Vitamin - D level and severity of COVID-19 among the Admitted Patients in a COVID Dedicated Tertiary Care Hospital - An Prospective Study

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Abstract:

Background *The impact of vitamin D on COVID-19 infection has been much discussed recently. Our aim was to evaluate the association between baseline serum 25(OH)D with severity of COVID-19.*

Method *This was an prospective study, where 174 COVID-19 in-patients of an academic hospital in an urban setting were enrolled from Aug, 2020 to Oct, 2020. After detailed clinical history taking and examination, patients were divided into mild, moderate, severe and critical categories. Vitamin D level was measured. Relation between level of vitamin D and disease severity was determined.*

Result *Mean age of the study population was 52.01 years. 13% mild, 22.99% moderate, 26.44% severe and 3.45% were critical cases. 76% of the patients had vitamin D deficiency. No statistical significance between the level of vitamin D and disease severity was seen (p= 0.430).*

Conclusion *Our study revealed there is no correlation between vitamin D deficiency and severity of COVID-19.*

Key words: *SARS-CoV-2, COVID-19, Vitamin-D, Disease severity*

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Introduction:

Coronavirus disease 2019 (COVID-19), a potentially severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared pandemic by World Health Organization (WHO) on 11th March 2020 following its outbreak as a cluster of pneumonia cases with unknown cause in Wuhan City, Hubei Province, China, in December 2019[1-4]. In most cases the clinical presentation is that of a respiratory infection with a symptom severity ranging from a mild influenza like illness, to a severe viral pneumonia leading to acute respiratory distress syndrome that is potentially fatal. The explanations for this extremely variable prognosis are unclear. So far 114 M cases of COVID-19 were detected around the globe, among which 2.53 M deaths occurred. In Bangladesh 546k cases were detected, where 8400 deaths occurred[5].

Vitamin – D, a fat soluble vitamin, has the classic endocrine effect on calcium and phosphate metabolism and bone health. It is important for maintaining normal function of the cardiac muscle, immune function, inflammation, as well as cell proliferation and differentiation. Apart from sunlight exposure, oily fish – such as salmon, sardines, herring and mackerel, red meat,

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liver, egg yolks, fortified foods and dietary supplements are the sources of vitamin D[6-8].

Mortality from coronavirus disease 2019 (COVID-19) is higher amongst people who are older, male, obese, diabetic, hypertensive, or who are from black, Asian, or minority ethnic (BAME) demographics, all these factors are associated with increased prevalence of vitamin D deficiency, with reduced impact of vitamin D on the immune response[9]. Interest in the potential for vitamin D supplementation to reduce risk of acute respiratory infections (ARI) has increased since the emergence of the COVID-19 pandemic[10]. Findings of laboratory studies showed that vitamin D metabolites support innate immune responses to respiratory viruses[11]. Many observational studies have reported independent associations between low circulating levels of 25-hydroxyvitamin D and increased risk of ARI caused by other pathogens[12,13]. Randomized controlled trials (RCTs) of vitamin D for the prevention of ARI have produced heterogeneous results, with some showing protection, and others reporting null findings. One meta-analyzed individual participant data from 25 RCTs showed a protective overall effect that was stronger in those with lower baseline 25(OH)D levels, and in trials where vitamin D was administered daily or weekly rather than in more widely spaced bolus doses[11-15]. We therefore sought data from these more recent studies for inclusion in an updated meta-analysis of aggregate (trial-level) data to determine whether vitamin D reduced ARI risk overall, and to evaluate whether effects of vitamin D on ARI risk varied according to baseline 25(OH)D concentration and/or dosing regimen (frequency, dose size, and trial duration). Many studies show that vitamin D has a potential role in the prevention or treatment of acute respiratory infection. Lower circulating 25(OH)D concentration has also been reported to associate susceptibility and severity to SARS- Cov-2 infection.

\A potential crude association is found between the mean Vitamin D levels in various European countries with COVID-19 cases and COVID-19 mortality[16]. It is found that treatment with Cholecalciferol booster therapy regardless of baseline serum 25(OH)D levels, appeared to be associated with a reduced risk of mortality in acute in-patients admitted with COVID-19[17]. From one study it has been found that Lower latitude and typically 'sunny' countries such as Spain and Italy (Northern region), had low mean 25(OH)D and high deficiency, as well as higher infection and death rate of COVID-19. On the other hand, Countries having higher latitude (Norway, Finland, Sweden) which receive less UVB sunlight had higher mean 25(OH)D, low deficiency, and lower infection and mortality rate of COVID19[18].

From another study it was yielded that Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalized with COVID-19 are associated with greater disease severity[19]. The National Institute for Health and Care Excellence (NICE) conducted a rapid review which confirms that currently there is not enough available evidence to determine that there is a causal relationship between vitamin D and COVID-19[20]. Hypovitaminosis D is common among the real-world clinical subjects in Bangladesh[21]. The prevalence of vitamin D deficiency among the Bangladeshi population was found to be100% in all age groups, particularly in female sex, urban & obese population[22]]. So Bangladesh will be an ideal place to evaluate whether there is any relationship of low Vitamin D level to increased severity of disease in COVID-19 infection.

This study was aimed at determining the Vitamin-D levels among all mild, moderate, critical & Severe COVID-19 cases admitted in a dedicated COVID 19 care hospital in Bangladesh and to observe any relationship between vitamin D level and severity of COVID-19 infection.

Methods:
This was an observational prospective study conducted from August, 2020 - October, 2020 at 500 Bedded General Hospital, Mugda, Dhaka, Bangladesh, which is a COVID dedicated tertiary care hospital since April 20, 2020. Total 174 patients were recruited by purposive sampling. Figure 1 shows the entire method of study population selection.

To be included in this study, patients of both sexes need to fulfill all four of the following criteria – confirmed case of COVID-19 by positive RT-PCR, the patient has to be more than 18 years old, and the patient has to give informed written consent. Patients meeting the following criteria were excluded from the study – patients having history of taking vitamin D supplement within the last one month, patient having advanced malignancy and/ or CLD, chronic pancreatitis, on drugs that can reduce

vitamin D, patient on dialysis, and if the patient is pregnant. Institutional ethics committee approved data collection and analysis. A preformed questionnaire was used for data collection.
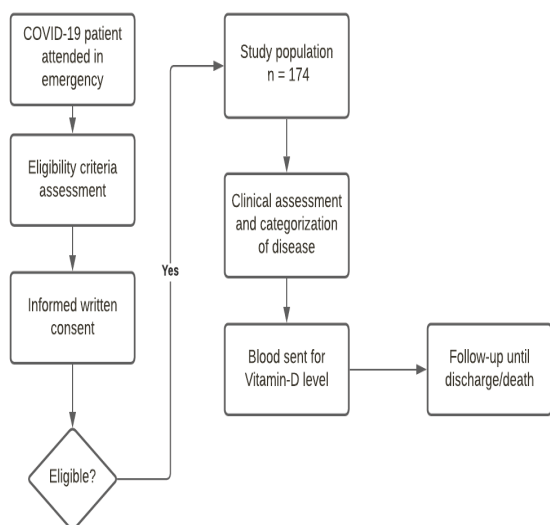

Fig.-1: *Study population selection*

Patients were tested for SARS-CoV-2 by taking nasopharyngeal/oropharyngeal swabs using Sansure kits (Changsha, Hunan, China). RT-PCR was performed on Quantstudio 5, Thermofisher, USA in our hospital lab. Vitamin D was analyzed by chemiluminescence immunoassay (CLIA) method using Maglumi 2000 Plus, Snibe (Shenzhen, China) in other designated labs. About 10% samples of vitamin - D were rechecked in another laboratory for quality assurance.

Vitamin D insufficiency was defined as serum 25(OH)D level <30 ng/ml.[26] Patients' disease severity was labeled as mild, moderate, severe and critical as per WHO guideline Supportive care and treatment was given according to the National Guideline for Management of COVID-19 Version 7. All patients were followed up to discharge or death.

Results:
Total 174 cases were included in this study. Male (n=107, 61.49%) patients were higher than females (n=67, 38.51%). Most of the patients were above 40 years of age.

According to disease severity, there were 47.13% mild, 22.99% moderate, 26.44 % severe, and 3.45 % critical

cases. In terms of clinical characteristics, fever was the most common symptom 84%, followed by cough 73.5% and sore throat 51%. Diarrhea , one of the most important GI symptoms, was found in 15% cases. Diabetes mellitus (DM) and hypertension (HTN) were two most common comorbidity. Almost half of the study subjects had hypertension (49.43%) and diabetes (47.7%).

75.86% of the study population had either deficient or insufficient levels of vitamin D (0-30 ng/mL) and 24.14% had sufficient levels of vitamin D (>30 ng/mL). Table 1 shows the vitamin D level among various groups of patients with their statistical significance (if any).

There was no difference in case severity of disease among both sexes $\div^2$=1.59, df 3, p=0.660. An independent T test revealed

Table-I

Mean vitamin D level and its statistical significance among various group of patients		
Variable (%)	Mean Vitamin D Level (ng/mL ± SD)	p Value
Male (61.49)	27.47 ± 8.81	<0.001
Female (38.51)	22.90 ± 6.64	
Age <40 years (26.44)	24.85 ±7.33	0.441
Age >40 years (73.56)	25.95 ±9.84	
Patient with DM (47.7)	25.92 ±6.12	0.698
Patient without DM (52.3)	25.43 ±6.34	
Patient with HTN (49.43)	26.13 ± 5.63	0.462
Patient without HTN (50.57)	25.20 ±5.71	
Patient requiring ICU (7.47)	26.74 ± 5.84	0.628
Patient not requiring ICU (92.53)	25.57 ± 8.49	
Patient who didn't survive (4.6)	28.24 ± 5.11	0.371
Patient who survived (95.4)	25.54 ± 8.89	
Mild case (47.13)	26.68 ± 10.46	0.430
Moderate case (22.99)	24.13 ± 5.30	
Severe case (26.44)	25.15 ± 6.04	
Critical case (3.45)	25.94 ± 5.85	

the average vitamin D level of male was significantly higher than female, p<0.001. Vitamin D level in patients admitted in ICU was rather higher than patients who didn't require ICU admission. This difference was not statistically significant (p=0.628).

An ANOVA test was conducted using the level of vitamin D as dependent variable and Severity of disease (mild, moderate, severe,

critical) as independent variable. It revealed that there was no statistically significant difference of level of vitamin D in different

groups of disease severity. *F(3,170) =0 .925, p= 0.430.*

Quantitative data were expressed as mean ± 2SD. Categorical variable is expressed as number (%). *p* - value of <0.05 was considered statistically significant. Independent sample t-test, Pearson's chi square test and ANOVA were performed. All statistical analysis were done by using SPSS version-21 (IBM SPSS Inc, Chicago IL)

Discussion

Our study demonstrated no association between level of vitamin D and severity of SARS CoV-2 infection. Faul et al [23] in their study on 33 patients with SARS-CoV-2-related pneumonia reported that VitD deficiency (baseline 25(OH)D < 12 ng/mL) was associated with a significantly increased risk for IMV, which does not match with our findings. Study from the UK that included 449 subjects (from the UK Biobank) with confirmed COVID -19 infection did not find an association between level of vitamin D and the risk of viral infections as well as COVID -19 infection[24]. We found Fever(84%) was the most common symptom followed by cough(73.5%). Similar findings observed by Chaomin Wu et al. where fever (93.5%) and cough (81.1%) were two most common symptom[25] . We observed more than three quarter of study population had vitamin D insufficiency. Ranil Jayawardena et al. observed three quarter of the Asian countries, more than 50% of the adult population were vitamin D deficient. The lowest rate of vitamin D deficiency was reported in Vietnam with only 2.0% and the highest was reported in Oman at 87.5% . As expected, an inverse relationship was observed between the prevalence of VDD and mean VD levels and the countries, Oman and Vietnam had the lowest (32.5/ nmol/l) and the highest (83.8/ nmol/l) mean VD levels respectively. Mean vitamin D level in male was 27.47±8.81 and female was 22.90 ± 6.64 , which was statistically significant (P=,0.001). In one study by Monica Verdoia et al. noticed female gender was associated with lower vitamin D levels (14.5 ± 10.9 vs. 15.9 ± 9.5, p = 0.007) and independently associated with severe vitamin D deficiency (41.9% vs. 30.4%, p < 0.001 [26]. Another study by GK Acherjya et al. conducted study in Jashore, Bangladesh and noticed the mean serum 25(OH)D levels was 18.60±6.59ngm/dl. mean serum 25(OH)D level in case of male participants was 19.72±7.10ngm/dl whereas in female the

corresponding figure was 17.74±6.07gm/dl and no significant difference observed among the man and women (p=0.059) [27].

Conclusion:

From this study we came to know that vitamin D deficiency is very common in our country, as only one fourth of study population had sufficient level of vitamin D. Females have significantly low level than males. No relation could be established between level of vitamin D with severity of disease or mortality. Our finding contrasted with many other studies, so further study with large sample to be conducted to resolve the issue.

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