

CD4⁺CD25⁺FOXP3⁺ Tregs and systemic lupus erythematosus disease activity among systemic lupus erythematosus patients

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ABSTRACT

BACKGROUND Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that impacts several organ systems. Regulatory T cells (Tregs) are essential for maintaining immunological tolerance, and their dysregulation has been found linked to the pathogenesis of SLE. This study aimed to evaluate the correlation between CD4⁺CD25⁺FOXP3⁺ Treg levels and disease activity, as measured by the MEX-SLEDAI score, in patients with SLE.

METHODS A cross-sectional study was conducted involving 40 SLE patients treated in the Allergy and Immunology outpatient clinic and inpatient ward of Mohammad Hoesin Hospital from June 1, 2024 to August 31, 2024. Inclusion criteria were adults (≥18 years) diagnosed with SLE who provided informed consent. Exclusion criteria included other history autoimmune or immunocompromised conditions, pregnancy or lactation, hormonal contraceptive use, and active severe infection. CD4⁺CD25⁺FOXP3⁺ Treg cell levels were measured by flow cytometry. Disease activity was assessed using the MEX-SLEDAI score. Spearman's correlation test was used to analyze the association between Treg levels and disease activity.

RESULTS Of 40 enrolled subjects (39 women, 1 man), 75% were aged 20–44 years. Mucocutaneous manifestations were the most common clinical feature (95%). Nephritis and hematologic involvement were most frequently observed in patients with severe disease activity. A strong negative correlation was identified between CD4⁺CD25⁺FOXP3⁺ Treg cell levels and MEX-SLEDAI scores ($R = -0.72$, $p < 0.001$), indicating that lower Treg levels were associated with higher disease activity.

CONCLUSIONS CD4⁺CD25⁺FOXP3⁺ Treg levels show a significant negative correlation with MEX-SLEDAI disease activity in SLE. Lower Treg cell levels reflect more severe disease activity.

KEYWORDS disease progression, flow cytometry, systemic lupus erythematosus, Treg cells

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which the immune system attacks the body's own cells, resulting in multisystem inflammation and organ damage. SLE manifests as episodes of aggravation and remission, necessitating consistent evaluation of disease activity. The Mexican systemic lupus erythematosus disease activity index (MEX-SLEDAI) is a validated instrument for assessing

disease activity, particularly in resource-constrained environments.^{1,2}

The pathophysiology of SLE entails the disruption of immunological tolerance to self-antigens, characterized by increased activation of autoreactive B and T cells, along with the overproduction of autoantibodies and proinflammatory mediators. These processes facilitate persistent inflammation, tissue

damage, and cellular impairment in various organs. Regulatory T cells (Tregs), a subset of CD4⁺ T cells, play a crucial role in preserving immunological homeostasis by inhibiting autoreactive lymphocytes. Tregs promote immunological tolerance, reduce inflammation, and mitigate autoimmune responses. Dysregulation and functional impairment of Tregs have been observed in multiple autoimmune diseases, including SLE, making them crucial factors in the pathogenesis of SLE.^{3,4}

Research findings on Treg levels in patients with SLE are inconsistent. Reduced Treg counts are correlated with increased disease severity. Li et al⁴ demonstrated that a decreased frequency of Tregs contributes to active SLE, likely due to impaired interleukin (IL)-2 signaling, which is essential for Treg differentiation and function. In contrast, Bonelli et al⁵ observed elevated Treg numbers in active SLE, indicating compensatory proliferation due to increased immune activation, despite the possibility that these Tregs may lack functional efficacy. Research is underway to improve Treg populations, with a study by Zhou et al⁶ demonstrating that low-dose IL-2 therapy markedly elevated Treg counts in patients with SLE. Despite these developments, the role of Tregs in SLE remains unclear because studies have reported contradictory results and global research correlating Treg levels with disease activity remains limited. In Indonesia, studies on Treg levels in SLE have been conducted, but have not specifically examined their association with disease activity using the MEX-SLEDAI index. Therefore, this study aimed to analyze the correlation between CD4⁺CD25⁺FOXP3⁺ Treg levels and MEX-SLEDAI disease activity in patients with SLE.

METHODS

Study design

This observational cross-sectional study was conducted in the Allergy and Immunology outpatient clinic and inpatient ward of Mohammad Hoesin Hospital, Palembang, from June 1 to August 31, 2024.

Population and sampling

The study population comprised patients diagnosed with SLE based on the 2019 American College of Rheumatology/European Alliance of Associations for Rheumatology (EULAR) criteria. The participants were recruited from both inpatient and outpatient settings using consecutive sampling until the target sample

size was reached. This study was designed to capture the full range of disease activity by including both clinically stable outpatients and hospitalized patients with more active disease. This approach allows a comprehensive understanding of disease severity and reflects real-world clinical practice, thereby enhancing the generalizability of the findings across the SLE spectrum. Eligible participants were adults aged ≥18 years with a confirmed diagnosis of SLE who provided written informed consent. Exclusion criteria included concomitant autoimmune or immunocompromised conditions, pregnancy or breastfeeding, hormonal contraceptive use, or severe active infection at the time of recruitment. Patients with insufficient or hemolyzed blood samples were excluded to ensure laboratory integrity.

Sample size calculation

The sample size was calculated using a correlation formula with an anticipated correlation coefficient of 0.5, a significance level of 0.05, and a statistical power of 80%. Based on these parameters, a minimum of 34 participants was necessary. To address potential data loss, 40 patients with SLE were enrolled in this study.

Assessment of disease activity (MEX-SLEDAI)

Disease activity, the dependent variable in this study, was assessed using the MEX-SLEDAI. This scoring system evaluates clinical and laboratory features occurring within the preceding 10 days and consists of seven domains: neurological involvement, renal manifestations, mucocutaneous lesions, musculoskeletal symptoms, serositis, fever, and hematological abnormalities. Two allergy and immunology specialists (NK, 18 years of clinical experience and Y, 10 years of clinical experience), conducted independent assessments of each patient to reduce inter-observer variation, and any disagreements were addressed through discussion. Total scores were classified into three categories—mild (2–5), moderate (6–9), and severe (10–13)—facilitating the stratification of disease activity levels within the study population.

Blood collection and Treg analysis

Peripheral blood samples of 12 ml were collected from each participant using BD Vacutainer® cell preparation tube (Becton, Dickinson and Company, USA). Peripheral blood mononuclear cells were isolated by density gradient centrifugation to enhance

lymphocyte recovery. Flow cytometry (FCM) analysis was performed using a BD FACSLytic flow cytometer (Becton, Dickinson and Company). The gating strategy began with the identification of lymphocytes based on forward and side scatter characteristics, followed by the selection of the CD4⁺ T-cell population. CD25⁺ expression indicated activated T cells, whereas intracellular staining for FOXP3 validated the Treg subset. Treg levels were measured as the proportion of CD4⁺CD25⁺FOXP3⁺ cells in the overall CD4⁺ T-cell population.

Statistical analysis

All statistical analyses were performed using the SPSS software version 26 for Windows (IBM Corp., USA). Descriptive statistics were used to summarize the demographic and clinical characteristics. The correlation between CD4⁺CD25⁺FOXP3⁺ Treg levels and MEX-SLEDAI scores was assessed using Spearman's rank correlation test due to abnormal data distribution. Bivariate analysis was performed to determine the factors related to disease activity, and clinically or statistically significant variables were included in a multivariate linear regression model to account for confounding effects. A *p*-value of <0.05 was considered statistically significant, and the results are reported with 95% confidence intervals.

Ethical considerations

Ethical approval for this study was granted by the Health Research Ethics Committee of Mohammad Hoesin General Hospital (No. DP.04.03/D.XVIII.6.8/ETIK/101/2024). All participants were given a comprehensive overview of the study's objectives and procedures and subsequently provided written informed consent. Participants were also informed that they could request access to their individual laboratory results at any time.

RESULTS

Forty patients with SLE were included and stratified into mild, moderate, and severe disease activity groups based on the MEX-SLEDAI scores. Most patients were female, and most were between 20 and 44 years of age. There were no significant differences in age or sex between disease activity groups. The corticosteroid dose was significantly correlated with disease activity, and increasing steroid doses were

associated with an increased probability of severe SLE. The median MEX-SLEDAI score increased significantly across the disease activity categories, confirming the appropriate classification of disease severity. The demographic and clinical characteristics of the study population are summarized in Table 1. Musculoskeletal and mucocutaneous manifestations were the most frequent across all disease activity groups, with a similar prevalence in the mild and severe groups. In contrast, nephritis, hematologic abnormalities, and neurological involvement were more frequently observed in moderate and severe disease categories. Nephritis was observed in 7% of patients in the mild disease group, but this was based on a history of nephritis with negative proteinuria at the time of the study, indicating no active renal involvement. In the moderate disease group, nephritis was found in 50% of the patients, and in the severe disease group, it was present in 43%.

A significant negative correlation was observed between CD4⁺CD25⁺FOXP3⁺ Treg levels and MEX-SLEDAI scores, indicating that lower Treg levels were associated with higher disease activity (Table 2). In multivariate linear regression analysis, after adjusting for confounding variables, CD4⁺CD25⁺FOXP3⁺ Tregs remained significantly associated with SLE severity, confirming an independent inverse correlation with disease activity. The regression analysis yielded the equation $y = 7.62 - 1.26x$ with a low R^2 value of 0.104 (Figure 1). The steroid dose also remained a significant predictor, indicating a positive association with disease severity. In contrast, body mass index (BMI) and immunosuppressant use were not statistically significant.

FCM analysis was performed to identify Tregs. Figure 2 shows representative dot plots used to quantify FOXP3-expressing Tregs within the CD4⁺ T-cell population.

DISCUSSION

In this study, we found a strong negative correlation between CD4⁺CD25⁺FOXP3⁺ Treg levels and SLE disease activity as measured by the MEX-SLEDAI score. Lower Treg levels were associated with higher MEX-SLEDAI scores, suggesting a potential role of Treg deficiency in disease progression. This finding is consistent with Treg function in autoimmune disease. The identified association remained significant after adjusting for potential confounders

Table 1. Demographic and clinical characteristics of patients with SLE degrees activity

Variables	Mild (n = 14)	Moderate (n = 13)	Severe (n = 13)	Total (n = 40)	p
Age (years), n (%)					0.277 [‡]
<20	0 (0)	0 (0)	1 (8)	1 (2)	
20–44	10 (71)	10 (77)	10 (77)	30 (75)	
45–59	4 (29)	3 (23)	2 (15)	9 (23)	
≥60	0 (0)	0 (0)	0 (0)	0 (0)	
Sex, n (%)					0.650 [‡]
Female	14 (100)	13 (100)	12 (92)	39 (98)	
Male	0 (0)	0 (0)	1 (8)	1 (2)	
Education level, n (%)					0.353 [‡]
Elementary	0 (0)	0 (0)	2 (15)	2 (5)	
Junior high	0 (0)	1 (8)	2 (15)	3 (7)	
Senior high	11 (79)	8 (62)	6 (46)	25 (63)	
Bachelor degree	3 (21)	4 (31)	3 (23)	10 (25)	
Occupation, n (%)					1.000 [‡]
Private sector	2 (14)	1 (8)	1 (8)	4 (10)	
Civil servant	1 (7)	1 (8)	1 (8)	3 (7)	
Housewife	10 (71)	9 (69)	10 (77)	29 (73)	
Unemployed	1 (7)	2 (15)	1 (8)	4 (10)	
Immunosuppressant use, n (%)					0.019 [‡]
2 agents	7 (50)	0 (0)	4 (31)	11 (27)	
3 agents	6 (43)	12 (92)	7 (54)	25 (63)	
4 agents	1 (7)	1 (8)	2 (15)	4 (10)	
Daily corticosteroid dose (prednisone-equivalent) (mg), n (%)					<0.001 [‡]
<7.5	12 (86)	10 (77)	1 (8)	23 (58)	
7.5–30	2 (14)	2 (15)	7 (54)	11 (27)	
>30	0 (0)	1 (8)	5 (38)	6 (15)	
BMI, n (%)					0.290 [‡]
Underweight	0 (0)	0 (0)	1 (8)	1 (2)	
Normal weight	9 (64)	10 (77)	11 (85)	30 (75)	
Overweight	5 (36)	3 (23)	1 (8)	9 (23)	
Hypertension, n (%)	1 (7)	2 (15)	3 (23)	6 (15)	0.487 [‡]
Organ involvement*, n (%)					
Musculoskeletal	13 (38)	8 (24)	13 (38)	34 (85)	0.521 [‡]
Mucocutaneous	14 (37)	12 (32)	12 (32)	38 (95)	0.280 [‡]
Nephritis [†]	1 (7)	7 (50)	6 (43)	14 (35)	0.012 [‡]
Hematologic	0 (0)	4 (31)	9 (69)	13 (33)	0.010 [‡]
Neurological	0 (0)	1 (25)	3 (75)	4 (10)	0.108 [‡]
MEX-SLEDAI score, median (min–max)	4 (2–5)	6 (6–9)	12 (10–13)	7 (2–13)	<0.001 [§]

BMI=body mass index; MEX-SLEDAI=Mexican systemic lupus erythematosus disease activity index; SLE=systemic lupus erythematosus

*In the organ involvement, one patient may present with multiple manifestations of organ involvement, the percentage was calculated according to the total number of organ involvement occurrences; [†]in the mild disease group, nephritis was based on the patient's history of nephritis with negative proteinuria at the time of assessment, indicating no active renal involvement; [‡]Fisher exact test; [§]Kruskal–Wallis test

in multivariate analysis, highlighting Treg depletion as an independent factor related to disease activity in this cohort.

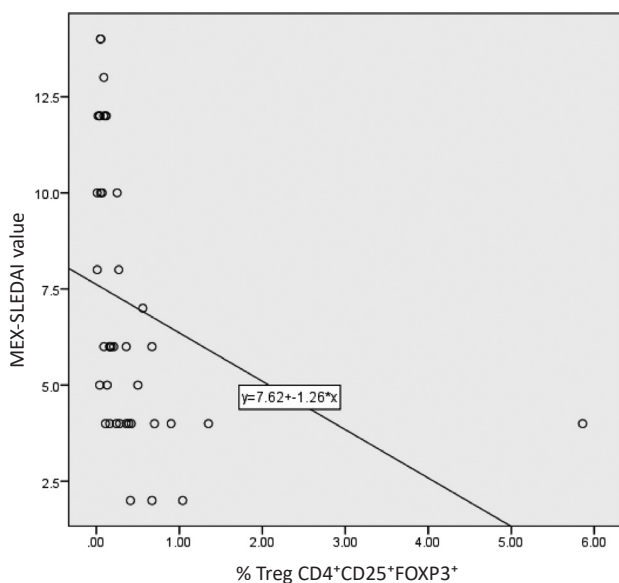
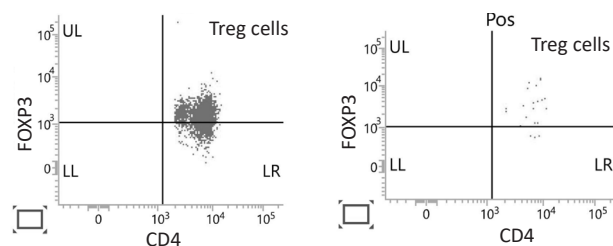
This association between Tregs and disease activity is consistent with the established role of Tregs in maintaining peripheral tolerance and

Table 2. Bivariate and multivariate analyses of CD4⁺CD25⁺FOXP3⁺ Treg cells and confounding variables on the degree of SLE

Variables	Bivariate analysis*		Multivariate analysis†			
	<i>r</i>	<i>p</i>	β	(95% CI)	SE	<i>p</i>
CD4 ⁺ CD25 ⁺ FOXP3 ⁺ Treg cells	-0.72	<0.001	-0.357	-2.355 to -0.501	0.440	0.003
BMI	-0.313	0.049	-1.95	-3.330 to 0.275	0.888	0.094
Steroid dose	0.654	0.001	0.585	1.7 to 3.96	0.552	0.001
Immunosuppressant treatment	0.203	0.208	0.156	-0.448 to 2.35	0.690	0.176

β =regression coefficient; CI=confidence interval; SE=standard error; BMI=body mass index; SLE=systemic lupus erythematosus; Treg=regulatory T cell

*Spearman's correlation; †linear regression

**Figure 1.** The scatter diagram of correlation between CD4⁺CD25⁺FOXP3⁺ Treg cells and MEX-SLEDAI disease activity. MEX-SLEDAI=Mexican systemic lupus erythematosus disease activity index; Treg=regulatory T cell**Figure 2.** The results of FCM examination in this study, where the image on the left shows high Treg cells in mildly SLE and the right shows low Treg cells in severely active SLE. The scatter plots show CD4 expression on the x-axis and FOXP3 expression on the y-axis. Tregs were defined as CD4⁺FOXP3⁺ cells located in the upper right quadrant. The left panel shows a distinct cluster of CD4⁺FOXP3⁺ cells, indicating a higher frequency of Tregs, whereas the right panel demonstrates fewer events in this quadrant, suggesting a lower Treg frequency. CD4=cluster of differentiation 4; FOXP3=forkhead box P3; FCM=flow cytometry; SLE=systemic lupus erythematosus; Treg=regulatory T cell

limiting autoreactive immune responses in SLE. Tregs suppress effector T-cell activation, inhibit B-cell-mediated autoantibody production, and reduce the production of pro-inflammatory cytokines, thereby restraining tissue damage in target organs.^{3,4,7} When Treg frequency or function is reduced, unchecked autoreactive responses may emerge, perpetuate chronic inflammation, and contribute to the worsening of disease activity. The strong negative correlation observed in this study suggests that Treg depletion reflects not only immunological dysregulation, but also clinically meaningful worsening of SLE, as captured by the MEX-SLEDAI score.

These findings are consistent with those of several previous studies that have reported reduced Treg numbers or impaired Treg function in patients with active SLE. Li et al⁴ and a subsequent meta-analysis showed that Treg depletion is significantly associated with active disease, supporting a central role of Treg deficiency in SLE pathogenesis.⁸ A study by Yang et al⁸ similarly reported that lower CD4⁺CD25⁺FOXP3⁺ Treg levels were correlated with higher SLEDAI scores and with immunological abnormalities such as anti-double-stranded DNA positivity, hypocomplementemia, and cytopenias. In addition, Li et al⁴ demonstrated that Treg depletion is consistently linked to active SLE across multiple cohorts, thereby strengthening the external validity of our observations. Conversely, some authors have reported increased numbers of phenotypically defined Tregs in active SLE, which are thought to represent functionally impaired or unstable populations unable to adequately suppress effector responses.⁵

These discrepancies may be related to the different gating strategies, markers, or disease stages at the time of sampling. Variations in the study design and patient characteristics may also contribute to

the inconsistent findings reported across studies. Nevertheless, the overall body of evidence, including our data, supports the notion that effective Treg-mediated immune regulation is diminished in patients with active SLE. This reduction may occur through numerical deficiency, functional impairment, or a combination of both.^{4–6,8,9}

The biological plausibility of these findings is further supported by mechanistic work on FOXP3⁺ Tregs and IL-2 signaling. FOXP3 is a key transcription factor that defines the Treg lineage and is essential for its development and function.^{9,10} Alterations in FOXP3 expression or function, including gene polymorphisms or epigenetic changes, have been associated with Treg instability and the loss of suppressive capacity in SLE.^{9,10} Patients with SLE often have reduced IL-2 production, which is critical for Treg survival and expansion.^{4,6,11} IL-2 deficiency favors an imbalance between effector T cells and Tregs, promoting inflammation and disease flares. The clinical relevance of this pathway is underscored by emerging data showing that low-dose IL-2 therapy can expand Treg populations and improve disease activity in SLE.^{6,12} Our finding of lower Treg levels in patients with higher MEX-SLEDAI scores is consistent with these mechanistic insights and supports further exploration of IL-2-based or Treg-targeted therapies in this population.

In addition to Treg levels, we characterized the demographic and clinical profiles of this cohort to better contextualize the immunological findings. The overwhelming majority of patients were women of reproductive age, which is consistent with Indonesian data from Palembang and other local studies, as well as global epidemiological reports showing that SLE predominantly affects women with a female-to-male ratio of approximately 9:1.^{13,14} This pattern is thought to be driven in part by the immunostimulatory effects of estrogens on B cells, dendritic cells, and cytokine production, which may amplify autoimmune responses in genetically susceptible women.^{15,16} Although this sex and age profile is typical for SLE, neither sex nor age showed a significant correlation with disease activity in this cohort, in agreement with previous studies that did not find a consistent association between these variables and SLE activity.^{17,18}

We also observed that most patients received a combination of immunosuppressive therapy and universal corticosteroid treatment, reflecting real-world practice in a tertiary referral center. Three-drug

regimens were the most frequent, and a considerable proportion of patients with mild activity still received multiple immunosuppressants, likely reflecting prior episodes of moderate or severe disease and efforts to prevent relapse.^{13,14} Although steroid dose was associated with disease severity in the multivariate analysis, these variables were inherently influenced by clinical decisions and disease history, making it difficult to disentangle cause and effect. Nevertheless, the finding that higher steroid doses correlated with more severe disease underscores the current EULAR recommendations to minimize long-term glucocorticoid exposure and taper to <7.5 mg/day prednisone-equivalent whenever possible to limit irreversible organ damage.^{19–21}

BMI was significantly associated with disease activity in this study, adding to the growing literature on the interplay between metabolic status and SLE.²² The results complement data from the Southern California Lupus Registry and the Hopkins Lupus Cohort, which have reported complex association between obesity, low BMI, and disease activity, potentially mediated by glucocorticoid exposure, inflammatory adipokines, and differences in body composition.²³ Although the direction of effect across studies is not uniform, these observations together suggest that BMI and metabolic factors may modulate disease expression in SLE, and they highlight the need to consider nutritional and cardiometabolic status as part of comprehensive SLE management.^{22,23} Hypertension was present in a minority of our patients and more frequent among those with severe activity, consistent with the known increased cardiovascular risk in SLE, although we did not find a statistically significant association with MEX-SLEDAI in this sample.²⁴

With respect to clinical manifestations, mucocutaneous and musculoskeletal involvement were the most common features across all disease activity categories, in keeping with the well-described predominance of rash and arthritis in SLE.²⁵ In contrast, nephritis, hematologic abnormalities, and neurological manifestations clustered in patients with moderate-to-severe activity, supporting the validity of the MEX-SLEDAI classification in capturing organ-threatening disease.² In the mild group, the single case labeled as nephritis represented a history of lupus nephritis rather than active renal disease, as proteinuria was negative at the time of assessment; this has been clarified in the Results and table footnote to avoid misinterpretation.

Collectively, the clinical profile of this cohort aligns with that of previous regional and international reports and provides a robust backdrop for interpreting immunological findings.^{13,18,25}

The essence of this study lies in demonstrating, for the first time in an Indonesian cohort using the MEX-SLEDAI index, that CD4⁺CD25⁺FOXP3⁺ Treg levels are inversely associated with SLE disease activity. This finding supports the use of Tregs as a potential adjunct biomarker for disease monitoring and highlights a possible therapeutic target in SLE management. By linking a practical clinical index (MEX-SLEDAI), which is particularly useful in resource-limited settings, with a mechanistically relevant immunological marker, this study bridges the gap between basic immunology and bedside assessment in a real-world population.

This study had some limitations. This study was conducted at a single tertiary center with a relatively small sample size, which may limit the generalizability of the findings to other regions or ethnic groups with different genetic and environmental backgrounds. Treg levels were measured at a single time point; therefore, we could not evaluate temporal changes in Treg dynamics during flares, remission, or their response to therapeutic adjustments. Flow cytometric assessment was based on a single-gating strategy, and functional assays for Treg suppressive capacity were not performed, which may have underestimated the complexity of Treg biology in SLE. Finally, although multivariate analysis was used to adjust for major confounders, residual confounding due to unmeasured factors could not be excluded. Despite these limitations, this study provides novel local data on the correlation between Tregs and MEX-SLEDAI disease activity in SLE, and supports further longitudinal, multicenter studies to validate Treg-based biomarkers and explore the potential of Treg-targeted interventions, including low-dose IL-2 therapy, in Indonesian and other diverse patient populations.^{4,6,12}

In conclusion, this study demonstrates a significant negative correlation between CD4⁺CD25⁺FOXP3⁺ Treg levels and disease activity in patients with SLE, as measured by the MEX-SLEDAI score. These findings highlight the potential of Tregs as valuable biomarkers for monitoring disease activity and underscore the importance of immune regulation in SLE pathogenesis. Further research is required to explore Treg-targeted therapies for disease management.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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