Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1056650
J Health Sci Med 2022; 5(2): 457-461

Vitamin D levels and in-hospital mortality of COVID-19

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Cite this article as: Saygılı ES, Karakılıç E. Vitamin D levels and in-hospital mortality of COVID-19. J Health Sci Med 2022; 5(2): 457-461.

ABSTRACT

Introduction: Vitamin D deficiency may be linked to an increased susceptibility risk of COVID-19. However, the data on the link between vitamin D levels and COVID-19 related in-hospital mortality is debatable. This study investigated whether vitamin D levels are associated with intensive care unit (ICU) admission and COVID-19 related in-hospital mortality.

Material and Method: We conducted a retrospective study with hospitalized COVID-19 patients between March 2020 and March 2021. 25 OH Vitamin D (Vit-D) levels <12 ng/mL were accepted as Vit-D deficiency. The patients were evaluated in two groups as Vit-D deficient and Non-Vit-D deficient. Groups were matched 1:1 by propensity score matching (PSM) regarding age and gender.

Results: A total of 192 patients, 52.6% (101) of whom were female, with a median age of 71 (IQR:61-78), were included in the study. Before PSM analysis, the Vit-D deficient group patients were older, female predominant, have more mortality rates. After PSM, 122 cases (61 cases for each group) remained, and mortality between Vit-D groups was statistically similar (34% vs. 26%, p=0.32). In the univariate logistics regression analysis before PSM, Vit-D level was a significant for mortality (OR:0.972 CI:0.945-0.999, p=0.044); after PSM statistical significance was lost (OR:0.96 CI:0.934-1.005, p=0.087). ICU admission rates were similar between groups.

Conclusion: Although mortality was higher in the group with Vit-D deficiency in the first analysis, it lost its significance on mortality after adjusting groups for age and gender. There was no relationship between vitamin D deficiency and COVID-19 in-hospital mortality.

Keywords: Vitamin D, COVID-19, mortality, critical care, hospitalization

INTRODUCTION

The benefits of vitamin D on bone health are well known. However, many studies have been conducted on the extra-skeletal effects of vitamin D (1). Serum total 25-OH Vitamin D (Vit-D) is often used to determine an individual's vitamin D level. Vitamin D is a pluripotent hormone that regulates immunity. (2,3).

With its various roles, such as interfering with adaptive and cell-mediated immunity and increasing antioxidant-related gene expression, vitamin D has played an adjunct position in preventing and treating acute respiratory infections (4,5). It is thought to prevent the progression to Acute Respiratory Distress Syndrome (ARDS) in viral diseases due to suppression of cytokine storm (5,6).

Although there are data on susceptibility and decreasing the severity of viral infections, conflicting results have been obtained in studies evaluating the effect of Vit-D levels on COVID-19 outcomes (7–9). This study was conducted to assess the relationship between Vit-D level, intensive care unit (ICU) admission and COVID-19 related in-hospital mortality.

MATERIAL AND METHOD

The study was carried out with the permission of the Çanakkale Onsekiz Mart University Medical Faculty Ethics Committee (Date: 09.06.2021, Decision No: 06-05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 192 patients hospitalized in Çanakkale Onsekiz Mart University Hospital diagnosed with COVID-19 between March 2020-March 2021 and whose Vit-D levels were measured during hospitalization were retrospectively included in the study. The diagnosis of COVID-19 was made by PCR positivity and/or radiological findings. Patients under 18 years old and pregnant were excluded from the study.

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Received: 12.01.2022 **Accepted:** 23.01.2022

The patients' laboratory values and clinical results were obtained from the hospital records. Those with Vit-D levels <12 ng/mL (30 nmol/L) were accepted as Vit-D deficiency (10). The patients were evaluated in two groups: Vit-D deficient and Non-Vit-D deficient (Vit-D levels ≥12 ng/mL). Participants in the Vit-D deficient group were matched 1:1 by propensity score matching (PSM) method to individuals in the Vit-D levels ≥12 ng/mL group in terms of age and gender. Participants were eligible for matching if their propensity scores were on the same support with a caliper width of 0.2 (11).

Serum 25(OH) vitamin D level was measured using the electrochemiluminescence immunoassay method in Cobas e 600 autoanalyzer device (Roche Diagnostics, F. Hoffmann-La Roche Ltd Kaiseraugst, Switzerland).

The CKD-EPI equation was used to compute the estimated glomerular filtration rate (eGFR) (12). Acute renal failure (ARF) was diagnosed by KDIGO(Kidney Disease: Improving Global Outcomes) criteria(13). Chronic kidney disease (CKD) was defined as a decreased estimated glomerular filtration rate (eGFR: <60 mL/min/1.73 m²). An album corrected the calcium called corrected calcium.

Statistical Analysis

Continuous variables are presented as the median and interquartile range (IQR: the difference between the 25th and 75th percentiles). Numbers and percentages were used to express categorical variables. Mann Whitney U test was used to compare the difference between groups of continuous variables. To determine the significance of the difference between categorical variables, Pearson's chi-square was performed. The Odds ratios (OR) were calculated using a 95% confidence interval (95 % CI). Statistical analyzes were performed using SPSS Version 19 (IBM, Armonk, NY, USA). Statistical significance was defined as two-sided p values of less than 0.05.

RESULTS

A total of 192 patients, 52.6% (101) of whom were female, with a median age of 71 (IQR:61-78), were included in the study. The intensive care unit admission rate in the study group was 35.4% (68), and the in-hospital mortality rate was 27.6% (53). The median hospital stay of the patients was 11 days (IQR: 6-17), and the median Vit-D level was 13.4 ng/mL (IQR: 7.9-22.9).

Data analysis without PSM

Before PSM analysis, Vit-D deficient group consisted of 82 (43%), and the Non-Vit-D Deficient group consisted of 110 (57%) participants. The Vit-D deficient group patients were older, female predominant, have more mortality rates and longer hospitalization lengths than Non-Vit-D Deficient group. ICU admission rates were similar between groups (43% vs. 30%, p=0.069). Vit-D deficient group patients have higher CRP levels, lower lymphocyte count, higher neutrophil/ lymphocyte ratio, higher parathormone, lower GFR, lower albumin and total protein levels. Diabetes, chronic obstructive pulmonary disease, hypertension, coronary artery disease, hyperlipidemia and cerebrovascular diseases history were similar in both groups. However, a history of CKD (33% vs 16%, p= 0.029) and ARF (63% vs 43%, p= 0.029) were higher in the Vit-D deficient group. The characteristics of the Vit-D deficient group and the non-Vit-D deficient group are shown in **Table 1**.

Data analysis after PSM

After age and gender matching with the PSM method, 122 cases (61 cases for each group) remained. After PSM, the effect of the Vit-D group on mortality lost its statistical significance. ICU admission rates were similar between groups (43% vs. 31%, p=0.19). The Vit-D deficient group had a longer hospital stay and lower lymphocyte levels. CKD history was higher, and GFR values were lower in the Vit-D deficient group. However, the ARF ratio was similar in both groups. Other comorbidities were similarly distributed in both groups. The characteristics of the groups after PSM are shown in **Table 2**.

In-hospital Mortality Analysis According to Vit-D Level

When the groups' mortality was evaluated with the Kaplan-Meier analysis, no significant difference was observed (Before PSM Log Rank p=0.309; After PSM Log Rank p=0.529). In the univariate logistics regression analysis before PSM, Vit-D level was a significant factor in predicting mortality (Beta: -0.029, Odds Ratio: 0.972 CI: 0.945-0.999, p=0.044); after PSM statistical significance was lost (Beta: -0.032, Odds Ratio: 0.96 CI: 0.934-1.005, p=0.087). Mortality rates according to Vitamin D groups before and after PSM are given in **Figure 1**.

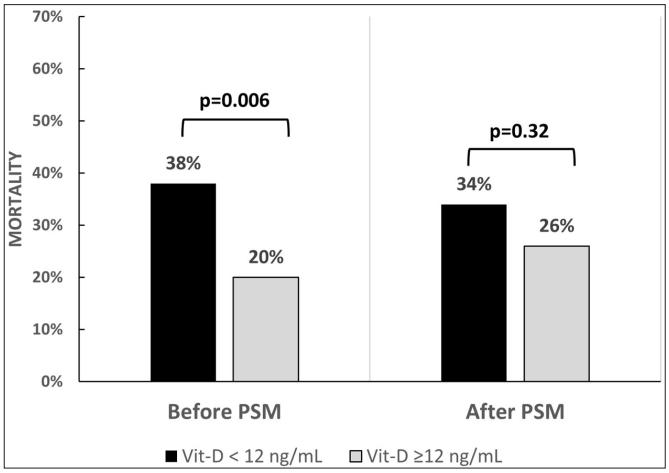

Figure 1. Mortality rates according to Vitamin D groups before and after PSM

Table 1. Comparison of groups with and without Vit-D deficiency before PSM

	Vit-D < 12 ng/mL n=82 (43%)	Vit-D ≥12 ng/mL n=110 (57%)	p
Female gender, n (%)	55 (67%)	46 (42%)	0.001
Age (years)	75 (67-81)	66 (59-76)	0.001
In-hospital mortality, n (%)	31 (38%)	22 (20%)	0.006
ICU Admission, n (%)	35 (43%)	33 (30%)	0.069
Length of hospitalization (days)	13 (8-18)	10 (6-16)	0.049
25 OH Vitamin D (ng/mL)	8 (5-10)	22 (15-31)	0.001
Serum glucose (mg/dl)	141 (104-166)	126 (103-165)	0.32
CRP (mg/dL)	5.1 (1.5-12.3)	1.7 (0.4-5.6)	0.002
Fibrinogen (mg/dl)	538 (427-647)	485 (393-784)	0.52
Procalcitonin (ng/ml)	0.35 (0.11-0.61)	0.11 (0.08-0.39)	0.23
White blood cell (10^3/Ul)	8.6 (5.8-12.2)	7.4 (5.8-9.9)	0.37
Lymphocyte (10^3/Ul)	0.70 (0.48-1.00)	1.03 (0.50-1.62)	0.004
Neutrophil (10^3/Ul)	7.4 (4.2-10.3)	6.1 (3.9-9.3)	0.30
Neutrophil/lymphocyte ratio	9 (5-17)	6 (3-14)	0.034
Parathormone (pg/ml)	224 (105-435)	118 (30-193)	0.032
eGFR (mL/dk/1.73m²)	32 (13-68)	75 (44-96)	0.001
Ionized calcium (mmol/l)	1.10 (1.04-1.17)	1.13 (1.06-1.21)	0.11
Albumin (g/dL)	2.86 (2.44-3.26)	3.38 (2.82-3.77)	0.001
Corrected calcium (mg/dL)	8.89 (8.49-9.36)	9.16 (8.62-9.43)	0.11
Phosphorus (mg/dl)	3.65 (2.96-5.23)	3.59 (3.00-4.24)	0.52
Total protein (g/dl)	5.61 (5.05-6.48)	6.10 (5.68-6.64)	0.014
Lactate dehydrogenase (U/l)	346 (253-463)	286 (224-379)	0.041
Uric acid (mg/dl)	5.70 (4.20-8.00)	5.20 (3.30-6.40)	0.024
Magnesium (mg/dL)	2.02 (1.63-2.32)	1.99 (1.79-2.18)	0.64

The numbers are given as the median (Interquartile Range). ICU: intensive care unit, eGFR: estimated glomerular filtration rate

Table 2. Comparison of groups with and without Vit-D deficiency after PSM

	Vit-D < 12 ng/mL N = 61 (50%)	Vit-D ≥12 ng/mL N = 61 (50%)	p
Female gender, n (%)	39 (64%)	39 (64%)	0.99
Age (years)	73 (64-79)	72 (65-78)	0.96
In-Hospital Mortality, n (%)	21 (34%)	16 (26%)	0.32
ICU Admission, n (%)	26 (43%)	19 (31%)	0.19
Length of hospitalization (days)	13 (8-19)	10 (5-15)	0.048
Serum Vitamin D (ng/mL)	7 (5-9)	23 (16-30)	<0.001
Serum glucose (mg/dl)	140 (110-165)	118 (104-163)	0.30
CRP (mg/dL)	5 (1-9)	3 (1-7)	0.19
Fibrinogen (mg/dl)	538 (431-612)	505 (422-763)	0.79
Procalcitonin (ng/ml)	0.18 (0.10-0.44)	0.16 (0.08-0.58)	0.98
White Blood Cell (10^3/uL)	8.5 (4.8-11.3)	7.2 (5.5-9.8)	0.70
Lymphocyte (10^3/uL)	0.70 (0.43-1.00)	1.00 (0.51-1.55)	0.015
Neutrophil (10^3/uL)	6.1 (4.8-9.7)	5.8 (3.5-9.1)	0.41
Neutrophil/lymphocyte ratio	9 (5-17)	5 (3-16)	0.087
Parathormone (pg/ml)	210 (79-428)	107 (48-181)	0.14
eGFR (mL/dk/1.73m²)	33 (14-71)	57 (31-89)	0.011
Ionized calcium (mmol/l)	1.11 (1.06-1.17)	1.10 (1.06-1.18)	0.90
Albumin (g/dL)	2.87 (2.52-3.29)	3.13 (2.54-3.71)	0.10
Corrected calcium (mg/dL)	8.83 (8.42-9.36)	9.00 (8.52-9.32)	0.50
Phosphorus (mg/dl)	3.64 (2.86-4.76)	3.51 (2.74-4.17)	0.50
Total protein (g/dl)	5.63 (5.06-6.60)	6.08 (5.68-6.55)	0.15
Lactate dehydrogenase (U/l)	325 (244-475)	287 (221-430)	0.29
Uric acid (mg/dl)	5.6 (4.1-7.9)	5.1 (3.2-6.7)	0.35
Magnesium (mg/dL)	1.98 (1.62-2.30)	1.82 (1.73-2.06)	0.37

The numbers are given as the median (Interquartile Range). ICU: intensive care unit, eGFR: estimated glomerular filtration rate

DISCUSSION

We found that mortality was higher in the Vit-D deficient group in the first evaluation before PSM. However, when the two groups were equalized by performing PSM in terms of age and gender, which are among the most significant markers of COVID-19 mortality, the mortality risk in the Vit-D deficient group lost its statistical significance. The true effect of Vit-D can be determined only after adjusting for crucial cofounders of mortality, such as age and gender. In this respect, PSM provides a more appropriate interpretation of the results (14).

The presence of vitamin D receptors (VDRs) and the activating enzyme 25-hydroxyvitamin D-1alpha-hydroxylase in immune cells partly explains vitamin D's immunological effects. Vitamin D, VDR and Retinoid X Receptor complex allow transcription of genes with antimicrobial activity such as cathelicidins and defensins (15). Because of the wide interindividual variation in gene expression in human cells in response to vitamin D treatment, some people may benefit more or less from it than others (3).

Low vitamin D levels may be linked to an increased susceptibility risk of COVID-19 (16,17). However, the data on the link between vitamin D levels and COVID-19 mortality is debatable. Although a meta-analysis with a high number of patients shows the association of low vitamin D with mortality(9), a more recent meta-analysis in which excluded biased studies could not show a relationship (7).

The lymphocyte count was also lower in the Vit-D deficient group after PSM. Low lymphocyte count may be due to impaired immune-modulatory effects caused by low vitamin D levels. Low lymphocyte levels have been detected frequently in COVID-19 (18,19). A correlation was found between lymphopenia and disease severity. ACE-2 receptors in lymphocytes are targets for COVID-19, which trigger programmed cell death processes in lymphocytes, and inhibit lymphocyte proliferation by increased inflammatory cytokines are possible causes of lymphopenia (20).

In the evaluation made after PSM, the hospitalization duration was longer in the Vit-D deficient group. In previous studies, no difference was found in the length of hospitalization (21,22). Using different cut-off levels for vitamin D deficiency in studies may explain this situation.

Although albumin levels were lower in the Vit-D Deficient group before PSM, there was no significant difference between them after PSM. It is known that albumin levels decrease as age increases (23). The Vit-D deficient group was older before PSM, and the difference after the equalization of age and gender with PSM may explain similar albumin levels. As an acute phase reactant, CRP levels were high in the Vit-D deficient group before PSM but lost their significance after PSM. Although some studies in the literature show that the acute phase reactants are higher in vitamin D deficiency (24), others do not support this data (25). In the studies, the groups were not balanced with PSM, and different criteria in the definition of vitamin D deficiency may explain this difference in acute phase reactants.

The kidneys may be the target of SARS-COV2; renal dysfunction may also significantly impact COVID-19 outcomes (26). Age and male gender are independent risk factors for renal dysfunction in COVID-19 patients (27). In our study, while ARF ratio was higher in Vit-D deficient group before PSM, it lost its significance among the groups after PSM. Chronic kidney disease was higher in the Vit-D deficient group before and after PSM. Vit-D deficiency is quite common in patients with CKD may explain this situation (28).

Calcium has essential roles in intracellular and metabolic signaling pathways, and it is critical for viral survival and virulence. (29). In a recent meta-analysis, patients with low calcium levels were shown to have higher COVID-19 disease severity and mortality (30). Although vitamin D deficiency is known as a cause of hypocalcemia, severe calcium deficiency is rarely reported (31). No difference was observed between the Vit-D groups regarding corrected calcium levels in our study.

Although our study is real-life data, its retrospective design and the fact that it was conducted during the pandemic are its main limitations. There are no other vitamin D-related measurements, such as the free fraction of 25-OH vitamin D, 1,25 dihydroxy vitamin D, and vitamin D binding protein. Some studies have analyzed patients' Vit-D levels prior to the diagnosis of COVID-19 (32,33). Although we used Vit-D levels during hospitalization to exclude this bias, the status of taking vitamin d supplements was not evaluated. Since our study is single-centered, it may not represent the general population.

CONCLUSION

Although mortality was higher in the group with vitamin D deficiency in the first analysis, it lost its significance on mortality after adjusting for age and gender. There was no relationship between vitamin D deficiency and COVID-19 in-hospital mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Çanakkale Onsekiz Mart University Medical Faculty Ethics Committee (Date: 09.06.2021, Decision No: 06-05).

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.

Financial Disclosure: The authors declared that this study had received no financial support.

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.

Acknowledgment: We acknowledge and thank all the doctors, nurses and other medical personnel at our hospital who provided care to patients during the COVID-19 pandemic. Especially, we would like to thank Dr. Erdal Mert for his support.

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