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Association between 25(OH)D₃ Levels and the Presence of COVID-19 Symptoms

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Background: Recently, there have been studies reporting a relationship between vitamin D levels in the blood and the immune system. This study aimed to analyze the association between vitamin D levels and symptoms of coronavirus disease 2019 (COVID-19).

Materials and methods: This study was an analytical survey study with a cross-sectional approach, with lecturers at Universitas Malahayati that have been infected with COVID-19 in 2022 as subjects. Total 47 subjects were included. Subjects were fasted overnight, then blood samples were taken from subjects in the next morning. The blood was centrifuged, then the serum was separated for examination by the direct competitive chemiluminescence immunoassay (CLIA) method using Architect 25-OH Vitamin D Reagent. Data was analyzed using logistic regression.

Results: None of the subjects had normal blood levels of 25(OH)D₃ and almost half (48.9%) of the subjects had symptoms when infected with COVID-19. There was a significant relationship between the level of 25(OH)D₃ ($p=0.001$) and the status of the COVID-19 vaccine ($p=0.013$) with the presence of symptoms in COVID-19 patients.

Conclusion: The lower the level of 25(OH)D₃ in the blood and the more incomplete the COVID-19 vaccine, the greater the onset potential of COVID-19 symptoms. It is necessary to maintain vitamin D intake and increase the coverage of the COVID-19 vaccine, especially at booster doses.

Keywords: vitamin D, COVID-19, vaccination, health protocol

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is the cause of the coronavirus disease 2019 (COVID-19), continues to mutate until it becomes a new variant¹, such as omicron which is currently found in many countries. Although not as many as when there was delta

variant, COVID-19 cases are still being reported. Based on data from the COVID-19 handling unit of the Republic of Indonesia, until mid-2022, 150,000 mortality cases caused by COVID-19 infection were reported in Indonesia.²

Not all Indonesians, especially who live outside the Java island have received a complete COVID-19

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vaccination. Although the coverage of second dose vaccination in Indonesia is around 70%, coverage of booster vaccine administration is still low, around 25% of the total population of Indonesia.³ While truly effective drugs for this disease are still being explored, several things can be done to avoid COVID-19 infection, such as implementing health protocols, maintaining distance, washing hands with soap, always wearing masks, avoiding crowds and reducing mobility.⁴⁻⁶ There are many ways to maintain or increase endurance, such as increasing the consumption of nutritious foods, taking multivitamins, avoiding stress, getting enough rest, taking regular exercise and avoiding exposure to pollution, including avoiding exposure to cigarette smoke and others that are all related to lifestyle.⁷

There have been recent studies reporting positive relationship between vitamin D levels in the blood and the immune system, although the exact mechanism is still unclear. It is known that vitamin D plays an important role in regulating bone and tooth mineralization, as well as preventing various degenerative diseases, such as cancer, heart disease, hypertension, obesity, stroke and diabetes mellitus.⁸⁻¹⁵ Many important functions of vitamin D have been reported. However, vitamin D deficiency is a problem reported worldwide.^{16,17} This is due to changes in the individuals' behavior, such as avoiding sunlight and being more active indoors.^{18,19} Recent research reports that vitamin D is able to prevent COVID-19 infection.²⁰ A study also reports that sun exposure is proven to improve the healing process of COVID-19 patients.²¹

Vitamin D can be obtained from foods and biosynthesis in the skin. Vitamin D is reported to have many effects on the immune system, including increasing the macrophage activity, activating neutrophils and T lymphocytes, as well as increasing the level of immunity markers.^{22,23} Administration of vitamin D plays an important role in activating the immune system in COVID-19 patients, both in pediatric and adult patients.²⁴

Information about the importance of vitamin D to prevent COVID-19 has spread widely to the community. Many health facilities such as hospitals provide sunbathing therapy to get additional vitamin D and reduce the symptoms felt by COVID-19 patients.^{25,26} Since vitamin D is known to play a role in increasing the activity of the immune system, however it is still controversial whether Indonesians who are living in the tropical zone will be more resistant to infectious diseases than other people living in sub-tropical countries. This is showed by the increase in morbidity and

mortality due to COVID-19 is still occurring in Indonesia, even though countries with temperate climates still report higher disease severity.²⁷ The purpose of this study was to analyze the association between levels of 25(OH)D₃ and the presence of symptoms in COVID-19 patients.

Materials and methods

Study Design and Subjects

This was an analytical observational study with a cross-sectional approach that analyzed the relationship between 25(OH)D₃ levels in the blood and the symptoms due to COVID-19 infection. This research was conducted from March to July 2022 which was carried out in the integrated laboratory of Universitas Malahayati, while the measurement of vitamin D levels in the blood was carried out at the Prodia Clinical Laboratory, Bandar Lampung. This research has obtained an ethics approval from the Health Research Ethics Commission, Universitas Malahayati (No. 2499/EC/KEP-UNMAL/V/2022 dated May 20, 2022). The population of this research was all lecturers at Universitas Malahayati. As much as 47 lecturers were known to had been infected with COVID-19 in 2022, hence included in the study as subjects. The sampling technique was total sampling.

Data Collection and Measurement of 25(OH)D₃ Level

Vitamin D/25(OH)D₃ levels were measured by direct competitive chemiluminescence immunoassay (CLIA) using Architect 25-OH Vitamin D Reagent (Abbott Diagnostics, Lake Forest, IL, USA). The subjects fasted overnight and in the morning 5 mL of blood was taken. The blood sample was centrifuged at a speed of 3,700 rpm for 15 minutes, then the serum was separated and put into the apparatus for examination using CLIA. In this study, several other variables were also analyzed, *i.e.* the presence of symptoms, age, gender, completeness of the COVID-19 vaccination, and compliance to health protocols. Interviews with research subjects were conducted to obtain these data.

Data Analysis

The data was analyzed with SPSS version 25 (IBM Corporation, Armonk, NY, USA) to see the relationship between the levels of 25(OH)D₃, completeness of the COVID-19 vaccination, implementation of the health protocol, age and gender of the subjects, and the presence of COVID-19 symptoms. Univariate analysis was performed to see the frequency distribution of each variable. Bivariate test with chi-square test was used to analyze the relationship

between all independent variables with the presence of COVID-19 symptoms. The chi-square test was also used to select variables that will be included in the multivariate test. Multivariate test using logistic regression test was performed to find out the most dominant variable associated with the presence of COVID-19 symptoms.

Results

None of the subjects had normal blood levels of vitamin D. Most of the subjects (57.4%) had low levels of vitamin D. Nearly half (48.9%) of the subjects experienced symptoms when infected with COVID-19. Most of the subjects (72.3%) were female and 76.6% of the subjects were under 45 years old. There were 31.9% of the subjects whose vaccination status was not complete. It also appeared that only 29.8% subjects were obedient to the health protocol. It was found that there were 51.1% of the subjects who were asymptomatic when infected with COVID-19 (Table 1). Symptoms suffered by COVID-19 patients were cough (23.4%), headache (21.3%), fever and joint pain (6.4%) (Table 2).

The results of the bivariate analysis (Table 3) showed that blood vitamin D levels ($p=0.001$) and completeness of the COVID-19 vaccination ($p=0.010$) were significantly associated with the presence of COVID-19 symptoms, whereas the results of the multivariate test showed that vitamin D levels ($p=0.001$) and completeness of vaccination status ($p=0.013$) were the dominant variables associated with the presence of COVID-19 symptoms (Table 4).

Discussion

The percentages of subjects with symptoms (48.9%) and without symptoms (51.1%) were almost the same. This strengthens the notion that the symptoms felt by COVID-19 patients in 2022 are milder when compared to the symptoms felt by COVID-19 patients last year.²⁸ In the present study, most of the subjects (72.3%) were women. Interestingly, previous studies have reported that COVID-19 prevalence is higher in men than women, because men do more risky behaviors than women, such as smoking, drinking alcohol and staying up late.²⁹ This difference occurred allegedly because the population in this study was mostly female lecturers in the health sector who did not have the habit of smoking and drinking alcohol. In addition, dual roles of women, both as housewives and workers, require them to do a lot of strenuous work. In general, women have a

Table 1. Characteristics of subjects.

Variable	n (%)
Presence of symptoms	
Asymptomatic	24 (51.1)
Symptomatic	23 (48.9)
Gender	
Man	13 (27.7)
Women	34 (72.3)
Age	
Low risk (<45 years old)	36 (76.6)
High risk (\geq 45 years old)	11 (23.4)
Blood levels of 25(OH)D₃	
Normal (>30–100 ng/mL)	0 (0)
Sufficient (>20–30 ng/mL)	7 (14.9)
Less (10–20 ng/mL)	27 (57.4)
Very poor (<10 ng/mL)	13 (27.7)
Completeness of COVID-19 vaccination	
Complete (\geq 2 doses)	32 (68.1)
Incomplete (<2 doses)	15 (31.9)
Compliance with health protocols	
Obedient	14 (29.8)
Disobedient	33 (70.2)

stronger immune system, because they are influenced by the presence of estrogen. However, the function of the immune system will decrease with increasing age and the amount of stress in work and daily life.³⁰

Most subjects (76.6%) were in the <45 years old (low risk) group. Previous studies report that age is positively correlated with the incidence of COVID-19 infection. The older a person is, the higher the risk of COVID-19 infection and the higher the severity of the symptoms.³¹ However, individuals at the productive ages also have a high risk of getting infected with COVID-19. At this age, they are required to work actively and carry out many activities in various places, hence the possibility of being exposed to the

Table 2. Distribution of COVID-19 symptoms.

Symptoms	n (%)
Symptomatic	
Cough	11 (23.4)
Headache	10 (21.3)
Fever and joint pain	3 (6.4)
Asymptomatic	23 (48.9)
Total	47 (100.0)

Table 3. Results of bivariate analysis.

Variable	Showing Symptoms During COVID-19 Infection (n)		p-value
	No	Yes	
Gender			
Man	8	5	0.374
Women	16	18	
Age			
Low risk (<45 years old)	16	20	0.101
High risk (≥45 years old)	8	3	
Blood levels of 25(OH)D₃			
Normal (>30–100 ng/mL)	0	0	0.001*
Sufficient (>20–30 ng/mL)	5	2	
Less (10–20 ng/mL)	19	8	
Very poor (<10 ng/mL)	0	13	
Completeness of COVID-19 vaccination			
Complete (≥2 doses)	19	13	0.010*
Incomplete (<2 doses)	5	10	
Compliance with health protocols			
Obedient	9	5	0.238
Disobedient	15	18	

**p*<0.05.

COVID-19 virus is greater. This may cause many young people to be infected with COVID-19.

None of the subjects had normal blood vitamin D levels. Many of them were in poor condition (57.4%) or even very poor (27.7%). There were only 14.9% of the subjects that had sufficient levels of vitamin D. These results strengthen the notion that there has been a global pandemic of vitamin D deficiency.^{16,32} This phenomenon occurs not only in sub-tropical areas, but also in tropical areas, such as Indonesia. Changes in the individuals' behavior, such as avoiding sunlight and being more active indoors are thought to be one of the contributing factors. Previous studies have also reported that there is a deficiency in vitamin D levels both in adolescence and old age.^{8,33}

There were 31.9% and 70.2% of the subjects that have not completed COVID-19 vaccination and were not compliant in implementing the health protocol, respectively. These results corroborate the results of another research which reports that preventive measures are still low.³⁴ The easing of health protocols, along with the low number of

new COVID-19, are suspected to have contributed to the low level of public compliance with the current health protocol.

There was a significant relationship between vitamin D levels and the presence of symptoms in COVID-19 patients. The lower the level of vitamin D, the greater the possibility for COVID-19 symptoms to develop. All of the subjects who have a very low vitamin D levels (<10 ng/mL) experienced COVID-19 symptoms. This result is in line with studies that report a high prevalence of vitamin D deficiency in hospitalized patients with COVID-19 with an increased risk of developing COVID-19 symptoms.³⁵ Vitamin D modulates both innate and adaptive immune systems.^{24,25,36}

There was no significant relationship between gender and the presence of symptoms in COVID-19 patients. Although women in their reproductive period are benefitted from the presence of estrogen, which helps the immune system³⁰, however, in this study, both men and women showed no different results. It has been

Table 4. Results of multivariate analysis.

Variable	B	Wald	Sig	OR	CI (95%)
25(OH)D ₃ levels	2.967	11.37	0.001*	9.4	3.46–10.9
Completeness of COVID-19 vaccination	2.139	6.149	0.013*	8.9	1.56–14.6

**p*<0.05.

reported that more women suffer from COVID-19 than men at working ages.³⁷

Age of the subjects was also not significantly related to the onset of symptoms in COVID-19 patients. High risk (≥ 45 years old) and low risk (< 45 years old) age groups have the same risk for the onset of COVID-19 symptoms. Previous research has reported that age affects the severity of COVID-19.³⁸ Older patients tend to experience more severe symptoms compared to the younger ones.

Completeness of the COVID-19 vaccination was significantly related to the presence of COVID-19 symptoms. Based on previous research, COVID-19 vaccine is proven to be effective in preventing infection with COVID-19. Furthermore, vaccination during recovery from COVID-19 infection is very effective in preventing reinfection.²³

Compliance with health protocols was also not significantly related to the presence of COVID-19 symptoms. Compliance with health protocols has proven to be able to prevent COVID-19 exposure. Many studies have reported this case.²³ Unfortunately, compliance with current health protocols seems to decline. A decrease in adherence to health protocol is more visible in groups of people who have been vaccinated.²³ There is a wrong assumption: when they have been vaccinated, they will be immune to the virus. In this study, it also appeared that 70.2% of the subjects did not comply with the health protocol. Subjects who disobeyed the health protocol did not avoid crowds and/or eating and drinking together, while the most common practice is to wash hands and use masks.

Multivariate analysis results showed that the variables of $25(\text{OH})\text{D}_3$ levels in the blood and the completeness of the COVID-19 vaccine are the most dominant variables related to the presence of COVID-19 symptoms. The levels of $25(\text{OH})\text{D}_3$ were significantly related to the presence of COVID-19 symptoms. This variable had the largest odds ratio (OR) value, which was 9.4. This showed that individuals who have low levels of $25(\text{OH})\text{D}_3$ will have a risk to experience COVID-19 symptoms 9.4 times higher than those who have normal $25(\text{OH})\text{D}_3$ levels.

The completeness of the COVID-19 vaccination was also the dominant variable associated with the presence of COVID-19 symptoms, with an OR value of 8.9. This shows that people who were not fully vaccinated against COVID-19 will have a risk to experience COVID-19 symptoms 9.4 times higher than those who have been fully vaccinated. In addition to preventing COVID-19 infection, vaccines have also been reported to reduce the severity of

COVID-19.³⁹ Booster vaccines are also needed to increase the effectiveness of primary COVID-19 vaccines in preventing and reducing COVID-19 severity.⁴⁰ Serious efforts are still needed to educate and socialize the COVID-19 vaccination program, hence its coverage continues to increase.

Conclusion

$25(\text{OH})\text{D}_3$ levels in the blood and the completeness of the COVID-19 vaccination are significantly related to the presence of symptoms that appear in COVID-19 infection. Lower $25(\text{OH})\text{D}_3$ level and incomplete COVID-19 vaccine will increase the possibility of an individuals to experience symptoms when infected with COVID-19.

Some efforts are needed to increase $25(\text{OH})\text{D}_3$ levels in the blood, either by increasing the consumption of foods containing vitamin D or optimizing UVB exposure, hence the biosynthesis of vitamin D in the skin runs optimally. The COVID-19 vaccination program must also be encouraged in order to increase the coverage of COVID-19 vaccination, especially for booster doses, hence the onset of COVID-19 symptoms can be minimized.

Authors Contribution

DH, NA and NM were involved in concepting and planning the research and aided in interpreting the results. DH, SA and MP performed the data collection. DH and NA calculated the experimental data and performed the analysis. DH and SA drafted the manuscript. MP designed the tables. All authors took parts in giving critical revision of the manuscript and have read and approved the final manuscript.

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