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## Nutritional status of patients with COVID-19

Jae Hyoung Im<sup>a</sup>, Young Soo Je<sup>b</sup>, Jihyeon Baek<sup>a</sup>, Moon-Hyun Chung<sup>c</sup>, Hea Yoon Kwon<sup>a,\*</sup>,  
Jin-Soo Lee<sup>a,\*</sup><sup>1</sup>

<sup>a</sup> Division of Infectious Diseases, Department of Internal Medicine, Inha University College of Medicine, Incheon, Republic of Korea

<sup>b</sup> Department of Laboratory Medicine, Seoul Clinical Laboratories (SCL), Yongin, South Korea

<sup>c</sup> The Korean Society of Infectious Diseases, Republic of Korea



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### ABSTRACT

The relationship between immunity and nutrition is well known and its role in coronavirus disease 2019 (COVID-19) is also being paid great attention. However, the nutritional status of COVID-19 patients is unknown. Vitamin B1, B6, B12, vitamin D (25-hydroxyvitamin D), folate, selenium, and zinc levels were measured in 50 hospitalized patients with COVID-19. Overall, 76% of the patients were vitamin D deficient and 42% were selenium deficient. No significant increase in the incidence of deficiency was found for vitamins B1, B6, and B12, folate, and zinc in patients with COVID-19. The COVID-19 group showed significantly lower vitamin D values than the healthy control group (150 people, matched by age/sex). Severe vitamin D deficiency (based on a cut-off of  $\leq 10$  ng/dl) was found in 24.0% of the patients in the COVID-19 group and 7.3% in the control group. Among 12 patients with respiratory distress, 11 (91.7%) were deficient in at least one nutrient. However, patients without respiratory distress showed a deficiency in 30/38 cases (78.9%;  $p = 0.425$ ). These results suggest that a deficiency of vitamin D or selenium may decrease the immune defenses against COVID-19 and cause progression to severe disease. However, more precise and large-scale studies are needed.

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### Introduction

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China in December 2019 and has since caused numerous fatalities and economic losses worldwide (Nicola et al., 2020). The mortality rate of COVID-19 varies significantly by country, race, and socioeconomic status (Aldridge et al., 2020). The differences are believed to be caused by a variety of factors, including ethnicity, medical systems, and age structure. Factors such as poor socioeconomic status or weak immunity appear to increase vulnerability to COVID-19 (Grant et al., 2020). It is well documented that older individuals, those with underlying illnesses, and those living in long-term care facilities are more vulnerable to COVID-19 (D'Adamo et al., 2020).

Decreased immunity is a significant risk factor for infection with respiratory viruses. A proper diet and good nutritional status are considered important elements for an optimal immune response to prevent infections (Calder et al., 2020; Chandra,

1983). Thus, a poor diet and deficiency of these nutrients will increase the disease burden. Evidence suggests that nutrients are involved in the development of COVID-19 (Rhodes et al., 2020a); however, no studies have been undertaken to assess nutrient deficiencies in COVID-19 patients directly. Therefore, this study was conducted to confirm the levels of various nutrients in COVID-19 patients.

### Methods

This study was conducted on adults with COVID-19 admitted to Inha University Hospital, South Korea, from February to June 2020. Foreigners and children younger than 15 years of age were excluded. A PCR assay (Allplex 2019-nCoV Assay Kit; Seegene, Republic of Korea) was performed on samples from the upper or lower respiratory tract to diagnose the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19. The severity of COVID-19 was classified as (1) without pneumonia, (2) pneumonia without oxygen treatment, (3) pneumonia with oxygen treatment, (4) high-flow oxygen treatment, (5) mechanical ventilation, and (6) extracorporeal membrane oxygenation (ECMO) or death.

\* Corresponding authors.

E-mail addresses: [haeyoon85@hanmail.net](mailto:haeyoon85@hanmail.net) (H.Y. Kwon), [ljinsoo@inha.ac.kr](mailto:ljinsoo@inha.ac.kr) (J.-S. Lee).

<sup>1</sup> The two corresponding authors contributed equally to the study.

The levels of all nutrients were analyzed within 7 days of admission (median number of days for analysis was 2 days after admission) and the following nutrients were investigated: vitamin B1, B6, B12, vitamin D (25-hydroxyvitamin D3), folate, selenium, and zinc. Specimens were sent to Seoul Clinical Laboratories Co. Ltd (Republic of Korea) for analysis, except those for the analysis of folate and vitamin B12, which were sent to Green Cross Co. Ltd (Republic of Korea). 25-Hydroxyvitamin D3 was tested using a validated liquid chromatography–tandem mass spectrometry method. High-performance liquid chromatography was used for vitamin B1 and B6, an electrochemiluminescence binding assay for folate and vitamin B12, and inductively coupled plasma–mass spectrometry for selenium and zinc. The equipment, cut-off values, and references are described in **Supplementary Material** Table S1.

The levels of 25-hydroxyvitamin D3 in COVID-19 patients were compared to those of a control group of individuals who attended Inha University for their annual medical check-up. The control group comprised those who were tested for 25-hydroxyvitamin D3 in February–June, the same season in which COVID-19 patients presented to the hospital. The control group was assigned 3:1 to each COVID-19 patient after age- and sex-matching. A control group was only used for the analysis of 25-hydroxyvitamin D3. The Student *t*-test and Chi-square test were used to compare the vitamin D levels of the two groups. Any *p*-value <0.05 was considered statistically significant. The data analysis was performed using SPSS version 18 software (SPSS Inc., Chicago, IL, USA).

## Result

During the study period, 83 patients with COVID-19 were hospitalized. Fifteen of these patients were excluded because they were children or foreigners. Therefore, the total number of potential candidates for this study was 68. Of these 68 patients, 12 were missing prescriptions and six were not examined within 1 week of hospitalization. Therefore, only 50 individuals were selected to have their nutrient levels assessed (zinc measurement was introduced from May, and only 25 individuals were tested for this). A total of 29 men and 21 women were included. Their median age was 57.5 years (interquartile range 34.5–68.0 years). The age distribution was as follows: two teenagers (15–19 years), eight in their 20 s, five in their 30 s, five in their 40 s, eight in their 50 s, 12 in their 60 s, and 10 were ≥70 years or older.

According to the data, vitamin D deficiency was the most prevalent, with a deficiency ( $\leq 20$  ng/dl) in 76% of the patients and a severe deficiency ( $\leq 10$  ng/dl) in 24%. Regarding the other nutrients, a deficiency of selenium was observed in 42% of the patients, pyridoxine in 6.1%, and folate in 4.0%. No patient was deficient in B1, B12, or zinc. At least one missing nutrient was revealed in 82% of the patients. The median value of each nutrient and the percentages of deficiency are shown in **Table 1**.

In the comparison between the two groups, the average 25-hydroxyvitamin D3 level among those with COVID-19 was

15.73 ng/dl, which was significantly lower than the average level in the control group, which was 25.03 ng/dl. The deficiency rate was 74.0% in the COVID-19 group and 43.3% in the control group. In terms of severe deficiencies, there were also differences between the two groups: 24.0% and 7.3%, respectively (**Table 2**).

Among the patients with mild COVID-19 (without pneumonia), vitamin D and selenium deficiencies were present in 66.7% and 44.4%, respectively. In contrast, the same deficiencies in patients whose disease severity was higher than the mechanical ventilation category were 80% and 100%, respectively. Of the 12 patients with respiratory distress, 11 were deficient in at least one nutrient. The percentages of nutrient-deficient patients according to the categories of infection severity are shown in **Table 3**.

## Discussion

In this study, vitamin D and selenium deficiencies were the most prevalent. Additionally, almost all COVID-19 patients with respiratory distress were classified as nutrient-deficient. It is unclear whether individual nutrient deficiencies affected immunity or whether the nutrient deficiency simply led to a decline in the patient's overall condition. However, as it is becoming increasingly clear that hyper-inflammation is a major factor in the course of progression to severe COVID-19, vitamin D and selenium deficiencies should be highlighted.

Vitamin D supports the production of antimicrobial peptides in the respiratory epithelium, reducing the likelihood of viral infections and decreasing the severity of symptoms ([Barlow et al., 2011](#); [Bartley, 2010](#)). Dysregulation of the renin–angiotensin system is one of the primary mechanisms of lung injury in COVID-19 ([Bourgonje et al., 2020](#); [Kong et al., 2013](#)). Furthermore, vitamin D upregulates anti-inflammatory mediators, which is vital when considering the hyper-inflammatory immune response caused by COVID-19 ([Daneshkhah et al., 2020](#)). These mechanisms suggest that vitamin D-deficient patients may be more susceptible to become infected with SARS-CoV-2 and be more likely to develop severe symptoms.

In this study, the COVID-19 group showed a high percentage of vitamin D deficiency when compared to the control group. Vitamin D supplements have been shown to be of uncertain benefit in treating or preventing most diseases, except rickets and osteomalacia ([Autier et al., 2017](#)). However, an important exception to this general trend is in the case of upper respiratory tract infections. A meta-analysis conducted in 2017 showed that vitamin D supplements protect against acute respiratory infections ([Martineau et al., 2017](#)). In the present study, even the control group showed an incidence of vitamin D deficiency of 43.3%, so it is difficult to conclude that vitamin D deficiency directly increases the risk of infection. However, considering the high mortality rate in long-term care facilities and in high latitude countries ([Rhodes et al., 2020a](#)), as well as the pathophysiology of COVID-19 ([Rhodes et al., 2020b](#)), a vitamin D deficiency is thought to exacerbate the

**Table 1**  
Nutrient deficiency in patients with COVID-19; median and percentage values.

	Median value (IQR)			Deficiency (percentage)		
	Female (n = 29)	Male (n = 21)	Total (n = 50)	Female	Male	Total
25-Hydroxyvitamin D3 (ng/dl)	14.0 (10–20.5)	14.0 (11.1–19.4)	14.2 (10.5–20.2)	22/29 (75.9%)	16/21 (76.2%)	38/50 (76.0%)
Vitamin B1 (nmol/l)	149.8 (127.4–186.7)	174.2 (159.2–236.2)	163.2 (131.8–198.9)	0/28 (0.0%)	0/21 (0.0%)	0/49 (0.0%)
Vitamin B6 (PLP) (μg/l)	11.9 (8.2–15)	11.8 (8.4–22)	11.85 (8.4–20.7)	2/29 (7.9%)	1/21 (4.8%)	3/50 (6.0%)
Folate (μg/l)	10.3 (7.8–15.4)	7.8 (4.9–11.5)	9.6 (7.3–14.3)	2/29 (7.9%)	1/21 (4.8%)	3/50 (6.0%)
Vitamin B12 (ng/l)	729.0 (533.0–965.0)	601.0 (543.0–956.0)	727 (535.5–962.8)	0/29 (0.0%)	0/21 (0.0%)	0/50 (0.0%)
Selenium (ng/mL)	96.7 (90.6–107.8)	101.4 (86.9–105.7)	98.3 (90.3–107.6)	13/29 (44.8%)	8/21(38.1%)	21/50 (42.0%)
Zinc (μg/dl)	86.3 (82.3–94.9)	91.4 (78.8–102.5)	87.2 (81.9–96.7)	0/18 (0.0%)	0/7 (0.0%)	0/25 (0.0%)

IQR, interquartile range; PLP, pyridoxal-5-phosphate.

**Table 2**  
Comparison of vitamin D levels between the COVID-19 group and the healthy control group.

	Control group (n = 150)	COVID-19 group (n = 50)	p-Value
Age (years), mean ± SD	52.4 ± 20.2	52.2 ± 20.7	0.965
25-Hydroxyvitamin D3 (ng/dl), mean ± SD	25.0 ± 13.2	15.7 ± 7.9)	<0.001
25-Hydroxyvitamin D3 deficiency, n/n (%)			
Deficiency (≤20 ng/dl)	65/150 (43.3%)	37/50 (74.0%)	0.003
Severe deficiency (≤10 ng/dl)	11/150 (7.3%)	12/50 (24.0%)	0.001

SD, standard deviation.

**Table 3**  
Percentage of nutrient deficiency according to severity.

	Without pneumonia	With pneumonia <sup>a</sup>				
		Pneumonia	Oxygen	High-flow nasal cannula	Mechanical ventilator	ECMO or death
Number	18	32	12	9	5	4
25-Hydroxyvitamin D3	12 (66.7%)	26 (81.3%)	9 (75.0%)	6 (66.7%)	4 (80.0)	3 (75.0%)
Vitamin B1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vitamin B6 (PLP)	2 (11.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Folate	1 (20.4%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vitamin B12	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Selenium	8 (44.4%)	13 (40.6%)	8 (66.7%)	6 (66.7%)	4 (100.0%)	3 (100.0%)
Zinc	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
One or more deficiency	13 (72.2%)	28 (87.5%)	11 (91.7%)	8 (88.9%)	5 (100.0%)	4 (100.0%)

ECMO, extracorporeal membrane oxygenation; PLP, pyridoxal-5-phosphate.

<sup>a</sup> Pneumonia includes cases with or without an oxygen supply. Oxygen includes high-flow nasal cannula, mechanical ventilator, and ECMO/death. High-flow nasal cannula includes mechanical ventilator and ECMO/death. Mechanical ventilator includes ECMO/death and one death.

severity of COVID-19. Further studies are needed to determine whether vitamin D supplementation could aid clinical progress in COVID-19 patients.

In selenium-deficient mice, there were no differences in influenza virus-specific antibodies compared to mice with adequate selenium levels. However, the levels of macrophages and CD8+ and CD4+T cells were lower, suggesting that selenium deficiency affects cellular immunity (Beck et al., 2003). Influenza virus-infected models in selenium-deficient mice (Beck et al., 2001) and in vitro influenza infection models of selenium-deficient human bronchial epithelial cells (Jaspers et al., 2007) have shown that inflammation may be increased in response to high oxidative stress levels. Among HIV-1-infected individuals, the lower the serum selenium concentration, the lower the number of CD4+T cells, leading to more significant HIV-1 disease progression (Baum et al., 1997; Look et al., 1997). Another study suggested that low selenium levels were associated with reduced natural killer (NK) cell-mediated cytotoxicity in HIV-1-infected individuals (Mantero-Atienza et al., 1991). In SARS-CoV-2 infection, there is an association between infection severity and T-cell and NK cell dysfunction and lymphopenia (Tay et al., 2020); therefore, selenium deficiency needs to be considered in severe cases of COVID-19. In a study involving previously healthy Koreans, the mean selenium levels were 103.2 µg/l in males and 120.8 µg/l in females. In the present study, the median selenium concentrations were 101.4 µg/l in males and 96.7 µg/l in females. Additionally, 42% of COVID-19 patients were found to have selenium levels below the cut-off. It is unknown whether selenium supplementation could influence the progression of severity of COVID-19.

In this study, only 6% of COVID-19 patients were deficient in pyridoxal-5-phosphate (PLP); however, 96% were deficient in pyridoxal or 4-pyridoxic acid (4PA). PLP, the active form of vitamin B6 (pyridoxine), is an essential cofactor in many inflammatory pathways and is gradually depleted during inflammation (Paul et al., 2013). In the present study, PLP had not dropped significantly. It is probable that the individuals in our study were less affected because it was conducted within 7 days of patient admission. However, 4-pyridoxic acid and pyridoxal may indicate

other micronutrient deficiencies that we did not measure. Additionally, some COVID-19 patients have longer treatment periods due to acute lung injury; therefore, even if the PLP levels are acceptable, it is necessary to study how the PLP status changes in patients with 4-pyridoxic acid/pyridoxal deficiency during severe COVID-19 infection.

This study had several limitations that are worth noting. First, it was a study conducted at a single center with a relatively small number of patients. However, compared to the averages in Korea, an apparent deficiency of vitamin D and selenium was observed. Second, in this study, nutrients such as vitamin D were only measured from February to June, and most of the patients with COVID-19 in this study lived in cities. However, this study did not aim to determine an exact fraction of the specific nutritional deficiency, but rather to show the general trend of deficiency and the importance of nutrition in the prevention of severe cases of COVID-19. Third, many indicators of nutritional status are unreliable during infections. Vitamin D binding protein is a positive acute phase reactant after infections; it may lower the level of 25-hydroxyvitamin D (Silva and Furlanetto, 2015). A decrease in other nutrients may also be the result of an infection. However, because this study was conducted in the early stages of infection, these outcomes should not be considered a result of COVID-19. Additional research is needed, including the use of a free vitamin D assay (Bikle et al., 2017).

In conclusion, this study investigated the status of various nutrients in patients with COVID-19. The results showed that many patients were deficient in vitamin D and selenium. Additionally, all severely ill patients with COVID-19 were deficient in more than one nutrient. Therefore, we suggest that nutritional deficiencies may possibly favor the onset of COVID-19 and increase the severity of the disease. Further research is needed on the impact of nutritional deficiencies in COVID-19.

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This study had no funding.

## Ethical approval

This study was approved by the local ethics committee, which waived the need for informed consent.

## Conflict of interest

All authors declare no conflict of interest related to this study.

## CRediT authorship contribution statement

**Jae Hyoung Im:** Conceptualization, Writing - original draft. **Young Soo Je:** Writing - review & editing. **Jihyeon Baek:** Writing - review & editing. **Moon-Hyun Chung:** Writing - review & editing. **Hea Yoon Kwon:** Writing - review & editing, Supervision. **Jin-Soo Lee:** Conceptualization, Supervision.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2020.08.018>.

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