

Vitamin D Deficiency Is Associated with COVID-19 Incidence and Disease Severity in Chinese People

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ABSTRACT

Background: Vitamin D might have beneficial potential in influencing the natural history of the coronavirus disease 2019 (COVID-19) due to its immunomodulatory and anti-inflammatory properties.

Objective: The aim was to investigate whether vitamin D deficiency is associated with COVID-19 incidence and disease severity in Chinese people.

Methods: In a cross-sectional study we retrospectively analyzed 335 COVID-19 patients (median: 56.0; IQR: 43.0–64.0 y) who were admitted to the Wuhan Tongji Hospital between 27 February and 21 March 2020. We also included an age- and sex-matched population of 560 individuals (median: 55; IQR: 49.0–60.0 y) who underwent the physical examination program. Their serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured during the same period from 2018–2019. Serum 25(OH)D concentrations were measured for all COVID-19 patients on admission. Severity of COVID-19 was determined based on the level of respiratory involvement. A general linear model with adjustment for covariates was used to compare 25(OH)D concentrations between the COVID-19 and 2018–2019 control groups. Adjusted ORs with 95% CIs for associations between vitamin D status and COVID-19 severity were estimated via multivariable logistic regression.

Results: In the general linear model adjusted for age, sex, comorbidities, and BMI, serum 25(OH)D concentrations were significantly lower among COVID-19 patients than the 2018–2019 controls [ln transformed values of 3.32 ± 0.04 vs. 3.46 ± 0.022 ln (nmol/L), $P = 0.014$]. Multivariable logistic regression showed that male sex (OR: 2.26; 95% CI: 1.06, 4.82), advanced age (≥ 65 y) (OR: 4.93; 95% CI: 1.44, 16.9), and vitamin D deficiency (<30 nmol/L) (OR: 2.72; 95% CI: 1.23, 6.01) were significantly associated with COVID-19 severity (all $P < 0.05$).

Conclusions: These findings suggested that vitamin D deficiency impacts COVID-19 hospitalization and severity in the Chinese population. *J Nutr* 2021;151:98–103.

Keywords: vitamin D, coronavirus disease, cross-sectional, deficiency, COVID-19 severity

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic of coronavirus disease 2019 (COVID-19). Infected persons display varied symptoms ranging from mild to severe illness, even death. Noticeably, the elderly, men, African Americans, Latinos, and patients with underlying

diseases seem to be more susceptible to COVID-19 and are disproportionately affected by severe COVID-19 (1, 2). To date, the mechanisms underlying this variability are still being elucidated.

Vitamin D is a pluripotent hormone that regulates cellular functions throughout the body. Generally, vitamin D deficiency is more prevalent among people with poor health status, the elderly, and ethnic groups with darker skin (3, 4). Vitamin D deficiency has been recognized as a pandemic, affecting almost 1 billion people worldwide (5). These 2 pandemics may be interrelated because they share some common epidemiological characteristics and risk factors (6). Over the last decade, vitamin D deficiency has been associated with infections and poor outcomes of several common viral infections, such as influenza, HIV type 1, and hepatitis (7–9). Science et al. (10) described an inverse relation between serum vitamin D

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Abbreviations used: ACE, angiotensin-converting enzyme; COVID-19, coronavirus disease 2019; RAS, renin angiotensin system; RTI, respiratory tract infection; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 25(OH)D, 25-hydroxyvitamin D.

concentrations and viral respiratory tract infections (RTIs) in a prospective cohort study. The authors observed that serum vitamin D concentrations <75 nmol/L increased the risk of viral RTI by 50% and concentrations <50 nmol/L increased the risk by 70% in 743 children from Canadian Hutterite communities. Similarly, data from meta-analysis of 25 eligible randomized controlled trials from 14 different countries (total 11,321 participants) suggested that vitamin D supplementation reduced the risk of RTIs (OR: 0.88; 95% CI: 0.81, 0.96) and patients with deficient vitamin D experienced the most benefit (OR: 0.30; 95% CI: 0.17, 0.53) (11). Another long-term prospective cohort study in 426 patients with chronic hepatitis B demonstrated that vitamin D deficiency was independently associated with adverse clinical outcomes (including cirrhotic complications, hepatocellular carcinoma, and/or death) (12). Vitamin D is anti-inflammatory; it modulates the immune system and is an inhibitor of the renin angiotensin system (RAS). Therefore, it could contribute to resistance against COVID-19 incidence or progression. However, this hypothesis still needs to be tested.

Currently, vitamin D deficiency and COVID-19 are global public health concerns and many studies have investigated the possible relation between these pandemics. A study from Switzerland revealed that vitamin D concentrations were significantly lower in patients with COVID-19 than in those without the disease (13). Many other studies have also indicated the correlation between vitamin D deficiency and COVID-19 infection, suggesting that vitamin D supplementation could reduce the risk of disease (14–16). However, the analyses of UK Biobank data neither supported this potential correlation nor indicated if vitamin D concentrations could explain the differences between ethnic groups regarding the incidence of COVID-19 (17). Thus, the association between vitamin D status and COVID-19 incidence is controversial. Here, we aimed to explore the association of the serum vitamin D status with COVID-19 incidence and severity in a Chinese population.

Methods

Study design and population

This retrospective cross-sectional study was conducted in Tongji Hospital of the Huazhong University of Science and Technology (Wuhan, China). We enrolled 335 consecutive patients with COVID-19 who were admitted to the hospital between 27 February and 21 March 2020. Data regarding demographic characteristics, treatment, ventilation condition, and outcome were retrospectively reviewed from electronic medical records. The follow-up period was extended to 2 May 2020. Six patients eventually died, and the remaining 329 patients survived and were discharged. Meanwhile, we reviewed 22,387 vitamin D measurements from the physical examination program in 2018–2019. The serum vitamin D status of the individuals in this program was influenced by sex, age, and sampling season (Supplemental Figure 1). We selected an age- and sex-matched population of 560 individuals who underwent vitamin D measurements during the same period (27 February to 21 March) from those (control) who underwent the physical examination program during 2018–2019. This work was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Diagnosis, definitions, and measurements

Patients with COVID-19 tested positive for SARS-CoV-2 infection as per nucleic acid tests of nasopharyngeal or oropharyngeal specimens. According to the diagnosis and treatment protocol for novel coronavirus pneumonia (version 7) released by the National Health Commission and State Administration of Traditional Chinese Medicine

(18), the COVID-19 patients were classified into 4 levels based on the severity of illness, as follows—1) mild: mild symptoms with no signs of pneumonia on imaging; 2) moderate: fever, respiratory symptoms with radiological evidence of pneumonia; 3) severe [i.e., meeting any of the following: respiratory distress, respiratory rate ≥ 30 breaths/min, hypoxemia, oxygen saturation (SpO_2) $\leq 93\%$ (at rest), or lung infiltrates of $> 50\%$ within 24–48 h]; and 4) critical (i.e., meeting any of the following criteria: respiratory failure requiring mechanical ventilation, shock, or multiple organ dysfunction requiring intensive care unit monitoring and treatment). In this study, mild and moderate cases were classified into the nonsevere group, while severe and critical cases were classified into the severe group. Nonsevere patients whose symptoms became progressively severe during hospitalization were defined as severe cases. With regard to vitamin D concentrations, patients were categorized into vitamin D-deficient (<30 nmol/L) and non-vitamin D-deficient (≥ 30 nmol/L) groups. BMI was calculated as weight (kilograms) divided by height (meters) squared (kg/m^2). The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation developed in 2009 (19).

Laboratory analysis

Blood samples were obtained from each COVID-19 patient upon admission. For the purpose of this study, serum 25-hydroxyvitamin D [25(OH)D] concentration, which represents the major circulating form of vitamin D, was determined using chemiluminescence immunoassay (DiaSorin, Inc.). Routine tests for COVID-19 to detect plasma concentrations of high-sensitivity C-reactive protein, calcium, phosphate, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase were measured using the Cobas 8000 system (ISE module, c701, c701, c701, and c502; Roche Diagnostics) and original reagents. Serum procalcitonin and IL-6 concentrations were evaluated with the Cobas e602 immunoassay analyzer using original reagents (Roche Diagnostics). D-dimer was assessed with a STA-R MAX coagulation analyzer (Diagnostica Stago) using commercially available kits. Complete blood count was conducted using the Sysmex XE-2100 hematology analyzer (Sysmex). All tests were performed in the Department of Laboratory Medicine, Tongji Hospital.

Statistical analysis

Statistical analysis was performed using GraphPad Prism (version 5.0; GraphPad Software, Inc.) and SPSS (version 20.0; IBM, Inc.). Data normality was analyzed using the Kolmogorov-Smirnov test. Normally distributed data were compared using the unpaired *t* test and expressed as means \pm SDs. Non-normally distributed data are expressed as medians and IQRs. Between-group comparisons were assessed using the Mann-Whitney *U* test, while between-group comparisons were analyzed using the Kruskal-Wallis test and Dunn's multiple-comparison test. Pearson's chi-square test or Fisher's exact test was performed to analyze the categorical data. A general linear model with adjustment for covariates was used to compare the serum 25(OH)D concentrations between COVID-19 patients and the 2018–2019 controls. A multivariable logistic regression model adjusted for confounding factors was used to estimate the ORs, 95% CIs, and *P* values for associations between serum 25(OH)D concentrations and COVID-19 severity. Multiple linear regression was used to determine the association between serum 25(OH)D and ln-transformed hospital stay, adjusted for age, sex, comorbidities, smoking status, and BMI. *P* values were 2-tailed, and *P* < 0.05 was considered statistically significant.

Results

Characteristics of the study population

A total of 335 COVID-19 patients and 560 controls from 2018–2019 were included in this study. Table 1 presents the background characteristics. The median ages for the COVID-19 and 2018–2019 control groups were 56.0 (IQR: 43.0–64.0) y and 55.0 (IQR: 49.0–60.0) y, respectively. The proportion of

TABLE 1 Baseline characteristics of 2018–2019 controls and patients with COVID-19¹

	Total			COVID-19		
	2018–2019 Controls	COVID-19	<i>P</i>	Nonsevere group ²	Severe group ³	<i>P</i> ⁴
<i>n</i>	560	335		261	74	
Age, y	55.0 (49.0–60.0)	56.0 (43.0–64.0)	0.18	54.0 (40.0–62.0)	62.5 (51.0–75.3)	<0.0001
Male, <i>n</i> (%)	257 (45.9)	148 (44.2)	0.62	105 (40.2)	43 (58.1)	0.006
BMI, ⁵ kg/m ²	24.6 ± 3.35	23.5 ± 3.13	<0.0001	23.6 ± 3.07	23.1 ± 3.37	0.4
Comorbidity status, ⁶ <i>n</i> (%)	145 (26.5) ⁷	147 (43.9)	<0.0001	97 (37.2)	50 (67.6)	<0.0001
Smoking status						
Never	Unknown	290 (86.6)		229 (87.7)	61 (82.4)	0.24
Former/current	Unknown	45 (13.4)		32 (12.3)	13 (17.6)	
Serum 25(OH)D, nmol/L	32.5 (25.3–41.8)	26.5 (20.7–33.8)	<0.0001	27.5 (21.8–34.5)	23.1 (18.1–28.3)	<0.0001
Serum vitamin D status, <i>n</i> (%)			<0.0001			0.0004
Deficient ⁸	228 (40.7)	218 (65.1)		157 (60.2)	61 (82.4)	
Nondeficient ⁹	332 (59.3)	117 (34.9)		104 (39.8)	13 (17.6)	

¹Values are medians (IQRs) or means ± SDs for continuous variables or frequencies (%) for categorical variables. COVID-19, coronavirus disease 2019; 25(OH)D, 25-hydroxyvitamin D.

²Nonsevere patients were those with mild respiratory illness with fever, cough, or pneumonia on chest radiography.

³Severe COVID-19 was defined as meeting any of the following: respiratory distress, respiratory rate ≥30 breaths/min, hypoxemia, oxygen saturation (SpO₂) ≤93% (at rest), lung infiltrates >50% within 24–48 h, respiratory failure requiring mechanical ventilation, shock, or multiple organ dysfunction requiring intensive care unit monitoring and treatment.

⁴Continuous values were compared by Mann-Whitney *U* test or unpaired *t* test; categorical variables were compared by Pearson's chi-square test.

⁵Observations were not available for all subjects: *n* = 533 (2018–2019 controls), *n* = 255 (COVID-19), *n* = 206 (nonsevere group), *n* = 49 (severe group).

⁶Including hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic lung diseases, chronic kidney disease, and tumors.

⁷Information on comorbidity status was available for 547 controls.

⁸Serum 25(OH)D concentrations <30 nmol/L.

⁹Serum 25(OH)D concentrations ≥30 nmol/L.

men was 44.2% in the COVID-19 group and 45.9% in the 2018–2019 control group. There was no significant difference between the 2 groups in terms of age distribution and sex proportion. While 2018–2019 controls had fewer subjects with comorbidity, their mean BMI was higher than that in COVID-19 patients.

Vitamin D status in 2018–2019 control and COVID-19 groups

The median 25(OH)D concentrations were significantly lower in the COVID-19 group (median: 26.5; IQR: 20.7–33.8 nmol/L) than in the 2018–2019 control group (median: 32.5; IQR: 25.3–41.8 nmol/L) (Table 1). The prevalence of vitamin D deficiency was higher among COVID-19 patients than among 2018–2019 controls (65.1% vs. 40.7%; *P* < 0.0001). After adjusting for confounders including comorbidities, BMI, age, and sex, the ln-transformed 25(OH)D concentrations in the COVID-19 group remained significantly lower than those in the 2018–2019 control group [3.32 ± 0.04 vs. 3.46 ± 0.022 ln (nmol/L), *P* = 0.014] (Figure 1). Back-transformed means were 27.7 nmol/L and 31.8 nmol/L, respectively.

Association between vitamin D status and severity of COVID-19

In the COVID-19 group, 261 (77.9%) patients were categorized as nonsevere and 74 (22.1%) were categorized as severe (Table 1). The severe COVID-19 patients were significantly older than the nonsevere COVID-19 patients [median (IQR): 62.5 (51.0–75.3) vs. 54.0 (40.0–62.0) y]. A greater proportion of men were in the severe group than in the nonsevere group (58.1% vs. 40.2%). However, there was no significant difference between the severe and nonsevere groups in terms of BMI distribution and smoking status. Ninety-seven patients (37.2%) in the nonsevere group and 50 patients (67.6%) in the severe group had ≥1 pre-existing comorbidities (*P* < 0.0001). The median hospital stay was 15.0 (IQR: 11.0–22.0) d in

the nonsevere group and 20.0 (IQR: 13.8–33.3) d in the severe group (Supplemental Table 1; *P* = 0.0001). During the follow-up period, 329 COVID-19 patients survived and were discharged and the remaining 6 died. In the linear regression

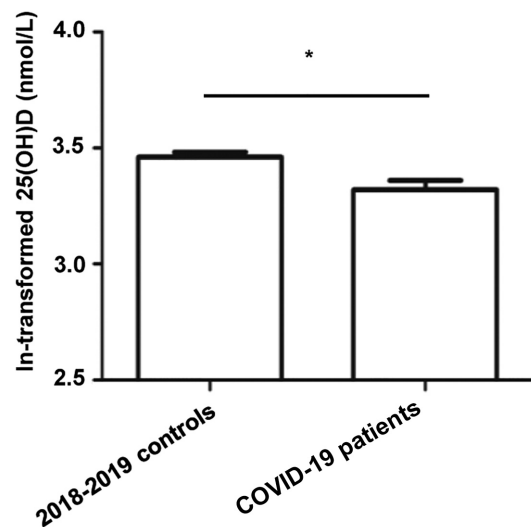


FIGURE 1 Vitamin D concentrations in 2018–2019 controls and patients with COVID-19. Values are estimated marginal means ± SEs from general linear models adjusted for comorbidities, BMI, age, and sex. *Different from 2018–2019 controls, *P* < 0.05. Serum 25(OH)D was ln-transformed. Back-transformed means are as follows: 2018–2019 controls, 31.8 nmol/L; COVID-19 patients, 27.7 nmol/L. The 2018–2019 controls consisted of an age/sex-matched population from the 2018–2019 physical examination program during the same period (27 February to 21 March), *n* = 560; patients with COVID-19 were those cases recruited between 27 February and 21 March 2020, *n* = 335. COVID-19, coronavirus disease 2019; 25(OH)D, 25-hydroxyvitamin D.

TABLE 2 Risk factors of disease severity in patients with COVID-19¹

	OR (95% CI)	P
Sex		
Female	Reference	
Male	2.26 (1.06, 4.82)	0.035
Age groups		
13–42 y	Reference	
43–55 y	2.99 (0.99, 9.03)	0.052
56–64 y	1.88 (0.59, 5.94)	0.29
65–92 y	4.93 (1.44, 16.9)	0.011
Comorbidities		
No	Reference	
Yes	1.30 (0.58, 2.91)	0.52
BMI (continuous)	0.95 (0.85, 1.06)	0.33
Smoking status		
Never	Reference	
Former/current	1.11 (0.44, 2.82)	0.83
Serum vitamin D status		
Nondeficient ²	Reference	
Deficient ³	2.72 (1.23, 6.01)	0.014

¹ORs, 95% CIs, and *P* values were adjusted by sex, age, comorbidities, BMI, smoking status, and vitamin D status; Reference = 1. COVID-19, coronavirus disease 2019; 25(OH)D, 25-hydroxyvitamin D.

²Serum 25(OH)D concentrations ≥ 30 nmol/L.

³Serum 25(OH)D concentrations < 30 nmol/L.

analysis, age was directly associated with the length of hospital stay among discharged patients, whereas serum 25(OH)D concentrations, sex, comorbidities, BMI, or smoking status were not associated with the length of hospital stay (Supplemental Table 2). In the severe group, 22 (29.7%) patients received corticosteroid treatment and 16 (21.6%) received ventilation assistance (5 with noninvasive ventilation and 11 with invasive ventilation) at the hospital (Supplemental Table 1). Serum 25(OH)D concentrations were lower in the severe group than in the nonsevere group (Table 1). Consistently, 82.4% of the severe COVID-19 patients and only 60.2% of the nonsevere COVID-19 patients were vitamin D deficient ($P = 0.0004$). Multivariable analysis revealed that male sex (OR: 2.26; 95% CI: 1.06, 4.82), advanced age (≥ 65 y) (OR: 4.93; 95% CI: 1.44, 16.9), and vitamin D deficiency (OR: 2.72; 95% CI: 1.23, 6.01) were significantly associated with COVID-19 severity (Table 2).

Vitamin D status in severe COVID-19 patients

Six of the 74 severe COVID-19 patients (8.1%), of whom 5 were males, eventually died. The remaining 68 patients survived and were discharged (Table 3). All patients who died had pre-existing comorbidities, and 83.3% of them were vitamin D deficient. The median hospital stay was 17.0 (IQR: 11.0–23.5) d in the discharged group and 19.5 (IQR: 8.75–39.3) d in the death group ($P = 0.74$). No significant difference in serum 25(OH)D concentrations was observed between those who died and those who were discharged (18.7 nmol/L vs. 23.2 nmol/L); this may be due to the small number of patients in the death group.

Discussion

The COVID-19 outbreak has become a global threat. Public health measures to reduce the risk of infection, severity, and death are desperately needed. Currently, there is no strong

evidence from the intervention trials to conclusively prove that vitamin D beneficially affects COVID-19 outcomes. However, a few retrospective observational studies evaluated the relation between vitamin D status and incidence of COVID-19 (17, 20, 21). Our study revealed that 25(OH)D concentrations on admission were significantly lower in COVID-19 patients than in the 2018–2019 controls, even after adjusting for comorbidities, BMI, age, and sex. An Israeli population study with 7807 participants demonstrated that vitamin D concentrations were significantly lower among the COVID-19–positive individuals than COVID-19–negative individuals (20). Similarly, a retrospective cohort study from the University of Chicago Medicine in the United States included 499 patients who underwent vitamin D measurement and treatment within 1 y before they were tested for SARS-CoV-2 (21). The study indicated that patients with vitamin D deficiency, who were not sufficiently treated, were at an increased relative risk of COVID-19 infection compared with patients with likely sufficient vitamin D concentrations. The vitamin D measurements in these 2 studies were not performed while SARS-CoV-2 tests were carried out. Thus, the actual vitamin D status may not have been reflected. Furthermore, a recent study from the United Kingdom, which recruited 348,598 Biobank participants, found that the vitamin D concentration was associated with COVID-19 infection in a univariate analysis, but not after adjustment for confounders, including ethnicity, age, sex, smoking status, health rating, household income, and BMI, to name a few (17). However, the baseline vitamin D concentration and health status in the study were obtained 10 y prior, which could have resulted in a time-lag bias. In our study, vitamin D deficiency was more common in COVID-19 patients than in 2018–2019 controls, indicating that vitamin D deficiency could be a risk factor for SARS-CoV-2 infection. However, this cross-sectional analysis does not allow us to draw conclusions regarding causality, and more research is needed. Overall, evidence suggests that vitamin D could be an etiological factor in COVID-19 infection.

Our data revealed significantly lower serum 25(OH)D concentrations in severe COVID-19 patients than in nonsevere patients. We observed that vitamin D deficiency was associated with COVID-19 severity, after adjusting for several potential confounders, such as age, sex, comorbidities, BMI, and smoking status. While stratifying the severe COVID-19 patients by outcomes, it was found that 25(OH)D concentrations in the death group were lower (but not significant) than that in the discharged group (18.7 nmol/L vs 23.2 nmol/L). This was likely due to the small number of patients in the death group. Recently, a single-center, retrospective, and observational study investigated the possible associations of vitamin D status with disease severity and survival (22). The authors examined 185 COVID-19 patients, of whom 28 patients had invasive mechanical ventilation and/or died. This study showed that vitamin D deficiency (< 30 nmol/L) was associated with higher risk of invasive mechanical ventilation and/or death [HR (95% CI): 6.12 (2.79, 13.42) and 14.73 (4.16, 52.19); $P < 0.001$, respectively]. It is noteworthy that the disease severity criteria in this study were different from ours as mentioned above. Altogether, vitamin D deficiency could act as an important risk factor for COVID-19 severity.

The role of vitamin D in barrier function and innate immunity could partially explain the relation of vitamin D deficiency with COVID-19 incidence and disease severity. Vitamin D promotes barrier integrity by upregulating a complex set of proteins (23) and inducing the expression of defense

TABLE 3 Baseline characteristics of patients with severe COVID-19 in the discharged and death groups¹

Variables	Discharged group (n = 68)	Death group (n = 6)	P ²
Demographic parameters			
Age, y	62.4 ± 15.3	64.8 ± 10.2	0.10
Male, n (%)	38 (55.9)	5 (83.9)	0.38
BMI, ³ kg/m ²	23.3 ± 3.38	22.6 ± 0.66	0.68
Comorbidity status ⁴	44 (64.7)	6 (100)	0.17
Smoking status			0.62
Never	57 (83.8)	4 (66.7)	
Former/current	11 (16.2)	2 (33.3)	
Serum 25(OH)D, nmol/L	23.2 (18.6–28.4)	18.7 (17.0–28.3)	0.38
Hospital stay, d	17.0 (11.0–23.5)	19.5 (8.75–39.3)	0.74
Serum vitamin D status, n (%)			1.0
Deficient ⁵	56 (82.4)	5 (83.3)	
Nondeficient ⁶	12 (17.6)	1 (16.7)	

¹Values are medians (IQRs) or means ± SDs for continuous variables or frequencies (%) for categorical variables. COVID-19, coronavirus disease 2019; 25(OH)D, 25-hydroxyvitamin D.

²Continuous values were compared by Mann-Whitney *U* test or unpaired *t* test; categorical variables were compared by Pearson's chi-square test (with continuity correction) or Fisher's exact test.

³Information on BMI was available for 45 cases in the discharged group and 4 in the death group.

⁴Including hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic lung diseases, chronic kidney disease, and tumors.

⁵Serum 25(OH)D concentrations <30 nmol/L.

⁶Serum 25(OH)D concentrations ≥30 nmol/L.

peptides, such as cathelicidin and β -defensins (24); both of these functions protect the host from pathogen invasion. Recently, the RAS has been suggested as a potential mechanism underlying the association between vitamin D and COVID-19 (25). SARS-CoV-2 infection can enhance angiotensin-converting enzyme (ACE)/angiotensin II expression and reduce ACE2/angiotensin-(1–7) concentrations (25). This is conducive for COVID-19 pathogenesis and subsequent disease severity and mortality. However, vitamin D negatively regulates the RAS by inhibiting renin, ACE, and angiotensin II and activating the ACE2/angiotensin-(1–7) axis, thereby exerting protective effects against COVID-19 (16, 26). Uncontrolled inflammation and cytokine release also play critical roles in COVID-19 pathogenesis and clinical manifestations. Increasing evidence indicates that vitamin D can suppress the expression of proinflammatory cytokines, such as IL-6, TNF- α , IFN- γ , IL-1 β , IL-8, and IFN- γ , in immune cells (27). It induces this effect by increasing intracellular glutathione concentrations and suppressing excessive reactive oxygen species, NF- κ B, and p38 mitogen-activated protein kinase expression. Furthermore, vitamin D exerts anti-inflammatory effects by promoting anti-inflammatory cytokine generation, such as transforming growth factor- β and IL-10 (27, 28). Therefore, vitamin D may reduce cytokine storm syndrome in COVID-19 patients and prevent multiple organ damage. Additionally, thrombotic or thromboembolic events are common in patients with severe COVID-19. The antithrombotic effects of vitamin D in other conditions have been well documented (29, 30) and may also apply to COVID-19. Taken together, vitamin D may play an important role in reducing the risk of COVID-19 development, progression, and severity.

Our study has several strengths. Most importantly, this is a real-world study investigating, for the first time, the vitamin D status of COVID-19 patients in a Chinese population. Additionally, sample collections from COVID-19 patients for serum 25(OH)D were completed within ~1 mo for reducing seasonal variation in vitamin D status. However, the study also had some limitations. First, the cross-sectional study design may be a major limitation. Although vitamin D deficiency was

associated with COVID-19 incidence and disease severity, we could not establish the causality. Better-designed clinical trials are warranted in the future. Second, we could not obtain a sufficient number of vitamin D measurements from population-wide tests during the study period (2020) due to the COVID-19 outbreak. Thus, we selected the 2018–2019 cohort as representative of vitamin D status of the general public. Third, information on smoking status was not available for the 2018–2019 controls. While we assessed the potential impact of vitamin D deficiency on COVID-19 incidence, this risk factor was not controlled for.

In conclusion, our study showed that individuals with vitamin D deficiency were more common among patients with COVID-19 infection and severe illness. Interventional trials would be helpful in clarifying the role of vitamin D in COVID-19 infection and disease severity.

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