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ORIGINAL RESEARCH

Association Between Vitamin A and D Status and the Risk of COVID-19 in the Elderly Population: A Single-Center Experience

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Background: Studies have confirmed that vitamins A and D are related to the coronavirus disease 2019 (COVID-19). However, little research has reported the relationship between vitamin A and D nutrition status and COVID-19 in the elderly population in China. Thus, the aim of this study was to explore the association between vitamin A and D status and the risk of COVID-19 in the elderly population.

Methods: From April 1st to September 20th, 2023, 32 COVID-19 patients who tested positive for severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection through polymerase chain reaction (PCR) were enrolled in this study. During the same period, 30 elderly individuals undergoing health checkups were enrolled as the control group. Clinical and laboratory data were obtained via electronic medical records. Vitamin A and D levels were detected using ultra-performance liquid chromatography-tandem mass spectrometry. Vitamin A deficiency is a retinol below 30 ng/mL, and vitamin D deficiency is a 25(OH)D below 20 ng/mL. Multivariate logistic regression analysis was used to assess the relationship between vitamin A and D levels, nutritional status, and the risk of COVID-19. Statistical analysis was performed using SPSS 24.0 (SPSS Inc. Chicago, Illinois).

Results: Compared with the subjects in the control group, COVID-19 patients had lower levels of vitamins A and D. Further analysis showed that the deficiency rate of vitamins A and D in patients with COVID-19 was higher than those in the control group. Correlation analysis revealed that vitamins A and D significantly negatively correlated with respiratory rate, neutrophil counts and positively correlated with lymphocyte count. Multivariate logistic regression analysis showed that vitamins A and D were the independent risk factors of CIVID-19.

Conclusion: Vitamins A and D were significantly lower in COVID-19 patients, and lower vitamins A and D were independently linked with a high risk of COVID-19, according to this single-center analysis.

Keywords: COVID-19, vitamin A, vitamin D, elderly population

Introduction

The coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), posing a severe threat to human life.[1–4] According to the WHO epidemiological update of COVID-19 on August 13, 2024, since December 2019, COVID-19 has affected over 775 million cases worldwide, resulting in over 7 million deaths[5,6] Due to a weakened immune system, the elderly were more susceptible to infection by SARS-CoV-2 and were more likely to develop severe symptoms.[7] Meanwhile, compared with young people, elderly patients with COVID-19 were prone to severe complications and had a higher mortality rate.[8]

Vitamins are a class of trace organic substances that maintain the normal physiological functions of the human body.[9] Current research has confirmed that vitamins are essential to the body's immune process. Vitamins can exert their effects

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by regulating the responses of various immune cells and the expression of immune factors, as well as by mediating antiviral and antibacterial immune responses.[10–12] Therefore, a deficiency in vitamins can lead to a decreased ability of the body to resist external pathogens, thereby promoting the occurrence and development of related infectious diseases. Adequate vitamin levels can help improve immune function and enhance the body's ability to fight infections.[13]

Vitamin A (VA) and vitamin D (VD) are important fat-soluble vitamins. Studies have confirmed that a VA or VD deficiency can lead to a decline in immune function, making individuals more susceptible to various diseases, including respiratory infections, diarrhea, and other bacterial or viral infections.[14–16] Supplementing VA or VD can significantly improve the clinical symptoms and length of hospitalization in patients with respiratory infections.[17–20] Accumulating clinical evidence has demonstrated an epidemiological association between VA and VD deficiencies and SARS-CoV-2 infection, with cohort studies consistently reporting significantly lower serum VA/VD levels in COVID-19 patients compared to controls.[21–24] However, few published data on the levels of VA and VD in elderly patients with COVID-19 in China, as well as the relationship between VA and VD and the risk of COVID-19. Thus, this study aimed to investigate the association between VA and VD and the risk of COVID-19 in the elderly population.

Materials and Methods

Study Design and Population

This study is a prospective single-center study conducted at Inner Mongolia Baogang Hospital (Inner Mongolia, China). From April 10 to August 20, 2023, 32 hospitalized patients with COVID-19 and 30 healthy individuals who underwent physical examinations during the same period were included in this study. The inclusion criteria of patients with COVID-19 in this study are as follows: (1) age $\geq$ 60 years old; (2) SARS-CoV-2 nucleic acid or antigen test positive. The inclusion criteria of healthy volunteers in this study are as follows: (1) age $\geq$ 60 years old; (2) SARS-CoV-2 nucleic acid test negative; (3) No symptoms of infection such as fever, cough, sore throat, etc. All subjects with the following conditions were excluded from this study: (1) subjects who refused to provide informed consent; (2) subjects with hematological diseases, cancers, and autoimmune diseases; (3) subjects without complete clinical and laboratory data. The study was conducted according to the Declaration of Helsinki policies and received approval from the Hospital Ethics Review Board of Inner Mongolia Baogang Hospital (2022-MER-110). Written informed consent was obtained from all the participants.

Clinical Definition

According to the diagnosis and treatment plan of novel coronavirus infection in China (Tenth version on trial),[25] the diagnosis of COVID-19 should be based on the comprehensive analysis of patients' epidemiological history, clinical manifestations, laboratory tests, etc. Positive detection of SARS-CoV-2 nucleic acid is the primary standard for diagnosing COVID-19. The diagnostic criteria are as follows:

(1) clinical symptoms associated with SARS-CoV-2 infection include sore throat, cough, fever, etc.

(2) have one or more of the following pathogenic and serological test results:

- SARS-CoV-2 nucleic acid test is positive.
- SARS-CoV-2 antigen test was positive.
- SARS-CoV-2 was positive in isolation and culture.
- The SARS-CoV-2 specific IgG antibody level in the convalescent stage is four times or more higher than in the acute stage.

All the patients included in this study with COVID-19 have the clinical symptoms of SARS-CoV-2 infection and positive SARS-CoV-2 nucleic acid test. Two independent clinicians confirmed the diagnosis of COVID-19.

Data Collection

Clinical data such as age, gender, body temperature, respiratory and heart rate, as well as laboratory test indicators such as the levels of white blood cell (WBC), neutrophil count, lymphocyte count, monocyte count, platelet count (PLT),

hemoglobin (HGB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (UREA), and creatinine (CREA), were collected through electronic medical records on the day of admission. WBC, neutrophil count, lymphocyte count, monocyte count, PLT, and HB were measured using the manufactured MACCURA fully automated blood analyzer (Maccura Biotechnology, Sichuan, China). ALT, AST, UREA, and CREA were measured using the automatic Beckman biochemical analyzer (Beckman Coulter, California).

Measurement of VA and VD

Serum VA and VD were detected using the ultra-high performance liquid chromatography-tandem mass spectrometry analysis system (Waters Xevo TQ-S Micro, Waters Corporation, Massachusetts). The sample pretreatment process follows the instructions of the commercial reagent kit for VA and VD (Tianjin Hanahao Biotechnology Co., Ltd. China), and 5 μL of the sample was injected for analysis. The electric spray ionization source is used for positive mode collection. The capillary voltage is 3.0kv, the ion source temperature is 150 °C, the desolvent temperature is 500 °C, the desolvent gas is 1000L/Hr, and the cone hole gas is 50L/Hr. Use Masslynx software (Waters Corporation, Massachusetts) to complete data collection and qualitative and quantitative analysis. According to the WHO global prevalence of VA deficiency among high-risk populations 1995–2005[26] and the current Chinese health industry standard WS/T 553–2017,[27] VA deficiency is retinol below 30 mcg/dL. According to the current Chinese health industry standard WS/T 677—2020[28] and the Endocrine Society Clinical Practice Guideline,[29] VD deficiency was 25 hydroxyvitamin D below 20 ng/mL.

Statistical Analysis

Normal distribution data were presented as means ± standard deviation (SD) and analyzed using *t*-tests. Non-normally distributed data were expressed as medians with interquartile ranges and analyzed using the Mann–Whitney *U*-test. Categorical variables were reported as frequencies (percentages) and analyzed using the Chi-square test. Spearman correlation analysis was employed to assess the relationships between VA, VD, and other clinical and laboratory indices. Multivariate logistic regression analysis was conducted to determine whether VA and VD were independent risk factors for COVID-19. Variables with a p-value below 0.05 in the univariate logistic analysis were included in the multivariate logistic regression model. All statistical analyses were performed using IBM SPSS version 24.0 (SPSS Inc., Chicago, Illinois, USA). A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Study Population Characteristics

This study included 32 patients with COVID-19 and 30 health volunteers, all aged over 60 years. Patients with COVID-19 were defined as the COVID-19 group. Health volunteers were classed as the control group. The basic characteristics of the control and COVID-19 groups of the study subjects are summarized in Table 1. Compared with the control group, patients with COVID-19 were older and had higher respiratory and heart rates, while no significant differences were observed in sex distribution, body temperature, or the prevalence of hypertension, diabetes, and heart disease comorbidities between the groups. Biochemical and hematologic parameters analysis showed that the levels of the neutrophil count, ALT, and AST in the COVID-19 group were significantly higher than in the control group, and the lymphocyte count, PLT, and HGB in the COVID-19 group were significantly lower than in the control group. Further analysis revealed that the VA and VD levels were significantly lower in the COVID-19 group.

The Nutritional Status of VA and VD in Two Groups

According to the screening method for VA and VD deficiency in Chinese population (WS/T 553–2017 and WS/T 677—2020), we divided them into the VA deficiency group (< 30 mcg/dL), VA sufficiency group (≥ 30 mcg/dL), VD deficiency group (< 20 ng/mL), and VD sufficiency group (≥ 20 ng/mL) based on their levels of VA and VD. As shown in Table 2, the VA sufficiency rate in the control group was 96.7%, while that in the COVID-19 group was only 18.8%. The VA deficiency rate in patients with COVID-19 was significantly higher than that in the control group (81.3% vs 3.3%, P < 0.001).

Table 1 Basic Characteristics of Study Subjects of Control and COVID-19 Groups

Variables	Control (n=30)	COVID-19 (n=32)	P*
Age (years)	68.5 (66.7, 73.0)	76.5 (68.5, 82.0)	**0.002**
Male, n (%)	13 (43.3%)	18 (56.3%)	0.309
Temperature (°C)	36.5 (36.5, 36.7)	36.7 (36.3, 37.7)	0.425
Respiratory (rate/minute)	20.0 (18.0, 21.0)	21.0 (20.0, 21.0)	**0.012**
Heart rate (rate/minute)	79.0 (72.7, 83.2)	83.5 (76.0, 97.0)	**0.012**
Hypertension, n (%)	11.00 (40.0%)	18.00 (56.3%)	0.204
Diabetes mellitus, n (%)	2.00 (6.7%)	8.00 (25.0%)	0.052
Heart disease, n (%)	9.00 (30.0%)	7.00 (21.9%)	0.469
Hematologic parameters			
WBC (×10^9cell/L)	5.86 (4.82, 7.60)	6.08 (4.90, 7.74)	0.486
Neutrophil (×10^9cell/L)	2.92 (2.38, 4.19)	5.19 (3.66, 6.59)	**< 0.001**
Lymphocyte (×10^9cell/L)	2.00 (1.83, 2.44)	0.89 (0.59, 1.07)	**< 0.001**
Monocyte (×10^9cell/L)	0.35 (0.31, 0.48)	0.45 (0.29, 0.57)	0.197
PLT (×10^9cell/L)	226.0 (190.7, 260.5)	179.0 (132.8, 211.3)	**0.005**
HGB (g/L)	149.00 (141.00, 154.25)	137.00 (121.50, 146.00)	**< 0.001**
Biochemical parameters			
ALT (U/L)	21.5 (17.0, 28.0)	29.0 (19.2, 44.5)	**0.027**
AST (U/L)	21.0 (18.7, 23.5)	29.5 (20.0, 41.7)	**0.001**
UREA (mmol/L)	5.5 (4.4, 6.2)	6.2 (5.0, 7.6)	0.101
CREA (μmol/L)	71.7 (56.6, 80.0)	72.8 (54.2, 84.0)	0.800
VA (mcg/dL)	53.45 (44.88, 67.38)	18.91 (15.06, 25.73)	**< 0.001**
VD (ng/mL)	20.0 (15.7, 23.5)	11.7 (8.0, 20.3)	**< 0.001**

Note: *Boldface highlights results with statistically significant differences.
Abbreviations: COVID-19, corona virus disease 2019; WBC, white blood cell; PLT, platelet; HGB, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UREA, urea nitrogen; CREA, creatinine; VA, vitamin A; VD, vitamin D.

Table 2 The Nutritional Status of VA and VD in the Control and COVID-19 Groups

Variables	Control (n=30)	COVID-19 (n=32)	P*
VA status			**< 0.001**
VA sufficiency (≥ 30 mcg/dL)	29 (96.7)	6 (18.8%)	
VA deficiency (< 30 mcg/dL)	1 (3.3%)	26 (81.3%)	
VD status			**0.042**
VD sufficiency (≥ 20 ng/mL)	15 (50.0%)	8 (25.0%)	
VD deficiency (< 20 ng/mL)	15 (50.0%)	24 (75.0%)	

Note: *Boldface highlights results with statistically significant differences.
Abbreviations: COVID-19, corona virus disease 2019; VA, vitamin A; VD, vitamin D.

Meanwhile, the VD sufficiency rate in the control and COVID-19 groups was 50% and 25.0%. The VD deficiency rate in patients with COVID-19 was significantly higher than that in the control group (75.0% vs 50.0%, P = 0.042).

Correlation Between VA and VD and Clinical Parameters

To further explore the relationship between VA and VD and the clinical parameters, a correlation analysis was performed. As shown in Table 3, VA significantly negatively correlated with age (r = −0.295, P = 0.020), respiratory rate (r = −0.358, P = 0.004), heart rate (r = −0.336, P = 0.008), neutrophil count (r = −0.461, P < 0.001), and AST (r = −0.302, P = 0.017), and positively correlated with lymphocyte count (r = 0.657, P < 0.001), HGB (r = 0.398, P = 0.001) and VD (r = 0.649, P < 0.001). There was no significant correlation between VA and temperature, PLT, ALT, UREA, and CREA. VD significantly negatively correlated with temperature (r = −0.270, P = 0.034), respiratory rate (r = −0.311, P = 0.014), heart

Table 3 Correlations Between VA, VD, and Clinical Parameters

Variables	VA		VD	
	r	P*	r	P*
Age (years)	−0.295	**0.020**	−0.234	0.067
Temperature (°C)	−0.140	0.278	−0.270	**0.034**
Respiratory rate (rate/minute)	−0.358	**0.004**	−0.311	**0.014**
Heart rate (rate/minute)	−0.336	**0.008**	−0.305	**0.016**
Neutrophil (×10^9cell/L)	−0.461	**< 0.001**	−0.456	**< 0.001**
Lymphocyte (×10^9cell/L)	0.657	**< 0.001**	0.405	**< 0.001**
PLT (×10^9cell/L)	0.235	0.066	−0.006	0.963
HGB (g/L)	0.398	**0.001**	0.124	0.336
ALT (U/L)	−0.230	0.072	−0.222	0.082
AST (U/L)	−0.302	**0.017**	−0.162	0.209
UREA (mmol/L)	−0.118	0.360	0.016	0.902
CREA (μmol/L)	−0.012	0.925	0.022	0.868
VA (mcg/dL)	—	—	0.649	**< 0.001**
VD (ng/mL)	—	—	—	—

Note: *Boldface highlights results with statistically significant differences.
Abbreviations: COVID-19, corona virus disease 2019; PLT, platelet; HGB, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UREA, urea nitrogen; CREA, creatinine; VA, vitamin A; VD, vitamin D.

rate (r = −0.305, P = 0.016), and neutrophil count (r = −0.456, P < 0.001), and positively correlated with lymphocyte count (r = 0.405, P < 0.001). No correlation was found between VD and age, PLT, HGB, ALT, AST, UREA, and CREA.

VA and VD, and the Risk of COVID-19

Multivariable binary logistic regression analysis was performed to assess whether VA and VD were independent risk predictors for COVID-19. Variables in univariate regression analysis with P < 0.05 were included in multivariable binary logistic regression analysis, including age, respiratory rate, neutrophil counts, PLT, AST, and ALT. As shown in Table 4, After adjusting the above variables, VA (OR = 0.832, 95% CI = 0.739–0.936, P = 0.002) and VD (OR = 0.875, 95% CI = 0.765–1.001, P = 0.049) were independent risk factors for COVID-19. Meanwhile, compared with the VA-sufficient subjects, the risk of COVID-19 in the VA-deficient population is high (OR = 147.518, 95% CI = 5.874–3704.664, P = 0.002).

Table 4 Regression Analyses to Determine the Independent Risk Factors of COVID-19

Variables	Univariate		Multivariate[#]	
	OR (95% CI)	P*	OR (95% CI)	P*
VA (mcg/dL)	0.817 (0.970–0.990)	**<0.001**	0.832 (0.739–0.936)	**0.002**
VD (ng/mL)	0.852 (0.777–0.935)	**0.001**	0.875 (0.765–1.001)	**0.049**
VA status				
VA sufficiency (≥ 30 mcg/dL)	1		1	
VA deficiency (< 30 mcg/dL)	125.667 (14.175–1114.113)	**<0.001**	147.518 (5.874–3704.664)	**0.002**
VD status				
VD sufficiency (≥ 20 ng/mL)	1		1	
VD deficiency (< 20 ng/mL)	3.000 (1.025–8.777)	**0.045**	1.063 (0.945–1.195)	0.313

Notes: *Boldface highlights results with statistically significant differences. [#]Adjusted for age, respiratory rate, neutrophil counts, PLT, ALT, and AST.
Abbreviations: COVID-19, corona virus disease 2019; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; VA, vitamin A; VD, vitamin D.

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Discussion

Immunodeficiency is a common triggering factor for COVID-19, caused by the SARS-CoV-2 virus.[30] Vitamins' nutritional status is closely related to the body's immune function.[31] VA is a fat-soluble vitamin that primarily exists in the body as retinol. It is crucial in maintaining normal vision, promoting cell differentiation, and enhancing immune function.[32] VA contributes to the integrity of the pulmonary mucosa and regulates immune system functions, thus protecting against pulmonary infections.[33] Furthermore, the VA regulates inflammatory responses, reduces lung inflammation, and alleviates pneumonia symptoms.[33] Deficiency in VA can result in the degeneration and shedding of respiratory epithelial cells, which increases the susceptibility of the respiratory tract to pathogen invasion and elevates the risk of pneumonia.[16] Clinical studies have shown that peripheral blood VA levels in patients with COVID-19 are significantly reduced, and there is a negative correlation between VA levels and the severity of COVID-19.[22,34] Patients with VA deficiency experienced higher mortality rates and exhibited more severe symptoms following infection.[21] In this study, we observed a significant reduction in VA levels among elderly patients with COVID-19, along with a marked increase in deficiency rates. Furthermore, compared with the published data,[22,34] our data showed that VA levels in healthy elderly individuals are reduced. Notably, elderly patients with COVID-19 exhibit even more significant reductions in VA levels.

VD is also a fat-soluble vitamin critical in various physiological processes within the human body. It is essential for regulating the skeletal system, maintaining calcium balance, and supporting the immune, nervous, and cardiovascular systems.[35] By binding to VD receptors, VD enhances the function of immune cells, including macrophages and dendritic cells, thereby strengthening the body's defense against pathogens.[36] Additionally, VD inhibits pro-inflammatory cytokine production while promoting the expression of anti-inflammatory factors.[37] This dual action helps to mitigate excessive inflammatory responses associated with infections. Furthermore, VD stimulates the synthesis of specific antimicrobial peptides, such as defensins, which enhance the body's defense against bacterial, viral, and other pathogenic infections.[38] These peptides can directly disrupt the cell membranes of pathogens, thereby reducing the risk of infection. Recent studies indicate that VD may also lower viral replication by interfering with the replication process, potentially alleviating the severity of infections.[39] Multiple clinical studies have demonstrated that COVID-19 patients had a lower VD level than those without COVID-19, and COVID-19 patients with VD deficiency had a higher risk of invasive mechanical ventilation, requiring ICU admission and mortality rate.[22,40–44] In this study, our data showed that patients with COVID-19 had a lower VD level and a higher VD deficiency rate than those in the control group. Meanwhile, compared to prior studies involving younger cohorts (subjects aged ≤60 years), elderly COVID-19 patients in our analysis demonstrated significantly lower vitamin D levels and a higher prevalence of vitamin D deficiency.[45–48] Notably, even control subjects in this elderly population exhibited lower vitamin D concentrations than the matched control groups in published literature,[45,49] likely attributable to accelerated age-related declines in synthesis and absorption.

In this study, we first investigated the association between VA and VD levels and the risk of COVID-19 in Chinese elderly subjects and found that COVID-19 patients had lower levels of VA and VD, along with higher deficiency rates. Correlation analysis revealed significant negative correlations between VA and VD levels and respiratory rate, heart rate, and neutrophil count. Additionally, further analysis identified VA and VD as independent risk factors for COVID-19 in this population in Chinese elderly subjects.

Our study also has several limitations. First, the current study's sample size was constrained by the single-center design (restricting recruitment to hospitalized patients at Inner Mongolia Baogang Hospital during the brief secondary infection wave [April–August 2023]), inconsistent community nucleic acid/antigen testing practices during the study period, and a substantial proportion of mild cases self-managing without clinical documentation; therefore, further research with a larger sample is needed to validate our findings. Second, as a cross-sectional, single-center investigation, it cannot predict future events and may contain inherent biases. Third, the absence of age-matched cohorts introduces potential residual confounding, limiting causal inference; prospective age-matched cohort designs would further strengthen causal inference. Lastly, we have not evaluated the severity of COVID-19, so we cannot provide data on the relationship between VA and VD and the severity of COVID-19.

Conclusions

In conclusion, our data from this single-center demonstrated that elderly patients with COVID-19 had lower levels of VA and VD and higher deficiency rates of VA and VD. Meanwhile, multivariate analysis revealed that VA and VD were independent risk factors for COVID-19 in Chinese elderly subjects. The findings indicate that adequate VA and VD may help prevent SARS-CoV-2 virus infection.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval

The study was conducted according to the Declaration of Helsinki policies and received approval from the Hospital Ethics Review Board of Inner Mongolia Baogang Hospital (2022-MER-110). Written informed consent was obtained from all the participants.

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Disclosure

The authors report no conflicts of interest in this work.

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