

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

GURDEEP KAUR*, GAURAV SHARMA†, JAINENDRA SHARMA‡, SHWETA BIYANI‡, RANJNA VEERWAL†

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

*Professor, Dept. of Medicine

†Senior Resident, Dept. of General Medicine

‡Associate Professor, Dept. of Biochemistry

RNT Medical College, Udaipur, Rajasthan

Address for correspondence

Dr Gaurav Sharma

Senior Resident

Dept. of General Medicine

RNT Medical College, Udaipur, Rajasthan

E-mail: gauravsharma1280@gmail.com

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.

REFERENCES

1. Weir EK, Thenappan T, Bhargava M, Chen Y. Does vitamin D deficiency increase the severity of COVID-19? *Clin Med (Lond)*. 2020;20(4):e107-e108.
2. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5):2620-9.
3. Johnstone J, Parsons R, Botelho F, Millar J, McNeil S, Fulop T, et al. Immune biomarkers predictive of respiratory viral infection in elderly nursing home residents. *PLoS One*. 2014;9(9):e108481.
4. Fisher SA, Rahimzadeh M, Brierley C, Gratton B, Doree C, Kimber CE, et al. The role of vitamin D in increasing circulating T regulatory cell numbers and modulating T regulatory cell phenotypes in patients with inflammatory disease or in healthy volunteers: A systematic review. *PLoS One*. 2019;14(9):e0222313.
5. Prietl B, Treiber G, Mader JK, Hoeller E, Wolf M, Pilz S, et al. High-dose cholecalciferol supplementation significantly increases peripheral CD4⁺ Tregs in healthy adults without negatively affecting the frequency of other immune cells. *Eur J Nutr*. 2014;53(3):751-9.
6. Lu D, Zhang J, Ma C, Yue Y, Zou Z, Yu C, et al. Link between community-acquired pneumonia and vitamin D levels in older patients. *Z Gerontol Geriatr*. 2018;51(4):435-9.
7. Science M, Maguire JL, Russell ML, Smieja M, Walter SD, Loeb M. Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. *Clin Infect Dis*. 2013;57(3):392-7.
8. Peterson CA, Heffernan ME. Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH)D concentrations in healthy women. *J Inflamm (Lond)*. 2008;5:10.
9. Manion M, Hullsiek KH, Wilson EMP, Rhame F, Kojic E, Gibson D, et al; Study to Understand the Natural History of HIV/AIDS in the Era of Effective Antiretroviral Therapy (the 'SUN Study') Investigators. Vitamin D deficiency is associated with IL-6 levels and monocyte activation in HIV-infected persons. *PLoS One*. 2017;12(5):e0175517.
10. Alhassan Mohammed H, Mirshafiey A, Vahedi H, Hemmasi G, Moussavi Nasl Khameneh A, Parastouei K,

- et al. Immunoregulation of inflammatory and inhibitory cytokines by vitamin D3 in patients with inflammatory bowel diseases. *Scand J Immunol.* 2017;85(6):386-94.
11. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol.* 2020;127:104362.
 12. Mohammad S, Mishra A, Ashraf MZ. Emerging role of vitamin D and its associated molecules in pathways related to pathogenesis of thrombosis. *Biomolecules.* 2019;9(11):649.
 13. Vranić L, Mikolašević I, Milić S. Vitamin D deficiency: consequence or cause of obesity? *Medicina (Kaunas).* 2019;55(9):541.



Oral Contraceptive Pills may Check PCOS-related Diabetes Risk

A retrospective, population-based study has found that some of the oral contraceptives are tied to a lower risk for type 2 diabetes and prediabetes among women with polycystic ovary syndrome (PCOS). An analysis of 64,051 women with PCOS revealed that they had around two-times greater risk for developing type 2 diabetes (adjusted hazard ratio [aHR] 2.04) and dysglycemia (aHR 1.87) compared to the general population, reported researchers online in *Diabetes Care*.

However, combined oral contraceptive pills (COCPs) were found to counter this risk over a median follow-up of 3.5 years. Women who were prescribed COCPs had a 16% to 17% reduced risk for type 2 diabetes. The risk reduction appeared to be similar for contraceptives with an antiandrogenic progestin component (aHR 0.84) and without it (aHR 0.83)... (Source: *Medpage Today*)

Nurse Survey Highlights Mental Health Difficulties During COVID-19 Pandemic

A COVID-19 survey on mental health and wellness by the American Nurses Foundation has shown that over half of the nurses working in critical care reported that they were not emotionally healthy.

Out of 9,572 nurses surveyed in the third of a series of pandemic-related polls, around 75% nurses across all roles stated that they were stressed, while 10% reported feeling worthless. Around 51% of nurses, 25 to 34 years of age, reported feeling 'not emotionally healthy'.

Among critical care nurses, 80% reported that they felt stressed or exhausted in the last 14 days, and nearly half reported feeling depressed. About 39% reported feeling numb, and 15% felt worthless. Regarding behavior, 71% of the nurses reported increased difficulty in sleeping in the previous 14 days, 45% reported that they were overeating, 29% reported an increase in alcohol consumption, 6% reported that they had increased suicidal thoughts and 2% reported increase in self-harm behavior... (Source: *Medpage Today*)

Excessive Screen Time Leads to Developmental Delays: Study

Excessive exposure to television or mobile phone screens for children less than 5 years old could have adverse effects on their development, suggested a study by Chennai-based researchers, published in *PLOS One*.

The researchers evaluated the performance of children and their understanding of commands from their mothers. It was found that children exposed to several hours of television or mobile phone screens were not able to comprehend what they were being told.

A total of 718 children, aged 6 months to 5 years, were included in the study. Around 70% of them had been exposed to excessive screen time, noted the researchers. Though the study was done in 2019, lead study author, Samya Varadarajan said that it could also apply to the current scenario, as children are forced to study through online classes during the pandemic... (Source: *The Hindu*)

हेमेटिनिक डेक्सॉरेंज with traditional root



बोचपायुड इतय त्राए to तेड चलोएडइ

Rx in Anaemia associated with

* Pregnancy & Lactation

* Menorrhagia

* Nutritional & Iron Deficiency

* Chronic Gastrointestinal Blood Loss

* General Weakness

* Chemotherapy-induced anaemia

* Lack of Appetite

* Chronic Kidney Disease



FRANCO-INDIAN
PHARMACEUTICALS PVT. LTD.
20, Dr. E. Moses Road, Mumbai 400 011.