

Relationship Between Systemic Lupus Erythematosus Disease Activity Index Scores and Subclinical Cardiac Problems

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Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune connective-tissue disease involving multiple organs and systems. Some evidence has demonstrated that disease activity could be associated with increased risk of organ damage.

Objectives: The aim of this study was to determine the association between systemic lupus erythematosus Disease Activity Index (SLEDAI) scores and subclinical cardiac involvement.

Methods: This cross-sectional study was conducted on 45 SLE patients (88% female; mean age: 31.2 ± 8.2 years) from 2011 to 2013 in Mashhad, Iran. The patients had no clinical signs and symptoms of cardiac problems or risk factors for cardiovascular disease and were selected consecutively. All patients underwent complete echocardiographic examinations (using two dimensional (2D) tissue Doppler and 2D speckle tracking). Disease activity was evaluated by using the SLEDAI.

Results: Patients with higher SLEDAI scores had higher pulmonary artery pressure rates ($r = 0.34$; $P = 0.024$; 95% CI (0.086 to 0.595)) and SLE durations ($r = 0.43$; $P = 0.004$; 95% CI (0.165 to 0.664)). The correlation between disease duration and left ventricular mass was also significant ($r = 0.43$; $P = 0.009$; 95% CI (0.172 to 0.681)), even after adjusting for age ($r = 0.405$; $P = 0.016$). There was no correlation between SLEDAI scores or disease duration and the left/right ventricle systolic function parameters. This was true while assessing the right ventricle's diastolic function. A statistically significant correlation was found between mitral E/E' as an index of left ventricle diastolic impairment and the SLEDAI scores ($r = 0.33$; $P = 0.037$; 95% CI (0.074 to 0.574)) along with disease duration ($r = 0.45$; $P = 0.004$; 95% CI (0.130 to 0.662); adjusted for age: $r = 0.478$; $P = 0.002$).

Conclusions: Echocardiography is a useful noninvasive technique for screening subclinical heart problems in SLE patients. Although disease activity in general should suggest a closer follow-up, regular scanning would enable earlier detection of cardiovascular involvement and should not be confined to cases with higher SLEDAI indices or longer disease durations.

Keywords: Systemic Lupus Erythematosus, Ventricular Dysfunction, Echocardiography, Cardiac Disease

1. Background

Systemic lupus erythematosus (SLE) is an autoimmune connective-tissue disease with multiple system involvement. The heart is affected in more than 50% of cases. Coronary heart disease, stroke, and myocardial involvement including alteration in the structure and function of the left ventricular (LV), as well as an increase in wall thickness and mass, have been increasingly reported among SLE patients (1-3).

In Iran, a prevalence rate of 40 per 100,000 has been reported for SLE in a study by Davatchi et al. (4). In an SLE registry in Iran, a total of 2,280 patients were evaluated. Cardiovascular involvement was detected in 17.2% of patients. Pericarditis, valvular abnormalities, and myocarditis were

reported in 9.2%, 3.8% and 2.8% of patients, respectively (5).

Disease duration and activity, the number of involved organs, and laboratory test results affect the disease's prognosis (6, 7). Disease activity could be associated with increased risk of organ damage (8, 9). In 1985, the systemic lupus erythematosus disease activity index (SLEDAI), one of the standard scales which combines laboratory and clinical findings, was introduced for evaluating outcomes and disease activity among SLE patients (10).

One of the major challenges facing clinicians managing patients with SLE is to predict the disease course and prevent irreversible organ damage, which impacts patient outcomes. Echocardiography is one of the simplest and most noninvasive techniques used for the diagnosis of subclinical heart disease. SLE now has a higher prevalence in

patients with cardiac abnormalities than was previously reported; many of them were clinically silent and without manifestations of SLE activity (11-13).

2. Objectives

The aim of this study was to determine if there is a correlation between the SLEDAI scores and subclinical left ventricular dysfunction using echocardiography in a group of Iranian SLE patients. These results may have clinical advantages in providing prognostic information which may be an essential addition to the clinical data and standard echocardiographic variables, the latter of which are already used for determining risk stratification and early therapeutic intervention for the improvement of patient outcomes.

3. Methods

3.1. Patients

This cross-sectional study was conducted on 48 patients with a confirmed diagnosis of SLE by an expert rheumatologist from 2011 to 2013. They were selected consecutively from the patients visiting the rheumatology clinic at Imam Reza hospital, Mashhad University of Medical Sciences. This teaching hospital is the general referral site for northeastern Iran, a government center affiliated with the university and responsible for research and academic-related affairs as well. The sample size was measured using a prevalence comparison formula based on the longitudinal strain of the left ventricle that was determined by retrieval of information from each patient's records. The sample size was calculated as 44, including the predicted dropout rate (10%) of the patients.

3.2. Inclusion and Exclusion Criteria

All patients met the diagnostic criteria of the systemic lupus international collaborating clinics (SLICC) (14). All of the included patients had no clinical signs or symptoms of cardiac problems, histories of heart disease, or histories of conventional risk factors for atherosclerosis (e.g., hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking, obesity, and postmenopausal state).

The following exclusion criteria were applied: (i) poor left ventricle (LV) endocardial definition in echocardiography; (ii) atrial fibrillation; or (iii) moderate to severe valvular disease or reduced LV ejection fraction (< 55%) in echocardiography.

3.3. Clinical Manifestations and Treatment Modalities

All patients were placed on corticosteroid therapy and prescribed a total daily dose of prednisolone between 25 - 30 mg. Hydroxychloroquine (400 mg/day) was also administered. Disease duration was calculated from the time of diagnosis to the time of study entry. A questionnaire based on the SLEDAI was used to evaluate the level of disease activity, and other demographic and clinical variables of the patients were collected upon the first visit in a separate questionnaire.

This study was carried out in accordance with the code of ethics of the world medical association (declaration of Helsinki) for experiments involving humans. Written informed consent was obtained from each participant prior to study entrance.

3.4. Echocardiographic Assessment

All SLE cases were referred to the echocardiography department within two or three days after SLEDAI assessment. Echocardiography (conventional, Doppler imaging, 2D-STE) was performed with a single vivid seven-dimensional ultrasound scanner (GE Vingmed, Horten, Norway) with a 4-MHz transducer. LV end-diastolic and end-systolic diameters (LVEDD, LVESD) and volumes, inter-ventricular septal diameters and posterior wall thickness (IVSd, PWT), ejection fractions, LV masses, and left atrial volumes were all measured. Mitral inflow E and A waves' velocities and deceleration times were determined using pulse-Doppler radar. Tissue Doppler imaging was used for measuring the peak systolic (S') and early diastolic (E') velocities of the mitral annulus on the septal sides. The E/A and E/E' were also computed.

Three echocardiographic parameters were used to assess RV systolic function: the right ventricular index of myocardial performance (RIMP), the S' wave of the tricuspid annulus, and the longitudinal systolic strain in the mid segment of the RV free wall. In addition, the E wave velocity of the tricuspid inflow, E/A, E' peak velocity in the lateral annulus of the tricuspid valve, and E/E' were measured as echocardiographic parameters to assess RV diastolic function.

Pulmonary artery pressure was estimated through the tricuspid regurgitation peak pressure gradient. Global left ventricular longitudinal strain (GLS) was assessed with the automated functional imaging (AFI) method using three apical views (apical long-axis, 4- and 2- chamber views) in grayscale.

3.5. Statistical Analysis

Statistical analyses were performed using SPSS software (SPSS statistics for windows, version 11.0, Chicago:

SPSS, Inc.). Continuous variables were presented as means \pm standard deviation. The Kolmogorov-Smirnov test was used to evaluate whether the variables were normally distributed. Pearson's correlation test was used to detect the relationship between continuous variables. A partial correlation analysis was run to determine the relationship between each echocardiographic parameter and disease duration while controlling for age. Bootstrap estimation was used for reporting p values and confidence intervals (CI) for explaining the correlation between variables. The level of significance was set at 0.05.

4. Results

Forty-eight SLE patients with no history of cardiac problems were initially enrolled in the study, but three patients were excluded because of poor endocardial definition shown in the echocardiography. The study group included 38 (84.4%) females. The mean age of the study population was 31.38 ± 8.09 years.

The calculated mean SLEDAI score was 8.3 ± 5.1 (range: 0 - 30). The mean SLE disease duration was 5.5 ± 3.4 years (range: 2 - 20 years). Disease severity was estimated as mild to moderate according to the SLEDAI score.

The details of the SLEDAI scoring system are presented in Table 1; the mean age of the patients and the disease duration were defined for each item. Anti-dsDNA and low complement were detected in 15 (33.33%) and 16 (35.5%) of SLE patients, respectively. None of the patients had psychological problems. Pericarditis was defined in one case (with mild pericardial effusion, incidentally diagnosed by echocardiography) and pleurisy in two patients.

Eighty percent ($N = 36$) of SLE patients were CRP negative, and the remaining were diagnosed as positive ($N = 9$; 20%). Comparing these two groups, there was not a significant difference in the echocardiographic parameters.

The measured echocardiographic parameters and their correlation with SLEDAI scores and disease duration are presented in Table 2. The LV ejection fractions, mitral annuls S', and global LV longitudinal strains were 57.21 ± 4.90 , 6.92 ± 1.17 , and -18.56 ± 2.50 , respectively. Pulmonary artery pressure (PAP) was 24.42 ± 5.24 mmHg according to the echocardiographic study. Only one patient (2.22%) had pulmonary hypertension with a PAP level of 42 mmHg. This included patient had not had any history of cardiac symptoms or problems. It was found that patients with higher SLEDAI scores had higher pulmonary artery pressure rates ($r = 0.34$; $P = 0.024$; 95% CI (0.086 to 0.595)). Moreover, a positive correlation was found between disease duration and SLEDAI scores ($r = 0.43$, $P = 0.004$; 95% CI (0.165 to 0.664)).

Table 1. Details of SLEDAI Scoring System^a

Item	Number of Patients (N = 45) ^b	Age, y	Duration, y
Seizure	0	0	0
Psychosis	0	0	0
Organic brain syndrome	0	0	0
Visual disturbances	2	32.5 ± 3.5	6.5 ± 0.7
Cranial nerve disorder	0	0	0
Lupus headache	3	37.6 ± 6.4	3.7 ± 2
Cerebrovascular accident	0	0	0
Vasculitis	5	31.6 ± 5.5	7.5 ± 3.6
Arthritis	17	33.7 ± 7	6.1 ± 2.9
Myositis	3	40.3 ± 9.5	9 ± 3.6
Urinary casts	4	37.2 ± 3	13.7 ± 4
Hematuria	5	33.2 ± 6	10.8 ± 6.3
Proteinuria	12	31.4 ± 6.7	7.5 ± 4.8
Pyuria	1	23	2
New rash	9	30.3 ± 8.3	6.2 ± 5.4
Alopecia	6	32.5 ± 6.4	3.8 ± 1.3
Mucosal ulcers	6	29.1 ± 6	6 ± 2.9
Pleurisy	2	30	4.5 ± 3.5
Pericarditis	1	23	2
Low complement	16	31.6 ± 7.1	4.8 ± 2.7
Presence of Anti-dsDNA	15	33.7 ± 8.5	6.1 ± 3.2
Fever	3	37 ± 11.3	6.3 ± 4
Thrombocytopenia	6	30.5 ± 2.9	5 ± 1.9
Leukopenia	7	28.9 ± 5.1	5.7 ± 2

^aValues are expressed as mean \pm SD.

^bAbsolute number of patients having the mentioned item.

There was no relationship between the SLEDAI scores or disease duration and left/right ventricular systolic function parameters. This was also true for the right ventricular diastolic function parameters. In contrast, a significant correlation was observed between mitral E/E', as an index of left ventricle diastolic impairment, the SLEDAI scores ($r = 0.33$; $P = 0.037$; 95% CI (0.074 to 0.574)), and disease duration ($r = 0.45$; $P = 0.004$; 95% CI (0.130 to 0.662)). The correlation between disease duration and left ventricular mass was also significant ($r = 0.43$; $P = 0.009$; 95% CI (0.172 to 0.681)). Two SLE patients (4.44%) had increased interventricular septal thickness.

Table 2. Correlation Between Echocardiographic Parameters and Both SLEDAI Scores and Disease Durations^a

ECHO Parameters	Measurement	SLEDAI Score			Disease Duration		
		r	P	95% CI	r	P	95% CI
RV systolic function							
RIMP	0.27 ± 0.08	0.04	0.813	(-0.311 to 0.325)	0.05	0.766	0.235 to 0.312)
Tricuspid annulus S', cm/s	11.85 ± 1.66	-0.07	0.637	(-0.367 to 0.211)	-0.03	0.847	(-0.243 to 0.349)
RV longitudinal strain (%)	-33.20 ± 9.11	0.36	0.828	(-0.372 to 0.313)	0.10	0.533	(-0.224 to 0.517)
RV diastolic function							
Tricuspid E velocity, m/s	0.49 ± 0.12	0.12	0.481	(-0.116 to 0.364)	0.29	0.122	(-0.524 to -0.099)
Tricuspid annulus E'	11.92 ± 2.56	-0.03	0.831	(-0.372 to 0.270)	-0.35	0.029	(-0.524 to -0.099)
Tricuspid deceleration time, msec	176.28 ± 33.68	-0.40	0.015	(-0.629 to -0.050)	-0.01	0.914	(-0.390 to 0.354)
Tricuspid E/E' ratio	4.15 ± 1.46	0.16	0.366	(-0.133 to 0.437)	0.12	0.490	(-0.487 to 0.182)
Tricuspid E/A ratio	1.45 ± 0.38	0.34	0.038	(-0.540 to -0.181)	0.33	0.051	(-0.492 to -0.167)
LA volume, mL	46.12 ± 15.78	0.42	0.005	(-0.009 to 0.719)	0.41	0.008	(0.132 to 0.710)
PAP, mmHg	24.42 ± 5.24	0.34	0.024	(0.086 to 0.595)	0.20	0.191	(-0.057 to 0.449)
LV size							
IVSd, cm	0.79 ± 0.15	0.18	0.277	(-0.111 to 0.491)	0.15	0.361	(-0.177 to 0.496)
LVIDd, cm	4.47 ± 0.47	0.04	0.815	(-0.349 to 0.366)	0.43	0.008	(0.060 to 0.769)
LVIDs, cm	3.03 ± 0.39	0.01	0.950	(-0.286 to 0.343)	0.50	0.002	(0.188 to 0.725)
LV mass, gr	111 ± 29.54	0.12	0.452	(-0.226 to 0.506)	0.43	0.009	(0.172 to 0.681)
LVEDV, mL	93.88 ± 20.14	0.08	0.61	(-0.301 to 0.423)	0.28	0.071	(-0.011 to 0.644)
LVESV, mL	40.14 ± 9.54	0.05	0.756	(-0.250 to 0.363)	0.22	0.171	(-0.135 to 0.664)
LV Systolic function							
LVEF	57.21 ± 4.90	-0.003	0.986	(-0.238 to 0.251)	-0.05	0.740	(-0.349 to 0.189)
Mitral annulus S'	6.92 ± 1.17	-0.229	0.145	(-0.501 to 0.154)	-0.09	0.575	(-0.333 to 0.225)
GLS average	-18.56 ± 2.50	0.17	0.280	(-0.121 to 0.470)	0.08	0.612	(-0.236 to 0.342)
LV Diastolic function							
Mitral E velocity, m/s	0.75 ± 0.16	0.01	0.919	(-0.359 to 0.366)	0.12	0.458	(-0.210 to 0.386)
Mitral E/A ratio	1.40 ± 0.45	0.11	0.451	(-0.394 to 0.173)	-0.1114	0.481	(-0.292 to 0.110)
Mitral deceleration time, msec	176.42 ± 36.84	0.12	0.436	(-0.174 to 0.341)	0.04	0.807	(-0.308 to 0.498)
Mitral septal E', cm/s	9.92 ± 2.09	-0.41	0.007	(-0.662 to -0.075)	-0.37	0.017	(-0.539 to -0.162)
Septal E/E' ratio	7.77 ± 1.70	0.33	0.037	(0.074 to 0.574)	0.45	0.004	(0.130 to 0.662)

Abbreviations: GLS, global longitudinal strain; IVSd, interventricular septum diameter in diastole; LA, left atrium; LVEDV, left ventricle end diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end systolic volume; LVIDd, left ventricle internal diameter in diastole; LVIDs, left ventricle internal diameter in systole; MPI, myocardial performance index; PAP, pulmonary artery pressure; RIMP, right ventricular index of myocardial performance; RV, right ventricle; SLEDAI, Systemic lupus erythematosus disease activity index.

^aAll echocardiographic parameters are expressed as mean ± SD. Bootstrap estimation data: Relationship (correlation), CI (confidence interval), and P values are presented. P values < 0.05 are defined as significant.

A partial correlation analysis was conducted to determine the relationship between each echocardiographic parameter and the disease duration while adjusting for age. Statistically significant correlations were found when considering LV mass ($r = 0.40$; $P = 0.016$), LVIDd ($r = 0.43$, $P = 0.009$), LA volume ($r = 0.36$, $P = 0.021$), and mitral sep-

tal E/E' ($r = 0.47$; $P = 0.002$) against disease duration after controlling for age.

Patients with arthritis (37%) had higher interventricular septal thickness (0.82 ± 0.23 ; $P = 0.001$) compared to those without. The difference in pulmonary artery pressure levels had borderline significance (25 ± 6.6 ; $P = 0.06$).

In five of the patients with vasculitis, increased LV mass was detected, in contrast to the patients without vasculitis, yet the difference was not statistically significant ($P = 0.051$). However, the mitral E/E' (marker of LV diastolic dysfunction) was greater in these subjects (0.07 ± 0.001 ; $P = 0.03$). Furthermore, the 12 patients with proteinuria had higher LV end diastolic volumes (98.65 ± 27.32 ; $r = 0.12$; $P = 0.024$), end systolic volumes (41.71 ± 12.52 ; $r = 0.18$; $P = 0.045$), and tricuspid valve E/E' (0.07 ± 0.02 ; $r = 0.25$; $P = 0.03$). In addition, two patients with visual disturbances (mild retinopathy appearing as perivascular hard exudates and cotton-wool spots) had greater LV masses ($r = 0.15$; $P = 0.021$) and increased pulmonary artery pressure rates ($r = 0.13$; $P = 0.012$).

No other significant differences were detected between the echocardiographic results and the other SLEDAI parameters.

5. Discussion

SLE is an autoimmune disease that affects multiple organs, and cardiovascular complications are the most common reason for late mortality in such patients (15). In the present study, echocardiographic parameters were used to determine the relationship between disease duration (both before and after controlling for age) and SLEDAI. A statistically significant relation was found between LV mass, LVIDd, and mitral septal E/E' (as an index of LV diastolic function). LA volume showed a significant correlation, but only after adjusting for age.

In a cohort study on SLE patients, the cardiovascular event rate (CVE) was higher than the corresponding rate for the general population. However, CVE rates were not related to disease duration after adjusting for age (16). In the present study, we excluded SLE patients with atherosclerosis risk factors or clinical and echocardiographic evidence of significant valvular, coronary, or pericardial heart disease to eliminate the confounding variables that could affect the cardiovascular system. However, we did not classify the patients into groups with longer disease durations and greater disease severity. All patients were using similar doses of corticosteroids (ranging between 25 - 30 mg/day).

We found that the SLEDAI score had significant correlation with pulmonary artery pressure; however, in studies conducted by Kamel et al. (17) and Robbins et al. (18), no significant correlation was found. These discrepancies could be due to differences in genetic factors, the age distribution of the patients, and the duration of the SLE disease. Moreover, patients with visual disturbances had higher pulmonary artery pressure than others in our study. No similar study was found in the literature; therefore, fur-

ther research is required to determine the involved mechanisms regarding this issue.

In the present study, SLEDAI scores and disease duration showed a significant association with LV diastolic function parameters. We also found greater LV diastolic dysfunction in patients with vasculitis; this was assumed to be the result of an increased afterload. The disease duration in patients with vasculitis was more than five years. Hence, careful screening could play an important role in diagnosing and treating patients with vasculitis and longer disease durations.

Furthermore, larger LV mass was detected with increases in disease duration. This could be due to the effects of inflammatory mediators such as leukocytes and myocytes, which can result in the remodeling and hypertrophy of the heart. The frequency of LV hypertrophy was low in our study, which is in agreement with the studies conducted by Cervera et al. (19) and Omdal et al. (20), where this condition was reported in only six out of 70 and three out of 35 SLE patients, respectively.

As previously mentioned, cardiovascular involvement could be detected even in asymptomatic patients without conventional atherosclerosis risk factors (11-13).

Disease duration and activity can affect pulmonary artery pressure, LV mass, and diastolic function. However, we did not find any relationship between the ventricular systolic function indices, SLEDAI scores, and disease duration. On the other hand, subclinical abnormalities in LV longitudinal systolic function have been detected in multiple studies. Therefore, regular echocardiographic evaluation seems to be highly beneficial for identifying early cardiovascular involvement, and it should not be limited only to those cases with a higher SLEDAI scores or longer disease durations.

5.1. Study Limitations

Although subclinical LV dysfunction was detected in the SLE patients, this study was not able to identify the underlying pathophysiologic mechanisms. Another limitation was the small sample size and follow-up period for the study group due to restrictions on the selection of the cases and the limited time allotted for follow-up. Other cardiovascular events or symptoms necessitating further evaluation were not detected. Nevertheless, it seems prudent to follow the patients for a longer duration in order to clarify the clinical implications of the subclinical LV dysfunction in otherwise asymptomatic SLE patients. In addition, other organ involvement and the relationship between the various organs (possible confounders) were not taken into account. Finally, all patients were selected from a single referral teaching hospital, thus limiting the generalizability of the study's findings.

5.2. Conclusion

It was shown that echocardiography can enable the early detection of cardiovascular involvement in asymptomatic SLE patients. Although disease activity in general should suggest closer follow-up, such screening should not be limited to patients with higher SLEDAI scores or longer disease periods. Associated vasculitis or proteinuria should be considered as necessitating more precise surveillance and follow-up.

Footnotes

Authors' Contribution: Study concept and design, Zahra Mirfeizi, Hoorak Poorzand; acquisition of data, Hoorak Poorzand, Zahra Mirfeizi, Aida Javanbakht; analysis and interpretation of data, Hoorak Poorzand, Zahra Mirfeizi, Aida Javanbakht; drafting of the manuscript, Aida Javanbakht, Hoorak Poorzand; critical revision of the manuscript for important intellectual content, Hoorak Poorzand, Zahra Mirfeizi; statistical analysis, Aida Javanbakht, Hoorak Poorzand, Mohammad Khajedaloei; administrative, technical, and material support, Hoorak Poorzand, Zahra Mirfeizi; study supervision, Zahra Mirfeizi, Hoorak Poorzand.

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