



Prevalence of vitamin D deficiency in patients with COVID-19 admitted to a tertiary hospital in Rio Grande do Sul

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Abstract

Background: Increasing data suggests a connection between vitamin D (vitD) and COVID-19. VitD may impact COVID-19 by affecting innate cellular immunity and exacerbating cytokine storms linked to severe respiratory syndrome from the virus. **Objective:** To assess the prevalence of vitD deficiency in COVID-19 patients hospitalized at Hospital Ernesto Dornelles and examine its links to in-hospital mortality, the need for Intensive Care Unit (ICU), patient demographics, and hospital stay duration. **Methods:** A cross-sectional study was performed, in which 3518 hospitalized patients with a confirmed diagnosis of COVID-19 were evaluated to obtain the prevalence of vitD deficiency, from March 2020 to August 2022. Data collection was performed using electronic medical records, excluding patients without serum levels of vitD measured during hospitalization, and including those with the exam in their medical records, which were later placed for statistical analysis. **Results:** 486 patients had their serum level of vitD measured, with a mean age of 68.3 years, 57.2% female, and 42.8% male. The prevalence of vitD deficiency was 60.1% (292 patients). There was no difference between the groups with and without vitD deficiency when comparing age, gender, and

comorbidities. The median length of hospital stay, the need for ICU admission, and the outcome of death were significantly higher in the group with vitD deficiency ($p < 0.001$; $p = 0.005$; $p = 0.03$). After adjusting for confounding factors, only the risk of ICU admission remained 1.38x higher in the group with vitD deficiency than in the group without ($p = 0.015$), as well as age and CRF were factors with a higher risk for ICU admission. **Conclusions:** The prevalence of vitD deficiency in patients with COVID-19 was 60%, being associated with a higher risk of ICU admission, possibly presenting or not an association with higher mortality rates and length of stay. Therefore, further studies are needed to establish a cause-and-effect association.

Keywords: COVID-19. SARS-CoV-2. Vitamin D. Prevalence. 25-hydroxyvitamin D. Vitamin D Deficiency.

Introduction

The infection caused by the new coronavirus, COVID-19, had its first documentation in Wuhan, China, in December 2019 [1]. SARS-CoV-2 is an RNA virus capable of causing severe respiratory syndromes, which is characterized by acute respiratory distress secondary to severe lung damage. Several authors have

demonstrated abnormally high levels of pro-inflammatory cytokines in patients who develop severe types of COVID-19, characterizing an inflammatory "storm" and increasing the risk of death [2-5].

Older adults [4] and/or immunosuppressed patients are the most susceptible to the negative outcomes of COVID-19, including mortality and other complications [1,6]. The risk also increases with multiple comorbidities [1] and according to the individual's nutritional status and the presence of specific essential nutrients [7].

Multiple observational cohorts suggest that people with low vitamin D levels are at increased risk of SARS-CoV-2 infection and worse clinical outcomes after infection [5,8,9]. Vitamin D is already well established as related to reducing the risk of respiratory tract infections, including influenza [1,3,10,11], by increasing the physical barrier mechanism of the epithelium, as well as through modulation of native and adaptive immunity [12].

Vitamin D, also known as calciferol, is a fat-soluble vitamin, found in two forms: D2 (ergocalciferol) and D3 (cholecalciferol). These are hormone precursors that play an important role in bone metabolism, calcium and phosphate regulation, and in the immune, cardiovascular, and neuromuscular systems [8,13,14].

Calciferol is biologically inert and for its activation must undergo two hydroxylations. The first occurs in the liver, converting vitamin D into 25-hydroxyvitamin D [25-(OH)D], calcidiol. The second will occur mainly in the kidney, forming 1,25-dihydroxyvitamin D [1,25-(OH)2D], calcitriol – active metabolite of vitamin D [8,14,15]. Serum 25-(OH)D concentration is currently the main indicator of vitamin D status. The Department of Bone and Mineral Metabolism of the Brazilian Society of Endocrinology Metabolism (SBEM) proposes that levels greater than 20 ng/mL are desirable for the general healthy population, in risk groups between 30 and 60 ng/mL [16].

The Food and Nutrition Board (FNB) of the National Academies of Science, Engineering, and Medicine (NASEM) has concluded that people are at risk of deficiency when serum 25-(OH)D levels are below 12 ng/mL, inadequacy with serum levels between 12-20 ng/mL, sufficiency with levels greater than or equal to 20 ng/mL. However, the Endocrine Society has stated that for clinical practice, levels greater than 30 ng/mL are required for the effects of vitamin D to be maximized [8,14].

The old adult population, due to the loss of the skin's ability to synthesize vitamin D, less sun exposure, and intestinal malabsorption, is more likely to suffer

from vitamin D deficiency. In addition, obesity is also associated with lower levels of vitamin D due to the sequestration of this vitamin by the adipose tissue resulting in its lower availability [1,14].

Currently, available data are still limited, although suggest that a sufficient level of serum vitamin D is associated with a significantly lower risk of infection with the new coronavirus [17]. Research suggests that individuals with severe COVID-19 have 65% greater vitamin D deficiency compared to individuals with mild COVID-19 [12]. Furthermore, vitamin D deficiency has been linked to increased hospitalization [1], mortality, and severity of COVID-19 [8,18,19].

Vitamin D may play several roles in COVID-19, including that hypovitaminosis D may reduce innate cellular immunity and stimulate cytokine storms related to worsening Severe Acute Respiratory Syndrome associated with the new coronavirus; vitamin D supports antimicrobial peptides produced in the epithelium of the respiratory tract, producing improbable viral infections and symptoms of COVID-19 and vitamin D can help reduce the inflammatory response triggered by SARS-CoV-2 infection. Dysregulation of this response, especially of the renin-angiotensin system, is a characteristic of COVID-19, and the degree of hyperactivation is associated with a worse prognosis [13,20].

Considering that vitamin D deficiency has increasingly become a global problem and its relation with COVID-19 remains unknown, the need for studies on this association becomes relevant [21]. This study proposes to analyze the prevalence of vitamin D deficiency in patients hospitalized for Respiratory Syndrome, secondary to the new coronavirus, in a tertiary hospital in Rio Grande do Sul (RS) - Brazil. Also, to analyze the association of vitamin D deficiency with in-hospital mortality, the need for Intensive Care Unit (ICU) admission; the epidemiological profile; and the length of hospital stay.

Materials and Methods

Design

A cross-sectional, observational, and descriptive study following the STROBE guidelines [22] to analyze the prevalence of vitamin D deficiency in patients with a confirmed diagnosis of COVID-19.

Sample

A total of 3518 patients were admitted to the Ernesto Dornelles Hospital, a tertiary care hospital located in the city of Porto Alegre - RS, with a confirmed diagnosis of COVID-19, admitted to the ward,

emergency and ICU, from March 2020 to August 2022. The absence of data regarding serum levels of vitamin D measured during hospitalization was used as exclusion criteria. Therefore, patients with measured serum levels of vitamin D were included in the study as a random sample for convenience, as shown in Figure 1. These were divided into two groups: 1) with vitamin D deficiency [25-(OH)D serum level < 20 ng/mL]; 2) without vitamin D deficiency [25-(OH)D $\geq$ 20 ng/mL].

Data Collection

Data collection was performed using electronic medical records from the Phillips® TASY system at Hospital Ernesto Dornelles. The primary objective was to assess the prevalence of vitamin D deficiency in this sample, considering deficiency levels below 20 ng/mL. The secondary objective was to evaluate the epidemiological profile with the following data: gender, age, associated comorbidities (diabetes mellitus - DM, systemic arterial hypertension - SAH, hypothyroidism, chronic obstructive pulmonary disease - COPD/asthma, neoplasm, coronary artery disease - CAD, chronic renal failure - CRF, obesity). Also, in the secondary objective, the following outcomes and their association with vitamin D deficiency were evaluated: in-hospital death rate, length of hospital stay (permanence) and stay in the Intensive Care Unit (ICU).

Data Analysis

Data analysis was performed with support from a professional in the statistical area of Hospital Ernesto Dornelles. Data were collected and tabulated in Excel and later exported to SPSS version 20.0 for statistical analysis. Categorical or qualitative variables were described by frequencies and percentages. Quantitative variables were evaluated using the Kolmogorov-Smirnov test concerning their normality. Quantitative variables with normal distribution were described by mean and standard deviation. Variables with asymmetrical distribution were described by the median and interquartile range and compared between those with and without vitamin D deficiency using the Mann-Whitney test.

In order to assess the association of categorical variables, the Chi-square test with Yates' continuity correction was used, and the quantitative variables with normal distribution for Student's t test for independent samples. Those variables with a p value of less than 0.20 in the bivariate analysis were included for adjustment in the multivariable regression models for each outcome (death, ICU stay and length of hospital stay). Poisson regression with robust variance was performed for the binary outcomes and multiple linear regression for the

quantitative outcome (hospital stay). A significance level of 5% was considered.

Ethical Considerations

The present study respected the anonymity of the patients, following the current ethical and legal regulations (Resolution CN 466/12). The project was submitted to the Research Ethics Committee of Hospital Ernesto Dornelles. The Informed Consent Form (ICF) was not applied since it is an observational and retrospective study, performed through a review of electronic medical records, not incurring additional risks to patients.

Data from medical records were kept confidential and were only used for this research. The privacy and individual rights of research subjects were always respected. There was no concrete benefit to the research participants, however, the project contributed to data analysis referring to patients with COVID-19 and vitamin D deficiency.

According to Resolution 466/12, it is considered that every study carries the risk, although minimal, of breaching confidentiality of information.

Results

A total of 3518 patients admitted to the Ernesto Dornelles Hospital, with a confirmed diagnosis of COVID-19, from March 2020 to August 2022 were evaluated. Of these, 3032 patients were excluded for not having the serum level of vitamin D measured. Therefore, for convenience, 486 patients with serum vitamin D levels were analyzed. The mean age of the sample was 68.3 years with $SD \pm 14.6$, with 278 female patients (57.2%) and 208 male patients (42.8%). Of these, 151 patients (31.1%) had diabetes mellitus (DM), 289 (59.5%) systemic arterial hypertension (SAH), 64 (13.2%) hypothyroidism, 67 (13.8%) chronic obstructive pulmonary disease/asthma, 55 (11.3%) some neoplasm, 67 (13.8%) coronary artery disease, 39 (8%) chronic renal failure, 63 (59.1%) stroke/dementia and 72 (14.8%) obesity (Table 1).

The prevalence of patients with vitamin D deficiency was 60.1%, representing 292 patients in total. When comparing patients with and without vitamin D deficiency, there was no difference in the groups between age ($p=0.166$), gender ($p=0.783$), and comorbidities - DM ($p=0.45$); SAH ($p=0.359$); hypothyroidism ($p=0.999$); COPD/asthma ($p=0.839$); neoplasm ($p=0.111$); CAD ($p=0.999$); CRF ($p=0.165$); stroke/dementia ($p=0.314$); obesity ($p=0.398$) (Table 1).

Figure 1. Flowchart.

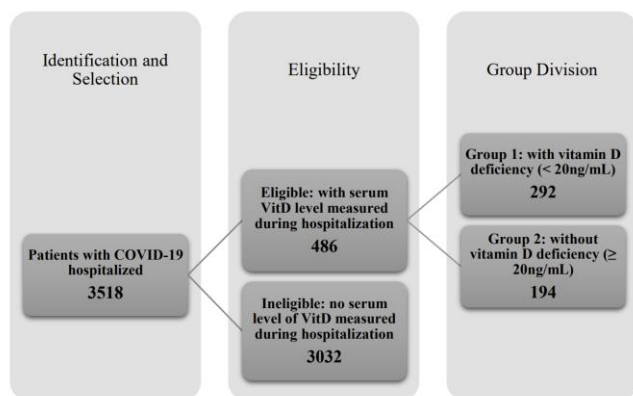


Table 1. Description of sample characteristics and comparison of patients with and without 25-(OH)D deficiency.

Characteristics	Total Sample	With VitD deficiency	Without VitD deficiency	P
Age, mean±SD	68.3±14.6	69.0±14.6	67.2±14.5	0.166
Gender, n (%)				
Female	278 (57.2)	169 (57.9)	109 (56.2)	0.783
Male	208 (42.8)	123 (42.1)	85 (43.8)	
Comorbidities, n (%)				
DM	151 (31.1)	95 (32.5)	56 (28.9)	0.450
SAH	289 (59.5)	179 (61.3)	110 (56.7)	0.359
Hypothyroidism	64 (13.2)	38 (13)	26 (13.4)	0.999
COPD/asthma	67 (13.8)	39 (13.4)	28 (14.4)	0.839
Neoplasm	55 (11.3)	39 (13.4)	16 (8.2)	0.111
CAD	67 (13.8)	40 (13.7)	27 (13.9)	0.999
CRF	39 (8)	28 (9.6)	11 (5.7)	0.165
Stroke/dementia	63 (13)	42 (14.4)	21 (10.8)	0.314
Obesity	72 (14.8)	47 (16.1)	25 (12.9)	0.398

SD: standard deviation; DM: diabetes mellitus; SAH: systemic arterial hypertension; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; CRF: chronic renal failure; stroke: cerebrovascular accident.

The median length of hospital stay was significantly longer in the group with vitamin D deficiency than in the group without deficiency (16 x 11, $p<0.001$). The need for ICU admission was significantly higher in the group with vitamin D deficiency than in the group without (40.9% vs. 28%, $p=0.005$). The outcome of death was significantly higher in the group with than in the group without deficiency (25.4% x 16.7%, $p=0.03$) (Table 2).

Table 2. Description of sample outcomes and comparison of patients with and without vitamin D deficiency.

	Total Sample	With VitD deficiency	Without VitD deficiency	P
Length of hospital stay (median, IQR)	14 (8-26)	16 (9-31)	11 (8-20)	<0.001
ICU admission, n (%)	173 (35.7)	119 (40.9)	54 (28)	0.005
Death	106 (21.9)	74 (25.4)	32 (16.7)	0.030

IQR: interquartile rang

Table 3. Association of vitamin D deficiency with the outcomes death, ICU stay and length of hospital stay adjusted for confounding factors.

	Death		ICU admission		Length of hospital stay	
	PR (CI95%)	p	PR (CI95%)	p	B (CI95%)	p
Group1 - With VitD deficiency	1.35 (0.94 a 1.9)	0.097	1.38 (1.06 a 1.8)	0.015	3.59 (-2.3 a 9.5)	0.232
Age	1.04 (1.03 a 1.06)	<0.001	1.01 (1.00 a 1.02)	0.045	-0.02 (-0.22 a 0.175)	0.814
Neoplasm	1.6 (1.1 a 2.4)	0.017	1.15 (0.8 a 1.57)	0.380	15.4 (6.2 a 24.7)	0.001
CRF	1.8 (1.2 a 2.7)	0.003	1.8 (1.4 a 2.4)	<0.001	6.7 (-4.07 a 17.4)	0.223

PR: prevalence ratio obtained by Poisson Regression with robust variance; B: Multiple Linear Regression coefficient; ICU: Intensive Care Unit; CRF: chronic renal failure.

After adjusting for potential confounding factors (age, neoplasia, and CRF), the risk of death did not differ between the groups with and without vitamin D deficiency (05%CI 0.94-1.91; $p=0.097$), only the risk number of ICU stays remained 1.38x higher in the group with vitamin D deficiency than in the group without (CI05% 1.06 – 1.8; $p=0.015$), as well as age and CRF were factors with greater risk for ICU admission (Table 3).

Therefore, it was observed that the neoplasia increases, on average, by 15 days in the length of hospital stay, regardless of the other variables, and vitamin D deficiency had no significant association after adjusting for confounding factors (Table 3).

Discussion

COVID-19 has multiple clinical aspects and varied outcomes from asymptomatic presentation to death. Estimates indicate that the pathophysiology that causes the severe types of SARS-CoV-2 infection is intertwined with the release of pro-inflammatory cytokines. Thus, vitamin D is related to the metabolism of the immune system and influences the systemic inflammatory response. Consequently, several studies have linked vitamin D deficiency to unfavorable outcomes of COVID-19.

The study performed showed a significant prevalence of 25-(OH)D deficiency in patients with COVID-19, of 60.1%, in a sample of 486 patients, in a tertiary hospital in Rio Grande do Sul. However, a cause-and-effect association cannot be defined, as only patients with confirmed infection were evaluated in this study. Analyzes show that older adults are at greater risk of acquiring severe forms of infection with the new coronavirus and suffer more from vitamin D deficiency [4], the mean age of the population in this sample was

68.3 years, considered older adult population and consequently more likely to have vitamin D deficiency.

Preliminary results of the studied sample showed that vitamin D deficiency could be related to worse clinical outcomes: longer hospital stay, higher rates of ICU admission and higher mortality. However, when adjusting the analysis for potential confounding factors, no significant difference was observed in mortality and length of hospital stay, only the risk of ICU admission remained significant, configuring greater severity of cases. A systematic review and meta-analysis showed that among patients hospitalized with moderate to severe COVID-19, vitamin D deficiency (defined as 25-(OH)D < 10 ng/mL) was associated with a trend towards longer hospital stays, although, when adjusted in the multivariate Cox regression model, this association lost its significance [23]. Another systematic review and meta-analysis of 31 observational studies found no significant associations between serum 25-(OH)D levels below 20 ng/mL and mortality, ICU admission, or need for ventilation among patients with COVID-19 [8].

The association between greater severity of the disease and admission to an ICU was considered, thus, it can be inferred that in this analyzed population, patients with vitamin D deficiency had a higher risk of severity when compared to those without vitamin D deficiency. This finding is similar to previous studies that associate vitamin D deficiency with a higher risk of disease severity. Dramé et al. [4] showed that mortality was consistently higher among study participants with hypovitaminosis D and their results suggest that older adults with vitamin D supplementation during the acute phase of COVID-19 were at lower risk of adverse outcomes (mortality, needs for high-flow oxygen therapy or ICU support).

Yisak et al. [10] also showed in 09 analyzed articles that in 77.8% of them the levels of vitamin D were related to the infection, severity, and mortality of COVID-19, while two of them failed to show any association. Patients with COVID-19 diagnosed in the health system of the University of Cincinnati showed that disease severity was associated with vitamin D deficiency and the odds of ICU admission were also higher in these individuals [10]. A retrospective observational analysis aimed to investigate vitamin D levels and their correlation with the severity of COVID-19 in Belgium, as determined by the chest CT result, and found higher rates of vitamin D deficiency among severe cases of COVID-19 (58.6% versus 45.2%, $P = 0.0005$). Another study evaluating the prevalence of vitamin D deficiency in patients with COVID-19 also showed that mean serum 25-(OH)D levels were an indicator of disease severity [10].

As a limitation of this study, its retrospective observational design, dependent on data collection from electronic medical records, whose exams were requested by assistant physicians at different times, without predefined research protocols, resulted in the evaluation of approximately 14% of patients with COVID-19 during this period. Other factors not analyzed and with potential bias in the results obtained were:

1) Time of illness at hospital admission: after 7 days of onset of symptoms, the chance of clinical worsening increases [2,3,5];

2) Type of treatment offered at hospitalization: patients who received treatment with plasma, immunoglobulin, or immunobiologicals, these being able to interfere with the outcomes;

3) Vaccine status for COVID-19: the sample includes data collected after the start of vaccination in 2021, and the severity of the disease decreased considerably after the preventive measure [24,25] and;

4) Previous use of vitamin D supplementation: patients were already on vitamin D replacement.

Conclusion

Among older adults patients hospitalized with COVID-19 in this study sample, there was a 60% prevalence of vitamin D deficiency. Vitamin D deficiency in this population was associated with a higher risk of hospitalization in the ICU, possibly presenting or not an association with higher mortality rates and length of stay. Currently, the existing data supporting the association between vitamin D deficiency and the clinical outcomes of SARS-CoV-2 infection are conflicting. Therefore, further investigations and studies are needed to establish a cause-and-effect association.

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Ethical Approval

This study was approved by the Research Ethics Committee of Hospital Ernesto Dornelles, Rio Grande do Sul, Brazil.

Informed consent

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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It was applied by Ithenticate@.

Peer review process

It was performed.

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