The performances of the ACR 1997, SLICC 2012, and EULAR/ACR 2019 classification criteria in pediatric systemic lupus erythematosus

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Running head: Classification of pediatric SLE

Abstract

Objective: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease. The ACR (American College of Rheumatology) 1997, SLICC (Systemic Lupus International Collaborating Clinics) 2012, and EULAR (European League Against Rheumatism)/ACR 2019 SLE classification criteria are formed based on data mainly from adult patients. We aimed to test the performances of the SLE classification criteria among pediatric SLE patients.

Methods: Pediatric SLE patients (n=262; 80.9% female) were included from three different centers in Turkey. As controls, 174 children (60.9% female) with other diseases who had ANA (antinuclear antibody) test results were included. The gold standard for SLE diagnosis was expert opinion.

Results: The sensitivities of the ACR 1997, SLICC 2012, and EULAR/ACR 2019 criteria were 68.7%, 95.4%, and 91.6%, respectively. The specificities of the ACR 1997, SLICC 2012, and EULAR/ACR 2019 criteria were 94.8%, 89.7%, and 88.5%, respectively. 18 SLE patients met the SLICC 2012 but not the EULAR/ACR 2019 criteria. Among these, hematologic involvement was prominent (13/18; 72.2%). Eight SLE patients fulfilled the EULAR/ACR 2019 but not the SLICC 2012 criteria. Among these, joint involvement was prominent (6/8; 75%).

Conclusion: This is the largest cohort study of pediatric SLE testing the performances of all three classification criteria. The SLICC 2012 criteria yielded the best sensitivity, while the ACR 1997 criteria had the best specificity. SLICC 2012 criteria performed better than EULAR/ACR 2019 criteria. Separation of different hematological manifestations in the SLICC 2012 criteria might have contributed to the higher performance of this criteria set.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystemic involvement and the presence of autoantibodies (1). Childhood-onset or pediatric SLE is relatively less common compared to the adult-onset disease, and it is defined as developing the clinical disease before the age of 18 years (2). Around 10-20% of all SLE cases have pediatric SLE (3). Although pediatric and adult diseases are similar in most aspects, several involvements such as renal, neurologic, and hematological are more common, and the disease activity is usually higher in pediatric SLE as compared to the adult disease (4, 5).

To date, three classification criteria sets have been defined for SLE (Table 1). The ACR (American College of Rheumatology) criteria was published in 1982 and revised in 1997 to delete the LE cell criterion and include antiphospholipid antibodies (6, 7). According to the ACR 1997 criteria, a patient is classified with SLE in the presence of at least 4 out of 11 criteria (6, 7). In 2012, SLICC (Systemic Lupus International Collaborating Clinics) criteria set was published (8). In SLICC 2012, the major revisions to the ACR 1997 were the expansion of the mucocutaneous and neurologic manifestations, the inclusion of alopecia and hypocomplementemia, and the allocation of cytopenias and autoantibodies each in different criteria (8). Furthermore, the SLICC 2012 criteria allow classification with SLE if lupus nephritis is proven with biopsy in the presence of antinuclear antibody (ANA) or anti-double stranded DNA (anti-dsDNA). Other than that, the SLICC 2012 classifies a patient as having SLE when she/he has four or more criteria out of 11 clinical and six immunologic criteria (8). However, all of the criteria could not be immunologic or clinical. With the SLICC 2012 criteria, the sensitivity increased at the expense of specificity, which was observed in most studies (9). However, in a few studies, the SLICC 2012 and ACR 1997 criteria sets exhibited similar specificity (10-12). Most recently, in 2019, the EULAR/ACR (European League

Against Rheumatism/American College of Rheumatology) SLE classification criteria set was developed with the aim of combining the high specificity of the ACR 1997 criteria with high sensitivity (13, 14). In this criteria set, ANA has been defined as the required entry criterion; unexplained fever has been included, the items have been weighted and ordered in domains allowing only the highest-ranked item to be counted in each domain (13, 14). EULAR/ACR 2019 criteria also excluded some subtypes of cutaneous and neuropsychiatric manifestations, which were included in the SLICC 2012 criteria (8, 13, 14). In EULAR/ACR 2019 criteria, there are seven clinical and three immunological domains, and the patient is classified with SLE when she/he gets 10 or more points (13, 14). This cut-off is reached by class III or IV lupus nephritis alone. However, different from the SLICC 2012, the presence of class II or V lupus nephritis and positive ANA is not sufficient for SLE classification (13, 14). In the SLICC 2012 criteria, specific diseases were mentioned to exclude for a feature to be counted in favor of SLE in several criteria such as exclusion of Behçet's disease for oral ulcer or exclusion of infection in case of serositis (8). In the EULAR/ACR 2019 criteria, a general attribution rule has been defined. That is, the items should not be counted for SLE if there is a more likely explanation (13, 14).

The patient cohorts of the three criteria sets did not represent pediatric SLE. Currently, there are no classification criteria specific for pediatric SLE. Thus, it is essential to test the performance of the existing criteria sets in large cohorts of pediatric SLE patients. To date, there is only one pediatric SLE study (including 122 SLE patients) analyzing the performances of all three criteria sets (15).

In this study, we aimed to test the performances of the ACR 1997, SLICC 2012, and EULAR/ACR 2019 classification criteria in a large cohort of pediatric SLE patients.

Patients and Methods

Patients

Three centers from Turkey participated in this study. SLE patients were enrolled at the Pediatric Rheumatology Units of Hacettepe University, Ankara (n=111), Erciyes University, Kayseri (n=102); and Umraniye Training and Research Hospital, Istanbul (n=49). The control group consisted of 174 patients who had ANA test results available (positive or negative) admitted to the Hacettepe University, Ankara, Turkey. These were the patients referred to the Pediatric Rheumatology Unit at least for once from the general pediatrics out-patient clinics. In the control group, the most prevalent diagnoses were primary systemic vasculitides such as polyarteritis nodosa, Behçet's disease, or immunoglobulin A vasculitis, juvenile dermatomyositis, and juvenile idiopathic arthritis. The complete list of the diagnoses of the patients in the control group is present in Appendix 1. The diagnosis of all patients was before 18 years of age.

The gold standard for the diagnosis of SLE was expert opinion at each center (SO, HP, BS). All three experts are experienced in SLE and have been seeing pediatric SLE patients for at least ten years.

Patient and control data were collected on standardized case report forms. Demographic features, clinical, and laboratory characteristics, including the items of different criteria sets were evaluated. ANA test result was defined as positive if staining reactivity was seen at ≥1:80 serum dilution. The sensitivity and specificity of the criteria sets were evaluated based on the features of the patients at the time of disease diagnosis.

The study was approved by the ethical committee of Hacettepe University (GO 20/369-14) and performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consents were obtained from all parents/patients before inclusion in the study.

Statistical analysis

The SPSS version 15.0 (SPSS, Inc., Chicago, Illinois) is used for statistical analysis. Visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov) were used to investigate whether or not the numeric variables are normally distributed. Descriptive analyses were presented using proportions, medians, minimum, and maximum values as appropriate. Differences in proportions between independent groups were evaluated by the Chi-square test or Fisher's exact test where appropriate. Proportion differences between dependent groups were assessed utilizing the McNemar test. The Mann-Whitney U test was used to compare the non-normally distributed continuous data between two groups. We used the Receiver Operating Characteristics (ROC) curve to demonstrate the best performing cut-off value for the EULAR/ACR 2019 criteria in our study group (only ANA positive patients were included). P value <0.05 was considered as significant, and the confidence interval was 95%.

Results

Two hundred sixty-two SLE patients and 174 control patients were included in this study. The characteristics of patients in SLE and control groups were summarized in Table 2. The list of comorbid diseases in SLE patients is available in Appendix 2. Females were more prevalent, and the median age at symptom onset and diagnosis were older in the SLE group compared to controls ($p<0.001$ for all). Besides, most of the items included in the criteria sets differed significantly between SLE and control groups (Table 2).

The sensitivity of the SLICC 2012 criteria was the highest, while the highest specificity was that of the ACR 1997 criteria (Table 3). The SLICC 2012 criteria performed better than the EULAR/ACR 2019 criteria with higher sensitivity and specificity (95.4% vs. 91.6% and 89.7% vs. 88.5%, respectively). Of note, when we picked ≥11 as the threshold for the

EULAR/ACR 2019 criteria, its specificity (89.7%) was the same as the specificity of the SLICC 2012 and its sensitivity (88.2%) was lower than that of the SLICC 2012 criteria (95.4%). Eighteen SLE patients met the SLICC 2012 criteria but did not fulfill the EULAR/ACR 2019 criteria (Table 4). On the other hand, eight SLE patients were fulfilling the EULAR/ACR 2019 but not the SLICC 2012 criteria. Joint involvement was more frequent among SLE patients fulfilling the EULAR/ACR 2019 criteria (p=0.008) while oral ulcers, thrombocytopenia, and hematologic involvement were more common among SLE patients who met the SLICC 2012 criteria (p values were 0.031, 0.031, and 0.009; respectively) (Table 4). In the control group, nine patients were misclassified by the EULAR/ACR criteria with SLE, but not by SLICC 2012; and seven patients were misclassified by the SLICC 2012 but not by the EULAR/ACR criteria (Table 5). Thrombocytopenia, hemolysis, hematologic involvement, and low C3 and C4 levels were more frequent among controls who met the SLICC 2012 criteria (p values were 0.005, 0.019, 0.005, 0.041, and 0.041; respectively) and ANA positivity was more frequent among controls fulfilling the EULAR/ACR 2019 criteria (p=0.019). There were three ANA negative SLE patients in our SLE cohort. All of these patients were classified as having SLE by the SLICC 2012 criteria, while only one fulfilled the ACR 1997 criteria. Four out of 10 patients with mixed connective tissue disease were classified as having SLE by all three criteria sets. Of note, the SLICC 2012 misclassified six patients with mixed connective tissue disease with SLE while the ACR 1997 and EULAR/ACR 2019 misclassified only four of them. Four out of five patients with hemolytic uremic syndrome (HUS) were classified with SLE by the SLICC 2012, while only one of these patients was misclassified by the ACR 1997 or EULAR/ACR 2019.

The area under the ROC curve for EULAR/ACR 2019 criteria was 0.96 (Figure 1), which indicates good discrimination (standard error 0.009; 95% CI 0.943-0.978). When we picked

≥11 as the threshold for the EULAR/ACR 2019 criteria, the sensitivity slightly decreased (from 91.6% to 88.2%), and the specificity slightly increased (from 88.5% to 89.7%).

Finally, we evaluated the performances of the three criteria sets by including only ANA positive SLE patients (n=259) and controls (n=127). Again, the sensitivity of the SLICC 2012 criteria was the highest, while the highest specificity was that of the ACR 1997 criteria. The sensitivities of the ACR 1997, SLICC 2012 and EULAR/ACR 2019 were 69.1%, 95.3%, and 92.6%; respectively while the specificities were 93.7%, 88.9%, and 84.2%; respectively.

Discussion

This is the largest cohort study analyzing the performances of all three SLE classification criteria sets in pediatric SLE. In our cohort, the SLICC 2012 criteria had the highest sensitivity (95.4%), and the ACR 1997 criteria had the highest specificity (94.8%). The SLICC 2012 performed better than the EULAR/ACR 2019 criteria with a higher sensitivity (95.4% vs. 91.6%, respectively) and specificity (89.7% vs. 88.5%, respectively). In SLE patients who met the SLICC 2012 but not the EULAR/ACR 2019 criteria, hematologic involvement was prominent while in patients fulfilling the EULAR/ACR 2019 but not the SLICC 2012 criteria, arthritis was the prominent manifestation.

The classification criteria in SLE have been developed based on data from adult patients and not validated in children (6-8, 13, 14). However, pediatric SLE differs from adult SLE in certain aspects. In 2011 and 2012, Livingstone et al. performed two meta-analyses comparing the clinical manifestations, autoantibodies, disease activity, and damage between pediatric and adult SLE (4, 5). 5993 adults and 905 children were included in the comparison of clinical features (4) and, 6429 adults and 1090 pediatric SLE patients were included in the comparison of autoantibodies, disease activity, and damage (5). They demonstrated that fever, some hematologic abnormalities such as thrombocytopenia and hemolytic anemia,

lymphadenopathy, central nervous system involvement, renal disease, anti-dsDNA, and anticardiolipin antibodies were more common among childhood patients while Raynaud phenomenon, pleurisy, sicca syndrome, and rheumatoid factor positivity were more common among adult SLE patients (4, 5). Hematologic involvement was present in 55% of our SLE cohort which may have contributed to the sensitivity of the SLICC 2012 criteria since the hematologic manifestations are allocated into separate items in SLICC 2012 (8). In addition, the increased frequency of renal involvement in pediatric SLE could contribute further to the high sensitivity of the SLICC 2012 criteria since SLICC 2012 is the only one allowing SLE classification in the presence of any class lupus nephritis and positive serology.

Several studies have compared the performances of all three criteria sets (10, 16-21). Rubio et al. showed that the SLICC 2012 criteria performed best with regards to sensitivity (100%) compared to the ACR 1997 (94%) and the EULAR/ACR 2019 criteria (94%) in their cohort, including 217 adult SLE patients (17). Adamichu et al. compared the criteria sets in a cohort of 690 adult SLE patients and 401 controls (10). They demonstrated that the SLICC 2012 criteria had the highest sensitivity (91.3% vs. 85.7% for the ACR 1997, and 88.6% for the EULAR/ACR 2019). However, the highest specificity was that of the EULAR/ACR 2019 criteria (97.3% vs. 93% for the ACR 1997, and 93.8% for the SLICC 2012).

There is only one previous pediatric SLE study analyzing the performances of all three criteria sets (15). In that study, including 122 pediatric SLE patients and 89 controls, Rodrigues Fonseca et al. (15) found that the SLICC 2012 had the highest sensitivity (89.3%), and the ACR 1997 had the highest specificity (83.2%), consistent with our results. Of note, in their study, all controls had a positive ANA test. In our control group, we have also included patients with negative ANA test results since we have ANA negative SLE patients in our SLE cohort.

In most of the previous studies comparing the performances of the SLICC 2012 and ACR 1997, the SLICC 2012 criteria had higher sensitivity but lower specificity compared to the ACR 1997 criteria, consistent with our results. In 2018, Hartman et al. performed a systematic review of studies comparing the performances of the ACR 1997 and SLICC 2012 criteria (9). In adult SLE (5236 SLE patients vs. 1313 controls), the 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. On the other hand, in pediatric SLE (568 SLE patients vs. 339 controls), the SLICC 2012 had higher sensitivity (99.9% vs. 84.3%, respectively) but much lower specificity (82% vs. 94.1%, respectively) than the ACR 1997 criteria. Of note, the SLICC 2012 criteria had the advantage of classifying juvenile SLE patients earlier in the disease course (9). We evaluated the performance of the criteria sets at the time of diagnosis in our study. Thus, the higher performance of the SLICC 2012 criteria could be partially due to the above-mentioned advantage. In the largest pediatric SLE cohort study, including 772 patients, Tao et al. demonstrated that the sensitivity of the SLICC 2012 was higher than that of the ACR 1997 criteria (96.3% vs. 92.4%, respectively) (22). However, they were not able to analyze the specificity since they did not have a control group.

Arthritis was present in six out of eight SLE patients who fulfilled the EULAR/ACR 2019 criteria but not the SLICC 2012. Although the definition for arthritis is the same in the SLICC 2012 and EULAR/ACR 2019 criteria, the latter gives it a higher weight (13, 14). A patient gets six out of the required 10 points from only arthritis according to the EULAR/ACR 2019 criteria. Arthritis is a common feature of SLE (23). It is present in around 60-70% of children with SLE at the time of presentation (24). Thus, giving arthritis a higher weight could be an advantage for pediatric SLE patients leading to early diagnosis. However, in our study, the EULAR/ACR 2019 criteria misclassified six out of 10 patients with mixed connective tissue disease as having SLE, and five of these patients had arthritis. Therefore, the high weight of

arthritis in the EULAR/ACR 2019 could also introduce a challenge while differentiating SLE from its close mimickers.

Hematologic involvement was frequent among patients who fulfilled the SLICC 2012 criteria but not the EULAR/ACR 2019 criteria (n=13; 72.2%). Hematologic manifestations are more frequently observed in pediatric than adult SLE (4). These have been described in up to 86% of children with SLE (25). In the SLICC 2012 criteria, different components of the hematologic involvement such as hemolytic anemia, leukopenia/lymphopenia, and thrombocytopenia are allocated into different criteria (8). Thus, a patient could meet three out of the required four criteria with only hematologic involvement according to the SLICC 2012 criteria (8). On the other hand, in the EULAR/ACR 2019 criteria, all these manifestations are included in the hematologic domain, and the highest rank a patient could get from this domain is four which occurs in the presence of autoimmune hemolysis or thrombocytopenia (13, 14). This specific difference between the two criteria sets might have contributed significantly to the higher sensitivity of the SLICC 2012 over EULAR/ACR 2019 criteria. It is worth mentioning that the SLICC 2012 misclassified four out of five HUS patients with SLE while the other two criteria set each misclassified only one of these patients. The hematologic manifestations that are common between HUS and SLE were the main reasons for this misclassification. Thus, the separation of the different hematologic manifestations into different criteria also causes difficulty while differentiating SLE from other diseases with similar hematologic involvement (26).

The analysis of disease controls misclassified with SLE by the SLICC 2012 and EULAR/ACR 2019 criteria sets (Table 5), showed that the hematologic involvement and arthritis were the prominent features among these patients, respectively. Thus, the separation of hematologic manifestations in different criteria in the SLICC 2012 and attribution of a high

weight to arthritis in the EULAR/ACR 2019 criteria probably also contribute to the lower specificity of these criteria sets compared to the ACR 1997 criteria.

The main limitation of our study was its retrospective design. Some medical information might have been missed during data extraction from medical files. All autoantibodies included in the criteria sets were not routinely tested in all patients. This fact could have led to an underestimation of the performances of the criteria sets. In the EULAR/ACR criteria set, a general attribution rule has been defined as counting an item in favor of SLE only if SLE is the most likely explanation (13, 14). For instance, in case of pneumonia, pleural effusion is most probably due to infection, and it should not be counted for SLE. To follow the attribution rule, it would be ideal to evaluate the patients in the clinical context when they present to the pediatric rheumatology clinic. This is somewhat restricted in a retrospective study. Another limitation is that we were not able to test the performances later in their disease course of these patients. Analysis in the follow-up might have provided valuable data about the performances of the criteria sets, since pediatric SLE has an additive course. Lastly, the gold standard for SLE diagnosis was the expert opinion which may cause a deficiency in the standardization of the diagnosis. However, the treating physician's diagnosis is the gold standard in all previous studies, as well, since a true gold standard is lacking for SLE diagnosis.

In conclusion, in the largest pediatric SLE cohort study testing the performances of the three classification criteria, we showed that the SLICC 2012 had the highest sensitivity, and the ACR 1997 had the highest specificity. SLICC 2012 performed better than the EULAR/ACR criteria, probably based on the difference in the items regarding hematologic involvement. The high sensitivity of the SLICC 2012 criteria set is a significant advantage for children since early diagnosis and timely treatment are very important in pediatric SLE.

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Figure legend

Figure 1. Area under the receiver operating characteristic (ROC) curve for the EULAR/ACR (European League Against Rheumatism/American College of Rheumatology) 2019 criteria in ANA (antinuclear antibody) positive pediatric systemic lupus erythematosus (SLE) patients and controls

Table 1. The ACR (American College of Rheumatology)1997, SLICC (Systemic Lupus International Collaborating Clinics) 2012, and EULAR/ACR 2019 classification criteria sets for systemic lupus erythematosus (SLE)

ACR[a] 1997	**SLICC[a] 2012**	**EULAR[a]/ACR 2019**
-	-	**Entry criterion:** ANA[a] positivity
1. Malar rash 2. Discoid rash 3. Photosensitivity 4. Oral ulcers 5. Arthritis 6. Serositis 7. Renal disorder (proteinuria or urinary casts) 8. Neurologic disorder (seizures or psychosis) 9. Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia)	**Clinical criteria** 1. Acute cutaneous lupus 2. Chronic cutaneous lupus 3. Oral or nasal ulcers 4. Nonscarring alopecia 5. Synovitis 6. Serositis 7. Renal involvement (proteinuria or erythrocyte casts) 8. Neurologic involvement (seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial	**Clinical domains and criteria** 1. Constitutional Fever 2. Hematologic Leukopenia Thrombocytopenia Autoimmune hemolysis 3. Neuropsychiatric Delirium Psychosis Seizure 4. Mucocutaneous Nonscarring alopecia

10. Immunologic disorder (Anti-dsDNA[a]; anti-Smith; false (+) serologic test for Syphilis; anticardiolipin antibodies; lupus anticoagulant) 11. ANA positivity	neuropathy, acute confusional state) 9. Hemolytic anemia 10. Leukopenia or lymphopenia 11. Thrombocytopenia	Oral ulcers Subacute cutaneous or discoid lupus Acute cutaneous lupus 5. Serosal Pleural or pericardial effusion Acute pericarditis 6. Musculoskeletal Joint involvement 7. Renal Proteinuria Renal biopsy class II or V lupus nephritis Renal biopsy class III or IV nephritis
	Immunologic criteria 1. ANA positivity 2. Anti-dsDNA positivity 3. Anti-Smith positivity	**Immunology domains and criteria** 1. Antiphospholipid antibodies

	4. Antiphospholipid antibody positivity 5. Low complement 6. Direct Coombs' test positivity in the absence of hemolytic anemia	Anti-cardiolipin Anti-β2glycoprotein I Lupus anticoagulant 2. Complement proteins Low C3 or low C4 Low C3 and low C4 3. SLE[a]-specific antibodies Anti-dsDNA or anti-Smith

[a]ACR, American College of Rheumatology; ANA, anti-nuclear antibody; anti-dsDNA, anti-double stranded DNA; EULAR, European League Against Rheumatism; RPR, rapid plasma reagin; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics

Table 2. The characteristics of patients in systemic lupus erythematosus (SLE) and control groups

Characteristics, n (%) or median (min-max)	**SLE[a] group (n=262)**	**Control group (n=174)**	**P value**
Sex, female	212 (80.9)	106 (60.9)	<0.001
Age at disease onset, months	151.5 (4-215)	108 (1-204)	<0.001
Age at diagnosis, months	160 (7-215)	112 (4-204)	<0.001
Comorbid diseases	46 (17.6)	2 (1.1)	<0.001
Fever (>38.3^{0}C)	66 (25.2)	29 (16.7)	0.035
Pleural effusion	19 (7.3)	4 (2.3)	0.023
Pleuritis	6 (2.3)	0 (0)	0.085*
Pericardial effusion	15 (5.7)	0 (0)	0.001
Pericarditis	13 (5)	0 (0)	0.003
Joint involvement	133 (50.8)	72 (41.4)	0.055
Non-scarring alopecia	27 (10.3)	0 (0)	<0.001
Oral ulcers	71 (27.1)	23 (13.2)	0.001
Nasal ulcers	2 (0.8)	0 (0)	0.51*

Malar rash	128 (48.9)	13 (7.5)	<0.001
Discoid rash	10 (3.8)	1 (0.6)	0.056*
Photosensitivity	70 (26.7)	8 (4.6)	<0.001
Generalized maculopapular rash	24 (9.2)	11 (6.3)	0.28
Annular papulosquamous cutaneous eruption	5 (1.9)	1 (0.6)	0.40*
Bullous lupus	2 (0.8)	0 (0)	0.51*
Hypertrophic verrucous lupus	2 (0.8)	0 (0)	0.51*
Lupus panniculitis profundus	3 (1.1)	2 (1.1)	1*
Chilblain lupus	3 (1.1)	0 (0)	0.27*
Discoid lupus/lichen planus overlap	2 (0.8)	0 (0)	0.51*
Delirium	2 (0.8)	1 (0.6)	1*
Psychosis	4 (1.5)	0 (0)	0.15*
Seizure	15 (5.7)	2 (1.1)	0.016
Focal neurologic defect	4 (1.5)	4 (2.3)	0.71*
Peripheral neuropathy	5 (1.9)	3 (1.7)	1*
Cranial neuropathy	1 (0.4)	3 (1.7)	0.30*

Acute confusional state	5 (1.9)	1 (0.6)	0.40*
Coma	1 (0.4)	0 (0)	1*
Leukopenia (<4000/mm^3)	60 (22.9)	6 (3.4)	<0.001
Lymphopenia (<1000/mm^3)	32 (12.2)	3 (1.7)	<0.001
Lymphopenia (<1500/mm^3)	66 (25.2)	6 (3.4)	<0.001
Thrombocytopenia (<100,000/mm^3)	67 (25.6)	16 (9.2)	<0.001
Evidence of hemolysis	65 (24.8)	7 (4)	<0.001
Hematologic involvement	145 (55.3)	24 (13.8)	<0.001
Low C3	159 (60.7)	24/133 (18)	<0.001
Low C4	182 (69.5)	33/131 (25.2)	<0.001
Low CH50	6/55 (10.9)	1/6 (16.6)	0.53*
Proteinuria	69 (26.3)	14 (8)	<0.001
Urinary casts	34 (14.9)	9 (5.2)	0.002
ANA[a] positivity (≥1/80)	259 (98.9)	127 (73)	<0.001
Anti-dsDNA[a]	164 (62.6)	7/144 (4.8)	<0.001
Anti-Smith	37/203 (18.2)	4/70 (5.7)	0.012
Anti-cardiolipin antibodies	53/235 (22.5)	2/83 (2.4)	<0.001

Anti-β2 glycoprotein	29/153 (18.9)	1/44 (2.3)	0.007
Lupus anticoagulant	27/160 (16.8)	1/41 (2.4)	0.017
Direct Coombs	94/241 (39)	2/20 (10)	0.01
False RPR positivity	6/34 (17.6)	Not checked	-
Biopsy proven lupus nephritis	97 (37)	0 (0)	<0.001
SLE according to the ACR[a] 1997 criteria	180 (68.7)	9 (5.2)	<0.001
SLE according to the SLICC[a] 2012 criteria	250 (95.4)	18 (10.3)	<0.001
SLE according to the EULAR[a]/ACR 2019 criteria	240 (91.6)	20 (11.5)	<0.001

[a]*ACR, American College of Rheumatology; ANA, anti-nuclear antibody; anti-dsDNA, anti-double stranded DNA; EULAR, European League Against Rheumatism; RPR, rapid plasma reagin; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics*

[*]*These comparisons were done utilizing the Fisher's exact test while Chi-square test was used for the rest of the comparisons*

Table 3. Categories of patients according to the ACR (American College of Rheumatology) 1997, SLICC (Systemic Lupus International Collaborating Clinics) 2012, and EULAR (European League Against Rheumatism)/ACR 2019 SLE (systemic lupus erythematosus) classification criteria

Criteria set	**SLE[a] group (n=262)**	**Control group (n=174)**	**Sensitivity (%)**	**Specificity (%)**	**P values[b]**
SLE according to the ACR[a] 1997 criteria	180	9	68.7	94.8	ACR 1997 vs. SLICC[a], p<0.001
Not-SLE according to the ACR 1997 criteria	82	165			
SLE according to the SLICC 2012 criteria	250	18	95.4	89.7	SLICC vs. EULAR[a]/ACR (≥10) 2019, p=0.28
Not-SLE according to the SLICC 2012 criteria	12	156			
SLE according to the EULAR/ACR 2019	240	20	91.6	88.5	EULAR/ACR 2019 (≥10) vs.

criteria (threshold≥10)					p<0.001
Not-SLE according to the EULAR/ACR 2019 criteria (threshold≥10)	22	154			
SLE according to the EULAR/ACR 2019 criteria (threshold≥11)	231	18	88.2	89.7	EULAR/ACR 2019 (≥11) vs. ACR 1997, p=0.08 SLICC vs. EULAR[a]/ACR 2019 (≥11), p=0.36
Not-SLE according to the EULAR/ACR 2019 criteria (threshold≥11)	31	156			

[a]*ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics*

[b]*p values are for the comparison of sensitivities/specificities among classification criteria.*

Table 4. SLE (systemic lupus erythematosus) patients who met either one of the SLICC (Systemic Lupus International Collaborating Clinics) 2012 or EULAR (European League Against Rheumatism)/ACR 2019 criteria but not the other

Characteristics, n (%)	**SLE[a] patients who met SLICC[a] 2012 but not EULAR/ACR[a] 2019 (n=18)**	**SLE patients who met EULAR/ACR 2019 but not SLICC 2012 (n=8)**	**P values**
Sex, female	14 (77.8)	7 (87.5)	1
Age at dx[a], months, median (min-max)	183.5 (96-215)	156 (62-204)	0.24
Fever (>38.3^{0}C)	1 (5.6)	1 (12.5)	0.52
Pleuritis	0 (0)	1 (12.5)	0.30
Pericarditis	0 (0)	1 (12.5)	0.30
Joint involvement	3 (16.7)	6 (75)	0.008
Non-scarring alopecia	2 (11.1)	0 (0)	1
Oral ulcers	8 (44.4)	0 (0)	0.031
Malar rash	5 (27.8)	4 (50)	0.38
Discoid rash	3 (16.7)	0 (0)	1
Photosensitivity	6 (33.3)	2 (25)	1
Delirium	1 (5.6)	0 (0)	1
Psychosis	1 (5.6)	0 (0)	1
Focal neurologic defect	1 (5.6)	0 (0)	1
Acute confusional state	1 (5.6)	0 (0)	1

Leukopenia (<4000/mm^3)	7 (38.9)	0 (0)	0.062
Lymphopenia (<1000/mm^3)	2 (11.1)	0 (0)	1
Lymphopenia (<1500/mm^3)	7 (38.9)	1 (12.5)	0.36
Thrombocytopenia (<100,000/mm^3)	8 (44.4)	0 (0)	0.031
Evidence of hemolysis	5 (27.8)	0 (0)	0.28
Hematologic involvement	13 (72.2)	1 (12.5)	0.009
Proteinuria	3 (16.7)	0 (0)	0.52
Low C3	3 (16.7)	1 (12.5)	1
Low C4	8 (44.4)	1 (12.5)	0.19
ANA[a] positivity (≥1/80)	15 (83.3)	8 (100)	0.52
Anti-dsDNA[a]	1 (5.6)	3 (37.5)	0.07
Anti-Smith	0 (0)	1 (12.5)	0.31
Anti-cardiolipin antibodies	6 (33.3)	0 (0)	0.26
Anti-β2 glycoprotein	3 (16.7)	0 (0)	0.50
Lupus anticoagulant	3 (16.7)	0 (0)	0.52
Direct Coombs	6 (33.3)	0 (0)	0.14

Biopsy proven lupus nephritis	3 (16.7)	0 (0)	0.52
SLE according to the ACR 1997 criteria	7 (38.9)	2 (25)	1

[a]*ACR, American College of Rheumatology; ANA, anti-nuclear antibody; anti-dsDNA, anti-double stranded DNA; dx, diagnosis; EULAR, European League Against Rheumatism; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics*

Table 5. Control group patients who met either one of the SLICC (Systemic Lupus International Collaborating Clinics) 2012 or EULAR (European League Against Rheumatism)/ACR 2019 criteria but not the other

Characteristics, n (%)	**Controls who met SLICC[a] 2012 but not EULAR/ACR[a] 2019 (n=7)**	**Controls who met EULAR/ACR 2019 but not SLICC 2012 (n=9)**	**P values**
Sex, female	5 (71.4)	7 (77.8)	1
Age at dx[a], months, median (min-max)	40 (4-192)	132 (36-192)	0.09
Fever (>38.3^{0}C)	0 (0)	4 (44.4)	0.08
Joint involvement	2 (28.6)	7 (77.8)	0.12
Oral ulcers	1 (14.3)	0 (0)	0.43
Malar rash	0 (0)	1 (11.1)	1
Generalized maculopapular rash	0 (0)	3 (33.3)	0.21
Photosensitivity	1 (14.3)	0 (0)	0.43
Delirium	0 (0)	1 (11.1)	1
Seizure	0 (0)	1 (11.1)	1
Focal neurologic defect	1 (14.3)	1 (11.1)	1
Peripheral neuropathy	1 (14.3)	0 (0)	0.43
Cranial neuropathy	1 (14.3)	0 (0)	0.43
Acute confusional state	0 (0)	1 (11.1)	1

Leukopenia (<4000/mm^3)	1 (14.3)	0 (0)	0.43
Lymphopenia (<1000/mm^3)	1 (14.3)	0 (0)	0.43
Thrombocytopenia (<100,000/mm^3)	5 (71.4)	0 (0)	0.005
Evidence of hemolysis	4 (57.1)	0 (0)	0.019
Hematologic involvement	5 (71.4)	0 (0)	0.005
Proteinuria	3 (42.9)	1 (11.1)	0.26
Low C3	5 (71.4)	2 (22.2)	0.041
Low C4	5 (71.4)	2 (22.2)	0.041
ANA[a] positivity (≥1/80)	3 (42.9)	9 (100)	0.019
Anti-dsDNA[a]	0 (0)	2 (22.2)	0.47
Anti-cardiolipin antibodies	1 (14.3)	0 (0)	1
Lupus anticoagulant	1 (14.3)	0 (0)	0.33
SLE[a] according to the ACR 1997 criteria	1 (14.3)	0 (0)	0.43

[a]ACR, American College of Rheumatology; ANA, anti-nuclear antibody; anti-dsDNA, anti-double stranded DNA; dx, diagnosis; EULAR, European League Against Rheumatism; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics

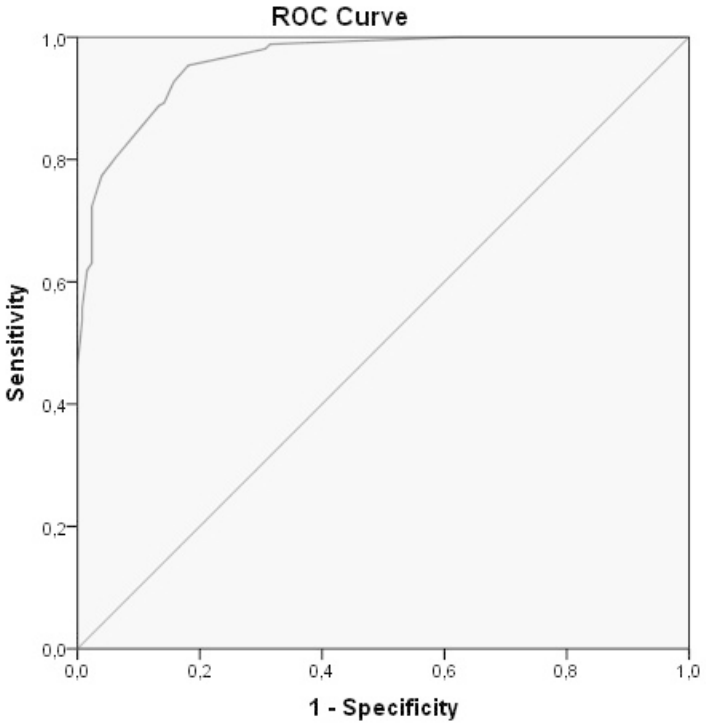

Figure 1. Area under the receiver operating characteristic (ROC) curve for the EULAR/ACR (European League Against Rheumatism/American College of Rheumatology) 2019 criteria in ANA (antinuclear antibody) positive pediatric systemic lupus erythematosus (SLE) patients and controls

165x133mm (96 x 96 DPI)