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THE LEVELS OF FERRITIN SERUM AS A BIOMARKER TO DISTINGUISH BETWEEN ACTIVE AND INACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Introduction: The Characteristic recurrence of SLE (Systemic Lupus Erythematosus) patients cannot be predicted. Lack of a reliable parameter that can predict an active clinical phase precludes the way to explore effective preventive strategies for disease relapse, while clinicians should balance the toxicity effect of prolonged use of immunosuppressive therapy.

Aim: Knowing the function of serum ferritin as a biomarker to distinguish between active and inactive SLE

Methods: Cross-sectional research was conducted at the hospital general of Haji Adam Malik Medan from August to September 2019 in 65 SLE patients. Patients conducted a serum ferritin test and in value by using the Mex-Sledai score. Data analysis using the Mann-Whitney test in SPSS 20th.

Result: Median (Min-max) serum ferritin levels of active SLE group 1519 (18.6-2218) ng/mL while inactive SLE Group is 250 (10.5-2000) ng/mL. There are significant differences in serum ferritin levels between active and inactive SLE groups (p = 0,004). ROC curve plot on was found the value of the serum ferritin cutoff can be used to diagnose active SLE. Cutoff value for ferritin levels is (486.0 ng/mL) with a sensitivity value (100.0%) and specificity (90.5%).

Conclusion: Serum ferritin levels can be used as a biomarker to distinguish active and inactive SLE.

Introduction

The systemic lupus erythematosus (SLE) is a complex and systemic autoimmune disease that has characteristic recurrence that can not be predicted in the remission and active phase. The Lupus Foundation of America estimates approximately 1,5 million cases occur in America and at least 5 million cases occur in the world. Every year in the estimate happened about 16 thousand new cases of SLE.[1] The active phase of SLE can occur without any observation or a slight alteration of the conventional resultant biomarkers that settle persistently at an abnormal level and may not relate to the apparent clinical symptoms of SLE disease activity. Therefore, the novel biomarkers for SLE disease activity should be developed.[2]

Serum Ferritin is an acute-phase protein that increases inflammation, autoimmune diseases, and liver disease. Increased serum ferritin in autoimmune diseases.[2] Lim et al found that changes in the SLEDAI score before and after receiving treatment are significantly related to serum ferritin levels. E Beyan et al reported that in patients SLE serum ferritin can be a useful marker to measure the activity of the disease in patients SLE.[3] A significant association between the serum ferritin and the activities of SLE disease and its pathogenicity in observation to know its role as an important biomarker of disease activity. It is important to obtain a good biomarker and can be relied on to predict the severity of the disease. This research was conducted to investigate the association of ferritin serum with the MEX-SLEDAI score.[2]

Method

This research was using cross-sectional design, undergone in RSUP H. Adam Malik Medan between July-October 2019. Samples were taken consecutively in patients who met the criteria for signing informed consent. The inclusion criteria of this research were active and inactive SLE patients, receiving information, and participation

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approval to undergo this whole research, also matches the exclusion criteria were stress massif (severe trauma, surgery, cardiac shock, burns), patients with other autoimmune diseases, patients with hematological malignancy, severe hepatic cirrhosis (Child-Pugh C), acute renal failure, recurrent transfusion history and patient uncooperative.

Formulae was using analytical numerical formula unpaired two groups, with a confidence rate of 95%, then it takes a total sample number were 65 people. The MEX-SLEDAI has a score range from 0 to 32, lupus is active if MEX-SLEDAI scores >5, and inactive phase if MEX-SLEDAI score ≤ 5. The samples were processed using statistical software 20th.

Result

This research following with 65 people SLE patients over 18 years old who came to RSUP H. Adam Malik Medan.

Table 1. A correlation characteristics respondent between active and inactive SLE groups

VARIABLE	N (%)	SLE GROUPS		*p-value*
		Active SLE (n=23)	Inactive SLE (n=42)	
Age (mean ± SD) years	-	30 ± 8,9	30 ± 8,3	0,954
Sex				0,041*
Male	3 (4,6)	3 (13,0)	0 (0)	
Female	62 (95,4)	20 (87,0)	42 (100,0)	
Ethnic				0,249
Javanese	19 (29,2)	6 (26,1)	13 (31,0)	
Bataknese	31 (47,7)	9 (39,1)	22 (52,4)	
Acehnese	15 (23,1)	8 (34,8)	7 (16,7)	
Occupation				0,984
Student	32 (49,2)	11 (47,8)	21 (50,0)	
Household	14 (21,5)	5 (21,7)	9 (21,4)	
Entrepreneur	19 (29,2)	7 (30,4)	12 (28,6)	
Laboraty Findings				
Hb (g/dL)	10,6 ± 2,1	8,9 ± 2,1	11,4 ± 1,5	0,000*
WBC (/µL)	7847,1 ± 2,2	6850,4 ± 2,3	8392,9 ± 1,9	0,007*
Trombosit (10^3/µL)	277,0 ± 77,4	258,5 ± 71,36	290,2 ± 68,9	0,064
Ureum (mg/dL)	26,3 ± 9,6	27,4 ± 10,5	25,7 ± 9,2	0,675
Creatinine (mg/dL)	0,7 ± 0,2	0,8 ± 0,2	0,7 ± 0,2	0,275
ANA	100,5 ± 69,7	119,5 ± 72,7	90,1 ± 66,6	0,115
Anti DsDNA	367,9 ± 492,0	625,1 ± 712,9	227,0 ± 218,4	0,008*

Note : *p <0,05, SD*:* Standard Deviation; Hb: Haemoglobin; WBC: White Blood Cell; ANA: Antinuclear Antibodies; Anti dsDNA: Anti double stranded Deoxyribo Nucleic Acid

Characteristics respondent based on table 1. the average age of respondents was (30.4 ± 8.5) years with the most common were female (95.4%). The majority of respondents were Bataknese (47.7%), occupation were a student (49.2%). The most respondents was an inactive SLE (62.4%), which is the average value of the MEX-SLEDAI score (5.4 ± 3.6) and median 4 (2-12). Based on laboratory finding, respondents had an average of Hb (10.6 ± 2.1) g/dL, WBC (7847.1 ± 2.2)/mL, platelets (277.0 ± 77.4) 103/mL Ureum (26.3 ± 9.6) mg/dL, creatinine (0.7 ± 0.2) mg/dL, ANA (100.5 ± 69.7), anti dsDNA (367.9 ± 492.0) and ferritin serum (662.5 ± 721.2) ng/mL. There were found significant correlation such as gender (p=0,041), the average of Hb [10.09 ± 1.281 vs. 9.53 ± 1.047; (p=0.000)] and also WBC [6850.4 ± 2.3 vs. 8392.9 ± 1.9, (p=0.007)] in active SLE respondents were lower than SLE inactive groups while the average of anti dsDNA value in the active SLE group was higher than the inactive SLE [(625.1 ± 712.9 vs. 227.0 ± 218.4; (p=0.008)].

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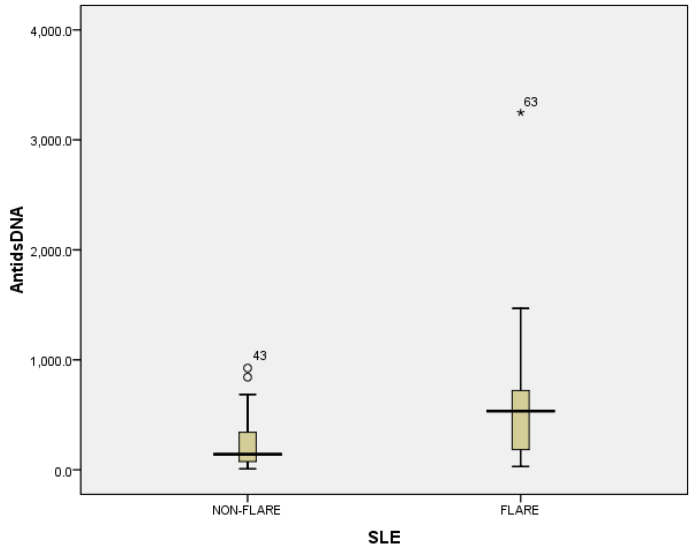

Figure 1. Correlation Anti DsDNA levels between active and inactive SLE group

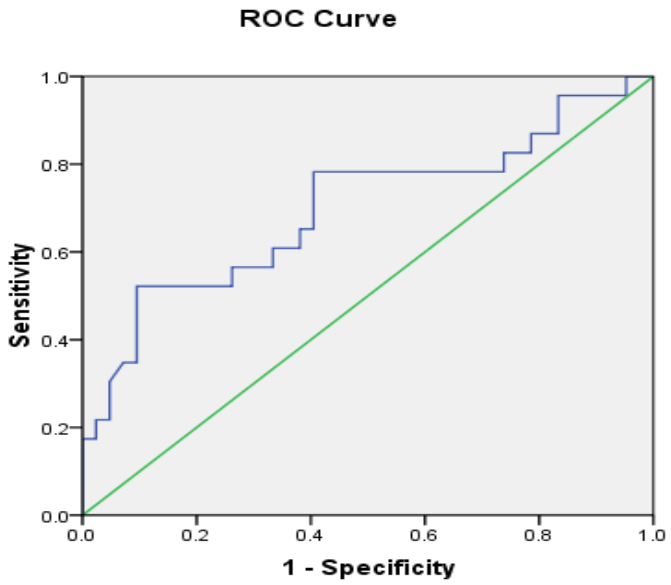

Figure 2. ROC curve of Anti dsDNA levels in active SLE group

Based on the ROC (Receiver Operating Characteristic) curve plot of figure 2. a cutoff value of anti dsDNA (177.5) is obtained to diagnose active SLE with a sensitivity (78.3%) and specificity (59.5%).

Table 2. A correlation value of Hb, WBC, platelets, Ureum, creatinine, and ANA toward anti dsDNA in respondents with SLE

VARIABLE	Anti dsDNA	
	p	*r*
Hb (g/dL)	0,000*	-0,474
WBC (/µL)	0,154	-0,179
Trombosit (10^3/µL)	0,896	0,017
Ureum (mg/dL)	0,187	0,166
Creatinine (mg/dL)	0,014*	0,304
ANA	0,000*	0,442
Ferritin (ng/mL)	0,023*	0,281

Note: *p <0,05

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Based on table 2. There was found significant relationship with moderate correlation of Hb value (p = 0.000, r=0.474), a low correlation of the creatinine value (p=0.014, r=0.304), medium correlation of ANA value (p=0.000, r=0.442) and low correlation of ferritin serum (p=0.023, r=0.281) statistically toward the value of Anti dsDNA in SLE respondents.

Table 3. Ferritin Serum levels in an active and inactive SLE group

Ferritin Serum	SLE Active (n=21)	SLE Inactive (n=44)	*p-value*
Ferritin (ng/mL), n (%)			0,000*
<500	0 (0)	38 (90,5)	
≥500	23 (100,0)	4 (9,5)	
Mean ± SD	1.477,0 ± 592,1	216,5 ± 218,7	0,000*
Median (Min-Max)	1775,0 (522,0 - 2.218,0)	150,5 (10,5 – 937,0)	

Note: *p <0,05

In table 3. shows a significant relationship between the ferritin serum levels (p=0.000) toward active and inactive SLE groups, where the value of ferritin serum inactive SLE group majority has a value <500 (90.5%), whereas the active SLE group has all a value of ferritin serum >50 (100.0%) that shows a statistically significant result (p=0.000).

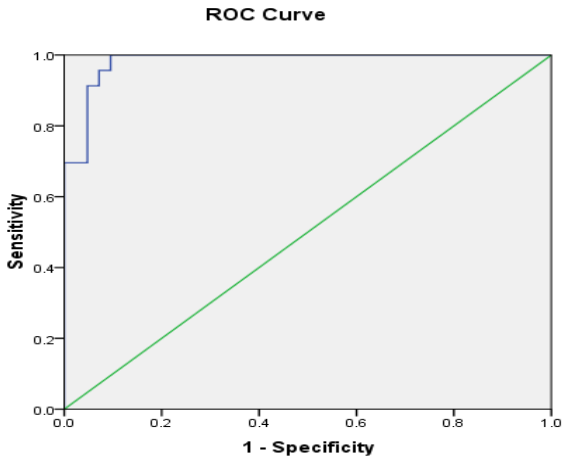

Figure 3. ROC curve of ferritin serum levels in active SLE group.

Based on figure 3. ROC curve plot on was found cutoff value of ferritin serum that can be used to diagnose active SLE. Cutoff value for ferritin levels is (486.0 ng/mL) with a sensitivity (100.0%) and specificity (90.5%).

Discussion

In general, SLE is more attacking females than males with a ratio of 12:1.[4] These results are also supporting by previous studies that SLE most common found in female including the study of Ho et al[5] in Taiwan (87.7%), Bador et al[6] in Malaysia (84%), Yu et al[7] in China (82,5%).

Cytopenia including anemia, thrombocytopenia, lymphopenia, leukopenia, often occurs in patients with SLE. Anemia in patients with SLE varies widely between chronic disease anemia, hemolytic anemia, blood loss, renal insufficiency, infections and myelodysplasia, and aplastic anemia. The often occurrence of anemia in SLE due to erythropoiesis suppression due to chronic inflammation. There may be anemia due to autoimmune or not, anemia obtained in the form of chronic disease anemia, iron deficiency, and autoimmune hemolytic anemia. A positive Comb test on 10% of SLE patients is significant hemolysis. Erythrocyte antibodies in patients usually type "warm" IgG antibodies.[8]

Leukopenia reported approximately 50% of cases of lupus sufferers with increased disease activity, being lymphocytopenia occurs approximately 20% of cases. In SLE patients with leukopenia usually, bone marrow production is generally normal, so there is neutropenia in patients with SLE active due to the use of immunosuppressive or the presence of autoantibodies that inhibit the colonization granulocyte Forming Unit in the bone marrow.[9]

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Based on table 1. the value of anti dsDNA between active SLE patients is higher than inactive SLE respondents. Based on table 2. it can be explained that there is a significant relationship with a moderate correlation between the value of Hb, low-correlation of creatinine, moderate correlated ANA, and low correlation of ferritin serum value toward anti dsDNA in respondents with SLE. Anti dsDNA antibodies are specific antibodies for SLE, commonly associated with glomerulonephritis. The involvement of anti-dsDNA antibodies to lupus nephritis is supported by the presence of evidence: 1. Clinical observation in most patients showed that active nephritis was associated with the increase of the anti-dsDNA title and decreased total value of hemolytic complement, 2. Anti dsDNA antibodies prefer to settle in the kidneys, so it is suspected that the immune complex DNA antibody anti dsDNA is a major inflammatory mediator. Anti dsDNA antibodies bind to the DNA part of the basal glomerular membrane through Histon or interact with other glomerular antigens such as C1q, nuclei, heparan sulfate, and laminin. Bonding anti dsDNA antibodies with antigens will initiate local inflammation and activation of the complement so that the immune complex forms in the kidneys.[10]

In table 2., there was found a significant relationship between Hb value, creatinine value, ANA value, ferritin serum value toward anti dsDNA value in SLE respondents. Based on the ROC curve plot on figure 2., a cutoff value of Anti dsDNA is obtained to diagnose active SLE. This research found that cutoff value for anti dsDNA is (177.5) with a sensitivity (78.3%) and specificity (59.5%). The measurement of anti dsDNA antibodies can be beneficial in monitoring the activity of the disease and can be found to increase 10 weeks or more before relapse (Flare).[11] Research conducted in Medan RSUP Haji Adam Malik (2016) expressed the increasing of anti dsDNA was not related to clinical manifestations, but associated with hematological disorders, increased renal function and proteinuria in SLE.[12] In the condition of the clinic, there is a positive anti dsDNA to support SLE diagnosis, while the negative anti dsDNA does not exclude the existence of SLE.[13]

In table 3. showed that an average value, standard deviation (SD), median, minimum and maximum value of serum ferritin in an active, and inactive SLE group statistically significant toward SLE status ($p = 0.000$). This results following other studies that reported higher levels of ferritin serum in an active SLE group compared to inactive SLE, Tripathy et al[14] ($p = 0.001$), Beyan et al[15] ($p < 0.001$), Vanarsa et al[16] ($p = 0.0013$) and, Lim et al[2] ($P < 0.01$).
Based on the ROC curve plot in figure 3. Shows the value of ferritin cutoff can be used to diagnose active SLE. This research was found cutoff value for ferritin levels is (486.0 ng/mL) with a sensitivity (100.0%) and specificity (90.5%). It is also almost similar to the research done in Athens, the Greek researched patients with classical fever symptoms is not clear the cause to know whether the cause of infection or inflammation was concluded that patients with symptoms of classical fever with a value of ferritin serum <500 µg/l in independent are associated with infection and in patients with classical fever with a ferritin serum >500 µg/L associated with inflammation.[17] There are different research results conducted by Orbach et al was not found a significant relationship between serum levels of ferritin in an active SLE and inactive SLE groups ($p=0.13$). The differences in the results of the research conducted by Orbach et al may be caused by limitations in the number of fewer patient samples amounting to 23 people so that the possibility of bias can occur.[18]

SLE has the characteristic of recurrence that cannot be predicted to be remission or active phase. The lack of a reliable parameter that can predict an active clinical phase precludes the way to explore effective preventive strategies for disease relapse, while clinicians should balance the toxicity effect of long-term use of immunosuppressive therapy.[19] Although the prognosis of SLE has increased significantly it is necessary to find biomarkers to monitor the activity of SLE disease.[3] Conventional serological markers such as anti-dsDNA and complement level are not ideal because they are not sensitive specific enough to monitor the activity of the disease. The active phase of the SLE can occur without any observation or a slight alteration of the marker that settle persistently in the abnormal level and may not relate to the apparent clinical symptoms of SLE disease activity.[2]
Ferritin is an acute-phase protein that is increased in autoimmune diseases. Increased serum ferritin among autoimmune diseases including SLE.[17] Ferritin has a regulatory effect on the immune system and plays a specific role in SLE. Ferritin synthesis induced by interleukin I (IL-I), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α), then the ferritin synthesized in reticuloendothelial tissue such as liver hepatocytes cells. Ferritin was produced in all the reticuloendothelial tissues, so if the condition of the body with high ferritin values, it can be found in the pleural fluid or urine of patients.[3]

The limitations of this study were the number of samples amounting to 65 people between active and inactive SLE groups so that the possibility of bias can occur in this research.

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Conclusion

Based on the results and discussion of this study, it can be concluded that ferritin serum levels can be additional biomarker than can be used to distinguish of active and inactive SLE.

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