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ORIGINAL ARTICLE

Analysis of serum levels of B cell activating factor and soluble B cell activating factor receptor with disease activity in systemic lupus erythematosus

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ABSTRACT

BACKGROUND
Systemic lupus erythematosus (SLE) is caused by B-cell hyperactivity, which stimulates the production of autoantibodies, leading to the formation of immune complexes and resulting in tissue damage. Increased B-cell activation is associated with disease activity in SLE. The cytokine B-cell Activating Factor (BAFF) and its soluble BAFF receptor (sBAFF-R) play a crucial role in B-cell activation and survival. Their serum levels may serve as potential biomarkers for SLE severity. This study aimed to compare serum levels of BAFF and sBAFF-R between SLE patients with mild, moderate, and severe disease activity.

METHODS
A cross-sectional study was conducted involving 33 female SLE patients. Subjects were divided into mild, moderate, and severe disease activity groups. Disease activity was assessed using Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI) scores. Serum BAFF and sBAFF-R levels were measured using ELISA. Data were analyzed using the Kruskal–Wallis and Mann-Whitney tests. A p-value < 0.05 was considered statistically significant.

RESULTS
The median serum BAFF level in SLE patients was 0.51 ng/mL, and 4.66 ng/mL in sBAFF-R level.There was a statistically significant difference in serum BAFF and sBAFF-R levels between mild, moderate, and severe disease activity among SLE patients ($p<0.0001$).

CONCLUSION
Increased serum levels of BAFF and sBAFF-R may influence disease activity in SLE. Serum concentrations of BAFF and sBAFF-R were found to be associated with disease severity, including mild, moderate, and severe categories. These findings suggest that serum BAFF and sBAFF-R levels may serve as potential biomarkers for assessing SLE activity.

Keywords: B-cell activating factor, biomarker, MEX-SLEDAI, receptor, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with a substantial global epidemiological burden. According to the latest comprehensive systematic review and statistical modeling by Tian et al.[1] the global prevalence of SLE is estimated at 43.7 per 100,000 individuals, affecting approximately 3.41 million people worldwide, the majority of whom are women. The global annual incidence is estimated at 5.14 per 100,000 person-years, corresponding to about 400,000 new cases each year. The prevalence of SLE in Asia based on research by Tanaka et al.[2] ranges from 3.7 to 127 per 100,000 people, with the prevalence of SLE in China being 10-70 per 100,000 people, in Hong Kong 58.8 per 100,000 people, in Korea 18.8-21.7 per 100,000 people, and in Japan 3.7-37.7 per 100,000 people. Worldwide prevalence ranges from 15.87 to 108.92 per 100,000 people and incidence from 1.5 to 11.0 per 100,000 person-years, depending on geographic region and genetic background.[3]

B cells play a critical role in several aspects of SLE pathogenesis. The development and survival of B cells depend on stimulation by B cell activating factor (BAFF) from the tumor necrosis factor (TNF) superfamily.[4] B cell activating factor, produced by dendritic cells, monocytes, and neutrophils, is essential for B cell maturation and autoantibody production in SLE.[5] Du et al.[6] demonstrated that BAFF receptor (BAFF-R) signaling is essential for the activation of transitional B cells and autoantibody production. BAFF promotes B cell proliferation and IgG autoantibody generation through direct interaction with BAFF-R.

In SLE, monitoring of disease activity is required, which is related to the activation of B cells in producing autoantibodies. Evaluation of disease activity is useful as a guide in providing therapy from the beginning of the diagnosis. Several instruments have been developed and validated for assessing SLE disease activity, such as the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI) which has a sensitivity of 87.5% and a specificity of 100%.[7,8] The Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI) is a validated and simplified version of the original SLEDAI proposed by Uribe et al.[9] The validity and reliability of MEX-SLEDAI have been demonstrated in multiethnic populations, showing good correlation with established disease activity measures.

The study by Sari et al.[10] conducted on 79 patients with systemic lupus erythematosus (SLE), reported elevated serum levels of BAFF in SLE patients compared to healthy controls. Research conducted by Salazar-Camarena et al.[11] in examining the relationship between serum BAFF levels and SLE disease activity based on the MEX-SLEDAI score gave positive correlation results. Therefore the score can be used as a biomarker in determining SLE disease activity, with the sensitivity and specificity of serum BAFF being 82.2% and 94.1%, respectively.[12] The study by Vincent et al.[13] showed that serum BAFF levels were significantly elevated in patients with systemic lupus erythematosus (SLE) and were associated with disease activity, flares, and organ damage. In contrast, soluble BAFF-R (sBAFF-R) levels did not show significant differences between patient and control groups and were not correlated with disease activity, indicating their limited potential as a clinical biomarker in SLE.

Although the Indonesian study by Vitri et al.[14] found a statistically significant correlation between serum BAFF levels and SLE disease activity, the strength of this association was low, suggesting that additional immunological or genetic factors may influence disease activity. Thus, the novelty of this study does not lie solely in the geographic setting, but also in its more comprehensive approach.

Several studies have evaluated the role of the BAFF/sBAFF-R axis in SLE pathogenesis and activity. Duan et al.[15] in a study involving 75 SLE patients, reported that the BAFF/sBAFF-R3 axis was overactivated in SLE patients, suggesting an abnormal B-cell survival mechanism. A cross-sectional study by Zaki et al.[16] involving 40 SLE patients and 20 healthy controls found that both circulating BAFF levels and sBAFF-R expression (measured via flow cytometry) were significantly associated with disease activity, such that the investigators proposed their potential use as peripheral blood biomarkers. However, methodological differences, such as the use of flow cytometry to assess membrane-bound receptor expression, limit comparability with studies using serum-based assessments such as ELISA. Additionally, Zollars et al.[17] observed that BAFF gene transcript levels in peripheral blood more strongly predicted disease activity

than serum BAFF levels, underscoring the complexity of BAFF pathway regulation in SLE.

The novelty of the present study lies in its simultaneous assessment of serum BAFF and sBAFF-R levels using ELISA, stratified across clinically defined disease activity categories (mild, moderate, and severe) in an Indonesian SLE population. This approach allows for a nuanced evaluation of the BAFF/BAFF-R axis in relation to disease severity using accessible and non-invasive biomarkers. By addressing a gap in the local and regional literature, this study aimed to advance understanding of SLE immunopathogenesis and to support the potential utility of BAFF and sBAFF-R as composite serological biomarkers in clinical practice. Therefore, this study aimed to compare serum levels of BAFF and sBAFF-R between mild, moderate, and severe disease activity in SLE patients.

METHODS

Research design

A cross-sectional study was conducted in the inpatient and outpatient installations of the allergy, immunology, and rheumatology division of internal medicine at M.Djamil Padang Hospital from June 2024 to September 2024.

Research subjects

In this study, participants were recruited using a consecutive sampling method. The minimum sample size was calculated using a two-sample comparison formula, with assumptions of a significance level (α) of 0.05 ($Z\alpha$=1.96), a statistical power of 99% (β = 0.01, $Z\beta$=2.326), an estimated standard deviation of 1.157, and a clinically meaningful mean difference of 2.07, resulting in a large effect size (Cohen's d ≈ 1.79). This calculation yielded a sample size of 11 subjects per group and a total 33 subjects, evenly distributed into three groups (n = 11 per group). The assumptions used in the sample size calculation were adapted from the findings of Salazar-Camarena et al.[11] who investigated the association of serum BAFF and APRIL levels and the expression of three receptors [BAFF-R, TACI, BCMA] with clinical manifestations in systemic lupus erythematosus. In our study, participants were classified into three groups based on disease activity levels: mild, moderate, and severe. The subjects taken for the study sample were persons who met the inclusion criteria and did not meet the exclusion criteria. The inclusion criteria were SLE patients who met the 1997 ACR diagnostic criteria, namely female patients aged 18-50 years, who were willing to take part in the study and sign the informed consent form. On the other hand, the exclusion criteria were patients with other autoimmune diseases (rheumatoid arthritis, Sjögren's syndrome, multiple sclerosis), B cell malignancy, co-infection with human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV), and sepsis.

Demographic and clinical assessment

Demographic and clinical data were recorded, including age, organ involvement (mucocutaneous, arthritis, lupus nephritis, serositis, hematologic, and neuropsychiatric lupus), pharmacologic treatment (methylprednisolone 4 mg, prednisone 5 mg, hydroxychloroquine), immunosuppressive agents (azathioprine, mycophenolic acid, mycophenolate mofetil), and duration of treatment. Disease activity in patients with systemic lupus erythematosus (SLE) was assessed using the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI), a validated and simplified version of the original SLEDAI proposed by Uribe et al.[9] This instrument excludes laboratory-based parameters such as complement levels and anti-dsDNA, making it more practical for use in outpatient clinics and resource-limited settings. According to the MEX-SLEDAI scoring system, disease activity is categorized as mild (score 2–5), moderate (6–9), and severe (≥10). Its simplicity, low cost, and ease of use allow for consistent and timely evaluation of disease activity in clinical settings, particularly where access to advanced laboratory diagnostics is limited.[7]

Laboratory procedures

The serum concentrations of B-cell Activating Factor (BAFF) and soluble B-cell Activating Factor Receptor (sBAFF-R) were measured using a sandwich enzyme-linked immunosorbent assay (ELISA). Commercial ELISA kits were obtained from Bioassay Technology Laboratory (BT LAB), China, namely the Human BAFF ELISA Kit (Catalog No. E1967Hu) and the Human BAFF-R ELISA Kit (Catalog No. E0268Hu). All procedures were conducted at the Biomedical Laboratory, Faculty of Medicine, Andalas University, following the standardized protocols provided by the

manufacturer. Serum levels of BAFF and sBAFFR were expressed in ng/mL.[11] This study did not involve the use of flow cytometry or cell surface co-expression markers such as CD19/BAFF-R; therefore, no corresponding cellular expression data or figures are presented. This clarification is provided to prevent any misinterpretation regarding the scope of the methodology used in this study.

Statistical analysis

BAFF and sBAFF-R levels were the primary outcomes of interest based on the degree of disease activity assessed using the MEX-SLEDAI score. Predictor variables included age, MEX-SLEDAI score, organ involvement, treatment, and duration of treatment. Before evaluating the independent variables, we performed a normality test to determine the subsequent parametric test. Based on the Kolmogorov-Smirnov test, the data on BAFF and its sBAFF-R were not normally distributed. Therefore the Kruskal Wallis test was used and a p value of less than 0.05 was considered statistically significant. When the Kruskal-Wallis test indicates a significant difference among the three SLE disease activity groups, it is typically followed by post-hoc tests such as Dunn's test to pinpoint which specific group pairs differ.

Ethical considerations

This study was approved by the Health Research Ethics Committee of Dr. M. Djamil Padang General Hospital under number: DP.04.03/D.XVI.XI/278/2024.

RESULTS

Characteristics of the study subjects

The subjects of this study were also divided based on age group. The mean age of the subjects was 25.03 ± 6.08 years. The largest distribution of SLE patients based on age category was in the 20-40 year age group, totaling 27 people (81.8%), categorized into mild, moderate, and severe SLE groups. The mean MEX-SLEDAI score of SLE patients was 8.72 ± 5.21. The most frequently involved organ in SLE was the mucocutaneous junction, with 27 people (81.8%), followed by arthritis, lupus nephritis, serositis, and hematologic SLE. The mucocutaneous junction was also the area most involved in mild and moderate SLE, accounting for 11 people (100%) and 7 people (63.6%), respectively. On the other hnad, in severe SLE the organs most involved were the mucocutaneous junction, the joints (arthritis), and the kidneys (lupus nephritis), totaling 9 people (81.8%). The most common medication for SLE was hydroxychloroquine, followed by methylprednisolone 4mg tablets and mycophenolic acid. The mean duration of treatment of SLE patients was 19.78 ± 25.84 months (Table 1).

BAFF and sBAFF-R levels according to degree of disease activity in SLE patients

The results of the Shapiro-Wilk normality test showed that the BAFF level data in this study were not normally distributed. The median serum BAFF level in SLE patients was 0.51 ng/mL, with the lowest level of 0.16 ng/mL and the highest level of 3.15 ng/mL. The Shapiro-Wilk normality test also showed that the sBAFF-R level data in this study were not normally distributed. The median serum sBAFF-R level in SLE patients was 4.66 ng/mL, with the lowest level being 1.61 ng/mL and the highest level 42.42 ng/mL.

Table 1. Baseline demographc and clinical characteristics of patients with systemic lupus erythematosus (n=33)

Characteristics	SLE(n=33)
Age (years)	25.03 ± 6.08
Age category	
< 20 years	5 (15.2)
20 – 40 years	27 (81.8)
> 40 years	1 (3.0)
MEX-SLEDAI score	8.72 ± 5.21
Organ involvement	
Mucocutaneous	27 (81.8)
Arthritis	20 (60.6)
Serositis	10 (30.3)
Lupus nephritis	15 (45.5)
Hematology	7 (21.2)
Lupus neuropsychiatry	3 (9.1)
Treatment Corticosteroids	
Methylprednisolone 4 mg	15 (45.5)
Methylprednisolone 8 mg	2 (6.1)
Methylprednisolone 16 mg	6 (18.2)
Methylprednisolone 24 mg	2 (6.1)
Prednisone 5 mg	1 (3.0)
Hydroxychloroquine	25 (75.8)
Azathioprine	4 (12.1)
Mycophenolic acid	7 (21.2)
Mycophenolate mofetil	4 (12.1)
Duration of treatment (months)	19.78 ± 25.84

Note: Data presented as mean ± SD, except age category, organ involvement, and treatment (n,%)

To assess differences across disease activity categories, the Kruskal–Wallis test was performed. The results revealed a statistically significant increase in both BAFF and sBAFF-R levels corresponding with the severity of disease activity. Specifically, median BAFF levels increased from 0.36 ng/mL in the mild SLE group, to 0.51 ng/mL in the moderate group, and 1.11 ng/mL in the severe group ($p<0.0001$). Similarly, median BAFF-R levels rose from 0.77 ng/mL (mild) to 4.72 ng/mL (moderate) and 10.16 ng/mL (severe), also with statistically significant differences ($p<0.0001$) (Table 2).

To further explore the pairwise differences across disease activity groups, a post hoc multiple comparison analysis was conducted following the Kruskal–Wallis test. As shown in Table 3, BAFF levels differed significantly between mild and moderate activity ($p=0.026$), between mild and severe activity ($p<0.001$), and between moderate and severe activity ($p=0.035$). Similarly, BAFF-R levels showed significant differences between mild and severe activity ($p<0.001$), and between moderate and severe activity ($p=0.023$). However, the difference between mild and moderate groups was not statistically significant for BAFF-R levels ($p=0.157$) (Table 3).

These results confirm that both BAFF and sBAFF-R levels increase significantly in accordance with disease activity severity in SLE patients, and that BAFF levels demonstrate more consistent and statistically significant differentiation across all activity levels compared to BAFF-R. This supports the role of BAFF and its receptor as potential biomarkers for assessing disease activity in clinical settings.

DISCUSSION

This study shows that there are differences in BAFF and sBAFF-R levels at various degrees of SLE disease activity. This is in line with research showing increased BAFF levels in active SLE. Research conducted by Salazar-Camarena et al.[11, 12] found that serum BAFF showed a strong correlation with disease activity SLE, with a sensitivity of 82.2% and a specificity of 94.1%, suggesting its use as a biomarker for SLE disease activity. These results support the potential role of serum BAFF and sBAFF-R as independent biomarkers of disease activity in SLE.

Table 2. Comparison of BAFF and sBAFF-R levels between degrees of disease activity in SLE

Group	Mild SLE (n=11)	Moderate SLE (n=11)	Severe SLE (n=11)	p value
	Median (min – max)	Median (min – max)	Median (min – max)	
BAFF (ng/mL)	0.36 (0.16 – 0.45)	0.51 (0.40 – 0.58)	1.11 (0.55 – 3.15)	p < 0.0001
sBAFF-R (ng/mL)	0.77 (1.61 – 4.23)	4.72 (3.58 – 6.43)	10.16 (4.66 – 42.42)	p < 0.0001

Note : Data presented as median (min-max); BAFF : B cell activating factor;sBAFF-R : soluble B cell activating factor receptor;SLE : systemic lupus erythematosus

Table 3. Multiple comparison test of BAFF and sBAFF-R levels according to SLE disease activity grades

Group	SLE degree of activity	Mean rank difference	p-value
BAFF	Mild >< Moderate	-10.82	0.026*
	Mild >< Severe	-21.23	<0.001*
	Moderate >< Severe	-10.41	0.035*
BAFF-R	Mild >< moderate	-8.00	0.157
	Mild >< Severe	-19.00	<0.001*
	Moderate >< Severe	-11.00	0.023*

Note :* Statistically significant difference ($p<0.05$) based on Dunn's post-hoc test;BAFF: B cell activating factor;sBAFF-R: soluble B cell activating factor receptor; SLE: systemic lupus erythematosus

Several previous studies have evaluated the role of BAFF and sBAFF-R in the immunopathogenesis and clinical activity of systemic lupus erythematosus (SLE), supporting the findings of the present study. Vincent et al.[13] demonstrated that serum BAFF levels were significantly elevated in SLE patients and correlated with disease activity, flares, and organ damage. However, they found that sBAFF-R levels did not significantly differ between SLE patients and healthy controls, suggesting limited utility of soluble BAFF-R alone as a clinical biomarker.

A study by Vitri et al.[14] in the Indonesian population also found a statistically significant but weak correlation between serum BAFF levels and disease activity, implying that additional immunological or genetic factors may modulate this relationship. Compared to that study, our findings suggest a stronger and more consistent association, possibly due to a more comprehensive analysis that includes both BAFF and its receptor (sBAFF).

In contrast to Vitri's study, our study identified that both BAFF and sBAFF-R levels varied with disease activity, suggesting that BAFF-R may still have a role in immunopathogenesis and disease stratification, particularly when evaluated alongside BAFF levels. Supporting this, Duan et al.[15] observed reduced BAFF-R expression on B cells in SLE patients using flow cytometry, which they hypothesized as a compensatory downregulation in response to chronic BAFF stimulation. Zaki et al.[16] further supported this by showing that both circulating BAFF levels and sBAFF-R expression were significantly associated with disease activity. However, methodological differences—such as the use of flow cytometry for membrane-bound receptors versus ELISA for soluble receptors—may account for discrepancies in findings across studies.

Additionally, Zollars et al.[17] highlighted that BAFF transcript levels in peripheral blood might even outperform serum BAFF levels in predicting disease activity, underscoring the complexity of BAFF pathway regulation in SLE. Despite these complexities, the consistent finding of elevated BAFF levels in active disease across multiple studies reinforces its clinical potential as a biomarker.

In line with these findings, Marín-Rosales et al.[18] found that serum BAFF levels were significantly higher in active SLE patients and positively associated with disease activity. They also reported increased expression of the TNF superfamily member 13b (TNFSF13B) gene, encoding BAFF, in patients with higher disease scores, indicating a potential link between transcriptional upregulation and elevated serum protein levels.

In contrast to the findings of Salazar-Camarena et al.[11] who reported decreased BAFF-R expression in peripheral B-cell subsets of SLE patients compared to healthy controls as measured by flow cytometry, our study demonstrated that serum concentrations of both BAFF and sBAFF-R were significantly elevated in patients with higher disease activity based on the MEX-SLEDAI score. The discrepancy may be attributed to methodological differences, where Salazar-Camarena's study [11] evaluated membrane-bound receptor expression, while our research focused on the quantification of soluble forms in serum using ELISA.

The increase in sBAFF-R concentrations observed in our study may reflect enhanced receptor shedding or an alternative regulatory mechanism in response to persistent BAFF stimulation. These findings underscore the potential utility of serum BAFF and sBAFF-R as accessible and non-invasive biomarkers for disease monitoring, particularly in clinical settings lacking advanced immunophenotyping tools. Furthermore, the combined elevation of both ligand and receptor in serum suggests that sBAFF-R may serve not only as a passive byproduct of immune activation but also as an active participant in the dysregulated BAFF signaling axis in SLE pathogenesis.

Soluble BAFF-R is the main specific BAFF receptor that is expressed by more than 90% of B cells which can increase the survival of B cells.[4] B cells are produced from myeloid cells mainly through dendritic cells (DC) which follow the lymphoid stem cell and lymphoblast pathways.The development and survival of B cells depend on stimulation by B cell activating factor (BAFF) from the tumor necrosis factor (TNF) superfamily.[4] BAFF functions as an important modulator of autoimmunity through B cell activation.[4] As shown by Du et al.,[6] autoantibody production by activated transitional B cells essentially involves sBAFF R signaling. Through direct interaction with BAFF R, BAFF promotes the proliferation of B cells and the production of IgG autoantibodies.

Several studies have also examined the relationship between BAFF inhibitors which can be used as targeted therapy for SLE patients. Durcan et al.[19] stated that there are a number of targeted therapies that have been developed and tested in SLE. Parodis et al.[4] stated that to inhibit the B cell response in SLE, there is one main pathway currently used, namely inhibition of BAFF.

The European Alliance of Associations for Rheumatology (EULAR) recommendations on the management of SLE state that targeted therapy or second-line therapy such as belimumab (a BAFF inhibitor) is recommended for SLE patients who do not respond to first-line therapy such as hydroxychloroquine and corticosteroids, regardless of the degree of SLE disease activity. However, belimumab is recommended as first-line therapy for SLE with severe disease activity.[20]

Roth et al.[21] stated that there is a relationship between treatment response and increased initial serum BAFF levels. The response parameters were numerically higher in patients with BAFF levels >2 ng/mL compared to BAFF <2 ng/mL indicating that initial BAFF levels are the values used to predict response to treatment in SLE patients.

Serum BAFF and sBAFF-R are important parts in the process of B cell proliferation and differentiation that can potentially be predictive biomarkers in determining the degree of disease activity in SLE patients.[11] The lack of uniformity of ELISA tools and reagents used in various countries is also a factor that causes variation in research results.

The primary limitation of this study is the absence of established cut-off values for serum BAFF and sBAFF-R levels, which limits their immediate applicability as standardized biomarkers in clinical settings. Additionally, the cross-sectional design restricts interpretation to a single time-point, preventing assessment of dynamic changes in biomarker levels in relation to disease progression or treatment response.

Despite these limitations, this study provides valuable clinical insight. The significant differences in serum BAFF and sBAFF-R levels across mild, moderate, and severe disease activity categories suggest their potential role as adjunctive biomarkers for stratifying disease activity in SLE. This is especially relevant in resource-limited settings, where comprehensive immunological testing may not be readily available.

Future studies should adopt a longitudinal design to evaluate the temporal fluctuations of BAFF and sBAFF-R levels and their responsiveness to therapy. Furthermore, large-scale studies are warranted to determine clinically relevant cut-off values, validate their prognostic utility, and explore their integration into composite disease activity indices for more accurate and accessible monitoring of SLE.

CONCLUSION

This study demonstrated that increased serum BAFF and sBAFF-R levels can affect disease activity in SLE. Higher serum BAFF and sBAFF-R levels were associated with greater disease severity. These findings suggest that BAFF and sBAFF-R have the potential to be biomarkers in determining the severity of SLE.

Conflict of Interest

Competing interests: No relevant disclosures.

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Author Contributions

R conceptualized and drafted the manuscript as well as designed the experimental framework. DE was responsible for the collection of patient samples and clinical data. MD conducted data analysis. Manuscript revisions were carried out by both DE and MD. All authors reviewed and approved the final version of the manuscript.

Data Availability Statement

The data supporting the findings of this study

are fully included within the article, and no supplementary source data are necessary.

Declaration of Use of AI in Scientific Writing

Nothing to declare

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