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# COMPARISON OF THE CARDIOVASCULAR DISEASE (CVD) RISK BETWEEN SYSTEMIC LUPUS ERYTHROMATOSIS (SLE) PATIENTS AND NORMAL CONTROL GROUP

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## ABSTRACT

***Objective:*** To compare cardiovascular disease risk between Systemic Lupus Erythromatosis (SLE) patients and normal healthy controls.

***Study Design:*** Comparative cross-sectional study.

***Place and Duration of Study:*** Rheumatology Ward & OPD, PIMS Hospital Islamabad, from Dec 2018 to Feb 2019.

***Methodology:*** Patients of age between 18-50 years, both genders having a diagnosis of Systemic Lupus Erythromatosis, were enrolled as cases group and matched healthy controls were picked from the medical out door. All the enrolled patients were selected by non-probability consecutive sampling. The calculation of Framingham risk score for all cases and controls was done using online calculator. It was based upon patients age, blood pressure, lipid parameters (total cholesterol, HDL), history of hypertension, diabetes and smoking. Among SLE cases, this score was further multiplied by a factor 1.5 as per European League against Rheumatism (EULAR) recommendations to find the correct cardiovascular risk.

***Results:*** The mean body mass index was noted (22.87 ± 2.55 vs. 23.86 ± 4.02 kg/m$^2$) in control and cases group. There was statistically significant ($p$-value<0.05) difference in systolic and diastolic blood pressure of cases and control group. Mean cholesterol level (179.63 ± 32.69 vs. 167.50 ± 32.17mg/dL) and mean triglyceride levels (156.69 ± 53.90 vs. 106.82 ± 58.35mg/dl) were significantly ($p$-value<0.05) higher in cases group as compared to control group. There was statistically significant ($p$-value <0.05) difference in mean value of Framingham risk Score of Systemic Lupus Erythromatosis patients (6.77 ± 6.37 vs. 1.82 ± 2.84) and normal healthy controls.

***Conclusion:*** Quite a large proportion of Systemic Lupus Erythromatosis patients in cases group had high risk of cardiovascular disease as compared to normal healthy controls on the basis of Framingham risk score.

**Keywords:** Cardiovascular disease (CVD), Framingham risk Score, Systemic Lupus Erythromatosis (SLE).



## INTRODUCTION

Systemic lupus erythromatosis (SLE) is a multisystem, autoimmune disease with involvement of different organs like skin, joints, kidneys and brain. It has a worldwide reported frequencies range from 20 to 240 per 100,000 persons and reported incidence rates range from 1 to 10 per 100,000 person[1]. SLE is diagnosed on the basis of history, examination and certain investigations and SLICC Classification criteria. Antineutrophilic antibodies (ANA), anti dsDNA, anti-Ro and anti-Smith antibodies may be positive in SLE patients. The leading causes of death in SLE are infection (50.0%), cardiovascular disease (CVP) (20.8%) and malignancy (12.5%)[2].

There are several risk assessment tools, which are being used to assess the cardiovascular risk in general population. These tools include systemic coronary risk evaluation (SCORE), American heart association risk score ASCVD risk score, Reynolds risk score and another famous scoring system to calculate CVD risk is Framingham risk score[3]. These risk assessment tools are usually used in general population and their use in specific autoimmune diseases like SLE is suspicious[4]. However these tools or scoring systems can be used in SLE population to identify the risk of CVD in terms of low, moderate and high risk. This quantification will help in earlier screening of high-risk patients for better intervention to manage these risk factors[5].

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Cardiovascular risk assessment in patients having autoimmune diseases like RA and SLE should be done on the basis of national guidelines and SCORE risk prediction model, as recommended by European League against Rheumatism (EULAR). The calculated risk score should be multiplied by 1.5 to adjust the increased risk associated with SLE[6,7]. The patients identified with moderate risk or high risk for CVD on the basis of risk stratification according to calculated score, should be counseled regarding the aggressive modifications in lifestyle[8]. Many SLE patients underestimate their risk for CVD. It very important to follow the recommended guidelines in such high-risk patients. The awareness regarding changes in their daily habits and lifestyle can have a significant impact on decreasing the morbidity and mortality associated with CVD among SLE patients[9].

This present study was designed to identify CVD risk associated with SLE by applying Framingham risk score and EULAR recommendations for correct identification of CVD in SLE patients in our study population[10]. So, this study was planned to calculate increased CVD risk in SLE patients in comparison to matched healthy participants, which would help the physicians in earlier identification of high-risk patients and proper management of SLE patient on their routine follow up visits.

## METHODOLOGY

This comparative cross sectional study was started after taking approval form hospital ethical board. Patient of SLE, admitted or visiting to the OPD were placed in cases group and normal healthy persons without SLE consisting on attendants of the patients were enrolled as controls. The SLE patients were diagnosed on the basis of "American College of Rheumatology" criteria for SLE. The study was conducted in rheumatology ward, OPD of PIMS hospital, Islamabad from December 2018 to February 2019.

A pilot study was conducted on 20 cases and 20 controls prior to actual study and then with the help of mean Framingham risk score from this pilot study actual sample size was calculated with the help of WHO sample size calculator on the basis of results from this pilot study. A total sample size of 124 participants was calculated consisting on 62 patients of SLE and 62 healthy controls. A 5% level of significance was used with 80% power of test, population standard deviation of 8.5, and mean value of Framingham risk score of 2.25 in control group and 6.53 in cases based upon the pilot study.

All the patients were selected by non-probability consecutive sampling method. Patients of age between 18-50 years, both genders having a diagnosis of SLE, were enrolled in SLE group and controls were picked from the medical out door. Patients were matched with respect to age and gender in control group. All patients having SLE but disease duration of less than 1 year and who were already taking lipid lowering therapies, had any previous cardiovascular events like stroke or myocardial ischemia or BMI >30 or participants who did not give consent were excluded from the study.

Demographic information like age, gender, weight, height, duration of disease and medications used were noted in a predesigned performa. History of comorbid diseases like diabetes, hypertension, stroke, ischemic heart disease was recorded. Lipid profile parameters were taken from lab reports by taking sample in fasting condition. Framingham risk score was calculated for both cases and control groups. The calculation of the Framingham risk score was based upon age, blood pressure value, lipid profile parameters i.e. total cholesterol level, HDL, history of smoking, hypertension and diabetes using online calculator. Additionally, the calculated score of SLE patients was further multiplied by 1.5 as recommended by EULAR as a correction factor for cardiovascular risk. This calculated risk gave a 10-year CVD risk for each SLE patient. This risk can be further divided into three categories including (low risk: less than 10, moderate risk: 10-20 and high risk having a score of > 20. The control group was selected from the medical outdoor OPD consisting on healthy attendants,

who do not have any disease and their Framingham risk was also calculated using the same calculator as for SLE group except its multiplication by the factor 1.5.

Data was entered and analyzed using SPSS version 23.0. Mean and Standard deviation was calculated for numeric variables and frequencies with percentages were calculated for categorical data. The comparison of the mean Framingham risk score of SLE group and control group was done using independent sample t-test and *p*-value ≤0.05 was considered significant.

## RESULTS

In this study, a total of 124 participants were included, 62 patients of SLE in cases group and 62 healthy participants in control group. The mean age in control group was 31.95 ± 7.18 years and in cases group was 33.15 ± 9.10 years. The mean values of weight, height and BMI were (61.62 ± 7.27 vs. 61.85 ± 8.75 kg), (1.63 ± 0.05 vs. 1.59 ± 0.08 m) and (22.87 ± 2.55 vs. 23.86 ± 4.02 kg/m$^2$) in control group and cases group respectively. There was statistically significant (*p*-value <0.05) difference in systolic and diastolic blood pressure of cases and control group. Systolic blood pressure (126.45 ± 14.07 vs. 115.16 ± 10.20) and diastolic blood pressure (81.37 ± 8.55 vs. 70.29 ± 10.55) was significantly higher in SLE patients' group in comparison to normal healthy controls. Two out of four lipid profile parameters also showed a significant association with SLE, in patients with SLE mean cholesterol level (179.63 ± 32.69 vs. 167.50 ± 32.17) and mean triglyceride levels (156.69 ± 53.90 vs. 106.82 ± 58.35) were significantly (*p*-value<0.05) higher in cases group as compared to control group. The mean values of HDL (45.19 ± 10.11 vs. 48.35 ± 11.10) and LDL (109.05 ± 35.96 vs. 98.66 ± 29.03) were noted comparable in cases and control groups as elaborated in table-I.

**Table-I: Distribution of demographic characteristics and lipid profile of Systemic Lupus Erythromatosis case and healthy controls (n=62).**

| Groups | Control Group | Systemic Lupus Erythromatosis Group | *p*-value |
|---|---|---|---|
| | Mean | Mean | |
| Age (Years) | 31.95 ± 7.18 | 33.15 ± 9.10 | 0.419 |
| Weight (Kgs) | 61.62 ± 7.27 | 61.85 ± 8.75 | 0.869 |
| Height (Meters) | 1.63 ± 0.05 | 1.59 ± 0.08 | 0.006* |
| Body Mass Index | 22.87 ± 2.55 | 23.86 ± 4.02 | 0.104 |
| Systolic Blood Pressure | 115.16 ± 10.20 | 126.45 ± 14.07 | <0.001** |
| Diastolic Blood Pressure | 70.29 ± 10.55 | 81.37 ± 8.55 | <0.001** |
| Cholesterol | 167.50 ± 32.17 | 179.63 ± 32.69 | 0.039* |
| High Dendisty | 48.35 ± 11.10 | 45.19 ± 10.11 | 0.099 |
| Lower Dendisty | 98.66 ± 29.03 | 109.05 ± 35.96 | 0.079 |
| Triglycerides | 106.82 ± 58.35 | 156.69 ± 53.90 | <0.001** |

*Difference is statistically significant at 5% level of significance, **Difference is highly significant at 1% level of significance.

**Table-II: Comparison of framingham risk Score between Systemic Lupus Erythromatosis cases and normal controls (n=62).**

| | Control Group | Systemic Lupus Erythromatosis Group | *p*-value |
|---|---|---|---|
| **Framingham Risk Score** | | | |
| Mean ± SD | 1.82 ± 2.84 | 6.77 ± 6.37 | <0.001** |
| **Framingham Risk Score** | | | |
| Low risk | 61 (98.40%) | 46 (74.20%) | <0.001** |
| Moderate risk | 1 (1.60%) | 15 (24.20%) | |
| High risk | - | 1 (1.60%) | |

**Difference is highly significant at 1% level of significance.

Among the cases group 61 (98.39%) patients were ANA positive. Organ involvement was observed in a large number of patients and 28 (45.16%) patients in cases group presented with any organ involvement. Among these patients 14 (22.58%) had cytopenia, 13 (20.97%) had Lupus Nephritis, only one (1.61%) patient presented with ILD, and no patients APS in our sample of cases. HCQ was present in almost all patient 61 (98.38%). Prednisolone was being used by 61 (98.39%) patients with dose of <7.5 mg in 40 (74.19%) patients and >7.5mg in 22 (35.48%) patients. Among the patients of SLE in our study hypertension was observed in 15 (24.19%) patients, diabetes mellitus was present in 4 (6.45%) patients and only one case had a history of smoking.

The analysis of the study showed that there was significant ($p$-value<0.05) difference in mean value of Framingham risk Score of SLE patients and normal healthy controls. The average value of Framingham risk Score was noted significantly greater in SLE patients 6.77 ± 6.37 as compared to normal healthy controls with mean value of 1.82 ± 2.84, showing a highly significant increase in Framingham risk Score of SLE patients. Similarly, according to the results, a very strong association ($p$-value<0.05) was found between Framingham risk Score and SLE disease status. In normal healthy control participants 61 (98.40%) had low risk of CVD in comparison to patients of SLE in which only 46 (74.20%) patients had low risk of CVD. Only participant found to have moderate risk on the basis of Framingham risk Score, on the other hand in SLE cases group 15 (24.20%) patients showed moderate risk as given in table-I.

## DISCUSSION

SLE is a chronic and multisystemic auto-immune disorder which mainly affect the female population. With passage of time in patients with SLE many other sever diseases like CVD increases significantly. After a period of 5 years, most common cause of death among SLE patients is CVD. Many epidemiological studies have identified some non-conventional/disease specific factors along with classical conventional risk factors, which stimulate the enhanced chances of atherosclerosis in inflammatory diseases like SLE[11].

The results of this present study showed that almost all the patients in cases group were females and that's why in control group almost 90% female participants were enrolled in control group. Many studies in literature also support this highly predominance of females in SLE disease, like Boulos *et al* found in his study that majority (82%) of the SLE patients were females[12]. The rate of morbidity and mortality significantly increases in patient with SLE as compared to general population. The main causes for such increase are lupus nephritis, infection and CVD[13]. The incidence of mortality due to CVD increases many times in patient with SLE. The main origin of CVD and other cardiac related manifestations is accelerated atherosclerosis, which increases the significance of proper management with respect to preventive aspect in patients with SLE for better prognosis. Lupus related atherosclerosis and its clinical indicators are caused by sevral traditional and disease related risk factors in SLE patients. Traditional risk factors include deranged lipid levels, increasing age and smoking, do not fully explain the increased risk for CVD, indicating a strong involvement of auto-immunity due to accelerated atherosclerosis[14].

The results of this present study showed that there was no significant difference in weight, and BMI of cases and control group but a significantly less mean hight was found in cases group. These results are not in accordance to previous studies in which overweight was found a major contributor to atherosclerosis in SLE patients, like in a study, Sacre *et al* found that overweight was a major contributor (OR = 4.13, $p$-value 0.047) to atherosclerosis in SLE patients[15].

According to the results of this present study it was observed that in patients with SLE mean cholesterol and triglyceride levels were significantly higher in cases group as compared to control group. But the mean values of HDL and

LDL were noted comparable in cases and control groups. These results have an agreement with findings in literature in which abnormal plasma concentration of lipids was common in patients with SLE. Dyslipidemia usually refers to elevated total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL) level[16].

A systematic review which included 28 studies found that the risk of CVD among SLE patients is at least doubled when compared with the general population. This increased risk of CVD was firstly recognized in seventies and was confirmed by many subsequent studies. These studies have reported the prevalence of coronary heart disease in SLE patients ranging from 6 to 10%[17].

CVD risk increased many times in patients of SLE, and many studies support this argument. A study conducted in Swedish population having SLE disease showed that the risk of CVD in SLE patients increased nine times as compared to age matched general population[18]. Another study conducted in Toronto showed as CVD risk increase of five times among SLE patients in comparison to normal healthy population. Yassin *et al* found that women of 35-44 years age and having SLE disease had 50 times more risk of having CVD as compared to normal healthy population in this age group. These findings are also supported by Framingham offspring study[19,20].

Parallel results were found in this present study, showing a significantly ($p$-value<0.001) higher mean value (6.77 ± 6.37 vs. 1.82 ± 2.84) of Framingham risk score and a considerably greater proportion (24.2% vs. 1.6%) of patients in moderately high-risk category of Framingham risk score.

The risk of cardiovascular events increases considerably in patients of systemic lupus erythematosus due to atherosclerosis. This increase in risk can not be explained completely on the basis of traditional cardiac risk factors. It was an established belief that lipids accumulate in arterial wall to form plaque. But recent researches have clearly revealed that main cause of atherosclerotic plaque is inflammation. Preventive strategies for modifiable cardiac risk factors can help in lowering the chance of cardiovascular events by reducing the possibility of atherosclerosis among SLE patients. Plaque formation due to inflammation is a main reason for atherosclerosis and treatment to neutralize the immunologic responses that results in plague formation can considerably reduce the chance of CVD among SLE patients[21,22].

## CONCLUSION

A considerably large proportion of SLE patients in cases group had high risk of CVD as compared to normal healthy controls on the basis of Framingham risk score. It highlights importance to create a high awareness of this risk among SLE patients, and the attainment of target cholesterol and blood pressure levels in these high-risk patients. Further attention should be paid to optimal CVD risk categorization and management in SLE patients.

## CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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