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Low vitamin D at ICU admission is associated with cancer, infections, acute respiratory insufficiency, and liver failure

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ABSTRACT

Objectives: Vitamin D deficiency may be associated with comorbidities and poor prognosis. However, this association in patients in the intensive care unit (ICU) has not been fully elucidated. The aim of this study was to investigate whether the serum concentrations of 25-hydroxyvitamin D (25[OH]D) within the first 48 h after ICU admission are associated with prognostic indicators (Acute Physiology and Chronic Health Evaluation [APACHE] II, Sequential Organ Failure Assessment [SOFA] score, Charlson comorbidity index [CCI]), clinical complications, serum C-reactive protein (CRP) concentrations, mechanical ventilation duration, and mortality.
Methods: Seventy-one patients were admitted to the ICU, and their concentrations of 25(OH)D in the first 48 h were analyzed. To evaluate the prognostic factors in the ICU, APACHE II scores, SOFA scores, CCI questionnaires, mechanical ventilation time, CRP, and mortality were used.
Results: The mean concentration of 25(OH)D was 17.7 $\pm$ 8.27 ng/mL (range 3.5–37.5 ng/mL), with 91.6% presenting with deficiency at admission. Although no associations were found between serum 25(OH)D concentrations with mechanical ventilation time, CRP, mortality, and APACHE II and SOFA severity scores, we found associations with the CCI when adjusted by age (model 1: odds ratio [OR], 1.64; 95% confidence interval [CI], 1.14–2.34) and by age, sex and body mass index (model 2: OR, 1.59; 95% CI, 1.10–2.34). In addition, among the comorbidities present, 25(OH)D concentrations were inversely associated with cancer (crude model OR, 3.42; 95% CI, 1.21–9.64) and liver disease (crude model OR, 9.64; 95% CI, 2.28–40.60).
Conclusion: We found a strong association between 25(OH)D concentrations and the prognostic indicator CCI and clinical complications (acute respiratory insufficiency, acute liver failure, and infections), but no associations with the prognostic indicators APACHE II and SOFA score, CRP, mechanical ventilation duration, or mortality. The main comorbidities associated with low 25(OH)D were cancer and liver disease, suggesting that the determination of 25(OH)vitamin D is relevant during the ICU stay.

Introduction

25-hydroxyvitamin D [25(OH)D] is synthesized by the skin from 7-dehydrocholesterol in response to sun exposure [1] and also can be obtained through the diet [2]. Both dietary and endogenous vitamin D concentrations are considered biologically inactive. To become active, vitamin D undergoes hydroxylation, initially in the liver by 25-hydroxylase, forming 25(OH)D; subsequently, 25(OH)D undergoes further hydroxylation by 1 α-hydroxylase in the kidney and forms 1,25-dihydroxyvitamin D, the active form of vitamin D [3,4]. Despite its role in calcium metabolism, phosphorus metabolism, and the regulation of bone growth, vitamin D has a pleiotropic

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action [4–7]. Vitamin D has an anti-inflammatory action by attenuating the expression of inflammatory biomarkers [8]. Thus, serum 25(OH)D concentrations are inversely associated with inflammatory markers such as C-reactive protein (CRP) [9]. Vitamin D concentrations decrease in acute diseases, such as in patients in the intensive care unit (ICU), or in the case of chronic comorbidities, such as liver disease and cancer [10].

The prevalence of vitamin D deficiency in ICU patients is 26% to 74% [11–13]. A prospective study of patients admitted to a surgical ICU showed that low 25(OH)D concentrations (<12 ng/mL) were associated with a higher mortality [13]. Likewise, inadequate vitamin D (<30 ng/mL) concentrations in ICU patients may be associated with an increased risk for clinical complications such as infection, organ failure evaluated by the Sequential Organ Failure Assessment (SOFA) score [14,15], ICU length of stay [11,16], duration of mechanical ventilation (MV) [7], and mortality [2,11,13]. In addition to traditional severity indicators, such as the SOFA score and Acute Physiology and Chronic Health Evaluation (APACHE) II, the Charlson Comorbidity Index (CCI) also has been used as a prognostic indicator in ICU patients [17–19]. In a cohort study of 310 ICU patients, vitamin D paired with the CCI questionnaire was more strongly associated with mortality than when CCI was used alone, demonstrating the benefit of the evaluation of vitamin D on disease prognosis [18].

Although some studies have shown an association between vitamin D concentrations and the clinical outcome of ICU patients [7,13,16,20–27], others found no association between vitamin D and prognostic indicators such as SOFA, APACHE II, mortality, and comorbidities [16,22, 28,29]. Therefore, we formed the hypothesis that low 25(OH)D concentrations in ICU patients are associated with a higher inflammatory state, duration of MV, and a greater number of comorbidities.

This study aimed to investigate whether 25(OH)D concentrations obtained within the first 48 h of ICU admission are associated with prognostic indicators (APACHE II, SOFA score, and CCI), clinical complications, higher CRP concentrations, duration of MV, and mortality in ICU patients.

Although the present study had small sample size and major the studies evaluated the clinical prognostic indicators (APACHE II and SOFA score) in ICU patients, our research is promising because this was, to our knowledge, the first study in Brazil to evaluate the 25(OH) D concentrations and association with comorbidities.

Methods

Design of the study and recruitment

This was a cross-sectional study carried out at the Clinical ICU at University Hospital between May and November 2017. The study was approved by the Research Ethics Committee at Clinical Hospital (UFG-EBSERH).

The determination of sample size was based on the equation proposed by Lwanga and Lemeshow [30]. Using a significance level of 5% and statistical power of 80%, considering that 37% of critically ill patients with vitamin D deficiency use mechanical ventilation and present a relative risk of 2, the minimum sample size determined was 71 patients.

ICU patients >18 y of age with serum 25(OH)D determinations made within 48 h of ICU admission were included. Exclusion criteria were previous use of vitamin D supplements to avoid influencing serum vitamin D levels [31], pregnancy, and parenteral nutrition or palliative care. After exclusions, 91 patients were admitted. Of these, 13 were excluded because of the unavailability of 25(OH)D levels, 5 because they were on parenteral nutrition and 2 because of pregnancy (Fig. 1).

Data collection

Data were collected from medical records and included age; sex; comorbidities; admission category (medical or surgical); ICU length of stay in days; body mass index (BMI), which was calculated by dividing the weight (kg) by the square of the height (m^2); NUTrition Risk in the Critically Ill (NUTRIC score), which assesses the nutritional risk of critically ill patients and identifies those who require more intensive nutritional therapy [32]; CCI, which evaluates the risk for mortality based on present comorbidities and the age of the patient [17]; APACHE II, which evaluates the risk for mortality based on routine physiological measurements, age, and previous health status [33]; SOFA score, which evaluates the evolution of organ failure [34]; use of MV at admission; days in MV; time of fasting after admission (in hours); clinical complications up to 28 d in the ICU [35,36]; and

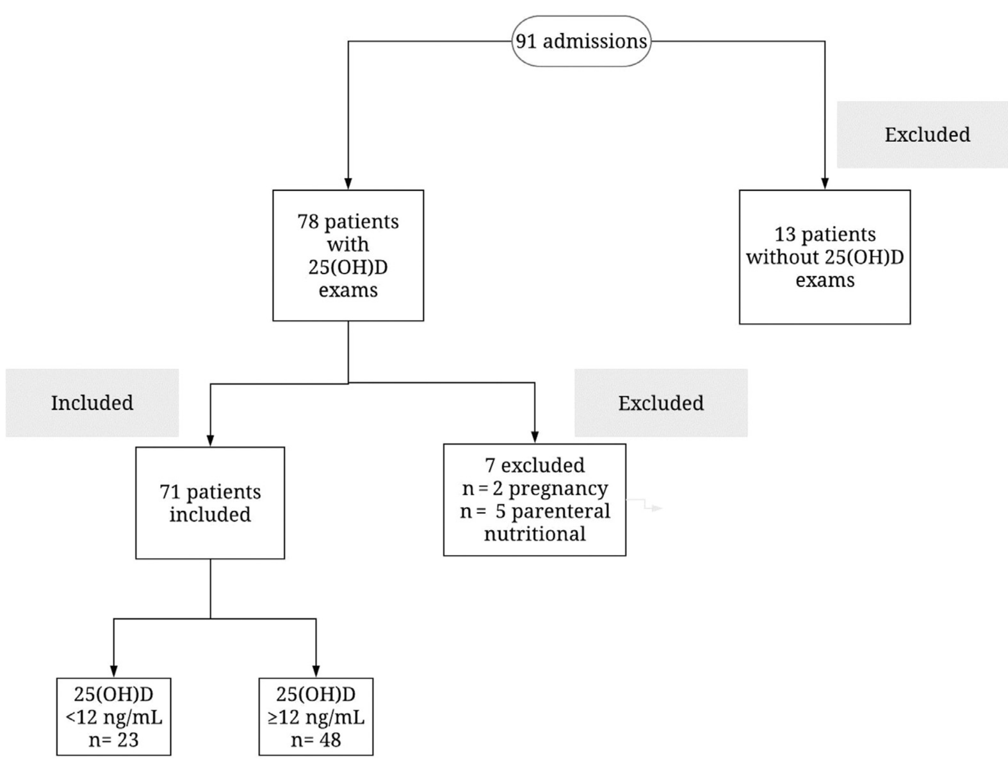

Fig. 1. Flowchart of the study. 25(OH)D, 25-hydroxyvitamin D.

comorbidities, such as acute renal failure, acute liver failure, infections, sepsis, cardiorespiratory arrest, and acute pulmonary insufficiency.

Laboratory

Blood samples were obtained within the first 48 h at ICU admission. The 25(OH) vitamin D concentration was measured by an immunoassay and the high-sensitivity (hs) CRP concentration was quantified by immunoturbidimetry.

Statistical analyses

The descriptive statistical analysis was performed with a cutoff of 12 ng/mL for the serum concentrations of vitamin D, according to a Brazilian study that evaluated ICU patients [13]. The continuous data were presented as the mean and SD, with categorical data as absolute (n) and relative (%).

Comparisons of the characteristics of the sample were made using the unpaired Student's *t* test in the presence of normality of the data and Mann–Whitney U test in the absence of normality. The χ^2 test and Fisher exact test were made to assess the homogeneity and possible differences of the groups in relation to the proportions (%).

When considering the outcomes for MV, CRP, SOFA score, APACHE, CCI, and clinical outcomes (death or discharge during the ICU stay), logistic regression was performed to verify the association between these variables and serum vitamin D concentrations. In addition, a new logistic regression was performed to evaluate the association between comorbidities present at admission and low serum vitamin D concentrations. For this, binary models (crude) were constructed and adjusted for age (model 1) and age, sex, and BMI (model 2). The results are presented as the odds ratio (OR) and 95% confidence interval (CI). For all analyses, $P < 0.05$ was considered significant. Analyses were performed using the Stata version 14 (StataCorp., College Station, TX, USA) and Medcalc®, Seoul, Korea software version 18.11.

Results

The mean of serum 25(OH)D concentrations in patients at admission was 17.7 ± 8.27 ng/mL (range 3.5–37.5 ng/mL), with only 8.4% of patients (n = 6) having sufficient vitamin D levels (≥30 ng/mL) and 91.6% presenting with deficiency. Figure 2 shows the blood 25(OH)D concentration distribution among patients.

The mean age was 53 ± 18 y old. The majority of patients belonged to the medical admission category 63.38% and were women 57.74% (*P* = 0.003; Table 1). Regarding severity scores, mean APACHE II score was 21.37 ± 9.6 points, SOFA score was 6.7 ± 4.3 points, and CCI score was 3.87 ± 2.3 points. Mean BMI was 23.43 ± 6.1 kg/m^2 and the NUTRIC score was 4.83 ± 2.2 points. The mean CRP value was 33.1 ± 15.29 mg/dL (data not shown).

Table 1 presents the demographic factors, clinical and comorbidities indicators at admission, and the clinical complications of patients during the first 28 d after ICU admission. The patients were dichotomized according to serum 25(OH)D concentrations from a previous Brazilian study [13]. Those with values <12 ng/mL had a higher frequency of comorbidities, such as cancer (*P* = 0.017) and liver disease (*P* = 0.001). In addition, those with low 25(OH)D concentrations also had more clinical complications, such as acute respiratory failure (*P* = 0.003), acute liver failure (*P* = 0.002), and infections (*P* = 0.034). However, there was no difference between the groups in terms of admission categories, fasting hours, clinical outcomes (death or discharge), MV days, and ICU stay (Table 1).

Although there was no association between serum 25(OH)D concentrations and admission with hs-CRP concentrations, SOFA score, APACHE II, duration of MV, and clinical outcomes, an association was found with CCI when adjusted for age (model 1; OR, 1.64; 95% CI,

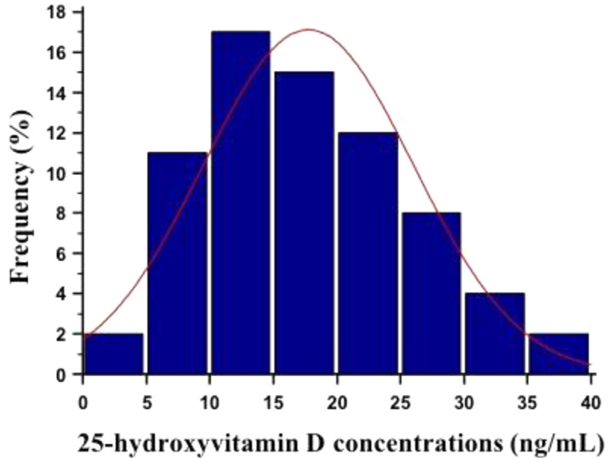

Fig. 2. Distribution of serum 25-hydroxyvitamin D concentrations.

Table 1
Sociodemographic and clinical data of patients at ICU admission (N = 71)

Variables	<12 ng/mL (n = 23)	≥12 ng/mL (n = 48)	*P*-value
25-hydroxyvitamin D (ng/mL)*	9.22 ± 2.22	21.85 ± 6.85	**<0.001**
Age (y)*	49.91 ± 18.13	55.35 ± 18.32	0.182
Sex†, n (%)			**0.003**
Female	19 (82.60)	22 (45.83)	
Male	4 (17.40)	26 (54.17)	
SOFA score‡	7.73 ± 5.25	6.28 ± 3.71	0.209
APACHE II*,§	23.17 ± 10.93	20.49 ± 895	0.311
Charlson Comorbidity Index‖	4.57 ± 2.71	3.54 ± 2.10	0.086
NUTRIC score‖	5.10 ± 2.41	4.70 ± 2.20	0.521
NUTRIC score‖, n (%)			0.845
Low risk (1–4)	10 (47.61)	18 (45)	
High risk (>4)	11 (52.39)	22 (55)	
Body weight (kg)*	58.71 ± 15.30	63.26 ± 16.12	0.171
Height (m)	1.61 ± 0.08	1.63 ± 0.10	0.248
BMI (kg/m^2)*	22.85 ± 6.06	23.71 ± 6.17	0.539
hs-CRP (mg/dL)*,¶	18.83 ± 14.05	16.39 ± 15.76	0.387
Admission category, n (%)			0.454
Surgery	7 (30.43)	19 (39.58)	
Clinical	16 (69.57)	29 (60.42)	
Comorbidities, n (%)			
Cancer	14 (60.86)	15 (31.25)	**0.017**
Renal disease†	4 (17.39)	15 (31.25)	0.172
Diabetes†	5 (21.73)	8 (16.67)	0.744
Liver disease†	9 (39.13)	3 (6.25)	**0.001**
COPD†	5 (21.73)	5 (10.41)	0.275
Clinical complications, n (%)			
Cardiorespiratory arrest	11 (47.82)	14 (29.16)	0.123
Acute respiratory insufficiency†	22 (95.65)	30 (62.50)	**0.003**
Acute renal failure	13 (56.52)	22 (45.83)	0.399
Acute liver failure†	11 (47.82)	5 (10.41)	**0.002**
Infections†	19 (82.60)	26 (54.16)	**0.034**
Sepsis	17 (73.91)	24 (50.00)	0.056
Mechanic ventilation, n (%)			0.179
No	11 (47.82)	31 (64.58)	
Yes	12 (52.18)	17 (35.42)	
Fasting from admission (h)*	34.43 ± 47.91	14.50 ± 21.43	0.177
Mechanic ventilation duration (d)*	3.87 ± 6.46	2.71 ± 5.31	0.196
ICU length of stay (d)*	7.04 ± 6.84	5.40 ± 5.95	0.351
Mortality, n (%)			0.084
Alive	12 (52.18)	35 (72.91)	
Died	11 (47.82)	13 (27.08)	

APACHE, Acute Physiology and Chronic Health Disease Classification System; BMI, body mass index; COPD, chronic obstructive pulmonary disease; hs-CRP, high-sensitivity C-reactive protein; ICU, intensive care unit; NUTRIC score, NUTrition Risk in the Critically Ill; SOFA, Sepsis-Related Organ Failure Assessment
Data are presented as mean ± standard deviation for continuous variables and absolute values in (n) and percentage in (%)
Clinical complications' percentages refer to prevalence of complications in each group
Values in bold are statistically significant.
**P*-value: Means comparison by unpaired Student's *t* test for continuous variables (Mann–Whitney U test).
†Comparison of proportions by χ^2test (Fisher exact test).
‡n = 62.
§n = 70.
‖n = 61.
¶n = 66.

Table 2
Association of serum of the 25-hydroxyvitamin D concentrations with clinical outcomes at ICU admission

Variables	OR (95% CI) 25(OH)D (continuous variables)	*P*-value
C-reactive protein		
Crude	1.01 (0.97-1.04)	0.530
Model 1	1.01 (0.98-1.04)	0.422
Model 2	1.02 (0.98-1.06)	0.167
Mechanical ventilation duration		
Crude	1.03 (0.95-1.12)	0.425
Model 1	1.03 (0.95-1.12)	0.421
Model 2	1.06 (0.96-1.12)	0.208
SOFA score		
Crude	1.08 (0.95-1.22)	0.208
Model 1	1.08 (0.95-1.22)	0.204
Model 2	1.10 (0.96-1.26)	0.143
APACHE II		
Crude	1.02 (0.97-1.08)	0.274
Model 1	1.03 (0.98-1.09)	0.177
Model 2	1.03 (0.97-1.09)	0.238
Charlson Comorbidity Index		
Crude	1.20 (0.97-1.50)	0.091
Model 1	1.64 (1.14-2.34)	**0.006**
Model 2	1.59 (1.10-2.34)	**0.001**
Mortality		
Crude	2.46 (0.87-6.95)	0.087
Model 1	2.73 (0.93-7.95)	0.065
Model 2	2.08 (0.66-6.59)	0.210
ICU length of stay		
Crude	1.04 (0.96-1.12)	0.303
Model 1	1.04 (0.96-1.12)	0.307
Model 2	1.05 (0.96-1.15)	0.225

25(OH)D, 25-hydroxyvitamin D; APACHE, Acute Physiology and Chronic Health Disease Classification System; ICU, intensive care unit; SOFA, Sepsis-Related Organ Failure Assessment.
Model 1: adjusted by age.
Model 2: adjusted by age, sex, and body mass index.
P-value: means differences in variables.
Values in bold are statistically significant.

1.14–2.34) and by age, sex, and BMI (Model 2; OR, 1.59; 95% CI, 1.10–2.34). A higher CCI score was identified when vitamin concentrations were <12 ng/mL; that is, when the CCI was worse (Table 2).

Next, we performed a new logistic regression analysis to identify which comorbidities were associated with low serum 25(OH)D concentrations at admission (Table 3). We found that low serum 25(OH)D concentrations are inversely associated with cancer (crude model OR, 3.42; 95% CI, 1.21–9.64) and liver disease (crude model OR, 9.64; 95% CI, 2.28–40.60). In addition, this association remained even after adjusting for age, sex, and BMI (Table 3, models 1 and 2).

Table 4 demonstrates that serum 25(OH)D concentrations were also positively associated with clinical complications in the next 28 d of ICU admission. These included acute respiratory insufficiency and acute liver failure (crude model OR, 13.20; 95% CI, 1.63–106.45; and crude model OR, 7.88; 95% CI, 2.29–27.12), respectively, as well as when adjusted by age (model 1) and age, sex, and BMI (model 2). In addition, a positive association was found for infections (crude model OR, 4.01; 95% CI, 1.18–13.59) and model 1 (OR, 4.00; 95% CI, 1.17–13.64), but not when adjusted by sex, age, and BMI (model 2).

Discussion

This observational study demonstrated that patients with 25(OH)D concentrations <12 ng/mL at ICU admission had a higher number of comorbidities when assessed by CCI. In addition, low 25(OH)D concentrations were strongly associated with cancer and liver disease. This study was one of the few carried out in Brazil and the first one performed in the midwest region that evaluated serum 25(OH)D concentrations in ICU patients.

Furthermore, a few studies of ICU patients have reported that, in addition to comorbidities, the inadequacy of serum 25(OH)D concentrations may greatly influence ICU patient disease severity, increasing the risk for clinical complications and mortality [13,31,37,38].

Table 3
Association of serum 25-hydroxyvitamin D concentrations with clinical conditions and comorbidities at ICU admission

Variables	OR (95 % CI) 25(OH)D (continuous variables)	*P*-value
Cancer		
Crude	3.42 (1.21–9.64)	**0.017**
Model 1	3.64 (1.26–10.51)	**0.016**
Model 2	4.15 (1.24–13.94)	**0.021**
Acute renal failure		
Crude	0.46 (0.13–1.59)	0.223
Model 1	0.50 (0.14–1.79)	0.292
Model 2	0.66 (0.17–2.54)	0.546
Diabetes mellitus		
Crude	1.38 (0.39–4.83)	0.606
Model 1	1.47 (0.41–5.20)	0.548
Model 2	1.47 (0.37–5.83)	0.581
Liver diseases		
Crude	9.64 (2.28–40.60)	**0.0008**
Model 1	10.36 (2.38–45.11)	**0.001**
Model 2	17.26 (2.75–108.18)	**0.0001**
COPD		
Crude	2.38 (0.61–9.27)	0.208
Model 1	2.37 (0.60–9.35)	0.214
Model 2	3.65 (0.77–17.19)	0.101

25(OH)D, 25-hydroxyvitamin D; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.
Model 1: adjusted by age.
Model 2: adjusted by age, sex, and body mass index.
P-value: means differences in variables.
Values in bold are statistically significant.

Table 4
Association of serum 25-hydroxy-vitamin D concentrations with clinical complications in next 28 d at ICU admission

Variables	OR (95% CI) 25(OH)D (continuous variables)	*P*-value
Acute respiratory insufficiency		
Crude	13.20 (1.63–106.45)	**0.015**
Model 1	12.30 (1.50–100.40)	**0.019**
Model 2	12.53 (1.44–108.79)	**0.021**
Acute liver failure		
Crude	7.88 (2.29–27.12)	**0.001**
Model 1	7.53 (2.17–26.11)	**0.001**
Model 2	6.87 (1.75–26.95)	**0.005**
Infections		
Crude	4.01 (1.18–13.59)	**0.025**
Model 1	4.00 (1.17–13.64)	**0.026**
Model 2	3.57 (0.99–12.88)	0.051
Sepsis		
Crude	2.83 (0.95–8.42)	0.060
Model 1	2.84 (0.94–8.53)	0.062
Model 2	2.53 (0.79–8.03)	0.114

25(OH)D, 25-hydroxyvitamin D; ICU, intensive care unit.
Model 1: adjusted by age.
Model 2: adjusted by age, sex, and body mass index.
P-value: means differences in variables.
Values in bold are statistically significant.

Although serum 25(OH)D concentrations are influenced by insufficient sun exposure, skin pigmentation, dietary intake, and liver disease [39], and are worsened by other factors inherent in an ICU stay, such as fluid overload [40,41] and inflammation [42], it is still unclear whether serum vitamin D deficiency influences the development of comorbidities. However, recent studies have shown that serum 25(OH)D concentrations may be used as a biological marker of health worsening [10,39]. The present study found that 25(OH)D concentrations at admission were associated with the presence of comorbidities such as cancer (crude model OR, 3.42; 95% CI, 1.21–9.64), liver disease (crude model OR, 9.64; 95% CI, 2.28–40.60), and acute liver failure.

Because of its pleiotropic action, vitamin D acts in several cellular pathways, such as proliferation, differentiation, angiogenesis, metastasis, and apoptosis, that regulate processes, thus playing an important role in the inhibition of carcinogenesis [43]. In a cohort study, Giovannucci et al. [44] found that patients with low serum 25(OH)D concentrations had an increased incidence of cancer of the digestive tract and higher risk for mortality.

Vitamin D deficiency can occur in the case of liver failure, and reduced concentrations also may contribute to liver damage [45,46]. Vitamin D deficiency may lead to increased hepatic injury by increasing inflammatory processes and the development of liver fibrosis [47]. Although studies show an association between low vitamin D levels and inflammation [48,49], we found no association between serum CRP and 25(OH)D concentrations at ICU admission. This is probably due to the heterogeneity of the ICU population and because CRP is correlated with both infections and organ failure, which justifies its increase in critically ill patients [50,51].

Although some studies have shown that there are associations between 25(OH)D concentrations and severity scores such as SOFA and APACHE II [3,14], the present study and others [22,52] did not find any association between the APACHE II and SOFA severity scores and 25(OH)vitamin D concentrations, which suggests that further clarification is needed.

Although evidence suggests that CCI is not routinely used in clinical practice and is not as effective as other severity scores when compared with APACHE II and SOFA in predicting ICU mortality, this index shows good accuracy in identifying severity and risk for mortality in the ICU, mainly because it considers the preexisting comorbidities [19,49,53].

Similar to the present findings, Atalan et al. [52] evaluated the 25(OH)D concentrations at ICU admission for 491 patients and also found no association between the APACHE II score and an amount of organ dysfunction with vitamin D. In another study conducted by Long-Xiang et al. [22], patients in the ICU with a diagnosis of sepsis, alongside controls, also were evaluated; no associations were found between APACHE II and SOFA severity scores with 25 (OH)D concentrations. Regarding the clinical outcomes, studies have shown that reduced 25(OH)D concentrations may predict a higher mortality risk in ICU patients, likely because of the higher inflammatory state and risk for infections [2,24,54]. Likewise, the present study found a higher frequency of infectious complications in patients with 25(OH)D concentrations $<$12 ng/mL (crude model OR, 4.01; 95% CI, 1.18–13.59). Despite that, no difference was found between the groups in the evaluation of serum concentrations of CRP and mortality (Table 4). Another factor related to the worse prognosis in ICU patients is the prolonged time on MV.

Vitamin D deficiency may result in an increased risk for chest fractures, decreased lung capacity, increased risk of infections, elevated inflammatory status, and increased risk of pulmonary parenchymal degradation [55], which reduces breath capacity. Likewise, in a cohort study performed with 210 critical patients from a surgical ICU who were using MV at admission, the authors observed that serum 25(OH)D concentrations were inversely associated with MV duration [7]. In the present study, no association was found between MV duration and 25(OH)D concentrations, but there was an association with acute respiratory insufficiency, which is a clinical complication that may have an effect on MV.

A limitation of the present study was that the serum 25(OH)D concentrations were only measured at ICU admission, which limits the identification of whether the ICU duration would reduce 25(OH)D concentrations and how the clinical evolution of the patients with low concentrations would occur. Moreover, in the present study, it was not possible to collect data on dietary intake because of the lack of data recorded in medical and dietitian records. In addition, we did not measure the renal megalin expression, which could have influenced the endocytosis of 25(OH)D filtered from the glomerular ultrafiltrate and thus reduce 25(OH)D concentrations [56]. Although we evaluated duration of MV, data were not recorded in hours, thus a patient with a minimum of 12 h was considered to have had 1 d on MV. We also had a limited sample size, which may hamper the generalization of the results. In addition, serum vitamin D levels were assessed within 48 h of ICU admission, which may have influenced serum vitamin D status because of diarrhea, hemodilution, and plasma protein losses such as vitamin D-carrying protein [57].

Conclusion

We found a strong association of 25(OH)D concentrations with the prognostic indicator (CCI) and clinical complications (acute respiratory insufficiency, acute liver failure, and infections), but no associations with the prognostic indicators APACHE II and SOFA score, CRP, MV duration, and mortality. In addition, the main comorbidities associated with low 25(OH)D were cancer and liver disease, suggesting that the determination of 25(OH)D is relevant during the ICU stay.

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