

Original Article

DOI: <https://doi.org/10.47648/jswmc2022v12-02-53>

Case Control Study to Evaluate the Relationship between Vitamin D-Deficiency and Severity of COVID-19 Infection and Outcome

*Ahmad S¹, **Salam MU², Patwary MI³, Talha KA⁴, Bhuiya MI⁵, Taher MA⁶, Ahmed R⁷, Goswami A⁸, Jumma MA⁹

Abstract:

Background: Coronavirus disease (COVID-19) is a systemic disorder caused by severe acute respiratory syndrome corona virus (SARS-COV-2). No established curative treatment for this disease is yet invented. Vitamin D deficiency (VDD) significantly facilitates in worsening COVID 19 infections. Till now, there is no definite verification on its impact on COVID-19 infection.

Objective: To evaluate the relationship amid vitamin D-deficiency and severity of COVID-19 infection and its outcome.

Methods: The present case-control study was conducted at a medical college hospital, Sylhet, Bangladesh. Total 100 cases and 100 controls were enrolled. Patients categorization were formulated on the ground of severity of COVID infection clinically and Vitamin D level at admission. The relationship among these two categories with different variables was analyzed. All data were processed and analyzed by SPSS (statistical package for social science) version 25.

Results: In this study the mean age was 58.46±14.50 years in COVID 19 patients (case group) and 41.96±5.66 years in control group. Majority (64%) was male and 36% was female among COVID 19 patients. Leading risk factor (64%) was DM (diabetes mellitus) followed by smoking (24%) and hypertension (16%). Significant vitamin D deficiency was seen in case group (COVID 19) than control group which was 37% and 22% respectively. Further observed, vitamin D insufficiency was also more in case group (39%) than control group (31%). However, sufficient vitamin D levels were more in control group than case group which was 47% and 24% respectively. The average vitamin D level was 24.10±11.30 in case group and 28.55±11.80 in control group which carried significant statistic value (P<0.05). Thus, Vitamin D level was significantly associated with the COVID 19 disease severity evident by 45.1 % deficiency in severe cases compared to 17.2% among the moderate cases.

Conclusion: This study shows the serum level of vitamin D was lower in patients with the COVID 19. It is also found that vitamin D status is remarkably related to COVID-19 severity. Vitamin D supplementation may have a vital role in limiting the impact of this pandemic. More clinical studies are demanded to establish the relationship between COVID 19 patients and the serum level of vitamin D.

Key words: Vitamin D, COVID-19, Severity of infection.

JSWMC 2022 [12(02)] P: 60-66

Introduction:

Coronavirus disease 2019 (COVID-19) also recognized as Wuhan virus, novel coronavirus 2019 (nCoV-19), human coronavirus 2019 (hCoV-19), is a severe acute respiratory syndrome.^{1,2}

7. Dr. Rajbir Ahmed, Registrar, Department of Medicine, SWMCH
8. Dr. Ashis Goswami, Medical Officer, Dept. of Medicine, SWMCH
9. Dr. Mashuq Ahmad Jumma, Assistant Registrar, Dept. of Medicine, SWMCH

1. Dr. Shahed Ahmad, Assistant professor, Dept. of Medicine, SWMCH
2. Dr. Mahjuba Umme Salam, Professor and head, Dept. of Medicine, SWMCH
3. Dr. Md. Ismail Patwary, Professor, Dept. of Medicine, SWMCH
4. Dr. Khandaker Abu Talha, Associate Professor, Dept. of Neurosurgery, SWMCH
5. Dr. Monharul Isalm Bhuiya, Assistant Professor, Dept. of Medicine, SWMCH
6. Dr. Md Abu Taher, Registrar, Department of Medicine, AHHPL

Corresponding author: Dr. Shahed Ahmad,
Assistant professor, Dept. of Medicine, SWMCH
Email: doc.s.s.ahmad@gmail.com

Mahjuba Umme Salam,
Professor and Head, Dept. of Medicine, SWMCH
Email- mahjubasalam@yahoo.com

COVID-19 is still now pandemic in Bangladesh and worldwide. Bangladesh confirmed first case of COVID-19 on 8th March 2020.³

The role of different vitamins and minerals in regulation of immunity has been a time demanding issue particularly in this COVID-19 era. One of the important micronutrients, vitamin D has a role in facilitating both the innate and adaptive invulnerableresponse^{4,5}. Given the fact, vitamin D deficiency is widely common in all parts of the world.⁶ Important part of vitamin D in refereeing the invulnerable structure response to infections including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.⁴

Vitamin D has an enormous impact on pathogenicity, clinical presentation, outcome, complications, and treatment of number of diseases.⁷ Sepsis related death rates are accelerated by vitamin D deficiency. Besides, a recent systematic review demonstrated associations between vitamin D deficiency and the chance of having breast, colon and prostate cancer. Vitamin D-mediated characteristic immunity is vital in host defenses to respiratory tract pathogens through accelerated expression of hCAP-18(human Cathelicidin Antimicrobial Peptides). Previous studies reported, vitamin D has some antiviral properties, and vitamin D supplementation might reduce the risk of respiratory infections.⁴

Vitamin D generally diminish the susceptibilities of microbial infections and death by regulating innate and adaptive immune response, and as a result of its antiviral and anti-inflammatory properties.⁸ Vitamin D also has a paramount consequence on intensifying the expression of Angiotensin-converting enzyme 2(ACE-2), which is an important receptor in the COVID 19 pathogenesis.⁹ This micronutrient can also intensify the expression of genes related to antioxidation, regulate adaptive immunity, and improves cellular immunity.¹⁰

Moreover, vitamin D Supplementation decrease acute viral respiratory infections.¹⁰ There have been several studies to find out the role of vitamin D considering the mechanism of action, particularly in the perspective of the COVID-19 disease but being in an area of uncertainty and persistent point of attention.¹¹ However, it is yet to be evaluated, on a prospective basis and considering possible confounding factors, whether VDD or low 25OHD levels are related to the severity of COVID-19.¹² Therefore, this

study is to evaluate the relationship of vitamin D-deficiency with severity of COVID-19 infection and its outcome.

Materials and methods

This was a case-control study that took place in the department of Medicine, Sylhet Women's Medical College Hospital, Sylhet, Bangladesh from July 2021 to October 2021. Patients with COVID 19 and non COVID 19 individuals who met eligibility criteria were included in this study. Total 200 participants were engaged comprising 100 COVID -19 patients as case and remainings were control. Subsequently, detailed history taking that includes age, sex, duration of disease, clinical symptoms, and vitamin D level and other laboratory investigations were recorded. Vitamin D level was estimated using a chemiluminescence based immunoassay analyzer. Data was collected on a self-formulated data collection sheet. Vitamin D level was ranked as deficiency 0 to <20 ng/ml, insufficiency 20-<30 ng/ml, sufficiency 30-100 ng/ml, and potential toxicity >100 ng/ml.

According to WHO classification, COVID-19 infection was categorised into mild, moderate or severe infection. Mild infection of COVID-19 is defined as respiratory symptoms without evidence of pneumonia or hypoxia, and moderate or severe infection is with clinical and radiological proof of pneumonia. In moderate cases, SpO₂ ≥90% on ambient room air while one of the following two was mandatory to define the cases severe is respiratory rate >30 breaths/min or SpO₂ < 90% on room air.¹³ Data analysis were performed on SPSS25 (SPSS inc. Chicago, IL, USA). Descriptive analysis was performed where means and standard deviations values were presented for all continuous variables, whereas numbers and percentages were used for categorical variables. Chi-square test was also used. Significance level was set at <0.05.

Category	Defination
Mild	Respiratory symptoms without evidence of pneumonia or hypoxia
Moderate	Clinical and radiological proof of pneumonia with SpO2 \geq 90% on ambient room air
Severe	Clinical and radiological proof of pneumonia with respiratory rate $>$ 30 breaths/min or SpO2 $<$ 90% on room air

Results

The mean age was 58.46 \pm 14.50 years in COVID 19 patients (case group) and mean age was 41.96 \pm 5.66 years in the control group. Majority (64%) was male whereas 36% were female among the COVID 19 patients. In contrast, 58 % male and 42% female participated as control (Table I). Leading (64%) risk factors were diabetes mellitus (DM) followed by (24%) smoking and (16%) were hypertension (HTN) (Table III). Most prominent presenting symptoms of COVID 19 patients were fever (92%) and cough (84%), However; least common manifestation was diarrhea (7%). Significant vitamin D deficiency was noticed in the case group (COVID 19) than the control group which was 37% and 22% respectively. It is also noticeable that vitamin D insufficiency was more in case group than control group, 39% and 31% respectively. However, sufficient vitamin D levels were more in the control group (47%) than the case group (24%). The average vitamin D level was 24.10 \pm 11.30 in the case group and 28.55 \pm 11.80 in the control group which was statistically significant (P< 0.05) (Table V). Vitamin D deficiency was 45.1 % in severe cases compared to 17.2% among moderate cases (Table VI). It is also noticeable that mortality is more in Vitamin D deficiency group in comparison to insufficiency group that is 75% and 25.5% respectively (Table VII). Therefore, it could be concluded that vitamin D status is remarkably related to COVID-19 severity and vitamin D sufficiency might have a high survival among moderate and severe covid 19 sufferers.

Table I: Demographic characteristics of the study subject (n=200)

Characteristics	Case (n=100)		Control (n=100)		P value
	No	%	No	%	
Age in years					
21-30	5	5	30	30	0.001
31-40	12	12	24	24	
41-50	7	7	20	20	
51-60	31	31	10	10	
>60	45	45	16	16	
Mean \pm SD	58.46 \pm 14.50		41.96 \pm 5.66		
Sex					
Male	64	64	58	58	0.219
Female	36	36	42	42	

Data were analyzed using chi-square test

Table II: Symptoms of covid 19 patients (n=100)

Symptoms	Frequency	Percentage (%)
Fever	92	92
Cough	84	84
Breathlessness	62	62
Diarrhea	7	7
Headache	15	15
Malaise	44	44
Fatigue	51	51

Table III: Risk factor of covid 19 patients (n=100)

Risk factor	Frequency	Percentage (%)
Diabetes mellitus	64	64
Systemic hypertension	16	16
COPD	1	1
CKD	3	3
IHD	6	6
Smoking	24	24

Table IV: Severity of the covid 19 patients (n=100)

Severity	Frequency	Percentage (%)
Moderate	29	29.0
Severe	71	71.0

Table V: Vitamin D level of the study subject (n=200)

Vitamin D level	Case (n=100)		Control (n=100)		P value
	No	%	No	%	
Deficiency	37	37	22	22	0.002
Insufficiency	39	39	31	31	
Sufficient	24	24	47	47	
Mean±SD	24.10±11.30		28.55±11.80		

Data were analyzed using chi-square test

Table VI: Association of vitamin D level and severity of Covid 19 patients (n=100)

Vitamin D level	Moderate (n=29)		Severe (n=71)		P value
	No	%	No	%	
Deficiency	5	17.2	32	45.1	0.009
Insufficiency	12	41.4	27	38.0	
Sufficient	12	41.4	12	16.9	
Mean±SD	26.87±12.64		23.37±10.71		

Data were analyzed using chi-square test

Table VII: Association of vitamin D level and outcome of Covid 19 patients (n=100)

Vitamin D level	Survived (n=96)		Died (n=4)		P value
	No	%	No	%	
Deficiency	31	34.4	3	75.0	0.017
Insufficiency	38	39.6	1	25.5	
Sufficient	24	25.0	0	00	
Mean±SD	25.17±10.41		26.62±1.87		

Data were analyzed using chi-square test

Discussion

The theatrical development of COVID 19 pandemic along with its advanced illness and mortality rates, urged us to examine the possible indicators leading to severe medical outcomes.¹² The Vitamin D might have variable effects on multiple organs and plays an vital role as immunomodulator, antiviral and anti-inflammatory.¹⁴ Vitamin D, through its autophagy method via acidification of endolysosomes also accelerate the degradation of corona virus.¹⁵ This COVID 19 infection hinders the formation of ACE2 receptors whereas vitamin D stimulates ACE2. It can also adhere to SARS-CoV-2 and negate it to get in contact with ACE2 receptors.¹⁶

This study exhibits; the mean age was 58.46±14.50 years in COVID 19 patients (case group) and 41.96±5.66 years in the control group. Maximum patients were >60 years. This finding was also consistent with other studies.^{17,18} Teama et al. reported that the average age was 50 years.¹⁹ According to the data, the older group of population worldwide were the mostly sufferers from COVID 19 in majority of countries.¹⁶

This study demonstrates that the majority were male (64%) whereas 36% were female in COVID 19 patients (case group). Therefore, the finding of the study is in well agreement with the interpretation of the other research works²⁰. Several studies reported differences in the immune system could also explain why severe COVID-19 is much more common in men than in women.^{8,17,18}

In the current study we found the predominant symptoms were fever (92%) then cough (84%), shortness of breath (62%), fatigue (51%) and malaise (44%). In previous studies, cough and fever were globally regarded as main factors.^{17,18} and in consideration of symptom factors, cough were the main symptoms of severe COVID-19.^{18,19,20}

In this study major (64%) risk factors were DM followed by (24%) smoking and (16%) HTN. Diabetes and hypertension were significantly linked to COVID-19 severity and mortality in

the Nimavat et al study.¹⁵ Changes on glucose homeostasis, immunological status, inflammation and stimulation of the RAAS (renin–angiotensin–aldosterone system) are all possible pathogenetic linkages between COVID-19 and diabetes mellitus.^{21,22} More than a half (58%) of severely ill COVID-19 patients admitted to Critical Care Department in the United States were having diabetes mellitus that is demonstrating a link between severe COVID-19 and diabetes mellitus.^{23,24} Elder population group, people with hypertension were associated with severe COVID-19.^{25,26} In another Chinese study, mortality in COVID-19 was apparently high among the hypertensive patients (48 %).²⁷ In this study, vitamin D deficiency was noticed significantly in the case group (COVID 19) than the control group which was 37% and 22% respectively. It also spotted that vitamin D insufficiency also was more in case group than control group, 39% and 31% respectively. But sufficient vitamin D levels were more in the control group (47%) than the case group (24%). The average vitamin D level was 24.10 ± 11.30 in the case group and 28.55 ± 11.80 in the control group which were statistically significant between two groups ($P < 0.05$). These findings of the this study were also consistent with similar kind of previous studies.^{17,18,19}

In this study, Vitamin D level was greatly related with the severity of COVID 19 disease. The deficiency was 45.1 % in severe cases compared to 17.2% among moderate cases. The results of the study are in well agreement with the interpretations of the other research works.^{15,17,19,20} In a study by Ye et al. observed a large proportion of the patients with Vitamin D deficiency among severe diseases compared to mild to moderate disease. An Indian cross sectional study among patients with COVID 19 infections described 58.97 % of patients with Vitamin D deficiency and 89.1 % with insufficiency.²⁸ Similar type of other case-control study infers significant association between VDD and severe COVID-19 infection.^{29,30}

In this study patients who were also with low level of vitamin D level which was consistent with Nimavat et al. ¹⁵Previous European studies

reported vitamin D insufficiency was linked to death from COVID-19 in that countries.³¹ From another study, Munshi et al. showed that patients with poor prognosis had very low Vitamin D level.³²

Many studies and trials have been enrolled worldwide to establish the benefits of Vitamin D in COVID-19 patients. These results would be supportive towards establishing further strategies. However, existing evidence favours that COVID-19 patients had low levels of Vitamin D. Therefore, supplementation of Vitamin D in COVID-19 patients may play a vital role to halt the progression of disease and in reduction of mortality and might create a new era of prevention and treatment of COVID-19.

Conclusion

This study shows low serum level of vitamin D in COVID 19 patients which was statistically significant. It is also reflected that vitamin D deficiency was more common in severe COVID 19. Thus, from this presented study, the inference could be drawn that there is a relation between vitamin D deficiency and severity of COVID 19. Nevertheless, those who develop COVID-19, should be screened for Vitamin D and proper treatment should be given accordingly.

Declarations

Funding: The study was not supported by any funding sources.

Conflicts of Interest: No conflict of interest was declared by any co-authors.

References

1. WHO. Naming the coronavirus disease (COVID-19) and the virus that causes it. Retrieved from WHO: [https://www.who.int/emergencies/diseases/novel-coronavirus2019/technical-guidance/naming-the-coronavirus-disease-\(covid-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it). 2020a:75-80
2. Cucinotta D and Vanelli M. WHO Declares COVID-19 a Pandemic. 2020;91(6), 157-160.

3. Institute of Epidemiology, Disease Control and Research (IEDCR). Corona info. corona.gov.bd (in Bengali). Archived from the original on 22 March 2020;215-220.
4. Rbab Taha 1 Shahd Abureesh 2 Shuruq Alghamdi 2 Rola Y Hassan 3 Mohamed M Cheikh 4,5 Rania A Bagabir6 Hani Almoallim 2,7 Altaf Abdulkhaliq. The Relationship Between Vitamin D and Infections Including COVID-19: Any Hopes? *International Journal of General Medicine* 2021;14 3849–3870.
5. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res.* 2020;32(7):1195–1198.
6. Lips P, Cashman KD, Lamberg-Allardt C, et al. Current Vitamin D status in European and Middle East countries and strategies to prevent Vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol.* 2019.
7. Marino R, Misra M. Extra-skeletal effects of vitamin D. *Nutrients.* 2019;11(7):1460.
8. Hribar CA, Cobbold PH, Church FC. Potential role of vitamin d in the elderly to resist covid-19 and to slow progression of parkinson's disease. *Brain Sci.* (2020) 10:6–13.
9. Cristian P, Simina I, Lee S. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res.* (2020) 32:1195–8.
10. Teshome A, Adane A, Girma B and Mekonnen ZA (2021) The Impact of Vitamin D Level on COVID-19 Infection: Systematic Review and Meta-Analysis. *Front. Public Health* 9:624559:1-10.
11. D'Avolio A, Avataneo V, Manca A, Cusato J, De Nicolò A, Lucchini R, et al. 25-hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. *Nutrients.* (2020) 12:1–7.
12. Campi I, Gennari L, Merlotti D, Mingiano C, Frosali A. Vitamin D and COVID-19 severity and related mortality: a prospective study in Italy *BMC Infectious Diseases* 2021;21:1-13.
13. World Health Organization. *Clinical Management of COVID-19: Interim Guidance.* World Health Organization; 2020:13–15.
14. Tsujino I, Ushikoshi-Nakayama R, Yamazaki T, Matsumoto N, Saito I. Pulmonary activation of vitamin D3 and preventive effect against interstitial pneumonia. *J. Clin. Biochem. Nutr.* 2019;65:245–251.
15. Nimavat N, Singh S, Singh P, Singh SK, Sinha N. Vitamin D deficiency and COVID-19: A case-control study at a tertiary care hospital in India. *Ann Med Surg (Lond)* . 2021;68:1-6.
16. Jakovac H. COVID-19 and vitamin D-Is there a link and an opportunity for intervention? *Am. J. Physiol. Endocrinol. Metab.* 2020;318:E589.
17. Vasheghani M, Jannati N, Baghaei P, Rezaei M, Aliyari R, MMarjani M. The relationship between serum 25-hydroxyvitamin D levels and the severity of COVID-19 disease and its mortality *Scientific Reports* 2021;1-5.
18. PiumikaSooriyaarachchi a, b , Dhanushya T. Jeyakumar b, c , Neil King a , Ranil Jayawardena. Impact of vitamin D deficiency on COVID-19. *Clinical Nutrition ESPEN* 2021;44:372-378.
19. TeamaMAEM, Abdelhakam DA, Elmohamadi MA, Badr FM. Vitamin D deficiency as a predictor of severity in patients with COVID-19 infection. *Science Progress* 2021;104(3):1–14.
20. Singh S, Nimavat N, Singh AK, Ahmad S, Sinha N. Prevalence of Low Level of Vitamin D Among COVID-19 Patients and Associated Risk Factors in India – A Hospital-Based Study. *International Journal of General Medicine* 2021;14 2523–2531.
21. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat. Rev. Endocrinol.* 2021;17:11–30.
22. Bhatraju P.K., Ghassemieh B.J., Nichols M. Covid-19 in critically ill patients in the seattle region - case series. *N. Engl. J. Med.* 2020;382.
23. Malek Mahdavi A. A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: implications for a potential treatment for COVID-19. *Rev. Med. Virol.* 2020;30:e2119.

24. Tay MZ, Poh C.M., Rénia L., MacAry P.A., Ng L.F.P. The trinity of COVID-19: immunity, inflammation and intervention. *Nat. Rev. Immunol.* 2020;20:363–374.
25. Arentz M, Yim E, Klaff L. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *J. Am. Med. Assoc.* 2020;323:1612–1614.
26. Clark CE, McDonagh STJ, McManus RJ, Martin U. COVID-19 and hypertension: risks and management. A scientific statement on behalf of the British and Irish Hypertension Society. *J. Hum. Hypertens.* 2021;35:304–307.
27. Zhou F, Yu T, Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395:1054–1062.
28. Ye K, Tang F, Liao X. Does serum vitamin D level affect COVID-19 infection and its severity?-A case-control study. *J. Am. Coll. Nutr.* 2020.
29. Mamani M, Muceli N, Ghasemi Basir HR, Vasheghani M, Poorolajal J. Association between serum concentration of 25-hydroxyvitamin D and community-acquired pneumonia: a case-control study. *Int. J. Gen. Med.* 2017;10:423–429.
30. Talebi F, Rasooli Nejad M, Yaseri M, Hadadi A. Association of vitamin D status with the severity and mortality of community-acquired pneumonia in Iran during 2016-2017: a prospective cohort study. *Reports Biochem. Mol. Biol.* 2019;8:85–90.
31. Carpagnano GE, Di Lecce V, QuarantaVN. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. *J. Endocrinol. Invest.* 2020.
32. Munshi R, HusseinMH, ToraihEA. Vitamin D insufficiency as a potential culprit in critical COVID-19 patients, *J. Med. Virol.* 2021;93:733–740.