International Journal of Research and Review
Vol. 10; Issue: 8; August 2023
Website: www.ijrrjournal.com
Original Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Analysis of Vitamin D Level among COVID-19 Patients: A Cross-sectional Study

Siti Ayu Saputri[1], Irawaty Djaharuddin[1,2], Muhammad Ilyas[1,2], Harun Iskandar[1,2], Jamaluddin Madolangan[1], Edward Pandu Wiriansya[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[2]Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia

Corresponding Author: Siti Ayu Saputri

DOI: https://doi.org/10.52403/ijrr.202308108

ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the virus responsible for causing coronavirus disease (COVID-19). Vitamin D has been proposed as a potentially modifiable risk factor that could influence the severity of COVID-19 infection. In the case of respiratory tract infections, the failure of cellular damage mechanisms and impaired oxygen diffusion can lead to acute respiratory failure. This study aimed to describe the effects of vitamin D levels in COVID-19 patients.

Methods: A cross-sectional study was taken on 360 COVID-19 older than 18 years old unrepeated patients in Dr. Wahidin Sudirohusodo Hospital and its network, Makassar, South Sulawesi, Indonesia. Vitamin D level was analyzed from blood. Age, gender, body mass index (BMI), comorbidity, severity degree of COVID-19, and vitamin D level are also analyzed.

Results: According to the findings of the study, several factors were identified to have notable correlation with the severity of COVID-19 symptoms. However, the study did not establish any connection between vitamin D levels and the severity of COVID-19 symptoms.

Conclusion: Individuals affected by COVID-19 often have insufficient levels of vitamin D, although the severity of symptoms experienced by patients is not associated with their serum vitamin D levels.

Keywords: *Vitamin D, COVID-19, severity*

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the virus responsible for causing coronavirus disease (COVID-19). It has high transmission rate, allowing it to spread worldwide rapidly.[1] As of April 2022, the death toll due to COVID-19 has exceeded 6.2 million cases.[2] COVID-19 symptoms can range from mild to moderate, severe, and even critical, requiring intensive care and leading to fatalities. Certain risk factors have been identified that contribute to the severity of COVID-19.[3] These include advanced age, obesity, and underlying health conditions such as diabetes mellitus, hypertension, cardiovascular disease, chronic lung disease, and cancer.[4]

Vitamin D has been proposed as a potentially modifiable risk factor that could influence the severity of COVID-19 infection.[5] Research suggests that vitamin D deficiency may be associated with various systemic infectious diseases, including acute respiratory infections.[6] Vitamin D has an immunomodulatory effect on infections that trigger cytokine storms.[7] In the case of respiratory tract infections, the failure of cellular damage defense mechanisms and impaired oxygen diffusion can lead to acute respiratory failure.[8]

However, studies examining the relationship between vitamin D and COVID-19 in Indonesia are still limited. Although there

have been numerous observational studies investigating the link between vitamin D levels and the severity of COVID-19, more research is needed to fully understand the impact of vitamin D on COVID-19 outcomes in the Indonesian populations.

MATERIALS & METHODS

A cross-sectional study was taken on 360 COVID-19 more than 18 years old unrepeated patients from June 2020 until June 2021 in Dr. Wahidin Sudirohusodo Hospital and its network, Makassar, South Sulawesi, Indonesia. This study was approved by the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University (No: 145/UN4.6.4.5.31/PP36/2022).

STATISTICAL ANALYSIS

Demographic and clinical data were collected. Age, gender, body mass index (BMI), comorbidity, severity degree of COVID-19, and vitamin D level are also analyzed. Baseline data were descriptively summarized, and the differences in each variable between groups were calculated using Chi-Square tests, Fischer-Exact tests, and Mann-Whittney test. Significant values were determined at $p<0.05$. All statistical analyses were performed using the Statistical Program for Social Sciences (IBM SPSS 24, IL, USA).

RESULT

According to the findings of the study, several factors were identified to have a notable correlation with the severity of COVID-19 symptoms (Table 1). These factors include older age, male gender, obesity, and the presence of comorbidities, particularly hypertension and type 2 diabetes mellitus. However, the study did not establish any connection between vitamin D levels and the severity of COVID-19 symptoms (Table 2, 3 & 4). Furthermore, even among individuals with comorbidities, there was no significant distinction between the COVID-19 group experiencing severe symptoms and those with non-severe symptoms (Table 5).

Table 1. Patients Characteristic according to Severity of COVID-19

Variable	Severity of COVID-19 [n (%)] (ng/mL)		*p-value*
	Severe	Non-severe	
	(N=90)	(N=270)	
Age (years)	57.34 ± 14.03	42.78 ± 14.04	**<0.001$**
18-39	10 (11.1%)	136 (50.4%)	**<0.001***
40-59	36 (40.0%)	93 (34.4%)	0.409*
≥60	44 (48.9%)	41 (15.2%)	**<0.001***
Gender			
Male	62 (68.9%)	120 (44.4%)	**<0.001***
Female	28 (31.1%)	150 (55.6%)	
Body mass index			
Obesity	8 (8.9%)	3 (1.1%)	**0.001#**
Non-obesity	82 (91.1%)	267 (98.9%)	
Comorbidity			
Without comorbid	18 (13.4%)	187 (60.7%)	**<0.001***
Hypertension	44 (32.8%)	40 (13.0%)	**<0.001***
Diabetes mellitus type 2	39 (29.1%)	19 (6.2%)	**<0.001***
Cardiovascular disease	14 (10.4%)	24 (7.8%)	0.465*
Chronic kidney disease	9 (6.7%)	17 (5.5%)	0.786*
Chronic lung disease	0 (0.0%)	5 (1.6%)	0.329#
Liver disease	1 (0.7%)	0 (0.0%)	0.303#
Cerebrovascular disease	2 (1.5%)	0 (0.0%)	0.091#
Malignancy	7 (5.2%)	13 (4.2%)	0.828*
Pregnancy	0 (0.0%)	3 (1.0%)	0.557#

***Chi-Square test; #Fisher-Exact test; $Mann-Whitney test, bold p<0.05**

Table 2. Analysis of COVID-19 Risk Factors According to Serum Vitamin D Level

Variable	Serum vitamin D level [25(OH)D] (ng/mL)		*p-value*
	(Mean ± SD)	(Min-max)	
Age (years)			
18-39	22.04 ± 8.50	21.0 (8.0-83.0)	**<0.001***
40-59	26.74 ± 13.00	25.0 (8.0-126.0)	**0.009***
≥60	26.78 ± 9.57	25.0 (11.1-58.0)	**0.012***
Gender			
Male	27.86 ± 12.23	25.2 (8.0-126.0)	**<0.001***
Female	21.76 ± 7.99	20.45 (8.0-63.0)	
Body mass index			
Obesity	27.36 ± 9.74	24.0 (13.0-44.0)	0.303*
Non-obesity	24.77 ± 10.82	23.0 (8.0-126.0)	
Comorbidity			
Without comorbid	23.78 ± 9.17	22.0 (8.0-83.0)	0.305*
Hypertension	25.68 ± 14.46	22.95 (8.0-126.0)	0.671*
Diabetes mellitus type 2	24.23 ± 9.86	23.0 (8.0-58.0)	0.875*
Cardiovascular disease	27.30 ± 18.24	22.8 (10.0-126.0)	0.462*
Chronic kidney disease	21.30 ± 7.38	22.35 (8.0-36.0)	0.197*
Chronic lung disease	33.80 ± 18.43	39.0 (9.0-56.0)	0.178*
Liver disease	24.60	24.60	0.772*
Cerebrovascular disease	31.00 ± 5.65	31.0 (27.0-35.0)	0.155*
Malignancy	26.77 ± 7.55	25.55 (14.4-46.0)	0.084*
Pregnancy	17.86 ± 4.75	17.0 (13.6-23.0)	0.161*

SD = standard of deviation, min = minimal, max = maximal, *Mann-Whitney test, bold p<0.05

Table 3. Analysis of COVID-19 Severity According to Serum Vitamin D Level

Serum vitamin D level [25(OH)D]	COVID-19 severity		*p-value*
	Severe	Non-severe	
	(ng/mL)	(ng/mL)	
Deficiency (≤20 ng/mL)	16.10 ± 3.22	16.07 ± 3.39	0.916*
Insufficiency (21-29 ng/mL)	24.58 ± 2.45	24.32 ± 2.59	0.558*
Sufficiency (≥ 30 ng/mL)	40.60 ± 19.94	36.86 ± 8.85	0.964*

***Mann-Whittney test**

Table 4. Analysis of COVID-19 Risk Factors According to Serum Vitamin D Level

Variable	Serum vitamin D level [n (%)]			*p-value*
	Deficiency	Insufficiency	Sufficiency	
	(≤20 ng/mL)[9]	(21-29 ng/mL)[9]	(≥ 30 ng/mL)[9]	
	(N= 126)	(N=144)	(N= 90)	
Age (years)	43.15±16.27	46.29±14.83	51.21±13.77	**<0.001#**
18-39	68 (54.0%)	57 (39.6%)	21 (23.3%)	**<0.001***
40-59	32 (25.4%)	59 (41.0%)	38 (42.2%)	**0.010***
≥60	26 (20.6%)	28 (29.4%)	31 (34.4%)	**0.020***
Gender				
Male	38 (30.2%)	77 (53.5%)	67 (74.4%)	**<0.001***
Female	88 (69.8%)	67 (46.5%)	23 (25.6%)	
Body mass index				
Obesity	3 (2.4%)	3 (2.1%)	5 (5.6%)	0.279*
Non-obesity	123 (97.6%)	141 (97.9%)	85 (94.4%)	
Comorbidity				
Without comorbid	79 (49.4%)	86 (48.3%)	40 (38.5%)	0.177*
Hypertension	30 (18.8%)	31 (17.4%0	23 (22.1%)	0.621*
Diabetes mellitus type 2	25 (15.6%)	16 (9.0%)	17 (16.3%)	0.106*
Cardiovascular disease	11 (6.9%)	17 (9.6%)	10 (9.6%)	0.623*
Chronic kidney disease	9 (5.6%)	14 (7.9%)	3 (2.9%)	0.226*
Chronic lung disease	1 (0.6%)	1 (0.6%)	3 (2.9%)	0.154*
Liver disease	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.476*
Cerebrovascular disease	0 (0.0%)	1 (0.6%)	1 (1.0%)	0.503*
Malignancy	3 (1.9%)	10 (5.6%)	7 (6.7%)	0.119*
Pregnancy	2 (1.3%)	1 (0.6%)	0 (0.0%)	0.467*

***Chi-Square test; #Kruskal-Wallis test, bold p<0.05**

Table 5. Analysis of Serum Vitamin D Levels in Comorbidity According to COVID-19 Severity

Serum vitamin D level [25(OH)D]	COVID-19 Severity (ng/mL)		*p-value*
	Severe	Non-severe	
With comorbid	26.45 ± 15.28	26.07 ± 9.55	0.491*
Without comorbid	22.92 ± 8.84	23.87 ± 9.22	0.596*

***Mann-Whitney test**

DISCUSSION

The study revealed a significant association between age and the severity of COVID-19. The average age of patients with severe COVID-19 (57.34 ± 14.03 years) was higher compared to those with non-severe cases (42.78 ± 14.04 years). In the elderly population, immune system dysfunction, such as immunosensitization, can increase susceptibility and the severity of clinical manifestations of COVID-19.[10] This occurs due to immunosenescence, which leads to changes in immune function, exacerbates inflammation, and contributes to multiorgan failure.[11,12]

Moreover, men exhibit higher susceptibility to COVID-19 compared to women. When considering the severity of COVID-19, there is a significant difference. Men are more commonly affected by severe cases, while women tend to have a higher proportion of non-severe COVID-19.[13,14]

Obesity significantly influences the severity of COVID-19, with obese individuals experiencing more severe symptoms compared to those without obesity.[15] Conversely, individuals with non-obese nutritional status are more likely to experience milder COVID-19 symptoms.[16] In obesity, the presence of a large amount of adipose tissue results in an increased expression of the angiotensin receptor blocker (ACE2), which serves as the receptor for SARS-CoV-2. Consequently, adipose tissue becomes a favorable host for a large viral load, leading to increased viral release.[17,18]

This study indicates that every COVID-19 patient with severe symptoms has at least one comorbidity. The most prevalent comorbidities among COVID-19 patients in this study were hypertension, type 2 diabetes mellitus, cardiovascular disease, kidney failure, and malignancy. However, only hypertension and type 2 diabetes mellitus demonstrated a significant relationship with the severity of COVID-19.[19–21]

The mechanisms underlying the connection between pre-existing hypertension and COVID-19 have not been fully understood. However, they may be related to endothelial dysfunction and an imbalance in the renin-angiotensin system (RAS). Patients with diabetes mellitus are at a higher risk of developing severe or critical COVID-19, requiring intensive care unit (ICU) treatment, and having a threefold increased risk of death from COVID-19. SARS-CoV-2 infection can complicate diabetes through several mechanisms, including increased glucose levels causing oxidative stress and inflammation, binding to ACE2 and damaging tissue, and inhibiting lymphocyte proliferation due to hyperglycemia.[22–24]

Regarding vitamin D deficiency, this study found that it was more prevalent among younger individuals rather than older individuals, contrary to previous studies suggesting that vitamin D levels decrease with age.[25] The relationship between age and vitamin D levels has been extensively investigated across different countries, with older individuals being at higher risk of vitamin D deficiency.[26]

In terms of gender, the study found that women were more likely to experience serum vitamin D deficiency and insufficiency [25(OH)D] compared to men. Possible mechanisms related to this disparity include differences in sun exposure patterns between genders.[27,28]

When considering nutritional status, there was no significant difference in serum vitamin D levels between the obese and non-obese groups in this study. These results differ from previous studies that have reported a relationship between vitamin D deficiency and obesity. The variance may be attributed to differences in sun exposure.[29,30]

Vitamin D plays a crucial role in calcium and bone homeostasis, as well as in the immune system. It exhibits a broad range of immunomodulatory, anti-inflammatory, antifibrotic, and antioxidant effects. Vitamin D has been shown to increase the production of anti-inflammatory molecules while reducing the production of pro-inflammatory molecules.[31] In this study, COVID-19 patients in the severe group had

a higher prevalence of non-deficient vitamin D levels compared to those in the non-severe group. Furthermore, vitamin D deficiency was associated with the severity of COVID-19, even after adjusting for potential factors such as age, sex, comorbidities, BMI, and smoking status.[31,32] Differences in study methodology, ethnicity, sample size, and uncontrolled factors that influence the severity of COVID-19, including comorbidities, may contribute to the results that differ from previous studies reporting a relationship between serum vitamin D levels and the severity of COVID-19. Additionally, genetic factors should be considered when examining the association between serum vitamin D levels and COVID-19 severity, as there is ample evidence pointing to genetic variations in proteins involved in vitamin D metabolic pathways.[33–35]

CONCLUSION

Certain factors such as older age, being male, obesity, and diabetes mellitus have been found to be linked to the severity of COVID-19. Moreover, individuals affected by COVID-19 often have insufficient levels of vitamin D, although the severity of symptoms experienced by patients is not associated with their serum vitamin D levels.

Declaration by Authors

Ethical Approval: Approved
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Sahin AR. 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of the Current Literature. EJMO [Internet]. 2020 [cited 2023 May 29]; Available from: https://www.ejmo.org/10.14744/ejmo.2020.12220/
2. Luciani S, Agurto I, Caixeta R, Hennis A. Prioritizing noncommunicable diseases in the Americas region in the era of COVID-19. Revista Panamericana de Salud Pública. 2022 Jul 20;46:1.
3. Goh KJ, Choong MC, Cheong EH, Kalimuddin S, Wen SD, Phua GC, et al. Rapid Progression to Acute Respiratory Distress Syndrome: Review of CurrentUnderstanding of Critical Illness from Coronavirus Disease 2019 (COVID-19) Infection. Ann Acad Med Singap. 2020 Mar 31;49(3):108–18.
4. Pepera G, Tribali MS, Batalik L, Petrov I, Papathanasiou J. Epidemiology, risk factors and prognosis of cardiovascular disease in the Coronavirus Disease 2019 (COVID-19) pandemic era: a systematic review. Rev Cardiovasc Med. 2022 Jan 17;23(1):1.
5. Tang Y, Zeng X, Feng Y, Chen Q, Liu Z, Luo H, et al. Association of Systemic immune-inflammation index With Short-Term Mortality of Congestive Heart Failure: A Retrospective Cohort Study. Frontiers in cardiovascular medicine. 2021;8.
6. Honardoost M, Ghavideldarestani M, Khamseh ME. Role of vitamin D in pathogenesis and severity of COVID-19 infection. Archives of Physiology and Biochemistry. 2023 Jan 2;129(1):26–32.
7. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of Infection and Public Health. 2020 Oct;13(10):1373–80.
8. Swenson KE, Swenson ER. Pathophysiology of Acute Respiratory Distress Syndrome and COVID-19 Lung Injury. Critical Care Clinics. 2021 Oct;37(4):749–76.
9. Chutterpaul P, Paruk F, Cassim B. Prevalence of vitamin D deficiency in older South Africans with and without hip fractures and the effects of age, body weight, ethnicity and functional status. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2019 Jan 2;24(1):10–5.
10. Dhama K, Patel SK, Kumar R, Rana J, Yatoo MohdI, Kumar A, et al. Geriatric Population During the COVID-19 Pandemic: Problems, Considerations, Exigencies, and Beyond. Front Public Health. 2020 Sep 22; 8:574198.
11. Grolli RE, Mingoti MED, Bertollo AG, Luzardo AR, Quevedo J, Réus GZ, et al. Impact of COVID-19 in the Mental Health in Elderly: Psychological and Biological

Updates. Mol Neurobiol. 2021 May;58(5):1905–16.
12. Wang Y, Pang SC, Yang Y. A potential association between immunosenescence and high COVID-19 related mortality among elderly patients with cardiovascular diseases. Immun Ageing. 2021 Jun 1;18(1):25.
13. Pradhan A, Olsson PE. Sex differences in severity and mortality from COVID-19: are males more vulnerable? Biol Sex Differ. 2020 Dec;11(1):53.
14. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ. 2020 Mar 26; m1198.
15. Aghili SMM, Ebrahimpur M, Arjmand B, Shadman Z, Pejman Sani M, Qorbani M, et al. Obesity in COVID-19 era, implications for mechanisms, comorbidities, and prognosis: a review and meta-analysis. Int J Obes. 2021 May;45(5):998–1016.
16. Jovanoski N, Chen X, Becker U, Zalocusky K, Chawla D, Tsai L, et al. Severity of COVID-19 and adverse long-term outcomes: a retrospective cohort study based on a US electronic health record database. BMJ Open. 2021 Dec;11(12):e056284.
17. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. European Journal of Internal Medicine. 2020 Jun;76:14–20.
18. Engin AB, Engin ED, Engin A. Two important controversial risk factors in SARS-CoV-2 infection: obesity and smoking. Environmental toxicology and pharmacology. 2020;78:103411.
19. Parveen R, Sehar N, Bajpai R, Agarwal NB. Association of diabetes and hypertension with disease severity in covid-19 patients: A systematic literature review and exploratory meta-analysis. Diabetes Research and Clinical Practice. 2020 Aug; 166:108295.
20. Schiffrin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. American Journal of Hypertension. 2020 Apr 29;33(5):373–4.
21. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med. 2020 Aug;2(8):1069–76.
22. Gazzaz ZJ. Diabetes and COVID-19. Open Life Sciences. 2021 Mar 25;16(1):297–302.
23. Abu-Farha M, Al-Mulla F, Thanaraj TA, Kavalakatt S, Ali H, Abdul Ghani M, et al. Impact of Diabetes in Patients Diagnosed With COVID-19. Front Immunol. 2020 Dec 1;11:576818.
24. Li G, Chen Z, Lv Z, Li H, Chang D, Lu J. Diabetes Mellitus and COVID-19: Associations and Possible Mechanisms. Kin T, editor. International Journal of Endocrinology. 2021 Apr 1;2021:1–10.
25. Getachew B, Tizabi Y. Vitamin D and COVID-19: Role of ACE2, age, gender, and ethnicity. Journal of Medical Virology. 2021 Sep;93(9):5285–94.
26. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020 Jul;32(7):1195–8.
27. Elham AS, Azam K, Azam J, Mostafa L, Nasrin B, Marzieh N. Serum vitamin D, calcium, and zinc levels in patients with COVID-19. Clinical Nutrition ESPEN. 2021 Jun; 43:276–82.
28. Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020 Jul 15;12(7):2097.
29. Li S, Cao Z, Yang H, Zhang Y, Xu F, Wang Y. Metabolic Healthy Obesity, Vitamin D Status, and Risk of COVID-19. Aging and disease. 2021;12(1):61.
30. Ekiz T, Pazarlı AC. Relationship between COVID-19 and obesity. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Sep;14(5):761–3.
31. Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, et al. Mechanisms In Endocrinology: Vitamin D and COVID-19. European Journal of Endocrinology. 2020 Nov; 183(5):R133–47.
32. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. JAMA Netw Open. 2020 Sep 3;3(9):e2019722.
33. Mohan M, Cherian JJ, Sharma A. Exploring links between vitamin D deficiency and COVID-19. Chowdhary A, editor. PLoS Pathog. 2020 Sep 18;16(9):e1008874.
34. Carpagnano GE, Di Lecce V, Quaranta VN, Zito A, Buonamico E, Capozza E, et al. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. J Endocrinol Invest. 2021 Apr;44(4):765–71.

35. Pereira B, Xu XN, Akbar AN. Targeting inflammation and immunosenescence to improve vaccine responses in the elderly. Frontiers in immunology. 2020; 11:583019.

How to cite this article: Siti Ayu Saputri, Irawaty Djaharuddin, Muhammad Ilyas, Harun Iskandar, Jamaluddin Madolangan, Edward Pandu Wiriansya. Analysis of vitamin D level among COVID-19 patients: a cross-sectional study. *International Journal of Research and Review*. 2023; 10(8): 843-849. DOI: *https://doi.org/10.52403/ijrr.202308108*

******