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Association between Polymorphism Locus rs7041 and rs4588 in VDBP Gene and Vitamin D Status with Mortality in Sepsis Patient

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Abstract: Vitamin D deficiency was associated with an increased mortality risk in patients with sepsis. Loci rs7041 and rs4588 polymorphisms of the Vitamin D Binding Protein (VDBP) gene receptor caused a significantly increased risk of vitamin D deficiency in subtropical countries (Yordania). Simultaneously, similar studies for the tropics (Indonesia) have not been found yet. This study aims to analyze the association between polymorphism locus rs7041 and rs4588 in the vitamin D binding receptor gene and vitamin D status with the mortality of sepsis patients. This study was an analytical observation type with a cohort design. The relationship between the two groups was analyzed using the chi-square test/fisher test. Mutant's polymorphism locus rs7041 in *not survived* patients is more than *survived* (65.0% vs. 35.0%) with a p-value of 0,025. The mortality risk was 1.625 times (RR 1.625 95% CI 1.044 – 2.529). The mutant's polymorphism locus rs4588 locus in *not survived* patients is more than *survived* (70.3% vs. 29.7%) with a p-value of 0,022. The mortality risk was 1.622 times (RR 1.622 95% CI 1.095 – 2.402). Polymorphism loci rs7041 and rs4588 in *not survived* sepsis patients were higher mutants than the wild type. The highest vitamin D deficiency occurred in the mutant locus rs4588 (55.5%), but it was not statistically significant $p > 0.05$. There was an association between Loci rs7041 and rs4588 polymorphisms and mortality of sepsis patients. No association was between Loci rs7041 and rs4588 polymorphisms with vitamin D status and between vitamin D status and mortality of patients with sepsis.

Keywords: polymorphism, rs7041, rs4588, vitamin D, vitamin D binding protein, mortality, sepsis.

維生素丁結合蛋白基因多態性位點 rs7041 和 rs4588 與維生素丁狀態與膿毒症患者死亡率的關聯

摘要：維生素丁缺乏與膿毒症患者死亡風險增加有關。維生素丁結合蛋白基因受體的位

點 rs7041 和 rs4588 多態性導致亞熱帶國家（約旦尼亞）維生素丁缺乏症的風險顯著增加。同時，尚未發現對熱帶地區（約旦）的類似研究。本研究旨在分析維生素丁結合受體基因多態性位點 rs7041 和 rs4588 以及維生素丁狀態與膿毒症患者死亡率之間的關聯。本研究是採用隊列設計的分析觀察類型。使用卡方檢驗/費歇爾檢驗分析兩組之間的關係。未存活患者中的突變體多態性位點 rs7041 多於存活患者（65.0%對 35.0%），p 值為 0,025。死亡風險是 1.625 倍 (RR 1.625 95% CI 1.044 – 2.529)。未存活患者中突變體的多態性位點 rs4588 位點存活率高於存活率（70.3%對 29.7%），p 值為 0,022。死亡風險為 1.622 倍（RR 1.622 95% CI 1.095 – 2.402）。多態性位點 rs7041 和 rs4588 在未存活的膿毒症患者中比野生型更高突變。最高的維生素丁缺乏發生在突變基因座 rs4588 (55.5%)，但沒有統計學意義 p > 0.05。基因座 rs7041 和 rs4588 多態性與膿毒症患者死亡率之間存在關聯。基因座 rs7041 和 rs4588 多態性與維生素丁狀態之間以及維生素丁狀態與膿毒症患者死亡率之間沒有關聯。

关键词：多态性、rs7041、rs4588、维生素丁、维生素丁结合蛋白、死亡率、败血症。

1. Introduction

Sepsis is a life-threatening organ dysfunction caused by failure to regulate the patient's response to infection, and macro and microvascular dysfunction cause organ dysfunction. Sepsis with a Sequential Organ Failure Assessment (SOFA) score of ≥ 2 increases the risk of death by more than 10%. In Indonesia, the sepsis incidence is 30.29%, with a mortality rate of 11.56 to 49%. In the Intensive Care Unit (ICU) of Dr. M. Djamil Padang General Hospital in 2022, there was an increase in the mortality of sepsis patients from 11.53% to 19.64%.

Vitamin D is a critical mediator in the immune system and plays an inhibitory role in the pathogenesis of sepsis. Vitamin D can regulate acquired and innate immune responses. This vitamin prevents the overexpression of inflammatory cytokines and is a critical mediator in leukocyte aggregation, formation of local inflammation, and anti-bacterial responses in innate immunity. Vitamin D deficiency is associated with an increased risk of initiating and developing viral and bacterial infections. Low serum vitamin D levels on admission to the ICU correlated with an increased incidence of sepsis and risk of death.

Vitamin D can circulate as Vitamin D Binding Protein (VDBP). VDBP is a primary transport protein that, with albumin, binds more than 99% of circulating vitamin D metabolites. Unbound vitamin D is 25-(OH)D. VDBP participates in transporting 25-(OH)D into cells via the megalin/cubilin complex. VDBP has a biological function: binding and transporting all metabolites of vitamin D. Vitamin D converts to 25-(OH)D in the liver. The next process is a change in 25-(OH)D to 1,25-(OH)2D and 24,25-(OH)2D in the kidney.

Gene polymorphism is a variation in the gene structure within a population representing the most basic biodiversity. Gene polymorphisms can show whether the population's life is safe or threatened. The population with low gene polymorphism tends to threaten its long-term life. The genetic material in the form of DNA can apply to uncover gene polymorphisms. DNA is a polymeric molecule consisting of chains of nucleotide monomers.

The most common polymorphisms in the VDBP gene are rs7041 and rs4588, located in exon 11 of domain III of the VDBP gene. The rs7041 and rs4588 genes correlate with serum vitamin D status but also with vitamin D metabolites. Two common functional polymorphisms in the GC gene (rs4588 and rs704) influence plasma levels of Gc protein and its affinity for vitamin D metabolites. The rs7014G/A gene polymorphism of the CYP2R1 gene, rs7041T/G, and rs4588C/A vitamin D binding protein gene carry an increased risk of vitamin D deficiency.

2. Materials and Methods

This study uses a prospective cohort design. Sampling and collection were conducted from July 2022 to September 2022 at the Intensive Care Unit room of RSUP Dr. M. Djamil Padang. The study involved 80 samples that met the inclusion and exclusion criteria. The patient/guardian of the patient has agreed to an alloanamnesis-informed consent.

The inclusion criteria: sepsis patients in the ICU of RSUP Dr. M. Djamil Padang caused by bacteria (not mycobacterium tuberculosis), known levels of Vitamin D, aged 18 to 85 years, procalcitonin value ≥ 2 ng/mL, APACHE II score > 10, SOFA score ≥ 2 and willing to participate in the study. Exclusion criteria were patients previously affected by particular diseases and treated with vitamin D. Each study sample was examined for

vitamin D levels. The study sample consisted of 40 samples with vitamin D deficiency and 40 without. Vitamin D deficiency if the level was 25-(OH)D <20 ng/ml and non-deficient vitamin D if 25-(OH)D level ≥ 20 ng/ml. Vitamin D levels were measured using the Biochem Canada Diagnostic Kit, catalog number CAN-VD-510, LOT 222590, in the Biomedical Laboratory of FK Andalas University. The number of this Research Ethics Review is LB.02.02/5.7/383/2022.

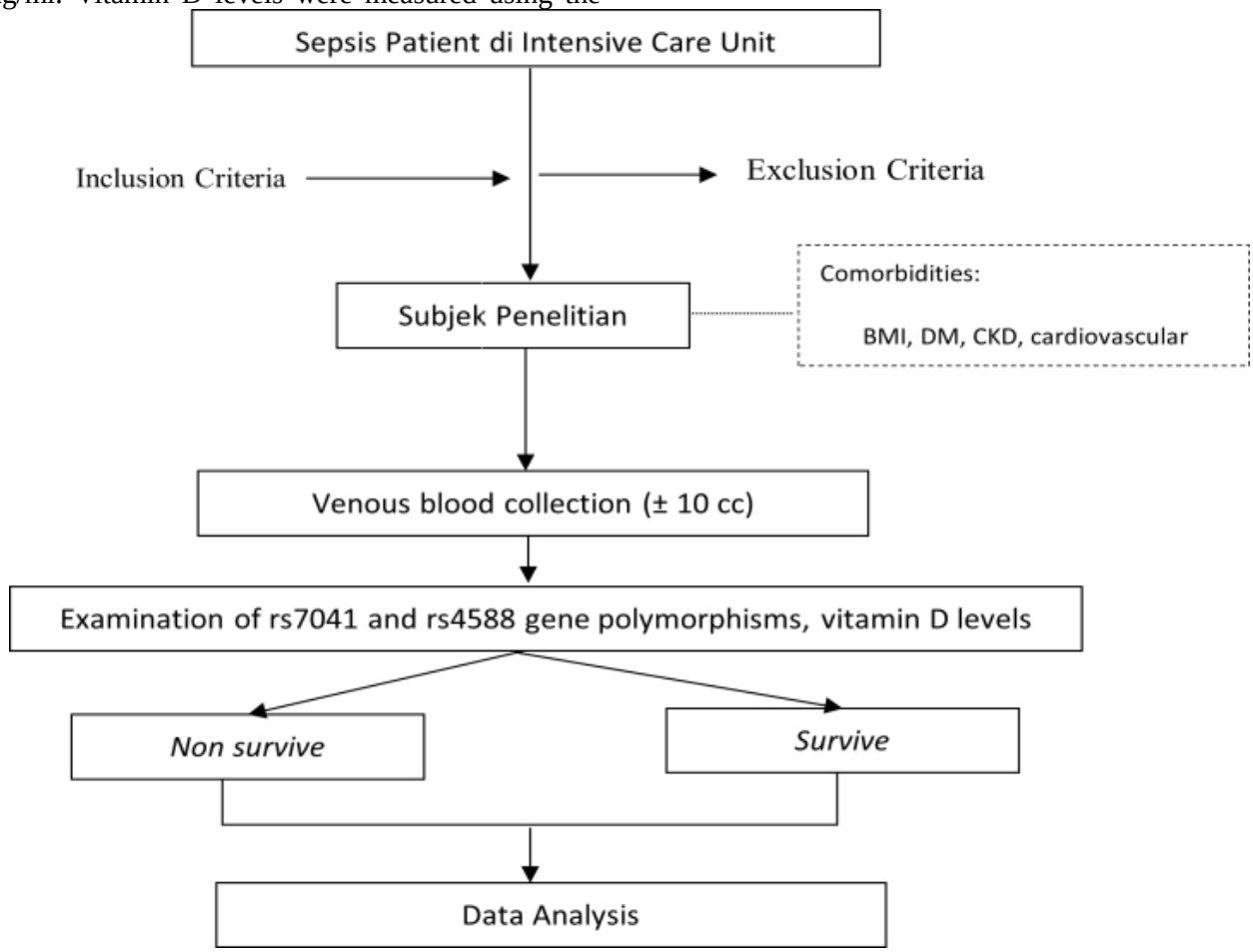

Fig. 1 Flowchart for research methodology (Developed by the authors)

3. Results

Characteristics of study subjects in sepsis patients consisted of age, sex, body mass index (BMI), APACHE II score, SOFA score and comorbidities, such as diabetes mellitus, chronic kidney injury, cardiovascular disease and COPD, as shown in Table 1.

Table 1 Characteristics of sepsis patients

Characteristics	**Sepsis patient mortality**			
	Not survived		**Survived**	
	n (%)	**Median (min – max)**	**n (%)**	**Median (min – max)**
Age (years old)	-	56 (18-85)	-	48.5 (18-73)
Sex				
Male	16 (38.1%)	-	21 (55.3%)	-
Female	26 (61.9%)		17 (44.7%)	
APACHE II Score	-	24 (13-33)	-	17 (9–31)
SOFA score	-	7 (12–18)	-	5 (1-20)
COMORBID				
BMI				
Underweight	1 (2.4%)	-	2 (5.3%)	-
Normoweight	14 (33.3%)		19 (50.0%)	
Obesitas	27 (64.3%)		17 (44.7%)	
Diabetes Mellitus	4 (9.5%)	-	1 (2.6%)	-
Chronic kidney Injury	7 (16.7%)	-	1 (2.6%)	-
Cardiovascular Disease	6 (14.3%)	-	3 (7.9%)	-
COPD	1 (2.4%)	-	3 (7.9%)	-

The polymorphisms in this study were loci rs7041 and rs4588 in the VDBP gene located in exon 11. Table 2 illustrates the relationship between locus rs7041 polymorphisms and mortality in patients with sepsis patients. The table shows a difference in mortality between mutants and wild type (65.0% vs. 40.0%). Statistically was found to be significant $p < 0.05$. The risk of mortality occurring was 1.625 times (RR 1.625 95% CI 1.044 – 2.529). The mutant of the rs7041 locus experienced more non-survival events than survival.

Table 2 Correlation of the polymorphism locus rs7041 with sepsis patient mortality

Variant locus rs7041	Sepsis patient mortality		p Value	RR	(95% CI)
	Not survived n (%)	Survived n (%)			
Mutant	26 (65.0%)	14 (35.0%)	0.025	1.625	1.044 – 2.529
Wild type	16 (40.0%)	24 (60.0%)			
Total	42	38			

Fig. 2 Visualization of the rs7041 locus polymorphism in the survivor group samples (Developed by the authors)

Table 3 describes the rs4588 locus polymorphism with sepsis patient mortality. From the table, it can be seen that there is a difference in mortality between mutants and wild type (70.3% vs. 43.4%).

Statistically was found to be significant $p < 0.05$. The risk of mortality at the rs4588 locus mutant was 1.622 times (RR 1.622 95% CI 1.095 – 2.402).

Table 3 Correlation of the polymorphism locus rs4588 with sepsis patient mortality

Variant locus rs4588	Sepsis patient mortality		p Value	RR	95% CI
	Not survived n (%)	Survived n (%)			
Mutant	19 (70.3%)	8 (29.7%)	0.022	1.622	1.095 – 2.402
Wild type	23 (43.4%)	30 (56.6%)			
Total	42	38			

The polymorphism of the rs4588 locus mutants experienced more non-survival events than survival (70.3% vs. 29.7%).

Fig. 3 Visualization of the SNP rs4588 polymorphism in the non-survival group samples (Developed by the authors)

Table 4 describes the locus polymorphisms rs7041 and rs4588 with sepsis patient mortality. From the table, it can be seen that there is a difference in mortality between mutants 1 locus and 2 loci with wild type and p-Value statistically significant p <0.05. The risk of mortality in the 2 locus mutant was 1.909 times (RR 1.909 95% CI 1.382 – 2.636) and 1.264 times in the 1 locus mutant (RR 0.808 95% CI 0.808 – 1.977). The highest percentage of mortality occurred in the 2 locus mutant compared with the 1 locus mutant (90.0% vs. 57.5%).

Table 4 Correlation of polymorphism loci rs7041 and rs4588 with sepsis patient mortality

Variant locus rs7041, rs4588	**Sepsis patient mortality**		**P Value**	**RR**	**(95% CI)**
	Not survived n (%)	**Survived n (%)**			
Mutant 1 locus	27 (57.4%)	20 (42.6%)	0.002	1.264	0.808 –1.977
Mutant 2 locus	9 (90.0%)	1 (10.0%)		1.909	1.382 –2.636
Wild type	6 (26.1%)	17 (73.9%)		Ref	
Total	42	38			

Table 5 describes the rs7041, and rs4588 locus polymorphisms with vitamin D status. It can be seen that the highest vitamin D deficiency occurred in the rs4588 locus mutant (55.5%) and none had a statistical significance p value > 0.05.

Table 5 Correlation between the polymorphism locus rs7041 and rs4588 with vitamin D status

	Vitamin D status		**p Value**
	Deficiency n (%)	**Non deficiency n (%)**	
Locus rs7041 polymorphism			
Mutant	16 (40.0%)	24 (60.0%)	0.740
Wild type	24 (60.0%)	16 (40.0%)	
Locus rs4588 polymorphism			
Mutant	15 (55.5%)	12 (44.5%)	0.478
Wild type	25 (47.2%)	28 (52.8%)	
Locus rs7041, rs4588 polymorphism			
Mutant	4 (40.0%)	6 (60.0%)	0.499
Wild type	36 (51.4%)	34 (48.6%)	

Table 6 describes the relationship between vitamin D status and mortality in patients with sepsis. Table 6 shows that there is a difference in mortality between vitamin D deficiency and non-deficiency of vitamin D in non-survivors (60.0% vs. 45.5%) but not statistically significant p > 0.05.

Table 6 Correlation between vitamin D status and mortality in sepsis patients

Vitamin D status	**Sepsis patient mortality**		**p value**
	Not survived n (%)	**Survived n (%)**	
Deficiency	24 (60.0%)	16 (40.0%)	0.179
Non-deficiency	18 (45.5%)	22 (55.5%)	
Total	42	38	

In examining the polymorphism of the re7041 and rs455 locus, a substitution mutation was found at the 443rd base position of the VDBP fragment using the 57,942nd base of the full-length data of the VDBP gene on chromosome 4 of Homo sapiens in Indonesia, namely, the G allele. This mutation differs from previous studies in Asian countries (China), namely, the A allele.

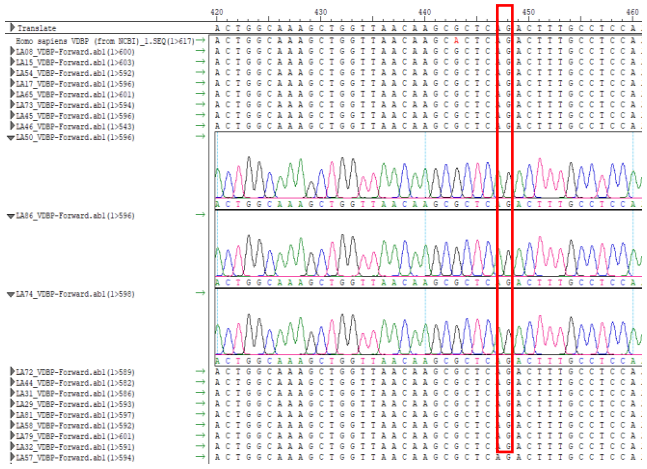

Fig. 4 The 443rd base substitution in the sequence data of non-survival and survival group samples (Developed by the authors)

4. Discussion

The frequency of nucleotide variants at the rs7041 locus was more mutant than the wild type (65.0% vs. 40.0%), and the rs7041 mutant had more non-survivors than survivors (65.0% vs. 35.0%). These results coincide with [1], where the rs7041 locus mutant correlated not only with serum vitamin D levels but also with vitamin D metabolism, thereby increasing the mortality of sepsis patients. Several factors cause high mortality in the mutant locus rs7041 caused by race/ethnicity. In black people, there are more T alleles; in white - more G alleles. The rs7041 locus polymorphism is associated with several diseases,

vitamin D levels, and mortality in patients with sepsis. The high mutant mortality at the rs7041 locus can be a reference in treating sepsis patients [2, 3].

The frequency of the rs4588 locus nucleotide variant was fewer mutants than the wild type (33.8% vs. 66.2%). However, the mortality of sepsis patients at the rs4588 locus mutant was higher than that of the wild type (70.3% vs. 43.4%). The rs4588 locus that survived was more wild type than the mutant (56.6% vs. 29.7%). These results coincide with [4], where the rs4588 locus mutant is associated with low vitamin D levels but not with disease severity. Likewise, the results of [5] showed that the heterozygous rs4588 "CA" genotype was significantly associated with disease susceptibility and risk of mortality [5]. Several studies have linked the rs4588 locus polymorphism to low vitamin D levels but not mortality. The high incidence of mortality in this study was due to several factors, one of which was low vitamin D levels in the rs4588 locus mutant. Patients with the rs4588 locus polymorphism had a large number of vitamin D deficiencies (70.3%) that will impact high mortality [6].

The mortality of sepsis patients in the 1 locus mutant was lower than that of the two-locus mutant (57.4% vs. 90.0%), but this result was higher than the wild type (57.4% vs. 26.1%). The results of the Chi-Square analysis showed a significant relationship $p < 0.05$. The risk of mortality in the 2 locus mutant was 1.909 times (RR 1.909 95% CI 1.382 – 2.636) and 1.264 times in the 1 locus mutant (RR 0.808 95% CI 0.808 – 1.977). The highest percentage of mortality occurred in the 2 locus mutant compared with the 1 locus mutant (90.0% vs. 57.5%). [2] found that the rs7041 and rs4588 locus polymorphisms were associated with decreased vitamin D levels [2]. Currently, no data show the relationship between the number of mutants at the rs7041 and rs4588 loci simultaneously on the mortality of sepsis patients. The rs7041 and rs4588 locus polymorphisms can apply as critical references in treating patients with sepsis. The percentage of mortality due to mutants, both 1 locus and 2 loci, can be used as a reference and predictive of sepsis patient outcomes. DNA repair action can be one of the actions to reduce the mortality rate of patients with sepsis.

The mutant rs7041 polymorphism had the highest vitamin D status in non-deficient compared to deficient (60.0% vs. 40.0%). The results of the Chi-Square analysis show that there is no significant relationship. This result coincides with [7], which showed that 25-(OH)D levels were significantly higher among patients with the primary homozygous rs7041 genotype. This result coincides with [16], where the rs7041 locus polymorphism had a higher average vitamin D level than no mutation (24.1 vs. 17.8). The rs7041 polymorphism with the variant homozygous (TT) allele was associated with low VDBP levels ($p = 0{,}007$). This difference may be due to disease factors affecting VDBP levels [7].

The mutant rs4588 polymorphism on vitamin D status was the highest in deficiency compared with non-deficiency (55.5% vs. 44.5%). The results of the Chi-Square analysis showed that there was no significant relationship. Vitamin D deficiency in the study sample was found only in the rs4588 locus polymorphism. This result coincides with other studies, where the nucleotide variant locus rs4588 is associated with lower levels of vitamin D. A study in Poland showed low levels of vitamin D at the rs4588 locus polymorphism. Different results are from [8], where individuals with the AA genotype (mutant) at the rs4588 locus experienced normal vitamin D levels.

Vitamin D status was the highest in non-deficient compared with deficiency (60.0% vs. 40.0%) at locus mutations rs7041 and rs4588. The results of the Chi-Square analysis showed no significant relationship. These results coincide with [5] and [9], where vitamin D levels in genotypes rs7041 "GG" and rs4588 "CC" was not deficient.

In theory, vitamin D exerts its biological function through binding to VDBP so that nucleotide variations may contribute to vitamin D deficiency and result in disease progression in sepsis patients. Vitamin D circulates in the blood as a protein combined with VDBP encoded by the GC gene and albumin. The expression level of VDBP mRNA decreased along with the serum albumin level, implying that VDBP and albumin deficiency may play a role in vitamin D deficiency [9].

This study did not find a significant relationship between polymorphism and vitamin D status because of, theoretically, another factor for vitamin D deficiency besides polymorphism of albumin levels. The mean albumin in this study sample was 2.6 ± 0.71. Nucleotide variants cause another factor. Combination nucleotide variants (Gc1s, Gc1f, and Gc2) provide different binding affinities for vitamin D metabolites. The highest genotype frequencies of sepsis patients in this study were Gc1f/Gc1s (31.3%) and Gc1f/Gc1f (28.8%), having a higher binding affinity than other genotypes [6].

This study found that the incidence of not surviving was more in vitamin D deficiency than in non-deficiency (60.0% vs. 45.5%). Vitamin D deficiency has a high risk of non-survival compared to survival (60.0% vs. 40.0%. RR = 1.833 95% CI (0.871 – 2.041). These results coincide with [10] that vitamin D levels < 8.1 ng/ml, at the time of admission, have a higher risk of death within 28 days [10]. [11] found that 66.6% of patients who did not survive had a deficiency of 25-(OH)D levels. Serum vitamin D levels <20 ng/mL predicted higher mortality, with a specificity of 62.1%. This study is also in line with the study in which Vitamin D deficiency patients had increased mortality within 30 days after admission to the hospital for sepsis

or sepsis shock [11].

Increased mortality in ICU admissions with vitamin D deficiency is related to the pleiotropic function of vitamin D. Vitamin D inhibits vascular smooth muscle cell proliferation, protects normal endothelial function, and modulates inflammatory processes. This Vitamin D deficiency has potential risks associated with (1) vitamin D-stimulatory effects on innate immunity, (2) suppression of immune regulators, and (3) negative effects on pathways that function to reduce potential inflammatory damage [12].

The research in a meta-analysis study [13] also found a relationship between lower serum 25-(OH)D and higher mortality in sepsis patients, especially in Vitamin D deficiency [13]. This result coincides with [10], where the group of patients with vitamin D deficiency <8.1 ng/ml had a higher risk of death within 28 days (RR: 1.95) [10]. The increased mortality in sepsis patients with vitamin D deficiency may be due to altered glucose and calcium metabolism and/or immune and endothelial cell dysfunction (20). [14] found other results that vitamin D deficiency was not associated with 28- or 90-day mortality but associated with long-term ventilator use and ICU stay.

Factors that influence vitamin D deficiency with the length of stay in sepsis patients are lack of sun exposure, malnutrition, decreased kidney hydroxylation, and increased tissue conversion of 25-(OH)D3 to 1,25-(OH)2D3. Decreased serum vitamin D levels on the first day of hospitalization may be due to reduced serum albumin or vitamin D-binding protein levels or receiving intravenous volumes to correct hypovolemia or hypotension [15]. Vitamin D deficiency will increase the mortality of sepsis patients due to a low immune system and suppression of the immune regulatory system. Patients with vitamin D deficiency with sepsis patients must be treated immediately.

5. Conclusion

An association was between rs7041 and rs4588 loci polymorphisms and mortality of sepsis patients, but there was no association with vitamin D status. This study's implications are expected to concern and manage vitamin D supplementation in sepsis patients who experience polymorphisms of the rs7041 and rs4588 loci and vitamin D deficiency. The strength and novelty of this study are:

1) The discovery of polymorphisms at the rs7041 and rs4588 loci in the vitamin D binding protein receptor gene on the mortality of sepsis patients and the first time conducted in a tropical country (Indonesia).

2) Polymorphism of rs7041 and rs4588 locus in vitamin D binding protein receptor gene in exon 11 with two-locus mutant has higher mortality risk than one locus mutant and wild type.

3) Mortality of rs4588 locus polymorphism is higher than rs7041 locus polymorphism.

4) A substitution mutation was found at the 443rd base position of the VDBP fragment using the 57,942nd base of the full-length data of the VDBP gene on chromosome 4 of Homo sapiens in Indonesia, namely allele G. This mutation is different from previous studies in Asian countries (China), namely allele A.

6. Limitations of the Study

The limitations of this study are that not all DNA chains can be examined because of the extended base chain, and the polymorphism of the rs7041 and rs4588 loci are not only limited to sepsis patients but also involved with other diseases, so further examination is necessary. This study recommends further investigation with longer base chains and other diseases associated with the rs7041 and rs4588 polymorphisms.

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