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Risk Factors for Disease Activity Fluctuation in Pediatric Non-Nephritis Systemic Lupus Erythematosus: A Retrospective Cohort Study at Dr. Soetomo General Academic Hospital

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ABSTRACT

Objective. This study aimed to identify the risk factors associated with disease activity fluctuation in children with non-nephritis systemic lupus erythematosus (SLE) at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Disease activity fluctuation was defined as the variation in serial SLEDAI and Mex-SLEDAI scores during 12 months of follow-up. Methods. This retrospective cohort study analyzed 36 pediatric patients with non-nephritis SLE aged 6–18 years who met the ACR/SLICC/EULAR criteria between January 2023 and June 2024. Data were extracted from medical records, including demographic, clinical, immunologic, and treatment variables. Disease activity was assessed using SLEDAI, Mex-SLEDAI, and hospitalization frequency. Statistical analyses included bivariate testing and multivariate modeling using Partial Least Squares–Structural Equation Modeling (PLS-SEM). Results. Most patients were female (86.1%) with a median age of 14 years. Younger age, infection, and treatment non-adherence were the most significant factors influencing disease activity fluctuation (β=0.32; $p<0.05$). Elevated ANA and anti-dsDNA titers, high ESR, and low complement C4 were also associated with increased disease activity. PLS-SEM analysis showed that younger age, infection, and non-adherence had the strongest predictive value for SLEDAI and Mex-SLEDAI fluctuations (R^2=0.222 and 0.427, respectively). Conclusions. Younger age, infection, and treatment non-adherence were the major determinants of disease activity fluctuations in pediatric non-nephritis SLE. Comprehensive infection control, close monitoring of younger patients, and interventions to enhance long-term adherence are essential for disease stabilization and improved outcomes.

KEYWORDS: Characteristics Respondent, Bivariate Analysis, Multivariate analysis with β coefficients in the SEM-PLS model.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by fluctuating clinical activity, alternating between remission and relapse. Pediatric SLE tends to present more aggressively than in adults, often with a higher risk of organ damage and disease progression. Global incidence ranges from 0.3 to 31.5 per 100,000 individuals per year, with approximately 15–20% of cases occurring in children and adolescents.(1,2) In Indonesia, lupus remains an important cause of pediatric morbidity and mortality.

In this study, disease activity fluctuation is defined as the variation in the degree of systemic lupus erythematosus (SLE) activity during the observation period, reflected by changes in clinical and immunological parameters such as the SLE Disease Activity Index (SLEDAI) and Mexican SLEDAI (Mex-SLEDAI) scores. These fluctuations represent alternating phases of remission and flare, driven by dynamic immune dysregulation and external triggers such as infection or therapy non-adherence. The magnitude of fluctuation reflects the instability of disease control, which may predispose pediatric patients to cumulative organ damage and worse long-term outcomes.

Disease activity fluctuation in SLE is multifactorial, influenced by genetic, immunologic, inflammatory, and environmental factors. Previous studies have reported that persistent immunologic activity (high ANA and anti-dsDNA), hypocomplementemia, infection, and non-adherence to therapy contribute to higher flare rates.(3,4) However, evidence from pediatric SLE populations, particularly in Indonesia, remains scarce.

This study aimed to identify clinical and immunological risk factors associated with disease activity fluctuation in pediatric non-

nephritis SLE at Dr. Soetomo General Academic Hospital, Surabaya. We hypothesized that immunologic markers, infection, and treatment non-adherence would significantly predict variability in disease activity. The findings are expected to provide insights for improving long-term management strategies in this population.

MATERIAL AND METHODS

This analytical observational study with a retrospective cohort design was conducted to identify clinical and immunological risk factors associated with disease activity fluctuation in pediatric systemic lupus erythematosus (SLE) across 12 months of follow-up. The study was carried out at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Medical records of children diagnosed with SLE between January 2023 and June 2024 were followed up 12 months, and data were collected during July–August 2025.

The study population included children aged 6–18 years diagnosed with SLE who were treated and followed up for at least 12 months. Inclusion criteria were patients who had completed the induction phase of therapy and had complete medical record data related to study variables. Patients with lupus nephritis or irregular follow-up visits were excluded. A total sampling technique was applied, and all eligible patients were included, resulting in 36 subjects.

Sample size estimation was based on guidelines by Hair et al. (2017, 2022) for Partial Least Squares Structural Equation Modeling (PLS-SEM), assuming six independent variables, a 5% significance level, 80% power, and an expected R^2 of 0.50, which indicated a minimum sample size of 21 subjects.

The dependent variable was disease activity fluctuation, evaluated by variation in hospitalization frequency, SLEDAI, and Mex-SLEDAI scores during a 12-month follow-up period. Independent variables included demographic characteristics (age, sex), comorbidities (autoimmune overlap, organ involvement), immunological markers (ANA, anti-dsDNA), inflammatory parameters (C3, C4, ESR), disease characteristics at diagnosis (complexity, severity, INA-CBGs level), and initial therapy (hydroxychloroquine, methylprednisolone pulse, immunosuppressant use). Infection and follow-up adherence were considered potential confounding factors.

ANA and anti-dsDNA levels were measured using ELISA at the Clinical Pathology Laboratory of Dr. Soetomo Hospital, with elevated values defined as ≥40 AU/mL and ≥30 IU/mL, respectively. Complement levels were determined by immunoturbidimetry (normal C3: 82–185 mg/dL; C4: 15–53 mg/dL). ESR > 20 mm/h was considered elevated. All immunologic assays were performed using standardized ELISA kits with uniform calibration procedures across all measurement periods. Follow-up adherence was defined as regular attendance at ≥10 monthly visits or ≤2 missed appointments without rescheduling. (5–7) To reduce information bias, only complete and verified medical records were used. Selection bias was minimized through total sampling of all eligible pediatric SLE cases.

Data were extracted from medical records and analyzed using SPSS version 29 and SmartPLS software. The Shapiro–Wilk test was applied to assess data normality. Normally distributed variables were compared using the independent t-test, while non-normal data were analyzed with Mann–Whitney or Kruskal–Wallis tests. Multivariate analysis was performed using Structural Equation Modeling (SEM); the PLS-SEM approach was applied due to non-normal data distribution. Missing data were handled using pairwise deletion. Sensitivity analyses were conducted by excluding patients with overlapping autoimmune diseases to test model robustness.

This study was approved by the Ethics Committee of Dr. Soetomo General Academic Hospital (No. 3725/105/4/VI/2025, July 2 2025). The study received no external funding, and all costs were covered by the investigators.

RESULTS AND DISCUSSION

This study aimed to identify clinical and immunological factors associated with disease activity fluctuation in pediatric systemic lupus erythematosus (SLE). Disease fluctuation was evaluated using three main indicators: SLEDAI, MexSLEDAI, and hospitalization frequency. The findings highlight several important determinants of disease instability in children with SLE. Although the minimum required sample size was 21, the final sample comprised 36 subjects due to availability of complete follow-up data.

Characteristics of Participants: Among 36 subjects, 86.1% were female, with a median age of 14 years. Most patients (80.5%) had ≥2 comorbidities, and 19.4% developed infections during follow-up. Hydroxychloroquine was prescribed in 97.2%, immunosuppressants in 88.9%, and MP-pulse therapy in 50%. Follow-up adherence was 80.5% (table 1).

Table 1. Characteristics Respondent

Characteristics	n(%)	*Mean (± SD)/**Median (IQR)	Normality test Shapiro-Wilk (p-value)
Age			0, 011
Group age			
• 6-12 years old	12 (33,3)	14,00 **	
• 13-17 years old	24 (66,7)		
Gender			

• Female • Male	31 (86,1) 5 (16.1)		
ANA titer tes • < 400 • ≥ 400	 18 (50) 18 (50)	 185,0 **	<0,001
Anti-ds DNA titer		185,0**	<0,001
Disease severity • Mild • Moderate • Severe	 7 (19,4) 13 (36,1) 16 (44,4)		
Complexity disease • Number of diagnosis: 1 • Number: of diagnosi 2-3 • Number of diagnosi ≥ 4	 6 (16,6) 29 (80,5) 1 (2,7)	2**	<0,001
Severity level INA CBGs • level 0 • level 1 • level 2 • level 3	 9 (25) 14 (38,9) 12 (33,3) 1 (2,7)		
Major organ involvement • Yes • No	 5 (13,8) 31 (86,1)		
Coexisting autoimmune disease • Yes • No	 2 (5,50) 34 (94,4)		
LED titer		60,83 ± 34,39*	0,182
Complement C3 titer		60,5**	< 0,001
Complement C4 titer		10,5**	< 0,001
Hydroxychloroquine therapy • Yes • No	 35 (97,2) 1 (2,8)		
MP purge therapy • Yes • No	 18 (50) 18 (50)		
Sparing agent therapy • Yes • No	 32 (88,9) 4 (11,1)		
Follow-up adherence • Adherent • Not adherent	 29 (80,5) 7 (19,4)		
Infection • Yes • No	 7 (19,4%) 29 (80,5%)		
SLEDAI		9,25 ± 6,42*	0,55
MexSLEDAI		0**	< 0,001
Hospitalization		0**	< 0,001

Normality test: variables with a normal distribution are presented as mean (± SD). Normality test: variables with a non-normal distribution are presented as median (IQR = interquartile range)

Bivariate Analysis (table 2): Elevated ANA and anti-dsDNA levels were positively correlated with higher SLEDAI scores ($p<0.05$). ESR showed a positive association, while C4 showed a negative correlation with disease activity. Infections significantly increased the risk of flare and hospitalization. Patients with autoimmune comorbidities had less fluctuation. Non-adherence to follow up significantly raised disease activity ($\beta=0.32$; CI 95% 0.12–0.51; $p=0.012$). Adjusted β coefficients with 95% CI for all predictors are shown in Table2.

Table 2. Bivariate Analysis

No	Independent variable	Dependent variable	Statistical test	Results

1	Demographic a. Age	SLEDAI	Spearman	r = -0.121 p= 0,482
		MEXSLEDAI		r = -0,049 p= 0,777
		Hospitalization		r= 0,056 p=0,747
	b. Sex	SLEDAI		r=0,291 p=0,085
		MEXSLEDAI		r=0,166 p=0,334
		Hospitalization		r=0,142 p=0,409
2.	Comorbidities a. Infection	SLEDAI	Independent T-Test	Group 1: Mean±SD =8,42±6,14 Group 2: Mean±SD=12,71±6,89 p=0,113 (95% CI : 0,39 – 2,94)
		MEXSLEDAI	Mann Whitney	Group 1 Median= 0 Group 2 Median= 1 p=0,087
		Hospitalization	Mann Whitney	Group 1 Median= 0 Group 2 Median= 0 p=0,106
	b. Major organ involvement	SLEDAI	Independent T-Test	Group 1: Mean±SD= 9,00±6,62 Group 2: Mean±SD=10,80±5,40 p=0,569 (95% CI: -2,08 – 1,22)
		MEXSLEDAI	Mann Whitney	Group 1 Median= 0 Group 2 Median= 0 p=0,292
		Hospitalization	Mann Whitney	Group 1 Median= 0 Group 2 Median= 0 p=0,502
	c. Coexisting autoimmune disease	SLEDAI	Independent T-Test	Group 1: Mean±SD= 2,4±1,6 Group 2: mean±SD=1,25±1,06 p= 0,337 (95% CI: -1,25 – 3,54)
		MEXSLEDAI	Mann Whitney	Group 1 Median= 0 Group 2 Median= 0 p=0,183
		Hospitalization	Mann Whitney	Group 1 Median= 0 Group 2 Median= 0 p= 0,612
3.	Immunological Parameters a. ANA level	SLEDAI	Spearman	r= 0,469 p= 0,004
		MEXSLEDAI		r= 0,068 p= 0,693
		Hospitalization		r= 0,085 p= 0,622
	b. Anti-dsDNA	SLEDAI	Spearman	r= 0,455 p= 0,005
		MEXSLEDAI		r= 0,048 p= 0,779
		Hospitalization		r= 0,077 p= 0,657
4.	Inflammatory parameters a. Complement C3	SLEDAI	Spearman	R= -0,238 p= 0,162
		MEXSLEDAI		R= 0,103 p= 0,552
		Hospitalization		R= 0,030 p= 0,863
	b. Complement C4	SLEDAI	Spearman	R= -0,381

				p= 0,022
		MEXSLEDAI		R= -0,034 p= 0,842
		Hospitalization		R= -0,128 p=0,458
	c. ESR	SLEDAI	Pearson	r= 0,346 p= 0,039 (95% CI: 0,03 – 0,60)
		MEXSLEDAI	Spearman	r= 0,243 p= 0,154
		Hospitalization		r= -0,017 p= 0,922
5.	Disease status at initial diagnosis			
	a. Disease complexity	SLEDAI	Spearman	r=0,045 p= 0,795
		MEXSLEDAI		r= 0,058 p= 0,739
		Hospitalization		r=0,061 p=0,722
	b. Disease severity	SLEDAI	ANOVA	Mild: mean± SD= 8, 3± 6,0 Moderate: mean± SD 9,3 ± 6,4 Severe: mean± SD 9,7± 6,6 p=0,649
		MEXSLEDAI	Kruskal Wallis	Mild: 0.00 (0–0.09) Moderate: 0.04 (0–0.10) Severe: 0,04 (0–0.08) p=0,537
		Hospitalization	Kruskal Wallis	Mild: 0 (0-0) Moderate: 0 (0-0) Severe: 0 (0-0) p= 0,883
	c. INA-CBGs severity level	SLEDAI	ANOVA	Level 0: mean± SD 10,2 ±7,5 Level 1 : mean± SD8,6±5,5 Level 2: mean± SD 9,0 ± 6,1 Level 3: 7,0 0=0,452
		MEXSLEDAI	Kruskal Wallis	Level 0: 0,02 (0-3) Level 1: 0,07 (0-0,11) Level 2: 0,04 (-0-0,007) Level 3: 0,02 (0-0,02) p= 0,270
		Hospitalization	Kruskal Wallis	Level 0: 0 (0-0) Level 1: 0 (0-0) Level 2: 0 (0-0) Level 3: 0 (0-0) p= 0,076
6.	Treatment at initial diagnosis			
	a. Methylprednisolone pulse (MP-Pulse)	SLEDAI	independentT Test	Group 1 (No): 2,19 ± 1,71 Group 2 (Yes) 2,47 ± 1,56: p=0,614 (95% CI : -5,35 – 3,46)
		MEXSLEDAI	Mann Whitney	Mean Rank Group 1= 19,19 Mean Rank Group 2=18,81 p= 0,672
		Hospitalization	Mann Whitney	Mean rank Group 1= 19,50 Mean rank group 2:17,50 p=0,296
	b. Sparing agent	SLEDAI	IndependentT Test	Group 1 (No): 0,94 ± 1,13 Group 2(Yes): 2,51 ± 1,60 p= 0,614 (95% CI: -12,8 – 0,5)
		MEXSLEDAI	Mann Whitey	Group 1 mean rank (No): 16,63 Group 2 Mean rank (Yes): 18,73) p=0,696

		Hospitalization	Mann Whitney	Group 1 Mean Rank: 21,00 Group 2 Mean Rank= 18,19 p=0,355
	c. Hydroxychloroquine	SLEDAI	Independent T Test	Group 1 (No): 5,0 (-) Group 2: 2,26 ± 1,58 p= 0,095 (95% CI: -1,82 – 23.93))
		MEXSLEDAI	Mann Whitney	Group 1 Mean Rank: 33,00 Group 2 Mean Rank= 18,09 p=0,135
		Hospitalization	Mann whitney	Group 1 Mean Rank: 34,50 Group 2 Mean Rank= 18,04 p=0,005
7.	Follow-up adherence	SLEDAI	Independent T Test	Not adherent: Mean ± SD=3,68 ± 1,41 Adherent Mean ± SD: 2,01 ± 1,51 Mean difference= 1,67 (95% CI: 0,39 – 2,94) p=0,012 (p<0,05)
		MEXSLEDAI	Mann Whitney	Not adherent Mean Rank = 20,07 Adherent Mean Rank: 18,12 p=0,638 (p>0,05)
		Hospitalization	Mann Whitney	Not adherent Mean Rank = 16,50 Adherent Mean Rank: 18,98 p=0,304 (p>0,05)

Multivariate Analysis PLS-SEM (figure 2): Each construct included five indicators: (1) mean value during follow-up; (2) standard deviation; (3) range between highest and lowest values; (4) RMSSD (Root Mean Square of Succesive Differences), representing short-term variability between consecutive observations; and (5) coefficient of variation (CV = SD/Mean). PLS-SEM demonstrated that younger age, infection, and non-adherence were the most influential predictors of SLEDAI and Mex-SLEDAI fluctuation. Hospitalization was primarily influenced by age, adherence, and therapy type (R^2 = 0.222, 0.427, and 0.138, respectively) (table 3,4 and 5).

Table 3. Multivariate analysis with β coefficients in the SEM-PLS model

No.	Construct	Indicator number	Indicator	*1st Loading*	*2nd Loading*	*3rd Loading*
1	Demographic	1	Gender	-0.575	removed	removed
1	Demographic	2	Age	0.637	1.000	1.000
2	Comorbidity	1	Infection	-0.609	-0.691	-0.692
2	Comorbidity	2	Coexisting autoimmune disease	0.663	0.800	0.799
2	Comorbidity	3	Major organ involvement	0.461	removed	removed
3	Immunological parameters	1	ANA	0.977	1.000	1.000
3	Immunological parameters	2	Anti-dsDNA	0.326	removed	removed
4	Inflamation parameters	1	C3 Complement	0.662	0.277	removed
4	Inflamation parameters	2	C4 Complement	0.528	removed	removed
4	Inflamation parameters	3	LED	0.760	0.972	1.000
5	Disease status at initial diagnosis	1	Complexity	0.834	0.802	0.803
5	Disease status at initial diagnosis	2	Severity level	0.705	0.780	0.779
5	Disease status at initial diagnosis	3	Severity level INA-CBGs	0.602	0.780	removed
6	Type of therapy	1	HCQ	0.777	0.795	0.803
6	Type of therapy	2	MP_Pulse	0.746	0.732	0.723
6	Type of therapy	3	Sparing_Agent	0.102	removed	removed

7	Follow-up adherence	1	Follow-up adherence	1.000	1.000	1.000
8	SLEDAI	1	SLEDAI_Mean	0.618	0.697	0.701
8	SLEDAI	2	SLEDAI_SD	0.984	0.966	0.964
8	SLEDAI	3	SLEDAI_Range	0.986	0.972	0.970
8	SLEDAI	4	SLEDAI_CV	0.405	removed	removed
8	SLEDAI	5	SLEDAI_RMSSD	0.971	0.951	0.950
9	Mex-SLEDAI	1	Mex_Mean	0.834	0.842	0.844
9	Mex-SLEDAI	2	Mex_SD	0.990	0.994	0.994
9	Mex-SLEDAI	3	Mex_Range	0.954	0.960	0.960
9	Mex-SLEDAI	4	Mex_CV	0.683	0.652	0.646

*SD = standard deviation; RMSSD = Root Mean Square of Succesive Differences; CV = Coefficient of variation; HOSPITALIZATION = hospitalization;

Table 4. Indicator–construct association strength in the outer model

Construct	Indikator - construct	Outer loading
Demographic	Age <- Demographic	1.00000000
Type of therapy	HCQ <- Type of therapy	0.80293434
	MP_Pulse <- Type of therapy	0.72321120
Follow up adherence	Therapy adherence <- Follow-up adherence	1.00000000
Comorbidity	Infection <- Comorbidity	-0.69167047
	Coexisting autoimmune disease <- Comorbidity	0.79948615
Imunological Parameters	ANA <- Immunological paramaters	1.00000000
Inflammation Parameter	LED <- Inflamation parameter	1.00000000
Disease status at initial diagnosis	Complexity <- Disease status at initial diagnosis	0.80312145
	Severity level <- Disease status at initial diagnosis	0.77881894
SLEDAI	SLEDAI_Mean <- SLEDAI	0.70133794
	SLEDAI_Range <- SLEDAI	0.97030004
	SLEDAI_RMSSD <- SLEDAI	0.94954197
	SLEDAI_SD <- SLEDAI	0.96405734
Mex-SLEDAI	Mex_CV <- Mex-SLEDAI	0.64612938
	Mex_Mean <- Mex-SLEDAI	0.84411250
	Mex_Range <- Mex-SLEDAI	0.96048754
	Mex_RMSSD <- Mex-SLEDAI	0.98249649
	Mex_SD <- Mex-SLEDAI	0.99426044
HOSPITALIZATION	HOSPITALIZATIOn _Total <- HOSPITALIZATION	1.00000000

*SD = standard deviation; RMSSD = Root Mean Square of Succesive Differences; CV = Coefficient of variation; HOSPITALIZATION = hospitalization;

Table 5. Final path coefficient of demographic factors with disease activity fluctuation

Contruct	Indicator	No	Path Coefficient	β	β1
Demographic	Age (1.00000000)	1	Demographic -> SLEDAI	-0.24420225	-
		2	Demographic -> Mex-SLEDAI	0.10746992	-
		3	Demographic -> SLEDAI -> Mex-SLEDAI	-0.12268042	-
		4	Demographic -> SLEDAI -> HOSPITALIZATION	0.06494368	-

		5	Demographic -> Mex-SLEDAI -> HOSPITALIZATION	0.04251063	-
		6	Demographic -> SLEDAI -> Mex-SLEDAI -> HOSPITALIZATION	-0.04852727	-
Comorbidity	Infection (-0.69167047)	1	Comorbidity -> SLEDAI	-0.22992828	0,15903460
		2	Comorbidity -> Mex-SLEDAI	-0.10905030	-
		3	Comorbidity -> SLEDAI -> Mex-SLEDAI	-0.11550958	0,07989456
		4	Comorbidity -> SLEDAI -> HOSPITALIZATION	0.06114763	-
		5	Comorbidity -> Mex-SLEDAI -> HOSPITALIZATION	-0.04313576	-
		6	Comorbidity -> SLEDAI -> Mex-SLEDAI -> HOSPITALIZATION	-0.04569078	0,03160296
Comorbidity	Coexisting autoimmune disease (0.79948615)	1	Comorbidity -> SLEDAI	-0.22992828	-0,183824
		2	Comorbidity -> Mex-SLEDAI	-0.10905030	-
		3	Comorbidity -> SLEDAI -> Mex-SLEDAI	-0.11550958	-0,092348
		4	Comorbidity -> SLEDAI -> HOSPITALIZATION	0.06114763	
		5	Comorbidity -> Mex-SLEDAI -> HOSPITALIZATION	-0.04313576	-
		6	Comorbidity -> SLEDAI -> Mex-SLEDAI -> HOSPITALIZATION	-0.04569078	-0,036529
Immunological parameter	ANA (1.00000000)	1	Immunological parameter -> SLEDAI	0.04503250	-
		2	Immunological parameter -> Mex-SLEDAI	-0.27112600	-
		3	Immunological parameter -> SLEDAI -> Mex-SLEDAI	0.02262308	-
		4	Immunological parameter -> SLEDAI -> HOSPITALITY	-0.01197604	-
		5	Immunological parameter -> Mex-SLEDAI -> HOSPITALITY	-0.10724616	-
		6	Immunological parameter -> SLEDAI -> Mex-SLEDAI -> HOSPITALITY	0.00894875	-
Disease status at initial diagnosis	Complexity (0.80312145)	1	Disease status at initial diagnosis -> SLEDAI	0.05834860	0,046574
		2	Disease status at initial diagnosis -> Mex-SLEDAI	0.19439025	-
		3	Disease status at initial diagnosis -> SLEDAI -> Mex-SLEDAI	0.02931272	0,023287
		4	Disease status at initial diagnosis -> SLEDAI -> HOSPITALIZATION	-0.01551736	-
		5	Disease status at initial diagnosis -> Mex-SLEDAI -> HOSPITALIZATION	0.07689269	-
		6	Disease status at initial diagnosis -> SLEDAI -> Mex-SLEDAI -> HOSPITALIZATION	0.01159489	0,008833
Disease status at initial diagnosis	Severity level (0.77881894)	1	Disease status at initial diagnosis -> SLEDAI	0.05834860	0,045124
		2	Disease status at initial diagnosis -> Mex-SLEDAI	0.19439025	-
		3	Disease status at initial diagnosis -> SLEDAI -> Mex-SLEDAI	0.02931272	0,022562
		4	Disease status at initial diagnosis -> SLEDAI -> HOSPITALIZATION	-0.01551736	-
		5	Disease status at initial diagnosis -> Mex-SLEDAI -> HOSPITALIZATION	0.07689269	-

		6	Disease status at initial diagnosis -> SLEDAI -> Mex-SLEDAI -> HOSPITALIZATION	0.01159489	0,008558
Type of therapy	HCQ (0.80293434)	1	Type of therapy -> SLEDAI	0.14524381	0,11629
		2	Type of therapy -> Mex-SLEDAI	-0.27737195	-
		3	Type of therapy -> SLEDAI -> Mex-SLEDAI	0.07296645	0,057744
		4	Type of therapy -> SLEDAI -> HOSPITALIZATION	-0.03862646	-
		5	Type of therapy -> Mex-SLEDAI -> HOSPITALIZATION	-0.10971680	
		6	Type of therapy -> SLEDAI -> Mex-SLEDAI -> RAWAT INAP	0.02886249	0,023123
Type of therapy	MP-Pulse (0.72321120)	1	Type of therapy -> SLEDAI	0.14524381	0,104835
		2	Type of therapy -> Mex-SLEDAI	-0.27737195	-
		3	Type of therapy -> SLEDAI -> Mex-SLEDAI	0.07296645	0,0527067
		4	Type of therapy -> SLEDAI -> HOSPITALIZATION	-0.03862646	-
		5	Type of therapy -> Mex-SLEDAI -> HOSPITALIZATION	-0.10971680	-
		6	Type of therapy -> SLEDAI -> Mex-SLEDAI -> HOSPITALIZATION	0.02886249	0,020244
Follow-up adherence	Therapy adherence (1.00000000)	1	Follow-up adherence -> SLEDAI	-0.21363693	-
		2	Follow-up adherence -> Mex-SLEDAI	0.09200344	-
		3	Follow-up adherence -> SLEDAI -> Mex-SLEDAI	-0.10732526	-
		4	Follow-up adherence -> SLEDAI -> HOSPITALIZTION	0.05681508	-
		5	Follow-up adherence -> Mex-SLEDAI -> HOSPITALIZTION	0.03639273	-
		6	Follow-up adherence -> SLEDAI -> Mex-SLEDAI -> HOSPITALIZATION	-0.04245340	-
SLEDAI	SLEDAI (1.00000000)	1	SLEDAI -> HOSPITA LIZATION	-0.26594220	-
		2	SLEDAI -> Mex-SLEDAI	0.50237220	-
		3	SLEDAI -> Mex-SLEDAI -> HOSPITALIZATION	0.19871753	-
Mex-SLEDAI	Mex-SLEDAI (1.00000000)	1	Mex-SLEDAI -> HOSPITALIZATION	0.39555837	-

Consistent with established epidemiologic data, most patients were female and in the adolescent age group, supporting the role of hormonal and immunological differences in SLE pathogenesis. Although age and sex did not show significant associations in bivariate analyses, the PLS-SEM model revealed that younger age was significantly correlated with higher disease fluctuation. This aligns with previous cohort studies indicating that younger age at diagnosis is a strong predictor of flare risk, likely due to more active immune responses and incomplete immune regulation during adolescence.(4,8,9) These findings suggest that closer clinical monitoring is warranted in younger patients to anticipate disease instability Sensitivity Analysis: Excluding patients with other autoimmune diseases did not change the direction or strength of associations, confirming model stability.

In terms of comorbidities, infection showed a strong positive association with hospitalization and disease activity, supporting its role as both a trigger and amplifier of immune dysregulation in pediatric SLE. Conversely, the presence of other autoimmune comorbidities, such as autoimmune thyroiditis or antiphospholipid syndrome, was associated with lower disease fluctuation. This may reflect closer monitoring and more structured therapy in these patients, which can enhance stability despite increased clinical complexity. These findings underscore the need for integrated management strategies emphasizing infection control and comprehensive follow-up.

Regarding immunologic parameters, elevated ANA and anti-dsDNA levels were significantly correlated with higher SLEDAI scores, indicating their continued relevance as serologic markers of disease activity. This is consistent with prior evidence that anti-dsDNA antibodies and complement consumption (C3/C4 reduction) are key indicators of flare.(1,10,11) However, these antibodies did not correlate with MexSLEDAI or hospitalization, likely because those indices emphasize clinical rather than serologic manifestations. Therefore, serologic and clinical assessments should be interpreted together to capture both immunologic and symptomatic domains of disease activity.

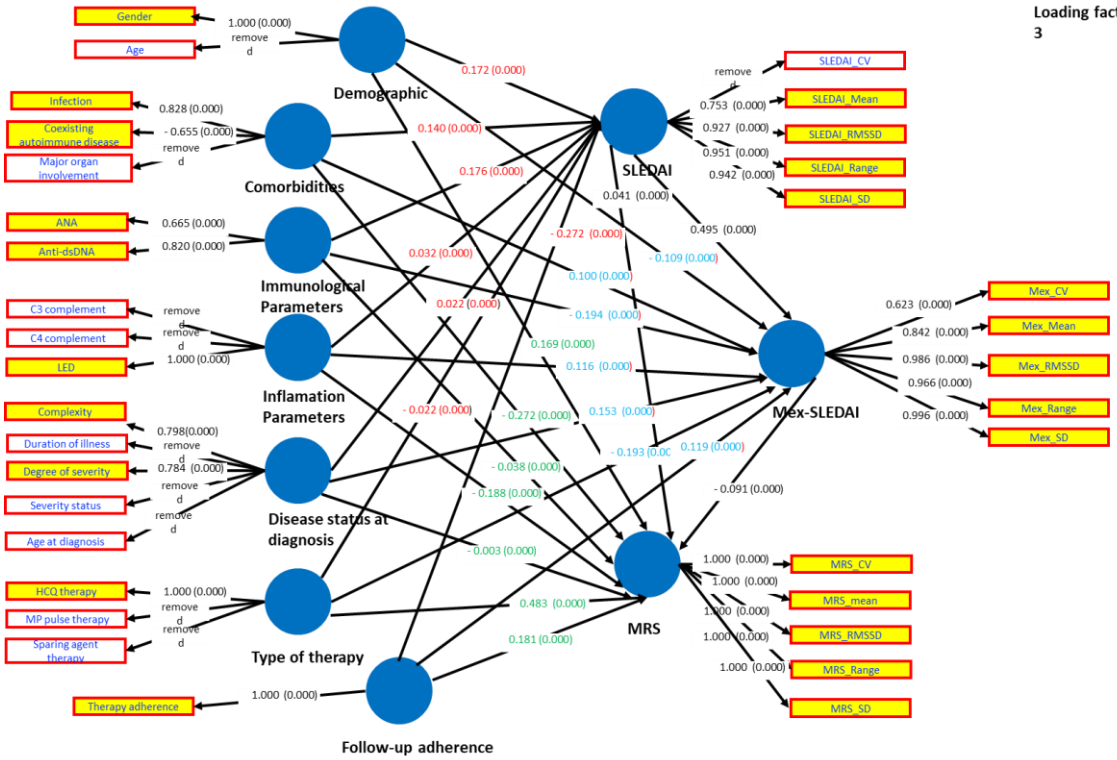

Figure. 2. Result of final loading factors PLS-SEM

Among inflammatory markers, decreased C4 and elevated ESR were significantly associated with increased disease fluctuation, confirming the role of complement activation and systemic inflammation in SLE exacerbations. (12,13) These findings support the utility of serial ESR and complement monitoring as part of longitudinal disease assessment in children, although their sensitivity may vary across disease phases.

Initial disease severity, complexity, and INA-CBGs severity levels did not show significant correlations with disease fluctuation. This aligns with prior studies suggesting that initial disease presentation does not necessarily predict long-term activity, as disease progression is largely driven by immunologic and inflammatory dynamics. (1,12) The INA-CBGs classification, while administratively valuable, may not fully capture the biological complexity of lupus progression.

Therapeutic factors also played a notable role. The absence of hydroxychloroquine (HCQ) use was significantly associated with increased hospitalization, supporting its established protective effect in preventing flares and maintaining remission. (4,9,14) HCQ remains a cornerstone of SLE management and should be continued whenever possible to reduce disease variability and improve long-term outcomes.

Follow-up adherence emerged as one of the strongest determinants of disease stability. Non-adherence was significantly associated with higher SLEDAI scores, emphasizing the importance of consistent medication use and regular follow-up. This finding corroborates previous studies showing that poor adherence leads to increased flare risk, hospitalizations, and healthcare utilization. (6,7) Hence, promoting adherence through patient education, psychosocial support, and simplified treatment regimens is essential in pediatric populations.

CONCLUSION

Younger age, infection, and follow-up non-adherence are major determinants of disease activity fluctuation in pediatric non-nephritis SLE. These findings highlight the multifactorial nature of disease variability, involving both biological and behavioral components. Regular monitoring of immunologic and inflammatory markers, infection prevention, and adherence support should be prioritized in long-term management to minimize disease instability and improve outcomes in pediatric lupus. These predictors may guide individualized monitoring schedules in pediatric SLE.

LIMITATIONS

This study has several limitations. The retrospective design may introduce data completeness bias. The relatively small sample

size limits generalizability, and findings are based on a single tertiary referral center. Despite these limitations, the use of PLS-SEM allowed comprehensive modeling of complex interactions between multiple clinical and laboratory variables. Residual confounding may persist due to unmeasured psychosocial and environmental factors.

The authors declare no conflicts of interest related to this study.

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