

RESEARCH STUDY

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Correlation between Vitamin D Levels and Completion of COVID-19 Vaccines with Recurrent COVID-19 Infections in Lecturers at the University of Malahayati

Hubungan Kadar Vitamin D dan Kelengkapan Vaksin COVID-19 dengan Kejadian Infeksi COVID-19 Berulang pada Dosen Universitas Malahayati

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ABSTRACT

Background: There is a continued increase in the fatality rate of COVID-19 pandemic despite the apparent containment of the virus. In September 2022, the death toll from this disease has exceeded 150 thousand individuals. Furthermore, Vitamin D has been observed for its correlation with the immune system.

Objectives: This study aimed to analyze correlation between blood vitamin D levels, completeness of COVID-19 vaccine, and compliance with health protocols for recurrent infection.

Methods: This analytical observational study with a cross-sectional method examined correlation between blood vitamin D levels, vaccine completeness status, as well as compliance with health protocols, age, and gender. The population consisted of 62 lecturers at Malahayati University, Bandar Lampung, who were willing to volunteer as subjects. The method used was non-probability sampling and the inclusion criteria were individuals infected with COVID-19 in 2022, resulting in 47 samples. The collected data was analyzed using the chi-square test and logistic regression test.

Results: The results showed that there was a significant correlation between the completeness status of COVID-19 vaccine (p-value=0.001) with an OR of 8.24 and 8.47, as well as low levels of vitamin D in the blood (p-value=0.007) and recurrent infection.

Conclusions: The possibility of recurrent COVID-19 infection was increased when there were lower levels of vitamin D in the bloodstream and a less comprehensive response to vaccine.

INTRODUCTION

In September 2022, the global COVID-19 pandemic was reported to be under control. Despite the persistent mutations of the SAR-CoV-2 virus and the subsequent development of new variants such as the Omicron, efforts were carried out to address and mitigate the situation. According to the Ministry of Health,, the reported death toll reached a total of 150 thousand individuals across the country¹.

The preventive efforts conducted by the Government of Indonesia include increasing vaccination coverage. However, it is important to state that not all individuals have attained complete vaccination. This is because only 70% has received their second vaccine dose, and the coverage for booster shots is still very low, at 25%. Therefore, an alternative for the public is to avoid exposure to COVID-19 virus by adhering to health protocols, such as maintaining physical distance, regularly washing hands with soap, consistently wearing

masks, avoiding crowds, and reducing unnecessary mobility. In this context, immune system resilience needs to be maintained and enhanced to prevent susceptibility to infectious diseases²⁻⁴. Lifestyle changes are also believed to play a role in the decline of the immune system⁵.

Many recent studies report a positive correlation between blood vitamin D levels and the immune system but the mechanisms still raise many questions. Vitamin D is known to play a crucial role in maintaining dental and bone health, as well as preventing various degenerative diseases such as cancer, heart disease, hypertension, obesity, diabetes mellitus, and others^{4,6-9}. However, the deficiency is a global issue and has been declared a pandemic¹⁰. Recent results suggest that vitamin D can prevent infection with COVID-19 pandemic¹¹. Ultraviolet B rays from sunlight have also been proven to enhance the healing of patients¹². Vitamin D is reported to have many effects on the immune system, including the ability

to enhance the function of macrophages, and neutrophils, as well as to activate T lymphocytes. This makes the immune system more prepared and robust when a virus or antigen enters the body^{13,14}. The results are further supported by studies proving that vitamin D intervention plays a crucial role in activating the immune system in pediatric and adult patients¹⁵.

Information about the importance of vitamin D in preventing the pandemic has spread widely to the public. Therefore, many healthcare facilities recommend sun exposure to obtain additional vitamin D and reduce symptoms experienced by patients^{12,16}. This study warrants further exploration to determine whether vitamin D enhances the immune system. Indonesia shows greater resilience to infectious diseases compared to sub-tropical countries. However, there is no significant difference between tropical and sub-tropical regions since all countries report similar figures for illness, recurring infection, and deaths. The conditions have sparked interest in studying and analyzing correlation between blood vitamin D levels and the occurrence of recurring COVID-19 infection. Moreover, study specifically addressing the connection between the two variables has not been extensively reported. The public can use a simple and cost-effective method to minimize recurring COVID-19 infection when the two variables are correlated. Information on the role of vitamin D in preventing recurring COVID-19 infection needs to be clarified when there is no correlation. Therefore, this study aims to analyze correlation between blood vitamin D levels, completeness of COVID-19 vaccination, and compliance with health protocols in the occurrence of recurring infection. The hypothesis is that the higher the blood vitamin D levels, the more complete the vaccination, and the more compliant with health protocols, the lower the possibility of experiencing recurring infection.

METHODS

Study Design and Subjects

The design used was an analytical observational method with a cross-sectional design. The study was conducted from early March to the end of July 2022 at the integrated laboratory of Malahayati University. Meanwhile, the measurement of blood vitamin D levels was carried out by assessing level of 25(OH)D₃ in the blood at the Prodia Clinical Laboratory in Bandar Lampung. This study obtained ethical approval from the Health Research Ethics Committee of Malahayati University Bandar Lampung with No: 2499/EC/KEP-UNMAL/V/2022 dated May 20, 2022.

The population consisted of 62 permanent faculty members at Malahayati University in Bandar Lampung who voluntarily agreed to participate. During the blood sampling and interviews, only 47 samples were obtained from individuals who had been infected with COVID-19.

Therefore, the total number of samples that met the inclusion criteria was 47 and the study used a non-probability sampling method.

Data Collection and Measurement

The measurement of blood vitamin D levels was conducted using the direct competitive chemiluminescence immunoassay (CLIA) method and the examination used the Architect 25-OH Vitamin D reagent (Abbott Diagnostics, Lake Forest, IL, USA). The subjects were subjected to fasting from 10:00 PM until the next morning at 08:00 AM and a total of 5 mL of blood was collected. Subsequently, the collected blood was centrifuged at a speed of 3700 rpm for 15 minutes. The separated serum was transferred into tubes and measured at a Clinical Laboratory in Bandar Lampung.

Several variables were also analyzed, such as age, gender, completeness of COVID-19 vaccination, and adherence to health protocols. Direct interviews were conducted to obtain data on recurring infection and the subjects were questioned after being diagnosed. Similarly, information on the completeness of vaccination was directly inquired. To strengthen the data, validation was performed by directly checking the Peduli Lindungi application for information related to certificates. Regarding adherence to health protocols, the subjects were directly asked about their habits in implementing the 5 M's, namely wearing masks, washing hands with soap, avoiding crowds, avoiding eating/drinking together, and avoiding unnecessary physical mobility. Individuals were categorized as compliant with health protocols after adhering to all five specified health measures. Conversely, those who did not follow any of the 5 M's were classified as non-compliant.

Data Analysis

The collected data were analyzed to investigate correlation between blood 25(OH)D₃ levels, completeness of COVID-19 vaccination, adherence to health protocols, and occurrence of recurring infection. The analysis was carried out using the chi-square test and further proceeded with logistic regression with a significance level of $p < 0.05$. Meanwhile, data analysis was conducted with the assistance of SPSS version 25.

RESULTS AND DISCUSSION

The collected data from the 47 study subjects were tabulated in Tables 1 through 3. Furthermore, none of the study subjects had blood 25(OH)D₃ levels within the normal range, and 40% experienced recurring infection. Approximately 72% of those who had COVID-19 were female, and 76% were under the age of 45. Table 1 also shows that there are still 32% of subjects with incomplete vaccination status and only 30% are compliant with health protocols.

Table 1. Respondent Characteristics

Respondent Characteristics	n	%
Recurrent COVID-19 Infection		
No	28	60
Yes (Repeat)	19	40
Gender		

Respondent Characteristics	n	%
Male	13	28
Female	34	72
Ages		
Low Risk (≤45 years)	36	76
High Risk (>45 years)	11	24
Blood Vitamin D Levels/25(OH)D₃ Levels		
Normal (>30 ng/mL)	0	0
Sufficient (20 - 30 ng/mL)	7	14.8
Less (10 - 19 ng/mL)	27	57.5
Very Less (<10 ng/mL)	13	27.7
Completeness for COVID-19 Vaccine		
Complete (≥2 times)	32	68
Incomplete (<2 times)	15	32
Compliance with Health Protocols		
Obedient	14	30
Not obey	33	70

n: Total of Respondents; %: Percentage of Respondents Total; >: More than; <: Less than; ≥: More than or equal to; ≤: Less than or equal to

The number of samples who have experienced recurring COVID-19 infection is 40% of the total subjects and the majority are female (72%), playing a dual role as homemakers and employees. This dual role demands female to conduct a considerable amount of energy-draining tasks. The situation needs to be monitored because a decline may be experienced in the immune system with increasing age and stress¹⁹. However, previous studies reported that males were at higher risk and experienced more infection compared to females. This is because males engage in more risky behaviors, such as smoking, alcohol consumption, and staying up late²⁰.

From Table 1, 76% of people infected with COVID-19 are under 45 years of age. At a young or productive age, there is a high risk of being infected because the age group is required to actively work and carry out many activities. These activities increase the potential for young age groups to be exposed to a greater extent of COVID-19 virus. Meanwhile, previous studies reported that age was positively correlated with the incidence. The risk of contracting COVID-19 rises, and the severity of symptoms tends to increase with age in association with a weakened immune system. Furthermore, none of the subjects had normal blood 25(OH)D₃ levels (above 30

ng/mL). The majority were in an insufficient state (57.5%), and even severely insufficient (27.7%), with only 14.8% having blood 25(OH)D₃ levels within the sufficient range (20 - 30 ng/mL). These results support the suspicion that a deficiency in vitamin D has occurred in sub-tropical and tropical regions^{10,22}. Changes in sun avoidance behavior, such as wearing long clothing, using sunscreen lotion, and indoor activities, are the contributing factors. Several previous studies have also reported a deficiency in vitamin D levels, both in adolescents and the elderly^{23,24}. Similarly, the results show the same pattern, with a very small number of samples having levels within the normal range^{25,26}. This situation is believed to be increased by poor intake of foods containing vitamin D. Some individuals still refrain from consuming fish and eggs due to fears of allergies, and there is a misconception that drinking milk is only for babies and children. Approximately 32% of the subjects have not completed COVID-19 vaccination, and 70% are not compliant with health protocols. These reinforce results reporting the low level of preventive measures taken by the community²⁷. The relaxation of health protocols is also suspected to contribute to the decreasing adherence of the community.

Table 2. Results of Bivariate Test Analysis: Correlation of Several Variables with Recurrent COVID-19 Infection

Variable	Recurrent COVID-19 Infection		p-value	OR 95% CI
	No	Yes		
Gender				
Male	8	5	0.865	
Female	20	14		
Age				
Low Risk (≤45 years)	20	16	0.506	
High Risk (>45 years)	8	3		
Blood Vitamin D Levels/25(OH)D₃ Levels				
Normal (>30 ng/mL)	0	0	0.045	
Sufficient (20 - 30 ng/mL)	5	2		
Less (10 - 19 ng/mL)	19	8		
Very Less (<10 ng/mL)	4	9		
Completeness for COVID-19 Vaccine				
Complete (≥2 times)	24	8	0.002*	8.2 2.04-33.3
Incomplete (<2 times)	4	11		

Variable	Recurrent COVID-19 Infection		p-value	OR 95% CI
	No	Yes		
Compliance with Health Protocols				
Obedient	11	3	0.084	
Not obey	17	16		

*: Significant (Meaningful); n: of Respondents; %: Percentage of Respondents Total; >: More than; <: Less than; ≥: More than or equal to; ≤: Less than or equal to; p-value: Probability Value; OR: Odds Ratio; 95% CI: 95% Confidence Interval

In Table 2, the results of bivariate testing show that gender, age, and adherence to health protocols are not significantly associated with the occurrence of recurring infection. However, blood 25(OH)D₃ levels are significantly associated with the occurrence (p-value=0.045). The lower the blood vitamin D levels, the greater the potential for recurring infection. Subjects with severely insufficient 25(OH)D₃ levels (below 10 ng/mL) predominantly experienced recurring infection. These results are consistent with a study reporting a high incidence of vitamin D deficiency in hospitalized patients and an increased risk of developing signs and symptoms in individuals with vitamin D deficiency²⁸. Vitamin D is believed to modulate both the innate and adaptive immune systems^{14,15,29}. The completeness of COVID-19 vaccination is significantly associated with recurring infection (p-value: 0.002), with an odds ratio (OR) of 8.2. Therefore, someone who is not fully vaccinated is 8.2 times more likely to experience recurring infection. Previous studies have shown that vaccine is effective in preventing infection when administered to patients during the recovery period¹⁴. The Government of Indonesia has carried out various efforts to continually increase the coverage of vaccination. These efforts include socialization, education, and a "door-to-door" vaccination program including various institutions such as the Indonesian National Defense Forces (TNI), the National Police (POLRI), and the State Intelligence Agency (BIN). However, in September 2022, only 72% and 25%

had received their second and third dose, respectively³⁰.

Other variables are not associated with the occurrence of recurring COVID-19 infection and gender has a p-value of 0.865. This result shows that there is no significant correlation between gender and the occurrence of recurring infection. Theoretically, females of reproductive age may benefit from estrogen, which aids the immune system¹⁹ but both genders showed similar results in this study. A different scenario is reported in the working female population, where increased numbers suffer from the pandemic compared to males.³¹

In Table 2, adherence to health protocols is not significantly associated with the occurrence of recurring infection (p-value 0.084). Therefore, the occurrence is not related to adherence to health protocols. Adherence to health protocols has proven to prevent potential exposure to COVID-19 virus. Even though many studies have reported this result, adherence seems to have declined. The study shows a decrease in this variable, which is more apparent in the vaccinated population¹⁴. The misconception that being vaccinated provides complete immunity has led to a decline in adherence to health protocols. In this study, 70% of the samples are not compliant with health protocols. Avoiding crowds or gatherings and eating or drinking together are protocols mostly violated. Meanwhile, handwashing and wearing masks are still widely practiced.

Table 3. Results of Multivariate Test Analysis: Logistic Regression on Several Variables on Recurrent COVID-19 Infection

Variable	p-value	OR	CI (95%)
Vitamin D Deficiency	0.007*	8.47	1.79 - 39.9
Completeness for COVID-19 Vaccine	0.001*	8.24	3.58 - 19.9
Compliance with Health Protocols	0.057	5.59	0.95 - 32.9

*: Significant (Meaningful); p-value: Probability Value; OR: Odds Ratio; 95% CI: 95% Confidence Interval

The results of the multivariate analysis show that the variables blood 25(OH)D₃ levels (p-value=0.007) and completeness of COVID-19 vaccination (p-value= 0.001) are the most dominant associated with the occurrence of recurring infection. The completeness of vaccination is the dominant variable associated with recurring infection and an OR of 8.24. An individual with incomplete vaccination is at a significantly higher risk of experiencing recurring infection. In addition to preventing infection, vaccine has also been proven to reduce the severity experienced by patients when infected³². Vaccination against the pandemic induces the body to produce specific antibodies for infection. Therefore, the antibodies promptly address the antigen after entering the body. Booster doses are also highly necessary to enhance the effectiveness of vaccine in preventing and reducing the severity levels³³. Currently, many people are reluctant or have not completed their COVID-19

vaccination, specifically the booster vaccine. This is evident from the low achievement of the vaccination, particularly outside of Java and Bali³⁴. Genuine efforts are needed to educate and socialize the vaccination program to ensure its coverage continues to increase.

Blood 25(OH)D₃ levels are also a dominant variable (p-value=0.007) with an OR of 8.47. From these results, an individual with low 25(OH)D₃ or vitamin D levels in the blood is potentially 8.47 times more likely to experience recurring infection within the normal range. Vitamin D modulates the immune system by enhancing the function of macrophages, neutrophils, and T lymphocytes^{13,14}.

Public awareness of the importance of maintaining vitamin D intake needs to be optimized hence the blood levels consistently fall within the normal range. Food and beverages rich in vitamin D, such as fish, fish oil, eggs, and milk³⁵ as well as outdoor activities, need

to be continuously promoted to ensure that these levels remain within the normal range³⁶. Outdoor activities should be encouraged to maximize exposure to UVB rays, allowing the biosynthesis in the skin to function properly³⁷ and preventing various diseases associated with the deficiency^{23,38,39}.

Limitations in this study include the reduced number of samples. The number of samples fulfilling the criteria is only 47 individuals infected with COVID-19 in 2022 out of 62. The limited number fulfilling the inclusion criteria is suspected to have caused a wide range in the 95% CI values, resulting in weak data quality. Further studies with larger and more diverse populations are needed to better depict the real conditions of the community.

CONCLUSIONS

In conclusion, blood vitamin D levels and completeness of COVID-19 vaccination were significantly associated with the occurrence of recurrent infection. Meanwhile, lower blood vitamin D levels and incomplete vaccination increased the potential for individuals to experience recurrent infection. Efforts were needed to continually promote increased vaccination coverage, specifically for booster doses, to reduce the occurrence of recurrent infection. There was also a need to enhance blood vitamin D levels by increasing the intake of foods and drinks rich in vitamin D or by optimizing exposure to UVB rays from the morning sunlight to ensure optimal skin biosynthesis.

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Conflict of Interest and Funding Disclosure

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