Original Article

Study of Cardiovascular Manifestations and Risk Factors in Systemic Lupus Erythematosus

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ABSTRACT

Background : Systemic lupus erythematosus (SLE) is a chronic autoimmune disease and is associated with several cardiovascular manifestations, of which accelerated atherosclerosis with coronary heart disease is a significant cause of morbidity and premature death. The present study was undertaken to study the cardiovascular manifestations and risk factors associated with cardiovascular diseases (CVD) in patients with SLE.

Method : Total 60 diagnosed cases of SLE were included in the study. Electrocardiogram, chest X-ray and 2D-echocardiography was done to find out cardiovascular manifestations. Traditional and non-traditional risk factors for CVD were assessed. Increased CIMT was considered as a marker of atherosclerosis and CVD which was correlated with traditional and Non-traditional risk factors.

Results : Cardiovascular system involvement was seen in 55% of patients of which most common was pulmonary hypertension (57.5%) followed by valvular involvement and pericardial effusion (39.33% each). Renal manifestations were the commonest systemic involvement (80%) followed by musculoskeletal (66.7%) and cutaneous manifestations (60%)of SLE. Most common traditional risk factor was dyslipidemia (16.67%) and raised CRP was the commonest non-traditional risk factor (51.67%). Increased CIMT was found in 16.7% cases (mean CIMT - 1.5 ± 0.05 mm) and all these patients had nontraditional disease related risk factors. There was a strong positive association between duration of disease > 5 years with premature atherosclerosis in SLE patients.

Conclusion : 2D-echocardiography is a non-invasive investigation which can be used to find out cardiovascular involvement and should be performed routinely in all patients of SLE for early diagnosis and management of CVD.

Keywords : Systemic lupus erythematosus; Cardiovascular manifestations; Atherosclerosis; Electrocardiogram; 2D-echocardiography; Traditional; Risk factors

Introduction :

Systemic lupus erythematosus (SLE) is a chronic multi-systemic autoimmune disease in which organs and cells undergo damage mediated by tissue binding autoantibodies & immune complex. 90% of patients are women of child bearing age[1]. Patients present with variable clinical features ranging from mild joint & skin involvement to life threatening renal, haematological, cardiovascular, pulmonary & neurological manifestation[2]. Cardiovascular involvement is a frequent and significant cause of morbidity in patients with SLE. Prevalence of cardiovascular manifestations in patients with SLE has been estimated to be approximately 50%[3]. Patients with SLE have two-fold increased risk of developing atherosclerosis & premature coronary artery disease than normal population of same age group[4]. Inflammation is prominent feature of atherosclerotic lesion & systemic inflammations as reflected by raised C reactive protein level in SLE are associated with increased risk of CVD[5]. Also other risk factors associated with CVD in SLE are dyslipidaemia, homocysteinemia, high cumulative dose of prednisolone[6].

The present study was aimed to further strengthen the association between SLE and the various cardiovascular manifestations and the involved risk factors. The prevalence of cardiovascular manifestations in SLE might be underestimated and under reported when compared to other system involvement like the renal system, which is screened routinely in patients of SLE. Hence early diagnosis

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and screening of cardiovascular involvement in SLE, with the help of simple tools like 2D echo may help in prevention of significant morbidity and mortality due to cardiac involvement in patients with SLE.

Materials and Methods :

After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this cross sectional observational study was conducted in Department of Medicine at Tertiary Care Centre in Central India during the period of 24 months from November 2018 to October 2020. Total 60 patients diagnosed with SLE according to "American Rheumatism Association (ACR 1997) diagnostic criteria for SLE"[7], those who gave consent at the time of presentation, follow up patients and patients with flare of underlying disease were included in the study. Patients with rheumatic heart disease, congenital heart disease, chronic obstructive pulmonary disease and patient not willing for study were excluded.

The clinical history of symptoms, duration of onset of disease, drug history, and number of flares was recorded. The vitals, general examination, head to toe examination and cardiovascular examination for every patient was carried out. Routine blood investigations were done to identify other systems involvement. Electrocardiogram, chest X-ray and 2 D echocardiography was done to find out cardiovascular manifestations in study population. Traditional and non-traditional risk factors for cardiovascular disease were assessed. Traditional risk factors included were age, hypertension, diabetes mellitus, dyslipidemia, increased BMI, family history of CVD and homocysteine. Non-traditional risk factors included were raised CRP, duration of disease > 5 years and duration of steroid therapy more than 5 years. C reactive protein is used as a marker of increased inflammatory activity in SLE patients. Common carotid artery intima to media thickness was calculated by B mode ultrasonography and colour Doppler sonography as a marker of atherosclerosis. Increased CIMT was considered as a marker of atherosclerosis and CVD. The assessment of correlation of cardiovascular system involvement with traditional and Non-traditional risk factors was done.

Statistical Analysis :

Collected data were analyzed using Statistical software STATA version 14.0. Continuous variables were presented as Mean ± SD. Categorical variables were expressed in frequency and percentages and were compared by performing chi-square test. $P < 0.05$ was considered as statistical significance.

Observation and Results :

The maximum numbers of patients were in the age group of 11-20 years (46.67%) with female predominance (76.67%). 18 (30%) patients have been received steroid therapy for more than 5 years as shown in table 1. The mean age of patient was 23.33 ± 9.16 years, ranged from 13-50 years. The mean duration of onset of disease was 2.83 ± 2.46 years. 18 (30%) patients have duration of onset of disease more than 5 years as shown in ***Table 1.***

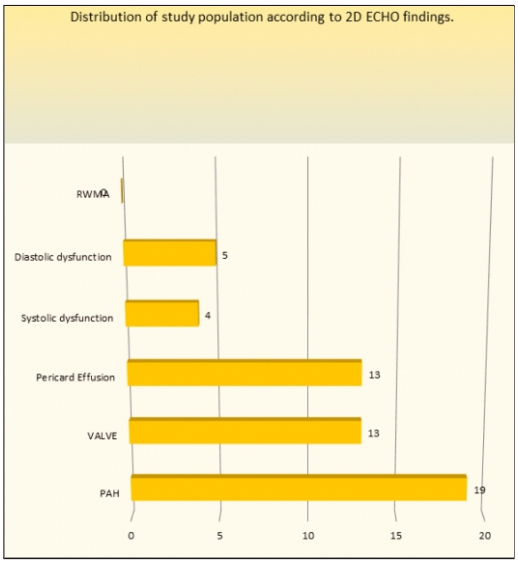
Table 1 : **Demographic data and duration of onset of disease and steroid therapy**

Demographic data		No. of patients	Percentage
Age in years Mean 23.33 ± 9.16	11-20	28	46.67
	21-30	19	31.67
	31-40	11	18.33
	41-50	02	3.33
Gender	Male	14	23.33
	Female	46	76.67
Duration (years)	0-2	33	55
	3-4	09	15
	≥5	18	30
Steroid therapy ≥5 Years	Yes	18	30
	No	42	70

Out of the 60 patients studied, 33 (55%) patients have cardiovascular system involvement on the basis of 2 D Echo findings of them only 6 (18%) patients were symptomatic and 27 (82%) were asymptomatic. Most common cardiovascular system abnormality detected was pulmonary arterial hypertension (PAH) (57.5%) ***(Table 3)*** of them 8 patients had mild PAH, 8 had moderate PAH while 3 patients had severe PAH. Followed by Valvular

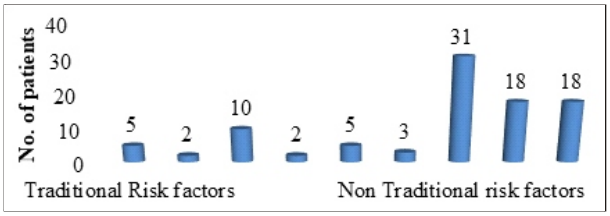
Involvement (39.3), Pericardial effusion (39.3%) followed by diastolic and systolic dysfunction (27%). Few patients have shown 2 or more cardiovascular lesion at the same time. However, most common ECG abnormality was sinus tachycardia (38.33%) whereas commonest chest X-ray finding was normal X-ray (80%) as shown in ***Table 3.***

Figure 1 : **Distribution of 2 D ECHO Findings, n=60**



20% of patients had one or more traditional risk factors while 83.33% of patients had one or more non-traditional risk factors for CVD. Most common traditional risk factor was dyslipidemia (16.67%) and raised CRP was the commonest non-traditional risk factor found in 51.67% of patients as depicted in ***Figure 2.***

Figure 2 : **Distribution of patients according to presence of traditional and non-traditional risk factors for cardiovascular diseases**
Figure No. 9 Distribution of study population according to 2D ECHO findings (N= 60)



Renal system was most commonly involved, followed by musculoskeletal and skin involvement and most of the patients (50%) had abnormal laboratory finding of anaemia. Out of 60 patients studied, 12 (20%) patients were CKD and 48 (80%) patients had increased urine protein creatinine ratio. All patients had normal LFT values.

Table 2 : **Electrocardiogram, chest X-ray and 2 D echocardiography findings for cardiovascular manifestations**

Findings		No. of patients	Percentage
2D ECHO findings	PAH	19	57.5
	Valvular involvement	13	39.3
	Pericardial Effusion	13	39.3
	LV Systolic dysfunction	04	12.1
	LV Diastolic dysfunction	05	15.3
	RWMA	00	00.0
	Total	33	100
ECG Findings	Low voltage complex	06	10.0
	Right axis deviation	03	5.0
	Sinus Tachycardia	23	38.33
	Normal	28	46.66
Chest X-ray	Pulmonary oedema	01	1.67
	Pleural effusion	02	3.33
	Cardiomegaly	03	5.00
	Cardiomegaly with pleural effusion	06	10.0
	Normal	48	80.0

Table 3 : **Distribution of study population according to other systems involvement and abnormal laboratory parameters**

Parameters		No. of patients	Percentage
Other system involvement	Renal	48	80
	Haematology	31	51.67
	Skin	36	60
	Musculoskeletal	40	66.67
	CNS	06	10.0
	Thyroid	11	18.33
	GIT	20	33.33

Out of 60 patients studied, 10 (16.7%) patients had increased CIMT in the range of 1.4 to 1.6 mm, with mean of 1.5 ± 0.05 mm and all these patients had non-traditional risk factors. When correlating traditional risk factors and increased CIMT, we found that all the 12 patients who had one or more traditional risk factors had normal CIMT and out of 10 patients with increased CIMT, no one has traditional risk factor. Thus there was **negative correlation** between traditional risk factors and increased CIMT and premature atherosclerosis in SLE patients in our study. Also on correlating the non-traditional risk factors i.e. increased inflammatory activity and increased CIMT we found negative correlation as shown in ***Table 4.*** There was **strong positive association** between duration of onset of disease and increased CIMT. So, patients with duration of onset of disease > 5 years had increased risk of developing premature atherosclerosis in SLE patients, ***(Table 4).***

Table 3 : **Distribution of study population according to other systems involvement and abnormal laboratory parameters**

Variables		Total cases	Increased CIMT	Normal CIMT	P-Value
Traditional risk factors	Present	12	00 (0.0%)	12 (100%)	0.188
	Absent	48	10 (20.83%)	38 (79.17%)	NS
Non-Traditional Risk factors	Present	50	10 (20%)	40 (80%)	0.236
	Absent	10	00 (0.0%)	10 (100%)	NS
Duration of disease	> 5 years	18	10 (55.56%)	08 (44.44%)	< 0.001 HS
	< 5 years	42	00 (0.0%)	42 (100%)	

NS : Not Significant, HS : Highly significant, CIMT : Carotid intima media Thickness

Discussion :

In the present study the mean age of patients was 23.33 ± 9.16 years and maximum numbers of patients were in 2nd and 3rd decades of life with female predominance which is comparable with the study carried out by *Kini et al*[3] and *Santhanam et al*[8]. ANA was positive in all the patients with 90% of patients had significant (1:160) ANA titre and most common ANA pattern was homogenous (70%). Anti-ds DNA antibodies found in 80% of patients followed by Anti-Smith antibodies (30%) then Anti-RNP antibodies (16.66%), anti-histone antibodies (8.33%). Coomb's test was positive in 5% of cases. These findings are similar to previous studies[8,10,& 11].

As similar to the literatures[3,12-14], in current study echocardiographic abnormality was noted in 55% of patients and most of them were asymptomatic. Most common abnormality was pulmonary arterial hypertension followed by valvular lesions and pericardial effusion. On studying various clinical manifestations of patient we found that renal system involvement was most common (80%) followed by musculoskeletal (66.7%) and cutaneous system involvement (66%). Haematological, gastrointestinal & neuropsychiatric manifestations were seen in 51.67%, 33.33% and 10% of patients respectively. Thyroid function abnormality was seen in 18% of patients. The most common

traditional risk factor was dyslipidemia (16.67%) followed by hypertension (8.33%) while raised CRP was the commonest nontraditional risk factor (51.67%) followed by duration of disease > 5 years and steroid therapy for > 5 years seen in 30% of patients each. These findings are in accordance with the other studies[3,15].

On laboratory investigations, anaemia was found in 30 (50%) patients of them 16 patients had anaemia of chronic disease with raised serum ferritin level and normocytic normochromic picture on CBC, 10 patients had microcytic hypochromic anaemia, 4 patients had haemolytic anaemia with positive coombs test. Leukopenia, thrombocytopenia and pancytopenia were found in 13.33%, 20% and 13.33% of patients respectively. CKD was found in 20% of patients while proteinuria in 80% of patients and liver function test was normal in all patients. These results are correlated with the previous studies[14,16].

The most common ECG abnormality was sinus tachycardia (38.33%) which is comparable with the study done by *Kini et al*[3]. 10 (16.7%) patients had increased CIMT on carotid artery doppler study with mean CIMT of 1.5 ± 0.05 mm. When correlating traditional risk factors and increased CIMT, we found that all the 12 patients who had one or more traditional risk factors had normal CIMT and out of 10 patients with increased CIMT, no one has traditional risk factor. Thus there was **negative correlation** between traditional risk factors and increased CIMT and premature atherosclerosis in SLE patients in our study. Also on correlating the non-traditional risk factors i.e. increased inflammatory activity and increased CIMT we found negative correlation. Similar findings are reported in a study conducted by *Roman et al*[17]. There was a **strong positive association** between duration of disease > 5 years with premature atherosclerosis in SLE patients, thus the longer duration of disease was associated with increased CIMT and premature atherosclerosis in SLE patients which is correlated with the other studies[17-19].

Conclusion :

Cardiovascular manifestations are common, under-diagnosed in patients of SLE and most of the patients were asymptomatic in early stages, and found to have subclinical 2 D echocardiographic findings. Cardiovascular system involvement was seen in 55% of patients of which most common was pulmonary hypertension (57.5%) followed by valvular involvement and pericardial effusion (39.33% each).

Hence 2D-echocardiography is a non-invasive investigation which can be used to find out cardiovascular involvement and should be performed routinely in all patients of SLE for early diagnosis and management of CVD as these are the significant cause of morbidity and mortality. Nontraditional disease related risk factors are responsible for premature atherosclerosis in a patient with SLE. Patients with longer duration of disease (> 5 years) are at increased risk of developing cardiovascular manifestations in SLE.

The study also suggested that the appropriate use of immunosuppressive and / or immunomodulator drugs to decrease disease related inflammatory activity can decrease the risk premature atherosclerosis in patients with SLE. Though traditional risk factors are not primarily responsible for premature atherosclerosis in SLE, presence of traditional cardiovascular risk factors in a patient with SLE should be treated aggressively because of their proven role in cardiovascular diseases.

Study Limitations :

This was a cross sectional observational single centre study, with small sample size but adequate to decide the power of the study. Long term follow up of the patients need to be done to study the association between various traditional and non-traditional risk factors with premature atherosclerosis in a patients with SLE.

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