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Research Article
Role of Vitamin D Levels in COVID-19 Disease Severity: A Multicenter Retrospective Study from Qatar

[1]Abdelelah S. Jazar, [1]Raed B. Alalaween, [1]Reem K. Al-Saadi, [1]Noora M. Aljaffali, [1]Zohair A. Al Arabi, [2]Mai A. Ghabashi and [3]Firas S. Azzeh

[1]Dietetics and Nutrition Services Department, Hamad Medical Corporation, Doha, Qatar
[2]Department of Clinical Nutrition, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia
[3]Department of Biology, Preparatory Year Program, Batterjee Medical College, Jeddah 21442, Kingdom of Saudi Arabia

Abstract

Background and Objective: Up to now, evidence remains inconclusive about how vitamin D (VD) status relates to the severity of COVID-19 among hospitalized patients. The present study aims to explore the impact of VD status on the severity of COVID-19 among hospitalized patients in Qatar and examine its effects on health factors related to the disease. **Materials and Methods:** A retrospective, cross-sectional, multicenter study was conducted at Hamad Medical Corporation in Qatar from March, 2020 to May, 2021. Demographics, laboratory values, comorbidities, clinical outcomes and some inflammatory markers were retrieved from the hospital's system. The severity of COVID-19 disease was determined by an elevated neutrophil-lymphocyte ratio (NLR). A patient with VD levels less than 20 ng/mL was considered deficient. Data were analyzed using SPSS v22, with significance set at $p<0.05$, employing Mann-Whitney, Chi-squared and correlation tests as appropriate. **Results:** The VD deficiency was common (68.6%), with longer ICU stays observed in deficient patients compared to those with normal VD status (19.7 vs. 11.2; $p = 0.04$). There was a trend of higher NLR with lower VD levels. No significant difference in interleukin-6 levels was found between the deficient and sufficient VD groups (60.6 ± 64.1 vs. 41.2 ± 45.2 pg/mL; $p = 0.472$). **Conclusion:** This study highlights the link between VD status and COVID-19 disease severity. The findings suggest that suboptimal levels of VD in COVID-19 patients may be potentially associated with increased length of stay in the ICU and have a minor impact on the pro-inflammatory state.

Key words: COVID-19, Hamad Medical Corporation, neutrophil-lymphocyte ratio, vitamin D

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Corresponding Author: Firas S. Azzeh, Department of Biology, Preparatory Year Program, Batterjee Medical College, Jeddah 21442, Saudi Arabia

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

Ethical Approval: The Institutional Review Boards of HMC approved the study with a waiver of informed consent (approval number MRC-01-23-165).

INTRODUCTION

Even though the COVID-19 pandemic ended several years ago, many patients who contracted the virus continue to suffer from various side effects to this day[1]. Hospitalization of such patients could increase symptoms related to coronavirus infection (such as fever, cough and shortness of breath), higher risk of developing secondary infections such as pneumonia, prolonged length of hospital stay and excess mortality[2]. Therefore, preserving immune system function and implementing measures to enhance its effectiveness can help prevent the decline in health status of individuals affected by or previously infected with COVID-19[3] with a key focus on maintaining optimal vitamin D (VD) levels[4].

In addition to its primary physiological function in maintaining serum calcium homeostasis and bone integrity, VD also has immunoenhancing and anti-inflammatory actions[5]. Numerous studies have shown that having sufficient levels of VD may help mitigate the severity of COVID-19 disease[6-8]. Conversely, suboptimal serum VD could worsen the disease severity, including increasing the risk of mortality[9]. In COVID-19 patients, VD deficiency has been linked to elevated C-reactive protein (CRP), dyspnea, prolonged hospital stay, the need for mechanical ventilation and an increased likelihood of respiratory failure[10]. Ye *et al.*[11] observed that VD deficiency is notably a determinant risk factor for individuals with severe or critical COVID-19 disease activity compared to those with milder symptoms. On the other hand, some studies indicated that VD status did not have a significant impact on the severity of COVID-19 disease[12-14], even in pregnant women[15]. Nevertheless, there is still a lack of conclusive evidence on the association between VD and COVID-19 disease severity. Hence, this research aimed to investigate the influence of VD status on the severity of COVID-19 disease among hospitalized patients in Qatar, along with its effects on various health factors like length of hospitalization, inflammatory markers and mortality percentage.

MATERIALS AND METHODS

Study design and population: This retrospective multicenter cross-sectional research was performed on symptomatic COVID-19 patients entered Hamad Medical Corporation (HMC), Qatar. From the start of the pandemic till May 2021, COVID-19 patients were admitted to hospitals numbered 11233 (Ministry of Public Health, 2023). A minimum sample size of 296 COVID-19 patients was included in the study based on a statistical power of 95.7%, confidence level of 95% and margin of error of 5%. Both genders were included in the study from Hamad General Hospital (N = 141), Hazm Mebaireek General Hospital (N = 110), Cuban Hospital (N = 39) and Communicable Disease Center (N = 6). Patients who had been diagnosed with conditions such as parathyroid disease, cancer, chronic kidney disease and chronic liver disease, as well as pregnant women and children, were excluded. In addition, patients who had taken any VD supplementation within the six months preceding the test for COVID-19 were also omitted from the research (Fig. 1).

Data collection: Data of eligible COVID-19 patients, covering demographic details (such as sex, age, body mass index (BMI; kg/m^2) and nationality), laboratory results, existing health conditions, clinical outcome, disease severity and mortality were gathered from the integrated nationwide digital-health information platform (Business Intelligence and Operational Performance Unit, HMC) between March, 2020 to May, 2021. Disease severity of patients with COVID-19 was determined by an elevated neutrophil-lymphocyte ratio (NLR)[16]. The prior study classified patients according to their NLR into five groups based on the level of inflammation as follows: (i) normal/no inflammation, (ii) subclinical or low inflammation, (iii) mild-to-moderate inflammation, (iv) moderate-to-severe inflammation and (v) severe/critical inflammation. The corresponding values for these groups were: <2.3, 2.3-2.9, 3-6.9, 7-10.9 and >11, respectively.

Laboratory measurements: The hospital ensured the COVID-19 patients' verification by obtaining positive results from real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tests. Serum VD as 25(OH)D levels were used to assess patients' VD status. The VD assessment was considered valid if it was conducted during the patient's hospitalization. Based on the Institute of Medicine (IOM), patients were categorized into two groups based on their VD: The low VD group <20 ng/mL and the normal VD group $\geq$20 ng/mL (IOM, 2010). Baseline laboratory values, including neutrophil and lymphocyte count, lactate dehydrogenase (LDH), CRP, procalcitonin and Interleukin-6 (IL-6), were abstracted from the Electronic Health Record (EHR) software-Cerner.

Statistical analysis: Data analysis was performed using IBM-SPSS software version 22 and results were considered statistically significant when the p-value was less than 0.05.

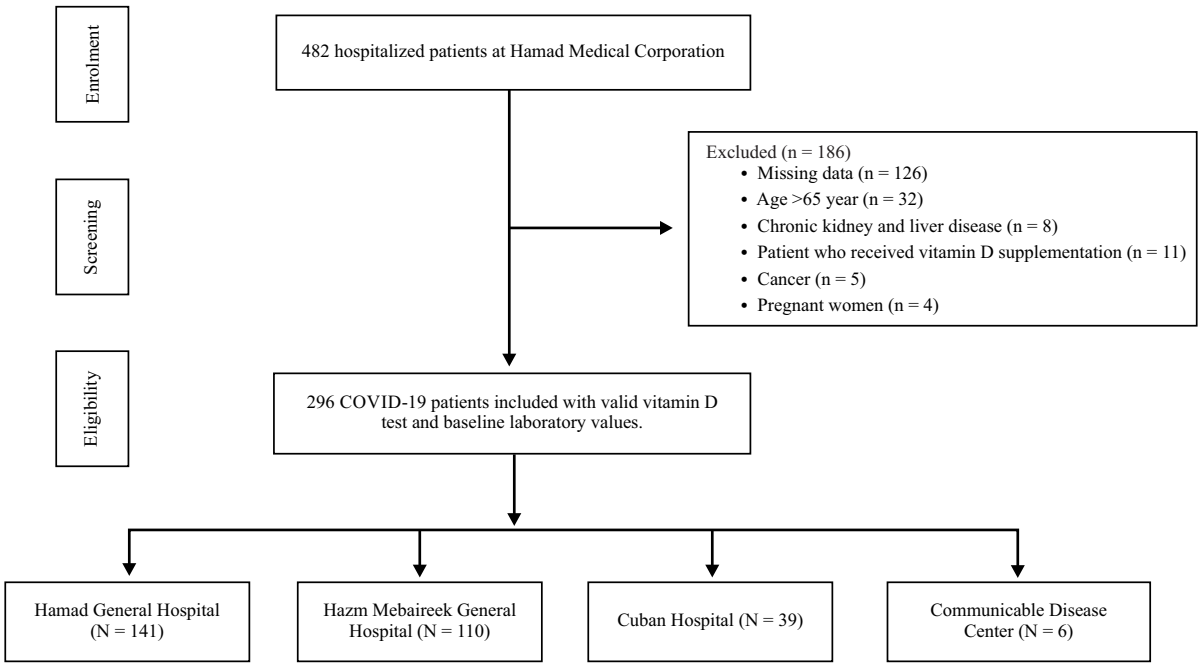

Fig. 1: Patient flow diagram

Categorical variables were presented as frequencies and percentages, while Means±Standard Deviation (SD) displayed continuous variables. The median and Interquartile Range (IQR) values were also employed in consideration of data appropriateness. The p-values are determined by the Mann-Whitney test or the Chi-squared test for continuous and categorical variables, respectively. The correlation test assessed the association between serum VD and NLR.

RESULTS

The descriptive results of the present study are summarized in Table 1. Among the participants, the majority were females, constituting 84.5% (250/296) of the total sample size. The mean age and BMI of the participants were 46.6±9.5 years and 29.8±5.3 kg/m^2, respectively. Regarding weight status, only 13.2% (39/296) of the participants were classified as having a normal weight, whereas 47% (116/296) were overweight and 39.2% (116/296) fell into the obesity category. Approximately 61% (183/296) of the patients with COVID-19 had at least one concurrent chronic disease. The average hospital stay was 17.2±14.9 days, while the average ICU stay was 16.9±19.8 days. Notably, the majority of patients, accounting for 68.6% (203/296), exhibited VD deficiency. Figure 2 provided an overview of the severity of inflammation among the participants, categorized according to their NLR. Among the total of 296 participants, it was found that only 14.2% (42/296) did not exhibit any signs of inflammation, while the remaining 85.8% (254/296) showed varying degrees of inflammation. Specifically, 14.2% (42/296) had low levels of inflammation, 39.9% (118/296) displayed mild-to-moderate inflammation, 19.6% (58/296) had moderate-to-severe inflammation and another 12.2% (36/296) exhibited severe or critical inflammation.

Table 2 displays a number of hospitalization-related factors in relation to VD status. Age and BMI values did not significantly differ between the two groups. The duration of ICU stay was observed to be significantly higher in VD-deficient patients compared to their counterparts who had a normal level of VD (19.7 vs 11.2; p = 0.04). The levels of IL-6, a pro-inflammatory cytokine, were higher among VD-deficient patients as compared to those with sufficient levels, despite the lack of statistical significance in the observed difference (60.6±64.1 vs 41.2±45.2 pg/mL; p = 0.472). Additionally, Fig. 3 illustrates a correlation between VD levels and NLR. Although the correlation was not statistically significant, a positive trend was observed, indicating that lower VD levels were associated with higher NLR. Furthermore, Fig. 4 depicts the median NLR value (IQR) for VD-deficient and normal VD levels among participants as 4.9 (5.3) and 4 (4.4), respectively, with no significant difference noted between the groups (p = 0.145).

Table 1: Baseline characteristics of study participants (n = 296)

Variable	Mean±SD or frequency (%)
Sex	
Male	46 (15.5%)
Female	250 (84.5%)
Nationality	
Qatari	11 (3.7%)
Non-Qatari	285 (96.3%)
Age (years)	46.6±9.5
Height (cm)	167.3±8.1
Weight (kg)	83.8±17.3
BMI (kg/m^2)	29.8±5.3
Underweight	2 (0.7%)
Normal weight	39 (13.2%)
Overweight	139 (47%)
Obese	116 (39.2%)
LOS (days)	17.2±14.9
ICU admission (days)	16.9±19.8
Serum vitamin D (ng/mL)	17.2±14.9
Chronic diseases	
Yes	183 (61.8%)
No	113 (38.2%)
Ventilation support	
Yes	85 (28.7%)
No	211 (71.3%)
ECMO	
Yes	11 (3.7%)
No	285 (96.3%)
Dialysis	
Yes	11 (3.7%)
No	285 (96.3%)
Deceased	
Yes	15 (5.1%)
No	281 (94.9%)
Vitamin D status	
Deficient	203 (68.6%)
Normal	93 (31.4%)

LOS (days) stands for Length of Stay (in days)

Table 2: Effect of vitamin D status on ICU and hospital stay, some inflammatory parameters and mortality percentage

	Vitamin D status		
Variable	Deficient (n = 203, 68.6%)	Normal (n = 93, 31.4%)	p-value
Age (years)	45.6±9.6	48.8±8.8	0.251
BMI (kg/m^2)	29.5±4.8	30.6±6.1	0.49
LOS (days)	18.5±16.8	14.8±8.8	0.227
ICU admission (days; n = 96)	19.7±22.6	11.3±11	0.04
LDH (U/L)	459.5±249.5	449.3±246.1	0.738
CRP (mg/L)	87.8±78.8	87.5±72.8	0.74
IL-6 (pg/mL)	60.6±64.1	41.2±45.2	0.472
Neutrophil (10^3/UL)	5.6±3	5.3±3.2	0.132
Lymphocyte (10^3/UL)	1.2±0.6	1.2±0.6	0.958
NLR	6.1±4.4	5.7±4.7	0.145
Deceased			
Yes	11 (5.4%)	4 (4.3%)	0.783
No	192 (94.6%)	89 (95.7%)	

Bold values indicate significant results at p<0.05, P-values are determined by the Mann-Whitney test or Chi-squared test, Values are presented as Mean±Standard Deviation (SD), LOS: Length of stay, ICU: Intensive care unit, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IL-6: Interleukin-6, NLR: Neutrophil-to-lymphocyte ratio, BMI: Body mass index and p-values were calculated to compare deficient and normal vitamin D groups

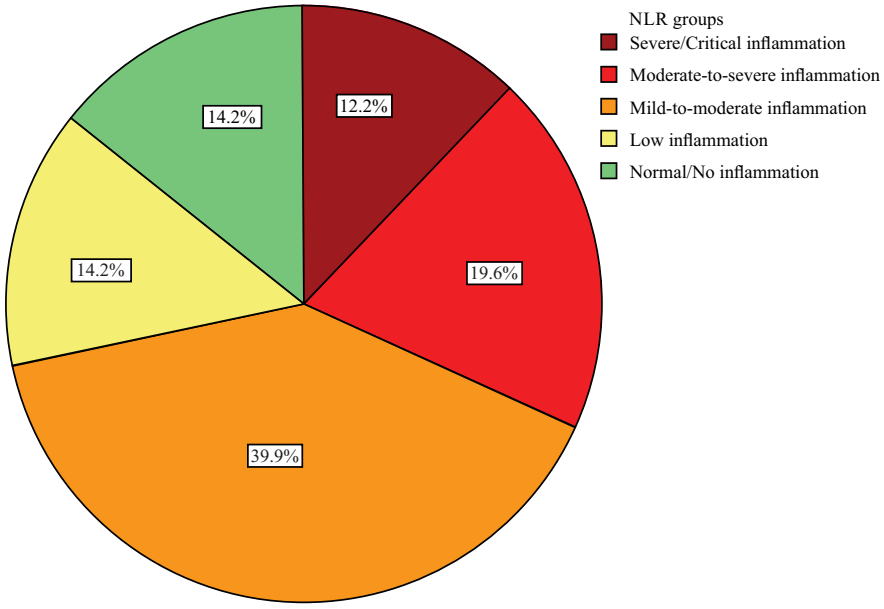

Fig. 2: NLR categories for the study participants

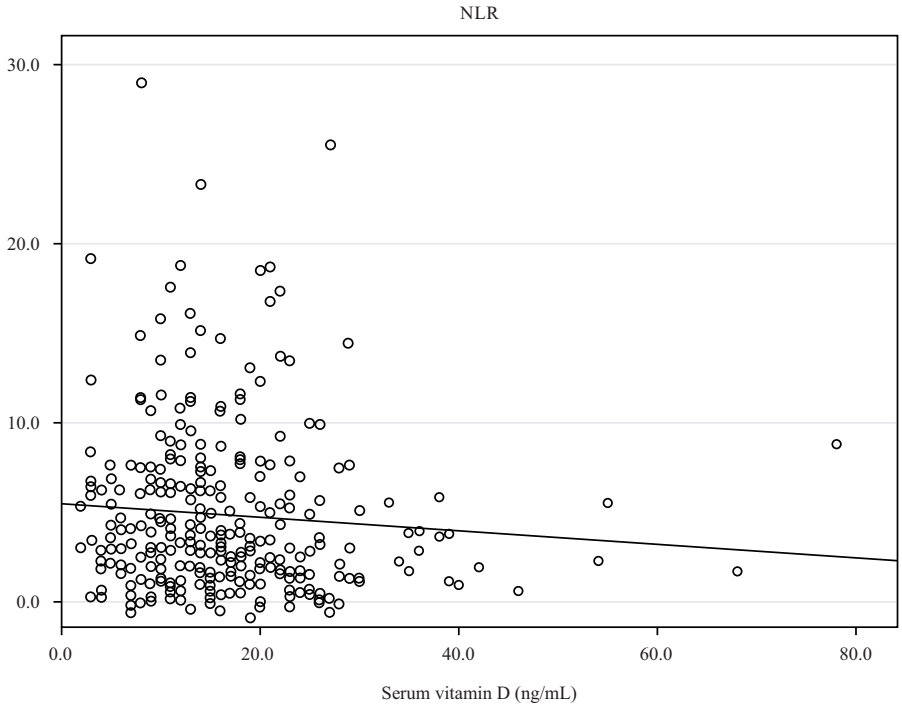

Fig. 3: Correlation curve between vitamin D and NLR ($r^2 = 0.006$, $p = 0.171$) and y-axis: NLR

DISCUSSION

This study provides insights into the relationship between VD status and inflammatory biomarkers among hospitalized patients diagnosed with COVID-19 in Qatar. The findings indicate a significant prevalence of VD deficiency among approximately two-thirds of the patients, which is consistent with existing literature on the subject[17-20]. Additionally, a substantial majority (83.8%) of the patients exhibited varying degrees of inflammation, aligning with the conclusions drawn from a systematic review and meta-analysis that highlighted the common occurrence of inflammatory status among individuals with COVID-19[21].

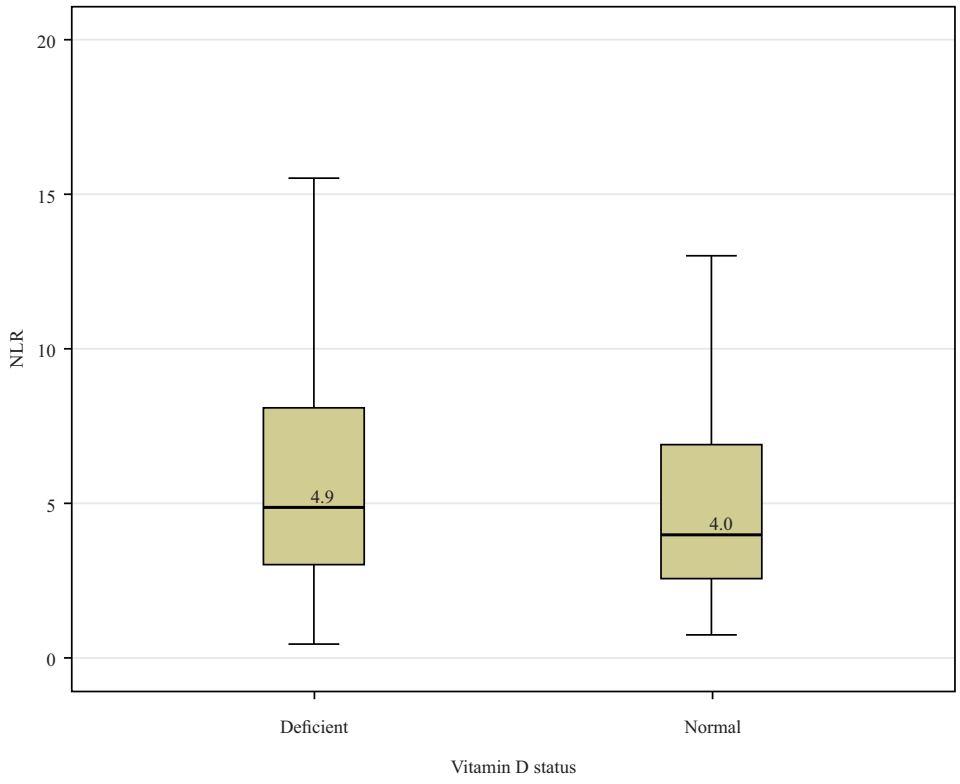

Fig. 4: Median NLR ratio for deficient and normal vitamin D groups

Importantly, this study sheds light on the potential impact of VD deficiency on crucial clinical parameters related to hospitalization in COVID-19 patients in Qatar. Importantly, the duration of hospitalization at the ICU was found to be significantly prolonged in patients with COVID-19 who exhibited VD deficiency compared to individuals with sufficient VD levels. Such finding proposes a potential relationship between VD deficiency and the exacerbation of COVID-19 severity among hospitalized patients. This is supported by findings from several studies conducted around the world, including countries such as China[7], India[22], Italy[23], Poland[24] and Denmark[14].

Additionally, a previous systematic review and meta-analysis that included 31 observational studies detected a positive trend between low serum levels of VD and increased health risks in COVID-19 hospitalized patients. Specifically, it was found that patients diagnosed with COVID-19 and possessing low levels of VD were approximately 5 times more likely to require ICU admission compared to those with higher levels (RR = 4.9, 95% CI; 0.5-44.3)[25]. Another recent systematic review and meta-analysis of 13 observational studies found that the odds of mortality were doubled in COVID-19 patients who had low VD levels compared to those with higher levels (OR = 2.1, 95% CI; 1.0-4.3)[26]. However, it is important to acknowledge that the evidence supporting the relationship between VD insufficiency and COVID-19 severity is limited, as these findings were primarily derived from observational studies that could be prone to confounding factors and biases, which can limit the ability to establish a causal relationship.

The proposed positive trend between insufficient VD levels and the severity of COVID-19 infection could be explained by the potential adverse influence of VD deficiency on the inflammatory status[27]. Particularly, VD deficiency has been found to affect the NLR, which is a marker of systemic inflammation[16]. In the present study, it was observed that patients with VD deficiency exhibited a modestly elevated NLR in comparison to individuals with normal VD levels (6.1 vs. 5.7). This observation suggests a potential shift towards a pro-inflammatory state in the immune system, which could potentially worsen complications associated with COVID-19 infection[28], providing a possible explanation for the prolonged ICU stays observed among study participants.

Moreover, in the current study, COVID-19 patients with VD deficiency had a slightly greater level of IL-6 in comparison to those with normal levels of VD. Consistent with this finding, elevated IL-6 levels have been consistently observed in hospitalized COVID-19 patients, notably in cases of severe disease[29]. Several studies have demonstrated an association

between elevated levels of proinflammatory cytokines, including IL-6 levels and unfavorable clinical outcomes, such as increased risk of ICU admission, mechanical ventilation and mortality. These observations suggest that the upregulation of pro-inflammatory cytokine production, including IL-6, as a result of VD deficiency, may contribute to the aggravation of COVID-19 disease severity[30-32].

In contrast, adequate VD levels play a role in modulating the immune system and it has anti-inflammatory effects[33]. It is suggested that maintaining optimal VD levels may potentially help mitigate the pro-inflammatory response associated with COVID-19 infection and subsequently improve clinical outcomes[34]. A recent systematic review and meta-analysis, encompassing 16 studies, suggests that VD supplementation could potentially improve survival rates among patients admitted with moderate to severe COVID-19. In particular, the analysis showed that VD supplementation was correlated with a reduction in mortality among patients with COVID-19, with an odds ratio of 2.3. Additionally, the supplementation was found to be effective in preventing COVID-19, with an odds ratio of 1.92[35]. Nevertheless, it is noteworthy to mention that while some studies suggest a potential benefit of VD supplementation in COVID-19, more research is needed to fully understand its role and effectiveness. For instance, future research is recommended to explore the mechanisms by which VD influences the immune response to COVID-19 and longitudinal studies would be needed to investigate the sustained benefits of VD supplementation, including its effects on long-term immunity, post-COVID complications and overall health outcomes.

Overall, the present study exhibits many strengths, including the incorporation of data from multiple healthcare centers to enhance the generalizability of the findings. Additionally, the study involved an adequate sample size that ensured statistical power. Also, it utilized an integrated nationwide digital-health information platform for data collection, ensuring the accuracy and completeness of the gathered information. However, it is essential to take into consideration certain drawbacks of the study. Firstly, as a cross-sectional study, it provides a snapshot of the relationship between VD deficiency and hospitalization-related factors in COVID-19 patients, but it does not establish causality or determine the direction of the relationship. Moreover, the study primarily relies on serum 25 (OH)D levels as a biomarker of VD status but did not consider other factors that may influence VD metabolism or individual variations in response to supplementation. Also, potential confounding factors, such as comorbidities or socioeconomic factors, were not fully accounted for in the analysis, which may affect how the results are interpreted. Therefore, it is of utmost importance to interpret the results within the context of the aforementioned limitations. Further research, including prospective studies with larger and more diverse populations, is warranted to strengthen the evidence base and provide more conclusive insights into the role of VD in COVID-19 outcomes. As well, interventional trials examining the effects of VD supplementation on NLR and inflammatory markers in COVID-19 patients could also shed light on the potential therapeutic benefits of addressing VD deficiency in mitigating systemic inflammation.

CONCLUSION

This study highlights the link between VD deficiency and the severity of COVID-19 disease. The findings of the study suggest that there is a positive correlation between VD deficiency and longer length of stay in the ICU among patients diagnosed with COVID-19. That is, VD deficiency may exhibit a higher NLR ratio, indicating a potential pro-inflammatory state. These findings contribute to the growing understanding of the role of VD in modulating the inflammatory response in the context of COVID-19. Further investigations are warranted to fully elucidate the complex relationship between VD, NLR and the clinical outcomes of COVID-19 patients at the genetic level.

SIGNIFICANCE STATEMENT

This study underscores the importance of vitamin D status in shaping the clinical course of COVID-19, showing that patients with deficient levels were more likely to experience longer ICU stays and signs of heightened inflammation. While not all inflammatory markers differed significantly, the observed association between low vitamin D and higher neutrophil-lymphocyte ratios suggests a potential role of this nutrient in modulating the immune response during infection. These findings add to the global evidence that vitamin D deficiency, already widespread in many populations, may contribute to worse outcomes in COVID-19 and highlight the need for greater attention to simple, preventive strategies such as monitoring and correcting vitamin D levels to support overall resilience against infectious diseases.

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