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Research Article

Increase in Serum Ferritin Level as a Marker of Disease Activity in Pediatric Systemic Lupus Erythematosus (pSLE) Patients

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ABSTRACT

Ferritin is an acute-phase reactant that is elevated in autoimmune disorders, including systemic lupus erythematosus (SLE). However, their correlation with disease activity scores has not been confirmed. Pandemic Covid-19 makes children visitation to hospital to get the treatment of SLE were delayed. This study aimed to evaluate correlation between serum ferritin and disease activity and its role in screening for flare in pediatric SLE (pSLE) patients during pandemic Covid-19. This is a cross-sectional study conducted in Saiful Anwar General Hospital Malang. Sampling was carried out sequentially on pediatric patients who met the criteria for Systemic Lupus International Collaborating Clinics (SLICC) and were recorded between July 2021-May 2022. All patients were interviewed and assessed for disease activity using SLE Disease Activity Index 2000 (SLEDAI-2k). A score <4 was categorized as inactive disease. Biochemical, serological tests including markers of disease activity and ferritin level were measured by standard laboratory procedure. Comparison, correlation and ROC curve analyses were performed with SPSS software. There were 38 females pSLE participated in this study. The mean age of the patients were 12.6 ± 3.02 years. Serum ferritin significantly higher in active disease compared to inactive disease 84.50 ng/mL (68.00-151.75 ng/mL) ng/mL and 815.00 ng/mL (451.25-1570.00 ng/mL), a value of $p<0.05$ was determined to be statistically significant. A significant correlation was found between serum ferritin with SLEDAI 2K ($r = 0.890$, $p = 0.000$). Correlation was also found between serum ferritin and IgM anti-double stranded-DNA ($r = 0.325$, $p = 0.046$), but not with other laboratory and serological parameters. In ROC curve analysis, we found that Area Under The Curve (AUC) 0.989, 95%CI 0.964-1.014, p value 0,000, with cut off value 297.50 with sensitivity 85% and specificity 94.4%. Ferritin was increased in active disease as compared to inactive disease and correlated with SLEDAI score and IgM-dsDNA. Thus, ferritin may be potential as an affordable and available marker of disease activity in pSLE during pandemic Covid-19.

Keywords: Ferritin, Pandemic, pSLE, SLEDAI

Introduction

Systemic lupus erythematosus (SLE) is commonly known as “the disease of a thousand faces” because of the diversity of its symptoms. Symptoms can range from mild to severe, nonspecific, and mimic those of other diseases [1]. The incidence of SLE reaches 10–20 cases per 100,000 children and is generally more common in girls over the age of 10 years [2]. Systemic Lupus Erythematosus (SLE) is an autoimmune disease that causes systemic inflammation in various organ systems that are chronic and episodic. The rate of relapse and flare in SLE patients is 27-66%. Until

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now, for monitoring SLE activity, many researchers use the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score. The scoring system using SLEDAI has a sensitivity of 38% with a specificity of 81% [3]. In addition, in children, there is a severe complication of SLE, namely macrophage activation syndrome (MAS). The hallmark of this syndrome is excessive activation and proliferation of T lymphocytes and macrophages with massive hypersecretion of proinflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-α, and Tumor Necrosis Factor -alpha (TNFα). MAS may occur spontaneously as a complication of the underlying active disease (i.e. in Juvenile idiopathic arthritis and SLE), or may be precipitated by infection or a change in therapy [4]. However, the diagnosis of MAS in patients with active SLE may be difficult because the clinical features are almost the same. COVID-19 pandemic has made a huge impact in patients with other diseases. One of them are SLE sufferers who have difficulty in getting access to professional health care and availability of medicines, missed the doses of medicines, adherence, and fear of COVID-19 during the pandemic [5].

Ferritin is an acute phase reactant produced by liver cells whose levels increase in acute and chronic inflammation, for example, in autoimmune diseases, acute infections, cancer and other diseases [6]. Although ferritin is not sensitive to SLE, it can be considered that the SLEDAI assessment was the least expensive because it has excellent responsiveness in predicting disease damage and the number of variables evaluated [7]. Besides ferritin can detect severe SLE complications in the form of MAS so that it can start appropriate treatment quickly and prevent morbidity and mortality [8].

Material and Methods

Study Design

This is a cross-sectional study conducted at Allergy-Immunology Division, Pediatric Department, Saiful Anwar General Hospital Malang. Consecutive children who met the Systemic Lupus International Collaborating Clinics (SLICC) criteria were enrolled between July 2021 to May 2022. The ethics committee of the Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia, approved this study (No. 208/EC/KEPK/07/2021).

Clinical assessment

The collection of disease activity data for pediatric patients recorded using SLEDAI 2K was carried out at each visit. A score <4 was categorized as inactive disease. All patients have given written informed consent.

Measurement of ferritin using ELISA

Serum ferritin examination was performed using an enzyme-linked immunosorbent assay (ELISA). Blood samples were taken from the arm veins. Serum samples were diluted with a concentration of 1:20. The A450 nm was measured via a microplate reading. The normal value of ferritin in the blood varies between 23-336 ng/mL in boys and 11-306 ng/mL in girls [9].

Statistical analysis

The correlation between serum ferritin level and disease activity index in pediatric SLE patients was analyzed using the Statistical Product and Service Solution (SPSS) software version 25 with $p < 0.05$, indicating a significant difference.

Results and Discussion

Thirty-eight (all female) consecutive SLE patients with a mean age of 14 (11.5-15 years old) in SLE inactive and 12.50 (11-15 years old) in active SLE group. Demographic features and the frequency of hematologic parameters with SLEDAI score were shown at Table 1. Eighteen patients has inactive SLE and twenty patient has active SLE (The average score of SLEDAI is 8 (6-16.25).

Table 2 shows the correlation of serum ferritin with SLEDAI score and other variables. Serum ferritin correlated significantly with BMI, SLEDAI and IgM-dsDNA. A significant correlation was found between serum ferritin with SLEDAI 2K ($r = 0.890$, $p = 0.000$). A correlation was also found between serum ferritin and IgM anti-double stranded-DNA ($r = 0.325$, $p = 0.046$), but not with other laboratory and serological parameters. In ROC curve analysis, we found AUC 0.989, 95%CI 0.964-1.014 , p value 0,000, with a cut-off value 297.50 with sensitivity 85% and specificity 94.4% (Figure 1).

A correlation was found between serum ferritin and SLEDAI in Table 1. The study of SLE in children also found that ferritin levels in childhood SLE (cSLE) patients were significantly higher

Table 1. Characteristic of Subjects

Variables	SLE inactive (n=18)	SLE active (n=20)	p value
Sex, n (%)			
Female	18/18	20/20	
Age	14 (11.5-15)	12.50 (11-15)	0.461[a]
Weight	43.86±12.78	34.57±14.28	0.038[b]*
Height	1.48(1.37-1.51)	1.44 (1.29-1.52)	0.578[a]
BMI	21.08(17.87-23.46)	15.99(13.93-18.79)	0.006[a]*
Laboratory parameter			
Hb	9.56±2.89	9.31±3.23	0.639[b]
Leucocyte	3850(3150-5655)	5520 (3647-7900)	0.132[a]
Thrombocyte			0.148[a]
ANA	4.00(3.00-5.47)	5.00(3.51-9.42)	0.252[a]
IgM dsDNA	50.85(45.00-106.25)	83.50(15.75-189.55)	0.539[a]
IgG dsDNA	110.00(48.75-151.50)	123.20(37.85-200.00)	0.965[a]
Ferritin	84.50(68.00-151.75)	815.00(451.25-1570.00)	0.000[a]
SLEDAI score	0	8(6-16.25)	

*p < 0.05 was statistically significant, [a]Mann Whitney Test, [b]Independet T test

than in patients with SLE [10]. Healthy as controls with a mean of 416.1 ± 1022.9 ng/ml vs 36.1 ± 18.2 ng/ml, p < 0.001. Serum ferritin was also found to be significantly higher in active cSLE patients (SLEDAI >=4) compared with inactive were 890.4 ± 1474.8 ng/ml and 77.4 ± 74.1 ng/ml, respectively [11]. Another study by Almutairi *et al.* [4] also found serum ferritin was significantly higher in patients with active cSLE (676.5 (±2060) ng/ml) compared to inactive (52.9 (±49) ng/ml). This study also showed a significant correlation between serum ferritin and lupus disease activity as assessed by SLEDAI, r = 0.66, p < 0.001. However, serum ferritin was negatively correlated with fibrinogen (p=0.02), indicating that the relationship between the two was strong [4]. The study by Soliman *et al.*. [10] also found that serum ferritin was higher in patients with active cSLE compared with inactive (110.8 ± 25.5) compared with inactive (18.3 ± 3.9 ng/ml). This study also found a significant correlation between serum ferritin and lupus disease activity as assessed by SLEDAI, P 0.001) [10].

In this research, we found that AUC 0.989, 95%CI 0.964-1.014, p value 0,000, with cut off value 297.50 with sensitivity 85% and specificity 94.4%. Similar to the study of Soliman *et al.*.[10] also assessed a ferritin cut off of >27.3 ng/ml as a biomarker to differentiate between active and inactive SLE patients, which was AUC 0.81 (0.70-0.90), with sensitivity and specificity of 0.62, 0.88,

Table 2. Correlation between ferritin and other parameters

Variables	r	p
Age	.029	.863
Weight	-.327	.055
Height	.018	916
BMI	-.471	.003*
Hb	-.185	.265
Leucocyte	.170	.307
Thrombocyte	.097	.561
ANA	.091	.585
IgM dsDNA	.325	.046*
IgG dsDNA	.132	.428
SLEDAI score	.890	.000*

*p < 0.05 was statistically significant, r= correlation coefficient

p<0.0001 [10]. However, another study conducted on children by Hesselink *et al.*. [12] did not align with previous studies. This study shows that although the disease activity in patients is classified as severe, serum ferritin remains at normal levels, but the study only has a small sample, so it is considered less valid [12]. Research by Andreas *et al.* in 2020 [13] concluded that serum ferritin levels could be used as a biomarker to differentiate between active and inactive SLE. There was a

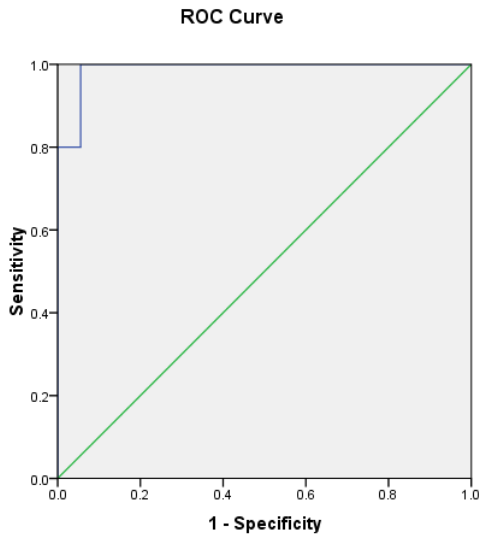

Figure 1. We found that AUC 0.989, 95%CI 0.964-1.014 , p value 0,000, cut off value of 297.50, sensitivity 85%, and specificity 94.4%.

significant difference in serum ferritin levels in the active and inactive SLE groups (p = 0.004). The cut-off value for ferritin levels was (486.0 ng/mL) with sensitivity (100.0%) and specificity (90.5%) [13]. In addition to assessing disease activity in the SLE, checking ferritin levels can detect early severe complications in SLE in the form of MAS that SLEDAI scores or others cannot assess. In a pediatric study by Smitherman *et al.* [14], ferritin 627 g/L has been shown to be 89% specific with a sensitivity of 95% for identifying patients with MAS. In this study also retrospectively sought data on hospitalizations within 12 months, all cases of MAS occurred within 30 days of SLE diagnosis. In this study, there were no data on the strength of the association between ferritin and MAS [14]. Another study by Almutairi *et al.*, found serum ferritin levels to be significantly correlated with SLEDAI ($p<0.0001$) and MAS markers (LDH, AST, triglycerides and CD25) [4].

Ferritin is an acute phase reactant that is important in iron storage and recycling. Ferritin can be found in circulating blood, but the greatest concentration is found in hepatocytes and the immune system in reticuloendothelial cells. Hyperferritinemia is associated with inflammation, infection, malignancy of renal failure, liver disease, metabolic syndrome, and autoimmune diseases (e.g., rheumatoid arthritis, Juvenile Idiopathy Arthritis). Iron, pro-inflammatory cytokines, hormones, and oxidative stress can regulate ferritin expression [4]. Ferritin has also been reported to exhibit various immunological activities, including binding to T lymphocytes, suppression of delayed-type hypersensitivity, suppression of antibody production by B lymphocytes, and decreased phagocytosis of granulocytes [15]. Hyperferritinemia in SLE correlates with disease activity [10]. Various pro-inflammatory cytokines such as IL-6, IL-1a and IFN-α were shown to regulate ferritin expression and translation and significantly correlated with SLEDAI [15]. Several limitations of this study are a single center experience, a small sample, and one visit assessment.

Conclusion

Overall ferritin levels correlated with pSLE disease activity as assessed by the SLEDAI scoring system. Ferritin was increased in active disease as compared to inactive disease of SLE. It may be potential as a cheap and available marker of disease activity in pSLE during the pandemic Covid-19. Ferritin levels can detect severe SLE complications in the form of MAS so that prompt and appropriate treatment can reduce morbidity and mortality. This shows that ferritin can be used as a laboratory test to assess SLE disease activity in the future.

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