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ORIGINAL ARTICLE

Cardiovascular Damage Index Score and Disease Activity among Patients with Systemic Lupus Erythematosus

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that can harm multiple organs, including cardiovascular system. Disease activity is crucial in determining risk of organ damage. This research aimed to assess Cardiovascular Damage (CV) Index score in SLE and its association with disease parameters, including disease activity. **Methods**A cross-sectional study involved 198 SLE patients at rheumatology clinics, Zagazig University Hospitals. Patients were divided into two groups based on SLE Disease Activity Index 2000 (SLEDAI-2K). Patients' clinic-demographic, laboratory, and echocardiographic data were recorded. Cardiovascular damage index was detected according to cardiac domain of Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI). Multivariable regression analysis was used to identify potential predictors of CV damage. **Results**: About (16.7%) of included SLE patients had CV damage. Statistically significant differences were detected between Group I (SLEDAI-2K ≥6) versus Group II (SLEDAI-2K <6) regarding left ventricular systolic dysfunction and diastolic dysfunction and pericardial effusion (65.3±5.68 vs 66.9±4.65), (5.40±1.78 vs 4.91±1.57), and (7.1% vs 0.00%), respectively. A significant positive correlation was observed between CV damage index and SLEDAI-2K (r=0.159, P=0.025*). CV damage significantly associated with SLEDAI-2K ≥ 6, smoking, dyslipidemia, pyuria, and hematuria. SLEDAI-2K ≥ 6, smoking, and dyslipidemia were independent predictors for CV damage in SLE. **Conclusion**: CV damage is detected in (16.7%) of lupus patients. It has a significant positive correlation with disease activity. SLEDAI-2K ≥ 6, smoking, and dyslipidemia are important contributors for developing CV damage in SLE. So, screening all SLE patients with echocardiography is important.

Keywords: Systemic lupus erythematosus, SLEDAI-2K, Cardiovascular system, Cardiovascular Damage Index, Echocardiography.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a persistent multisystemic immune-mediated illness and has considerable morbidity and mortality rates. Over the previous 50 years, the ten-year survival rates of lupus patients have notably improved; yet, the disease still has higher death rates than the general population [1].

Predicting the disease's progression and avoiding permanent organ damage, which influences patient outcomes, is an essential issue facing physicians who manage patients [2].

SLE remains a well-recognized risk factor for cardiovascular (CV) incidents, even after adjusting conventional Framingham risk variables [3]. Comparing to the general population of the same age without SLE, lupus

patients are thought to endure a nine to fifty-fold increased chance of getting CV events. Notably, this risk is significantly higher in females with lupus between 36 and 45 years old [4].

Accumulated organ damage is linked to decreased physical functioning, reduced health-related quality of life, and increased mortality in SLE patients [5]. A rise of two or more scores in Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) is linked to an increase in death rate in SLE by 7.7-fold between the first to the third year of illness [6].

Organ damage can be affected by disease activity. Longitudinal data by Bandeira et al. proved that the frequency of lupus flare-ups &overall level of disease activity throughout time were important predictors of developing damage to the organs. Therefore, evaluating the activity of the disease, cardiac organ damage, and organ-related symptoms is necessary for assessing the prognosis and course of the disease in SLE [7]. Echocardiography is an easy and non-invasive technique to diagnose heart abnormalities [8].

Since any interventions that can slow the progression of damage are likely to reduce future mortality, understanding variables contributing to CV damage in SLE is vital. So, the current research targeted to assess the Cardiovascular Damage Index score in lupus patients and its association with disease parameters including disease activity.

.METHODS

Study Design

A cross-sectional study was conducted in the follow-up and inpatient units at the Rheumatology & Rehabilitation Department, Faculty of Medicine, Zagazig University Hospitals-Egypt throughout one year.

Study participants

All the eligible patients in this work were >18years old and diagnosed to have SLE if they fulfilled Systemic Lupus International Collaborating Clinics (SLICC) criteria revision of the American College of Rheumatology (ACR) classification criteria for SLE with minimum disease duration of six months[9]. On the other hand, patients with histories of other autoimmune diseases and rheumatic heart problems, family history of cardiovascular diseases (CVD) in relatives, & clinical manifestations of cardiac events were excluded from this study. Moreover, patients with histories of cardiac conditions, or traditional risk factors of atherosclerosis (e.g., hypertension, diabetes mellitus (DM), or hyperlipidemia) before the diagnosis of SLE were also excluded.

Sampling and patient selection

The sample size was estimated utilizing the open epi-I program assuming that the percent of lupus patients who had no or mild activity and echo abnormalities is 40% versus lupus patients who had moderate or severe activity and echo abnormalities are 60% at a confidence interval of 95% and power of test 80%. In all, 198 lupus patients took part in the study & subdivided depending on SLE Disease Activity Index 2000 (SLEDAI-2K) score into two groups, each including 99 patients. Group I included 99 lupus patients with moderate to very high disease activity (SLEDAI-2K ≥6), and Group II included 99 lupus patients with no or mild disease activity (SLEDAI-2K <6).

Data was collected from patient records and clinic consultations including history taking, general, musculoskeletal, systemic, and echocardiographic examinations. Additionally, cardiovascular risk factors after the onset of SLE were detected such as hypertension, dyslipidemia, DM, smoking, & antiphospholipid syndrome. Hypertension was diagnosed on the basis of medical history, current medications, or recorded previous systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg [10]. The patients were diagnosed with DM if fasting blood sugar was above126 mg/dl (7 mmol/l) on two occasions, or if random plasma glucose was over200 mg/dl (11.1 mmol/l) with typical symptoms of hyperglycemia, or hemoglobin A1C (HbA1C) was over 6.5% [11]. The Adult Treatment Panel III (ATP III) defined

dyslipidemia as the existence of at least one of the subsequent lipid disturbances: Total cholesterol levels ≥ 200 mg/dl, Triglyceride levels ≥ 150 mg/dl, low-density lipoprotein cholesterol (LDL-c) levels ≥ 100 mg/dl, or high-density lipoprotein cholesterol (HDL-c) levels below 40 mg/dl for man or < 50 mg/dl for woman, or if the patient had been on anti-dyslipidemia drugs [12]. Diagnosis of antiphospholipid syndrome (APS) was established using the laboratory and clinical traits of APS [13].

The SLEDAI-2K score was employed to identify the disease activity in the patients [14]. As per Cook et al., SLE activity was classified into the following categories: No activity (SLEDAI: 0), Mild activity (SLEDAI: 1–5), Moderate activity (SLEDAI: 6–10), High activity (SLEDAI: 11–19), Very high activity (SLEDAI: 20) [15].

The cardiovascular damage index was computed based on the extracted data, using the cardiac domain of the SLICC Damage Index (SDI) for measuring irreversible damage. CV damage index was defined by the listed items (range 0–6): Angina or coronary artery bypass (score 1), Myocardial infarction ever (score 1 or score 2 if >I), Cardiomyopathy (ventricular dysfunction) (score 1), valvular disease (diastolic murmur, or systolic murmur >3/6) (score 1), Pericarditis for six months or pericardiectomy (score 1).Each item must persist for at least six months to be incorporated into this index [16].

Laboratory investigations involved complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lipid profile, antinuclear antibody (ANA), serum complement 3 (C3) and 4 (C4), antibody to double-stranded deoxyribonucleic acid (anti-ds DNA), antiphospholipid antibodies, urine analysis,& 24 h urinary proteins.

Transthoracic echocardiographic examination: assessment was done by (VividE9 commercial ultrasound scanner with phased-array transducers Horten, Norway) with a 1.5–3.6 MHz multifrequency phased array probe. The standard assessment was performed based on the American Society of Echocardiography and European Association of Echocardiography guidelines. Echocardiography was applied by an experienced and independent echocardiographer blinded to the patient's clinical data regarding the start of disease duration symptoms & medical history. Left ventricular ejection fraction (LVEF) m-mode, Simpson's method, elements indicative of diastolic function comprised early annular diastolic velocity (E), late annular diastolic velocity (A), E/A ratio, & isovolumetric relaxation time (IRT) were recorded. Tissue Doppler echocardiography velocities were acquired. A pulse wave Doppler sample gate was alternatively positioned at the medial then lateral mitral annulus in the apical four-chamber view to record the peak early diastolic (E′), atrial (A′), & systolic tissue velocities (S′) for each site in three successive cardiac cycles. These values determined the E/e′ ratio. We monitored valvular heart disease by Continuous wave Doppler, pulsed wave Doppler, &Color flow Doppler [17, 18].

Ethical approval and consent for participation

The Institutional Review Board (IRB) approved this research (ZU-IRB#9037) at the Faculty of Medicine, Zagazig University Hospitals in compliance with the 1964 Helsinki Declaration. Every participant signed a written informed consent.

Statistical analysis

A database software program, Statistical Package for Social Science software (SPSS) (Version 20.0. Armonk, NY: IBM Corp), was implemented to gather, code, present, and analyze the data. Quantitative data were presented as the mean ± standard deviation (SD) (and median with range for not normally distributed data). A number and percentage were used for the qualitative data presentation. For quantitative data, an independent samples t-test (t) was applied for normally distributed data, but non-parametric data was identified with the Mann-Whitney-U Test. The chi-square test ($\chi 2$) or Fisher's exact test was employed to detect the relationship between different

qualitative data. The independent factors affecting the development of CV damage among SLE patients were determined by Regression analysis. Spearman correlation (r) was employed to make the correlation between SLEDAI & CV damage index. The results were considered statistically significant if the significant probability (P value) was <0.05*& highly statistically significant if P ≤0.001**.

RESULTS

One hundred and ninety-eight SLE patients were involved in this study. Group I included 99 lupus patients with moderate to very high disease activity (SLEDAI-2K≥6), and Group II included 99 lupus patients with no or mild disease activity (SLEDAI-2K<6). The mean (±SD) age of the study population was 31.6 (±6.5) years old and the majority (167, 84.3%) was females with no significant difference between the two groups. Considering clinical features, (Table 1) showed that a highly significant difference was detected between both groups as regards the mean (±SD) of Body mass index (BMI), the median (range) scores for the SLEDAI-2K score, the use of steroids, anti-hypertensive drugs, & Angiotensin-converting enzyme inhibitors (ACE inhibitors) with the following variations in Group I versus Group II (25.3±2.9 vs 27.2±3.4), (17 (9-45) vs 1.0 (0.0-3.0)), (90.9% vs 61.6%), (35.4% vs 4.00%), and (56.6% vs 32.3%), respectively. Also, a significant variation was found between Group I and Group II regarding the use of methotrexate and azathioprine (8.1% vs 22.2%) and (21.2% vs 41.4%), respectively. However, the two groups did not significantly differ in other clinical variables.

On assessing the laboratory features, a highly significant difference was observed between participants having moderate to very high disease activity, compared to participants with no or mild disease activity ($p < 0.001$) as regards anti-dsDNA (68.7% vs 8.1%), the presence of low C3 (47.5% vs 15.2%), low C4 (29.3% vs 2.00%), high ESR (58.6% vs 16.2%), high CRP (27.3% vs 7.1%), leucopenia (25.3% vs 0.00%), hypoalbuminemia (57.6% vs 27.3%), pyuria (38.4% vs 10.1%) after exclusion of urinary tract infection, hematuria (13.1% vs 0.00%), cast with (14.1% vs 0.00%), and proteinuria (53.5% vs 30.3%). Both groups had no statistically significant differences regarding all other laboratory features (Table 2).

The echocardiographic parameters of the patients in both groups were compared. The ejection fraction for patients having moderate to very high disease activity was less than that in those with no or mild disease activity, which is statistically significant (Group I: 65.3±5.68, Group II: 66.9±4.65; p is less than 0.05). The E/e′ ratio was higher in the patients suffering moderate to very high disease activity in comparison to patients with no or mild disease activity, and it was statistically significant (GroupI:5.40±1.78 cm/s, Group II: 4.91±1.57 cm/s; p is less than 0.05). The frequency of pericardial effusion was higher in lupus participants having moderate to very high disease activity group than in participants with no or mild disease activity group and was statistically significant (Group I: 7 %, Group II: 0 %; $p<0.05$). Statistical analysis revealed no significant variation between the two groups for wall motion scores of each segment (WMSI), E/A ratio, pulmonary arterial hypertension (PHTN), diastolic dysfunction, valvular affection, and hypokinesia (Table 3).

SLE patients were distributed according to the CV damage index with a mean index of (0.27±0.65) and the majority (83.3%) of SLE patients had no damage and only (16.7%) of them had CV damage (Figure 1). The relationships between demographic & clinical variables and the development of CV damage detected that there were statistically significant associations between CV damage andSLEDAI-2K ≥6, smoking status, and dyslipidemia (P=0.004*, ≤0.001**, & ≤0.001**, respectively) where lupus individuals with SLEDAI-2K ≥6, smoking, and dyslipidemia were (3.2, 7.2, and 5.3) times more likely to develop CV damage, respectively. Also, a highly significant association was displayed

between the use of anti-hypertensive agents & occurrence of CV damage where lupus patients with cardiovascular damage used anti-hypertensive drugs more than lupus patients without CV damage. All other variables didn't reveal significant associations with CV damage (Table 4).

The relation between laboratory features and the development of CV damage identified statistically significant associations between CV damage and pyuria (after exclusion of urinary tract infection) (P=0.026*) & hematuria (p=0.029*) where SLE patients with pyuria and hematuria were (2.4 and 3.5) times more likely to develop CV damage, respectively. All remaining features weren't significantly associated with CV damage (Table 5).

The best-fitting logistic regression model to detect the independent factors that affect the development of CV damage among SLE patients showed that SLEDAI-2k ≥6, smoking, and dyslipidemia were statistically significant independent predictors for developing CV damage among SLE patients (Table 6).

Finally, the CV damage index significantly positively correlated with SLEDAI-2K among SLE patients (r=0.159, P=0.025*) (Figure 2).

Table 1 Demographic and clinical features among Systemic Lupus Erythematosus (SLE) patient groups (n=198).

Features	All SLE group (n=198)	Moderate to very high active SLE (n=99)	No or mild active SLE (n=99)	P value
Age (years)(mean ± SD)	31.6±6.5	31.03±6.4	32.1±6.7	[a]0.233
≤ Median (30)	100 (50.5%)	54 (54.5%)	46 (46.5%)	[b]0.255
> Median (30)	98(49.5%)	45 (45.5%)	53 (53.5%)	
Gender				
Female	167 (84.3%)	82 (82.8%)	85 (85.9%)	[b]0.557
Male	31(15.7%)	17 (17.2%)	14 (14.1%)	
BMI, kg/m2 (mean ± SD)	26.3±3.3	25.3±2.9	27.2±3.4	[a]≤0.001**
≤ Median (25.9)	103 (52.0%)	69 (69.7%)	34 (34.3%)	[b]≤0.001**
> Median (25.9)	95(48.0%)	30 (30.3%)	65 (65.7%)	
Smoking status	13(6.60%)	7 (7.10%)	6.0 (6.1%)	[b]0.774
Co-morbidities				
Hypertension	95(48.0%)	47 (47.5%)	48 (48.5%)	[b]0.887
Diabetes mellitus	10 (5.1%)	4.0 (4.00%)	6.0 (6.1%)	[b]0.516
Dyslipidemia	96(48.9%)	53 (53.5%)	43 (43.4%)	[b]0.155
Thyroid disorders	20 (10.1%)	10 (10.1%)	10 (10.1%)	[b]1.000
SLE duration (years)				
Median (range)	6 (1-23)	6 (1-23)	6 (1-23)	[c]0.485
≤ Median (6)	109 (55.1%)	56 (56.6%)	53 (53.5%)	[b]0.668
> Median (6)	89(44.9%)	43 (43.4%)	46 (46.5%)	
Clinical affection				
Malar Rash	112(56.6%)	56 (56.6%)	56 (56.6%)	[b]1.000
Photosensitivity	150(75.8%)	73 (73.7%)	77 (77.8%)	[b]0.507
Arthritis	89 (44.9%)	39 (39.4%)	50 (50.0%)	[b]0.116
Oral ulcer	98(49.5%)	50 (50.5%)	48 (48.5%)	[b]0.776
Hair Falling	52 (26.3%)	26 (26.3%)	26 (26.3%)	[b]1.000
Seizures	4.0 (2.00%)	1.0 (1.00%)	3.0 (3.00%)	[b]0.312
Psychosis	21(10.6%)	11(11.1%)	10 (10.1%)	[b]0.817
Fever>38°C	46 (23.2%)	21 (21.2%)	25 (25.3%)	[b]0.501
Lupus nephritis	97(48.9 %)	55 (55.6%)	42 (42.4%)	[b]0.064
Gastrointestinal manifestations	51 (25.8%)	28 (28.3%)	22 (23.2%)	[b]0.416
Pulmonary manifestations	50 (25.3%)	26 (26.3%)	24 (24.2%)	[b]0.744
Vasculitis	12 (6.1%)	8.0 (8.1%)	4.0 (4.00%)	[b]0.234
Pericarditis	11(5.6%)	5.0 (5.1%)	6.0 (6.1%)	[b]0.756
Pleuritis	20 (10.1%)	9.0 (9.1%)	11 (11.1%)	[b]0.637

Features	All SLE group (n=198)	Moderate to very high active SLE (n=99)	No or mild active SLE (n=99)	P value
Antiphospholipid antibody syndrome	51(25.8%)	30 (30.3%)	21 (21.2%)	[b]0.144
Medications				
Steroids	151 (76.3%)	90 (90.9%)	61 (61.6%)	[b]≤0.001**
Hydroxychloroquine	177 (89.4%)	91 (91.9%)	86 (86.9%)	[b]0.248
Methotrexate	30 (15.2%)	8 (8.1%)	22 (22.2%)	[b]0.006*
Azathioprine	62 (31.3%)	21 (21.2%)	41 (41.4%)	[b]0.002*
Cyclophosphamide	12 (6.10%)	9.0 (9.1%)	3.0 (3.00%)	[b]0.074
Cyclosporin	11 (5.6%)	7.0 (7.1%)	4.0 (4.00%)	[b]0.352
Mycophenolate mofetil	64 (32.3%)	33 (33.3%)	31 (31.3%)	[b]0.761
Statins	54 (27.3%)	31 (31.3%)	23 (23.2%)	[b]0.202
Anticoagulants	33 (16.7%)	20 (20.2 %)	13 (13.1%)	[b]0.182
Aspirin	9.0 (4.5%)	5.0 (5.1%)	4.0 (4.00%)	[b]0.733
Anti-hypertensive	39 (19.7%)	35 (35.4%)	4.0 (4.00%)	[b]≤0.001**
ACE inhibitors	88 (44.4%)	56(56.6%)	32(32.3%)	[b]≤0.001**
SLEDAI-2k Median (range)	6 (0.0-45)	17 (9-45)	1.0 (0.0-3.0)	[c]≤0.001**
No activity	42 (21.2%)	0.0 (0.00%)	42 (42.4%)	[b]≤0.001**
Mild activity	57 (28.8%)	0.0 (0.00%)	57 (57.6%)	
Moderate activity	16 (8.10%)	16 (16.1%)	0.0 (0.00%)	
High activity	47(23.7%)	47 (47.5%)	0.0 (0.00%)	
Very high activity	36 (18.2%)	36 (36.4%)	0.0 (0.00%)	

SD: Standard deviation, [a]Independent samples t-test, [b]Chi square test, [c]Mann-Whitney U Test, Statistically significant (P≤0.05*), Highly statistically significant (P≤0.001), SLE: Systemic Lupus Erythematosus, BMI: Body mass index, ACE inhibitors: Angiotensin-converting enzyme inhibitors, SLEDAI-2k: Systemic Lupus Erythematosus Disease Activity Index 2000.**

Table 2 Laboratory features among Systemic Lupus Erythematosus (SLE) patient groups (n=198).

Features	All SLE group (n=198)	Moderate to very high active SLE (n=99)	No or mild active SLE (n=99)	[a]P value
Positive ANA	197 (99.5%)	99 (100%)	98 (99.0%)	0.316
Positive Anti-dsDNA	76 (38.4%)	68 (68.7%)	8.0 (8.1%)	≤0.001**
Low complement 3	62 (31.3%)	47 (47.5%)	15 (15.2%)	≤0.001**
Low complement4	31 (15.7%)	29 (29.3%)	2.0 (2.00%)	≤0.001**
High ESR	74 (37.4%)	58 (58.6%)	16 (16.2%)	≤0.001**
High CRP	34 (17.2%)	27 (27.3%)	7.0 (7.1%)	≤0.001**
Anemia	18 (9.1%)	10 (10.1%)	8.0 (8.1%)	0.621
Leucopenia	25 (12.6%)	25 (25.3%)	0.0 (0.00%)	≤0.001**
Lymphopenia	27 (13.6%)	14 (14.1%)	13 (13.1%)	0.836
Thrombocytopenia	30 (15.2%)	14 (14.1%)	16 (16.2%)	0.692
Hypoalbuminemia	84 (42.2%)	57 (57.6%)	27 (27.3%)	≤0.001**
Pyuria	48 (24.2%)	38 (38.4%)	10 (10.1%)	≤0.001**
Hematuria	13 (6.6%)	13 (13.1%)	0.0 (0.00%)	≤0.001**
Cast	14 (7.1%)	14 (14.1%)	0.0 (0.00%)	≤0.001**
Proteinuria ≥ 500mg/24hr	83 (41.9%)	53 (53.5%)	30 (30.3%)	≤0.001**

[a]Chi square test, Statistically significant (P≤0.05*), Highly statistically significant (P≤0.001), SLE: Systemic Lupus Erythematosus, ANA: antinuclear antibodies, Anti-dsDNA: antibody to double-stranded deoxyribonucleic acid, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein.**

Table 3 Echocardiographic features of Systemic Lupus Erythematosus (SLE) patient groups (n=198).

Features	All SLE group (n=198)	Moderate to very high active SLE (n=99)	No or mild active SLE (n=99)	P value
EF (mean ± SD)	66.1±5.24	65.3±5.68	66.9±4.65	[a]0.035*
WMSI (mean ± SD)	0.99±0.15	0.97±0.20	1.01±0.03	[a]0.070
E/Aratio (mean ± SD)	1.29±0.30	1.26±0.31	1.32±0.28	[a]0.150
E/e'ratio (mean ± SD)	5.16±169	5.40±1.78	4.91±1.57	[a]0.039*
SPAP (mean ± SD)	25.7±8.43	26.5±9.00	25.0±7.78	[a]0.213
PHTN	30 (15.2%)	18 (18.2%)	12 (12.1%)	[b]0.234
Diastolic dysfunction	52 (26.3%)	31 (31.3%)	21 (21.2%)	[b]0.106
Valvular affection	22 (11.1%)	15 (15.2%)	7.0 (7.1%)	[b]0.070
Mitral stenosis	6.0 (3.00%)	4.0 (4.00%)	2.0 (2.00%)	[c]0.407
Mitral regurgitation	16 (8.1%)	10 (10.1%)	6.0 (6.1%)	[b]0.297
Aortic stenosis	5.0 (2.5%)	3.0 (3.00%)	2.0 (2.00%)	[c]0.651
Aortic regurgitation	11 (5.6%)	8.0 (8.1%)	3.0 (3.00%)	[b]0.121
Tricuspid stenosis	5.0 (2.5%)	3.0 (3.00%)	2.0 (2.00%)	[c]0.651
Tricuspid regurgitation	11 (5.6%)	8.0 (8.1%)	3.0 (3.00%)	[b]0.121
Pulmonary stenosis	5.0 (2.5%)	3.0 (3.00%)	2.0 (2.00%)	[c]0.651
Pericardial effusion	7.0 (3.5%)	7.0 (7.1%)	0.0 (0.00%)	[c]0.007*
Hypokinesia	7.0 (3.5%)	4.0 (4.00%)	3.0 (3.00%)	[c]0.700

SD: Standard deviation, [a]Independent samples t-test, [b]Chi square test, [c]Fisher's exact test, Statistically significant (P≤0.05*), Highly statistically significant (P≤0.001**), SLE: Systemic Lupus Erythematosus, WMSI: wall motion scores of each segment, PHTN: pulmonary arterial hypertension, EF: ejection fraction.

Table 4 Relation between demographic, clinical features, disease activity and the development of cardiovascular damage among Systemic Lupus Erythematosus (SLE) patients (n=198).

Features	Lupus patients with CV damage (n=33)	Lupus patients without CV damage (n=165)	P value	OR 95% CI
Age (years)				
≤ Median (30)(n=100)	16 (16.0%)	84 (84.0%)	[a]0.799	Ref
> Median(30)(n=98)	17 (17.3%)	81 (82.7%)		1.1(0.52-2.33)
Gender				
Female(n=167)	25 (15.0%)	142 (85.0%)	[a]0.137	Ref
Male(n=31)	8.0 (25.8%)	23 (74.2%)		2.0(0.80-4.91)
BMI, kg/m2				
≤ Median (25.9)(n=103)	16 (15.5%)	87 (84.5%)	[a]0.656	Ref
> Median (25.9)(n=95)	17 (17.9%)	78 (82.1%)		1.2(0.57-2.51)
Smoking status(n=13)	7.0 (53.8%)	6.0 (46.2%)	[b]≤0.001**	7.2(2.23-23.0)
Hypertension(n=95)	19 (20.0%)	76 (80.0%)	[a]0.227	1.6(0.75-3.38)
Diabetes mellitus(n=10)	2.0 (20.0%)	8.0 (80.0%)	[b]0.772	1.3(0.26-6.25)
Dyslipidemia(n=96)	26(27.1%)	70 (72.9%)	[a]≤0.001**	5.3(2.33-12.3)
Thyroid disorders(n=20)	6.0 (30.0%)	14 (70.0%)	[b]0.092	2.4(0.85-6.79)
Antiphospholipid antibody syndrome(n=59)	11 (18.6%)	48 (81.4%)	[b]0.627	1.3(0.55-2.71)
SLE duration years				
≤ Median (6) (n=109)	14 (12.8%)	95 (87.2%)	[a]0.110	Ref

Features	Lupus patients with CV damage (n=33)	Lupus patients without CV damage (n=165)	P value	OR 95% CI
> Median (6) (n=89)	19 (21.3%)	70 (78.7%)		1.8(0.87-3.93)
Steroids use (n=151)	26 (17.2%)	125 (82.8%)	[a]0.709	1.2(0.48-2.95)
Methotrexate use -ve(n=168) +ve(n=30)	 31 (18.5%) 2.0 (6.7%)	 137 (81.5%) 28 (93.3%)	 [a]0.111	 3.2(0.72-14.1) Ref
Azathioprine use -ve(n=136) +ve(n=62)	 24 (17.6%) 9.0 (14.5%)	 112 (82.4%) 53 (85.5%)	 [a]0.584	 1.3(0.55-2.91) Ref
Anti-hypertensive use(n=39)	11 (28.2%)	28 (71.8%)	[a]0.031*	2.5(1.07-5.62)
ACE inhibitors use(n=88)	19 (21.6%)	69 (69.7%)	[a]0.37	1.4(0.66-2.97)
SLEDAI-2K ≥6 (n=99) <6 (n=99)	 24 (24.2%) 9.0 (9.1%)	 75 (75.8%) 90 (9.9%)	 [a]0.004*	 3.2(1.41-7.31) Ref

[a]Chi square test, [b]Fisher's exact test, statistically significant (P≤0.05*), Highly statistically significant (P≤0.001**), OR: Odds ratio, CI: Confidence interval, SLE: Systemic Lupus Erythematosus, CV: cardiovascular, BMI: Body mass index, ACE inhibitors: Angiotensin-converting enzyme inhibitors, SLEDAI-2k: Systemic Lupus Erythematosus Disease Activity Index 2000.SLEDAI-2K≥6: Moderate to very high active SLE, SLEDAI-2K <6: no or mild disease activity.

Table 5 Relation between laboratory features and development of cardiovascular damage among Systemic Lupus Erythematosus (SLE) patients (n=198).

Features	Lupus patients with CV damage (n=33) No (%)	Lupus patients without CV damage (n=165) No (%)	P value	OR 95% CI
Positive ANA (n=197)	33 (16.8%)	164(83.2%)	[a]0.654	1.8(1.54-2.97)
Positive Anti-dsDNA(n=76)	16 (21.1%)	60 (78.9%)	[b]0.191	1.7(0.78-3.50)
Low complement 3(n=62)	14 (22.6%)	48 (77.4%)	[b]0.132	1.8(0.84-3.87)
Low complement 4(n=31)	6.0 (19.4%)	25 (80.6%)	[b]0.662	1.2(0.47-3.32)
High ESR(n=74)	14 (18.9%)	60 (81.1%)	[b]0.511	1.3(0.60-2.76)
High CRP(n=34)	7.0 (20.6%)	27 (79.4%)	[b]0.500	1.4(0.54-3.49)
Anemia(n=18)	5.0 (27.8%)	13 (72.2%)	[a]0.185	2.1(0.69-6.32)
Leucopenia (n=25)	7.0 (28.0%)	18 (72.0%)	[a]0.104	2.2(0.83-79.0)
Lymphopenia (n=27)	6.0 (22.2%)	21 (77.8%)	[a]0.405	1.5(0.56-4.13)
Thrombocytopenia (n=30)	7.0 (23.3%)	23 (76.7%)	[b]0.287	1.7(0.65-4.27)
Hypoalbuminemia (n=84)	16 (19.0%)	68 (81.0%)	[b]0.440	1.3(0.63-2.85)
Pyuria(n=48)	13 (27.1%)	35 (72.9%)	[b]0.026*	2.4(1.09-5.33)
Hematuria(n=13)	5.0 (38.5%)	8.0 (61.5%)	[a]0.029*	3.5(1.07-11.5)
Cast in urine (n=14)	3.0 (21.4%)	11 (78.6%)	[a]0.620	1.4(0.37-5.32)
Proteinuria ≥500mg/2h (n=83)	18 (21.7%)	65 (78.3%)	[b]0.107	1.8(0.87-3.92)

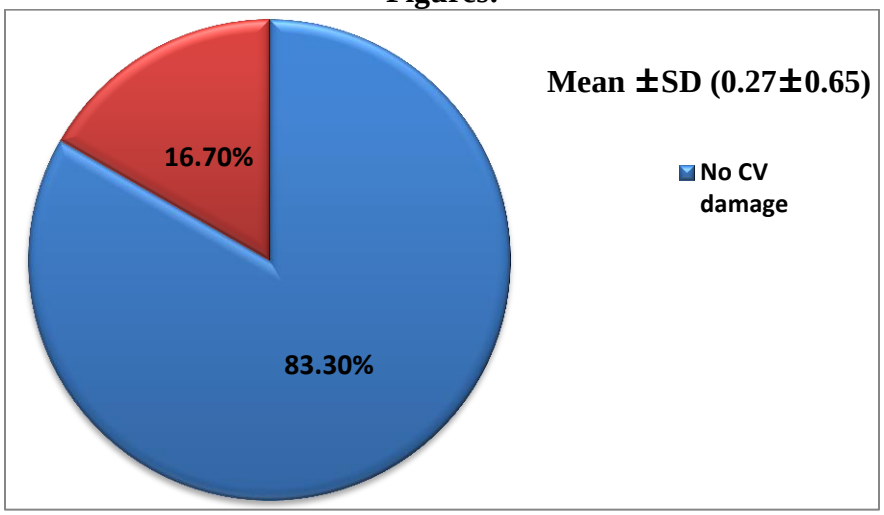
[a]Fisher's exact test, [b]Chi square test, Statistically significant (P≤0.05*), Highly statistically significant (P≤0.001**), OR: Odds ratio, CI: Confidence interval, SLE: Systemic Lupus Erythematosus, CV: cardiovascular, ANA: antinuclear antibodies, Anti-dsDNA: antibody to double-stranded deoxyribonucleic acid, ERS: Erythrocyte sedimentation rate, CRP: C-reactive protein.

Table 6 Logistic regression determining the independent factors affecting the development of cardiovascular damage among Systemic Lupus Erythematosus (SLE) patients (n=198).

Independent factors	B *coefficient*	S.E.	P value	Exp(B)	95% C.I. for EXP(B)	
					Lower	Upper
Positive smoking	1.783	0.658	0.007*	5.946	1.637	21.604
Presence of dyslipidemia	1.845	0.461	≤0.001**	6.327	2.562	15.625
SLEDAI-2K≥6	2.243	0.700	0.001*	9.425	2.388	37.193
Constant	0.089	0.675	0.893	1.093		

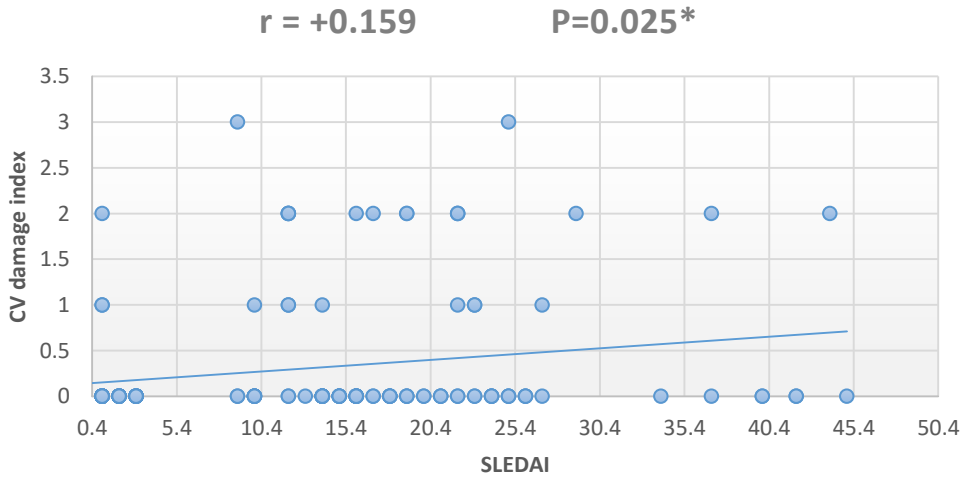
Chi-square test for model coefficient =37.011, P-value ≤0.001, SE: Standard Error, CI: Confidence interval, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, SLEDAI-2K ≥6: Moderate to very high active SLE, Variable(s) entered on the equation were SLEDAI-2K ≥6, smoking, dyslipidemia, anti-hypertensive, pyuria, and hematuria.**

Figures:



CV: cardiovascular damage, SD: Standard deviation.

Figure 1 Pie diagram for distribution of Systemic Lupus Erythematosus (SLE) according to cardiovascular (CV) damage index (n=198).



Statistically significant (P≤0.05*), Highly statistically significant (P≤0.001), SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, CV: cardiovascular damage.**

Figure 2 Correlation between SLEDAI-2K and cardiovascular damage (CV) index among Systemic Lupus Erythematosus (SLE) patients (n=198).

DISCUSSION

The precise mechanisms contributing to the raised possibility of CVD in SLE are still being researched. Some authors proposed the potential consequences of a systemic inflammatory state, particularly disease-related aspects, steroid treatments, along with the conventional risk factors [19]. Thus, this research aimed to assess the CV damage index score in patients with SLE and its association with disease parameters including disease activity.

The current study included (198) lupus patients distributed into two groups. Group I included lupus patients with moderate to very high disease activity (SLEDAI-2K ≥6), and Group II included lupus patients with no or mild disease activity (SLEDAI-2K <6).

In terms of echocardiographic features, the present results revealed significant differences between patients who had moderate to very high disease activity and those who had no or mild disease activity where the ejection fraction indicating left ventricular systolic dysfunction, E/e′ ratio indicating diastolic dysfunction, and pericardial effusion were more affected in lupus participants with moderate to very high disease activity.

Similarly, Mohammed et al. detected that SLEDAI significantly correlated with pericardial effusion [20]. Also, Yip et al. stated that lupus individuals suffering from decreased left ventricular systolic functions exhibited increased disease activity [21]. Nikdoust et al. found that patients suffering from severely active SLE had higher left ventricular end-diastolic volume than those with mild to moderately active SLE, reflecting diastolic dysfunction [22]. In contrast to these results, Attuquayefio et al. detected that no significant correlation was found between cardiac abnormalities detected by echocardiography and disease activity of SLE [23].

The present research also classified lupus patients based on the CV damage index into SLE patients with CV damage and those without CV damage. Most of SLE patients (83.3%) had no damage, and only (16.7%) of them had CV damage. This was similar to data from the published literature by Gladman et al. that showed a rate of CV damage in SLE was 5.0–16.4% [24], but Pons-Estel et al. detected that the rate of CV damage in lupus patients was 6.8% [25].

In this study, there was a significant association between SLEDAI-2K ≥6 and CV damage where SLE patients with SLEDAI-2K ≥6 were (3.2) times more probably to experience CV damage. A significant positive correlation was detected between SLEDAI-2K & CV damage index. In addition, SLEDAI-2K ≥6 was a significant independent indicator for developing CV damage among lupus patients.

These findings were in accordance with a study by Zen et al. that observed that prolonged remission has been related to a low damage accrual over time in SLE due to a decreased activity burden [26]. Cardiovascular involvement was considerably more prevalent in lupus patients suffering from high disease activity as chronic inflammation has been attributed to the accelerated process of atherosclerosis in SLE [27]. Conversely, Fasano et al. didn't identify any association between the mean SLEDAI and the incidence of CV damage, neither positively nor negatively [28].

This cardiac affection in lupus may be due to numerous inflammatory, immunological, and cytokine factors and antiphospholipid syndrome that affect the conduction system or cardiomyocytes. They could produce edema, diffuse fibrosis, myocyte necrosis, damaging the endothelium, ventricles remodeling, and premature atherosclerosis [29]. All of these factors cause increased cardiac mortality in SLE [30]. Furthermore, Li et al. predicted that the SLE disease activity might be a possible cause of decreased myocardial energy consumption [31].

Moreover, the study on hand detected highly significant associations between smoking, dyslipidemia, and CV damage in lupus patients. Smoking and dyslipidemia were statistically

significant independent predictors for the development of CV damage among SLE patients in this research.

These results were in agreement with numerous studies that have indicated that dyslipidemia has become more frequent among SLE patients and is linked to atherosclerotic cardiovascular events, which increase mortality [32]. Additionally, traditional risk factors of cardiovascular events included in the Framingham study such as smoking and dyslipidemia are prevalent in SLE patients, nevertheless, alone; they are insufficient to explain the elevated prevalence of cardiac affection in lupus patients [19]. On the contrary, Pons-Estel et al. detected that dyslipidemia and smoking were insignificantly associated with cardiac damage in SLE [25].

The current research showed a significant association between renal involvement, including pyuria and hematuria, and CV damage in lupus patients. Previous studies found that lupus patients with renal activity developed CV damage more than those without renal activity [25, 27]. This is because patients with active nephritis had significantly higher arterial stiffness factors [33]. Also, according to certain renal research, patients frequently display left ventricular hypertrophy & left atrial dilatation as a consequence of renal hypertension [34]. On the other hand, Pons-Estel et al. noted that serositis, cardiac symptoms, and pulmonary symptoms were more prevalent in SLE individuals who had CV damage than those who didn't [25].

The present study did not detect an association between CV damage and other demographic and laboratory factors such as obesity, antiphospholipid antibodies, & CRP. Similarly, Pons-Estel et al. found that antiphospholipid antibodies and obesity were insignificantly associated with CV damage in SLE, but they reported that high serum levels of CRP had been described to be linked to overall damage in SLE patients [25]. Lee et al. detected that CRP is insignificantly associated with the CV damage index in SLE [35].

In this work, there was no association between CV damage and glucocorticoids or hydroxychloroquine and this was consistent with observations of Pons-Estel et al. [25]. Nevertheless, the published data by Karp et al. supported the cautious administration of corticoids, but at the same time the broad administration of antimalarials to avoid CV damage in SLE [36].

These disparities in the cardiac findings in SLE could be partially explained by differences in patient characteristics, including age, race, antibody profiles, disease phenotype, and geographic distribution [34].

Overall, all these findings support the fact that inflammation plays a critical role in determining cardiovascular damage among lupus patients [19].

Limitations

The limitations of this research were a single-center analysis and a relatively small sample size. So, the data can't be generalized.

Conclusion

Cardiovascular damage is detected in (16.7%) of lupus patients. It has a significant positive correlation with SLE disease activity. There are significant associations between CV damage and SLEDAI-2K ≥ 6, smoking, dyslipidemia, pyuria, and hematuria among lupus patients.SLEDAI-2K ≥6, smoking, and dyslipidemia are independent predictors for developing CV damage in SLE. So, recognizing high-risk lupus patients is especially essential to tightly control the inflammatory process and modifiable traditional risk factors to avoid such cardiovascular damage. Screening all SLE patients with an echocardiography is important, particularly at presentation as a baseline and during flare-ups. A larger-scale prospective study may have added value in evaluating the prognostic significance of these results.

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Authors contribution: The authors were responsible for data collection and analysis, as well as writing and preparing the manuscript for publication. All authors reviewed and approved the final version

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