Serum Procalcitonin Levels in Systemic Lupus Erythematosus: Comparison Across Mild, Moderate, and Severe Disease Activity Stages

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Keywords: Systemic Lupus Erythematous, Procalcitonin, Inflammatory Marker.

Abstract
Introduction: SLE is still a disease with a high morbidity and mortality, where clinical syndrome occur due to immune system dysregulation and are characterized by the formation of antinucleous autoantibodies (ANA), especially anti-doublestranded DNA (antids-DNA) which subsequently form immune complexes and inflammation and tissue damage. Lately there have been many studies on Procalcitonin (PCT) as inflammatory marker.
Aim: to assess differences in serum procalcitonin levels between SLE mild, moderate and severe.
Methods: This is an observational study with cross sectional design in SLE patients at Haji Adam Malik Central Hospital (RSUP HAM) Medan from January 2016 to December 2018. The patients were divided into three degrees based on clinical manifestations: mild, moderate and severe SLE. Use Kruskal wallis to find the difference the procalcitonin level between mild, moderate, and severe. Using SPSS version 22.0, with the value $p < 0.05$ was significant.
Results: 157 SLE patients age > 18 years, SLE without infection 118 (75.2%). Distribution of respondents based on SLE severity Level Mild (34), Moderate (30), Severe (54). Mean and Standard deviation of PCT levels at each degree of SLE in a sequence are mild (0.17 ± 0.34), increasing at a moderate level (0.24 ± 0.19) and the greatest result at a severe degree ($1{,}13 \pm 2.93$). Based on bivariate analysis with Kruskal-Wallis from differences PCT levels between SLE mild, moderate, and severe showed statistical significance ($p = 0.014$).
Conclusion: Based on the increase in PCT levels along with an increase in the severity of SLE non-infectious, statistically there is a significant difference.

Introduction
Systemic Lupus Erythematosus (SLE) is a chronic autoimmune inflammatory disease with a spectrum of varied diseases and involves various organs. This disease is a clinical syndrome that occurs due to dysregulation of the immune system and is characterized by the formation of antinucleous autoantibodies (ANA), especially anti-doublestranded DNA (DNA antids) which subsequently form immune complexes and inflammation and tissue damage.[1] Procalcitonin production stimulated by cytokines proinflammatory factors such as tumor necrosis factor and IL-6, the level of PCT is directly proportional to the severity of inflammation or infection which means that the more severe the disease the higher the PCT level [2]

The diagnosis of SLE can be made based on clinical and laboratory features. ACR (The American College of Rheumbatology) in 1997, proposed 11 criteria for SLE classification, where if 4 criteria were obtained from the 11 criteria that occurred simultaneously or with a grace period, a diagnosis of LES could be established. The diagnostic criteria have a sensitivity of 96% and specificity of 100%. Delays in establishing a diagnosis will affect the success rate of management and survival of patients with SLE. One effort made to minimize the various possible errors in managing SLE is to establish a description of the severity of SLE. The level of severity consists of: Mild, moderate, and severe SLE.[3] Differences in PCT levels in SLE Mild, Moderate, and Severe evaluated from clinical manifestations that have not been done before. Many studies say that an increase in PCT levels is associated with the severity of autoimmune diseases without infection. The limited data on PCT relations with the severity of SLE in Indonesia is the basis of this study.

Methods
This Cross-Sectional study was conducted at the Haji Adam Malik General Hospital (RSUP HAM) in Medan from January 2016 to December 2018 to 157 SLE patients. PCT levels were examined. SLE Non-Infection is divided into mild, moderate and severe degrees based on clinical manifestations according to ACR criteria. Furthermore the serum PCT results are associated with SLE Mild, Moderate and Severe without infection event, by Kruskal Walis analysis.

Tabel 1. Severity of SLE disease [3,4]

Severity of SLE	**Criteria**
Mild	- Clinically calm - There are no life-threatening signs or symptoms - Normal or stable organ function, namely: kidney, lung, heart, gastrointestinal, central nervous system, joints, hematology and skin. Example: SLE with arthritis and skin manifestations
Moderate	- Mild to moderate nephritis (Lupus nephritis class I and II) - Thrombocytopenia (platelets 20-50x103 / mm3)Serositis mayor
Severe / life threatening	- Heart: Libman-Sacks endocarditis, coronary artery vasculitis, myocarditis, cardiac tamponade, malignant hypertension. - Lungs: pulmonary hypertension, pulmonary bleeding, pneumonitis, pulmonary embolism, pulmonary infarction, interstitial ibrosis, shrinking lung. - Gastrointestinal: pancreatitis, mesenteric vasculitis. - Kidney: proliferative and or membranous nephritis. - Skin: severe vasculitis, diffuse rash with ulcer or blister (blister). - Neurology: seizures, acute confusional state, coma, stroke, transverse myelopathy, mononeuritis, polyneuritis, optic neuritis, psychosis, demyelinating syndrome. - Hematology: hemolytic anemia, neutropenia (leukocytes <1,000 / mm3), thrombocytopenia <20,000 / mm3, thrombotic thrombocytopenia purpura, venous or arterial thrombosis.

Results

The study was participated by 157 patients during the period January 2016 to December 2018 in Haji Adam Malik General Hospital (RSUP HAM) ,Medan. The subjects of the study were patients who suffered from Systemic Lupus Erythematous according to the inclusion and exclusion criteria in this study. In this study SLE patients were divided into mild, moderate, and severe degrees and were assessed for serum Procalcitonin levels.

In this study, the average age of respondents was 31.7 ± 10.98, the gender of female respondents was more than 139 people (88.5%) compared to male respondents as many as 18 people (11.5%), Clinical manifestations in SLE patients in general were the 3 most experienced by 157 respondents, 131 people had arthritis (83.4%), malar rash 106 people (67.5%) and hematological disorders 87 people (55.4%), SLE patients with as many as 39 infections (24.8%) and those who did not have 118 infections (75.2%). (Table 2)

Infection status in SLE with mean age and standard deviation is in SLE patients with infection (28.3 ± 7.5), and SLE Non-Infected patients (32.8 ± 11.6), Female gender is more dominant than men men in SLE with Infection were 34 (87.2%) vs 5 (12.8%), SLE Non-Infection 105 (89.0%) vs 13 (11.0%), PCT levels in SLE patients were 1, 69 ± 3.6, while PCT levels in SLE Non-Infected patients are 0.63 ± 2.9. (Table 3)

In Table 4 shows that the age distribution of respondents based on the severity of SLE with age and SB is mild (35.06 ± 12.1), moderate (31.1 ± 8.1) and severe (32.4 ± 2.9). The Mean ± SD PCT levels at each of SLE in sequence were mild (0.17 ± 0.34), increased at a moderate level (0.24 ± 0.19) and the greatest result was at a severe level

(1 , 13 ± 2.93). Data analysis based on the Kruskal Wallis test between the mean PCT levels and degrees of SLE showed a statistically significant result (p = 0.014). (Table 5)

Tabel 2. Characteristics patients with SLE in RSUP HAM

Variabel	n : 157 (%)
Age (years) mean ± SD	31,7 ± 10,98
Minimum	15
Maximum	76
Range	61
Gender, n (%)	

Male	18 (11,5)
Female	139 (88,5)
Clinic Manifestation, n(%)	
Malar Rash	106 (67,5)
Discoid Rash	37(23,6)
Foto Sensitivitas	75(47,8)
Oral ulcer	39(24,8)
Arthritis	131 (83,4)
Serositis	38(24,2)
Renal	41 (26,1)
Neurologic	14 (8,9)
Hematologic	87 (55,4)
Immunologic	81 (51,6)
Max-Sledai Score (mean±SD)	7,9 4,84
Severity of SLE, n(%)	
Mild	41 (26,1)
Moderate	36 (22,9)
Severe	80 (51,0)
Activity of SLE, n(%)	
Flare	98 (62,4)
Non Flare	59 (37,6)
Infection Status, n(%)	
Infection	39 (24,8)
Non Infection	118 (75,2)
Anti- ds DNA (mean±SD)	484,4 ± 467,9
ANA – test (mean±SD)	101,4± 75
Procalcitonin Level (mean±SD)	
Infection	1,69 ± 3,6
Non Infection	0,63 ± 2,9

Tabel 3. Characteristics of Sle with infection and SLE Non-Infection patients in RSUP HAM

Variabel	SLE with Infection (n = 39)	SLE Non – Infection (n = 118)
Age (years) mean ± SD	28,3 ± 7,5	32,8± 11,6
Minimum	18	18
Maximum	44	76
Gender n(%)		
Male	5 (12,8)	13(11,0)
Female	34 (87,2)	105 (89,0)
Activity of SLE n(%)		
Flare	30 (76,9)	68 (57,6)
Non – Flare	9 (23,1)	50 (42,4)
Kadar PCT (mean±SD)	1,69 ± 3,6	0,63 ± 2,9

Tabel 4. Characteristics of Non-Infection SLE patients in RSUP HAM

Variabel	Mild (n = 34)	Moderate (n = 30)	Severe (((n = 54)
Age (year)	35,06 ± 12,1	31,1 ± 8,1	32,4 ± 2,9
Gender, n(%)			
Male	10(29,4)	3(10)	0(0)
Female	24(70,6)	27(90)	54(100)
Procalcitonin (mean±SD)	0,17 ± 0,34	0,24 ± 0,19	1,13 ± 4,29

Tabel 5. Difference procalcitonin level between SLE Mild, Moderate, and Severe, without infection

Variabel	Mild (n = 34)	Moderate (n = 30)	Severe (n = 54)	*P*
Procalcitonin				0,014*

Mean ± SD	0,17 ± 0,34	0,24 ± 0,19	1,13 ± 4,29

*P < 0,05

Discussion

In this study it was found that the prevalence of most SLE patients was women and many in productive age, according to the pathophysiology of the hormone estrogen and prolactin causing the autoimmune phenotype with increased maturity of high affinity B autoreactive cells. Where B cells and T cells combine to produce autoantibodies that play an important role in the inflammatory process in SLE patients[5]

This study shows that the most common clinical manifestation in SLE patients is arthritis, which is stated in a study in Grossman (2009) found anti-histone antibodies associated with arthritis in SLE patients. Anti-histone antibodies are one type of antibody found in many cell nuclei [1]

In this study we found data that SLE patients with infection were 48 (30.6%), infection caused morbidity and mortality in SLE patients due to immune system defects with decreased CD4 + T lymphocytes, deficiency of component system complement, neutropenia and leukopenia [5,6,7,8]

The limitation of this study is to use a minimal amount, due to the limited number of SLE patients who have PCT examinations. Using a retrospective study design, so that the data we obtained was based on the data contained in the patient's medical record, because PCT examination was used only in patients with sepsis causing PCT data in SLE patients to be difficult to obtain.

Procalcitonin expression occurs specifically on tissues. In the absence of infection, the CALC-1 gene transcription for PCT in non-neuroendocrine tissue is suppressed, except in C cells of the thyroid gland where its expression produces PCT, a precursor of CT in healthy and uninfected people. The synthesized PCT then undergoes post-translation processing to produce small peptides and mature CT, which are produced as a result of the transfer of C-terminal glycine from CT which is immature by peptidylglycine a-amidating monooxygenase (PAM). Adult CT is stored in the granules and secreted into the blood [9,10,11]

Conclusion

There was a significant difference between serum PCT levels in SLE mild, moderate, and severe, without infection (p <0.014).

Suggestion

It is recommended to continue the study with a prospective cohort study to obtain evidence of correlation PCT in autoimmune disease ,especially in SLE patient.

Acknowledgements

This study was funded by Haji Adam Malik Hospital (RSUP HAM) Medan.

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