The Relationship Between Plasma Vitamin D and Severity of Critical Disease Patients Admitted to the Intensive Care Unit

Pirhot L. M. Y. Siahaan[1]*, Anna Surgean Veterini[2], Bambang Pujo Semedi[2], Prananda Surya Airlangga[2], Edward Kusuma[2], Irwanto[2]

[1] Masters Student of Clinical Medicine Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[2] Lecturer at the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

*Corresponding

E-mail: pierhot11@gmail.com

Abstract

Introduction: Vitamin D is a micro-nutrient component that deserves to be taken into consideration for its various functions. In addition, according to various sources, it is said that vitamin D also has a role in the progress of critical patient conditions. Vitamin D deficiency condition often occurs not only in general patients but also in critical patients. Vitamin D deficiency in critically ill patients can be caused by a number of co-morbidities, systemic inflammation and multiorgan failure. Aim and Objective: The purpose of this study was to determine the relationship between plasma levels of vitamin D and the severity of the disease in critically ill patients treated in the Intensive Care Unit. Materials and Methods: This research is an observational analytic research. This research was conducted in the Intensive Care Unit of Dr. Soetomo Hospital Surabaya. The sample in this study were 32 people according to the inclusion and exclusion criteria. Data will be analyzed descriptive analytically. Results and Conclusion: The result showed that patient profiles, such as: age, gender, comorbidity status, smoking history, sun exposure, milk consumption, supplement or multivitamin consumption, BMI, SOFA Score, and APACHE II have significant differences between mild, moderate, and optimal levels of vitamin D deficiency ($p=0.001$). We hypothesized that nutrition has an effect on plasma vitamin D levels, but this research did not show a significant relationship between fish consumption and plasma vitamin D levels. Fish consumption had no significant difference ($p=0.371$). There was a significant negative correlation between vitamin D and SOFA score ($p<0.001$) and APACHE II ($p<0.001$). The critical patients profile in Dr Soetomo Hospital shows that mostly <50 years old, female, no history of smoking, exposed to sunlight >30 minutes, consumed fish, did not consume milk, and consumed supplements or multivitamins. The most common vitamin D levels in critically ill patients admitted to the Intensive Care Unit were optimal. The severity of critical illness patients based on SOFA Score between 0-1 and ≥ 2 is relatively similar. While based on APACHE II the most are 0-4. There is a significant relationship between vitamin D levels and the severity of critical illness patients treated in the intensive care unit according to SOFA Score and APACHE II.

Keywords: Critical Illness, Intensive Care Unit, Profile, Severity, Vitamin D

1. Introduction

Vitamin D, a fat-soluble vitamin, plays an important role in the regulation of bone metabolism and extraskeletal pleiotropic processes, such as immunomodulatory, antimicrobial and cardiovascular. Vitamin D deficiency is associated with a variety of diseases, including infections, diabetes, myocardial infarction, and autoimmune diseases. Vitamin D deficiency conditions often occur not only in general patients but also in critical patients (1). The incidence rate of vitamin D deficiency in critically ill patients ranges from 26 to 82% (2). More seriously, critically ill patients with vitamin D deficiency are accompanied by a series of more adverse clinical consequences, such as a higher likelihood of nosocomial infections, increased susceptibility to sepsis, prolonged ICU or hospital stay, and increased overall mortality (3).

Lee et al. (4) showed that 64.5% (n = 120) of critically ill surgical patients had a serum concentration of 25(OH)D <20 nmol/L, and Higgins et al. (2012) reported that 26% (50/196) of patients admitted to the medical/surgical intensive care unit (ICU) had a vitamin D level of 30 nmol/L. A retrospective cohort study showed that 54% (65/121) of patients with severe sepsis or septic shock had vitamin D levels lower than 15 mg/mL (5), and another prospective multicenter study demonstrated vitamin D deficiency in 78.8% (197/250) of patients (6). Furthermore, several studies document that vitamin D deficiency may be associated with poor outcomes in critically ill

doi.org/10.31838/hiv23.03.221 Received: 16.11.22, Revised: 02.12.22, Accepted: 04.01.23.

patients (1,4).
The hypothesis of this study is that there is a relationship between plasma levels of vitamin D and the severity of critical illness patients treated in the Intensive Care Unit.

2. Research Method

Researchers conducted observational analytic research using a cross-sectional research design. The purpose of the study was to determine the relationship between plasma levels of vitamin D and the severity of disease in critically ill patients treated in the Intensive Care Unit. The research was conducted in the Intensive Care Unit of Dr. Soetomo Hospital Surabaya between January and February 2022. The study was declared ethically feasible by the research and development of Ethics at the Faculty of Medicine, Airlangga University, and the Diklit section of Dr. Soetomo Hospital Surabaya. In the original study, 32 patients were included according to the inclusion and exclusion criteria. The inclusion criteria were patients aged between 18-65 years, admitted to the ICU for more than 24 hours, and patients with critical illness. While the exclusion criteria include patients who have received vitamin D therapy, incomplete patient medical record data, patients who are discharged or die within 24 hours, refuse to sign the research informed consent, and are on immunosuppressant treatment, glucocorticoids, cytostatics and a history of malignancy.

Data Collection

Blood samples were collected on the first day the patient was admitted to the intensive care unit. Serum samples were also collected and stored at −80 °C prior to analysis. Demographics, past medical history, and medications were obtained from patient charts and included age, race, sex, body mass index (BMI; determined prior to ICU admission or estimated as pre-ICU dry weight [in kg] divided by height [in cm] squared in ICU at admission), time of ICU admission, category of admission (cardiovascular, respiratory, neurological, metabolic, gastrointestinal, haematological, sepsis, postoperative), and comorbidities (coronary artery disease, hypertension, chronic obstructive pulmonary disease, diabetes, kidney disease, liver disease, cancer). Parameters assessed were plasma vit D levels, length of stay, age, gender, APACHE II, SOFA, CRP, Procalcitonin. The max SOFA score is calculated as the worst score for each organ component while the patient is in the ICU. The SOFA delta score was determined by subtracting the maximum SOFA score from the total incoming SOFA score. All samples were stored at -80 °C for later analysis and did not undergo more than 1 freeze-thaw cycle prior to testing. Serum 25(OH)D levels were assessed using the radioimmunoassay (RIA) method (DiaSorin, Antony, France) in the Laboratory. The coefficient of variation for the RIA 25(OH)D test is 0.046. Samples are run in 4 batches according to the day after receipt. The following 25(OH)D values were used for deficient, insufficient, and sufficient patients according to previously reported subgroups: moderate >60 nmol/L; insufficient, >30 to 60 nmol/L; and a deficiency of 30 nmol/L.

Statistics

Analysis was performed to determine the frequency distribution of patient risk factors (age, sex, BMI, and comorbid status) for critical illness and presented in tabular form. Categorical scale data will be expressed as a distribution of frequencies (n) and percentages (%). Numerical scaled data is expressed as the mean with a standard deviation. If the distribution is normal or median with a minimum-maximum value if the distribution is not normal. Numerical data obtained in this study were tested by normality test. The normality test aims to determine the distribution of normal data ($p > 0.05$). This normality test uses the Shapiro Wilk test because the sample size used is ≤50. A bivariate test was conducted to determine whether there were differences in the profile of patients in the category of vitamin D levels using the chi-square test and secondly serum vitamin D levels with the severity of critical illness patients using ANOVA. The results of the Anova test are said to be significant if the significance value is ($p < 0.05$). If the normality test shows that the distribution of data is not normal, a non-parametric test with the Kruskal Wallis test will be used. The correlation test between vitamin D serum levels and the severity of critical illness patients was analyzed using the Spearman correlation test. The correlation is stated to be very strong if the correlation coefficient (r) is 0.80-1.00, strong if r is 0.60-0.799, moderate if r is 0.40-0.599, weak if r is 0.20-0.399 and very weak if r is 0 .00-1.99. The p value is considered significant if $p \leq 0.05$.

3. Results and Discussion

Sample Characteristics

This study was conducted for two months, from January to February 2022 in the Intensive Care Unit room of Dr. Soetomo Hospital Surabaya. This study aims to determine the relationship between plasma vitamin D levels and disease severity in critically ill patients admitted to the Intensive Care Unit room. The samples obtained in this study amounted to 32 people according to the inclusion and exclusion criteria. The characteristics of the sample are shown in Table 1.

Table 1: Sample Characteristic			
Characteristics			P value
Age, n (%)	<50 years	17 (53,12)	0,512
	≥50 years	15 (46,88)	
Gender, n (%)	Man	14 (43,75)	0,289
	Woman	18 (56,25)	
Comorbid Status, n (%)	Yes	18 (56,25)	0,433
	No	14 (43,75)	
Body Mass Index, mean ± SD		25,68 ± 4,32	0,136
Vitamin D Levels, n (%)	>80 ng/mL	-	0,142
	25-80 ng/mL	21 (65,62)	
	10-24 ng/mL	11 (34,38)	
	<10 ng/mL	-	
SOFA Score, n (%)	0-1	15 (46,87)	0,415
	≥ 2	17 (53,13)	
APACHE II, n (%)	0-4	16 (50)	0,168
	5-9	5 (15,62)	
	10-14	-	
	15-19	11 (34,37)	
	20-24	-	
	25-29	-	
	30-34	-	
	≥ 35	-	

Table 1 shows that the age groups involved in this study varied evenly with almost equal numbers between the <50 years age group and the ≥50 years age group, consisting of 17 people (53.12%) and 15 people (46.88%). The most common gender was female, totaling 18 people (56.25%) while men totaled 14 people (43.75%). Most subjects involved in this study had comorbidities with a total of 18 people (56.25%). For plasma vitamin D levels, most subjects had optimal vitamin D levels as many as 21 people (65.62%) and 11 people (34.38%) had mild-moderate deficiency. There were no subjects with severe and toxic vitamin D deficiency. Based on the SOFA score, there were 15 people (46.87%) with a score of 0-1, while 17 people (53.13%) with a score ≥ 2. While based on APACHE II, there were 16 people (50%) with a score of 0-4, 5 people (15.62%) with a score of 5-9, and 11 people (34.37%) with a score of 15-19. Based on table 5.1 above, it can be seen that all samples are homogeneously distributed in terms of age, gender, comorbidity status, vitamin D levels, SOFA scores, and APACHE II.

Frequency Distribution of Patient Profile by Vitamin D Level Category

Table 2: Frequency Distribution of Patient Profile by Vitamin D Level Category					
Characteristics	Vitamin D Levels				P Value
	Severe deficiency (<10 ng/mL)	Mild Moderate Deficiency (10-24 ng/mL)	Optimal (25-80 ng/mL)	Toxic (>80 ng/mL)	
Age <50 years ≥50 years	-	8 (25) 3 (9,37)	9 (28,12) 12 (37,5)	-	0,001[a]
Gender Man Woman	-	6 (18,75) 5 (15,62)	13 (40,62) 8 (25)	-	0,001[a]
Comorbid Status Yes No	-	6 (18,75) 5 (15,62)	8 (25) 13 (40,62)	-	0,001[a]
BMI Less Weight (<18,5) Normal (18,5-22,9) Overweight (23-24,9) Obesity 1 (25-29,9) Obesity 2 (>30)	-	5 (15,62) 3 (9,37) 2 (6,25) 1 (3,12)	6 (18,75) 4 (12,5) 8 (25) 3 (9,37)	-	0,001[a]
SOFA Score 0-1 ≥2	-	-11 (34,37)	15 (46,87) 6 (18,75)	-	0,001[b]
APACHE II 0-4 5-9 10-14 15-19 20-24 25-29 30-34 ≥ 35	-	11 (34,37)	-16 (50) 5 (15,62)	-	0,001[b]

Table 2 shows that vitamin D levels found in the study subjects were only 25-80 ng/mL and 10-24 ng/mL. Meanwhile, levels >80 ng/mL and levels <10 ng/mL were not found. Based on age, vitamin D levels of 10-24 ng/mL were found more in the <50 years age group, as many as 8 people (25%). Meanwhile, vitamin D levels of 25-80 ng/mL were found more in the ≥50 years age group, as many as 12 people (37.5%). There was a significant difference in the age group <50 years and ≥50 years between vitamin D levels of 10-24 ng/mL and levels of 25-80 ng/mL (p=0.001). Based on gender, at vitamin D levels of 10-24 ng/mL, men and women have almost the same amount. While at vitamin D levels of 25-80 ng/mL found more in the male group, as many as 13 people (40.62%). There was a significant difference between male and female between vitamin D levels of 10-24 ng/mL and levels of 25-80 ng/mL (p=0.001). Based on comorbidity status, at vitamin D levels of 10-24 ng/mL, there were almost equal numbers between groups with comorbidities and groups without comorbidities. Meanwhile, vitamin D levels of 25-80 ng/mL were found more in the group without comorbidities, as many as 13 people (40.62%). There was a significant difference between the group with comorbidities and the group without comorbidities between vitamin D levels of 10-24 ng/mL and levels of 25-80 ng/mL (p=0.001). Based on BMI, vitamin D levels of 10-24 ng/mL were found more in the group with normal BMI, as many as 5 people (15.62%). Meanwhile, vitamin D levels of 25-80 ng/mL were found more in the group with obese BMI 1, as many as 8 people (25%). There was a significant difference in the BMI group between vitamin D levels of 10-24 ng/mL and levels of 25-80 ng/mL (p=0.001). Based on SOFA Score, vitamin D levels of 10-24 ng/mL were only found in the group with SOFA Score ≥2, as many as 11 people (34.27%). Meanwhile, vitamin D levels of 25-80 ng/mL were found more in the group with SOFA Score 0-1, as many as 15 people (46.87%). There was a significant difference between the group with SOFA Score 0-1 and the group with SOFA Score ≥2 between vitamin D levels of 10-24 ng/mL and levels of 25-80 ng/mL (p=0.001). Based on APACHE II, vitamin D levels of 10-24 ng/mL were only found in the group with APACHE II 25-29 as many as 11 people (34.37%). While vitamin D levels of 25-80 ng/mL were found more in the group with APACHE II 10-14, as many as 16 people (50%). There was a significant difference between groups with APACHE II 10-14, APACHE II 15-19, and APACHE 25-29 between vitamin D levels of 10-24 ng/mL and levels of 25-80 ng/mL (p=0.001).

Vitamin D Levels and Severity of Critical Illness Patients

The correlation between vitamin D levels and severity of critical illness patients can be seen in Table 3 and Table 4.

Table 3: Correlation between Vitamin D Level and APACHE II

			Spearman's rho		p
Vit. D	-	APACHE II Score	-0.654	***	< .001
* p < .05, ** p < .01, *** p < .001					

Based on table 3 above, it can be seen that the correlation coefficient value is – 0,654, this value indicates that there is a significant negative correlation between vitamin D levels and APACHE II (p<0.001).

Table 4: Correlation between Vitamin D Level and SOFA Score

			Spearman's rho		p
Vit. D	-	Patient SOFA Score	-0.714	***	< .001
* p < .05, ** p < .01, *** p < .001					

Based on table 4 above, it can be seen that the correlation coefficient is -0.714, so this value indicates that there is a significant negative correlation between vitamin D levels and the SOFA Score (p<0.001).

4. Discussion

This study showed that the majority of vitamin D levels in critical patients treated in the Intensive Care Unit had levels of 25-80 ng/mL. This is different from the results of a study conducted by Koekkoek and Van Zanten in 2016 which stated that vitamin D deficiency often occurs in critical illness with a prevalence between 40% and 70% (7). Especially in patients with burns (8). The average patient enters the ICU with conditions of malnutrition and pre-existing diseases. However, in this study the majority of research subjects were surgical patients undergoing surgery, some of which were elective surgeries. This explains why vitamin D levels of 25-80 ng/mL were found in this study. In addition, it is important to measure vitamin D levels in ICU patients before being given vitamin D supplements. So, not all ICU patients are given vitamin D supplements, but only in patients with vitamin D deficiency.

This study also demonstrated an association between the profile of the study subjects and their vitamin D levels. Based on the age of the study subjects, a significant difference was found in the age group <50 years and ≥50 years between vitamin D levels of 10-24 ng/mL and 25-80 ng/mL (p=0.001). Age is an essential factor that affects vitamin D levels. In general, old age tends to experience vitamin D deficiency due to many factors, not only due to reduced production of vitamin D in the skin but also due to decreased exposure to sunlight, decreased consumption of a diet high in vitamin D, impaired intestinal absorption, and loss or decreased hydroxylation in the liver and kidneys. This is in line with one study in Iraq which stated that young women showed significantly higher levels of vitamin D (9).

Based on gender, there was a significant difference between male and female sex groups between vitamin D levels of 10-24 ng/mL and 25-80 ng/mL (p=0.001). This is explained to be related to outdoor activities in men and their exposure to sunlight which is more frequent and longer than women. In addition, women also frequently apply sunscreen and they also breastfeed their babies. Higher adipose tissue in women than men has been hypothesized as a causal factor for low serum 25(OH)D concentrations in women (9,10).

Based on comorbid status, there was a significant difference between the group with comorbid and the group without comorbid between vitamin D levels of 10-24 ng/mL and 25-80 ng/mL (p=0.001). Patients with comorbidities tend to have vitamin D deficiency, especially in patients with malignancy, cardiovascular disease, and diabetes. Critical illnesses that occur in adults and children can result in vitamin D deficiency (11). Several diseases such as sepsis, acute respiratory syndrome, and acute kidney injury have been shown to be associated with vitamin D deficiency (3).

Based on BMI, there was a significant difference in BMI groups between vitamin D levels of 10-24 ng/mL and 25-80 ng/mL (p=0.001). Vitamin D is a fat-soluble hormone, so adipose tissue may be a place for vitamin D absorption, storage and subsequently results in a decrease in circulating free 25(OH)D levels. Individuals with normal body weight, who have less adipose tissue than obese people, tend to have an increased availability of vitamin D. The conflicting relationship between circulating 25(OH)D levels and high lipid profile biomarkers has been described in many studies. Vitamin D levels in individuals with high BMI tend to be lower than those with normal BMI. BMI >30 kg/m2 is one of the main factors affecting vitamin D levels (12,13)

This study also showed that there was a significant negative correlation between vitamin D levels and the severity of critical illness patients. The correlation coefficient value was -0.654, so this value indicates that there is a significant negative correlation between vitamin D levels and APACHE II (p<0.001). Meanwhile, a correlation coefficient of -0.714 was also obtained, so this value indicated that there was a significant negative correlation between vitamin D levels and the SOFA Score (p<0.001). Increased infection rates and decreased organ function may be factors associated with vitamin D deficiency that may contribute to prolonged ICU discharge time and poorer outcome in ICU patients. This is potentially due to the role of vitamin D on the immune system. In line with this, a recent report found significantly lower levels of endogenous antimicrobial cathelicidin peptide (LL-37) in vitamin D deficient critically ill patients, suggesting a role for vitamin D in maintaining innate immunity against infection in the ICU (14). Furthermore, 1,25(OH)D has been shown to have a stimulatory effect on the innate immune system by increasing interleukin-1 (IL-1) production and stimulating monocyte proliferation (15). Without this important innate immune system stimulatory effect, patients may be more susceptible to ICU infections. On the other hand, sufficient vitamin D levels have been associated with lower rates of autoimmune disorders, and perhaps sufficient vitamin D levels are necessary to regulate overactive pathological inflammatory immune responses (15). Therefore, patients may be more susceptible to pathological and overactive immune responses to common ICU infections.

5. Conclusion

The summary of this study is that the profile of critical patients admitted to the ICU room at Dr. Soetomo Hospital is <50 years old, female, has no history of smoking, exposed to sunlight for >30 minutes, consumes fish, does not consume milk, and consumes supplements or multivitamins. The most of vitamin D levels in critical patients treated in the intensive care unit had optimal levels. The severity of critical illness of patients admitted to the Intensive Care Unit based on APACHE II is mostly 0-4. Meanwhile, based on SOFA Score between 0-1 and ≥ 2 is almost the same. There is a significant relationship between vitamin D levels and the severity of critical illness of patients admitted to the intensive care unit as seen from APACHE II and SOFA Score. In addition, further research is expected by measuring vitamin D levels periodically to determine the role of vitamin D as a prognostic marker of the severity of critical illness patients.

Conflict of Interest:

The authors hereby declare that there is no conflict of interest in this study.

6. Acknowledgement

The authors express their gratitude to Dr. Soetomo General Hospital Surabaya for supporting and for successful completion of this project.

Source of funding

The present project was not funded by any external sources.

Author Contribution

A) Pirhot L. M. Y. Siahaan -contributed in designing the study, execution of the project, statistical analysis, manuscript drafting.

B) Anna Surgean Veterini -contributed in designing the study, execution of the project, statistical analysis, manuscript drafting.

C) Bambang Pujo Semedi -contributed in designing the study, execution of the project, statistical analysis, manuscript drafting.

D) Prananda Surya Airlangga -contributed in designing the study, statistical analysis, manuscript drafting.

E) Edward Kusuma -contributed in study design, guiding the research work, proofreading and manuscript correction.

F) Irwanto -contributed in study design, guiding the research work, proofreading and manuscript correction.

References

Higgins DM, Wischmeyer PE, Queensland KM, Sillau SH, Sufit AJ, Heyland DK. Relationship of vitamin D deficiency to clinical outcomes in critically ill patients. J Parenter Enter Nutr. 2012;36(6):713-720.

Amrein K, Christopher KB, McNally JD. Understanding vitamin D deficiency in intensive care patients. Intensive Care Med. 2015;41:1961-1964.

de Haan K, Groeneveld AB, de Geus HRH, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Crit care. 2014;18(6):1-8.

Lee J hyun, Doo S rin, Kim D, Park Y kyoung, Park E jeong, Lee J myeong. Vitamin D deficiency and mortality among critically ill surgical patients in an urban Korean hospital. Int J Vitam Nutr Res. Published online 2020.

Rech MA, Hunsaker T, Rodriguez J. Deficiency in 25-hydroxyvitamin D and 30-day mortality in patients with severe sepsis and septic shock. Am J Crit Care. 2014;23(5):e72-e79.

Anwar E, Hamdy G, Taher E, Fawzy E, Abdulattif S, Attia MH. Burden and outcome of vitamin D deficiency among critically ill patients: a prospective study. Nutr Clin Pract. 2017;32(3):378-384.

Koekkoek WAC, van Zanten ARH. Vitamin D deficiency in the critically ill. Ann Med. 2016;48(5):301-304.

Al-Tarrah K, Hewison M, Moiemen N, Lord JM. Vitamin D status and its influence on outcomes following major burn injury and critical illness. Burn trauma. 2018;6.

Al-horani H, Dayyih WA, Mallah E, et al. Nationality , Gender , Age , and Body Mass Index Influences on Vitamin D Concentration among Elderly Patients and Young Iraqi and Jordanian in Jordan. 2016;2016.

Arnold RH. COVID-19 – Does This Disease Kill Due to Imbalance of the Renin Angiotensin System (RAS) Caused by Genetic and Gender Differences in the Response to Viral ACE 2 Attack? Hear Lung Circ. 2020;29(7):964-972. doi:10.1016/j.hlc.2020.05.004

Rippel C, South M, Butt WW, Shekerdemian LS. Vitamin D status in critically ill children. Intensive Care Med. 2012;38:2055-2062.

Weir EK, Thenappan T, Bhargava M, Chen Y. Does vitamin D deficiency increase the severity of COVID-19? Clin Med (Northfield Il). 2020;20(4):e107.

Luo X, Liao Q, Shen Y, Li H, Cheng L. Vitamin D deficiency is inversely associated with COVID-19 incidence and disease severity in Chinese people. J Nutr. 2021;151(1):98-103. doi:10.1093/jn/nxaa332

Jeng L, Yamshchikov A V, Judd SE, et al. Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. J Transl Med. 2009;7:1-9.

Mora JR, Iwata M, Von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol. 2008;8(9):685-698.