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# The Performances of the ACR 1997, SLICC 2012, and EULAR/ACR 2019 Classification Criteria in Pediatric Systemic Lupus Erythematosus

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*ABSTRACT.* ***Objective.*** Systemic lupus erythematosus (SLE) is a chronic autoimmune disease. The American College of Rheumatology (ACR) 1997, Systemic Lupus International Collaborating Clinics (SLICC) 2012, and European League Against Rheumatism (EULAR)/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 patients with SLE.

***Methods.*** Pediatric patients with SLE (n = 262; 80.9% female) were included from 3 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. Eighteen patients with SLE met the SLICC 2012 but not the EULAR/ACR 2019 criteria. Among these, hematologic involvement was prominent (n = 13; 72.2%). Eight patients with SLE fulfilled the EULAR/ACR 2019 but not the SLICC 2012 criteria. Among these, joint involvement was prominent (n = 6; 75%).

***Conclusion.*** To our knowledge, this is the largest cohort study of pediatric SLE to test the performances of all 3 classification criteria. The SLICC 2012 criteria yielded the best sensitivity, whereas 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.

*Key Indexing Terms*: child, classification, diagnosis, systemic lupus erythematosus

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.[2] Approximately 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 hematologic, are more common, and the disease activity is usually higher in pediatric SLE compared to adult-onset SLE.[4,5]

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To date, 3 classification criteria sets have been defined for SLE (Table 1). The American College of Rheumatology (ACR) criteria were published in 1982 and revised in 1997 to delete the lupus erythematosus cell criterion and include antiphospholipid antibodies.[6,7] According to the ACR 1997 criteria, a patient is classified with SLE with the presence of at least 4 out of 11 criteria.[6,7] In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) 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 reallocation of cytopenia and autoantibodies to different criteria.[8] Further, the SLICC 2012 criteria allow classification of SLE if lupus nephritis (LN) is proven with biopsy in the presence of antinuclear antibody (ANA) or anti-dsDNA. Other than that, the SLICC 2012 classifies a patient as having SLE when one has ≥ 4 criteria out of 11 clinical and 6 immunologic criteria.[8] However, all 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] although, in a few studies, the SLICC 2012 and ACR 1997 criteria sets exhibited similar specificity.[10,11,12] Most recently, in 2019 the European League

*Table 1.* The ACR 1997, SLICC 2012, and EULAR/ACR 2019 classification criteria sets for SLE.

| ACR 1997 | SLICC 2012 | EULAR/ACR 2019[a] |
|---|---|---|
| Criteria | Clinical Criteria | Clinical Domains and Criteria |
| 1. Malar rash | 1. Acute cutaneous lupus | 1. Constitutional: fever |
| 2. Discoid rash | 2. Chronic cutaneous lupus | 2. Hematologic: leukopenia, thrombocytopenia, autoimmune hemolysis |
| 3. Photosensitivity | 3. Oral or nasal ulcers | 3. Neuropsychiatric: delirium, psychosis, seizure |
| 4. Oral ulcers | 4. Nonscarring alopecia | 4. Mucocutaneous: nonscarring alopecia, oral ulcers, subacute cutaneous or discoid lupus, acute cutaneous lupus |
| 5. Arthritis | 5. Synovitis | 5. Serosal: pleural or pericardial effusion, acute pericarditis |
| 6. Serositis | 6. Serositis | 6. Musculoskeletal: joint involvement |
| 7. Renal disorder: proteinuria or urinary casts | 7. Renal involvement: proteinuria or erythrocyte casts | 7. Renal: proteinuria, renal biopsy class II or V LN, renal biopsy class III or IV LN |
| 8. Neurologic disorder: seizures or psychosis | 8. Neurologic involvement: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state | |
| 9. Hematologic disorder: hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia | 9. Hemolytic anemia | |
| 10. Immunologic disorder: anti-dsDNA, anti-Sm, false positive serologic test for syphilis, ACA, LAC | 10. Leukopenia or lymphopenia | |
| 11. ANA positivity | 11. Thrombocytopenia | |
| | Immunologic Criteria | Immunology Domains and Criteria |
| | 1. ANA positivity | 1. aPL: ACA, anti-$\beta_2$-GPI, LAC |
| | 2. Anti-dsDNA positivity | 2. Complement proteins: low C3 or low C4, low C3, and low C4 |
| | 3. Anti-Sm positivity | 3. SLE-specific antibodies: anti-dsDNA or anti-Sm |
| | 4. aPL positivity | |
| | 5. Low complement | |
| | 6. Direct Coombs test positivity in the absence of hemolytic anemia | |

[a] Entry criterion: ANA positivity. ACA: anticardiolipin antibodies; ACR: American College of Rheumatology; ANA: antinuclear antibody; anti-$\beta_2$-GPI: anti-$\beta_2$-glycoprotein I; aPL: antiphospholipid antibody; EULAR: European League Against Rheumatism; LAC: lupus anticoagulant; LN: lupus nephritis; RPR: rapid plasma reagin; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics.

Against Rheumatism (EULAR)/ACR 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, and the items have been weighted and ordered in domains that allow only the highest-ranked item to be counted in each domain.[13,14] The 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, there are 7 clinical and 3 immunological domains, and the patient is classified with SLE when she/he gets ≥ 10 points.[13,14] This cutoff is reached by class III or IV LN alone. However, different from the SLICC 2012, the presence of class II or V LN and positive ANA is not sufficient for SLE classification.[13,14] In the SLICC 2012 criteria, specific diseases were mentioned that should be excluded for a feature to be counted in favor of SLE in several criteria, such as exclusion of Behçet 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 3 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 patients with pediatric SLE. To date, there is only 1 pediatric SLE study (including 122 patients with SLE) analyzing the performances of all 3 criteria sets.[15]

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

## METHODS

*Patients*. Three centers from Turkey participated in our study. Patients with SLE were enrolled at the pediatric rheumatology units of Hacettepe University in Ankara (n = 111), Erciyes University in Kayseri (n = 102); and Ümraniye Training and Research Hospital in Istanbul (n = 49). The control group consisted of 174 patients who had ANA test results available (positive or negative) and who had been admitted to Hacettepe University. These were the patients referred to the pediatric rheumatology unit at least once from the general pediatric outpatient clinics. In the control group, the most prevalent diagnoses were primary systemic vasculitides such as polyarteritis nodosa, Behçet disease, IgA vasculitis, juvenile dermatomyositis, and juvenile idiopathic arthritis. The complete list of the diagnoses of the

patients in the control group is presented in Supplementary Table 1 (available from the authors on request). All patients were diagnosed before 18 years of age.

The gold standard for the diagnosis of SLE was expert opinion (SO, HP, BS) at each center. All 3 experts are experienced in SLE and have been seeing patients with pediatric SLE for at least 10 years.

Patient and control data were collected on standardized case report forms. Demographic features and clinical and laboratory characteristics, including the items in 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.

Our 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 consent was obtained from all parents/patients before inclusion in the study.

*Statistical analysis*. SPSS version 15.0 (SPSS Inc.) was used for statistical analysis. Visual (histogram, probability plots) and analytic (Kolmogorov-Smirnov) methods were used to investigate whether the numeric variables are normally distributed. Descriptive analyses were presented using proportions, medians, and minimum and maximum values, as appropriate. Differences in proportions between independent groups were evaluated by the chi-square test or Fisher 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 abnormally distributed continuous data between 2 groups. We used the receiver-operating characteristic (ROC) curve to demonstrate the best-performing cutoff value for the EULAR/ACR 2019 criteria in our study group (only ANA-positive patients were included). $P < 0.05$ was considered significant, and the CI was 95%.

## RESULTS

Two hundred sixty-two patients with SLE and 174 controls were included in our study. The characteristics of patients in SLE and control groups were summarized in Table 2. The list of comorbid diseases in patients with SLE is available in Supplementary Table 2 (available from the authors on request). Females were more prevalent, and the median ages at symptom onset and diagnosis were older in the SLE group compared to controls ($P < 0.001$ for all). Further, 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, whereas 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 patients with SLE met the SLICC 2012 criteria but did not fulfill the EULAR/ACR 2019 criteria (Table 4). On the other hand, 8 patients with SLE fulfilled 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 patients with SLE who met the SLICC 2012 criteria (*P* values were 0.03, 0.03, and 0.009, respectively; Table 4). In the control group, 9 patients were misclassified as having SLE by the EULAR/ACR criteria but not by SLICC 2012, while 7 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, 0.02, 0.005, 0.04, and 0.04, respectively) and ANA positivity was more frequent among controls fulfilling the EULAR/ACR 2019 criteria ($P = 0.02$). There were 3 ANA-negative patients in our SLE cohort. All these patients were classified as having SLE by the SLICC 2012 criteria, while only 1 fulfilled the ACR 1997 criteria. Four out of 10 patients with mixed connective tissue disease (MCTD) were classified as having SLE by all 3 criteria sets. Of note, the SLICC 2012 misclassified 6 patients with MCTD as having SLE while the ACR 1997 and EULAR/ACR 2019 misclassified only 4 of them. Four out of 5 patients with hemolytic uremic syndrome (HUS) were classified with SLE by the SLICC 2012, while only 1 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 0.93–0.98). 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%; Table 3).

Finally, we evaluated the performances of the 3 criteria sets by including only ANA-positive patients with SLE (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

To our knowledge, this is the largest cohort study analyzing the performances of all 3 SLE classification criteria sets in pediatric SLE to date. 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%) and specificity (89.7% vs 88.5%). In patients with SLE 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.[6,7,8,13,14] However, pediatric SLE differs from adult SLE in certain aspects. In 2011 and 2012, Livingston, *et al* performed 2 metaanalyses comparing the clinical manifestations, autoantibodies, disease activity, and damage between pediatric and adult SLE.[4,5] Five thousand nine hundred ninety-three adults and 905 children were included in the comparison of clinical features,[4] and 6429 adult and 1090 pediatric patients with SLE were included in

*Table 2.* The characteristics of patients in SLE and control groups.

| Characteristics | SLE Group, n = 262 | Control Group, n = 174 | *P* |
|---|---|---|---|
| Sex, female | 212 (80.9) | 106 (60.9) | < 0.001 |
| Age at disease onset, months, median (min–max) | 151.5 (4–215) | 108 (1–204) | < 0.001 |
| Age at diagnosis, months, median (min–max) | 160 (7–215) | 112 (4–204) | < 0.001 |
| Comorbid diseases | 46 (17.6) | 2 (1.1) | < 0.001 |
| Fever (> 38.3°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 |
| Nonscarring 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) | > 0.99* |
| 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) | > 0.99* |
| Psychosis | 4 (1.5) | 0 (0) | 0.15* |
| Seizure | 15 (5.7) | 2 (1.1) | 0.02 |
| Focal neurologic defect | 4 (1.5) | 4 (2.3) | 0.71* |
| Peripheral neuropathy | 5 (1.9) | 3 (1.7) | > 0.99* |
| 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) | > 0.99* |
| 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 positivity (≥ 1/80) | 259 (98.9) | 127 (73) | < 0.001 |
| Anti-dsDNA | 164 (62.6) | 7/144 (4.8) | < 0.001 |
| Anti-Sm | 37/203 (18.2) | 4/70 (5.7) | 0.01 |
| Anticardiolipin antibodies | 53/235 (22.5) | 2/83 (2.4) | < 0.001 |
| Anti-$\beta_2$-GPI | 29/153 (18.9) | 1/44 (2.3) | 0.007 |
| Lupus anticoagulant | 27/160 (16.8) | 1/41 (2.4) | 0.02 |
| Direct Coombs | 94/241 (39) | 2/20 (10) | 0.01 |
| False RPR positivity | 6/34 (17.6) | Not checked | – |
| Biopsy-proven LN | 97 (37) | 0 (0) | < 0.001 |
| SLE (ACR 1997 criteria) | 180 (68.7) | 9 (5.2) | < 0.001 |
| SLE (SLICC 2012 criteria) | 250 (95.4) | 18 (10.3) | < 0.001 |
| SLE (EULAR/ACR 2019 criteria) | 240 (91.6) | 20 (11.5) | < 0.001 |

Values are expressed as n (%) unless stated otherwise. *These comparisons were done utilizing the Fisher exact test while chi-square test was used for the rest of the comparisons. ACR: American College of Rheumatology; ANA: antinuclear antibody; anti-$\beta_2$-GPI: anti-$\beta_2$-glycoprotein I; EULAR: European League Against Rheumatism; LN: lupus nephritis; RPR: rapid plasma reagin; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics.

*Table 3.* Categories of patients according to the ACR 1997, SLICC 2012, and EULAR/ACR 2019 SLE classification criteria.

| Criteria Set | | SLE Group, n = 262 | Control Group, n = 174 | Sensitivity, % | Specificity, % | *P** |
|---|---|---|---|---|---|---|
| ACR 1997 | SLE | 180 | 9 | 68.7 | 94.8 | ACR 1997 vs SLICC: < 0.001 |
| | Not SLE | 82 | 165 | | | |
| SLICC 2012 | SLE | 250 | 18 | 95.4 | 89.7 | SLICC vs EULAR/ACR (≥ 10) 2019: 0.28 |
| | Not SLE | 12 | 156 | | | |
| EULAR/ACR 2019 (threshold ≥ 10) | SLE | 240 | 20 | 91.6 | 88.5 | EULAR/ACR 2019 (≥ 10) vs ACR 1997: < 0.001 |
| | Not SLE | 22 | 154 | | | |
| EULAR/ACR 2019 (threshold ≥ 11) | SLE | 231 | 18 | 88.2 | 89.7 | EULAR/ACR 2019 (≥ 11) vs ACR 1997: 0.08; SLICC vs EULAR/ACR 2019 (≥ 11): 0.36 |
| | Not SLE | 31 | 156 | | | |

**P* values are for the comparison of sensitivities/specificities among classification criteria. ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics.

the comparison of autoantibodies, disease activity, and damage.[5] They demonstrated that fever, some hematologic abnormalities including thrombocytopenia and hemolytic anemia, lymphadenopathy, central nervous system involvement, renal disease, anti-dsDNA, and anticardiolipin antibodies were more common among pediatric patients, whereas Raynaud phenomenon, pleurisy, sicca syndrome, and rheumatoid factor positivity were more common among adult patients with SLE.[4,5] Hematologic involvement was present in 55.3% 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 of LN and positive serology.

Several studies have compared the performances of all 3 criteria sets.[10,16–21] Rubio, *et al* showed that the SLICC 2012 criteria performed best in regard to sensitivity (100%) compared to the ACR 1997 (94%) and the EULAR/ACR 2019 criteria (94%) in their cohort that included 217 adult patients with SLE.[17] Adamichou, *et al* compared the criteria sets in a cohort of 690 adult patients with SLE 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 1 previous pediatric SLE study analyzing the performances of all 3 criteria sets.[15] In that study, including 122 pediatric patients with SLE 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 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 patients with SLE 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 patients with SLE 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 patients with SLE 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%).[22] However, they were not able to analyze the specificity since they did not have a control group.

In our study, arthritis was present in 6 out of 8 patients with SLE 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 6 out of the required 10 points from only arthritis according to the EULAR/ACR 2019 criteria. Arthritis is a common feature of SLE,[23] and is present in approximately 60–70% of children with SLE at the time of presentation.[24] Thus, giving arthritis a higher weight could be an advantage for pediatric patients with SLE, leading to early diagnosis. However, in our study, the EULAR/ACR 2019 criteria misclassified 6 out of 10 patients with MCTD as having SLE, and 5 of these patients had arthritis. Therefore, the high weight of arthritis in the EULAR/ACR 2019 could also

*Table 4.* Patients with SLE who met either the SLICC 2012 or EULAR/ACR 2019 criteria, but not the other.

| Characteristics | Patients With SLE Who Met SLICC 2012 but Not EULAR/ACR 2019, n = 18 | Patients With SLE Who Met EULAR/ACR 2019 but Not SLICC 2012, n = 8 | *P* |
|---|---|---|---|
| Sex, female | 14 (77.8) | 7 (87.5) | > 0.99 |
| Age at diagnosis, months, median (min–max) | 183.5 (96–215) | 156 (62–204) | 0.24 |
| Fever (> 38.3°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 |
| Nonscarring alopecia | 2 (11.1) | 0 (0) | > 0.99 |
| Oral ulcers | 8 (44.4) | 0 (0) | 0.03 |
| Malar rash | 5 (27.8) | 4 (50) | 0.38 |
| Discoid rash | 3 (16.7) | 0 (0) | > 0.99 |
| Photosensitivity | 6 (33.3) | 2 (25) | > 0.99 |
| Delirium | 1 (5.6) | 0 (0) | > 0.99 |
| Psychosis | 1 (5.6) | 0 (0) | > 0.99 |
| Focal neurologic defect | 1 (5.6) | 0 (0) | > 0.99 |
| Acute confusional state | 1 (5.6) | 0 (0) | > 0.99 |
| Leukopenia (< 4000/mm$^3$) | 7 (38.9) | 0 (0) | 0.06 |
| Lymphopenia (< 1000/mm$^3$) | 2 (11.1) | 0 (0) | > 0.99 |
| Lymphopenia (< 1500/mm$^3$) | 7 (38.9) | 1 (12.5) | 0.36 |
| Thrombocytopenia (< 100,000/mm$^3$) | 8 (44.4) | 0 (0) | 0.03 |
| 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) | > 0.99 |
| Low C4 | 8 (44.4) | 1 (12.5) | 0.19 |
| ANA positivity (≥ 1/80) | 15 (83.3) | 8 (100) | 0.52 |
| Anti-dsDNA | 1 (5.6) | 3 (37.5) | 0.07 |
| Anti-Sm | 0 (0) | 1 (12.5) | 0.31 |
| Anticardiolipin antibodies | 6 (33.3) | 0 (0) | 0.26 |
| Anti-$\beta_2$-GPI | 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 LN | 3 (16.7) | 0 (0) | 0.52 |
| SLE according to the ACR 1997 criteria | 7 (38.9) | 2 (25) | > 0.99 |

Values are expressed as n (%) unless stated otherwise. ACR: American College of Rheumatology; ANA: antinuclear antibody; anti-$\beta_2$-GPI: anti-$\beta_2$-glycoprotein I; EULAR: European League Against Rheumatism; LN: lupus nephritis; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics.

introduce a challenge while differentiating SLE from its close mimickers.

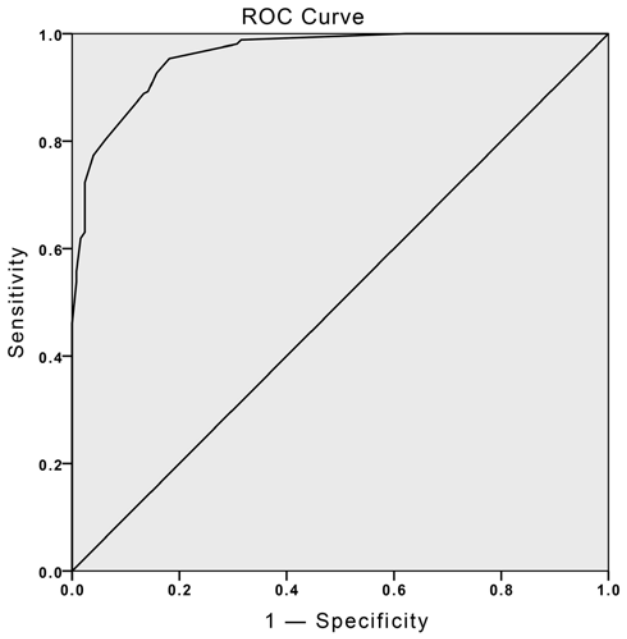
Hematologic involvement was frequent among patients who fulfilled the SLICC 2012 criteria but not the EULAR/ACR 2019 criteria (n = 13; 72.2%). Hematologic manifestations are more frequently observed in pediatric than adult SLE.[4] These have been described in up to 86% of children with SLE.[25] In the SLICC 2012 criteria, different components of hematologic involvement, such as hemolytic anemia, leukopenia/lymphopenia, and thrombocytopenia, are allocated into different criteria.[8] Thus, a patient could meet 3 out of the required 4 criteria with only hematologic involvement according to the SLICC 2012.[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 4, which occurs in the presence of autoimmune hemolysis or thrombocytopenia.[13,14] This specific difference between the 2 criteria sets might have contributed significantly to the higher sensitivity of the SLICC 2012 over the EULAR/ACR 2019 criteria. It is worth mentioning that the SLICC 2012 misclassified 4 out of 5 patients with HUS as having SLE while the other 2 criteria sets 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 into different criteria in the SLICC 2012 and the attribution of a high weight to arthritis in the EULAR/ACR 2019 criteria possibly also contributed to

*Table 5.* Patients in the control group who met either the SLICC 2012 or EULAR/ACR 2019 criteria, but not the other.

| | Controls Who Met SLICC 2012, but Not EULAR/ACR 2019, n = 7 | Controls Who Met EULAR/ACR 2019, but Not SLICC 2012, n = 9 | *P* |
|---|---|---|---|
| Sex, female | 5 (71.4) | 7 (77.8) | > 0.99 |
| Age at diagnosis, months, median (min–max) | 40 (4–192) | 132 (36–192) | 0.09 |
| Fever (> 38.3°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) | > 0.99 |
| Generalized maculopapular rash | 0 (0) | 3 (33.3) | 0.21 |
| Photosensitivity | 1 (14.3) | 0 (0) | 0.43 |
| Delirium | 0 (0) | 1 (11.1) | > 0.99 |
| Seizure | 0 (0) | 1 (11.1) | > 0.99 |
| Focal neurologic defect | 1 (14.3) | 1 (11.1) | > 0.99 |
| 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) | > 0.99 |
| 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) | 0.02 |
| 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) | 0.04 |
| Low C4 | 5 (71.4) | 2 (22.2) | 0.04 |
| ANA positivity (≥ 1/80) | 3 (42.9) | 9 (100) | 0.02 |
| Anti-dsDNA | 0 (0) | 2 (22.2) | 0.47 |
| Anticardiolipin antibodies | 1 (14.3) | 0 (0) | > 0.99 |
| Lupus anticoagulant | 1 (14.3) | 0 (0) | 0.33 |
| SLE according to the ACR 1997 criteria | 1 (14.3) | 0 (0) | 0.43 |

Values are expressed as n (%) unless stated otherwise. ACR: American College of Rheumatology; ANA: antinuclear antibody; EULAR: European League Against Rheumatism; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics.




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 2019 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 the 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.

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

Another limitation is that we were not able to test the performances later in the disease course of these patients. Analysis in the follow-up might have provided valuable data about the performance of the criteria sets, since pediatric SLE has an additive course. Last, the gold standard for SLE diagnosis was 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 to date, to our knowledge, testing the performances of the 3 classification criteria, we showed that the SLICC 2012 had the highest sensitivity, and that the ACR 1997 had the highest specificity. SLICC 2012 performed better than the EULAR/ACR 2019 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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