**Evaluation of the ACR and SLICC Classification Criteria in Juvenile-onset Systemic Lupus Erythematosus: A longitudinal analysis**

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**Abstract**

Objectives

The Systemic Lupus International Collaborating Clinics (SLICC) group proposed revised classification criteria for systemic lupus erythematosus (SLICC-2012 criteria). This study aimed to compare these criteria with the well-established American College of Rheumatology classification criteria (ACR-1997 criteria) in a national cohort of juvenile-onset systemic lupus erythematosus (JSLE) patients and evaluate how patients’ classification criteria evolved over time.

Methods

Data from patients in the UK JSLE Cohort Study with a senior clinician diagnosis of probable evolving, or definite JSLE, were analysed. Patients were assessed using both classification criteria within one year of diagnosis and at latest follow-up (following a minimum twelve month follow-up period).

Results

226 patients were included. The SLICC-2012 was more sensitive than ACR-1997 at diagnosis (92.9% vs 84.1% p<0.001) and after follow-up (100% vs 92.0% p<0.001). Most patients meeting the SLICC-2012 criteria and not the ACR-1997 met more than one additional criterion on the SLICC-2012.

Conclusions

The SLICC-2012 was better able to classify patients with JSLE than the ACR-1997 and did so at an earlier stage in their disease course. SLICC-2012 should be considered for classification of JSLE patients in observational studies and clinical trial eligibility.

Key words

Juvenile-onset systemic lupus erythematosus; ACR classification criteria; SLICC classification criteria

Introduction

Juvenile-onset systemic lupus erythematosus (JSLE) is a severe, multi-system inflammatory disease characterised by the presence of autoantibodies directed against nuclear auto-antigens.  Diagnosis and classification can prove challenging due to very varied clinical manifestations and disease course.  Classification criteria are important to ensure consistent definition, particularly in relation to clinical trials.

The American College of Rheumatology (ACR) initially established classification criteria in 1982[1], however they were updated in 1997[2] and although never validated these classification criteria (ACR-1997) are well established. However, there are concerns that the ACR-1997 criteria may limit classification of patients with early or evolving lupus, lupus nephritis or neurological lupus[3]. These limitations are of particular relevance in JSLE where there may be an evolving, but also generally more severe disease course than its adult-onset counterpart[4-6]. As the ACR-1997 criteria do not permit the classification of SLE with isolated lupus nephritis, and as lupus nephritis is more common in JSLE patients[5], under-representation of these patients when using the ACR-1997 criteria alone may be of more significance in this group.

The Systemic Lupus International Collaborating Clinics (SLICC) group revised SLE classification criteria in adults in an attempt to address some of the concerns with the ACR-1997 criteria[7].  SLICC-2012 has 17 criteria (compared to 11 criteria in ACR-1997), divided into 11 clinical criteria and 6 immunological criteria. Both classifications require patients to have at least 4 criteria to be classified with SLE but SLICC-2012 requires at least one clinical and immunological criterion. Important differences include: SLICC-2012 allows patients with lupus nephritis in the presence of antinuclear antibodies (ANA) or anti-double stranded DNA (anti-dsDNA) to be classified with SLE in the absence of any further criteria; the definition of cutaneous and neurological lupus have been extended; additional new criteria are included such as alopecia and low complement; the disaggregation of the ACR-1997 haematological and immunological criteria.

SLICC-2012 has been demonstrated to result in fewer misclassifications with a higher sensitivity than ACR-1997 in adult patients[7,8]. There are only two small studies in patients with childhood-onset lupus suggesting higher sensitivity [9,10].  Two studies suggest lower specificity of SLICC-2012[7,9]. A large study of adult patients with SLE demonstrated that the difference in sensitivity between ACR-1997 and SLICC-2012 decreased over time, indicating SLICC-2012 may enable classification of SLE at an earlier stage in the disease course[8].

This present study aims to compare the ACR-1997 and SLICC-2012 classification criteria in a large national cohort of children and young people with a clinician diagnosis of JSLE and determine how the classification criteria that individual patients meet, evolves over time.

Patients and Methods

Patients participating in the United Kingdom (UK) JSLE Cohort Study were included in this study[11].  The UK JSLE Cohort Study, started in 2006, collects data from almost all UK centres (n=21) treating patients diagnosed with JSLE.  It recruits patients who meet four or more ACR classification criteria for SLE. It also recruits patients with ‘probable,’ ‘evolving’ lupus in the opinion of the experienced consultant clinician looking after that patient, but currently fulfilling only 2 or 3 ACR criteria.  Data is collected prospectively at baseline, annually and at review visits.  The study has full ethical approvals and all patients / parents provided appropriate written assent / consent to participate.

Data collected at baseline and annually includes ACR-1997 classification criteria for SLE and disease activity data, collected using the paediatric adaptation of the 2004 update of the British Isles Lupus Assessment Group index (pBILAG-2004).  Disaggregated data for both of these is available.  The study does not collect data on non-JSLE patient cohorts. Having been started before the development of the SLICC-2012 criteria, the dataset does not currently collect the specific parameters of SLICC-2012 score separately.

Each patient’s SLICC-2012 score was therefore derived from disaggregated ACR-1997 and pBILAG-2004 data.  For all parameters of the SLICC-2012 criteria we matched as accurately as possible the definitions and data available. We additionally obtained detailed information regarding renal biopsies.

Each patient was classified using ACR-1997 and SLICC-2012 within one year of diagnosis (by a consultant paediatric rheumatologist or paediatric nephrologist) of JSLE and at their latest follow-up.  Patients were only included if they had a minimum of one year follow-up and sufficient data to facilitate classification by both sets of criteria.

Data are primarily expressed descriptively. McNemar’s test was used to compare the sensitivity of ACR-1997 and SLICC-2012 at diagnosis and after follow-up. Time to event analysis was performed using the Kaplan Meier method with the log-rank test used to compare the difference in time to classification using ACR-1997 and SLICC-2012. Results were considered significant if the p value was less than 0.05.

Results

**Patients**

226 patients were identified and included in this study.  The median age at diagnosis was 12.8 years (range 2.0 – 17.9 years, IQR 10.5 – 14.5 years) with a female-to-male ratio of 5:1.  The median follow-up was 3.6 years (range 1.0 – 14.8 years, IQR 2.3 – 5.3 years).

**Classification at diagnosis**

At diagnosis (by a consultant paediatric rheumatologist or paediatric nephrologist who assessed that they had definite, or probable, evolving JSLE), 187/226 met both ACR-1997 and SLICC-2012 (figure 1).  Thirteen patients met neither classification criteria at ‘diagnosis’.  A total of 190/226 met ACR-1997 at diagnosis compared to 210/226 meeting SLICC-2012. The SLICC-2012 was therefore more sensitive (84.1% vs 92.9% p<0.001).

*Figure 1: Summary of classification criteria met by patients at diagnosis and follow-up*

The median number of ACR-1997 criteria met at diagnosis was 4 (range 2 – 9, IQR 4 – 5).  The median number of SLICC-2012 criteria met at diagnosis was 6 (range 2 – 12, IQR 5 – 8).  Four patients with ≥4 SLICC-2012 criteria did not have at least one clinical and one immunological criterion and therefore did not meet SLICC-2012.

Three patients met ACR-1997 and not SLICC-2012. One patient had malar rash and photosensitivity fulfilling two criteria on ACR-1997 (plus two other criteria to give a total of 4 criteria) but only one criterion (acute cutaneous) on SLICC-2012 (to give a total of 3 criteria). One patient met the ACR-1997 criterion for low lymphocyte count but not the lower SLICC-2012 criterion. One patient met four criteria on both classification systems but did not meet any of the SLICC-2012 immunological criteria.

Twenty-three patients met SLICC-2012 but not ACR-1997 criteria. Only one patient met SLICC-2012 for biopsy-proven nephritis and positive ANA alone. Of the 22 patients meeting SLICC-2012 clinical and immunology criteria (but not ACR-1997 criteria), 14 patients met more than one ‘additional’ criterion on SLICC-2012 when compared to ACR-1997 (Table 1). Table 1 describes how patients met additional criteria on SLICC-2012 and highlights where a single additional criterion allowed a patient to meet SLICC-2012 but not ACR-1997). Additional criteria were noted (when comparing the criteria) as illustrated in this example: one patient met three criteria on the ACR-1997 but met an additional 4 criteria on SLICC-2012 (meeting 7 SLICC criteria in total); arthritis scored 1 point on each criteria; ANA scored 1 point on each criteria; anti-dsDNA and anti-Sm antibodies scored 1 point on ACR-1997 but 2 points on SLICC-2012; the patient also scored one additional point on SLICC-2012 for each of alopecia, low complement and positive direct coomb’s test in the absence of haemolytic anaemia. Hence, they were deemed to have four ‘additional’ criteria.

*Table 1: Summary of additional criteria met on SLICC-2012 compared to ACR-1997*

Of note, 6 patients met SLICC-2012 and not ACR-1997 only due to them meeting the ‘low complement’ criterion on SLICC-2012, increasing their score to 4 on SLICC-2012 (Table 1).

There were 40 patients who had lupus nephritis confirmed by renal biopsy at diagnosis (18%). 38 patients met SLICC-2012 criteria: 36 patients had positive antinuclear or anti-dsDNA antibodies and therefore automatically met SLICC-2012 classification with one of these patients meeting SLICC-2012 solely because of this (and this patient did not meet ACR-1997 criteria). Two patients with negative antinuclear and anti-dsDNA antibodies met SLICC-2012 clinical and immunology criteria. Thirty-six of the lupus nephritis patients met the ACR-1997 criteria. Two patients met neither classification criteria at diagnosis.

There were 18 patients with neurological features of JSLE at diagnosis. Seventeen patients met SLICC-2012 and 16 patients met ACR-1997 with one patient meeting neither classification criteria.

**Classification at latest follow-up**

At latest follow-up 208/226 met ACR-1997 and all patients met SLICC-2012. SLICC-2012 was therefore still more sensitive after follow-up (92.0% vs 100% p<0.001). Nine patients meeting SLICC-2012 but not ACR-1997 criteria at diagnosis had gone on to meet ACR-1997 during the follow-up period (figure 1).

The sensitivity of both criteria and their components at diagnosis and after follow up is shown in Table 2, with those that have greater than 60% sensitivity in bold. As the study does not collect data on other patient cohorts, specificity and positive and negative predictive value of both classification criteria could not be compared.

*Table 2: Sensitivity of ACR-1997 and SLICC-2012 at diagnosis and on latest follow-up*

The median ACR-1997 score at latest follow-up was 5 (range 2 – 10, IQR 4 – 7). The median SLICC-2012 classification score at latest follow-up was 8 (range 4 – 15, IQR 6 – 9).

Of the 18 patients meeting SLICC-2012 criteria but not ACR-1997 criteria, 11 patients met more than one additional criterion on SLICC-2012 (Table 1).

Time to event analysis demonstrated mean time to classification by ACR-1997 criteria to be 254 days (CI 152 – 356) compared to 38 days (CI 16 – 60 days) for SLICC-2012 criteria, which was statistically significant (p<0.001).

Discussion

This study demonstrates using national, real world data that the SLICC-2012 is more sensitive in classifying patients with a clinician diagnosis of JSLE than the ACR-1997, and does so at an earlier stage in their disease course.

As far as we are aware this is the largest comparison of these classification criteria in JSLE patients and the only study looking at how their classification evolves beyond the first year of diagnosis. Our results are consistent with previous studies demonstrating the SLICC-2012 criteria to have greater sensitivity[7-9]. Our results confirm that using SLICC-2012 for classification for clinical trials or observational studies would allow inclusion of more patients with a clinical diagnosis of JSLE.  The fact that the SLICC-2012 criteria are more sensitive and able to classify disease at an earlier stage in the disease course gives hope that proper diagnostic criteria might be developed in the future.

Interestingly the low complement criteria in SLICC-2012 particularly contributed to its increased sensitivity (Table 1). The impact of low complement at diagnosis on prognosis is not well understood. Further studies aiming to determine whether earlier classification using SLICC-2012 is able to impact on prognosis may be useful.

Previous research has shown that the difference in sensitivity between ACR-1997 and SLICC-2012 diminishes over time in adults with SLE, no longer being significant in patients with >20 years disease duration[8]. Our median follow-up was 3.6 years and the difference in sensitivity of ACR-1997 and SLICC-2012 remained consistent during this time. If our patients were to follow the pattern identified in the previous study it may be possible that many more would go on to meet the ACR-1997 if followed long-term into adulthood.

Specificity of classification criteria is also important, particularly in relation to clinical trials. Two studies of JSLE patients evaluate specificity of SLICC-2012. The first suggested the ACR-1997 to be significantly more specific (93.4% vs 85.3%, p<0.001), but despite this SLICC-2012 was better able to accurately classify patients with lupus or not[9]. . The second study suggested there was no significant difference in specificity (93.4% vs 93.5%, p=1)[10]. We suggest that the significant increase in sensitivity and earlier classification of JSLE demonstrated in our study would favour a move towards using the SLICC-2012 criteria for clinical trials involving JSLE patients.

The clinical phenotype of lupus is different in adults and children. Our study had relatively small numbers of patients with lupus nephritis and neurological lupus, but importantly did find that three patients in these groups could be classified using SLICC-2012 but not ACR-1997.  Although the SLICC-2012 was not developed for children, it does recognise a wider spectrum of presentations and sharing a classification system with adults is advantageous in allowing direct comparison.

There were some limitations to our study. There is an inherent lack of objective diagnosis as the standard of reference and treating clinician diagnosis was therefore used (based on meeting at least 2 ACR criteria and a strong senior, experienced clinical judgment). It may be argued that this could lead to inconsistency, however, it does allow evaluation of classification criteria in a real world setting. It is also the largest cohort of JSLE patients within which the SLICC-2012 criteria have been evaluated. We retrospectively classified patients for the SLICC-2012 using existing data, and some data was not available: mucosal lupus (distinct from oral and nasal ulceration), lupus erythematous tumidus and anti-β2 glycoprotein 1. However, lupus erythematous tumidus is only reported in adults and mucosal lupus is very rare in children[12]. This may mean that our reported sensitivities may even be slightly higher if these data were available. We defined criteria within a year of diagnosis as the sensitivity for ‘diagnosis’. This may lead to artificially higher sensitivity in both criteria than if classification criteria were performed at the exact point of diagnosis, however, a sub-analysis of 170 patients where data was available within a week of diagnosis demonstrated similar sensitivities (85.3% on sub-analysis vs 84.1% on main analysis met ACR-1997 and 94.7% vs 92.9% for SLICC-2012 respectively). As the UK JSLE Cohort Study focuses on patients with a diagnosis of definite or probable evolving JSLE and does not include other patient cohorts, comparing the specificity of both classification criteria was beyond the scope of this present study. A further large study with a comparator group would be important to understand fully how the SLICC-2012 would perform as eligibility criteria for clinical trials.

In summary, this study demonstrates that SLICC-2012 is more sensitive in classifying UK patients with clinically suspected JSLE and at an earlier stage of the disease course. We suggest the SLICC-2012 could be considered for classification of JSLE patients for the purpose of observational and clinical trial eligibility when additional data on specificity is available. Further studies should focus on specificity and prospective validation of the criteria, and consider whether our UK findings are replicated within international cohorts.

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Conflicts of Interest

There are no conflicts of interest

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Table 1: Summary of additional criteria met on SLICC-2012 compared to ACR-1997

|  |  |  |
| --- | --- | --- |
| **Additional points on SLICC-2012** | **Diagnosis** | **Follow-up** |
| **Number of patients** | **Number of patients for which score allows patient to meet SLICC-2012 independently** | **Number of patients** | **Number of patients for which score allows patient to meet SLICC-2012 independently** |
| Acute cutaneous, not malar rash/ photosensitivity | 3 | 1 | 2 | 0 |
| Chronic cutaneous, not discoid | 2 | 0 | 3 | 0 |
| Alopecia | 7 | 0 | 5 | 1 |
| Neurological, not meeting ACR | 1 | 0 | 0 | 0 |
| Multiple haematology criteriaa | 2 | 1 | 2 | 0 |
| Leukopenia/lymphopenia, not meeting ACR | 1 | 0 | 0 | 0 |
| Low complement | 16 | 6 | 16 | 6 |
| Direct Coombs’ test | 4 | 0 | 2 | 0 |
| Multiple immunology criteriab | 5 | 0 | 4 | 0 |
| **Total** | **41** | **8** | **34** | **7** |
| **a**Patients who have multiple haematological criteria which only score one point on the ACR-1997 but score >1 point on the SLICC-2012 e.g. presence of haemolytic anaemia and leukopaenia scores one point on ACR-1997 but 2 points on SLICC-2012bPatients who have multiple immunological criteria which only score one point on the ACR-1997 but score >1 point on the SLICC-2012 e.g. presence of anti-ds DNA and anti-Sm antibodies scores one point on ACR-1997 but 2 points on SLICC-2012 |

Table 2: Sensitivity of ACR-1997 and SLICC-2012 at diagnosis and on latest follow-up

|  |  |  |
| --- | --- | --- |
| **CRITERIA SET** | **SENSITIVITY AT DIAGNOSIS** | **SENSITIVITY AT FOLLOW-UP** |
| **ACR-1997** |
| **Overall met ACR-1997** | **84.1%** | **92.0%** |
| Malar rash | 52.1% | **64.6%** |
| Discoid rash | 8.4% | 13.7% |
| Photosensitivity | 18.6% | 32.3% |
| Oral ulcers | 34.1% | 45.6% |
| **Nonerosive arthritis** | **62.4%** | **67.3%** |
| Pleuritis/Pericarditis | 17.7% | 23.5% |
| Renal | 27.9% | 37.2% |
| Neurological | 5.3% | 11.1% |
| **Haematological** | **68.1%** | **77.9%** |
| **Immunological** | **76.6%** | **83.2%** |
| **ANA** | **93.4%** | **96.9%** |
| **SLICC-12** |
| **Overall met SLICC-2012** | **92.9%** | **100.0%** |
| **Acute cutaneous** | **64.6%** | **85.0%** |
| Chronic cutaneous | 19.0% | 36.3% |
| Oral ulcers | 34.1% | 45.6% |
| Nonscarring alopecia | 26.6% | 55.8% |
| **Synovitis** | **62.4%** | **67.3%** |
| Serositis | 17.7% | 23.5% |
| Renal | 27.9% | 37.2% |
| Neurologic | 8.0% | 16.4% |
| Haemolytic anaemia | 20.8% | 23.9% |
| Leukopenia | 43.4% | 44.7% |
| Thrombocytopenia | 19.9% | 21.7% |
| **ANA** | **93.4%** | **96.9%** |
| **Anti-dsDNA** | **61.5%** | **69.5%** |
| Anti-Sm | 17.3% | 22.1% |
| Antiphospholipid | 27.0% | 38.1% |
| **Low complement** | **71.7%** | **93.4%** |
| Direct Coombs' | 11.5% | 14.2% |
| Lupus nephritis + ANA | 15.9% | 23.0% |
| **Combined sensitivity**  |
| **Met ACR-1997 or** **SLICC-2012** | **94.2%** | **100.0%** |
| Criteria with >60% sensitivity noted in bold for comparison |