** Serum values of the laboratory parameters studied in all patients with a measurement of 25-Hydrovitamin D.

Patient N°	Age	Total serum Calcium (mg/dL)	Corrected total serum Calcium (mg/dL)	Phosphate (mg/dL)	Total serum proteins (g/L)	Creatinine (mg/dL)	25-Hydrovitamin D (ng/mL)	Parathormone (pg/mL)
1	65	7	7.94	3.2	52	0.62	10	117
2	71	8.5	9.71	4.6	51	1.3	6.3	14
3	54	7.3	8.34	4.5	51	0.31	13.3	108
4	75	8.3	9.09	4.1	58	0.95	10.2	118
5	70	9.5	10.16	4.3	62	1.2	16.5	23
6	68	7.4	8.66	3	47	0.76	11	51
7	61	8.8	9.69	3.3	57	2.81	9.4	323
8	55	7.6	8.47	3.4	55	0.59	13	65
9	59	7.7	8.63	3	54	0.45	10.7	85
10	70	6.7	7.70	2.8	50	0.6	8.6	206
11	54	7.3	8.04	5.1	57	0.74	4.1	101
12	68	8.2	8.62	3.2	65	0.56	<4	341
13	56	7.5	8.67	2.5	49	0.48	4.9	199
14	90	7.4	8.25	3.4	55	1.01	11.6	46
15	45	8.1	8.76	2.9	60	0.62	11.6	29
16	67	7.9	9.08	3.4	50	0.45	18	53
17	76	9.1	9.96	6.6	58	1.55	6.6	94

Given the retrospective nature of the study, it is not possible to determine whether the high observed proportion of patients with hypocalcemia (35.2%) and hypophosphatemia (64.7%) is a consequence of hypovitaminosis D and which is its clinical significance. However, it is known that they are related to arrhythmias and impaired myocardial contractility, metabolic encephalopathy, proximal myopathy, and respiratory failure. These clinical manifestations are also frequent in COVID-19 disease in critically ill patients [1].

A high incidence of nosocomial infections (76.5%), was observed (Table 1), vitamin D deficiency could have an important role in their development reducing concentrations of pro-inflammatory cytokines, as well as increasing concentrations of anti-inflammatory cytokines [2].

So far, studies showing the relationship between vitamin D deficiency and the progression of the disease due to COVID 19 are lacking.

Likewise, the interest in optimizing the levels of vitamin D as well as other vitamins and minerals, as part of prevention both in health workers and in the population continues to grow.

## Conclusion

Undiagnosed vitamin D deficiency is common in critically ill COVID-19 patients. As already recommended for populations with a high prevalence of vitamin D deficiency and critically ill patients, Vitamin D deficiency should be screened and supplemented if measured plasma levels are low (25-hydroxy-vitamin D < 12.5 ng/ml, or 50 nmol/l).

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