MAGNA MEDIKA
Berkala Ilmiah Kedokteran dan Kesehatan
e-ISSN 2774-2318
p-ISSN 2407-0505

Research Article
MAGNA MEDIKA
Berkala Ilmiah Kedokteran dan Kesehatan
Journal Page: https://jurnal.unimus.ac.id/index.php/APKKM

Factors Affecting Mortality of Sepsis Patients in General Hospital

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Article Info

Article history:
Received 18 February 2023
Revised 30 April 2023
Accepted 03 July 2023
Available online 18 August 2024

Keywords:
Sepsis, intensive care unit, vitamin D

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How to cite this article:
Aribowo Kornelis, Sari Wiwi Monika. Factors Affecting Mortality of Sepsis Patients in General Hospital. MAGNA MEDIKA Berk Ilm Kedokt dan Kesehat. 2024; 11 (2): 114-121

Abstract

Background: The high sepsis mortality rate is a significant problem that must be managed properly and comprehensively. Studies showed 30% mortality due to sepsis, 50% for severe sepsis, and 80% for sepsis shock. Data in Indonesia showed that 30.29% of sepsis patients were admitted, and 11.56% to 49% died. Vitamin D deficiency is associated with an increased risk of infection in sepsis.

Objective: This study aims to determine the factors that play a role in the death of sepsis patients.

Methods: This study used a cross-sectional analytic design. Data were taken from 42 patients who died from sepsis in the Intensive care unit of Dr. M. Djamil Padang Hospital from July 2022 to September 2022. Patients were previously checked for vitamin D levels, and data analysis was done using the Mann-Whitney test.

Results: The average age of sepsis patients is 56 years old, and the other characteristic is female (59.9%), vitamin D deficiency (82.5%), obesity (64.3%), and most comorbid with chronic kidney injury (CKD) (16.7%). Sepsis patients who died of vitamin D deficiency had a mean Hb of 11.5 g/dl; leukocytosis (14.490/mm3), thrombocytopenia (225.000/mm3), hypoalbumin (2.4 g/dl) and high risk to sepsis based on procalcitonin levels (15.47 ng/ml). There was no statistically significant relationship to the laboratory results (p-value>0.05).

Conclusion: Vitamin D deficiency, female, obesity, CKD, thrombocytopenia, and hypoalbumin increase the mortality risk of sepsis patients in the intensive care Unit. Recognizing demographic and laboratory risk factors helps clinicians prevent sepsis mortality.

e-ISSN 2774-2318
p-ISSN 2407-0505

INTRODUCTION

According to the *Third International Consensus Definitions for Sepsis and Septic Shock*, Sepsis is a life-threatening organ dysfunction caused by failure to regulate the patient's response to infection and macro and microvascular dysfunction, which causes organ dysfunction. Sepsis with a *Sequential Organ Failure Assessment* (SOFA) score ≥2 increases the risk of death by more than 10%.[1–3]

The *World Health Organization* (WHO) reported that in sepsis patients in the ICU, there are an estimated 58 cases per 100.000 people/year, and the incidence of in-hospital mortality is more than one-third (42%). Jawad et al. reported in a meta-analysis study that sepsis was around 240 cases per 100.000 people, whereas the incidence of severe sepsis was 56 cases per 100.000 people, and septic shock was 11 cases per 100.000 people. Mortality rates reached 30% for sepsis, 50% for severe sepsis, and 80% for septic shock.[4] In Indonesia, the incidence of sepsis is 30.29%, with a mortality rate of 11.56 to 49%. Tambajong, in 2016, of ICU patients at Prof Dr RD Kandou Hospital Manado found 82.8% were diagnosed with sepsis.[5]

Vitamin D is an essential mediator in the immune system and plays an inhibitory role in the pathogenesis of sepsis. Vitamin D can regulate both acquired and innate immune responses. It prevents the overexpression of inflammatory cytokines and is an essential mediator in leukocyte aggregation, local inflammation formation, and anti-bacterial responses in innate immunity.[6]

Deficiency Vitamin D, characterized by serum 25(OH)D concentrations less than 20 ng/mL, triggers *parathyroid hormone* (PTH) secretion. Subsequently, PTH will increase the conversion of 25-(OH)D to 1.25(OH)2D, which further aggravates the deficiency but maintains an average blood concentration of 1.25-(OH)2D. Continued PTH secretion causes the parathyroid glands to work optimally, leading to secondary hyperparathyroidism.[7,8]

Vitamin D deficiency increases the risk of viral and bacterial infections. Low serum vitamin D levels when patients enter the ICU correlate with increased incidence of sepsis and risk of death.[9] Research by Jhones et al. in 2001 showed a correlation between vitamin D deficiency and a severe sepsis infection.[10] Based on the above, researchers are interested in researching mortality risk factors for sepsis patients.

METHODS

The design of this study used an analytic study with a cross-sectional approach carried out on Sepsis patients in the Intensive Care Unit from July 2022 to September 2022. Samples were taken from populations that met the inclusion and exclusion criteria. The inclusion criteria are sepsis patients in the intensive care Unit of General Hospital Dr. M. Djamil Padang caused by bacteria (excluding mycobacterium tuberculosis), Aged 18 to 85 years, and procalcitonin levels ≥2 ng/mL. The exclusion criteria for this study were patients who had previously received vitamin D supplementation therapy. The research sample was directly examined for Vitamin D (because Vitamin D is not a routine examination in a hospital). Data analysis using univariate analysis and bivariate analysis using the Mann-Whitney test. Deficiency vitamin D deficiency if vitamin D is ≤30 ng/ml and Non-deficiency vitamin D if it is >30 ng/ml.

e-ISSN 2774-2318
p-ISSN 2407-0505

RESULTS

Based on Table 1, it was found that the average age of mortality of sepsis patients was 56 years. The gender was predominantly female (59.5%), followed by male (40.5%). Most sepsis patient mortality had vitamin D deficiency compared to normal (82.5% vs. 17.5%). Body mass index (BMI) was mainly obesity (64.3%), followed by norm weight (33.3%) and underweight (24.1%). The mean mortality of sepsis patients had an APACE II score of 22 points and a SOFA score of 7. The most common comorbidities based on mortality were Chronic Kidney Injury (16.7%), followed by Cardiovascular Disease (14.3%), diabetes mellitus (9.5%), and Chronic Obstruction Pulmonary Disease (2.4%).

Table 2 shows the average mortality of sepsis patients with deficiency vitamin D has Hb levels of 11.5 gr/dl, leukocytes 14.490/mm3, platelets 225.000/mm3, albumin 2.4 gr/dl and procalcitonin 15.47 ng/ml. In sepsis mortality, patients with normal vitamin D levels had an average Hb level of 10.25 gr/dl, leukocytes 17.730/mm3, platelets 254.000/mm3, albumin 2.8 gr/dl and procalcitonin 11.26 ng/ml. The statistical data did not significantly correlate the laboratory result variables with vitamin D levels. However, the table illustrates that patients with vitamin D deficiency had lower platelet and albumin levels than those with normal vitamin D levels. Hb levels, leukocyte values, and procalcitonin were higher in sepsis patients with vitamin D deficiency than those with normal vitamin D levels.

Table 1. Mortality Characteristics of Sepsis Patients

Characteristics	Sepsis Patient Mortality	
	f (%)	**Median (min-max)**
Age (years)		56 (18 - 85)
Sex		
Male	17 (40.5%)	
Female	25 (59.5%)	
Vitamin D Level		
Deficiency	66 (82.5%)	
Non-deficiency	14 (17.5%)	
Body Mass Index (BMI)		
Underweight	1 (2.4%)	
Normoweight	14 (33.3%)	
Obesity	27 (64.3%)	
Diabetes Mellitus		
Yes	4 (9.5%)	
No	38 (90.5%)	
Chronic Kidney Injury		
Yes	7 (16.7%)	
No	35 (83.3%)	
Cardiovascular Disease		
Yes	6 (14.3%)	
No	36 (85.7%)	
Chronic Obstruction Pulmonary Disease		
Yes	1 (2.4%)	
No	41 (97.6%)	
APACHE II Score		22 (12 - 67)
SOFA Score		7 (2 - 18)

doi: 10.26714/magnamed.11.2.2024.114-121
11 (2) August 2024

e-ISSN 2774-2318
p-ISSN 2407-0505

Table 2. Laboratory results of sepsis patient mortality based on vitamin D levels

Variable	Vitamin D Level		*p-Value*
	Deficiency vitamin D Median (min-max)	Non-deficiency Median (min-max)	
Hb gr/dl	11,5 (6,5-13,9)	10,25 (7,1-15,4)	0.182
Leukosit /mm^3	14,490 (3,110-29,720)	17,730 (925-35,750)	0.328
Platelet /mm^3	225,000 (78,000-442,000)	254,000 (26,700-609,000)	0.673
Albumin gr/dl	2,4 (1,2-3,8)	2,8 (1,4-3,7)	0.782
Procalsitonin ng/ml	15,47 (2,07-91,56)	11,26 (2,06-62,73)	0.701

DISCUSSION

This study found that the average age of sepsis patients who died was 56. This age was lower than Rech's research (69 years) and Chen's research (≥ 65 years). [11,12] Elder age is a predisposing factor for sepsis due to comorbidities, prolongation, recurrence of hospitalization, decreased immunity, and functional limitations, all of which were caused by aging. The diagnosis of sepsis in older people was more complicated than in younger because old age gives a less clear response and clinical symptoms of sepsis.[13]

Females in this study had the highest mortality risk compared to males (59.5% vs. 40.5%). These results align with Pietropaoli, where females experience higher mortality than males (35% vs. 33%). However, the results differed in Yoo's study, where males had the highest number of non-surviving sepsis patients (79.5%). In theory, females are at a lower risk of death than males because of the hormone estrogen.[14,15] However, this study had more females because the sample was Female-dominated.

Vitamin D deficiency had more deaths than usual (82.5% vs. 17.5%). According to Parekh, Xiao, and Yoo, vitamin D deficiency increases the mortality of sepsis patients.[16–18] However, different results were reported by Ratzinger in 2017 in a retrospective cohort study that low 25(OH)D levels could not predict the mortality of sepsis patients. [19] Vitamin D deficiency can increase the risk of morbidities, such as infection, acute kidney injury, myocardial infarction, and so on.[20]

Vitamin D affects the proliferation and differentiation of T cells and B cells and modulates immunoglobulin production through adaptive immunity.21 Macrophages and mature dendritic cells can induce adaptive T cell and B cell-mediated immunity after interacting with pathogens, resulting in an adaptive immune response. Macrophages and mature dendritic cells also express the enzyme CYP27B1 and synthesize calcitriol from calcifediol. One type of T cell is the Th cell (T helper). Calcitriol can suppress Th cell proliferation and modulate cytokine production from Th cells. Activation of Th cells after interacting with antigens and MHC II results in Th generation with different cytokine profiles, i.e., Th1 (IL-2, interferon-gamma, TNF-α) and Th2 (IL-3, IL-4, IL-5, IL-

e-ISSN 2774-2318
p-ISSN 2407-0505

10), which support cellular and humoral immunity, respectively. Calcitriol will decrease Th1 cytokines and increase Th2 cell responses. Th2 cells will interact with B cells that bind to antigens and activate them, resulting in proliferation and differentiation. The differentiated B cells (antibody-secreting cells/ASC) will produce antibodies (immunoglobulins) to fight the pathogen. Calcitriol reduces B cell proliferation, thus efficiently controlling the immune response process. Other Th cells affected by vitamin D are effector, memory, and IL-17-secreting Th17 cells. Calcitriol will suppress IL-17 production through direct transcriptional suppression of IL-17 gene expression. Other T cells also induced by calcitriol are regulatory T cells (Treg). T regulators suppress immune responses stimulated by other T cells to prevent excessive immune reactions or autoimmune responses.[21–23]

Mortality of sepsis patients was highest in obesity conditions (64.3%). This result is different from the existing theory. Obesity has a low risk of death because metabolism in sepsis patients will increase. Obesity has much adipose tissue and becomes a nutrient reserve due to increased metabolism. However, this study had more nonsurvivors of obesity because obese patients dominated the sample, and obese patients in this sample had comorbidities that aggravated the sepsis condition.[24,25]

The most common comorbidities that experienced mortality in sepsis patients were *chronic kidney injury* (16.7%). These results align with Jean's research, where Vitamin D deficiency in CKD patients increases the risk of sepsis patient mortality. Vitamin D deficiency is due to the progressive decrease in serum calcitriol simultaneously. Vitamin D deficiency causes secondary hyperparathyroidism (SHPT) and complications (tertiary hyperparathyroidism and hypercalcemia). It requires surgical parathyroidectomy or calcimimetics.[26] Patients with CKD are vulnerable to infection, and incoming therapy will aggravate kidney conditions so that CKD patients are more at risk for mortality. Proper management and attention to therapeutic doses were needed in the management of sepsis patients who have comorbid Diabetes mellitus.[27]

The mean APACHE II score in sepsis patients who died was 22 points. APACHE II score is a predictor of sepsis patient mortality. The higher the APACHE II score, the higher the risk of death. APACHE II score and the number of organ dysfunctions are still important parameters for increased mortality. [28,29]

The average SOFA score in sepsis patients who died was 7 points. These results align with Aygencel's research. The average SOFA score in nonsurvivors was 10 points. [30] An increase in SOFA score of 2 or more has greater prognostic accuracy for the incidence of mortality in the hospital.[31] SOFA scores can be a marker of bacterial infection in patients. A high SOFA score can be used to assess the organs' parameters. The SOFA score in this study was pretty close.[32]

The results of this study's research samples align with existing studies, namely Hb, leukocytes, platelets, procalcitonin, and albumin, which have levels that are not significantly different between Vitamin D deficiency patients and regular patients. Although the levels of the study samples were not significantly different, these levels can be an option to assess the parameters of sepsis patients.

e-ISSN 2774-2318
p-ISSN 2407-0505

CONCLUSION

There was no association between laboratory results and mortality of sepsis patients associated with vitamin D levels. However, vitamin D levels, gender, obesity, CKD, thrombocytopenia, and hypoalbumin increase the mortality risk of sepsis patients.

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