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Performance evaluation of the ACR 1997, SLICC 2012, and EULAR / ACR 2019 criteria of pediatric systemic lupus erythematosus

Esra Baglan[a,*], Semanur Ozdel[a], Tulin Gungor[b], Evra Celikkaya[b], Deniz Karakaya[b], Fatma Yazilitas[b], Evrim Kargin Cakici[b], Mehmet Bulbul[a,b]

[a] *University of Health Sciences, Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Department of Pediatric Rheumatology, Ankara, Türkiye*
[b] *University of Health Sciences, Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Department of Pediatric Nephrology, Ankara, Türkiye*

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Abstract

Aim: Systemic lupus erythematosus (SLE) is the prototype of chronic autoimmune diseases. One-fifth of all SLE disease occurs in childhood. In this study, it was aimed to compare the SLE classification criteria that have been used so far. These are the ACR (American College of Rheumatology) 1997, SLICC (Systemic Lupus International Collaborating Clinics) 2012, and EULAR (European League against Rheumatism) / ACR 2019 criteria.

Materials and Methods: Patients with 34 pediatric SLE and 32 antinuclear antibodies (ANA) (+) control groups who were followed up in Ankara Dr. Sami Ulus Obstetrics and Children's Hospital Pediatric Rheumatology Clinic were recruited to study. All of these patients were diagnosed by three pediatric rheumatologists. The control group consisted of ANA (+) patients with other rheumatologic diseases.

Results: The sensitivities of the ACR 1997, SLICC 2012, and EULAR/ACR 2019 criteria were 76.5%, 94.1%, and 88.2%, respectively. The specificities of the criteria for ACR 1997, SLICC2012, and EULAR/ACR 2019 were 93.8%.

Conclusion: Although SLICC 2012 showed the best sensitivity, all three classification criteria had the same specificity.

Introduction

One of the most important chronic autoimmune diseases is systemic lupus erythematosus (SLE). The term pediatric SLE describes the patients who are younger than 18 years of age. These patients constitute 10-20% of all SLE patients. The SLE seen in this period has more severe organ involvement hematologic, neurological, and nephrological compared to adulthood [1, 2] . To date, three sets of classification criteria have been defined for SLE. The American College of Rheumatology (ACR) first printed SLE criteria in 1971 to identify patients in clinical tests [3]. These criteria were separated into eleven categories with the addition of new immunological criteria in 1982 [4]. These were last updated in 1997 ACR criteria, where only the immunological criteria were changed [5]. The lupus erythematous (LE) cell criterion was excluded and adjusted to include antiphospholipid antibodies. According to the ACR 1997 criteria, a patient with four of the 11 classification criteria is diagnosed as SLE. The Systemic Lupus International Collaborating Clinics (SLICC) group modified the 1997 ACR criteria to include existing traditional wisdom using the iterative segmentation technique [6]. In SLICC 2012, mucocutaneous and neurological symptoms were expanded. SLICC 2012 classified patients as having SLE when they meet four or more criteria out of 11 clinical and 6 immunological criteria. Alopecia and hypocomplementemia were included in the criteria. Hematological signs of involvement and autoantibodies have been specified separately with different criteria [6]. In the presence of anti-double-stranded DNA (anti-dsDNA) or anti-nuclear antibody (ANA), SLICC 2012 allows classification by SLE if lupus nephritis is proven by biopsy. All criteria in the SLICC 2012 criteria cannot be immunological or clinical. The sensitivity observed in most studies in these criteria has increased at the expense of specificity [7]. In the

*Corresponding author:
Email address: eozb@yahoo.com (Esra Baglan)

SLICC 2012 criteria, specific diseases that exclude a feature that should be considered in favor of SLE were mentioned in various criteria such as excluding Behçet's disease for oral ulcer or excluding infection in the case of serositis [6]. There are also studies showing similar specificity in ACR 1997 and SLICC 2012 criteria points [8,9]. In 2019, the European League against Rheumatism (EULAR)/ ACR criteria were developed to combine the high specificity of the ACR 1997 criteria with high sensitivity. In these criteria, ANA was defined as an essential criterion. The criteria were scored between 2 and 6. Among the criteria for participation in the system, the criterion with the highest score is taken [10]. The EULAR / ACR 2019 criteria have also excluded some subtypes of cutaneous and neuropsychiatric symptoms that are included in the SLICC 2012 criteria [6,10]. There are seven clinical and three immunological areas in the EULAR/ ACR 2019 criteria. According to these criteria, a patient with positive ANA is diagnosed with SLE with the diagnosis of class 3 or 4 lupus nephritis biopsy [10].

This study aimed to test the performance of the ACR 1997, SLICC 2012, and EULAR/ ACR 2019 SLE classification criteria for pediatric SLE patients.

Materials and Methods

Thirty-four SLE cases diagnosed by 3 specialist doctors from Ankara Dr. Sami Ulus Obstetrics and Children's Hospital Pediatric Rheumatology Clinic were included in this single center study. ANA positive 32 children who applied to the hospital for various rheumatologic diseases were evaluated as the control group. The primary aim of the study is to compare the classifying criteria used in children so far.

Inclusion criteria for the study

1. Between the years 2017-2022; being diagnosed with SLE disease under the age of 18.
2. Be followed for at least 1 year.
3. To be included as a SLE patient and control, the diagnosis had to be made by a pediatric rheumatologist with at least one year of clinical follow-up and more than 5 years of experience in pediatric rheumatology.
4. As the control group; having other rheumatic diseases and ANA positivity at serum dilution of ≥1:80.

Exclusion criteria

1. Undiagnosed patients who applied to the rheumatology outpatient clinic were excluded from the study in terms of the control group.

All SLE patients who had been followed for 5 years from January 2017 and met the inclusion criteria were included in the study. For the control group, patients without a diagnosis of SLE but with another rheumatologic disease whose protocol number ended with an even digit were selected.

Demographic characteristics, clinical and laboratory characteristics detailed clinical data, and laboratory parameters such as hemogram, biochemistry, complement levels, and autoantibodies of the patient and control groups were evaluated. The specificity and sensitivity of the classification criteria were evaluated according to the characteristics of the children on the initial properties of the disease. The patients' files were reviewed by another rheumatologist who was blinded to diagnosis to identify each patient for SLE or not SLE. ANA negative patients who were diagnosed with SLE in the past were not included in the SLE cohort. Finally, all patients in both the SLE and non-SLE control groups were evaluated in terms of the ACR 1997, SLICC 2012, and ACR 2019 criteria. Since all patients were included in the study, no sample size calculation was made for patient selection. The randomization method and the single-blind method were used in the selection of the control group. A similar number of control groups was taken for the control group for the reliability of the statistical analyzes of the sample size.

Clinical Research Ethics Committee decision was taken with the number 2020-KAEK-141/121 from SBU Ankara Dr. Sami Ulus Children's Hospital.

Statistical analysis

Mean, standard deviation, median, minimum, and maximum values were given in descriptive statistics for continuous data. Number and percentage values were given in categorical data. The Shapiro-Wilk test was used to examine the conformity of continuous data with a normal distribution. It was determined that the continuous data (age of onset of complaint, age of diagnosis) did not comply with the normal distribution, and the Mann Whitney U test was used for comparisons between the patient and control groups. Chi-Square and Fisher's Exact tests were used for group comparisons (cross tables) of nominal variables. Fisher's exact test was used in cases where the expected frequency (have expected less count) was >25% in the chi-square analysis, and in other cases, the Pearson's Chi-Square test was used. IBM SPSS version 20 (Chicago, IL, USA) program was used in the evaluations and $p<0.05$ was accepted as the statistical significance limit.

Results

Thirty-four SLE patients, 32 control patients, were recruited to this study. In the control group, 14 patients had juvenile idiopathic arthritis, 9 patients had juvenile dermatomyositis, 5 patients had IgA vasculitis, 2 patients had Takayasu arteritis, and 2 patients had interferonopathy. The list of SLE patients and the control group is given in Table 1.

Two patients in the control group met all the SLE classification criteria (6.3%). Antiphospholipid antibody syndrome was the only comorbid condition accompanying SLE. There was no comorbid disease in the control group. Girls were predominant in both the SLE group and the control group.

The age of onset of disease and related complaints were greater in the SLE group ($p<0.05$). In addition, most of the items in criteria sets differed significantly between the two groups Table 2.

Six patients with SLE met the criteria of SLICC 2012 and were diagnosed with SLE, but these patients were not diagnosed with SLE according to the criteria of EULAR /

Table 1. Demographic and clinical data of patients with SLE and control group.

	SLE (n:34)	Control (n:32)	p
Gender	26 female(76.5%) 8 male(23.5%)	23 female(71.9%) 9 male(28.1%)	0.670
Age of onset of complaint	13.12 ± 2.85 13.5 (6-17)	10.19 ± 5.15 11 (2-17)	0.036
Age of diagnosis	13.21 ± 2.89 13.5 (6-17)	10.00 ± 5.41 11 (0-17)	0.030
Fever	11(32.4%)	2(6.3%)	0.008
Pleural effusion	5(14.7%)	0	0.054
Joint involvement	20(58.8%)	7(21.9%)	0.002
Alopecia	2(5.9%)	0	0.493
Oral ulcer	9(26.5%)	4(12.5%)	0.154
Nasal ulcer	2(5.9%)	0	0.493
Malar rash	16(47.1%)	0	0.000
Photosensitivity	16(47.1%)	1(3.1%)	0.000
Chillblain lesions	2(6.2%)	0	0.492
Delirium	1(3.1%)	0	1.000
Convulsion	3(9.7%)	0	0.113
Acute confusional state	4(12.5%)	0	0.113
Coma	2(6.2%)	0	0.492
Central nervous system involvement	6(18.8%)	2 (6.2%)	0.257

p<0.05 was accepted as the statistical significance limit.

ACR 2019. Only one of the patients diagnosed as SLE with EULAR / ACR 2019 criteria appropriate the SLICC 2012 criteria. Common involvements were seen in 18 (60%) of SLE patients meeting EULAR/ACR 2019 criteria and also 20 (58.8%) of patients meeting SLICC 2012 criteria.

While 9 (26.5%) patients diagnosed with SLE according to SLICC criteria had oral ulcers, 8 (26.7%) patients diagnosed with SLE with EULAR/ACR 2019 criteria had oral ulcers. Five (14.7%) patients who met the SLICC criteria had thrombocytopenia, 3 (10%) patients who were diagnosed with SLE with the EULAR / ACR 2019 criteria had thrombocytopenia. There was hematologic involvement in 28 (82.4%) patients who met the SLICC criteria, in 24 patients (85.7%) who met the ACR 1997 criteria (three criteria $p<0.05$).

Only 2 patients (6.3%) in the control group were misclassified as SLE according to all criteria, both of these patients were interferonopathies. One of them was Aicardi Goutries syndrome, the other was spondyloendochondrodysplasia. The common features of both interferonopathies were fever, joint involvement, and hematologic involvement. ANA was positive in both patients, C3 and C4 were low, and direct coombs were positive. Both patients had no proteinuria and no kidney biopsy was performed. Also, both patients responded well to the SLE treatment given before being diagnosed with interfereonopathy.

The sensitivities of the ACR 1997, SLICC 2012, and EULAR/ACR 2019 criteria were 76.5%, 94.1% and 88.2%, respectively. The specificity of all three classification criteria was the same with 93.8%.

Discussion

Unfortunately, there are currently no specific classification criteria for pediatric SLE patients. Therefore, it is important to compare and evaluate these sets of criteria in pediatric patients with SLE cohorts. To date, the largest pediatric SLE study comparing all three sets of criteria is conducted by Batu et al. In this study, these three classification criteria were compared in a cohort of pediatric SLE patients. In this study, SLICC 2012 criteria had the highest sensitivity (95.4%). The ACR 1997 criteria were found to have the highest specificity [11]. The removal of malar rash and photosensitivity in the SLICC 2012 criteria are the first and main changes in the criteria. It prevents patients with mucocutaneous lesions from being mistakenly diagnosed with SLE.

Second, hematological criteria are specified separately in SLICC 2012 criteria. According to the ACR 1997 criteria, a lymphocyte count as $<1{,}500$ / $mm^3$is required at least 2 times, while in the SLICC 2012 criteria $<1{,}000$ / $mm^3$is required only once. Third, the definition of synovitis by the SLICC 2012 classification criteria allows the inclusion of forms of erosive arthritis in the diagnosis of SLE. Finally, an important consideration in the SLICC 2012 criteria should also be sufficient to classify nephritis as having

Table 2. Laboratory data of patients with SLE and control group.

	SLE	Control	p
Leucopenia	18(52.9%)	0	0.000
Lymphopenia(<1000)	12(35.3%)	5(15.6%)	0.068
Lymphopenia(<1500)	15(44.1%)	1(3.1%)	0.000
Thrombocytopenia	3(8.8%)	2(6.2%)	1.000
Hemolysis	17(50%)	2(6.2%)	0.000
Hematological involvement	28(82.4%)	2(6.2%)	0.000
Low C3	31(91.2%)	2(6.2%)	0.000
Low C4	32(94.1%)	0	0.000
ANA positivity	30(88%)	4(12.5%)	0.000
Antids DNA positivity	27(79.4%)	0	0.000
ACA positivity	5(14.7%)	0	0.054
Antibeta2 positivity	2(5.9%)	0	0.493
Lupus anticoagulant	7(20.6%)	2(6.2%)	0.151
Direct coombs positivity	24(70.6%)	2(6.2%)	0.000
Biopsy-proven nephritis	28(%82.4)	0	0.000

p<0.05 was accepted as the statistical significance limit.

SLE in the presence of anti-dsDNA12 and ANA [12]. The increased frequency of renal involvement in pediatric SLE can be found in greater availability to the high sensitivity of the SLICC 2012 criterion because SLICC 2012 is the only criterion that allows for the classification of SLE in the presence of any class of lupus nephritis and positive serology.

In 2011 and 2012 Livingstone et al. compared pediatric SLE and SLE in adults. Lymphadenopathy, central nervous system involvement, kidney disease, anti-dsDNA, and anticardiolipin were more common. Raynaud's phenomenon, pleurisy, Sikka syndrome, and rheumatoid positivity were more common in adult SLE patients [1,2]. There was 55 % hematologic involvement in the SLE cohort of Batu et al. [11]. The reason for the high number of hematological findings may be that each of the hematological findings is separated into a separate group in SLICC.

Rubio et al. compared the performance of 3 sets of criteria in 217 adults with SLE. They showed that the SLICC 2012 criteria performed best in sensitivity (100%) compared to the ACR 1997 (94%) and EULAR/ACR 2019 criteria (94%) [13]. We also found a high sensitivity to SLICC in our cohort of patients.

In most previous studies comparing the ACR 1997 and SLICC 2012 criteria, the SLICC 2012 criteria have been shown to have higher sensitivity but lower specificity when compared to the ACR 1997 criteria. In 2018, Hartman et al. conducted a systematic review of studies comparing the first two classification criteria. In adult SLE (5,236 SLE and 1313 controls), SLICC 2012 had higher sensitivity (94.6% vs. 89.6%, respectively) and slightly lower specificity (95.5% vs. 98.1%, respectively) than the ACR 1997 criteria.) has been found.

On the other hand, in pediatric SLE (568 SLE patients and 339 controls), SLICC 2012 had a higher sensitivity (99.9% vs. 84.3%, respectively). It resulted in much lower specificity than the ACR 1997 criteria (82% vs. 94.1%). Rodrigues Fonseca et al. found in their study that SLICC 2012 had the highest sensitivity (89.3%). In their reports, it was shown that the ACR 1997 criteria had the highest specificity (83.2%) [14].

In the largest pediatric cohort study of SLE of 772 patients comparing the criteria of ACR1997 and SLICC 2012, Tao et al. showed that the sensitivity of SLICC 2012 was higher than the first criteria (96.3% versus 92.4%, respectively) [15]. Interestingly, the SLICC 2012 criteria had the advantage of classifying young SLE patients early in the course of the disease [7].

Since SLE is rarely seen in childhood, our case number is small, which is the main limitation of the study.

Conclusion

Separating hematologic symptoms with different criteria in SLICC 2012 and giving arthritis a high score in the EULAR / ACR2019 criteria may contribute to the lower specificity of these criteria sets compared to the ACR 1997 criteria. The classification criteria in SLE have been developed based on data from adult patients and have not been validated in children. However, pediatric SLE is different from adult SLE in some ways and new validated classification criteria are needed in children.

Ethics approval

Clinical Research Ethics Committee decision was taken with the number 2020-KAEK-141/121 from SBU Ankara Dr. Sami Ulus Obstetrics and Children's Hospital.

References

1. Livingston B, Bonner A, Pope J Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: A meta-analysis. Lupus 2011;1345–1355.
2. Livingston B, Bonner A, Pope J Differences in Autoantibody Profiles and Disease Activity and Damage Scores Between Childhood- and Adult-Onset Systemic Lupus Erythematosus: A Meta-Analysis. Seminars in Arthritis and Rheumatism 2012; 42:271–280.
3. Trimble RB, Townes AS, Robinson H, et al.Preliminary criteria for the classification of systemic lupus erythematosus (SLE) evaluation in early diagnosed SLE and rheumatoid arthritis. Arthritis & Rheumatism 1974; 17:184–188.
4. Satoh M, Hamamoto T, Shibata T, et al.An Evaluation on the 1982 Revised Criteria for the Classification of Systemic Lupus Erythematosus. Japanese Journal of Clinical Immunology 1987; 10:186–193. https://doi.org/10.2177/jsci.10.186.
5. RHEUMATISM AE Updating the American College of Rheumatology. 40:1997.
6. Petri M, Orbai AM, Alarcõn GS, et al.Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis and Rheumatism 2012; 64:2677–2686. https://doi.org/10.1002/art.34473.
7. Hartman EAR, van Royen-Kerkhof A, Jacobs JWG, et al. Performance of the 2012 Systemic Lupus International Collaborating Clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus. A systematic review and meta-an. Autoimmunity Reviews 2018; 17:316–322.
8. Adamichou C, Nikolopoulos D, Genitsaridi I, et al. In an early SLE cohort the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria classify non-overlapping groups of patients: use of all three criteria ensures optimal capture for clinical studies while their modification earlier classification and treatment. Annals of the rheumatic diseases 2020; 79:232–241.
9. Ma M, Hui-Yuen JS, Cerise JE, et al. Validation of the 2019 European League Against Rheumatism/American College of Rheumatology Criteria Compared to the 1997 American College of Rheumatology Criteria and the 2012 Systemic Lupus International Collaborating Clinics Criteria in Pediatric System. Arthritis Care and Research 2020;72:1597–1601.
10. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Annals of the Rheumatic Diseases 2019; 78:1151–1159.
11. Batu ED, Kaya Akca U, Pac Kısaarslan A, et al. The Performances of the ACR 1997, SLICC 2012, and EULAR/ACR 2019 Classification Criteria in Pediatric Systemic Lupus Erythematosus 2021;48(6):907-914.
12. Pons-Estel GJ, Wojdyla D, McGwin G, et al. The American College of Rheumatology and the Systemic Lupus International Collaborating Clinics Classification criteria for systemic lupus erythematosus in two multiethnic cohorts: A commentary. Lupus 2014;23:3–9.
13. Rubio J, Krishfield S, Kyttaris VC.Application of the 2019 European League Against Rheumatism/American College of Rheumatology systemic lupus erythematosus classification criteria in clinical practice: a single-center experience. Lupus 2020;29:421–425.
14. Fonseca AR, Rodrigues MCF, Sztajnbok FR, et al. Comparison among ACR1997, SLICC and the new EULAR/ACR classification criteria in childhood-onset systemic lupus erythematosus. Advances in Rheumatology 2019; 59:1–9.
15. Tao JJ, Hiraki LT, Levy DM, Silverman ED.Comparison of sensitivities of American college of rheumatology and systemic lupus international collaborating clinics classification criteria in childhood-onset systemic lupus erythematosus. Journal of Rheumatology 2019; 46:731–738.