Low Circulating Vitamin D in Intensive Care Unit–Admitted COVID-19 Patients as a Predictor of Negative Outcomes

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ABSTRACT

Background: Vitamin D deficiency has been associated with an increased risk of respiratory infections.

Objectives: The study aimed to evaluate the serum 25-hydroxyvitamin D [25(OH)D] concentration in patients admitted to the intensive care unit (ICU) as a predictor of coronavirus disease 2019 (COVID-19) mortality.

Methods: A single-center retrospective observational study was conducted. Forty adult patients (50% men) with confirmed COVID-19 who were admitted to the ICU were enrolled. The primary endpoint was mortality at day 60. Serum 25(OH)D concentration was measured on the day of admission to the ICU. We used the Mann–Whitney test, Fisher's exact test, Kaplan–Meier analysis, and receiver operator characteristic (ROC) analysis to assess serum 25(OH)D concentration as a predictor of COVID-19 mortality.

Results: All 40 patients had a low median (IQR) serum 25(OH)D concentration at admission [12 (9–15) ng/mL]. The median (IQR) serum 25(OH)D concentration was greater in survivors [13.3 (10.0–17.1) ng/mL, $n = 22$] than in nonsurvivors [9.6 (7.9–14.2) ng/mL; $n = 18$], $P = 0.044$. The area under the ROC curve was 0.69 (95% CI: 0.52, 0.86; $P = 0.044$). The 60-d mortality rate of those with serum 25(OH)D concentrations ≤ 9.9 ng/mL ($n = 14$, 71%) tended to be greater than that of those with concentrations >9.9 ng/mL ($n = 26$, 31%) ($P = 0.065$), and they had a 5.6-fold higher risk of death (OR: 5.63; 95% CI: 1.35, 23.45; $P = 0.018$).

Conclusions: The ICU patients had a low serum 25(OH)D concentration. Serum 25(OH)D concentrations ≤ 9.9 ng/mL on admission can be used to predict in-hospital mortality in patients with COVID-19. This trial was registered at clinicaltrials.gov as NCT04450017. *J Nutr* 2021;151:2199–2205.

Keywords: serum 25(OH)D concentration, SARS-CoV-2, COVID-19, outcome, intensive care unit

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the virus that causes coronavirus disease 2019 (COVID-19)—pandemic presents a global challenge affecting all aspects of human life and resulting in extensive social, economic, and human losses. Although moderately ill COVID-19 patients generally recover well, this is not the case for critically ill patients, where the results of the therapy are frequently disappointing. In this group of patients, disease progression is often complicated by acute respiratory distress syndrome (ARDS), multiple organ failure, infections, as well as the need for mechanical ventilation and admission to the intensive care unit (ICU) (1). The reported mortality rate in such patients varies significantly across different countries and may reach 85% (2–5). The risk factors, including race, age, comorbidities, genetics, and the availability of medical help, may contribute independently and cumulatively to the disease's severity (6).

Higher mortality and hospitalization rates have been previously reported in the northern-latitude regions of the world (6). This has been attributed to the low UV exposure and vitamin D deficiency in the populations in these areas.

Several studies on ICU patients have reported that low vitamin D concentrations are associated with a higher risk of negative outcomes such as death, organ failure, prolonged mechanical ventilation, a higher rate of ventilation-associated pneumonia, and sepsis (7–10).

We conducted a single-center retrospective study. The aim was to evaluate the serum 25-hydroxyvitamin D [25(OH)D] concentration in patients admitted to the ICU as a predictor of COVID-19 mortality.

Methods

Study design and participants

The retrospective observational single-center study (NCT04450017) was conducted in the Federal Scientific and Clinical Center of Specialized Types of Medical Care and Medical Technologies of the Federal Medical and Biological Agency of Russia, which was a designated hospital for COVID-19 patients. The diagnosis of COVID-19 was established according to the WHO interim guidance (11). Between 6 and 27 April, 2020, 663 consecutively admitted COVID-19 patients were screened. Of them, 121 were treated in the ICU. Forty patients who had their serum 25(OH)D concentration measured during admission and had a definite outcome (death or discharged) were included.

The study was approved and the requirement for informed consent was waived by the Ethics Commission (record 5 from Protocol No. 5, 2020).

To better define the relation between vitamin D insufficiency and COVID-19, we determined the serum 25(OH)D concentrations in COVID-19 outpatients and non-COVID-19 patients. The study was conducted at the same center through a retrospective analysis of 25 COVID-19 outpatients who were tested for serum 25(OH)D concentrations throughout the course of the disease. Furthermore, we retrospectively selected 100 random patients from the hospital database who represented the general population and had their serum 25(OH)D concentrations determined in our hospital in 2019 before the COVID-19 pandemic. Of these, only 50 patients could be reached and consented to participate in the study. We analyzed serum 25(OH)D concentrations and the incidence of COVID-19 in these patients, who represented 2 age groups (similar to our main study).

Laboratory assays and data analysis

Blood samples were collected within 24 h after admission for routine laboratory tests, such as blood count, coagulation profile, and serum biochemical tests (including renal and liver function), in the on-site laboratory. Plasma D-dimer concentration was determined using an ACL TOP 700 automatic coagulation analyzer (Instrumentation Laboratory, CTS Family) on a latex-enhanced photometric immunoassay. The plasma fibrinogen concentration was measured according to a photo-optical Clauss method, with an ACL TOP 700 automatic coagulation analyzer (Instrumentation Laboratory, CTS Family). The serum concentrations of C-reactive protein (CRP) and of ferritin were processed by the immunoturbidimetric method using an Architect c800. The serum concentrations of procalcitonin, IL-6, and troponin were analyzed using an electrochemiluminescence method on a Cobas e411 analyzer (Roche Diagnostics). The serum concentrations of albumin and total bilirubin were measured using an automated colorimetric method on a Cobas 8000 (Roche Diagnostics), whereas the serum creatinine was measured by an enzymatic method with calibration traceable to a reference procedure (isotope dilution-MS) and automatized on a Cobas 8000. Hematology analyses, including blood count, were performed using the flow cytometry method on an ADVIA 2120i (Siemens Healthineers). Immune phenotyping was performed by flow cytometric analysis (ACEA Novocyte flow cytometer, ACEA Bioscience). The serum 25(OH)D concentrations were assessed by chemiluminescence immunoassay on an ARCHITECT i 2000 SR instrument (Abbott Laboratories). The laboratory reference range was 5.0–160.0 ng/mL. All measurements were conducted within 2 h after blood sampling.

Vitamin D status was categorized using cutoffs based on serum 25(OH)D concentrations: <10.0 ng/mL represented severe deficiency, 10.0–19.9 ng/mL represented a deficiency, 20.0–29.9 ng/mL represented insufficiency, and ≥30.0 ng/mL represented sufficient 25(OH)D concentrations (12).

Statistical analysis

The statistical analysis was carried out using SPSS for Mac version 19 (IBM). Continuous and categorical variables were presented as median (IQR) or n (%), as appropriate. A comparison of quantitative characteristics was performed using the Mann–Whitney U test. The χ^2 tests (2 × 2) or Fisher's exact test (if there were <10 observations) were performed to assess the significance of the differences between the characteristics according to the categorical variables. The optimal 25(OH)D cutoff was determined using the receiver operator characteristic (ROC) curve. The strength of the association between the serum 25(OH)D concentration and the outcome was defined using the OR. The outcomes were compared using Kaplan–Meier survival analysis. A P value <0.05 was considered statistically significant.

Results

Forty patients [61 (52.5–80) y, 50% male] were enrolled in the present study (Table 1). All 40 patients had low serum 25(OH)D concentrations during admission to the ICU [12 (9–15) ng/mL]. The BMI was 27.7 (23–31) kg/m². The all-cause 60-d mortality rate was 45%. The serum 25(OH)D concentration was greater in survivors [13.3 (10.0–17.1) ng/mL; n = 22] than in nonsurvivors [9.6 (7.9–14.2) ng/mL; n = 18], P = 0.044 (Mann–Whitney test).

The area under the ROC curve was 0.69 (95% CI: 0.52, 0.86; P = 0.044). The cutoff value for the 25(OH)D concentration was 9.9 ng/mL. The predictive accuracy of mortality in patients with serum 25(OH)D concentrations <9.9 ng/mL had a sensitivity of 82% and a specificity of 56% (Figure 1).

These 2 groups [patients with serum 25(OH)D concentrations >9.9 and <9.9 ng/mL] had significantly different ages (P = 0.018), ratios of neutrophils to lymphocytes (P = 0.017), and D-dimer concentrations (P = 0.05).

Our data indicate that fewer NKT cells were found in the circulation in critically ill COVID-19 patients, and the NKT cell count was 67% less in the group of patients having serum 25(OH)D concentrations <9.9 ng/mL (P = 0.019). There were no between-group differences in other routine laboratory tests, including those for white blood cell count, neutrophils, lymphocytes, platelets, NK cells, albumin, total bilirubin, creatinine, troponin, ferritin, IL-6, procalcitonin, CRP, and fibrinogen (Table 1).

The durations of stay in the ICU [9 (2–22) d compared with 13 (5–17) d; P = 0.66] and hospital stay [16 (11–25) d compared with 14 (8–19) d; P = 0.14] did not significantly differ between the groups.

Kaplan–Meier survival curves for the 25(OH)D concentrations on admission to the ICU showed that the 60-d mortality rate was greater in those with serum 25(OH)D concentrations ≤9.9 ng/mL (n = 14, 71%) than in those with concentrations >9.9 ng/mL (n = 26, 31%) (P = 0.065) (Figure 2). Patients with serum 25(OH)D concentrations ≤9.9 ng/mL had a 5.6-fold higher risk of death than those with concentrations >9.9 ng/mL (OR: 5.63; 95% CI: 1.35, 23.45; P = 0.018).

The serum 25(OH)D concentrations of the COVID-19 outpatients and non-COVID-19 outpatients and the main outcomes are summarized in the Supplemental data. Among the 25 COVID-19 outpatients, 8 (32%) had an insufficiency and

TABLE 1 Characteristics of the COVID-19 patients admitted to the ICU[1]

	Total (n = 40)	25(OH)D > 9.9 ng/mL subgroup (n = 26)	25(OH)D ≤ 9.9 ng/mL subgroup (n = 14)	P value[2]
Age, y	61 [52.5–80]	56.5 [51–69]	76.5 [61–89]	0.018
Sex, male	20 (50)	13 (50)	7 (50)	0.87
BMI, kg/m^2	27.7 (23.1–31.3)	28.4 (23.0–31.6)	26.8 (23.4–29.0)	0.22
25(OH)D, ng/mL (N 30–80 ng/mL)	12.0 [8.7–15.0]	14.0 [12.1–18.8]	7.7 [5.2–8.6]	0.044
Routine tests				
White blood cell count, 10^9/L (N 4.5–9 10^9/L)	7.4 [6.1–9.6]	7.1 [5.6–8.9]	8.7 [6.4–16.0]	0.18
Neutrophils, 10^9/L (N 2–7.5 10^9/L)	6.4 [4.4–8.7]	6.1 [4.3–7.6]	7.6 [5.6–11.4]	0.14
Lymphocytes, 10^9/L (N 1.5–4.5 10^9/L)	0.9 [0.5–1.1]	1.0 [0.6–1.2]	0.7 [0.4–1.0]	0.06
NLR (N 0.78–3.53)	7.9 [5.0–13.9]	6.7 [4.7–10.5]	12.9 [7.8–20.6]	0.017
NKT cells (CD3+CD56+CD16+), % (N < 10)	0.6 [0.3–1.1]	1.5 [0.8–2.8]	0.5 [0.2–0.9]	0.019
NK cells (CD3-CD56+CD16+), % (N 9.9–22.0)	1.3 [0.9–2.6]	1.8 [0.9–2.6]	1.2 [0.9–3.5]	0.42
Platelets, 10^9/L (N 150–380 10^9/L)	209 [172–290]	197 [154–285]	230 [194–290]	0.25
Hemoglobin, g/L (N 120–170 g/L)	140 [121–150]	140 [130–158]	136 [112–147]	0.49
Albumin, g/L (N 35–50 g/L)	34 [32–37]	35 [33–37]	32 [26–35]	0.07
Creatinine, μM/L (N 53–97 μM/L)	81 [62–101]	86 [63–99]	70 [59–118]	0.69
Total bilirubin, μM/L (N 3.4–17.1 μM/L)	11.4 [9.3–15.0]	10.9 [9.0–13.5]	12.0 [9.2–18.6]	0.51
Troponin T, pg/mL (N <14 pg/mL)	13.0 [7.0–32.5]	10.6 [6.5–26.0]	21.0 [8.5–51.3]	0.26
Ferritin, μg/L (N 11–336 μg/L)	876 [375–1830]	1004 [486–2030]	409 [321–990]	0.09
IL-6, pg/mL (N <7 pg/mL)	85 [49.8–190]	85 [50–210]	88 [47–120]	0.65
D-dimer, μg/mL (N <0.5 μg/mL)	0.6 [0.4–1.8]	0.6 [0.3–1.8]	1.0 [0.6–2.2]	0.05
Fibrinogen, g/L (N 2–4 g/L)	5.2 [4.2–6.4]	4.9 [4.1–5.9]	5.9 [4.1–6.7]	0.27
Procalcitonin, ng/mL (N <0.05 ng/mL)	0.16 [0.06–0.30]	0.14 [0.05–0.30]	0.25 [0.10–0.65]	0.20
C-reactive protein, mg/L (N <5 mg/L)	141 [103–210]	126 [95–180]	183 [116–240]	0.23
Outcomes				
LOS ICU, d	11 [3–18]	9 [2–22]	13 [5–17]	0.66
Hospital stay, d	15 [10–22]	16 [11–25]	14 [8–19]	0.14
Nonsurvivors	18 (45)	8 (31)	10 (71)	0.044

[1] Values are median [IQR] for numerical data and n (%) for categorical data. ICU, intensive care unit; LOS, length of stay; N, reference range; NLR, ratio of neutrophils to lymphocytes; 25(OH)D, serum 25-hydroxyvitamin D.

[2] P values were calculated by Mann–Whitney U test, χ^2 test, or Fisher's exact test, as appropriate.

12 (48%) had a deficiency of 25(OH)D. No differences between the serum 25(OH)D concentrations were observed according to age group (P = 0.24). None of the patients were hospitalized for COVID-19 (**Supplemental Table 1**).

The prevalence of vitamin D insufficiency and deficiency among non-COVID-19 (n = 31) outpatients was 6 (19%) and 10 (32%), respectively. There were no intergroup (young compared with old) differences for any of the outcomes, including the rate of hospitalization due to COVID-19 progression and the incidence of COVID-19 (**Supplemental Table 2**). There were no differences between the serum 25(OH)D concentrations of the groups of patients with (n = 19) and without (n = 31) COVID-19 (P = 0.94) (**Supplemental Table 3**). The serum 25(OH)D concentrations of the COVID-19 and non-COVID-19 outpatients were significantly higher than those of the COVID-19 patients admitted to the ICU [22.5 (13.8–32.5) ng/mL and 12.0 (8.7–15.0) ng/mL, respectively; P < 0.001].

Discussion

The main findings of this study were that ICU patients with COVID-19 had deficient serum 25(OH)D concentrations and that a serum 25(OH)D concentration at admission ≤9.9 ng/mL was predictive of in-hospital mortality.

25(OH)D deficiency is common in critical illness with prevalence ranging from 40% to 70% (13). In critically ill patients, a precipitous decline in 25(OH)D concentration was reported to occur owing to compromised 25(OH)D metabolism, downregulation of vitamin D–binding protein and albumin, as well as owing to attenuated 25(OH)D conversion to 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] in the kidneys (7, 14). High-volume fluid infusion therapy in critically ill patients may similarly result in lowering of 25(OH)D and vitamin D–binding protein (15).

Vitamin D deficiency did not appear to be common in similar COVID-19 outpatients and non-COVID-19 outpatients. The serum 25(OH)D concentrations in COVID-19 and non-COVID-19 outpatients were significantly higher than the serum 25(OH)D concentrations in COVID-19 patients admitted to the ICU. It seems that COVID-19 can be a factor of the low serum 25(OH)D.

In our study, the patients with serum 25(OH)D concentrations ≤ 9.9 ng/mL were older. This is consistent with the well-known fact that older adult patients tend to have severe vitamin D deficiency. This occurs owing to the age-related downregulation of expression of vitamin D receptors, the decrease in 1,25(OH)$_2$D production in the kidneys, the decrease in vitamin D production in the skin, dietary insufficiency of vitamin D precursors, and the disruption of calcium metabolism (16). Older age is a common risk factor for vitamin D deficiency and unfavorable outcomes of COVID-19 infection (4, 16). We conducted subgroup analyses based on age to reduce possible confounding by this variable. There were no inter-age-group differences in serum 25(OH)D concentrations between the COVID-19 outpatients and the non-COVID-19
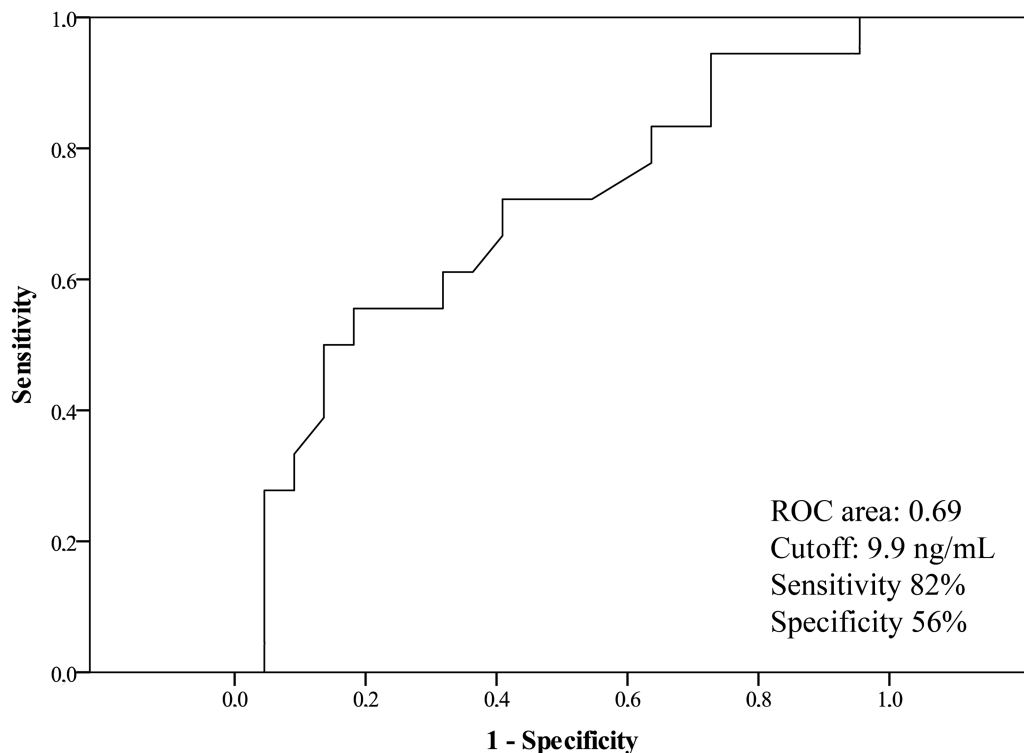
FIGURE 1 The ROC curve for serum 25(OH)D concentrations as a predictor of mortality risk in COVID-19 patients in the intensive care unit. The area under the ROC curve was 0.69 (95% CI: 0.52, 0.86; $P = 0.044$). The optimum cutoff value for 25(OH)D concentration was 9.9 ng/mL. The predictive accuracy of mortality in patients with 25(OH)D concentrations $\leq$ 9.9 ng/mL had a sensitivity of 82% and a specificity of 56%. ROC, receiver operator characteristic; 25(OH)D, 25-hydroxyvitamin D.

outpatients in the study. Furthermore, we did not reveal the relations between serum 25(OH)D concentrations and COVID-19 progression among COVID-19-positive outpatients and the incidence of COVID-19 in the general population. A larger cohort of COVID-19 patients is required to study the correlation between vitamin D deficiency, hospitalization, and mortality.

Several pathways are affected by vitamin D, and supplementation with vitamin D may reduce the risk of infection and death. Recent studies focused on the role of vitamin D in reducing morbidity due to acute upper respiratory tract infections and uncovered that it affected both cellular and humoral immunity, induced the expression of vitamin D–dependent antimicrobial peptides, and boosted antioxidant production (17, 18). Several studies have also demonstrated that vitamin D deficiency is associated with influenza, respiratory syncytial virus, and tuberculosis infections (19, 20).

Recently, several cytokines have been demonstrated to be associated with severe disease progression in COVID-19 patients (5, 21). Vitamin D is known to display potent immunomodulating activity, and it may affect pro- and anti-inflammatory cytokines. It inhibits monocyte production of proinflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, and TNFα (22). It may also downregulate the production of other proinflammatory cytokines, such as IL-17 and IL-21, and enhance the secretion of anti-inflammatory IL-10 (23). Several studies have demonstrated that vitamin D supplementation may reduce the severity of cytokine release syndrome in the context of flu and Crimean-Congo hemorrhagic fever (24, 25). Silberstein (26) hypothesized that vitamin D deficiency may underlie the variation in the severities of COVID-19, and that

treatment with vitamin D may offer a simpler alternative to tocilizumab.

Our data are consistent with the data of Shojaei et al. (27). The incidence of vitamin D deficiency in septic patients presenting to the emergency department was 60.2%. Age ($R = -0.261$, $P = 0.037$) and mortality ($R = -0.426$, $P = 0.025$) were significantly correlated with low serum 25(OH)D concentrations. The area under the ROC curve of serum 25(OH)D concentration and 1-mo mortality in their analysis was 0.701 (95% CI: 0.439, 0.964). In a meta-analysis including 1736 patients with sepsis, low 25(OH)D on admission was reported to be independently associated with increased mortality (28).

There are several protective mechanisms for vitamin D in the context of sepsis. First, 1,25(OH)$_2$D increases the expression of tight junction proteins. This strengthens the epithelial barrier (29) and prevents capillary leakage (30); both capillary leakage and a weak epithelial barrier are the hallmarks of sepsis. Second, this acts via the boosted expression of vitamin D–dependent antimicrobial peptides (cathelicidin and defensin) which, in turn, suppresses the growth of Gram-positive and Gram-negative bacteria, fungi, and enveloped and nonenveloped viruses. Thus, vitamin D may help dampen microbial load in patients with sepsis (31).

Vitamin D deficiency is prevalent in ARDS patients (32); furthermore, vitamin D deficiency is associated with increased risk of acute lung injury. The odds of ARDS in patients with 25(OH)D < 20 nmol/L were 3.5-fold those of patients with 25(OH)D $\geq$ 20 nmol/L (95% CI: 1.06, 11.6; $P = 0.040$) (33). Retrospective study of a cohort of 1985 critically ill patients identified an association of low prehospitalization
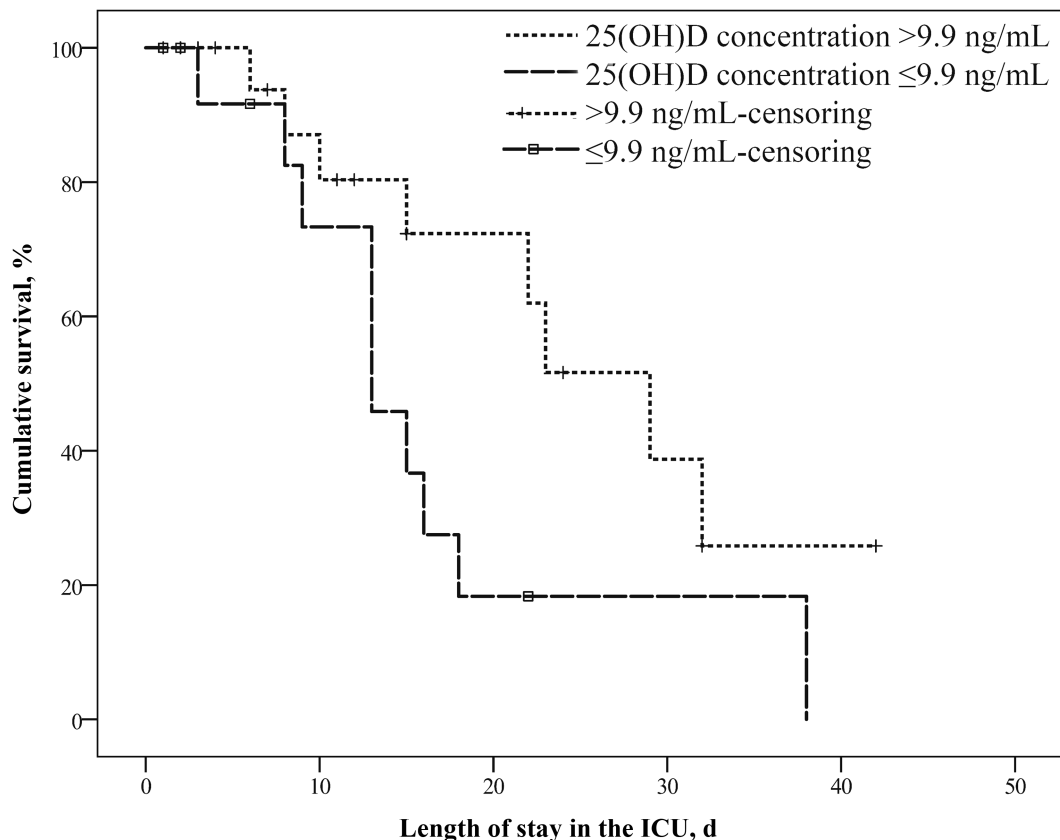
FIGURE 2 Survival curves for COVID-19 patients admitted to the ICU with serum 25(OH)D concentrations > 9.9 and ≤9.9 ng/mL. The Kaplan–Meier survival curve showed that the 60-d mortality rate of those with 25(OH)D concentrations ≤ 9.9 ng/mL ($n = 14$, 71%) tended to be greater than that of those with concentrations > 9.9 ng/mL ($n = 26$, 31%) ($P = 0.065$). ICU, intensive care unit; 25(OH)D, 25-hydroxyvitamin D.

concentrations of vitamin D with progression to acute respiratory failure (34).

Several animal studies have indicated that vitamin D demonstrates protective activity in ARDS. Kong et al. (35) reported that vitamin D reduces the severity of LPS-induced lung injury. Similarly, Xu et al. (36) demonstrated that vitamin D may help protect from acute lung injury by modulating expression of the renin–angiotensin system, including that of angiotensin-converting enzyme 2 (ACE-2), renin, and angiotensin II. Vitamin D is a well-known player in the renin–angiotensin system (37), and ACE-2 is the major cell entry receptor of SARS-CoV-2. Vitamin D deficiency is accompanied with the activation of the renin–angiotensin system, yet its permanent activation is associated with progression of chronic cardiovascular diseases and lung fibrosis (33).

Vitamin D deficiency is also associated with a number of other diseases that are known risk factors for a severe course and unfavorable outcomes in COVID-19 patients. Low concentration of vitamin D may lead to obesity and insulin resistance (38), and in elderly patients it contributes to insulinemia and glucose intolerance (39). Multiple studies support an association between vitamin D concentrations and heart failure, as well as outcomes in this patient cohort (40, 41).

Low vitamin D concentration was associated with a higher risk of thrombotic complications (42), which are very frequent (≤16.7%) among COVID-19 patients despite the anticoagulation therapy (43). Vitamin D directly controls the expression of >200 target genes (44), many of which may contribute to hypercoagulopathy. The present study has uncovered the association between severe vitamin D deficiency and increased D-dimer concentration.

According to numerous publications, vitamin D modulates immune cells and stimulates immune tolerance (45, 46). In this study, we paid attention to the immune status of patients with severe courses. NK cell concentrations in the peripheral blood inversely correlated with disease severity (47). In patients with moderate and severe COVID-19, lower concentrations of circulating NK cells were observed, and their functions were inhibited (47). During the early stages of COVID-19, NK-cell activation across distinct subsets was elevated in the peripheral blood, mirroring the activation signature of NK cells in the bronchoalveolar lavage fluid of patients with COVID-19. With a severe course of the disease, a sharp decrease in NK cells in the blood was observed. Further research is needed to determine the protective antiviral and the deleterious pathological roles of NK cells in COVID-19 patients (48). Another study demonstrated that in SARS-CoV-2 infection, the NK cells significantly reduced; however, the cells were strongly activated, and this activation correlated with the development of severe disease (49). Our data also indicate that fewer NKT cells were found in the circulation in critically ill COVID-19 patients with serum 25(OH)D concentrations ≤ 9.9 ng/mL. The good effects of vitamin D on protective immunity are due to its effects on the innate immune system. Lee et al. (45) reported that NK cell cytotoxicity and the counts of CD3− NK1.1+ cells were reduced in mice lacking 25(OH)D-upregulated protein 1. With in vitro treatment with 1,25(OH)₂D, enhanced lytic activity of NK cells has been observed against target tumor cells (46). Nonetheless, data that describe the opposite effects, namely the

negative regulation of NK cell activity and cell differentiation by vitamin D, are available (50). A larger cohort of COVID-19 patients is required to study the correlation between vitamin D deficiency and NK lymphopenia and activation.

Our study has several limitations. First, it is a small single-center study. Second, the low serum 25(OH)D concentration may have been influenced by seasonality, because the study was performed in April after a long period of limited sun exposure. Third, despite the observed prognostic potential of the serum 25(OH)D concentration, the effect of adding vitamin D to the therapy of this group of patients, especially the potential increase in therapeutic efficacy, is yet to be established.

In conclusion, we found that the ICU patients had a low serum 25(OH)D concentration on admission. Serum 25(OH)D concentrations ≤ 9.9 ng/mL on admission can be used to predict in-hospital mortality in patients with COVID-19 infection. An intervention study is warranted to elucidate the usefulness of vitamin D supplementation for the treatment and/or prevention of COVID-19.

Acknowledgments

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