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The association between vitamin D level and ICU mortality in COVID-19 patients: a single center survey

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ABSTRACT

Aim: Vitamin D, an immune modulator, may contribute COVID-19 infection. This study aims to assess the relationship between vitamin D value and clinical outcomes (need for mechanical ventilation (MV) support and intensive care unit (ICU) mortality) in critically ill patients diagnosed with COVID-19.

Material and Method: This study included critically ill adult patients diagnosed with COVID-19 infection. Serum vitamin D level was analyzed using liquid chromatography mass spectrometry. Vitamin D concentration was classified as normal (≥20 ng/mL) and deficiency (<20 ng/mL). The association between serum vitamin D value and the need for MV treatment and ICU mortality was analyzed by logistic regression model.

Results: Ninety-six critically adult COVID-19 patients with were recruited. The mean age of patients was 68.8±12.6 years. The mean APACHE II score of participants was 14.5±6.7. A total of 69.8% of participants had vitamin D deficiency. Patients with deficiency of vitamin D had significantly higher procalcitonin, BUN and creatinine concentrations than patients with normal vitamin D value (p=0.031, p=0.003, and p=0.001, respectively). Serum vitamin D level was negatively weak correlated with SOFA score (Rho=-0.238, p=0.020), serum creatinine (Rho=-0.299, p=0.003) and troponin levels (Rho=-0.330, p=0.004). Serum vitamin D value was not significantly associated with the need for MV support and ICU mortality (p>0.05).

Conclusion: Approximately 70% of our study sample has below the normal range of serum vitamin D value. Low serum vitamin D concentrations were associated with increased SOFA, creatinine, and troponin concentrations in patients with COVID-19 infection. Vitamin D deficiency was not a predictor of need for MV support and ICU mortality in COVID-19 patients.

Keywords: COVID-19, vitamin D, intensive care unit, mortality

INTRODUCTION

COVID-19, a global clinical viral disease, can progress to critical illness and acute respiratory failure, increasing the likelihood for ICU admission and the possibility of subsequent mortality (1–3).Vitamin D acts as an immune modulator through several mechanisms, including modulation of cytokine release, neutrophil activity, ACE-2 receptors, and pulmonary barrier function (4,5).Vitamin D has also been cited as having a possible impact concerning the treatment as well as the prevention of COVID-19 infection (6–9). Achieving normal vitamin D status has become a significant clinical goal in COVID-19 patients, based on the preliminary evidence of ICU admission, more extended ICU stay, and the mortality rate. Research suggests that a deficiency in vitamin D levels leads to worse outcomes in COVID-19 patients than in those with levels reported as average (10–13).Given the inconclusive clinical evidence, further primary studies would be apposite in clarifying how vitamin D status affects disease severity and mortality in COVID-19 patients (4–6,14).

This study aims to determine the relationship between vitamin D status and poor clinical outcomes (need for mechanical ventilation (MV) support and mortality) in critically ill patients receiving ICU treatment for COVID-19.

MATERIAL AND METHOD

The study was carried out with the permission of Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 15.04.2021; Decision No: 2021/370). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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This study was made retrospectively in a single-center ICU between August 2020 and January 2021. The inclusion criteria of the current study were as follows:

1. ≥18 years of age,
2. Diagnosed with COVID-19 (positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test and thorax CT consistent with COVID-19 infection),
3. Presence of acute respiratory distress syndrome (ARDS) (15),
4. ≥48 hours expect ICU stay.

Pregnant women, patients with rickets and osteomalacia were excluded.

Data were collected from patients' medical record. At ICU admission, demographic characteristics, symptoms related to COVID-19 on ICU admission, presence of comorbidity, the severity of illness scores (Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Glasgow Coma Scale (GCS), Charlson Comorbidity Index), need for Mechanical Ventilation (MV) support (Invasive) were recorded.

Troponin, C-reactive protein (CRP), procalcitonin, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), ferritin, D-dimer, PaO_2/FiO_2 ratio, lactate, leukocyte, neutrophil count, lymphocyte count, platelet count of patients was recorded. In addition, the length of ICU/hospital stay, and ICU mortality were noted.

Vitamin D Measurement

The concentrations of vitamin D of the participants were obtained from their medical records. Liquid Chromatography Mass Spectrometry (LC-MS/MS) (SCIEX Model 4500 Q TRAP) was utilized to determine 25(OH)D levels at the ICU admission.

According to vitamin D levels, we classified two groups: normal (Vit D ≥20 ng/mL) and deficiency (Vit D <20 ng/mL).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY). Continuous variables were presented as mean±SD or median (interquartile range, IQR) based on normality distribution. Categorical variables were shown as numbers (%). The difference between categorical variables was analyzed using the Chi-square test. The difference between continuous variables was analyzed with the two independent sample t test. Vitamin D level correlation with other parameters was analyzed using Spearman correlation analysis. The association between vitamin D levels and the need for MV and ICU mortality was assessed using logistic regression analysis adjusted with potential confounders (age and gender). A p-value <0.05 was accepted as statistically significant.

RESULTS

This study included 96 critically ill patients with respiratory failure related to COVID-19 infection in ICU. The mean age of the study sample was 68.8±12.6 years, and 52.1% of the cohorts were male. The mean APACHE II score was 14.5±6.7, and SOFA score was 5.5±2.2 at ICU admission. The most common reason for ICU admission was dyspnea (75.0%). In addition, the most common comorbidities of patients were hypertension (53.1%) and diabetes mellitus (39.7%). **Table 1** shows the patients' demographic and clinical characteristics.

MV support was required in 42.7% of patients. The median length of ICU stay was 10 (6.3-15) days, and the median length of hospital stay was 16 (11-26.5) days. The mortality rate of the participants was 57.3% in ICU (**Table 1**).

A total of 67 (69.8%) patients had vitamin D deficiency (<20 ng/mL). There was no statistically significant difference between groups in terms of age, symptoms on admission, and severity of illness (APACHE II score, SOFA score, GCS, Charlson comorbidity index) (p>0.05 for all). Approximately half of both groups treated with MV support. Patients with deficiency of vitamin D had similar length of ICU and hospital stay to patients with normal vitamin D status (p=0.606 and p=0.903, respectively).

Furthermore, the ICU mortality rates of the patients with deficiency of vitamin D and normal vitamin D status were 56.4%and 46.3%. The ICU mortality rate was similar between two groups (p=0.534) (**Table 1**).

As shown in **Table 2**, patients with deficiency of vitamin D had significantly higher procalcitonin than patients with average vitamin D value (median: 0.35 vs median: 0.15, p=0.031).Compared to patients with normal vitamin D values, patients with deficiency of vitamin D had significantly higher serum BUN (median: 33.0 (24.0-53.0) vs 24.0 (18.0-27.5), p=0.003) and creatinine value (1.2 (0.9-1.9) vs. 0.8 (0.7-1.1) ng/mL, p=0.001). There was no significant difference in serum CRP level and WBC count according to vitamin D classification (p>0.05 for all) (**Table 2**).

There was negatively weak-correlation between vitamin D levels and SOFA score (Rho=-0.238, p=0.020), serum creatinine (Rho=-0.299, p=0.003), and troponin (Rho=-0.330, p=0.004) levels (**Table 3** and **Figure 1**).

Table 1. Patient demographic and clinical parameters

	Total (n=96)	Normal Vitamin D (n=29)	Vitamin D Deficiency (n=67)	p value
Age (year), ±SD	68.8±12.6	68.6±13.46	68.9±12.31	0.925
Gender, n (%)				
Male	50 (52.1)	13 (26.0)	37 (74.0)	0.238
Female	46 (47.9)	32 (69.6)	14 (30.4)	
BMI (kg/m²), ±SD	27.9±4.5	28.3±4.33	27.8±4.53	0.600
Active smoking, n (%)	51 (53.1)	32 (62.7)	19 (37.3)	0.058
Comorbidity, n%)				
Hypertension	51 (53.1)	23 (45.1)	28 (54.9)	0.484
Diabetes mellitus	38 (39.6)	18 (47.4)	20 (52.6)	0.260
CAD	17 (17.7)	6 (35.3)	11 (64.7)	0.509
Asthma	14 (14.6)	7 (50.0)	7 (50.0)	0.423
COPD	11 (11.5)	3 (27.3)	8 (72.7)	0.105
Symptoms on admission, n (%)				
Dyspnea	72 (75.0)	32 (44.4)	40 (55.6)	0.521
Cough	14 (14.6)	5 (35.7)	9 (64.3)	0.160
Weakness	14 (14.6)	4 (28.6)	10 (71.4)	0.627
Fever	12 (12.5)	5 (41.7)	7 (58.3)	0.674
Myalgia	8 (8.3)	3 (37.5)	5 (62.5)	0.738
Indigestion	8 (8.3)	3 (37.5)	5 (62.5)	0.255
Severity of illness scores, ±SD				
APACHE II	14.5±6.7	13.1±7.0	15.1±4.5	0.176
SOFA	5.5±2.2	4.9±2.2	5.7±2.2	0.092
GCS	13.1±3.5	13.4±3.1	13.0±3.7	0.642
Charlson comorbidity index	4.2±2.0	3.9±1.9	4.3±2.0	0.345
MV support, n (%)	41 (42.7)	20 (48.8)	21 (51.2)	0.782
Length of stay, median (min-max)				
At ICU	10.0 (6.3-15.0)	10.0 (7.0-16.0)	10.0 (6.0-15.0)	0.606
In hospital	16.0 (11.0-26.5)	15.0 (9.5-28.0)	16.0 (11.0-24.0)	0.903
Mortality, n (%)				
ICU mortality	55 (57.3)	31 (56.4)	24 (43.6)	0.534
Hospital mortality	57 (59.4)	31 (54.4)	26 (45.6)	0.724

ICU: Intensive care unit, MV: Mechanical ventilation.

Table 2. Laboratory findings according to vitamin D status

	Total (n=96)	Normal Vitamin D (n=29)	Vitamin D Deficiency (n=67)	p value
Troponin (ng/mL)	23.0 (12.3-49.2)	17.5 (10.7-35.1)	27.4 (15.1-56.9)	0.094
CRP (mg/L)	110.7 (59.4-183.9)	88.0 (58.0-179.4)	125.0 (60.4-192.0)	0.346
Procalcitonin (µg/L)	0.29 (0.13-0.85)	0.15 (0.11-0.40)	0.35 (0.15-0.97)	0.031
BUN (mg/dL)	28.0 (21.0-46.0)	24.0 (18.0-27.5)	33.0 (24.0-53.0)	0.003
Creatinine (mg/dL)	1.0 (0.8-1.6)	0.8 (0.7-1.1)	1.2 (0.9-1.9)	0.001
LDH (U/L)	485.5 (373.5-619.0)	535.0 (387.0-620.5)	467.5 (370.8-620.3)	0.500
AST (IU/L)	39.0 (27.3-54.8)	41.0 (27.0-67.0)	38.0 (28.0-51.0)	0.336
Ferritin (µg/L)	742.0 (394.0-1589.0)	853.0 (482.0-1245.5)	716.5 (344.8-1847.5)	0.777
D-dimer (µg/L)	1604.5 (905.0-3604.8)	1630.0 (821.0-3501.5)	1579.0 (924.0-3652.0)	0.612
PaO_2/FiO_2	87.3 (70.3-158.3)	93.0 (68.0-167.0)	86.0 (71.0-143.0)	0.747
Lactate (mmol/L)	1.8 (1.4-2.6)	1.5 (1.3-2.6)	1.9 (1.4-2.6)	0.482
WBC (10^9/L)	11.3 (8.3-14.0)	12.7 (9.2-15.2)	11.2 (7.7-13.6)	0.298
Neutrophil (10^9/L)	10.0 (7.1-12.9)	10.7 (8.4-13.4)	9.8 (6.5-12.4)	0.307
Lymphocyte (10^9/L)	0.67 (0.47-0.97)	0.67 (0.51-0.83)	0.67 (0.45-0.98)	0.971
Platelet (10^9/L)	233.0 (169.3-300.3)	255.0 (174.0-329.0)	225.0 (157.0-283.0)	0.171

CRP: C-reactive protein; BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase; WBC: white blood cell, All data presented as median (IQR)

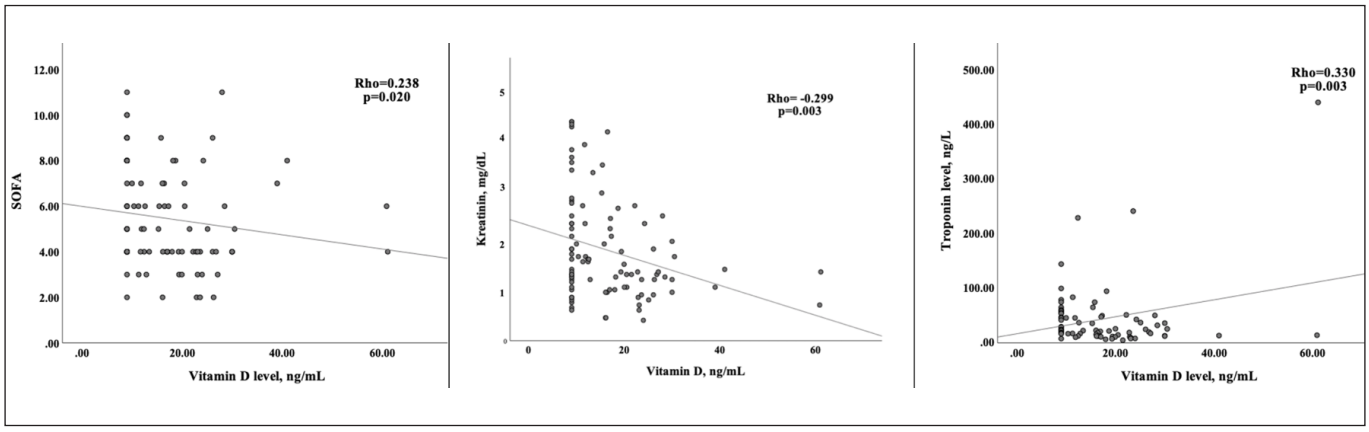

Figure 1. Correlation of vitamin D levels with SOFA score and serum creatinine and troponin levels

There was no statistically significant correlation between PaO_2/FiO_2 ratio and vitamin D level at baseline of the study (Rho= 0.008, p=0.940). Serum vitamin D levels were also not correlated with other severity of illness scores (APACHE II, GCS) and other laboratory findings (**Table 3**).

Table 3. Correlation of vitamin D levels with severity of illness scores and laboratory parameters

Variables	Vitamin D level	
	rho	p value
SOFA	-0.238	0.020
Charlson comorbidity index	-0.010	0.924
GCS	0.127	0.218
Troponin	-0.330	0.004
CRP	-0.140	0.174
Procalcitonin	-0.159	0.121
BUN	-0.177	0.085
Creatinine	-0.299	0.003
LDH	0.107	0.306
Ferritin	0.082	0.430
Ddimer	-0.105	0.308
PaO_2/FiO_2	0.008	0.940
Lactate	-0.060	0.561
Neutrophil	-0.058	0.572
Lymphocyte	-0.075	0.470

GCS: Glasgow Coma scale; CRP: C-reactive protein; BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase, r: correlation coefficient, Pearson correlation analysis

The results of the logistic regression analysis showed that the impact of vitamin D level on the need for MV support or mortality risk was not statistically significant, even after adjusting for age and gender (p>0.05 for both). In addition, there was no association between deficiency of vitamin D (<20 ng/mL) and both needs for MV support and ICU mortality (p>0.05). After adjusting for confounding variables (age and gender), vitamin D status was not associated with both needs for MV support and ICU mortality (p>0.05)(**Table 4**).

Table 4. Logistic regression analysis for vitamin D levels in predicting need for MV support and ICU mortality

	Need for MV support		ICU Mortality	
	OR (95% CI)	p value	OR (95% CI)	p value
Model 1				
Vit D, ng/mL	1.042 (0.972-1.118)	0.243	0.980 (0.914-1.051)	0.573
Vit D<20 ng/mL	1.770 (0.417-7.506)	0.438	0.950 (0.224-4.041)	0.945
Model 2				
Vit D, ng/mL	1.028 (0.960-1.100)	0.427	0.999 (0.931-1.071)	0.967
Vit D < 20 ng/mL	1.269 (0.293-5.501)	0.751	1.422 (0.312-6.475)	0.649

Model 2 adjusted for age and gender, MV: Mechanical ventilation; OR: Odds ratio; CI: Confidence interval

DISCUSSION

The findings revealed patients with a deficiency of 69.8% in our study sample. The vitamin D levels were negatively correlated with SOFA score, serum creatinine, and troponin levels. The level of vitamin D status of COVID-19 patients was not associated with the need for MV treatment and mortality.

Approximately 70% of our study sample had vitamin D deficiency. Bassatne et al. (14) performed a systematic review of 31 observational studies in 18724 patients with COVID-19 infection. It was suggested that 13-82% of COVID-19 patients had vitamin D deficiency. Karahan et al. (16) conducted a retrospective cohort study investigating relationship between vitamin D status and mortality in 149 COVID-19 patients in our country. Similar to our study, vitamin D deficiency was considered as Vit D <20 ng/mL. It was found that 69.1% of study participants had vitamin D deficiency in consistent with our results.

In our study sample, patients with vitamin D deficiency had significantly higher procalcitonin, BUN and creatinine value compared to patients with normal

vitamin D status. In addition, there is a correlation between serum vitamin D levels and serum BUN, creatinine, and troponin in ourpatients. A meta-analysis of 3637 COVID patients by Mohamed Ben-Eltriki et al. (17) indicated that patients with low vitamin D levels had higher troponin levels compared to the patients with average vitamin D levels. Similarly, Tarek M Yosef et al. (18) reported a negative correlation between vitamin D levels and serum BUN, creatinine in a case-control study involving 80 COVID-19 patients. According to a retrospective study of 71 COVID-19 patients, found a significant association between low vitamin D levels (<20 ng/ml) and increased troponin value (19). Similar to our results, Quintana et al. (20) reported that there was relationship between low vitamin D status and higher procalcitonin level in critically ill patients with COVID-19.

A total of 42.7% of study participants were treated with MV support. The mortality rate was 57.3% of the study participants. In our study, serum vitamin D level was not associated with the need for MV treatment and ICU mortality. A retrospective study with 270 patients with COVID-19 revealed that vitamin D levels were <20 ng/mLin 35.2% of patients, along with the need for MV (21.9%), ICU stay (32.2%) and mortality (26.7%) in almost one-third of the patients. Similarly, there was no significant correlation between vitamin D status and mortality, need for MV, or ICU admission in COVID-19 patients (8). Notably, in a meta-analysis of 20 clinical studies in 12.806 COVID-19 patients, low vs. high vitamin D serum levels were reported as having similar mortality rates, ICU admission rate, ventilator support requirement, and length of ICU stay (9). A retrospective multicenter study of 197 patients with COVID-19 revealed that 73.10% of the patients had deficiency levels of vitamin D compatible with our data (21). Multivariate analysis adjusted for demographics and comorbidities showed that the correlation between vitamin D status and COVID-19 severity parameters, including MV support and mortality, was not statistically significant. We think that mortality in patients with COVID-19 infection may be due presence of cerebrovascular disease, thromboembolic events, etc. Contrary to our study findings and the above-mentioned studies, several studies suggest that the vitamin D deficiency has a significant effect on hospital admission, ICU admission, or mortality in patients diagnosed with COVID-19 (10,13,22,23).A meta-analysis of 17 observational studies involving 2756 patients suggests a significant relationship between vitamin D deficiency and higher mortality rates (OR 2.47) compared to patients with normal vitamin D status(10).

Study Limitations

There are several limitations of the study. The study was designed as cross-sectionally and did not include a few time points in ICU. Our study sample was small. A prospective observational study design may improve reliable observation of clinical outcomes of critically ill patients with COVID-19 infection. The retrospective single-center design of this study can be regarded as a notable limitation that prevents generalizing our findings to the overall ICU-hospitalized COVID-19 population. Several studies revealed a correlation between vitamin D supplementation and poor clinical outcomes in COVID-19 patients (11,24). However, we did not follow the vitamin D supplementation of patients.

CONCLUSION

The findings of this study revealed that about 3/4 of patients hospitalized in the ICU diagnosed with COVID-19 had below average range vitamin D status. Moreover, serum vitamin D concentration was related to increased SOFA score, serum creatinine, and serum troponin value. Nonetheless, vitamin D status was not associated with the need for MV treatment and ICU mortality. Randomized controlled studies with long-term study periods involving vitamin D supplementation are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 15.04.2021; Decision No: 2021/370).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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