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Association between polymorphism loci rs7041, rs4588 in vitamin D-binding protein receptor gene with comorbid with mortality sepsis patients in intensive care unit General Hospital M. Djamil Padang, West Sumatra

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ABSTRACT

Background: Many factors influence the disease, one of which is comorbidity. Comorbid is a condition in which a person simultaneously suffers from two or more diseases. The disease is generally chronic. Patients with comorbid diseases are more at risk of experiencing increased healthcare costs, experiencing obstacles in the healing process, and even death. Loci rs7041 and rs4588 polymorphism of VDBP receptor gene contributed to the pathogenesis of sepsis patients. According to several previous studies, Vitamin D levels and comorbidities affected the mortality of sepsis patients. Several previous studies had linked VDBP with mortality in sepsis. This study aimed to determine the relationship between the loci rs7041 and rs4588 polymorphism and comorbidities with the mortality of sepsis patients.

Method: This research was a descriptive observational study with a prospective cohort design. The total data for this study were 80 samples, consisting of 40 samples of Vitamin D deficiency and 40 samples of non- deficiency Vitamin D. Data were analyzed using the Chi-Square test or the fisher test.

Result: The average age of patients with vitamin D deficiency was 56 years, for females (77,5%), mean APACE II score (20), and mean SOFA score (7). Non-deficient vitamin D with an average age of 50 years, males (70,0%), mean APACE II score (18) and mean SOFA score (5). Diabetes mellitus was the highest comorbidities in rs7041 locus polymorphism (80,0%), underweight in rs4588 locus polymorphism (66,7%) and obesity for non-survival events (64,3%). There was no significant association between comorbidities and rs7041 locus polymorphism, rs4588 locus polymorphism and severity sepsis patients with pValue > 0,05.

Conclusion: Obesity is the highest comorbid for mortality in sepsis patients, but loci rs7041 and rs4588 polymorphisms have no relation to comorbidities.

Keywords: mortalitas, obesitas, polimorfisme, rs7041, rs4588, sepsis.
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INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a failure to regulate the patient's response to infection. Changes in metabolic pathways such as pro- and anti-inflammatory reactions, nerves, hormones, metabolism, activation of coagulation, and macro and microvascular dysfunction lead to organ dysfunction.[1–3] Sepsis can develop into severe sepsis, septic shock, and even death if inadequate therapy or organ failure occurs.[4]

The VDBP genotype is an individual variant that has a composition with a specific VDBP gene resulting in a vitamin D-binding protein with different characteristics from the other variants.[5] The VDBP genotype frequency was not statistically different in patients who survived and non-survived.[6] The most common polymorphism in the VDBP gene are the rs7041 and rs4588 loci, which are located in exon 11 of domain III of the VDBP gene. Loci rs7041 and rs4588 correlate with serum vitamin D status and vitamin D metabolites. Plasma levels of Gc gene protein and its affinity for vitamin D metabolites are influenced by two common functional polymorphisms, namely loci rs4588 and rs7041.[7]

Many factors influence the disease, one of which is comorbidity. Comorbid is a condition in which a person simultaneously suffers from two or more diseases. The disease is generally chronic. Patients with Comorbid diseases are more at risk of experiencing increased healthcare costs, experiencing obstacles in the healing process, and even death.[8] Patients with diabetes mellitus have an increased risk of infection and sepsis. Diabetes mellitus is an independent risk factor for persistent kidney dysfunction in patients who experience *acute kidney injury* (AKI) in the ICU.[9] COPD patients with sepsis have a higher risk of severe COPD exacerbations, pneumonia, and death than those without sepsis.[4] Several studies have found that patients with cardiovascular disease have low vitamin D levels, such as stable angina or *acute myocardial infarction* (AMI) and hypertension, and are associated with long-term rehospitalization.[10,11] Patients with *chronic kidney injury* or with *hemodialysis* experience more vitamin D deficiency.[12] Based on the data above, researchers are interested in examining the relationship between comorbidities with mortality in sepsis patients.

METODE

This study used a prospective cohort design. Sampling and collection were carried out from July 2022 to September 2022 in the intensive care Unit of General Hospital M. Djamil Padang. This study was conducted on 80 samples. The inclusion criteria in this study were all sepsis patients in the ICU of RSUP Dr. M. Djamil Padang caused by bacteria (no mycobacterium tuberculosis), the known value of Vitamin D levels, aged 18 years to 85 years, procalcitonin value ≥ 2 ng/mL, lactate ≥ 1,6, APACHE II score > 10, SOFA score ≥ 2. Exclusion criteria were patients who had previously been treated with vitamin D supplements. The study sample consisted of 40 samples with vitamin D deficiency and 40 samples with non- deficiency vitamin D. Vitamin D deficiency if the level was 25(OH)D <20 ng/ml and non-deficiency vitamin D if 25(OH)D level ≥ 20 ng/ml. Vitamin D levels were examined with the Biochem Canada Diagnostic Kit, catalog number CAN-VD-510, LOT 222590, in the Biomedical Laboratory of Medical Andalas University. The number of this Research Ethics Review is LB.02.02/5.7/383/2022.

Data analysis was computerized. First, univariate analysis was performed to obtain the basic characteristics of the research sample. After that, a bivariate analysis was performed using the Chi-Square test / Fisher's Test. The relationship between the independent and dependent variables is statistically significant if the p-value <0,05.

RESULT

The characteristics of research subjects based on Vitamin D consisted of age, sex, APACHE II, and SOFA score. In table 1, the average age of patients with Vitamin D deficiency was 56 years; there were more females than males (77,5% vs. 22,5%), the mean APACE II score was 20, and the mean SOFA score was 7. Patients with non-deficient Vitamin D had an average age of 50 years; there were more males than females (70,0% vs. 30,0%), an average APACE II score of 18, and SOFA score of 5. The table showed that the average APACHE II and SOFA scores were higher in Vitamin D deficiency patients than in non-deficient patients.

The characteristics of sepsis patients based on Severity Sepsis Patients. It consisted of age, sex, APACHE II, and SOFA score. In table 2, the average age of patients with non-survive patients was 56 years; there were more females than males (61,9% vs. 38,1%), the mean APACE II score was 24, and the mean SOFA score was 7. Survive patients had an average age of 49 years; there were more males than females (55,3% vs. 44,7%), an average APACE II score of 17, and SOFA score of 5. The table showed that the average APACHE II and SOFA scores were higher in non-survive patients than for surviving patients.

Table 3 shows the association of comorbidities with the rs7041 locus polymorphism. Based on the table, diabetes mellitus was the highest comorbidity with the most mutations (80,0%). The highest risk of mutant occurred at the rs4588 locus was in comorbid diabetes mellitus, 1,667 times (1,667 95% CI (1,013 – 2,741)). There was no significant association between comorbidities and the rs7041 locus polymorphism with pValue > 0,05.

Table 4 shows the association of comorbidities with the rs4588 locus polymorphism. Based on the table, underweight was the highest comorbidity with the most mutations (66,7%). The highest risk of mutant occurred at the rs4588 locus and was in comorbid underweight 2,139 times (2,139 95% CI (0,899 – 5,086)). There was no significant association between comorbidities and the rs4588 locus polymorphism with pValue > 0,05.

Table 5 shows that obesity was the highest comorbid for non-survival events (64.3%). The risk of death from obesity was 1.841 times (1,841 95% CI (0,365 – 9,278)). There was no significant association between comorbidities and Severity Sepsis Patients with pValue > 0,05.

DISCUSSION

The average age of the non-survivors was 56 years and higher than the survivors, which was 49 years. This age was lower than Rech's study, where the mean of sepsis patients did not survive and survived (69 years vs. 61 years).[13] Old age was a predisposing factor for sepsis caused by comorbidities, prolonged and repeated hospitalizations, decreased immunity, and functional limitations caused by aging. The diagnosis of sepsis in the elderly was difficult because old age gives a less clear response and clinical symptoms of sepsis.[14] Age in sepsis patients affects the patient's body resistance. The higher the age, the greater the risk of death. A deficiency of vitamin D might exacerbate the severity of sepsis.[15]

The female sex experienced a higher incidence of non-survival than the male (61,9% vs. 38,1%). These results align with the Pietropaoli study, where females experienced higher mortality than males (35% vs. 33%). Different results were found in Yoo's study, where the sepsis patients who did not survive were mostly male (79.5%). The cause of females' lower risk of death than males in sepsis is caused by estrogen levels. Elevated estrogen levels may only be a substitute for disease severity because, in critical illness, estradiol concentrations are primarily determined by the adrenal stress response and peripheral aromatase activity. High

estrogen levels throughout a female's life could be associated with lower mortality and morbidity even after menopause.[16]

Females had a lower risk of death than men. One of the influencing factors was the hormone estrogen. However, this study had more females because the research sample was female-dominated.[17,18]

Cytokines play an extensive role in sepsis. Multiple organ dysfunction is caused by a severe inflammatory reaction resulting from systemic cytokine release.[19] The pro-inflammatory reaction is mediated by tumor necrosis factor (TNF-a), interleukin (IL) 1, and IL-6. The body also mounts a direct anti-inflammatory response largely mediated by IL-10. IL 10 is a potent anti-inflammatory cytokine that inhibits the production of other cytokines from activated macrophages and T-helper cells. Increased IL-10 production is an important regulatory mechanism in controlling protective cytokine-producing cells and increases survival in sepsis.[20] A prospective study in Germany showed a significantly better prognosis for females, which may be related to increased anti-inflammatory mediators IL-10.[21] The incidence of non-survival in this study was found more in females, even though Indonesia has a tropical climate. Females in this study dominated Vitamin D deficiency (77.5% vs. 22.5%).

The mean APACHE II score in septic patients was higher in non-survivors than survivors in this study (24 vs. 21), and this result was statistically significant (p = 0.000). These results align with Atalan's 2017 study. The APACE II score at levels of Vitamin D deficiency was higher than non-deficiency. This score is associated with non-survival events in septic patients treated in the intensive care unit. The same results were also found in Choudhry's study, and the APACHE II score was higher in the event of non-survivors compared to survivors with a mortality rate of up to 80,0% with an APACHE II score ≥ 30.[22]

APACHE II score was a predictor of death in sepsis patients. The higher the APACHE II score and the higher the risk of death. The APACHE II score and the number of organ dysfunctions were still important parameters for increased mortality.[22,23]

The mean SOFA score in the study was higher in nonsurvivors than in survivors (7 vs. 5). These results align with Aygencel's study, the mean SOFA score for nonsurvivors compared to survivors (10 vs. 6).[24] An increase in SOFA score of two or more has greater prognostic accuracy for in-hospital mortality.[25]

The SOFA score 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 is not too different.[26]

Diabetes mellitus was the highest comorbidity with the most mutations

Table 1. Characteristics of sepsis patients, based on vitamin D status.

Characteristic	Vitamin D Status	
	Deficient	Non-Deficient
Age (year) (Median ± SD)	52 ± 10,83	50 ± 14,13
Sex		
Male (n (%))	9 (22,5%)	28 (70,0%)
Female (n (%))	31 (77,5%)	12 (30,0%)
APACHE II Score (mean (min-max))	20 (11 – 30)	18 (9 – 33)
SOFA Score (mean (min-max))	7 (1 – 18)	5 (1 – 20)
Body Mass Index		
Underweight (n (%))	3 (7,5%)	0 (0,0%)
Normoweight (n (%))	14 (35,0%)	19 (47,5%)
Obesity (n (%))	23 (57,5%)	21 (52,5%)
Diabetes Mellitus (n (%))	4 (10,0%)	1 (2,5%)
Chronic Kidney Injury (n (%))	5 (12,5%)	3 (7,5%)
Cardiovascular Disease (n (%))	3 (7,5%)	6 (15,0%)
COPD (n (%))	0 (0,0%)	4 (10,0%)

Table 2. Characteristics of sepsis patients based on severity sepsis patients' status.

Characteristics	Severity Sepsis Patients	
	Non-Survive	*Survive*
Age (year) (mean (Min-max))	56 (18-85)	49 (18-73)
Sex		
Male (n (%))	16 (38,1%)	21 (55,3%)
Female (n (%))	26 (61,9%)	17 (44,7%)
APACHE II Score (mean (Min-max))	24 (13 - 33)	17 (9 – 31)
SOFA Score (mean (Min-max))	7 (12 – 18)	5 (1 - 20)

Table 3. Association of comorbidities with rs7041 locus polymorphism.

Characteristics	rs7041 Locus Polymorphism		*P* value	*RR* (95% CI)
	Mutant n (%)	*Wild type* n (%)		
Body Mass Index				
Underweight (≤18,4 kg/m^2)	1 (33,3%)	2 (66,7%)	0,706[a]	0,658 (0,131 - 3,310)
Normoweight (18,5–23,9 kg/m^2)	18 (54,5%)	15 (45,5%)		Reff
Obesity (≥24,0 kg/m^2)	21 (47,7%)	23 (52,3%)		1,432 (0,281 - 7,307)
Diabetes mellitus	4 (80,0%)	1 (20,0%)	0,359[a]	**1,667 (1.013 - 2.741)**
Chronic Kidney Injury	4 (50,0%)	4 (50,0%)	1,000[b]	1,000 (0,482 – 2,076)
Cardiovascular Disease	6 (66,7%)	3 (33,3%)	0,481[b]	1,392 (0,826 - 2,346)
COPD	2 (50,0%)	2 (50,0%)	1,000[b]	1,000 (0,366 - 2,733)

Note: a = chi-square test; b = fisher test; Ref is the reference standard

Table 4. Association of comorbidities with rs4588 locus polymorphism.

Characteristics	Polimorfisme lokus rs4588		*P* value	*RR* (95% CI)
	Mutant n (%)	*Wild type* n (%)		
Body Mass Index				
Underweight (≤ 18,4 kg/m²)	2 (66,7%)	1 (33,3%)	0,245[a]	**2,139 (0,899 - 5,086)**
Normoweight (18,5–23,9 kg/m²)	9 (27,3%)	24 (72,7%)		Reff
Obesity (≥24,0 kg/m²)	15 (34,1%)	29 (65,9%)		0,511 (0,208 - 1,257)
Diabetes mellitus	1 (20,0%)	4 (80,0%)	1,000[a]	0,600 (0,101 – 3,565)
Chronic Kidney Injury	4 (50,0%)	4 (50,0%)	0,427[a]	1,636 (0,753 - 3,554)
Cardiovascular Disease	2 (22,2%)	7 (77,8%)	0,710[a]	0,657 (0,186 - 2,329)
COPD	0 (0,0%)	4 (100,0%)	0,298[a]	N/A

Note : a = fisher test

Table 5. Association of comorbidities with Severity Sepsis Patients.

Characteristics	Severity Sepsis Patients		*P* value	*RR* (95% CI)
	Non-Survive n (%)	*Survive* n (%)		
Body Mass Index				
Underweight (≤18,4 kg/m²)	1 (2,4%)	2 (5,3%)	0,081[a]	0,626 (0,125 - 3,144)
Normoweight (18,5–23,9 kg/m²)	14 (33,3%)	19 (50,0%)		Reff
Obesity (≥24,0 kg/m²)	27 (64,3%)	17 (44,7%)		**1,841 (0,365 - 9,278)**
Diabetes mellitus	4 (9,5%)	1 (2,6%)	0,362[b]	1,579 (0,965 - 2,582)
Chronic Kidney Injury	7 (16,7%)	1 (2,6%)	0,059[b]	1,800 (1,264 – 2,563)
Cardiovascular Disease	6 (14,3%)	3 (7,9%)	0,487[b]	1,315 (0,785 – 2,202)
COPD	1 (2,4%)	3 (7,9%)	0,341[b]	0,463 (0,084 – 2,562)

Note : a = chi square test ; b = fisher test

locus rs7041 (80,0%). The highest risk of mutant occurred at the rs4588 locus was in comorbid diabetes mellitus, 1,667 times. These results align with Fawzy's study (2019), allele A at rs4588 was associated with poor blood sugar control, high serum GC globulin levels and albuminuria so that it would be developed into diabetes mellitus disease.[27] VDBP gene variation strongly influenced vitamin D bioavailability. The mechanism of this relationship was still unclear. Vitamin D3 also plays a role in insulin secretion. In a study by Baier et al. in pre-diabetic patients at Pima Indians, the Gc locus was reported to be associated with noninsulin-dependent diabetes mellitus. The metabolically active form of vitamin D was also involved in the feedback system of insulin regulation.[28] Vitamin D stimulated beta cells directly, and its role in calcium levels in pancreatic beta cells caused an increase in insulin secretion. The hypothesis was that vitamin D increased peripheral glucose uptake and insulin sensitivity. Patients with vitamin D deficiency had lower flow-mediated dilatation (FMD) and their CD 133+ count compared to those with normal serum levels of 25(OHD). Vitamin D deficiency supports progenitor endothelial cell depletion and endothelial dysfunction in type II DM.[29] Vitamin D deficiency was associated with decreased insulin release, insulin resistance and type 2 diabetes. Research showed that 1α, 25-dihydroxy vitamin D3 (1,25(OH)2D3) stimulates pancreatic cells to secrete insulin. The link between vitamin D deficiency and insulin resistance might be developed through inflammation, as vitamin D deficiency was associated with increased inflammatory markers. In addition, genetic polymorphisms of vitamin D-related genes could predispose to impaired glycemic control and type 2 diabetes.[30]

Vitamin D stimulates beta cells directly and, through its role in calcium levels in pancreatic beta cells, causes an increase in insulin secretion. The hypothesis was that vitamin D also increases peripheral glucose uptake and insulin sensitivity. Patients with Vitamin D D deficiency had lower *flow-mediated dilatation* (FMD) and CD 133+ count than those with normal serum 25(OHD) levels. Vitamin D D deficiency contributes to progenitor endothelial cell depletion and endothelial dysfunction in diabetes mellitus type II.[29] A deficiency of Vitamin D was associated with decreased insulin release, insulin resistance, and diabetes type 2 diabetes. Research showed that 1α, 25-dihydroxy vitamin D3 (1,25(OH)2D3) stimulates pancreatic cells to secrete insulin. The link between 25-hydroxyvitamin D deficiency and insulin resistance may develop through inflammation. A deficiency of 25-hydroxyvitamin D is associated with increased inflammatory markers.[30]

Patients with comorbid diabetes mellitus had higher mortality than those without diabetes mellitus (9,5% vs. 2,6%). These results differed from Jiang's study and Wang's meta-analysis, in which diabetes mellitus was not associated with mortality in sepsis patients but with an increased risk of acute kidney failure. However, high blood glucose levels, regardless of diabetes status, were associated with an increased risk of death in hospitals.[31,32] Patients with diabetes mellitus had an increased risk of infection and sepsis, constituting 20,1-22,7% of all sepsis patients.[33] Patients with

diabetes mellitus are susceptible infected, and the infection process will affect blood sugar levels and vice versa. Closely controlling sepsis patients with diabetes mellitus comorbid was needed.[31]

This study showed that obesity was the highest in non survive sepsis patients (64,3%). These results are different from Wheng's study (2022), which found a relationship between body weight and an increased risk of death (non-survival) related to sepsis in underweight, where the risk ratio of underweight is higher than obesity (RR = 1,841 vs. 0,626).[34] Likewise, in Wang's 2017 study, obesity was associated with lower mortality.[35] Obesity had a lower risk of death related to sepsis caused by sepsis. First, sepsis is an acute illness involving a high catabolic state, and excess body fat could be a source of fuel and energy during the disease. Clinically, obesity provided a nutritional reserve essential for survival in septic conditions.[36] Adipocytes store excess calories as triglycerides and release fuel (as fatty acids and glycerol) for use by other organs in times of caloric demand. Second, adipose tissue could regulate immunity by secreting proteins such as leptin and anti-inflammatory adipokines.[37] Obese people had elevated leptin levels in the early stages. Several factors regulated this level; for example, leptin could be increased by acute infection and proinflammatory cytokines. Bornstein et al. found that in cases of acute sepsis, the average plasma leptin level was three times higher in patients who survived compared to non-survivors, where leptin played a role in severe stress conditions such as acute sepsis.[38] Leptin plays a regulatory role in the immune system in sepsis.[39] The level of adiponectin, an anti-inflammatory adipokine, changed during sepsis. Higher adiponectin levels before sepsis, and decreased adiponectin levels after sepsis were associated with survival. In addition, compared to sepsis patients who survived, there were lower adiponectin concentrations in sepsis in the non-surviving group.[40] This study's mortality was caused by obesity because the study sample was dominated by patients with obese BMI (55%). Limitations in this study, comorbid samples in this study were still limited so they may not represent the existing population.

CONCLUSION

Obesity was the highest comorbid for mortality in sepsis patients, but locus rs7041 and rs4588 polymorphisms had no relation with comorbidities.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTION

All authors have contributed to this research process, including conception and design, literature search, clinical studies, data analysis, interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, and collection and assembly of data.

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