



Risk factors associated with blood vitamin D levels in COVID-19 patients

Faktor risiko yang berhubungan dengan kadar vitamin D darah pada penderita COVID-19

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Abstract

The two main factors associated with infectious diseases are the presence of antigens that enter the body and the immune system. It has been recently reported that vitamin D may be associated with the immune system. This study aimed to analyze the relationship between blood vitamin D levels and the occurrence of COVID-19 infection. This study used a cross-sectional approach for analytical survey research. The population in this study were all lecturers at Malahayati University. The total population participating in this study was 62 lecturers at Malahayati University. Direct competitive chemiluminescence immunoassays were used to measure vitamin D levels, while interviews collected other variables. Logistic regression analysis has been used to analyze the collected data. Results: There was a significant relationship between vitamin D levels and the incidence of COVID-19 infection ($p= 0,020$; $OR= 4,9$) & the habit of always wearing long clothes for more than 10 years is significantly related to blood vitamin D levels ($p= 0,021$; $OR= 5,07$). In conclusion, the lower the vitamin D level, the greater the risk of being infected with COVID-19, and the longer you wear long clothes, the higher the risk of having low blood vitamin D levels.

Keywords: Vitamin D, COVID-19, UVB rays, activity

Abstrak

Dua faktor utama yang berhubungan dengan terjadinya penyakit infeksi yaitu jumlah antigen yang masuk ke dalam tubuh serta kondisi sistem kekebalan tubuh. Akhir-akhir ini, dilaporkan bahwa vitamin D darah berhubungan dengan sistem imunitas. Adapun tujuan penelitian ini, untuk mempelajari faktor risiko yang mempengaruhi kadar vitamin D darah pada penderita COVID-19. Penelitian *observasional analitic* dengan pendekatan *cross sectinal* dilakukan di Universitas Malahayati Bandar Lampung tahun 2022. Total populasi yang berpartisipasi dalam penelitian ini ada 62 orang dosen di Universitas Malahayati. Teknik sampling dalam penelitian ini adalah total sampling. Adapun pengukuran kadar vitamin D dilakukan dengan mengukur Kadar $25(OH)D_3$ darah menggunakan metode *Direct competitive chemiluminescence immunoassay*, sedangkan variabel lainnya dikumpulkan dengan wawancara langsung. Data yang didapatkan selama penelitian, dianalisis dengan uji regresi logistik. Hasil penelitian didapatkan hubungan yang bermakna antara kadar vitamin D darah dengan kejadian infeksi COVID-19 ($p= 0,020$; $OR= 4,9$) & kebiasaan selalu menggunakan baju panjang selama lebih dari 10 tahun berhubungan bermakna dengan kadar vitamin D darah ($p= 0,021$; $OR= 5,07$). Kesimpulan, semakin rendah kadar vitamin D semakin

berisiko terinfeksi COVID-19 dan semakin lama selalu menggunakan baju panjang maka makin meningkatkan risiko untuk memiliki kadar vitamin D darah yang rendah.

Kata Kunci: Vitamin D, COVID-19, sinar ultraviolet B, aktivitas

Introduction

The COVID-19 pandemic in Indonesia has begun to be controlled; this can be seen by the decreasing number of new COVID-19 cases reported. However, the SAR-CoV-2 virus that causes COVID-19 disease continues to mutate and create new variants, so it still remains a threat to public health. As of September 2022, it has been reported that more than 150 thousand people have died throughout Indonesia (Satuan Tugas Penanganan COVID-19, 2022).

Several recent studies have reported that the immune system is affected by blood vitamin D levels, although the exact mechanism still requires a lot of further research. Initially, vitamin D was reported to play an important role in maintaining the health and strength of teeth and bones, but now, vitamin D is reported to be useful in the prevention of various degenerative diseases such as obesity, hypertension, diabetes mellitus, cancer, and many others (Hermawan, 2021; Al Rahmad, 2023; Manousaki & Richards, 2017; Maruotti & Cantatore, 2010; Sigmund, 2002; Vanlint, 2013).

However, the incidence of a global pandemic of blood vitamin D deficiency continues to occur and is reported worldwide (Holick, 2010). Changes in behavior to avoid direct sunlight exposure and always be active in closed spaces are thought to be risk factors that cause it (Alfredsson et al., 2020; Mendes, Hart, Botelho, & Lanham-New, 2018). Even though the results of recent studies report that COVID-19 infection can be prevented by giving vitamin D (Ali, 2020), The results also reported that the recovery rate of COVID-19 patients increased when given interventions in the form of sun or UVB exposure (Asyary & Veruswati, 2020).

There are two sources of vitamin D: those sourced from pro-vitamin D biosynthesis in the skin with the help of UVB exposure and those sourced from foods and drinks rich in vitamin D content (Dominguez et al., 2021). The working ability of macrophage cells, neutrophils, and T lymphocytes can be activated by vitamin D so as to increase the ability of the body's immune system when there are antigens that enter the body (Bui, Zhu, Hawkins, Cortez-Resendiz, &

Bellon, 2021; Prietl, Treiber, Pieber, & Amrein, 2013). The immune system in COVID-19 patients, both children and adults, was also reported to have improved when given Vitamin D (Panfili et al., 2021).

Based on the results of research on vitamin D that can prevent COVID-19 disease, many health facilities, such as hospitals, have tried to provide interventions in the form of sun basking therapy to convert pro-vitamin D into active vitamin D so as to reduce the symptoms experienced by COVID-19 patients (Saluy, Langingi, & Kaparang, 2022; Sharun, Tiwari, & Dhama, 2021).

However, the results of this study still need to be discussed in depth to answer the question: if it is true that vitamin D can boost the immune system, should people living in tropical regions, such as Indonesia, be more immune to infectious diseases compared to people living in sub-tropical areas? But in reality, if we look at the incidence of COVID-19 infections, there seems to be no difference because all countries report almost the same incidence. This condition causes the author to be interested in answering the question of whether there are really high blood vitamin D levels associated with COVID-19 infection and what factors affect vitamin D levels in the blood. The goal to be achieved in this study is to study and analyze risk factors related to blood vitamin D levels in patients with COVID-19.

Methods

Design and Subject

This study is an analytical survey study with a cross-sectional approach that tries to study and analyze risk factors related to vitamin D levels in the blood in patients with COVID-19. The study was conducted from March to July 2022 at an integrated health laboratory owned by Malahayati University Bandar Lampung. Meanwhile, the measurement of 25(OH)D3 blood levels was carried out at the laboratory of Prodia Clinic in Kota B. Lampung. This research has also obtained ethical approval from the Health Research Ethics Committee (KEPK) of

Malahayati University Bandar Lampung with letter number KEPK: 2499/EC/KEP-UNMAL/V/2022 on May 20, 2022.

The research population is all permanent lecturers and teaching staff at Malahayati University (Unmal) Bandar Lampung who are voluntarily willing to participate as research subjects; the number is 62. While the sampling technique used in this study is non-probability sampling (total sampling).

Data collection and measurement

Blood 25(OH)D3/vitamin D levels were measured using the direct competitive chemiluminescence immunoassay (CLIA) method. The total Liaison 25-OH Vitamin D reagent is produced by DiaSorin Liaison with catalog number 310600. This method is able to detect 25(OH)D3 levels in the range of 4 to 150 ng/mL. Before blood samples were taken, the study subjects were satisfied for one night, and in the morning, 5 cc of blood was drawn. Then the blood sample is centrifuged for 15 minutes at a speed of 1300-2000 g, and then the serum is taken and put into the device for further examination at Prodia Clinical Laboratory City, B. Lampung.

In this study, we also observed several other variants, such as gender, age of research subjects, activity patterns, habits of wearing long clothes, and habits of using sunscreen lotion. This data was obtained through direct interviews with respondents. Researchers asked directly related questions related to the pattern of daily activities: whether the study subjects were more indoors or outdoors, and whether they always used long or closed clothes when leaving the house or not. If so, how long has the habit of wearing long clothes been carried out? As well as asking if you always use sunscreen lotion when outdoors.

Data analysis

Proving the hypothesis and answering the purpose of the study, related to factors that have a relationship with vitamin D levels in patients with COVID-19, the author first uses the chi-square test. Variables with a pValue value less than or equal to 0,25 will be used as candidates and will be included in the modeling in the logistic regression test. Then the logistic

regression test was carried out, with a significance level of 95%.

Result and Discussion

In Table 1, it appears that most respondents have been infected with COVID-19, namely 47 samples (76%). It also appears that 41 respondents, or 66%, were female. Almost all (97%) respondents were under the age of 60. None of the respondents in the study had vitamin D levels within normal limits (above 30 ng/mL), and most (94 percent) were usually active indoors. There are 47% of respondents who have had the habit of wearing long clothes for more than 10 years, and there are 44% of respondents who always use sunscreen when leaving the room or house.

Table 1. Results of univariate analysis

Variable	n	%
Infected with COVID-19		
No	15	24
Yes	47	76
Gender:		
Male	21	34
Female	41	66
Age:		
Low Risk (under 60 years old)	60	97
High Risk (60 years and over)	2	3
Blood Vitamin D Levels:		
Normal (above 30 ng/mL)	0	-
Less (15-30 ng/mL)	32	52
Very Less (bellow 15 ng/mL)	30	48
Activity Pattern:		
Outdoor Activity	4	6
Indoor Activity	58	94
Long Shirt Habits (10 years and more):		
Not Always	33	53
Always	29	47
The Habit of Using Sunscreen Lotion Is		
Not Always Using	35	56
Always Using	27	44

In the results of the study (Table 1), it was seen that 76%, or 47 respondents, had been infected with COVID-19. The results also showed that women were more infected with COVID-19

(66%) when compared to men. This is different from previous studies and is interesting to analyze more deeply because previous studies reported that the type of men who were more infected with COVID-19 This is because men are more at risk of unhealthy behaviors compared to women, such as smoking, drinking alcohol, and staying up late (Abate et al., 2020). This difference allegedly occurred because the subjects of this study were lecturers and educators in the health sector who mostly did not have these risky habits.

Another factor that is also thought to be related is the dual role of women, both as housewives and as workers, who demand that they do a lot of work both at home and outside the home. This condition can cause women to experience fatigue. In theory, women have a stronger immune system when compared to men because there is a sex influence, such as estrogen, that helps strengthen the immune system. However, with increasing age and the amount of physical and psychological stress that women face at work and in their home lives, it can cause women to experience a decrease in their immune system (Ciarambino et al., 2021).

In Table 1, it appears that 97% of samples that have been infected with COVID-19 are under 60 years old (low-risk age). This result is different from previous reports that the older a person is, the greater the risk of being infected with COVID-19, and the likelihood of experiencing severe symptoms during COVID-19 infection is also higher (Perrotta et al., 2020). The difference in results with this previous

study is likely due to the fact that the study subjects, who are mostly young and productive, are required to actively work and carry out many activities in various locations, so that the possibility of exposure to or even being infected with the COVID-19 virus becomes greater.

In the results of the study (table 1), it was also found that none of the study subjects had blood vitamin D levels within normal limits (above 30 ng/mL), and most (52%) were in the category of less and even very less (48%). The results of this study support the hypothesis that there is a global pandemic of vitamin D deficiency (Hataikarn & Michael, 2013). Not only in sub-tropical regions such as Europe, but the phenomenon of vitamin D deficiency in the blood also occurs in tropical or hot regions such as Indonesia. This is thought to be related to changes in people's behavior patterns that always avoid sun exposure, such as always using long or closed clothes, always using sunscreen lotion when outdoors, and more active activity patterns indoors. This condition is supported by data showing that 94% of the total samples are active indoors, and almost 50% of the total study samples always wear long clothes and use sunscreen lotion when leaving the room. This result is also corroborated by several previous research results, which also reported that adolescents and the elderly also experienced a lack of vitamin D levels in their blood (Hermawan & Andoko, 2019; Hermawan & Widodo, 2021). This suggests that all age groups are deficient in vitamin D in the blood.

Table 2. Results of bivariate analysis of vitamin D & COVID-19 infection

Blood Vitamin D Levels	Infected with COVID-19		p-value	OR CI 95%
	No (%)	Yes (%)		
Less (between 15 – 30 ng/mL)	12 (36,0)	21 (64,0)	0,020	4,9
Very Less (below 15 ng/mL)	3 (10,0)	26 (90,0)		(1,23-19,8)

The results of bivariate analysis (table 2) showed that blood vitamin D levels were significantly associated with the incidence of COVID-19 infection (p-value 0,020) with an OR value of 4,9 (1,23-19,8). These results show that a person with low blood vitamin D levels will be more at risk of becoming infected with COVID-19 by 4,9 times when compared to those with higher blood vitamin D levels.

These results support previous studies that reported a high prevalence of vitamin D

deficiency in hospitalized COVID-19 patients and an increased risk of severe symptomatic symptoms in patients with vitamin D deficiency in their blood (Killeit, 2022). This is because Vitamin D has an effect on the body's immune system. Vitamin D is able to modulate the innate immune system as well as the acquired or adaptive immune system (Bui et al., 2021; Chirumbolo, Bjørklund, Sboarina, & Vella, 2017; Panfili et al., 2021).

Table 3. Risk factors affecting vitamin D levels based on bivariate analysis

Variable	Blood Vitamin D Levels:		p-value	OR CI 95%
	Very Less (bellow 15ng/mL)	Less (between 15- 30 ng/mL)		
Activity Pattern:				
Indoor activity	29 (50,0)	29 (50,0)	0,617	3,00 (0,29-30,5)
Outdoor activity	1 (25,0)	3 (75,0)		
Long Shirt Habits (10 years and more):				
Always	23 (70,0)	10 (30,0)	0,001	7,2 (2,33-22,3)
Not Always	7 (21,0)	22 (79,0)		
The Habit of Using Sunscreen Lotion Is				
Always Using	17 (63,0)	10 (37,0)	0,040	2,87 (1,01-8,13)
Not Always Using	13 (37,0)	22 (63,0)		
Gender				
Female	25 (61,0)	16 (39,0)	0,007	5,0 (1,50-11,3)
Male	5 (24,0)	16 (76,0)		
Age				
Senior (over 60 years old)	2 (100,0)	0 (0,0)	0,236	1,07 (0,97-1,18)
Adults (21 to 60 years old)	28 (47,0)	32 (53,0)		

In Table 3, factors related to blood vitamin D levels appear. From the results of the biavariate test, it was found that what was associated with blood vitamin D levels was the habit of wearing long clothes for more than 10 years (p-value 0,001), the use of sunscreen when outdoors (p-value 0,040), and gender (p-value 0,007). While the variables of activity patterns and age of respondents were not related to vitamin D levels in the blood.

The use of long clothes over 10 years was significantly associated with blood vitamin D levels, with an OR value of 7,2 (2,33-22,3). This shows that the habit of wearing long clothes for a long time has the potential to reduce vitamin D levels 7,2 times when compared to people who do not always use long clothes. The use of long clothes will reduce the area that will be exposed to UVB rays. UVB light is indispensable for the occurrence of biosynthesis 7-dehydrocholesterol into vitamin pre-D3 (Hall, 2015; Hermawan, 2016). Previous research reported the use of hijab on Muslim women in West Java caused exposure to UVB rays on the skin to be very limited, even at only about 8% (Judistiani et al., 2019). The surface area of the skin exposed to sunlight will affect the optimization of vitamin D biosynthesis in the skin (Chalcraft et al., 2020).

The habit of using sunscreen when outdoors is also associated with vitamin D levels in the blood, with an OR value of 2,87

(1,01-8,13). This shows that someone who always uses sunscreen lotion when outdoors will have a 2,87 times higher risk of lowering blood vitamin D levels when compared to someone who does not always use sunscreen lotion. The use of sunscreen has the ability to block ultraviolet rays and is also good for skin health if used correctly or not excessively; it even reported no effect on vitamin D levels (Passeron et al., 2019). But the use of octocrylene as a raw material for making sunscreen lately is reported to be able to inhibit the synthesis of vitamin D in the skin (Abdi et al., 2022).

In this study, sex was also associated with vitamin D levels in the blood (p-value 0,007) with an OR value of 5.0 (1,50-11,3). In Table 1, it can be seen that 75% of the samples that have very low vitamin D levels are female. This condition is thought to be related to the habit of avoiding sunlight, which is more common in women than men. Most of the subjects in this study were also Muslims, so the women wore hijab (long clothes). The use of hibab is reported to be able to reduce vitamin D levels because the area of skin exposed to the sun becomes very limited (Judistiani et al., 2019). The behavior of using sunscreen lotion when outdoors is also widely practiced by women when compared to men. This condition is also thought to affect many women who experience vitamin D

deficiency. The results of research in Riyadh, women in Riyadh have vitamin D deficiency, and even more than half of the

Saudi Arabia, showed that more than 60% of women have very low vitamin D levels (less than 10 ng/mL) (AlFaris et al., 2019).

Table 4. Multivariate analysis results

Variable	B	p-value	OR	CI (95%)
Gender	0,415	0,612	1,51	0,30 – 7,52
Long Shirt Habits (10 years and more)	1,625	0,021	5,07	1,28 – 20,1
The Habit of Using Sunscreen Lotion Is	0,390	0,542	0,54	0,42 – 5,17

In table 4, the results of the multivariate test showed that the variable habit of using long clothes for more than 10 years was the dominant variable associated with vitamin D levels in the blood (p-value 0.021) with an OR value of 5,07 (1,28–20,1). The regression equation model is as follows: Logit (Vitamin D Levels) = -1,409 + 0,415 sex + 1,625 habits of wearing long clothes + 0,39 habits of sunscreen use.

This shows that someone who has a habit of always wearing long clothes for a long period of time (more than 10 years) will be at a higher risk of having low blood vitamin D levels when compared to someone who does not always wear long clothes when leaving the house. The use of long clothes when outdoors will reduce the part of the body's skin exposed to sunlight (UVB). This condition will cause the process of vitamin D biosynthesis in the skin to run less optimally. Conversely, people who do not always wear long clothes when outside the home allow their body skin to be exposed to ultraviolet B and UVB rays so that the biosynthetic process of converting provitamin D into vitamin D can run better. As we know, the area of skin exposed to or in direct contact with sunlight and the duration of exposure to UVB rays affect the process of vitamin D biosynthesis in the skin (Hall, 2015; Chalcraft et al., 2020). Although there is still a discussion about the effect of sun exposure on skin health (Mostafa & Hegazy, 2013).

The way that can be done to get a good effect and avoid the negative effects of UVB exposure is to bask in the sun (UVB) for not too long, just between 10 and 20 minutes, but with a large enough exposure area and the right sunbathing time, which is between 8 a.m. and 10 p.m. Although the highest UVB intensity is in the time range between 10:00 and 12:00 noon (Judistiani et al., 2019) (Augustine, Nair, & Kulkarni B, 2021), in terms

of equality, sunbathing in the morning is more comfortable when compared to sunbathing during the day. Someone who always wears long clothes is advised to bask in the sun twice as long when compared to people who do not always wear long clothes, because when wearing long clothes, only about 8–13,5% of the surface area of his skin can be exposed to mahatari rays. For people who do not always wear long clothes when outside the home, the surface of the skin that can be exposed to mahatari rays can reach 48% (Judistiani et al., 2019).

The limitations of the study are that the limited number of samples only amounted to 62 lecturers of Malahayati University who were willing to be sampled voluntarily, so it might affect the conclusions drawn. There are several variables that are measured only based on the results of interviews or confessions from respondents, so the data may be less valid.

Conclusion

Vitamin D levels in the blood are significantly associated with the incidence of COVID-19 infection, while blood vitamin D levels are influenced by the habit of wearing long clothes for a long time (more than 10 years).

Suggestions also need efforts to be able to increase vitamin D levels in the blood, both by increasing the intake of foods that contain provitamin D and vitamin D and by optimizing the opportunity for the body to be exposed to UVB so that vitamin D biosynthesis in the skin occurs properly. Especially for women who always wear long clothes, it is advised to bask in the sun (UVB) twice as long, use sunscreen lotion wisely, and optimize the intake of foods and drinks containing vitamin D.

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