

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 SpO₂ 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 SpO₂ 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.¹ Treg levels can be particularly lower in severe COVID-19 infection.² 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-19.¹

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-19.¹

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 lungs and other vital organs. Thus, limiting the early

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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.² 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.³ 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.^{4,5} Low levels of vitamin D are associated with a significantly increased risk of pneumonia and viral respiratory tract infections.^{6,7}

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)- α .⁸ The levels of interleukin (IL)-6 have been found to be increased in those who were vitamin D deficient.⁹ Several animal studies and *in vitro* cell models have shown vitamin D3 to down-regulate the production of inflammatory cytokines, such as TNF- α and IL-6, while increasing inhibitory cytokines.¹⁰ 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.¹¹ 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.¹² Vitamin D deficiency has also been found to occur more frequently in patients with obesity and diabetes.¹³ 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 SpO₂ 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 SpO₂ 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 SpO₂ 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 SpO₂ 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 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

CLINICAL STUDY

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%)	
Total	33 (40.7%)	8 (9.9%)	25 (30.9%)	15 (18.5%)	81 (100.0%)	

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
Total	23.9295	81	19.26664	

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%)	
Total	18 (22.2%)	63 (77.8%)	81 (100.0%)	

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

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	

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 SpO₂ of patients was found to be statistically significant. It was observed that if patients had normal level of vitamin D, they maintained SpO₂ 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 SpO₂ and have more chance of mortality from COVID-19.

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Shots Don't Prevent Older Adults Against Long COVID

Research conducted in the US provided fresh evidence that long COVID can happen even after infections in vaccinated people with older adults at higher risk of long-term side effects. In the study, one-third of the elderly population showed signs of long COVID. A separate report published by CDC showed that after breakthrough infection 1 in every 4 adults aged 65 and above had 1 potential long COVID symptom in comparison to every 5th younger adult. The coronavirus vaccine helps in preventing initial infection and serious outcomes. About 1% of individuals develop a breakthrough infection, according to the study results published in *Nature Medicine* in which 13 million veteran reports were reviewed.

Overall, 32% had long COVID symptoms for up to 6 months in comparison to 36% of unvaccinated veterans after breakthrough infection. Long COVID symptoms such as breathing problems, and muscle aches, were the most common conditions. Strokes, brain fog and kidney failure were the high-risk factors observed among older adults. The author stated that this stressed the need to hasten long-term care for older adults along with the routine assessment of all COVID patients. (Source: <https://www.hindustantimes.com/lifestyle/health/long-covid-affects-more-older-adults-shots-don-t-prevent-it-101653540056217.html>)

Correcting Blood Sugar Levels can Improve Obesity-related Fertility Issues

A study published in *The Journal of Endocrinology* showed the association between the altered levels of the reproductive hormone in mouse model of obesity can be restored by reducing blood glucose levels. Several studies have highlighted the need for effective therapy in obese women facing fertility issues due to imbalance in reproductive hormones. Hence, the development of an effective therapy that treats obesity along with metabolic health is a major advancement in the field of medicine. Dapagliflozin is a common drug used to treat type 2 diabetes, where it reduces blood glucose levels and has a positive effect on other metabolic health factors. In the study, the researchers investigated the effect of dapagliflozin on metabolic health and reproductive hormones in mouse models of obesity. After 8 weeks of application, blood glucose levels, body mass index (BMI) and reproductive cycles were normalized with the hormone imbalance and ovulation restored in comparison to non-treated mice.

Professor Chen, the lead researcher stated that normalized blood glucose metabolism with dapagliflozin in obese mice is a promising development toward restoring reproductive functions. However, further examination is needed to understand the therapeutic benefits, target molecules, molecular pathways involved, etc. to better treat fertility issues among women. (Source: <https://www.hindustantimes.com/lifestyle/health/research-correcting-blood-sugar-levels-can-improve-obesity-related-fertility-issues-101653539743483.html>)

Pfizer: COVID-19 Vaccine Shows Robust Response in Children

Pfizer/BioNTech reported that 80% efficacy of its vaccine was demonstrated in 3 doses for toddlers and children below 5 years. The study included 1,678 children during the pandemic period when Omicron was predominant. Based on the study data Pfizer plans to submit an application for the Emergency Use Authorization (EUA) to the US FDA. Earlier Pfizer asked the US FDA to authorize its vaccine for younger children but delayed its application after the trial data for 2 vaccination doses did not produce a significant immune response. Although the safety of the vaccine was similar to the placebo. The US FDA advisory board meeting is scheduled on June 15th to evaluate and authorize their recommendations for the mRNA vaccines in children under 6 years old. The doses recommended for children from 6 months to 5 years are 3 µg, i.e., 1/10th of the vaccination dosage administered to an adult. (Source: <https://www.medscape.com/viewarticle/974473?src=>)