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Case-controlled Study

Vitamin D deficiency and COVID-19: A case-control study at a tertiary care hospital in India

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ABSTRACT

Background: As the pandemic COVID-19 affected developing and developed countries, there is no proven treatment options available yet. The anti-inflammatory, antiviral and immune modulator effect of Vitamin D could be beneficial to COVID-19.

Aim: To find out the possible association between Vitamin D and COVID-19.

Methods: The present case-control study was conducted at tertiary care hospital, AIIMS, Patna, Bihar, India. Total 156 cases and 204 controls were enrolled in the study after obtaining informed consent. Categorization of the patients were done based on clinical severity and level of Vitamin D. The association between these categories with different variables were analyzed using regression analysis and other statistical tests.

Results: The status of Vitamin D (optimal, mild to moderate deficiency and severe deficiency) differed significantly among cases and controls. Diabetes and hypertension were most prevalent comorbidities among cases. On regression analysis, the difference in Vitamin D level was significant (aOR, 3.295; 95%CI, 1.25–8.685). The association between Vitamin D status and clinical severity group was statistically significant among cases. Among all variables, age, diabetes, hypertension and clinical severity were associated with worst outcome.

Conclusion: Vitamin D status appears to be strongly associated with COVID-19 clinical severity. After COVID-19 confirmation, Vitamin D level should be measured in all patients and curative plus preventive therapy should be initiated.

1. Introduction

The world is facing the most challenging pandemic in the 21st century. The developed and developing countries are facing the burden equally and no proven treatment options available. The COVID-19 pandemic has become a global threat, with an inexplicable course of action and suboptimal response to the multitudes of therapies being tried. The pandemic has not affected only health but also had a great economic burden on the lives of entire world. Researchers are finding ways and measures by which we can control the risks and can reduce the death tolls which are a greater and clinical important aspect [1]. Vitamin D is termed as a steroid hormone which is produced when ultraviolet radiation from the sun falls on the skin. It is the endogenous production of Vitamin D, while exogenously it is taken from the food and other dietary supplements [2]. Vitamin D deficiency is now considered as a public health problem and globally affecting over a billion of population [3]. Many studies have revealed that if optimal serum level of Vitamin D is present, it decreases viral infections for example HIV, Dengue Hepatitis B and C, Pneumonia. Epidemiological study (RCT) have revealed that Vitamin D supplementation can decrease the risks of influenza especially in winters [4]. Thus, different findings have revealed the fact that vitamin D supplementation can decrease the risks of hospitalization in patients [5]. Recent clinical research has found a strong association between Vitamin D and acute respiratory infections such as epidemic influenza [6]. The SARS-CoV-2 is considered as a global threat and has various health and life threats. Recent study by Piroth et al. revealed that mortality is higher among COVID-19 than influenza [7]. Globally if we consider the differences in severity and fatality rates of COVID-19 cases, it is important to find the reasons for it. The most important factor to improve the immune system is healthy nutrition and, Vitamin D plays an important role in boosting our immune system. However, we have less knowledge about the role and

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association of Vitamin D and controlling the viral infections. Vitamin D reduces the viral infection incidences coincide with epidemic of Influenza, considered as "seasonal stimulus" due to effect of ultraviolet radiation and level of Vitamin D [8]. There are three ways by which vitamin D decreases the risks of infections. First is by controlling physical barriers, secondly by cellular natural immunity and thirdly by adaptive immunity [9].

A lot of research has recently focussed on the pleiotropic effects (immune modulatory, anti-inflammatory and antiviral) of Vitamin D, helpful against viral respiratory infections. It is quite possible, that these unique properties of Vitamin D may prove beneficial in COVID-19, which is primarily an infectious respiratory disorder, with an unprecedented inflammatory response. The aim of this study was to determine the association between Vitamin D status and COVID-19 clinical severity.

2. Materials and methods

2.1. Aim

The study aimed to find the possible relation between Vitamin D and COVID-19.

2.1.1. Study setting

The current study was carried out in tertiary care hospital, Patna, Bihar, India. Positive RT-PCR test positive for SARS-CoV-2, while the controls were selected who had RT-PCR negative test. All cases and controls were enrolled during August 01, 2020 to September 15, 2020. This study was performed in line with the principles of the Declaration of Helsinki and approved by the IRC and IEC, AIIMS Patna, vide Approval N0.-AIIMS/Pat/IEC/IRC/2020/501. Informed consent was obtained from all participants.

2.1.2. Study participants selection

Inclusion criteria: The individuals with a positive RT-PCR for SARS-COV-2 either from the Flu clinic or COVID-19 ward were included as cases. Individuals with a negative RT-PCR were included as controls.

Exclusion criteria: The individuals were taking Vitamin D supplements currently or had taken them in the last 6 months or status could not be ascertained, were also excluded from the study.

156 cases and 204 controls were included in the study, and 14 cases and 46 controls were excluded due to Vitamin D supplement status during screening phase of the study (July–August 2020).

2.1.3. Data collection and analysis

Data was collected on a pre-validated case recording form. Demographic data (age, sex, alcohol and smoking history, co-morbidities) of COVID-19 cases was collected and Vitamin D estimation was sent along with other routine investigations. Vitamin D level was estimated using a chemiluminescence based immunoassay analyzer [10]. The study subjects were classified into different severity categories according to World Health Organization (WHO) guidelines [11].

2.2. Cases and controls were divided into three groups by vitamin D status [12]

1 Optimal (Vitamin D $\geq$ 25 ng/mL)
2 Mild to moderate deficiency (Vitamin D = 10 ng/mL-24 ng/mL)
3 Severe deficiency (Vitamin D < 10 ng/mL).

2.3. Data processing and analysis

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. Pearson Chi-square was used to examine the associations between categorical variables; Fisher's exact test was also used when needed. Comparison of means between two groups were done using the Independent Samples T-test or Mann-Whitney, while a comparison between three groups was done using one-way ANOVA or Kruskal-Wallis. The Bonferroni post-hoc test was used for multiple comparisons. A binary logistic regression was carried out to identify which factors were independently associated with cases of COVID-19 using the Backward Likelihood method. All variables were initially entered in the model. Adjusted Odds ratios (aOR) were presented in tables with 95 % confidence intervals (CI). We evaluated the models using Nagelkerke R^2, Omnibus test, and Hosmer-Lemeshow goodness-of-fit test. Data analyses were performed on SPSS v.27 (SPSS inc. Chicago, IL, USA). [13]. Significance level was set at 0.05.

2.4. Classification of patient severity

The patients were classified according to the Ministry of Health and Family Welfare's criteria in India [14]. The patient's classification was based on the following clinical factors, according to the guideline:

a) Mild: Without evidence of breathlessness or hypoxia (normal saturation)
b) Moderate: the presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 <94 % (range 90–94 %) on room air, respiratory rate more or equal to 24 per minute
c) Severe: clinical signs of pneumonia plus one of the following; respiratory rate >30 breaths per minute, severe respiratory distress, SpO2 <90 % on room air

This study was prepared in compliance with the STROCSS criteria [15] and was registered with Research Registry registration ID - researchregistry7001, with accessible link: https://www.researchregistry.com/browse-the-registry#home/registrationdetails/60fe962ba204cf001e4b6527/

3. Results

Total 156 cases and 204 controls data were analyzed. There was no statistical difference between mean Vitamin D level among cases and controls (p = 0.757). But the status of Vitamin D among different categories of optimal, mild to moderate deficiency and severe deficiency was significant (p = 0.006). Alcohol consumption (23.7 %) and smoking (25.0 %) were more common among the cases than controls. Smoker is someone who smokes any tobacco product, either daily or occasionally. Alcohol use has been defined as following for male and female [16].

- For male, consuming 4 drinks on any day or more than 14 drinks per week
- For female, consuming 3 drinks on any day or more than 7 drinks per week

Diabetes (10.9 %) and hypertension (10.3 %) were the most prevalent comorbidities (Table 1) among the cases.

Table 2 show multivariable regression model for different variables among cases. Advanced age and smoking were significantly associated to COVID-19 in the multivariable regression model. The association between Vitamin D and COVID-19 was found significant [Nagelkerke R Square = 0.308, aOR 3.295 (1.25–8.685)].

Table 3 describes the characteristics and association between different variables with severity of COVID-19 cases. Age, BMI, hypertension, diabetes, Vitamin D status and death were significantly associated CVOID-19. Compared to mild clinical severity cases, moderate/severe patients had advanced age and increased BMI. Alcohol consumption and smoking were proportionally high among moderate/severe cases then mild ones. Comorbid conditions, mainly diabetes and hypertension were more prevalent among moderate/severe cases. The association between level of Vitamin D and clinical severity (mild,

Table 1
Main characteristics of COVID-19 cases and controls.

Variables	Controls n = 204 n (%)	Cases n = 156 n (%)	p
Sex (male)	145 (71.1)	118 (75.6)	0.334*
Age (years), mean ± SD	31.1 ± 8.6	41.6 ± 16.4	<0.001†
BMI (kg/m2), mean ± SD	22.9 ± 4.2	24.5 ± 4.8	0.001†
Vitamin D (ng/mL), mean ± SD	19.7 ± 8.4	20.0 ± 11.7	0.757†
Alcohol	16 (7.8)	37 (23.7)	<0.001*
Smoking	14 (6.9)	39 (25.0)	<0.001*
Diabetes Mellitus	0 (0)	17 (10.9)	<0.001*
Hypertension	0 (0)	16 (10.3)	<0.001*
Chronic Kidney Disease	0 (0)	4 (2.6)	0.034**
HTH	0 (0)	6 (3.8)	0.006**
Cancer	0 (0)	1 (0.6)	0.433**
CAD	0 (0)	4 (2.6)	0.034**
COPD	0 (0)	1 (0.6)	0.433**
AF	0 (0)	1 (0.6)	0.433**
HBsAG	0 (0)	1 (0.6)	0.433**
Vitamin D status[a]			0.006*
Optimal	44 (21.6)	33 (21.2)	
Mild to moderate deficiency	148 (72.5)	98 (62.8)	
Severe deficiency	12 (5.9)	25 (16.0)	
Symptoms severity			<0.001*
Asymptomatic	98 (48.0)	0 (0)	
Mild	106 (52.0)	109 (69.9)	
Moderate	0 (0)	20 (12.8)	
Severe	0 (0)	27 (17.3)	
Death	0 (0)	18 (11.5)	<0.001*

*Pearson Chi-square; **Fisher's Exact Test; †Independent Samples T-test.
BMI= Body Mass Index, HTH= Hypothyroidism, CAD= Coronary Artery Disease, COPD= Chronic Obstructive Pulmonary Disease, AF = Atrial Fibrillation, HBsAG = Hepatitis B surface antigen.
[a] Vitamin D status: Optimal (≥25 ng/mL), Mild to moderate deficiency (10 ng/mL-24 ng/mL), Severe deficiency (<10 ng/mL).

Table 2
Factors independently associated to COVID-19-multivariable regression.

Factors	B	SE	Wald c	p	aOR	95 % CI
Age	0.055	0.012	22.046	<0.001	1.057	1.033–1.081
Smoking	1.272	0.362	12.313	<0.001	3.566	1.753–7.256
Vitamin D status[a]						
Mild to moderate deficiency (vs Optimal)	0.344	0.316	1.184	0.277	1.41	0.759–2.618
Severe deficiency (vs. Optimal)	1.192	0.495	5.814	0.016	3.295	1.25–8.685

Variables entered: Age, SEX, BMI, Alcohol, Smoking, DM, HTN, CKD, HTH, Cancer, CAD, COPD, AF, HBSAG, Vitamin D_deficiency.
Nagelkerke R Square = 0.308, Omnibus test: p < 0.001, Hosmer and Lemeshow Test p = 0.205, Method: Backward LR.
B = regression coefficient, SE = standard error, 95 % CI = 95 % confidence interval.
[a] Vitamin D status: Optimal (≥25 ng/mL), Mild to moderate deficiency (10 ng/mL-24 ng/mL), Severe deficiency (<10 ng/mL).

moderate and severe) categories was statistically significant.

Table 4 describes the association between different factors with mortality among COVID-19 patients. Among these age (p=<0.001), hypertension (p=<0.001), diabetes mellitus (p = 0.03) and clinical severity (p=<0.001) were found significant. The mean age for survivors was 38.8 ± 14.4 years and 63.2 ± 14.9 for fatality. The difference between age group was statistically significant (p=<0.001). The mean level of Vitamin D among non-survivors was 18.8 ± 12.8 ng/ml, while among survivors it was 20.2 ± 11.6 ng/ml. Among all comorbidities, hypertension (38.9 %) and diabetes (27.8 %) were more prevalent among non-survivors.

Table 3
Main characteristics of COVID-19 cases according to symptoms severity.

	Symptoms severity among cases (N = 156)			p
	Mild (n = 109) n (%)	Moderate (n = 20) n (%)	Severe (n = 27) n (%)	
Sex (male)	78 (71.6)	17 (85.0)	23 (85.2)	0.195*
Age (years), mean ± SD	34.8 ± 11.5[a]	53.6 ± 15.4[b]	60.2 ± 14.8[b]	<0.001†
BMI (kg/m2), mean ± SD	23.6 ± 4.6[a]	28.2 ± 4.9[b]	25.4 ± 4.3[a,b]	<0.001‡
Vitamin D (ng/mL), mean ± SD	20.2 ± 10.4	20.3 ± 12.0	19.0 ± 16.1	0.183‡
Alcohol	20 (18.3)[a]	10 (50.0)[b]	7 (25.9)[a,b]	0.009*
Smoking	22 (20.2)	7 (35.0)	10 (37.0)	0.105*
Diabetes Mellitus	2 (1.8)[a]	5 (25)[b]	10 (37)[b]	<0.001**
Hypertension	1 (0.9)[a]	5 (25)[b]	10 (37)[b]	<0.001**
Chronic Kidney Disease	0 (0)[a]	0 (0)[a,b]	4 (14.8)[b]	0.001**
HTH	1 (0.9)[a]	2 (10)[b]	3 (11.1)[b]	0.011**
Cancer	0 (0)	1 (5.0)	0 (0)	0.128**
CAD	0 (0)[a]	3 (15)[b]	1 (3.7)[a,b]	0.002**
COPD	0 (0)	0 (0)	1 (3.7)	0.301**
AF	0 (0)	0 (0)	1 (3.7)	0.301**
HBsAG	0 (0)	1 (5.0)	0 (0)	0.128**
Vitamin D status				0.002**
Optimal	20 (18.3)[a]	5 (25)[a]	8 (29.6)[a]	
Mild to moderate deficiency	78 (71.6)[a]	11 (55.0)[a,b]	9 (33.3)[b]	
Severe deficiency	11 (10.1)[a]	4 (20.0)[a,b]	10 (37.1)[b]	
Death	0 (0)[a]	3 (15)[b]	15 (55.6)[c]	<0.001**

Each superscript letter (a, b and c) denotes a subset of severity categories whose column proportions do not differ significantly from each other at the 0.05 level. Groups that share the same letter are not significantly different. So, if 2 groups have "a", they are not different; if one has a and the other b, they are different. If a group has "a, b", they are not different from groups who have a nor from groups who have b.
*Pearson Chi-square; **Fisher's Exact Test; †One-Way ANOVA; ‡Kruskal-Wallis Test.

4. Discussion

The previous research shows a link between Vitamin D and repiratory infections. A studyby Cannell et al. revealed that those who were taking Vitamin D supplement were less likely to have respiratory infections [8,13,14]. The Vitamin D might have a pleotropic effect on multiple organs and plays an important role as immunomodulator, antiviral and anti-inflammatory [17–19]. Vitamin D also promotes the degradation of SARS-CoV-2 through autophagy mechanism via acidification process of endolysosomes [16,17]. COVID-19 suppresses the production of ACE2 receptors, and research suggests that vitamin D stimulates ACE2, which can bind to SARS-CoV-2 and prevent it from attaching to ACE2 receptors [18–20]. If remain untreated, COVID-19 can rapidly proceed to cytokine storm and hyper-inflammatory state in high-risk patients [21–25]. The anti-inflammatory effects of Vitamin D include inhibition of TNF-α (tumor necrosis factor-α) and IL-6 [26]. Traditionally known risk factor of COVID-19 like older age, high BMI, hypertension and diabetes, were also observed in the present study. The findings of Petre et al. point to the possibility that the elderly population has very low Vitamin D levels, making them more sensitive to COVID-19 [27].

The diabetes and hypertension were significantly associated with COVID-19 severity and mortality in the present study. Changes on glucose homeostasis, immunological status, inflammation and activation of the RAAS (renin–angiotensin–aldosterone system) are all possible pathogenetic linkages between COVID-19 and diabetes mellitus [28,29]. Diabetes mellitus was observed in 58 % and 33 % of severely ill COVID-19 patients admitted to Intensive Care Units (ICUs) in the United States, demonstrating a relationship between severe COVID-19 and diabetes mellitus [24,25]. Increased age and poor control of blood

Table 4
Main characteristics of COVID-19 cases according to death.

Variables	Deaths among cases (N = 156)		
	Alive n = 138 n (%)	Dead n = 18 n (%)	P
Sex (male)	102 (73.9)	16 (88.9)	0.244
Age (years), mean ± SD	38.8 ± 14.4	63.2 ± 14.9	<0.001[b]
BMI (kg/m2), mean ± SD	24.4 ± 4.8	25.1 ± 5.1	0.532[b]
Vitamin D (ng/mL), mean ± SD	20.2 ± 11.6	18.8 ± 12.8	0.333[c]
Alcohol	35 (25.4)	2 (11.1)	0.245*
Smoking	34 (24.6)	5 (27.8)	0.776*
Diabetes Mellitus	12 (8.7)	5 (27.8)	0.030*
Hypertension	9 (6.5)	7 (38.9)	<0.001*
Chronic Kidney Disease	2 (1.4)	2 (11.1)	0.066*
HTH	3 (2.2)	3 (16.7)	0.021*
Cancer	1 (0.7)	0 (0)	1*
CAD	2 (1.4)	2 (11.1)	0.066*
COPD	1 (0.7)	0 (0)	1*
AF	0 (0)	1 (5.6)	0.115*
HBsAG	1 (0.7)	0 (0)	1*
Vitamin D status[a]			0.167*
Optimal	28 (20.3)	5 (27.8)	
Mild to moderate deficiency	90 (65.2)	8 (44.4)	
Severe deficiency	20 (14.5)	5 (27.8)	
Symptoms severity			<0.001*
Mild	109 (79.0)	0 (0)	
Moderate	17 (12.3)	3 (16.7)	
Severe	12 (8.7)	15 (83.3)	

*Fisher's Exact Test.
[a] Vitamin D status: Optimal (≥25 ng/mL), Mild to moderate deficiency (10 ng/mL-24 ng/mL), Severe deficiency (<10 ng/mL).
[b] Independent Samples T-test.
[c] Mann-Whitney Test.

pressure show plausible association between COVID-19 severity and hypertension [30,31]. Another study from China reported that mortality among COVID-19 was apparently high among the patients with hypertension (48 % vs 23 % in survivors) [32].

In the present study Vitamin D level was significantly associated with the severity of disease. The deficiency was 37.1 % in severe cases compared to 20 % and 10.1 % among moderate and moderate cases respectively. A study by Kun ye et al. also reported higher percentage of patients among severe/critical disease with Vitamin D deficiency compared to mild/moderate disease [33]. A cross sectional study among COVID-19 patients from India reported 58.97 % of Vitamin D deficiency 89.1 % insufficiency [34]. A regression analysis, including all potential risk factors as independent variables, indicate statistically significant difference between Vitamin D deficiency and COVID-19 (aOR, 3.29; 95 % CI, 1.25–8.68) in the present study. Similar type of case control study reported significant association between Vitamin D deficiency and critical/severe COVID-19 (OR, 15.18; 95 % CI, 1.23–187.45) [35–37]. Several other studies in past also demonstrated the association between Vitamin D deficiency and severity of the respiratory tract infections [29–31]. A study by Panagiotou et al. reported that Vitamin D deficiency prevalence was higher among patients admitted to Intensive Therapy Unit than Non-ITU patients (81 % vs 60.9 %) [38]. A meta analysis conducted by Munshi et al. reported that patients with poor prognosis had very low level of Vitamin D compared to those with good prognosis [39].

A recent study found that nearly 75 % of hospitalized and 85 % of ICU care patients with COVID-19 symptoms had Vitamin D deficiency, which is consistent with our findings [40]. A study conducted to assess the inflammatory response and lung involvement, found that Vitamin D deficiency was associated with altered inflammatory response and higher lung involvement [41]. Vitamin D insufficiency was also linked to high infection rates and death from COVID-19 in European countries [42]. Other research from Indonesia discovered that 90 % of COVID-19 patients had Vitamin D insufficiency [43]. In the present study, out of total 18 fatalities, 7 had hypertension and 5 had diabetes. Yang and colleagues reported that of the 32 fatalities from a group of 52 hospitalized patients in ICU in China owing to COVID-19, 22 % had diabetes and another 22 % had cerebrovascular disorders [44]. Probably in the epithelial cells of the lungs, kidneys, and blood vessels, SARS-CoV-2 attaches to its target via ACE2. Increased expression of ACE2 may be responsible for high infection rate and mortality among patients of diabetes and hypertension, specifically those who have uncontrolled conditions [45,46].

Vitamin D supplementation, taken daily or weekly, lowers ARI (acute respiratory infection) by 32 %–60 %, according to a systemic review and meta-analysis of RCTs, indicating that it has a preventive and safe impact [47]. To understand the role of Vitamin D among COVID-19 patients more clearly, many clinical trials has been also initiated and registered. The results of these trials would be helpful to decide further strategies, but the current evidence also favors that patients of COVID-19 had low level of Vitamin D. For preventive and treatment purpose, supplementation with Vitamin D among COVID-19 patients will halt the progression of disease and subsequent mortality.

4.1. Strengths & limitations

This case control study is one of the few studies from this region to find an association between Vitamin D and COVID-19. Previous research has mostly used case reports and case series but comparison with a control group as reference is better design to find out (a) how Vitamin D level differ among cases and controls (b) what is the association between Vitamin D and clinical severity. Still our findings must be interpreted with caution because of certain limitations. Still it is not known and debate ongoing whether viral infection/inflammation reduce the Vitamin D level or low level of Vitamin D make person more susceptible, the findings of the such studies including this one, should be interpreted with care. Vitamin D supplement, smoking and alcohol consumption data were self-reported. This study found the association between Vitamin D and COVID-19 severity in India. Further clinical trials and multi-center studies may be needed to validate these findings and further investigate the beneficiary effect of Vitamin D and COVID-19.

5. Conclusion

The present study found association between low level of Vitamin D and COVID-19 severity. In many countries people are taking a diet which is deficient and lacks micronutrients. A health daily diet including micronutrients more than RDA can boost our immune system and makes it stronger against viral infections. Those who develop COVID-19, should be screened for Vitamin D levels and if found insufficient/deficient, proper treatment should be given.

Please state any conflicts of interest

All authors declare that they have no conflict of interests.

Please state any sources of funding for your research

There was not any direct fund to carry out the research.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki and approved by the IRC and IEC, AIIMS Patna, vide Approval N0.-AIIMS/Pat/IEC/IRC/2020/501.

Consent

Informed consent was obtained from the participant before enrolment in to study.

Author contribution

All authors contributed significantly and in agreement with the content of the article. All authors were involved in project design, data collection, analysis, statistical analysis, data interpretation and writing the manuscript. All authors read and approved the final, submitted version.

Registration of research studies

1 Research Registry registration ID - researchregistry7001

Guarantor

Shruti Singh.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no conflict of interests.

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List of Abbreviations

Severe acute respiratory syndrome 2 SARS-CoV-2
Respiratory Tract Infections RTI
COVID-19 Corona Virus Disease 2019
Acute Respiratory Distress Syndrome ARDS
Angiotensin Converting Enzyme 2 ACE2

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