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Original Research Article

Vitamin D status and its association with the severity of COVID-19 among hospitalized patients

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ABSTRACT

Background: Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), causing COVID-19, manifests with outcomes ranging from mild to severe, even fatal. The reason for severe symptoms remains unclear. Vitamin D is implicated in the pathogenesis of severe COVID-19, including ARDS, cytokine storms, and thrombotic complications. The aim of this study was evaluation of vitamin D status and its association with the severity of COVID-19 patients attending Bangabandhu Sheikh Mujib medical University (BSMMU).
Methods: This cross-sectional study, conducted at BSMMU, Dhaka from January to December 2021, included 103 adult COVID-19-positive patients from both genders. Disease severity was assessed using WHO guidelines, and vitamin D levels recorded. Data were collected using a pre-designed datasheet after obtaining written informed consent.
Results: Among 103 COVID-19 patients, 55.3% were vitamin D deficient, 26.2% insufficient, and 18.4% sufficient. Most were male (65%) in their sixth and seventh decades. The mean vitamin D level was 20.97±10.96 ng/ml with a median of 18.10 ng/ml. Vitamin D deficiency was highest among critical patients (84.6%), followed by severe (71.1%), moderate (41.9%), and mild (28.6%) cases ($p<0.001$). Severe patients had a significantly higher deficiency rate (74.5%) compared to non-severe (36.5%) cases ($p<0.001$). Symptoms such as cough (96.5%), fever (89.5%), and shortness of breath (78.9%) were prevalent in the vitamin D deficiency group.
Conclusions: This study reveals a 55% prevalence of vitamin D deficiency in COVID-19 patients, correlating independently with disease severity. Hypertension and diabetes are notable comorbidities. It underscores the importance of assessing vitamin D levels in clinical practice.

Keywords: COVID-19, Coronavirus disease 2019, SARS-CoV-2, ARDS

INTRODUCTION

Coronavirus disease (COVID-19) is a respiratory and systemic disorder caused by SARS-CoV-2 with a range of severity from mild respiratory symptoms to severe lung injury, multi-organ failure, and death. WHO declared COVID-19 outbreak as a pandemic, On March 11, 2020.[1] The outbreak of (COVID-19) is ongoing globally and

causing a major public health challenge. SARS-CoV-2 can present with the common cold to pneumonia and about 19% of patients with COVID-19 have severe symptoms and need for hospitalization.[2] A total of 448,686,646 confirmed cases and 6,030,081deaths has occurred worldwide up to March 8, 2022.[3]

In Bangladesh, the COVID-19 cases were first detected on March 8, 2020. Since then, the pandemic has spread day by day over the whole country and the number of affected people has been increasing. Till then March 8, 2022 total of 1,948,148 new cases were detected in Bangladesh.[3] SARS-CoV-2 is a beta coronavirus, it is a single-stranded RNA, enveloped virus that is 50-200 nm in diameter.[4] COVID-19 is more prevalent among older adults, nursing home residents, and health care workers, populations who all have increased risk of vitamin D deficiency.[5] Vitamin D is a seco-steroid that has immunomodulatory, antifibrotic, anti-inflammatory, and antioxidant actions. There is growing evidence that it may play a role in the pathophysiological processes of COVID-19.[6]

Vitamin D (Vit D) is a fat-soluble vitamin also called the sunshine vitamin. It is produced in human skin from 7-dehydrocholesterol due to exposure to ultraviolet B rays (UVB; 280-315 nm range) from sunlight. The subcutaneous production by UVB exposure is the major source of vitamin D and dietary sources include dairy products or fish liver 1,25-dihydroxy vitamin D [1,25-(OH)2 D] is the active form of vitamin D which plays a major role in calcium homeostasis.[7] Vitamin D enhances immune response both innate and acquired and suppress cytokine storm.[8] The virus enters the respiratory cells through the angiotensin-converting enzyme 2 (ACE-2) receptor on type II pneumocytes.[4] In COVID-19 patients the innate immune system generates both pro-inflammatory and anti-inflammatory cytokines. Vit D reduce pro-inflammatory cytokines by macrophages and increase anti-inflammatory cytokine and also decrease the production of T helper cell type 1 (Th1) cytokines such as interferon-γ and tumor necrosis factor-α (TNF-α).[8]

It is estimated that 1 billion people worldwide are vitamin D deficient (i.e., circulating 25(OH) D concentrations <20 ng/mL) and 50% population have insufficient vitamin D status (i.e., 25(OH) D <30 ng/dl). Aging decreases the ability of the skin to synthesize vitamin D and increased skin pigmentation reduces the efficacy of UV-B to stimulate the synthesis of vitamin D. The prevalence of vitamin D deficiency is highest in the elderly (61%), the obese (35% higher than in nonobese), nursing home residents (50-60% of nursing home and hospitalized patients), and those with higher melanin in their skin (40%).[9] Vitamin D Insufficiency highly prevalent in severe COVID-19 patients. Vitamin D insufficiency and COVID-19 share numerous associations including hypertension, diabetes, obesity, advanced age, and male sex, coagulopathy, and immune dysfunction.[10] Vitamin D status was defined as follows: deficiency 25(OH) D is 0 to <20 ng/ml, insufficiency 20 to 30 ng/ml, sufficiency >30-100 ng/ml.[11] Recent evidence shows that 46.5% of COVID-19 patients were suffering from vitamin D deficiency and in 43.3% of patients were suffering from vitamin D insufficiency.[12] The main aim of the study is to evaluate the vitamin D status and its association with severity of COVID-19 patients attending BSMMU.

Objectives

General objective

General objective was to explore the vitamin D status and its association with the severity of COVID-19 patients.

Specific objective

Specific objectives were to explore the proportion of Vitamin D deficiency, insufficiency, and sufficiency among COVID-19 patients, to investigate the factors associated with the severity of COVID-19 patients, to observe the Vitamin D level in different groups (mild, moderate, severe and critical) and in between severe and non-severe group of COVID-19 patients and to explore the independent association of vitamin D status with the severity of COVID-19 on adjusting the effects of covariates.

METHODS

Study design

A study design used was cross-sectional observational analytical.

Place of study

Study carried out at COVID-19 unit (Triage and inpatient), BSMMU, Dhaka.

Study period

Study conducted from January, 2021 to December, 2021.

Study population

Patients positive RT PCR for COVID-19 attending (Triage and Inpatient, COVID-19 Unit) BSMMU were selected.

Sample

Patients who fulfilled the inclusion and exclusion criteria were selected for study.

Sampling technique

Non- probability, consecutive sampling technique was applied. The sample size required for multivariate regression analysis was calculated as follows, using the formula suggested by an author.[13]

$n \geq 50 + 8(m)$

Here, n=sample size and m=number of independent variables

Taking m=6 (age, sex, tobacco smoking, diabetes, hypertension, vitamin D status)

$n \geq 50 + 8(6) = n \geq 98$

So, at least 98 patients needed for the study but we recruited 103 COVID-19 patients.

Sample size

At least 98 patients who fulfilled the inclusion criteria were selected.

Inclusion criteria

RT-PCR report positive for COVID-19 patients attended in COVID unit (Triage and inpatient) BSMMU with age≥18 years of both sexes and patients who gave informed written consent to participate were included in study.

Exclusion criteria

Patients taking vitamin D supplements or previously took within the last 3 weeks. Known case of chronic kidney disease, chronic pancreatitis, celiac disease, liver failure, Crohn's disease, cystic fibrosis, and gastric bypass surgery. The patient who previously taking a corticosteroid, phenobarbitone, were included in the exclusion criteria pregnant women and recent child birth were excluded.

Data collection procedure

Patients were thoroughly briefed on the study's purpose, procedures, risks, and their right to refuse participation before enrolling voluntarily. Adult COVID-19 positive patients aged >18, attending BSMMU Triage and Inpatient COVID-19 unit, were assessed if they met inclusion/exclusion criteria. A total of 103 COVID-19 infected patients (male and female) consented to participate. Demographic variables (age, sex, smoking), comorbidities (diabetes, hypertension, pre-existing lung or cardiovascular disease), and COVID-19 symptoms were recorded. Physical examinations included vital signs and oxygen saturation measured by pulse oximetry. Chest HRCT scans assessed pneumonia features. Disease severity was categorized as per WHO guidelines. Blood samples were drawn aseptically and serum isolated for 25(OH) D analysis via chemiluminescence micro particle immunoassay at BSMMU biochemistry department. All data were recorded in pre-designed data collection sheet.

Data analysis

Data analysis was conducted using SPSS version 23. Categorical variables were summarized with percentage distributions and frequency tables. The association between variables was assessed using Chi-square test and Fisher's exact test when applicable. Continuous variables were summarized using means, standard deviation, median, and range. Mean differences between severe and non-severe groups were estimated using unpaired t-test for normally distributed data or Mann-Whitney test for non-normally distributed data.

Ethical consideration

Before starting this study, the research protocol was submitted to the institutional review board of BSMMU, Dhaka. Voluntary informed written consent was taken from every patient after an explanation of the procedure and purpose of the study. Every patient was given the right to participate or refuse to participate. Every patient had the right to withdraw from the study at any time without compromising their medical care. The patient´s privacy was ensured and the patient´s information was not disclosed to anyone.

RESULTS

This cross-sectional study was conducted in department of respiratory medicine, BSMMU, Dhaka, from January, 2021 to December, 2021. A total of one hundred and three patients were included in this study based on inclusion and exclusion criteria. The main objective was to determine the vitamin D status in COVID-19 patients.

Table 1 is showing the distribution of the participants according to age. Majority of the participants were from 61-70 years of age, followed by 51-60 years of age. The mean ± SD age of the participants was 58.33±12.56 years. Median and range of age of the participants was 60 years, and 27-88 years, respectively.

Table 1: Distribution of the participants according to age, (n=103).

Age (in years)	N	Percentage
18-40	13	12.6
41-50	13	12.6
51-60	30	29.1
61- 70	36	35.0
>70	11	10.7
Total	103	100.0
Mean ± SD	58.33±12.56	
Median	60	
Range	27-88	

Table 2 is showing the distribution of COVID-19 patients according to vitamin D level. The mean ± SD vitamin D level of the participants was 20.97±10.96 ng/ml. Median (range) of vitamin D level was 18.10 (4.80-59.24) ng/ml. Majority (55.3%) of the participants/ study subjects had vitamin-D deficiency and mean ± SD of vitamin D level among these participants was 13.05±4.18 ng/ml. Vitamin

D level of only 19 (18.4%) participants was sufficient and mean ± SD of vitamin D level among these participants was 38.56±7.96 ng/ml. Median (range) of vitamin D level among the participants having vitamin D level sufficiency was 18.10 (4.80-59.24) ng/ml.

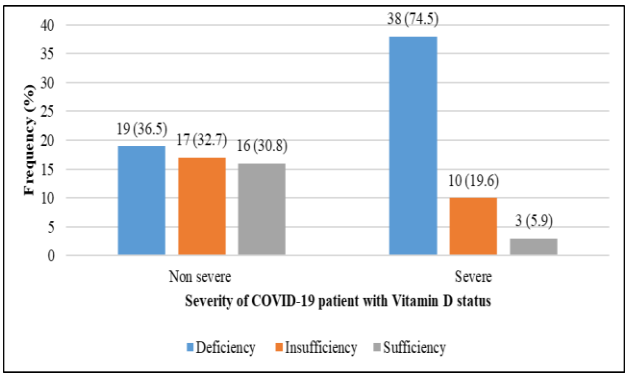

Figure 1: Vitamin D deficiency, insufficiency and sufficiency group between severe and non-severe group of COVID-19 patients.

Table 3 is showing the distribution of the COVID-19 patients according to age, sex, smoking status and vitamin D status. Majority [36 (35.0%)] of the participants were from 61-70 years age group followed by 51-60 years [30 (29.1%)]. Among patients with vitamin D deficiency, the highest number [20 (35.1%)] of patient were in age group of 51-60 years, followed by 16 (28.1%) in age range 61-70 years. The majority [8 (29.6%)] of the participants having vitamin-D insufficiency were from 61-70 years. There was a significant association (p=0.017) between age groups and vitamin D status. Majority of the patients suffering from vitamin D deficiency were male (64.9%). Gender distribution of COVID-19 patients in different category of vitamin D level was not statistically different (p=0.929). Among the patients with vitamin D deficiency, 23 (40.4%) were smoker. Different category of vitamin D and smoking status was not statistically associated (p=0.715).

Table 4 is showing that, among the COVID 19 patients the most common symptom was cough (98.17%), followed by fever (84.5%) and shortness of breath (65.0%). Common non-respiratory symptoms were loss of taste (63.1%) and loss of smell (59.2%). More prominent symptom in vitamin D deficiency group was cough, followed by fever and shortness of breath. The distribution of fever, shortness of breath, loss of smell and taste were significantly different in groups of vitamin D level.

Table 2: Distribution of the COVID-19 patients according to vitamin D level, (n=103).

Vitamin-D (ng/ml)	N (%)	Mean ± SD	Median (range)
Deficiency (< 20)	57 (55.3)	13.05±4.18	13.2 (4.80-19.40)
Insufficiency (20-30)	27 (26.2)	25.3±2.60	25.9 (20.90-29.92)
Sufficiency (>30)	19 (18.4)	38.56±7.96	34.9 (31.47-59.24)
Total	103 (100.0)	20.97±10.96	18.10 (4.80-59.24)

Table 3: Distribution of the COVID-19 patients according to age, sex, smoking status and vitamin D status, (n=103).

Variables		Vitamin D status			Total, N (%)	Value	Df	P value
		Deficiency (<20 ng/ml), (N=57) (%)	Insufficiency (20-30 ng/ml), (N=27) (%)	Sufficiency (>30 ng/ml), (N=19) (%)				
Age (in years)	18-40	8 (14.0)	3 (11.1)	2 (10.5)	13 (12.6)	18.589	8	0.017^{s}
	41-50	10 (17.5)	3 (11.1)	0 (0.0)	13 (12.6)			
	51-60	20 (35.1)	6 (22.2)	4 (21.1)	30 (29.1)			
	61-70	16 (28.1)	8 (29.6)	12 (63.2)	36 (35.0)			
	>70	3 (5.3)	7 (25.9)	1 (5.3)	11 (10.7)			
Sex	Male	37 (64.9)	17 (63.0)	13 (68.4)	67 (65.0)	0.147	2	0.929^{ns}
	Female	20 (35.1)	10 (37.0)	6 (31.6)	36 (35.0)			
Smoking status	Smoker	23 (40.4)	9 (33.3)	6 (31.6)	38 (36.9)	0.670	2	0.715^{ns}
	Non-smoker	34 (59.6)	18 (66.7)	13 (68.4)	65 (63.1)			

Chi-square test was performed to see the association between two groups. s=significant, ns= non-significant

Table 5 is showing that hypertension and diabetes mellitus were predominant co-morbidity in three groups. Among the patients with vitamin D deficiency 38 (66.7%) were hypertensive and 36 (63.2%) were diabetic. Among the patients with sufficient level of vitamin D 8 (42.1%) were hypertensive and 7 (36.8%) were diabetic. No significant association among past history of illness and category of vitamin D level was observed (p>0.05).

Distribution of the severity COVID-19 patients according to vitamin D status is presented in Figure 1. The maximum (74.5%) severe patients were in deficiency group than

19.6%were from insufficiency group and 5.9% were from vitamin D sufficiency group. Severity of COVID 19 and category of vitamin D level was significantly associated (p<0.001).

Table 4: Distribution of the COVID-19 patients according to symptoms in vitamin D level, (n=103).

Symptoms	Vitamin D status			Total, N (%)	Value	Df	P value
	Deficiency (< 20 ng/ml), (N=57) (%)	Insufficiency (20-30 ng/ml), (N=27) (%)	Sufficiency (>30 ng/ml), (N=19) (%)				
Fever	51 (89.5)	24 (88.9)	12 (63.2)	87 (84.5)	8.067	2	0.02^{s}
Cough	55 (96.5)	27 (100.0)	19 (100.0)	101 (98.17)	1.646	2	0.439^{ns}
Shortness of breath (SOB)	45 (78.9)	16 (59.3)	6 (31.6)	67 (65.0)	14.603	2	0.001^{s}
Chest pain	7 (12.3)	4 (14.8)	0 (0.0)	11 (10.7)	2.909	2	0.234^{ns}
Headache	12 (21.1)	8 (29.6)	5 (26.3)	25 (24.3)	0.786	2	0.675^{ns}
Fatigue	26 (45.6)	14 (51.9)	13 (68.4)	53 (51.5)	2.970	2	0.251^{ns}
Sore throat	18 (31.6)	14 (51.9)	11 (57.9)	43 (41.7)	5.594	2	0.061^{ns}
Diarrhea	10 (17.5)	5 (18.5)	8 (42.1)	23 (22.3)	5.236	2	0.072^{ns}
Nasal congestion	10 (17.5)	6 (22.2)	4 (21.1)	20 (19.4)	0.296	2	0.862^{ns}
Loss of smell	29 (50.9)	14 (51.9)	18 (94.7)	61 (59.2)	12.175	2	0.002^{s}
Loss of taste	32 (56.1)	15 (55.6)	18 (94.7)	65 (63.1)	10.014	2	0.007^{s}

Chi-square test was performed to see the association between three groups. s=significant, ns= not significant

Table 5: Distribution of the COVID-19 patients according to co-morbidities and vitamin D status, (n=103).

Past history of illness	Vitamin D status			Total, N (%)	Value	Df	P value
	Deficiency (<20 ng/ml), (N=57) (%)	Insufficiency (20-30 ng/ml), (N=27) (%)	Sufficiency (>30 ng/ml), (N=19) (%)				
Hypertension	38 (66.7)	14 (51.9)	8 (42.1)	60 (58.3)	4.157	2	0.125^{ns}
Diabetes mellitus	36 (63.2)	12 (44.4)	7 (36.8)	55 (53.4)	5.145	2	0.076^{ns}
Cardiovascular disease	9 (15.8)	2 (7.4)	1 (5.3)	12 (11.7)	2.176	2	0.337^{ns}
Pre-existing lung disease	4 (7.0)	4 (14.8)	1 (5.3)	9 (8.7)	1.750	2	0.417^{ns}

Chi-square test was performed to see the association between three groups. ns= not significant.

Table 6: Distribution of the COVID-19 patients according to severity and vitamin D status, (n=103).

Vitamin D status	Severity, N (%)				Total, N (%)	Value	Df	P value
	Mild	Moderate	Severe	Critical				
Deficiency (< 20 ng/ml)	6 (28.6)	13 (41.9)	27 (71.1)	11 (84.6)	57 (55.3)	29.63	6	<0.001^{s}
Insufficiency (20-30 ng/ml)	4 (19.0)	13 (41.9)	8 (21.0)	2 (15.4)	27 (26.2)			
Sufficiency (>30 ng/ml)	11 (52.4)	5 (16.2)	3 (7.9)	0 (0.0)	19 (18.4)			
Total	21 (100)	31 (100)	38 (100)	13 (100)	103 (100)			
Vitamin D level	28.47±8.72	23.66±12.59	17.11±8.92	13.69±5.58				

Chi-square test was performed to see the association between four groups. s=significant.

Distribution of the severity COVID-19 patients according to vitamin D status is presented in Table 6. The maximum (74.5%) severe patients were in deficiency group than 19.6%were from insufficiency group and 5.9% were from vitamin D sufficiency group. Severity of COVID 19 and category of vitamin D level was significantly associated (p<0.001). The mean ± SD level of vitamin D in non-severe group was 25.61±11.35 ng/ml and in severe group it was 16.25±8.28 ng/ml and this difference of vitamin D level was statistically significant (p<0.001).

Table 7 is showing that, the mean age of patient suffering from severe COVID-19 was59.45±10.86 years. And mean age patient suffering from non-severe COVID-19 was 57.25±14.05 years. The mean age of the participant suffering from severe illness due to COVID-19 was non-significantly higher (p=0.377). Majority of the participant of both severe and non-severe group was in between 61-70 years age group. Association between age and severity was not statistically significant (p=0.280). Among the patient suffered from COVID -19, majority were male (64.7%). There was no association of COVID-19 severity with sex (p=0.942). About 41.2% of the patient suffered from severe COVID-19 were smoker. And 32.7% patients suffered from non-severe COVID-19 were smoker. The smoking status and severity of COVID19 was not significantly associated (p=0.372).

Table 8 is showing that, mean lymphocyte count was significantly (p=0.001) higher in non-severe group (21.98±8.30) than severe group (16.29±8.48). Mean platelet count was significantly (p=0.028) less in non-severe group (239.92±79.79) than severe group (279.55±99.85). Mean CRP was significantly (p<0.001) higher in severe group (108.41±70.28) than non-severe group (37.93±36.36). Serum ferritin was significantly (p<0.001) higher in severe group (1135.30±624.22) than non-severe group (437.59±501.20).

Table 7: Distribution of age, sex, smoking status according to severity of COVID-19, (n=103).

Variables		Severity		Value	Df	P value
		Non-severe, (N=52) (%)	Severe, (N=51) (%)			
Age (in years)	18-40	10 (19.2)	3 (5.9)	5.077	4	[a]0.280 [ns]
	41-50	5 (9.6)	8 (15.7)			
	51-60	13 (25.0)	17 (33.3)			
	61-70	16 (30.8)	18 (35.3)			
	>70	6 (11.5)	5(9.8)			
	Mean ±SD	57.25 ±14.05	59.45±10.86	-0.888	101	[b]0.377[ns]
Sex	Male	34 (65.4)	33 (64.7)	0.005	1	0.942 [ns]
	Female	18 (34.6)	18 (35.3)			
Smoking status	Smoker	17 (32.7)	21 (41.2)	0.796	1	0.372 [ns]
	Non-smoker	35 (67.3)	30 (55.8)			

[b]Unpaired t test was performed to compare differences between two groups and [a] Chi-square test was performed to see the association between two groups. s=significant, ns= not significant.

Table 8: Laboratory parameters according to severity of COVID-19, (n=103).

General examination	Severity		Value	Df	P value
	Non-severe, (N=52)	Severe, (N=51)			
Hb	11.86±1.65	11.95±1.92	-0.287	101	0.775 [ns]
ESR	37.44±24.87	46.55±30.33	-1.668	101	0.098 [ns]
WBC (10^9 µg/L)	7.77±2.64	9.47±4.38	-2.393	101	[a]0.084 [ns]
Lymphocyte count	21.98±8.30	16.29±8.48	3.404	101	0.001 [s]
Platelet (10^9 µg/L)	239.92±79.79	279.55±99.85	-2.227	101	0.028 [s]
CRP	37.93±36.36	108.41±70.28	-6.411	101	<0.001 [s]
Serum ferritin	437.59±501.20	1135.30±624.22	-6.261	101	[a]<0.001[s]
D-dimer	0.68±1.31	1.31±1.31	-2.439	101	[a]<0.001[s]

Unpaired t test, [a]Mann-Whitney U test was performed to compare differences between two groups. s=significant, ns=non-significant.

Table 9: Effect of different parameters in developing severity of COVID-19, (n=103).

Variables	Odds ratio (95% CI)	P value
Diabetes	3.4 (1.3-8.7)	0.01
Hypertension	2.5 (0.95-6.4)	0.07
Vitamin D deficiency	8.6 (2.1-35.7)	0.003

Multivariate logistic regression was done to examine diabetes, hypertension, and vitamin D deficiency variables to determine those that best predict COVID-19 outcome (severity).

Table 9 is showing that COVID-19 patients with vitamin D deficiency are 8.6 (95% CI: 2.1-35.7) times at risk of developing COVID-19 severity. Among COVID-19 patients with diabetes are 3.4 (95% CI: (1.3-8.7) times at risk of developing COVID-19 severity. Among COVID-19 patients with hypertension are 2.5 (95% CI: 0.95-6.4) times at risk of developing COVID-19 severity but, non-significant.

DISCUSSION

Vitamin D deficiency and insufficiency is a worldwide condition, involving both adults and children, which has been associated with metabolic, autoimmune and infectious co-morbidities. Nowadays, the world is experiencing a pandemic caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus disease 19(COVID-19) is a respiratory tract infection whose clinical manifestations vary from mild to severe disease, sometimes requiring admission to intensive care (ICU) due to development of ARDS or sepsis showed that a low serum level of 25 hydroxyvitamin D (25(OH)D) was associated with a higher incidence of community-acquired pneumonia and more severe disease.[14,15] Vitamin D deficiency is common in critically ill patients and associates with adverse outcomes, as found in a cohort of patients with acute respiratory distress syndrome (ARDS).[16]

Vitamin D deficiency or insufficiency possibly affect SARS-CoV-2 severity and mortality by the paracrine and autocrine actions of vitamin D. The present study was a cross-sectional observational study conducted in the department of respiratory medicine, in the COVID unit, BSMMU, Dhaka. The study aimed to know about the vitamin D status among COVID-19 patients. A total of 103 patients diagnosed with COVID-19 infection were included in the study. In the present study maximum patients were found in the sixth and seventh decades for both males and females. The mean age of the participants was 58.33±12.56 years, range 27-88 years and median age was 60 years. It was also revealed that COVID-19 was more common among patients aged over 51 years and was less frequent in younger patients aged less than 30 years. This occur might be due to older age is associated with many co-morbidities, poor immune response and old patients are more prone to infection. These findings were similar to the observation done by an author.[17] Among the patients with vitamin D deficiency (40.4%) were smoker. Singh et al also found 25% patients were smoker on their study. We also found no association between smoking and severity. It was also consisted with a study.[18]

There was a hypothesis in a study that nicotine may have protective role against COVID-19 because of its anti-inflammatory properties and it also prevent acute lung injury in an animal ARDS.[18] In another study found strong association between smoking and COVID-19 severity.[19] So, the role of smoking in COVID-19 severity is controversial. In this study out of 103 COVID-19 patients, we found 57 patients were vitamin D deficient (55.3%) 27 patients were vitamin D insufficient (26.2%) and 19 patients were sufficient (18.4%). In a study conducted a retrospective case control study which included 166 adult RT-PCR positive COVID-19 patients.[20] The study revealed vit D deficiency was (49%), vit D insufficiency was (29%) and sufficiency was (22%) in adult COVID-19 patients. Our study matched with this research. In a study conducted a retrospective observational study which included 149 adult Rt-PCR positive COVID-19 patients.[21]

In this study, we found vitamin D not sufficient including both deficiency and insufficiency was 81.5% and sufficient was (18.4%). Our study matched with this. In severe (severe/critical) group our observation showed higher rate of vitamin D deficiency was 38 (74.9%) than in non-severe (mild/moderate) group 19 (36.5%). Only 3 (5.9%) were vitamin D sufficient in severe group and 16(30.8%) were sufficient vitamin D in non-severe COVID-19 patients. This result was statistically significant with a ($p<0.001$). Our observation those who were vitamin D deficient were in severe group of COVID-19 patients. We also observed that vitamin D deficiency was found (74.5%) in severe group and (36.5%) in non-severe group. There was a significant association between vitamin D status and clinical severity of COVID-19 (<0.001). Vitamin D reduces the risk of microbial infections and stimulates innate cellular immunity, through the induction of antimicrobial peptides, such as cathelicidins, IL-37 and defensing. It also inhibits the cytokine storm, reducing the production of pro-inflammatory cytokines such as IFNγ and TNFα. It also modulates the adaptive immune response, suppressing the Th1 response and promoting cytokines production by Th2 cells. That's why, vitamin D deficiency increases clinical severity of COVID-19. In a study shows that vitamin D deficiency reduces innate cellular immunity and may stimulate the cytokine storm, which are involved in worsening COVID-19-related ARDS.[16]

In this present study, in mildly affected patients the mean level of vitamin D ± SD (28.47±8.72) ng/ml, in moderately affected patients, the mean level of vitamin D ± SD (23.66±12.69) ng/ml, in severely affected patients, the mean level of vitamin D ± SD (17.11±8.92) ng/ml, in critically affected patients, the mean level of vitamin D ± SD (13.69±5.58) ng/ml. We also found that the mean level of vitamin D ± SD (25.61±11.35) ng/ml in non-severe group and mean level of vitamin D ± SD (16.25±8.28) ng/ml in severe group. This is similar with the results conducted by some author.[14,22] In our study, we found in critical group 11 (84.6%) patients were in vitamin D deficient with mean level of vitamin D ± SD (13.69±5.58) ng/ml that needed ICU admission. Prevalence of vitamin D deficiency in severe cases of COVID-19 was 64% more in vitamin D deficiency compared with mild cases. Our research consistent with this result.

In our study, the most common symptoms were cough (98.17%), fever (84.5%) and shortness of breath (65%). As our study revealed severe patients had higher vitamin D deficiency whom had high CRP, serum ferritin and high D-dimer level. In a study also found neutrophilia, lymphopenia, and higher CRP, D-dimer in severe patients. In multivariate logistic regression analysis, it revealed that the severity of COVID-19 infection was independently associated with diabetes mellitus and vitamin D deficiency.[6,20,21] In a study shows Vitamin D deficiency was associated with a 6-fold higher hazard of severe course

of disease and a 15-fold higher risk of death. After adjustment of diabetes mellitus and hypertension, vitamin D deficiency 25(OH) D<20 ng/ml, was an independent risk factor that was about 8.6-fold risk of developing severe disease (OR: 8.6; 95% CI: 2.1-35.7: p=0.003).[22]

Strengths

In our study data is taken from patients during attending hospital. So, no data was missing or wrong and there is less chance of biasness. We included patients with laboratory confirmed for COVID-19 infection. We were able to examine the independent associations between vitamin D deficiency and clinical severity in COVID-19.

Limitations

This is a single center-based study. Pediatric group not included in this study. It was not evaluated whether Vitamin D deficiency is due to COVID-19 or was pre-existing. There is the inability to independently assess the impact of other associated confounding variables such as obesity which are risk factors for both greater severity of COVID-19 infection and vitamin D deficiency.

CONCLUSION

The current study provides preliminary evidence that there is vitamin D deficiency around fifty five percent (55%) in people with COVID-19. Among patients with vitamin D deficiency, hypertension and diabetes were the most common co-morbidity for COVID-19. There is independent association of vitamin D deficiency with the severity of COVID-19. From this perspective, evaluating blood vitamin D levels could be considered in the clinical practice of health professionals.

Recommendations

A multicenter study with a large study population is needed to confirm the results of our study. Follow up will be needed to see the final outcome between two groups of as duration of hospital stay and mortality. Those who are affected COVID-19, should be screened for vitamin D levels and if found insufficient/deficient, optimal vitamin D supplementation should be given.

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