

# Correlation of Vitamin D Levels with COVID-19 Severity and Outcome

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## ABSTRACT

**Background and aims:** Low vitamin D levels have been associated with an increase in inflammatory cytokines and a significantly increased risk of pneumonia and viral upper respiratory tract infections. Vitamin D deficiency is associated with an increase in thrombotic episodes, which are frequently observed in coronavirus disease 2019 (COVID-19). These conditions are reported to carry a higher mortality in COVID-19. So, we conducted a study to prove the correlation of vitamin D levels with COVID-19 infection and severity. **Material and methods:** The present study was conducted at RNT Medical College, Udaipur, Rajasthan. This study was done over a period of 2 months after getting approval from Institutional Ethics Committee. Written and informed consent was obtained from patients. In this study, 81 patients admitted in COVID wards and ICU, with COVID reverse transcriptase-polymerase chain reaction (RT-PCR) positive reports were included. **Results:** Out of a total 81 patients, 37 (45.7%) were in the 41-60 years age group, 29 (35.8%) were more than 60 years of age and 15 (18.5%) were less than 40 years of age. Seventeen patients had severe vitamin D deficiency, 27 patients had moderate vitamin D deficiency, 20 patients had mild vitamin D deficiency and 17 patients had normal vitamin D level. Out of 17 patients who had severe vitamin D deficiency, 11 (64.7%) patients required invasive mechanical ventilation and out of these 17 patients, 13 (76.47%) patients died. Out of 17 patients who had normal level of vitamin D, 16 (94.1%) maintained SpO<sub>2</sub> at room air and only 1 patient required invasive mechanical ventilation. As the level of vitamin D increased from severely low to normal level, requirement of high oxygen support decreased and SpO<sub>2</sub> at room air increased. Mean of vitamin D among the patients who died was 10.4963 while mean of vitamin D level among patients who survived and were discharged was 27.2362. All 17 patients who had normal level of vitamin D were discharged from the hospital. Mean of serum ferritin and mean of interleukin (IL)-6 was high in patients who died and low in patients who were discharged. **Conclusions:** Vitamin D level plays an important role in COVID-19 disease. Vitamin D have significant role in protection from severe form of disease.

**Keywords:** COVID-19, vitamin D, T regulatory lymphocytes, acute respiratory distress syndrome, IL-6, serum ferritin

The severity of coronavirus disease 2019 (COVID-19) is influenced by several factors, including the evidence of pneumonia, severe acute respiratory distress, myocarditis, microvascular thrombosis and/or cytokine storm. All these conditions have underlying inflammation. A major defense against inflammation, and viral infection in general, is the T regulatory lymphocytes (Tregs). It has been reported that Treg levels can be low

in COVID-19 patients and can be increased with vitamin D supplementation.<sup>1</sup> Treg levels can be particularly lower in severe COVID-19 infection.<sup>2</sup> Low vitamin D level has been tied to an increase in inflammatory cytokines as well as a significant increase in the risk of pneumonia and viral respiratory tract infections. Additionally, vitamin D deficiency has also been tied to an escalation in thrombotic episodes, often seen in patients with COVID-19.<sup>1</sup>

Deficiency of vitamin D is common in patients with obesity and diabetes. Moreover, these are among the conditions known to be associated with a higher mortality in COVID-19.<sup>1</sup>

## MECHANISMS THAT LINK COVID-19 WITH VITAMIN D

The COVID-specific CD8 T cells and the specific antibodies produced by B cells are vital to eliminate the virus. However, unchecked non-specific inflammation and production of cytokines can result in injury to the

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lungs and other vital organs. Thus, limiting the early non-specific inflammation during COVID-19 illness may give time to the specific acquired immunity to develop.

As mentioned earlier, Treg levels have been reported to be low in some COVID-19 patients, and are markedly reduced in severe cases.<sup>2</sup> In a study by Johnstone et al conducted among older nursing home patients, high Treg blood levels were found to be tied to decreased risk of respiratory viral disease.<sup>3</sup> This implies that if Treg levels are increased, it may prove to be beneficial for decreasing the severity of viral disease and possibly of COVID-19 as well.

Vitamin D supplementation can increase Treg levels in both healthy individuals as well as those with autoimmune disorders.<sup>4,5</sup> Low levels of vitamin D are associated with a significantly increased risk of pneumonia and viral respiratory tract infections.<sup>6,7</sup>

Low vitamin D levels are tied to an increase in inflammatory cytokines. In healthy individuals, researchers have noted a significant inverse relationship between the serum 25-hydroxyvitamin D [25(OH)D] and tumor necrosis factor (TNF)- $\alpha$ .<sup>8</sup> The levels of interleukin (IL)-6 have been found to be increased in those who were vitamin D deficient.<sup>9</sup> Several animal studies and *in vitro* cell models have shown vitamin D3 to down-regulate the production of inflammatory cytokines, such as TNF- $\alpha$  and IL-6, while increasing inhibitory cytokines.<sup>10</sup> All these observations suggest that adequate levels of vitamin D can potentially decrease the incidence of cytokine storm, which is seen in COVID-19.

Thrombotic complications are also frequently encountered in COVID-19 patients.<sup>11</sup> A large number of patients with COVID-19 have been found to have elevated D-dimer levels. Vitamin D is known to regulate thrombotic pathways, and the deficiency of this vitamin is associated with an increase in thrombotic episodes.<sup>12</sup> Vitamin D deficiency has also been found to occur more frequently in patients with obesity and diabetes.<sup>13</sup> These conditions are associated with higher mortality in COVID-19 patients.

## MATERIAL AND METHODS

The present study was conducted at RNT Medical College, Udaipur, Rajasthan. This study was done over a period of 2 months after getting approval from Institutional Ethics Committee. Written and informed consent was obtained from patients. In this study, 81 patients admitted in COVID wards and intensive care unit (ICU), with COVID reverse transcriptase-polymerase chain reaction (RT-PCR) positive report, were included.

Patients admitted in COVID ICU and wards were tested for vitamin D level. Patient were grouped into: severe deficiency of vitamin D <10 ng/mL, moderate deficiency of vitamin D 10-20 ng/mL, mild deficiency of vitamin D 20-30 ng/mL and normal level >30 ng/mL. Association of vitamin D level was tested with outcome of patient in the form of discharge and death and maintenance of SpO<sub>2</sub> level.

## RESULTS

In the present study, out of total 81 patients 37 (45.7%) were in the 41-60 years age group, 29 (35.8%) were more than 60 years of age and 15 (18.5%) were less than 40 years of age. Most of patients were male (n = 59), 72.8% and 27.2% (n = 22) were female (Table 1).

Table 2 depicts the association of vitamin D level and SpO<sub>2</sub> maintained by patients. Among the patients who had severe vitamin D deficiency, all patients (100%) required mechanical ventilation. Out of 17 patients who had normal level of vitamin D, 16 (94.1%) maintained SpO<sub>2</sub> at room air. As the level of vitamin D increased from severely low to normal level, requirement of mechanical ventilation decreased. This association of vitamin D level and SpO<sub>2</sub> maintained by patients was found to be statistically significant, with Chi-square 88.163 and p value <0.0001.

Table 3 depicts means of vitamin D level as per the outcome of death and discharge. The mean of vitamin D level among the patients who died was 10.4963, while mean of vitamin D level among patients who survived and were discharged was 27.2362. As depicted in the table, patients who survived and were discharged had high mean level of vitamin D and patients who died had low mean level of vitamin D. The difference in mean of vitamin D level with outcome was statistically significant with p value 0.0015.

Table 4 depicts the association of vitamin D levels and outcome of patients in form of death and discharge of

**Table 1.** Distribution of Study Participants According to Age and Gender (n = 81)

Age Group	Frequency	Percentage (%)
Age Group (Years)		
<40	15	18.5
41-60	37	45.7
>60	29	35.8
Gender		
Male	59	72.8
Female	22	27.2

**Table 2.** Association Between Vitamin D Level and Peak Requirement of Oxygen Support in COVID RT-PCR Positive Patients (n = 81)

	Peak requirement of oxygen support				Total	Chi-square and p value
	Room air	Nasal prong/mask	NIV	Invasive mechanical ventilation		
Vitamin D level (ng/mL)						
0-10	0 (0.0%)	0 (0.0%)	6 (35.29%)	11 (64.7%)	17 (100.0%)	88.163,
11-20	5 (18.5%)	6 (22.2%)	14 (51.9%)	2 (7.4%)	27 (100.0%)	<0.0001
21-30	12 (60.0%)	2 (10.0%)	5 (25.0%)	1 (5.0%)	20 (100.0%)	
>30	16 (94.1%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	17 (100.0%)	
<b>Total</b>	<b>33 (40.7%)</b>	<b>8 (9.9%)</b>	<b>25 (30.9%)</b>	<b>15 (18.5%)</b>	<b>81 (100.0%)</b>	

**Table 3.** Association Between Mean of Vitamin D Level and Outcome of Death and Discharge (n = 81)

Outcome	Mean	N	SD	P value
Death	10.4963	18	5.76154	t = 3.3002
Discharge	27.2362	63	20.00015	0.0015
<b>Total</b>	<b>23.9295</b>	<b>81</b>	<b>19.26664</b>	

**Table 4.** Association Between Different Vitamin D Levels and Outcome of Death and Discharge (n = 81)

	Outcome		Total	Chi-square and p value
	Death	Discharge		
Vitamin D level (ng/mL)				
0-10	13 (76.47%)	4 (23.53%)	17 (100.0%)	29.018,
11-20	4 (14.8%)	23 (85.2%)	27 (100.0%)	<0.0001
21-30	1 (5.0%)	19 (95.0%)	20 (100.0%)	
>30	0 (0.0%)	17 (100.0%)	17 (100.0%)	
<b>Total</b>	<b>18 (22.2%)</b>	<b>63 (77.8%)</b>	<b>81 (100.0%)</b>	

patients. Out of 17 patients who had severely low vitamin D level, 13 (76.47%) patients died. All 17 patients who had normal level of vitamin D were discharged from hospital. As the level of vitamin D increased from severely low to normal level, chance of survival and discharge increased. This association of vitamin D level and outcome of patients in form of death and discharge of patients was found statistically significant, with Chi-square 29.018 and p value <0.0001.

Table 5 depicts that the mean of inflammatory marker IL-6 among the patients who died was 58.3231, while mean of IL-6 among patients who survived and were discharged was 40.7815. As depicted from the table, patients who survived and were discharged had low mean level of IL-6 and patients who died had high mean level of IL-6. However, the difference in mean of IL-6 level with outcome was statistically insignificant with p value 0.440.

**Table 5.** Association Between Inflammatory Markers (IL-6 and Serum Ferritin) and Outcome of COVID RT-PCR Positive Patients (n = 81)

	Outcome		't' value and p value
	Death	Discharge	
IL-6			
Mean	58.3231	40.7815	t = 0.7752
N	16	65	p = 0.440
SD	60.3941	85.2127	
Serum ferritin			
Mean	1050.7375	459.0000	t = 4.4711
N	16	65	p = 0.001
SD	644.5592	425.5343	

Table 5 also depicts that the mean of inflammatory marker serum ferritin among the patients who died was 1050.7375, while mean of serum ferritin among patients who survived and were discharged was 459.0000. As depicted in the table, patients who survived and were discharged had low mean level of serum ferritin and patients who died had high mean level of serum ferritin. The difference in mean of serum ferritin level with outcome was found statistically significant with p value 0.001.

### DISCUSSION

The present study was conducted at RNT Medical College, Udaipur, Rajasthan. In the present study, out of total 81 patients, 37 (45.7%) were in the 41-60 years age group, 29 (35.8%) were more than 60 years of age and 15 (18.5%) were less than 40 years of age. In our study, the association of vitamin D level and SpO<sub>2</sub> of patients was found to be statistically significant. It was observed that if patients had normal level of vitamin D, they maintained SpO<sub>2</sub> with room air/nasal prong/mask (low oxygen support) and they did not get severe form of disease. As depicted in our study, patients who survived and were discharged had high mean level of vitamin D and low mean level of serum ferritin and IL-6 and patients who died had low mean level of vitamin D and high mean level of serum ferritin and IL-6.

The difference in mean of vitamin D level with outcome and serum ferritin level with outcome was statistically significant. It was interpreted that if the patients had high mean level of vitamin D and low mean level of serum ferritin and IL-6, they had less severe disease, or in other words, patients who had low level of vitamin D and high

level of serum ferritin and IL-6 had more severe disease and higher death rate.

In the present study, it was found that as the level of vitamin D increased from severely low to normal level, chance of survival and discharge increased. This association of vitamin D level and outcome of patient in the form of death and discharge of patients was found statistically significant. It was interpreted that patients who had severe vitamin D deficiency had more chance of severe disease and death.

### CONCLUSIONS

In the present study, it was interpreted that vitamin D levels play an important role in COVID-19 disease. Vitamin D has a significant role in protection from severe form of the disease. Patients who have severe vitamin D deficiency have more chance of severe disease, more chance of requiring high oxygen support to maintain SpO<sub>2</sub> and have more chance of mortality from COVID-19.

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support its use for dyslipidemia management, in the settings of primary, secondary and tertiary intervention. While initial data is promising, we look forward to real-world evidence in Asian populations, as well as the result of the long-term cardiovascular outcome trial. The availability of bempedoic acid should encourage a change in modern statin-centric lipid management guidelines, and help them evolve into a more person-centered, rather than drug-centered, guidance.

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