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# Association between Vitamin D Levels and Mortality in Sepsis Patients Admitted to an Intensive Care at General Hospital Dr. M. Djamil, West Sumatera, Indonesia

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**Abstract**

**BACKGROUND:** Vitamin D deficiency is associated with an increased risk and progression of the disease, especially sepsis. Low serum Vitamin D levels when patients enter the Intensive Care Unit (ICU) can affect patient care outcomes.

**AIM:** This study aims to determine the relationship between Vitamin D levels and sepsis patients' treatment outcomes in the Intensive Care Unit.

**METHODS:** We analyzed 80 sepsis patients admitted from July 2022 to September 2022. This study used a cohort design. Sampling and collection were carried out from July 2022 to September 2022 in the Intensive Care Unit of Dr. M. Djamil Hospital, Padang. This study was conducted on 40 case samples and 40 control samples. The relationship between Vitamin D levels and treatment outcomes for sepsis patients was analyzed using the Chi-Square/Fisher Exact Test.

**RESULTS:** Patients with the most Vitamin D deficiency were women (77.5%), obese (57.5%), with the most comorbid Chronic Kidney Injury (12.5%), the mean APACHE II score was 21, and SOFA score of 7. Patients with non-deficiency Vitamin D most was male (7%), obese (52.5%), with the most comorbid Cardiovascular Disease (15.0%), the mean APACHE II score was 19, and SOFA score of 5. In 40 patients with Vitamin D deficiency, 24 patients (57.1%) non-survived, and 16 patients (42.1%) survived (RR = 1.833).

**CONCLUSION:** Vitamin D deficiency increases the risk of death in septic patients, so further intervention is needed.

## Introduction

Sepsis is the leading cause of death in the Intensive Care Unit (ICU) in the United States [1]. The incidence of sepsis is estimated at 31.5 million cases annually, and 19.4 million of them are severe sepsis, with a mortality rate of 5.3 million annually [2]. Data from the World Health Organization (WHO) reports that in sepsis patients in the ICU, it is estimated that there are 58 cases per 100,000 people/year and the incidence of hospital mortality is more than a third (42%). Jawad *et al*. reported in 2012 in a meta-analysis study that the incidence of sepsis ranged from 240 cases per 100,000 people, where the incidence of severe sepsis was 56 cases per 100,000 people, and sepsis shock was 11 cases per 100,000 people. The mortality rate is 30% for sepsis, 50% for severe sepsis, and 80% for sepsis shock [3].

Research Rhee *et al*. In 2017, the United States reported more than 170,000 cases of sepsis, and 55% of them required ICU care [4]. Research in the Asia Pacific region constitutes 60% of the world's population, with a total population of 4.6 billion. The incidence of sepsis in this region ranges from 120 to 1600 per 100,000, with a sepsis-related mortality rate of 35%. This figure is higher than in western and other high-income countries. The incidence of sepsis in Indonesia is still relatively high at 30.29%, with a mortality rate of 11.56 to 49%. Mortality in sepsis patients ranges from 15 to 40%, and in sepsis shock, from 20% to 72%—the 2016 Tambojang study on ICU patients at Prof. RSUP. Dr. R. D. Kandou Manado Indonesia received 82.8% diagnosis of sepsis, 11.4% severe sepsis, and 5.7% sepsis shock requiring vasopressors [5]. Data on sepsis in the ICU of Dr. M. Djamil Padang, Indonesian in the 2022 period showed an increase in the mortality of sepsis patients from 11.53% to 19.64% over the last 6 months.

Several studies have shown that lower levels of 25(OH)D in ICU patients are associated with increased infections, length of stay, higher health-care costs, higher hospital mortality, and higher mortality after discharge. The prevalence of Vitamin

D deficiency (25(OH)D < 20 ng/mL) is up to 70% in critically ill patients. A high risk of death in sepsis conditions with low serum 25(OH)D levels (<30 ng/mL) at hospital admission was associated with a higher risk of death. Low serum 25(OH)D level would be an independent predictor of poor prognosis for clinically critical patients [6], [7], [8].

## Methods

### *Study populations*

This study used a cohort design. Sampling and collection were carried out from July 2022 to September 2022 in the Intensive Care Unit of Dr. M. Djamil Hospital, Padang. Vitamin D levels were examined using the Biochem Canada Diagnostic Kit, catalog number CAN-VD-510, LOT 222590, at the Biomedical Laboratory of the Faculty of Medicine, Andalas University.

This study was conducted on 40 case samples and 40 control samples that met the inclusion and exclusion criteria and who had agreed to the informed consent of the study. In each sample, Vitamin D levels were checked. The inclusion criteria in this research were all patients with sepsis caused by bacteria, have known Vitamin D level, age between 18 until 60 years old, procalsitonin ≥2 ng/mL, lactate ≥1,6 mmol/L, APACHE score >10, and SOFA score ≥2. The exclusion criteria in this research were the patients who had received Vitamin D supplement, and sepsis caused by viral, parasite or fungal infection.

This research involves human as research subjects. The ethical implications of this research follow the provisions of the Declaration of Helsinki and have passed the ethical test of the ethic committee of RSUP Dr. M. Djamil in Padang with number: LB.02.02/5/7/383/2022. All medical matters relating to this research are confidential. Research subjects have the right to refuse to participate in the study if they do not agree. All research cost and other cost incurred as a result of this research are borne by the researcher.

### *Statistical analysis*

Data analysis was done computerized. First, a univariate analysis was conducted to obtain the basic characteristics of the research sample. After that, a bivariate analysis was carried out using the Chi-square test to obtain the relationship between each dependent variable and the independent variable. The relationship between the independent variable and the dependent variable is said to be statistically significant if $p < 0.05$.

## Results

The distribution of the basic characteristics of this study is shown in Table 1. The research sample comprised 40 sepsis cases with vitamin D deficiency and 40 samples of non-deficient controls. Sepsis patients treated in the ICU by Dr. M. Djamil Padang on vitamin D deficiency levels, the average age was 52 years. The most women were 31 people (77.5%), with BMI obesity of 23 people (57.5%), had the most comorbid Chronic Kidney Injury (CKD) 5 people (12,5%), the mean APACHE II score was 21 and SOFA 7 score. Sepsis patients with non-vitamin D deficiency had an average age of 61 years; most were men, 28 (70%), with an obese BMI of 21 (52.5%). The most comorbid Cardiovascular Disease was six people (15%), the mean APACHE II score was 19, and the SOFA score was 5.

**Table 1: Distribution of the basic characteristics of the research sample**

| Variable | Vitamin D level | | p |
|---|---|---|---|
| | Deficiency, n (%) | Nondeficient, n (%) | |
| Age (years) | 51.80 ± 10.825 | 49.98 ± 14.130 | 0.003 |
| Sex | | | |
| Men | 9 (22.5) | 28 (70.0) | 0.000 |
| Women | 31 (77.5) | 12 (30.0) | |
| BMI | | | |
| Underweight | 3 (7.5) | 0 | 0.653 |
| Normo weight | 14 (35.0) | 19 (47.5) | |
| Obesities | 23 (57.5) | 21 (52.5) | |
| DM | 4 (10.0) | 1 (2.5) | 0.359 |
| Chronic kidney injury | 5 (12.5) | 3 (7.5) | 0.712 |
| Cardiovascular disease | 3 (7.5) | 6 (15.0) | 0.481 |
| COPD | 0 | 4 (10.0) | 0.116 |
| APACHE II score | 20 (11–30) | 21.5 (9–33) | 0.964 |
| SOFA score | 7 (1–18) | 5 (1–20) | 0.143 |

DM: Diabetes mellitus, BMI; Body mass index, COPD: Chronic obstructive pulmonary disease.

From the table above, based on the level of Vitamin D which was characteristic basic BMI, comorbidities such as diabetes mellitus (DM), chronic kidney injury, cardiovascular disease, and COPD, APACHE II score, and SOFA score did not show a significant difference between sample deficiencies and non-deficiencies, or both groups have value $p > 0.05$. However, there was a significant relationship between age and sex against the level of vitamin D ($p < 0.05$).

Laboratory characteristics are as in Table 2. The average Hb in sepsis patients with Vitamin D deficiencies were 10.18 g/dl, leukocytes 16.040/$mm^3$, platelets 207.500/$mm^3$, procalcitonin 17.32 ng/mL, lactate 2.7 mmol/L, albumin 2.60 g/dl, bioavailable 25(OH)D 2.270 ng/dl, and VDBP 105.347 ug/mL.

**Table 2: Laboratory results of sepsis patients in intensive care unit**

| Variable | Vitamin D Level | | p |
|---|---|---|---|
| | Deficiency | Nondeficiency | |
| Hb, g/dl | 10.18 ± 2.21 | 11.66 ± 2.19 | 0.004 |
| Leukocytes, $\times 10^3/mm^3$ | 16.04 (3.25–43) | 13.145 (2.89–42.6) | 0.097 |
| Platelets, $\times 10^3/mm^3$ | 207.5 (10–610) | 220 (38–478) | 0.825 |
| Procalcitonin, ng/mL | 17.32 (2.41–200.0) | 12.26 (1.50–200.0) | 0.290 |
| Lactate, mmol/L | 2.7 (1.6–15.0) | 2.30 (1.6–5.4) | 0.368 |
| Albumin, g/dl | 2.60 ± 0.64 | 2.73 ± 0.70 | 0.123 |
| Bioavailable 25(OH) D, ng/mL | 2.270 (0.31–7.96) | 5.194 (1.88–37.83) | 0.000 |
| VDBP, ug/mL | 105.347 (25.81–290.89) | 132.015 (60.26–280.195) | 0.032 |

Hb: Hemoglobin, VDBP: Vitamin D binding protein.

Patients with non-deficient Vitamin D levels had a mean Hb of 11.66 d/dl, leukocytes 13.145/mm$^3$, platelets 220.000/mm$^3$, procalcitonin 12.26 ng/mL, lactate 2.30 mmol/L, albumin 2.73 g/dl, bioavailable 25(OH)D 5.194 ng/dl, and VDBP 132.015 ug/mL.

The table above showed that the values of leukocytes, platelets, procalcitonin, lactate, and albumin did not show a significant difference between samples of Vitamin D deficiency and non-deficiency levels, or both groups had p > 0.05. However, there were significant differences in the values of Hb, bioavailable 25(OH)D, and VDBP with Vitamin D levels (p < 0.05).

The relationship between Vitamin D levels and mortality showed in the Table 3. Of the sepsis patients in the ICU who experienced the most deficiency, 24 people (57.1%) did not survive, and 18 people (55.0%). The Chi-square analysis results showed no significant relationship between Vitamin D levels and survival rate in sepsis patients with p-value = 0.179 (RR = 1.833).

**Table 3: Relationship of Vitamin D levels in sepsis patients with the survival rate**

| Variable Vitamin D level | Survival rate | | p | RR |
|---|---|---|---|---|
| | Non-survive, *n* (%) | Survive, *n* (%) | | |
| Deficiency | 24 (57.1) | 16 (42.1) | 0.179 | 1.833 |
| Non-deficiency | 18 (42.9) | 22 (57.9) | | |

RR: Risk ratio.

## Discussion

Vitamin D has been shown to play an important role in many physiological processes involved in the pathogenesis of sepsis. Vitamin D has an important role in maintaining and regulating the innate and adaptive immune systems, which may therefore have a protective effect against severe infections and an overactive inflammatory response. Moreover, through interactions with widely distributed Vitamin D receptors and subsequent signaling pathways, Vitamin D can maintain the functional status of various susceptible organs during severe infections, such as the heart, lung, and kidney [9].

The pathophysiology of sepsis in Vitamin D deficiency may be innate immune dysfunction. In addition, decreased levels of 1,25(OH)2D at the tissue level may decrease its pleiotropic effect on immune regulation, mucosal, and endothelial function [10]. Sepsis due to bacteremia was significantly more common in patients with Vitamin D deficiency (19%) than in patients without deficiency (0%). Sepsis associated with pneumonia occurred significantly more frequently (p = 0.01) in non-deficient patients (46%) than Vitamin D-deficient (25%) [11].

Several factors can cause Vitamin D deficiency in sepsis patients with prolonged hospitalization: lack of sun exposure, malnutrition, decrease renal hydroxylation, and increased tissue conversion of 25(OH)D3 to 1,25(OH)2D3. Decrease serum Vitamin D levels on the first day of hospitalization may be due to decrease serum albumin or Vitamin D-binding protein levels or receiving intravenous volumes to correct hypovolemia or hypotension [12].

The average age for Vitamin D deficiency was 52 years old and was higher than for non-deficiency patients, which was 50 years old. In this study, the age was lower than in other studies. Bayat's study found that the age of Vitamin D deficiency was more than 65 years old [13]. Rech's study obtained the appropriate results where the mean age of septic patients was more than 65 years old [11]. This study found that age difference was lower compared to other studies because the mean age of the participants in our study was almost a decade younger than the previous study based on the sepsis management guidelines [14].

This study found that women had higher levels of Vitamin D deficiency in sepsis patients than men (77.5% vs. 22.5%). In line with the study of Mishal, found that serum 25(OH)D levels lower in women than men [15].

This result was different from Bayat's study, Vitamin D deficiency was higher in men than women [13] and similar with Yoo's study (55.6%) [6]. Deficiency in women occur due to menopause, due to estrogen levels and dressing styles (following religious and cultural teachings) that cover the body to a certain extent despite adequate sun exposure [15], [16].

The highest body mass index (BMI) was in conditions of Vitamin D deficiency and non-deficiency, namely, obesity (57.5% and 52.5%). In line with the Arabi's study, found that sepsis patients were obese (57.3%), followed by the normoweight (35.3%) [17] and similar with Gonzale's study [18]. Vitamin D is fat soluble, so in obese patients, there is a decrease in Vitamin D bioavailability, and a lot of Vitamin D 25(OH) D is trapped in adipose tissue [19].

This study found diabetes mellitus patients had lower of Vitamin D level (10.0%). The association between Vitamin D deficiency and insulin resistance developed through inflammation, as Vitamin D deficiency was associated with increased inflammatory markers [20].

Patient with chronic kidney disease (CKD) had lower of Vitamin D level (12.5%). In line with the Jean's study, found patient underwent hemodialysis had low Vitamin D level. Vitamin D deficiency occurred because of impaired Vitamin D synthesis in renal proximal tubular cells that increased fibroblast growth factor (FGF)-23 [21]. Abnormalities of vitamin D metabolism play a major role in the pathogenesis of secondary hyperparathyroidism in CKD [22].

Patients with cardiovascular disease had lower of Vitamin D level (15.0%). This result was different from existing research. Cosentino's study found low

Vitamin D levels in cardiovascular diseases such as stable angina, acute myocardial infarction (AMI), and hypertension [23]. Several mechanisms of Vitamin D deficiency in cardiovascular disease were caused by: First, experimental studies had shown that 1,25-(OH) D controlled the regulation of the renin-angiotensin axis by directly suppressing the expression of the renin gene. Renin overexpression could be produced through pharmacological inhibition of Vitamin D synthesis. Second, vascular smooth muscle cells and endothelial cells expressed receptors for Vitamin D. This process can convert circulating 25(OH)D to 1,25(OH)D. Vitamin D-24-hydroxylase, the enzyme that catalyzed the breakdown of 1 to 25(OH)D, progressed to significant atherosclerosis. Third, Vitamin D deficiency triggers secondary hyperparathyroidism. Parathyroid hormone (PTH) promotes myocyte hypertrophy and vascular remodeling. Another study showed that PTH had a pro-inflammatory effect, stimulating the release of cytokines by vascular smooth muscle cells [24].

This study found that COPD patients with sepsis had normal levels of Vitamin D. This result is different from existing research. Viral or bacterial infection often triggers acute exacerbations of COPD. This process causes an increase in the production of cathelicidin, so Vitamin D levels will decrease. Vitamin D can increase the production of cathelicidin. This process can reduce the frequency of exacerbations and exposure to infection in COPD patients [25].

The mean APACHE II score in this study was not much different between deficiency and non-deficiency of Vitamin D (20 vs. 21.5). This result is different from Ardehali's study, where in ICU patients with Vitamin D deficiency, the APACHE II score was higher than normal (12.75 vs. 8.41) [12]. The Aygencel's study also found that patients with high APACHE II had low levels of vitamin D deficiency (24 vs. 19) [26].

The mean SOFA score in this study was higher in Vitamin D deficiency than in non-deficiency (7 vs. 5). This result is in line with Ardehali's study, where the median SOFA score was significantly higher in the deficiency group compared to the normal non-deficient (8 vs. 5) [12]. This same result was also found in Aygencel's study; the mean SOFA score in Vitamin D deficiency was lower than in non-deficiency (8 vs. 6) [26].

This study found that the mean hemoglobin of sepsis patients in the ICU with Vitamin D deficiency was lower than non-deficiency (10.18 vs. 11.66) and statistically significant (p = 0.004). This result was in line with Sim's 2020 study, which found a relationship between Vitamin D deficiency and anemia. Vitamin D was related to hemoglobin levels, although the mechanism was unknown. One possibility was that Vitamin D modulates the level of systemic cytokine production, thereby reducing inflammation that causes anemia of chronic disease. Some additional confounding factors contributed to reduce erythropoiesis storage and total 25(OH)D levels were that patients with anemia might have more disease and weakness to prevent them from adequate sun exposure [27].

This study found that the mean value of leukocytes and procalcitonin in sepsis patients in the ICU with Vitamin D deficiency was higher than non-deficiency. These results align with Aygencel's study on leukocyte and procalcitonin levels. This value was directly associated to the mortality rate [26].

This study found that the mean VDBP in sepsis patients in the ICU with Vitamin D deficiency was lower than non-deficiency (105.347 vs. 132.015) and statistically significant (p = 0.032). In contrast to Kalousova's study, VDBP was not involved in Vitamin D deficiency [28]. However, another study found that circulating VDBP levels were positively associated with a total of 25(OH)D levels [29]. A total of 25(OH) D bound to VDBP was normally involved in regulating gene expression, which requires intracellular enzymatic cleavage of 25(OH)D. This process is thought to have limited biological activity during acute stress, for example, in sepsis [6]. VDBP levels were significantly lower in sepsis patients. VDBP levels in the previous studies were associated with the incidence of sepsis mortality [30].

This study found that sepsis patients with low Vitamin D level were higher risk for non-survival events (57.1% vs. 42.9%, RR = 1.833). These results align with Nainggolan's 2020 study that vitamin D levels <8.1 ng/mL at admission have a higher risk of death within 28 days [31]. Macrophage cells, lymphocytes, and dendritic cells play a role in the innate and adaptive immune systems, where macrophages, lymphocytes, and dendritic cells express the Vitamin D receptor and respond to 1,25(OH)2D stimulation. Increased mortality in ICU admission with hypovitaminosis D is related to the pleiotropic function of Vitamin D. Vitamin D inhibits vascular smooth muscle cell proliferation, protects normal endothelial function, and modulates the inflammatory process [32]. Vitamin D deficiency has potential risks related to (1) the stimulatory effect of Vitamin D on innate immunity, (2) suppression of immune regulators, and (3) negative effects on pathways that function to reduce the potential for inflammatory damage [13].

This study found that the risk ratio for mortality in sepsis patients with Vitamin D deficiency was 1.883 times higher than in non-deficiency. These results align with the Rech's study, where the risk of death in sepsis patients admitted to the ICU was 1.375 times compared to non-deficiency [11]. The same results were also found in a meta-analysis that found the risk of death in sepsis patients was 1.9 times [33].

Meta-analysis study by Li *et al*. found that an association between lower serum 25(OH)D and higher mortality in sepsis patients, especially in Vitamin D deficiency [9]. Study by Nainggolan *et al*. showed that

the group of patients with Vitamin D deficiency less than 8.1 ng/mL had a higher risk of death within 28 days (RR: 1.95) [31]. Different results were found in Chen's study, which found that Vitamin D deficiency was not associated with 28 or 90-day mortality but with longer ventilator use and ICU stay [34]. The mortality of sepsis patients had increased in Vitamin D deficiency. It might alter glucose and calcium metabolism and immune cell and endothelial cell dysfunction [26].

The study had several limitations. First, we could not control all the probable confounding factors in observational studies, which could affect the study's findings. Second, this single-centered study was performed at an Indonesian national referral hospital in Padang. Therefore, the patients might have more complex conditions or comorbidities than the general population. Furthermore, additional studies are going to be needed in a wider population.

## Conclusion

Vitamin D deficiency increases the risk of death in septic patients, so further intervention is needed.

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