Assessment of Cardiovascular Diseases in Lupus Patients

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Abstract: Aim of the work: The aim of the present study was to assess the cardiovascular diseases in SLE patients. **Patients and methods:** This is a cross sectional study of a total 50 SLE patients (44 females and 6 males), aged between20-40 with confirmed diagnosis of SLE based on the American College of Rheumatology (ACR) classification criteria for diagnosis of SLE were recruited from September 2016 to February 2017. Patients were collected from outpatient and inpatient of Rheumatology and Cardiology departments. The examination and investigations were performed at the Rheumatology, Cardiology and Radiology departments, Faculty of Medicine, Al-Azhar University, and New Damietta. All participants were examined by: resting 12 leads ECG, exercise ECG, echocardiography and carotid duplex. **Results:** Forty percent (n=20) of patients had cardiovascular manifestations while 60% of them did not develop cardiovascular manifestations at the time of enrollment in the study. Pericardial involvement was present in 10 patients (20%) (3 Pericarditis and 7 pericardial effusions). Valvular affection was detected in 10 patients (20%). Mitral regurge was present in 6 patients (12%), tricuspid regurge in 4 patients (8%). Aortic valve affection was not found in our patients. Mitral regurgitation was much more common than stenosis which was shown in 6 patients (12 %) and 0 patients (0%) respectively. Left ventricular hypertrophy was detected in 9 patients (18%). Pulmonary hypertension was present in 3 patients (6%). Eleven patients (22%) had up sloping ST segment depression in inferolateral leads (which is considered non-significant changes) while the others had normal stress test. As regard disease activity, 20 patients (40%) had mild activity, 18 patients (36%) had moderate activity, and 12 patients (24%) had severe activity. The results of the current study also revealed that the systemic lupus erethromatosus disease activity index (SLEDAI score) is significantly higher in SLE patients with cardiovascular manifestations than those without cardiovascular manifestations. The results of the current study also revealed that the disease duration is significantly longer in SLE patients with cardiovascular manifestations than those without cardiovascular manifestations. Vascular affection was found in the form of atherosclerotic plaque in 2 (4%) patients, the elevated intima-media thickness was found in 12 (24%) patients. **Conclusion:** Cardiovascular manifestations are common in SLE patients (40% of the patients). SLEDAI score is significantly higher in SLE patients with cardiovascular manifestations than those without cardiovascular manifestations. The disease duration is significantly longer in SLE patients with cardiovascular manifestations than those without cardiovascular manifestations.
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1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by presence of autoantibodies directed against different structures; therefore, tissue damage may result from deposition of immune complexes and antigens in various organs including the heart, lungs, kidneys, brain, skin, serous membrane, peripheral nerves, and blood components. SLE is a worldwide disease, with prevalence of 15 to 50/100,000 individuals, while in Saudi Arabia, prevalence was estimated to be 19.28 per 100,000 population **(1)** and symptoms usually appear between the second and third decades **(2)**.

Cardiovascular disease is the leading cause of morbidity and mortality in patients with SLE. The most prevalent diseases are coronary heart disease (12-90%), myocardial diseases (40-60%) and pericardium (25-50%), heart failure (5-31%), valvular heart diseases (13-65%) and conduction disorders (3-16%) **(3)**. It is estimated that 50% of patients with SLE have cardiac abnormalities, mostly oligosymptomatic but detectable when investigated with high-sensitivity imaging methods **(4).**

Autoimmune activity of SLE may induce epicardial, endocardial or pericardial disease (the most common one) with spectrum of clinical manifestations

ranging from asymptomatic patients to scenarios of acute left ventricular failure requiring hemodynamic support **(5).** Valvular heart diseases are less common and have prevalence similar to the general population (**6**).

The perception of subclinical cardiac damage is essential to stop the myocardial injury cycle and prevent the progression of heart disease **(7).** SLE itself confers the greater risk for premature coronary heart disease (CHD); and disease activity, cumulative damage, autoantibodies, soluble inflammatory factors, and medications seem to be involved as well so early detection and management may improve long term prognosis **(8)**.

It is important to monitor cardiac state in SLE patients because of increased risk of CAD, cardiotoxicity by drugs (mainly cyclophosphamide and hydroxychloroquine) and lupus myocarditis which should guide the management of these patients in a context of acute cardiopulmonary symptoms **(9).**

Because of the pleomorphic nature of this disease, its cardiac manifestations have not been fully emphasized. However, with prolonged survival of patients and improvement in diagnostic techniques, the cardiac affection associated with SLE has become more apparent **(10).**

Aim of the work

The aim of the present study was to assess the cardiovascular diseases in SLE patients.

2. Patients and methods

This is a cross sectional study.

Fifty SLE patients (44 females and 6 males), aged between 20-40 years with confirmed diagnosis of SLE based on the American College of Rheumatology (ACR) classification criteria for diagnosis of SLE were recruited from September 2016 to February 2017. Patients were collected from outpatient and inpatient of Rheumatology and Cardiology departments. The examination and investigations were performed at the Rheumatology, Cardiology and Radiology departments, Faculty of Medicine, Al-Azhar University, New Damietta.

Exclusion Criteria:

1- Patients who suffer from other diseases affecting the heart such as hypertension, diabetes, hyperlipidemia or Ischaemic heart disease or Rheumatic heart disease or congenital heart disease.

2- Patients who are not fit for stress ECG.

Baseline Evaluation:

Demographic data were analyzed along with history of comorbidities, drugs history including prednisolone, methotrexate, cyclophosphamide, hydroxychloroquine and azathioprine.

All patients had been assessed as follows:

1. Detailed history taking

2. Physical Examination

i. General Examination

ii. Systemic Examination

iii. Assessment of disease activity in the SLE patient by the SLE Disease Activity Index (SLEDAI)

3. Laboratory Investigations:

a- Routine investigations including:

-Complete blood count, Erythrocyte Sedimentation Rate and CRP.

-Liver function tests, Kidney function tests, blood sugar and urine analysis.

-Rheumatoid factor.

b- Autoimmune profile including antinuclear antibodies, lupus anticoagulant and anti dsDNA antibodies.

c- Anticardiolipin (IgG, IgM) antibodies using enzyme-linked immunosorbent assay (ELISA) technique.

Cardiovascular system assessment

All participants were examined by:

-Resting 12 leads ECG.

-Exercise ECG.

-Echocardiography.

-Carotid duplex**.**

Statistical analysis

All data was entered and analyzed through (Minitab version 17). Categorical variables were presented as numbers and percentages whereas continuous variables were expressed as median, range and Mean ± S.D.

3. Results

The mean age of the patients was 28.24±7.02 years (ranged from 20 – 40 years). The disease duration ranged from 1-17 years with a mean of 5.92±4.65 years. Data regarding drug intake showed that 42 (84%) patients were on systemic corticosteroids, 43 (86%) were on Hydroxychloroquine, 16 (32%) were on Azathioprine, 6 (12%) were on Cyclophosphamide and 5 (10%) were on Methotrexate (Table 1).

Based on **SLEDAI score**, all patients were active: 20 (40%) had mild disease activity, 18 (36%) were moderately active and 12 (24%) had severe activity.

By analysis of the clinical manifestation of the SLE patients, we found that the muco-cutaneous involvement was the most common clinical manifestation affecting patients: photosensitivity affecting 47 (94%) patients, alopecia affecting 50 (100%) patients, malar rash affecting 33 (66%), oral ulcers affecting 32 (64%) whereas discoid lesion affecting 3 (6%) patients. Musculoskeletal involvement was the 2nd most common clinical manifestation affecting patients: arthralgia affecting 50

(100%) patients and arthritis affecting 14 (28%) patients.

Constitutional manifestations were reported in 38 (76%) patients, with 18 (36%) patients had fever, 38 (76%) had fatigue and 15 (30%) had weight loss. Neuropsychiatric manifestations are also prevalent in SLE patients affecting 35 (70%) patients. lupus headache was found in 35 (70%) patients and psychosis in 18 (36%) patients. Pulmonary involvement was found in 3 (6%) patients. GIT involvement was found in 15 (30%) patients. Renal involvement was found in 46% of patients.

The presence of autoantibodies (ANA, anti-dsDNA, anticardiolipin and lupus anticoagulant) and the low concentrations of complement C3 and C4 components are shown in Table 2.

Overall, among the participants in the current study we found that 40% (n=20) of patients had cardiovascular manifestations while 60% of the patients did not develop cardiovascular manifestations at the time of enrollment in the present study. Pericardial disease was detected in 10 patients (20%) (3 Pericarditis and 7 pericardial effusion). Valvular affection was detected in 10 patients (20%) (6 mitral regurge and 4 tricuspid regurge), Left Ventricular Hypertrophy was detected in 9 patients (18%) and Pulmonary hypertension in 3 patients (6%), Aortic valve affection was not found in our patients. Four patient had LVH and MR, 2 patients had LVH, MR and pulmonary hypertension, 2 patients had LVH and TR, and one patient had LVH, TR and pulmonary hypertension as in Table 3.

The association of SLEDAI with cardiac valve abnormalities was found to be of high significance ($p<0.01$) especially mitral valve and left ventricular hypertrophy (Figure 1). The correlation of cardiac abnormalities and disease duration was found to be of high significance especially for Tricuspid regurge ($P<0.01$) and significant association in left ventricular hypertrophy and Pulmonary hypertension ($P<0.05$) (Figure 2).

Eleven patients (22%) had up sloping ST segment depression in inferolateral leads (which is considered non-significant changes) while the others had normal stress test.

Vascular affection was found in the form of Atherosclerotic plaque in 2 (4%) patients, the elevated intima-media thickness was found in 12 (24%) patients. The twelve patients having SLE related vascular manifestations (100%) were with positive CRP, ANA, lupus anticoagulants, anticardiolipins (IgG, IgM) antibodies (Figure 3).

Table (1): Demographic data of studied SLE patients

Patient (n=50)	**Mean ± SD**	**Range**
Age (years)	28.24±7.02	20-40
Disease duration (years)	5.92±4.65	1-17
	Number of Patients	**Percentage (%)**
Sex		
Male	6	12%
Female	44	88%
Severity of Disease		
Mild	20	40%
Moderate	18	36%
Severe	12	24%
Drug History		
Systemic Corticosteroids	42	84
HCQ	43	86
AZA	16	32
CYC	6	12
MTX	5	10

Table (2): Laboratory findings in the SLE patients

	Range	Mean ±SD
Hemoglobin concentration (gm/dl)	7.1-15.2	11.2 ±1.8
RBCs count (x10^6/mm^3)	2.6-4.7	3.8 ±0.6
Hematocrit (%)	28-46	35.2±5.3
Leucocytes count (x10^3/mm^3)	2.1 – 12	5.6 ±2.7
Platelets count (x10^3/mm^3)	92 – 420	280.06 ±106
Serum creatinine (mg/dl)	0.4 – 2.8	1.03 ± 0.7
	Number	Percentage
Elevated serum creatinine (n, %)	6	12%
Proteinuria (n, %)	18	36%
Hematuria (n, %)	14	28%
Casts (n, %)	12	24%
Pyuria	2	4%
CRP (+ve)	41	82%
ESR (High Rate)	23	46%
C3 (Low)	27	54%
C4 (Low)	26	52%
Anticardiolipin IgG (+ve)	15	30%
Anticardiolipin IgM (+ve)	18	36%
Lupus Anti-coagulant (+ve)	34	68%
ANA (+ve)	40	80%
Anti-dsDNA (+ve)	28	56%

Table (3): Cardiac Findings distribution of studied SLE patients

Cardiac Findings	**Number of Patients**	**Percentage (%)**
LVH & MR	4	8
LVH, MR & Pulmonary Hypertension	2	4
LVH & TR	2	4
LVH, TR & Pulmonary Hypertension	1	2
Pericardial effusion	7	14
Pericarditis	3	6
TR	1	2
Total	20	40

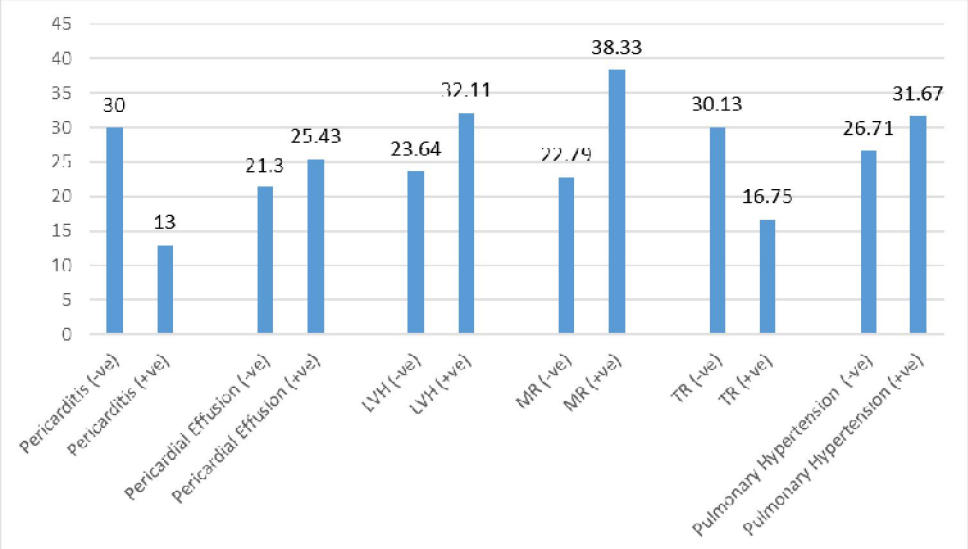

Figure 1: Association of cardiac abnormalities and SLEDAI Scoring in SLE patients

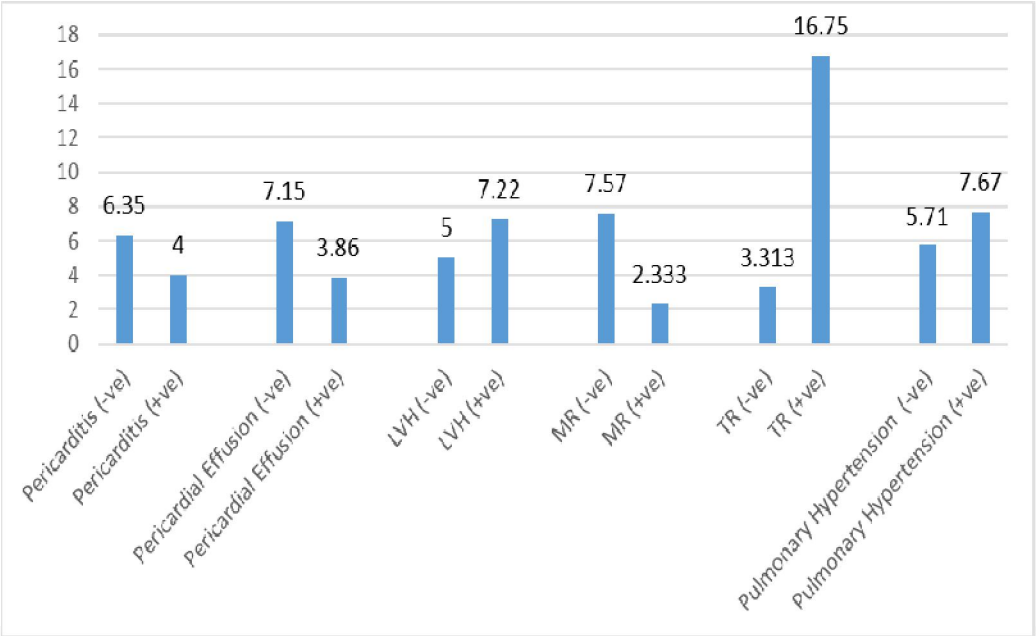

Figure 2: Association of cardiac abnormalities and disease duration in SLE patients

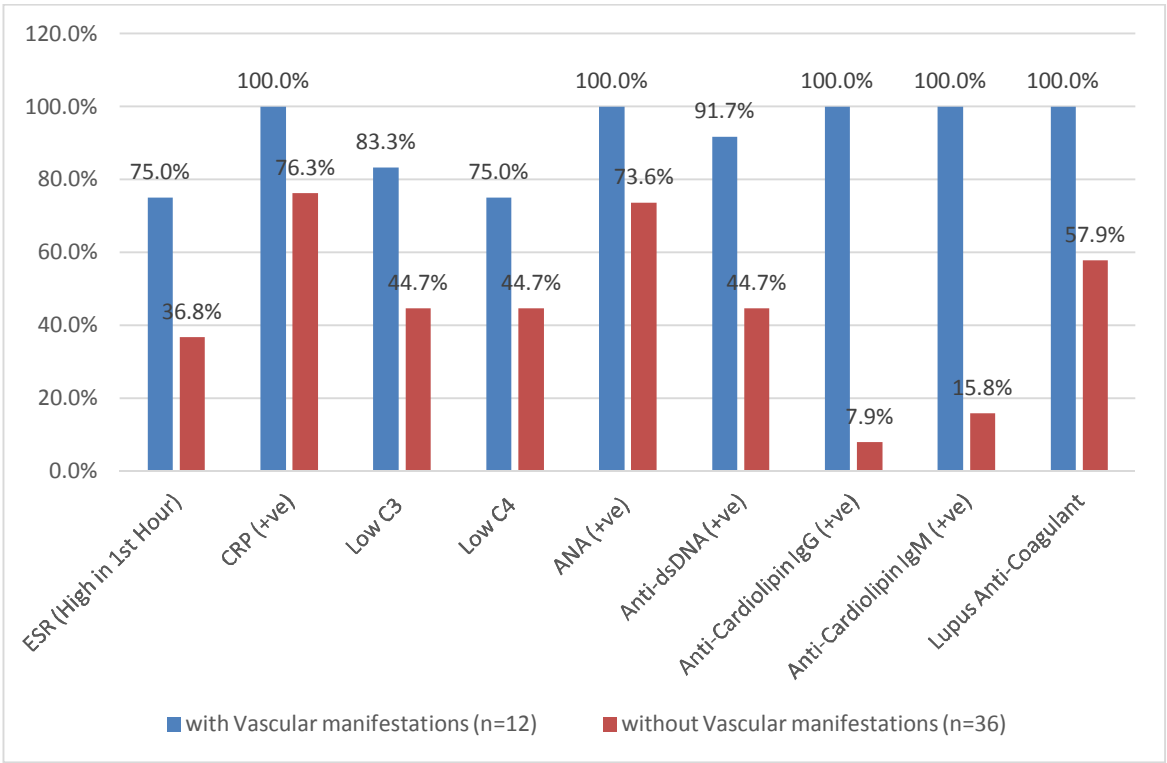

Figure (3): The association of SLE related features with the presence of SLE-related vascular manifestations.

4. Discussion

SLE is an autoimmune disease with genetic and environmental background, characterized by multi-organ involvement. Early mortality occurs because of infections and disease activity, whereas late mortality is mostly associated with cardiovascular involvement **(11).**

Autoimmune process in SLE can cause myocarditis, pericarditis, endocarditis, valvular lesions, and defect in the conduction system. The most

frequent valvular lesions reported in SLE patients were valve regurgitations with predilection to involve mitral and aortic valves **(12)**. Indeed, adverse effect of corticosteroid was also found to be another cause for cardiac disease in SLE. Cardiovascular system involvement in SLE might be associated with disease severity and activity **(13)**.

So early detection and management may improve long term prognosis **(14)**.

Our study revealed that 40% (n=20) of patients had cardiovascular manifestations while 60% of the patients did not develop cardiovascular manifestations. In agreement with our study **Hameed and his colleagues in 2007** found cardiac abnormalities among (58%) of the patients **(15)** and **Schur in 2009** found cardiac abnormalities in (50%) of patients **(16)** while **Moder et al in 1999** reported (90%) of their patients presented with cardiac abnormalities **(17)**, **Wei-Ren Lan et al in 2005** found 73.3% of their patients having cardiac abnormalities **(18)** and **Doria et al in 2005** reported that 70% of their patients had cardiac abnormalities **(13)**.

The lower incidence of cardiac involvement in the present study may due to the young age of the studied cases (mean age: 28 years) also could be explained by the exclusion criteria of the study **(13)**.

Pericardial involvement was present in 10 patients (20%) (3 Pericarditis and 7 pericardial effusion). This came in accordance with **Doria and Petri in 2004** who found pericardial effusion in 27% of lupus patients **(19)** but disagree with **Hameed and his colleagues in 2007 (15)** and **Schur in 2009 (16)** who found pericardial effusion in 42% & 55% respectively. The lower incidence of pericardial involvement in the present study may be explained by the protective effects of corticosteroids, as most of our patients (84%) were on systemic corticosteroid.

Valvular affection was detected in 10 patients (20%) in the current study. Mitral regurge was present in 6 patients (12%), tricuspid regurge in 4 patients (8%). Aortic valve affection was not found in our patients. **Leszczynski et al., 2003** studied 52 SLE patients with doppler echocardiography, their results showed echocardiographic disturbances in the form of valvular abnormalities in 18 patients (34.6%). The mitral valve was involved in 12 patients (23.1%) in the form of regurgitation, and leaflet thickening (15.5%) **(20).** The aortic valve was involved in 6 patients (11.5%) and the tricuspid valve in 3 patients (5.8%). **Mohammed et al in 2017** revealed mitral valve regurgitation in 16 patients (32%), aortic valves regurgitations were detected in five patients (10%) and tricuspid valve regurgitations were observed in 10 patients (20%) **(21)**. In agreement with the results of this current study stenotic lesions were not found in their population. The lower incidence of valvular involvement in the present study compared to the previous studies may be explained on the fact that our inclusion criteria included young patients aged from 20 – 40 and that the mean age among the cases was 28.24 years.

Left ventricular hypertrophy was detected in 9 patients (18%) in accordance with our results **Mohammed et al in 2017** revealed left ventricular hypertrophy in 11 patients (22%) **(21)** and **Ong et al. in 1992** reported that 20% of SLE patients were found to have left ventricular hypertrophy **(22).** Pulmonary hypertension was present in 3 patients (6%), this agreed with **Horwitz et al. in 1993, Tan et al., in 1982 and Pina et al., in 2003** who reported that the incidence of pulmonary hypertension in SLE patients was 1.8% to 14% **(23) (24) (25)**.

The association of SLEDAI with cardiac abnormalities was found to be of high significance ($p<0.01$) especially mitral valve involvement and left ventricular hypertrophy. This goes with the study of **Marcinkowski and his colleagues in 2003** who found an association between increased activity of the disease and the prevalence of mitral valve disease **(26),** and, also **Crozier and his colleagues in 1990** who found that mitral regurge tended to be more common with active disease **(27)**.

The disease duration ranged from 1-17 years with a mean of 5.92±4.65 years. The correlation of cardiac abnormalities and disease duration was found to be of high significance especially for tricuspid regurge ($P <0.01$) and significant association in left ventricular hypertrophy and pulmonary hypertension ($P<0.05$). In agreement with our study some studies had correlated major valvular involvement in SLE with disease duration **(Ioannis et al., 2007)** and **(Perez-Villa et al., 2005) (28) (29).**

Patients with cardiac manifestations with low c3 and c4 were 16 out of 20 (80%) while without cardiac manifestations patients with low C3 were 11 out of 30 (36.6%) and with low C4 were 10 out of 30 (33.3%) so there was significant association. **(13)**, There was higher percententage of positive ANA, Anti-dsDNA, Anticardiolipins IgG, IgM, Lupus Anticoagulant among SLE patients with cardiac manifestations in relation to SLE patients without cardiac manifestations, ANA was 100% positive in patients with cardiac manifestations while without was 80%, anti-ds DNA was positive in patients with cardiac manifestations in 85% while without was 36.6%, anticardiolipin IgG was positive in 75% of patients with cardiac manifestations while without was positive in 6.6% and lupus anticoagulant was positive in 95% with cardiac manifestation while without was positive in 15% which agreed with the study of **Pierez-Villa and his colleagues in 2005** who stated that the presence of abnormal intracardiac anatomy was

strongly associated with increased levels of anticardiolipin antibodies **(30)** and with the study of **Gabrielli and his collegues in 2009** who suggested a correlation between valvulopathy and higher levels of lupus anticoagulants and anticardiolipins antibodies **(31).**

Vascular affection was found in the form of atherosclerotic plaque in 2 (4%) patients, the elevated intima media thickness was found in 12 (24%) patients. A study by **Doria et al., in 2003** revealed a thickened intima in 28% of patients and atherosclerotic plaque in 17% of patients **(32).** While in **Ahmad et al., in 2007** the prevalence of plaque in SLE patients was 21% **(33)**. The twelve patients having SLE related vascular manifestations (100%) were with positive CRP, ANA, lupus anticoagulants, anticardiolipins (IgG, IgM) antibodies so there is significant association.

Conclusion

Cardiovascular manifestations are common in SLE patients (40% of the patients). SLEDAI score is significantly higher in SLE patients with cardiovascular manifestations than those without cardiovascular manifestations. The disease duration is significantly longer in SLE patients with cardiovascular manifestations than those without cardiovascular manifestations.

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