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ASSESSMENT OF THE CARDIOVASCULAR RISK IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: CHOOSING THE APPROPRIATE TOOL

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Abstract
Objectives. The aim of the research was to assess the cardiovascular risk in patients with systemic lupus erythematosus (SLE).
Materials and Methods. Cross-sectional study, including 96 patients with Systemic Lupus Erythematosus (The Systemic Lupus Collaborating Clinics classification criteria, 2012), was conducted at the Department of Internal Medicine, Institute of Cardiology, Chișinău, Republic of Moldova, between 2017-2019 years. We calculated and compared the 10-year cardiovascular risk by Systemic Coronary Risk Evaluation versus Systemic Lupus Erythematosus cardiovascular risk equation.
Results. A total number of 96 patients were included in the study, with female gender predominance (92 patients, 96%) and mean age, at the moment of the study, of 43.2±12.1 years. The Systemic Lupus Erythematosus duration was 89,9±44,1 months. The disease activity by Systemic Lupus Erythematosus Disease Activity Index was 8.08±7,1 points. Traditional cardiovascular risk factors were hypertension (50%), age (16.6%) and hypercholesterolemia (12.5%). Non-traditional risk factors were high disease activity (33.3%), antiphospholipidic syndrome (33.3%) and renal lupus (20.8%). The mean 10-year risk provided by Systemic Coronary Risk Evaluation was 7.8±9.0 points. Overall, 12.5% participants were deemed high risk, most of the subjects having moderate 45.8% or low 41.7% cardiovascular risk. According to Systemic Lupus Erythematosus Cardiovascular Risk Equation, we have established that 29.1% of patients had high cardiovascular risk, compared to only 12.5% by Systemic Coronary Risk Evaluation ($p<0.05$).
Conclusion. Patients with Systemic Lupus Erythematosus have a high cardiovascular risk, by combining traditional and non-traditional risk factors (disease activity, lupus nephritis and antiphospholipid syndrome). For clinical use, the specific tool for stratifying cardiovascular risk in Systemic Lupus Erythematosus is recommended.
Keywords: Systemic lupus erythematosus, Cardiovascular risk, SCORE, Systemic Lupus Erythematosus cardiovascular risk equation.

Introduction

Systemic lupus erythematosus (SLE) is a chronic and multisystemic disorder, linked to loss of immune tolerance to self-antigens and the production of a variety of autoantibodies, predominantly affecting women of childbearing age. Out of 10-20% of all SLE cases occur, approximately, in the first two decades of life. Its course is characterized by periods of exacerbation and remission with breakouts that are difficult to control. The most common cause of death in SLE patients, that are affected for more than 5 years, is cardiovascular disease (CVD) [1].

Coronary artery disease (CAD) is one of the cardiovascular manifestations observed in young SLE patients. The clinical manifestations of CAD in SLE can result from several pathophysiologic mechanisms, including atherosclerosis, arteritis, thrombosis, embolization, spasm, and abnormal coronary flow [2, 3, 4].

The striking clinical characteristic of most patients with SLE, who have a Myocardial Infarction (MI), is their young age. This demographic characteristic suggests that patients with SLE are at increased risk of MI and that reports of MI in patients with SLE do not simply represent chance occurrences. Fatal MI has been reported to be 3 times higher in patients with SLE than in age – and gender – matched control subjects [4, 6]. Recent case-control series have confirmed that the risk of MI in patients with SLE is increased between 9 and 50 fold over that in the general population [7]. It has been increasingly recognized that patients with SLE have a high cardiovascular mortality.

The impact of coronary heart disease (CHD) on morbidity and mortality in patients with established SLE has assumed increasing importance in their long-term management. SLE is a chronic inflammation of organism and inflammation is a prominent feature of atherosclerotic lesions [7]. To prove CVD features in SLE we observed the prevalence of clinically manifest ischemic heart disease has ranged between 8% and 16% in various studies [8-10].

Clinical epidemiological observations strongly suggest that, together with classical conventional risk factors, other mechanisms (non-conventional/disease-specific factors) promote accelerated atherosclerosis in inflammatory diseases like SLE [6-8]. SLE is now considered to be an independent risk factor for the development of atherosclerosis. Viewing atherosclerosis as an inflammatory disease, this association becomes stronger and better understood.

Based on the above, we aimed to conduct a cross-sectional study, which would allow characterizing the cardiovascular risk factors in patients with SLE.

Material and methods

The objective of the study was to assess the cardiovascular risk in patients with systemic lupus erythematosus. The study was conducted at the Department of Internal Medicine, Institute of Cardiology, Chișinău, Republic of Moldova, during 2017-2019 years.

Clinical and socio-demographic data were collected, according to The Systemic Lupus Collaborating Clinics classification criteria SLICC 2012, Systemic Lupus Erythematosus Disease Activity Index SLEDAI-2k, traditional and non-traditional cardiovascular risk factors were assessed. In the end of the study, we have appreciated the 10 year cardiovascular risk by Systemic Coronary Risk Evaluation SCORE versus SLE cardiovascular risk equation.

The research was approved by the Ethics Committee of State University of Medicine and Pharmacy "Nicolae Testemițanu" (session no. 78 of 08.06.2017). The study was conducted according to the ethical standards in the Helsinki Declaration of 1975, as revised in 2000 (5), as well as the national law.

The necessary number of subjects was calculated by applying the formula for cross-sectional studies: $n = P(1-P)(Z\alpha/d)^2$, where: $P = 0.000026$ (incidence of SLE), $Z\alpha = 1.96$, $d = 0.001$.

The statistical analysis was performed in Microsoft Excel 2010 and MedCalc statistical software, version 12.7.0. The results were presented as mean values ± standard deviation for normal distribution data and medians with range for skewed data. The statistical difference was calculated using t-Student criteria; the 95% confidence intervals were presented. The correlations were calculated by Pearson coefficient.

Results

A total of 96 patients were eligible according to the inclusion criteria and were enrolled in the study. The table 1 illustrates the general characteristic of the study group.

Table 1

General characteristics of the study group (n = 96)

Parameters	Result
Race: European	100%
Gender • Female, % • Male,%	 96 4
Residence • Rural, % • Urban, %	 58 42
Mean age at the time of the study, years (±SD)	43,2±12,1 (range 24-67)
Mean age at the disease onset, years (±SD)	31,2±13,8 (range14-56)
Mean disease duration, months (±SD)	89,7±45,5 (range 0,1-207)
Mean number of SLICC,2012 classification criteria	6,0±1,66 (range 4-10)

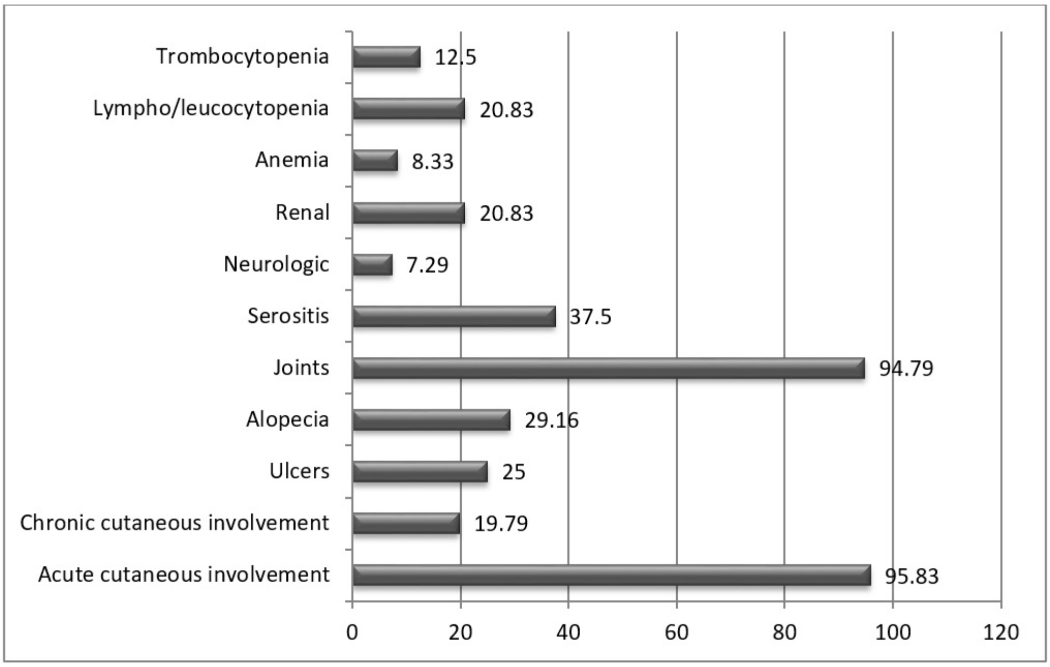

Figure 1. *Clinical manifestation of SLE in the study group (n=96).*

We have studied the clinical profile of our patients by applying SLICC, 2012 classification criteria, which includes clinical and immunological manifestations.

The most common clinical manifestations were acute/subacute cutaneous lupus and joint involvement, in 95.83% and 94.79% cases, respectively. Also, one of the frequent manifestations of the disease was serous involvement by pericarditis or pleuritis, in 37.50% of the cases. The least common findings were neurologic involvement and haemolytic anaemia, in only 7.29% and 8.33%.

The immunological changes are of a great importance in patients with SLE and are included in the SLICC criteria. So, we have collected information about the following immunologic markers: antinuclear antibody (ANA), anti-double stranded DNA antibodies, complement level – C3 and C4, anti-Smith antibodies, direct Coombs test and antiphospholipid Ab (anti-Cl ab, lupus anticoagulant and anti-beta2 glicoprotein 1 antibodies. In our patients, 91.66% had positive ANA, 87.50% positive anti-double stranded DNA antibodies. Also, 33.33% patients had antiphospholipid Ab, which is considered to be a non-traditional cardiovascular risk factor.

The next step was the assessment of the disease activity by SLEDAI, the value was 8.08±7.1 points, with variations from 0 to 20 points. We have classified SLEDAI disease activity according to the degrees of activity. As per expert consensus, SLE activity can be divided into 4 degrees: mild (less than 5 points), moderate (6-10 points) and severe activity (11-19 points) and very severe (more or equal to 20 points).

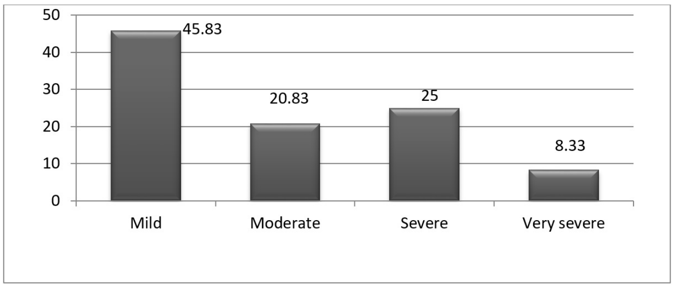

Figure 2. The classification of SLEDAI according to the of lupus activity (n=96).

According to the figure 2, most of the patients had mild or moderate disease activity, with a SLEDAI score up to 10 points (66.66%). Only 8.33% of patients had a very active disease, with a SLEDAI score of 20 points.

According to the study design, we aimed to investigate cardiovascular risk factors in patients with SLE, including traditional and non-traditional risk factors. As traditional risk factors, we can mention: the age (men >45 years, women >55 years), sex (male), current smocking, diabetes mellitus, systolic hypertension, and serum cholesterol levels (total cholesterol > 160mg/dl and high density lipoproteins HDL <40mg/dl).

Regarding the results from our study cohort, traditional risk factors were assessed.

Table 2

Conventional cardiovascular risk factors

Parameter	Relative value, %
Sex (male)	4.1
Age 9men >45 years, women >55 years)	16.6
Current smoker	8.3
Diabetes mellitus	3.12
Hypertension	50,0
Total cholesterol	12.5
Low HDL	4.1

Concerning cardiovascular risk score in our patients, we have applied the SCORE chart for the calculation. The stratification of the cardiovascular risk in our patients is shown in the following figure.

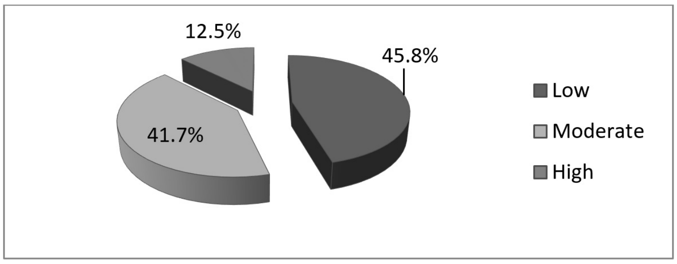

***Figure 3.** SCORE stratification in the study population (n=96)*

The mean 10-year risk provided by SCORE was 7.8±9.0. Overall, 12.5% participants were deemed high risk, most of the subjects having moderate 45.8% or low 41.7% cardiovascular risk.

Concerning non-traditional CV risk factors, the data from the literature cites several factors that have been proved to have a negative impact on cardiovascular outcomes in SLE patients. Among those, several quantifiable factors were cited:

- Renal involvement
- Inflammatory syndrome and/or SLE activity
- Presence of antiphospholipid (APL) syndrome

Renal involvement, included as well in SLICC, 2012 classification criteria, was established in 20.83% patients, which had increased level of creatinine and/or proteinuria. Concerning SLE activity, it was calculated by SLEDAI was found to be high and very high in 33.3% patients. Also, 8 (33.3%) of patients were found to have positive antiphospholipid antibodies, but only 3 patients had positive lupus anticoagulant.

After calculating Systemic Lupus Erythematosus Cardiovascular Risk Equation in our patients, we have established that 29.1% of patients had high cardiovascular risk, compared to only 12.5% by SCORE ($p<0.05$). Consequently, 16 (16.6%) patients were found to be high risk by Systemic Lupus Erythematosus Cardiovascular Risk Equation and low or moderate risk by SCORE.

We were interested to study the cases of two patients with different cardiovascular risk scores according to the both applied clinical tools.

Clinical case N1

Patient B.E., 39 years old woman, was hospitalized at the Institute of Cardiology by emergency.

At presentation, the patient complained of: dizziness and paraesthesia in the right upper and lower extremities and arthralgia.

Medical history: the patient was diagnosed with SLE 7 years ago, at the age of 32 years. The disease started with joint involvement (arthritis, arthralgia), fever, fatigue and skin eruptions. The immunological markers at the time of diagnosis: positive antinuclear antibodies ANA, high anti-DNAds Ab and positive Lupus Anticoagulant (LA). The patient was treated according to the protocol with high doses of corticosteroids and aspirin.

The evolution of the disease was marked by a relapsing course, with mild and moderate flares each year, manifested mainly by joint involvement.

Treatment regimen at admission: Methylprednisolone 8mg/day, Aspirin 75mg/day, Calcium D3 500mg/2 times a day.

Pathological antecedents: no antecedents of Arterial Hypertension, Diabetes Mellitus or dyslipidaemia.

Hereditary anamnesis: no particularities.

Bad habits: none.

Allergies: none.

Physical examination: grave general state. The inspection of the skin revealed no cutaneous eruptions. The lymph nodes were not enlarged. The thyroid gland – not enlarged. The ophthalmologic and neurologic exam was within normal limits. The auscultation of the chest – vesicular murmur. The heart beats were regular, heart rate 86 beats/minute, blood pressure 136/82 mm/Hg. The abdomen was smooth, non-tender, the liver and the spleen were not palpated. The micturitions were regular, not painful, Giordano sign – negative. Joint count: swollen joints – 2, tender joints – 5. Neurologic examination revealed hypoesthesia and of upper and lower right extremities, muscular force was 5/5 on the left side and 3/5 on the right side.

Laboratory tests results: Hemoglobin 116 g/dl, Leucocytes – $8,6x10^9/l$, Thrombocytes $236x10^9/l$; Erythrocytes sedimentation rate 25mm/h. Blood biochemistry: urea – 8.6 mg/dl, creatinine – 87 mmol/l, estimated creatinine clearance - 66 mL/min, total cholesterol – 4.6 mh/dl, high-density lipoproteins cholesterol – 1,3 mg/dl. Urine analysis – no micoalbuminuria, erythrocytes 0, leucocytes 2. Immunological testing: antinuclear antibodies ANA – 1:320, Anti-DNAds Ab – 86 U/ml (N<15 U/ml), low C3 and C4, positive lupus anticoagulant.

Electrocardiogram – normal sinusal rhythm, 72 beats/minute

Ecocardiography – no pericardial effusion, left ventricle ejection fraction 66%, no valve regurgitations

Chest radiography – normal result

Systemic Lupus Erythematosus specific assessment:

• SLEDAI – 8 points (arthritis 4, low complement 2, anti-DNAds Ab 2)

• SLICC/ACR Damage Index – 0 point

• SCORE risk score – low (0.2%)

• Systemic Lupus Erythematosus Cardiovascular Risk Equation – 8 points (by presence of lupus anticoagulant, SLEDAI > 2p and low complement level) – estimated 10 year risk is 8.9%.

Taking into account anamnesis, physical examination and laboratory results a brain CT was ordered, that confirmed an thromboembolic stroke.

Diagnosis: Systemic lupus erythematosus, SLEDAI 8 points, SLICC/ACR DI 0 point. Secondary antiphospholipidic syndrome complicated with embolic stroke.

In conclusion, we have presented a case of a young SLE patient, which was admitted to the hospital embolic stroke. The use of SCORE showed 0.2% change of cardiovascular events; meantime, the use of a more specific tool for SLE patients - Systemic Lupus Erythematosus Cardiovascular Risk Equation - estimated a 10 year risk of 8.9%.

Clinical case N2

Patient T.C., 33 years old woman, was admitted in the intensive care unit with the following complaints: dyspnoea at rest, digital ulcers, oral ulcers.

Medical history: The patient was diagnosed with SLE 8 months ago. The disease started with fatigue, fever and arthritis. The immunological markers at the time of diagnosis: positive ANA and high anti-DNAds Ab, high anti cardiolipin Ab titers.

The patient was prescribed high dose prednisolone and aspirin. It is to note that the patient has decreased by herself her prednisolone dosage, at the time of hospitalization – Methylprednisolone 4 mg/day and no aspirin intake.

Pathological antecedents: 1 miscarriage at the age of 27 years.

Hereditary anamnesis: no particularities.

Bad habits: current smocking.

Allergies: none.

Physical examination: grave general estate. Acrocyanosis. The inspection revealed digital ulcers. The lymph nodes were not enlarged. The thyroid gland – not enlarged. The ophthalmologic and neurologic exam was within normal limits. Respiratory rate – 23/minute. The auscultation of the chest – diffuse crepitations. SaO_2 at rest – 72%. The heart beats were regular, heart rate 102 beats/minute, blood pressure 123/85 mm/Hg. The abdomen was smooth, non-tender, the liver and the spleen were not palpated. The micturitions were regular, non-painful, Giordano sign – negative. Joint count: swollen joints – 0, tender joints – 2.

Figure 4. *Digital ulcers (lupus vasculitis)*

Laboratory tests results: Hemoglobin – 106 g/dl, Leucocytes – $4,1x10^9/l$, Thrombocytes – $166x10^9/l$; Erythrocytes sedimentation rate – 34 mm/h. Blood biochemistry: urea – 9,6 mg/dl, creatinine – 45 umol/l, estimated creatinine clearance – 79 mL/min, total cholesterol – 3,9 mh/dl, HDL cholesterol – 1,4 mg/dl. Urine analysis – micoalbuminuria – 2 mg/l, erythrocytes – 0, leucocytes – 3. Immunological testing: ANA – 1:640, Anti-DNAds Ab – 187 U/ml (N<15 U/ml), low C3 and C4, presence of positive anti-cardiolipin Ab and anti-beta2GP1 Ab.

Electrocardiogram – sinusal tachycardia, 102 beats/minute

Echocardiography – no pericardial effusion, ejection fraction 56%, pulmonary artery hypertension 56 mm/Hg

Chest radiography – signs of pulmonary thromboembolism

Chest computer tomography – confirmation of pulmonary artery thromboembolism

Assessment by clinical tools:

• SLEDAI – 14 points (vasculitis 8, oral ulcers 2, low complement 2, anti-DNAds Ab 2)

• SLICC/ACR DI – 1 point (pulmonary hypertension)

• SCORE – low (0.4%)

• Systemic Lupus Erythematosus Cardiovascular Risk Equation – 1 points (by presence of LA, SLEDAI >2p and low complement level, current smocking and low complement level) – estimated 10 year risk is 14.2%.

Taking into account anamnesis, physical examination and laboratory results a clinical diagnosis was established: Systemic lupus erythematosus, SLEDAI 14 points, SLICC/ACR DI 1 point, severe flare with lupus vasculitis. Comorbidities: Secondary antiphospholipid syndrome, complicated by pulmonary thromboembolism.

Discussions

Traditional CVD risk factors included age, Arterial Hypertension, Diabetes Mellitus, dyslipidemia, previous vascular event defined as previous history of cerebrovascular accidents or ischemic heart disease, menopause and smoking [8, 9, 10]. Among these factors Arterial Hypertension, dyslipidemia and hypercholesterolemia have been shown to be more prevalent in SLE [10]. Metabolic syndrome (MetS) is considered an independent predictor of cardiovascular morbidity and mortality that identifies substantial additional cardiovascular risk beyond the sum of the individual risk factors. In addition to the cardiovascular risk factors that comprise the MetS, there is a strong relationship with inflammation. Several studies have shown that the prevalence of MetS is increased in SLE [11].

An important finding is that SLE patients have an increased risk for cardiovascular events even after adjustment for Framingham risk factors (Arterial Hypertension, hypercholesterolemia, Diabetes Mellitus, older age, and postmenopausal status) [12], so it is necessary to develop other methods to determine the subgroup of SLE patients that are at highest risk for CVD disease. However, traditional CV risk factors alone cannot explain the excess risk of premature CV disease among SLE patients and this suggests that disease-related factors constitute an equal or even greater risk.

The results of our study showed a prevalence of traditional cardiovascular risk factors to be different for smoking and Arterial Hypertension published in other SLE studies [13, 14], where the smocking prevalence is higher, but the data for Arterial Hypertension is lower, however, the prevalence of diabetes dyslipidaemia was comparable [13, 14, 15].

The prevalence of diabetes (4.1%), was similar to the general population of females aged 45–54 years. In contrast, hypercholesterolemia (>5.5 mmol/L) was significantly less prevalent in the SLE sample (12.5% vs 33%; p value<0.01) [13, 14, 16, 17].

Conclusions

Patients with SLE have a high cardiovascular risk, by combining traditional and non-traditional risk factors (disease activity, lupus nephritis and antiphospholipidic syndrome). For clinical use, the specific tool for stratifying cardiovascular risk in SLE is recommended.

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