**Title**

**Limited sensitivity and specificity of ACR/EULAR-2019 classification criteria for SLE in JSLE? - Observations from the UK JSLE Cohort Study**

**Short title**

**EULAR/ACR-2019 Criteria in jSLE**

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**Abstract**

**Objectives:** This study aimed to test the performance of the “new” American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria, that include anti-nuclear antibodies (ANA) positivity as entry criterion, in juvenile-onset systemic lupus erythematosus (jSLE).

**Methods:** Performance of the ACR/EULAR-2019 criteria were compared with Systemic Lupus International Collaborating Clinics (SLICC-2012), using data from children and young people (CYP) in the UK JSLE Cohort Study (n=482), with the ACR-1997 criteria used as reference standard. An “unselected” cohort of CYP positive for ANA (n=129) was used to calculate positive/ negative predictive values of the criteria.

**Results:** At both first and last visit, the number of patients fulfilling the different classification criteria varied significantly (p<0.001). Sensitivity of SLICC-2012 criteria was higher when compared to ACR/EULAR-2019 at first and last visit (98% vs 94%, first visit, and 98% vs 96%, last visit; p<0.001), when all available CYP were considered. ACR/EULAR-2019 criteria were more specific when compared to SLICC-2012 (77% vs 67%, first visit, and 81% vs 71%, last visit; p<0.001). Significant differences between the classification criteria were mainly caused by the variation in ANA positivity across ages. In the “unselected” cohort of ANA positive CYP, ACR/EULAR-2019 criteria produced the highest false positive classification (6/129, 5%) .

**Conclusion:** In CYP, ACR/EULAR-2019 criteria are not superior to SLICC-2012 or ACR-1997 criteria. If classification criteria are designed to include CYP and adult populations, paediatric rheumatologists should be included in the consensus and evaluation process, as seemingly minor changes can significantly affect outcomes.

**Introduction**

Juvenile-onset systemic lupus erythematosus (jSLE) is a severe, multi-system autoimmune/inflammatory disease characterised by systemic inflammation, tissue and organ damage, and the presence of autoantibodies directed against nuclear auto-antigens(1). Presentation and outcomes vary significantly between individuals, which can complicate diagnosis, generation of evidence through clinical trials and treatment of patients(2).

Classification criteria are an important tool to ensure consistent case definition, particularly in relation to clinical trials. Widely accepted and used criteria for SLE were developed by the American College of Rheumatology (ACR) in 1982(3), updated in 1997 (ACR-1997). Criteria include 11 clinical and laboratory items, ≥4 required to be classified as SLE. Each element is weighted equally and (technically) patients can be classified as SLE in the absence of immunological anomalies(4). Due to concerns that the ACR criteria may miss some SLE patients, in particular those with lupus nephritis (LN) and autoantibody positivity but limited systemic involvement, the Systemic Lupus International Collaborating Clinics (SLICC-2012) group established further criteria, including 11 clinical and 6 immunological items(5). Each criterion is weighted equally, and a score of ≥4 is required for classification as SLE. Of note, SLICC-2012 also stipulated that patients with LN and anti-nuclear antibody (ANA) and/or anti-double-stranded DNA antibody (dsDNA) positivity can be defined as SLE, in the absence of other clinical criteria(5). Studies examining the performance of the SLICC-2012 criteria in international adult and jSLE cohorts identified higher sensitivity, but lower specificity when compared to the ACR-1997 criteria(6–8).

Recently, the ACR and the European League Against Rheumatism (EULAR) proposed a new set of classification criteria for SLE (ACR/EULAR-2019 criteria), validated in large adult SLE cohorts(9). ANA positivity is a mandatory entry criterion (ANA titre of ≥1:80 on human epithelial type 2 cells or equivalent positive test result). Thereafter, a weighted scoring system requires the patient to score ≥10 points to be classified as SLE. Similar to the SLICC-2012 criteria, ACR/EULAR-2019 criteria are separated into clinical and immunological features. Based on data from adult cohorts, ACR/EULAR-2019 criteria show better sensitivity and specificity when compared to previous criteria(9).

Data on performance of ACR/EULAR-2019 criteria in jSLE is limited to two relatively small cohorts that both suggested limited specificity when compared to ACR-1997 or SLICC-2012 criteria(10)(11). These studies did not include longitudinal assessment of the ACR/EULAR-2019 criteria.

This study aimed to: i) test performance of the ACR/EULAR-2019 classification criteria in the UK JSLE Cohort Study population longitudinally (first vs. last visit) and in relation to age at diagnosis (pre-/peri-/post-pubertal); ii) investigate ACR/EULAR-2019 criteria in an unrelated cohort of ANA positive individuals; and iii) compare performance of the ACR/EULAR-2019 classification criteria to that of the ACR-1997 and SLICC-2012 criteria.

**Methods**

***Participants --*** The UK JSLE Cohort Study(12), collects longitudinal clinical data from almost all UK paediatric rheumatology centres (n=22) treating children and young people (CYP) with jSLE. It primarily recruits patients who meet ≥4 ACR classification criteria for SLE(13). It also recruits patients with ‘probable’ lupus (fulfilling <4 ACR criteria) when an experienced consultant clinician anticipates that the patient will evolve into jSLE. As such, not all patients fulfil the ACR-1997 classification criteria for SLE.

The UK JSLE Cohort Study(13) patients included in this study fulfilled the following inclusion criteria: 1) had data collected between July 2016 and January 2019 (that included SLICC-2012 Classification criteria collected between these timepoints), 2) an ACR-1997 score of ≥2 at inclusion, and 3) aged <16 years at the time of recruitment. The performance of SLE classification criteria were tested both in CYP fulfilling ≥4 ACR-1997 classification criteria for SLE, and in CYP with a strong clinical history to suggest a diagnosis of jSLE but where <4 ACR-1997 criteria were fulfilled at recruitment to the UK JSLE Cohort Study (representing “possible” or “probable” jSLE cases). Throughout the manuscript, where all UK JSLE Cohort patients are included in the analysis (those fulfilling ≥4 ACR-1997 classification criteria and“possible” or “probable” cases with <4 ACR-1997 criteria at recruitment) they are described as the ‘**full** UK JSLE Study Cohort’.

Self-reported ethnicity information was collected according to UK National Census categorisations(14). Data of mixed-race patients were grouped with those of the associated ethnic minority group; a category of “other” was available for those not wishing to report ethnicity. The study has full ethical approval (National Research Ethics Service North West, Liverpool, UK, reference 06/Q1502/77). Research was carried out in accordance with the declaration of Helsinki.

***Data collected --*** Demographic and clinical data were collected at patients’ “first” clinical assessment at time of recruitment to the UK JSLE Cohort Study and their “last” study visit, which is the final or most recent clinical assessment. The UK JSLE Cohort Study collects the paediatric adaptation of the 2004 British Isles Lupus Assessment Group index (pBILAG-2004) disease activity score at each clinical encounter(12). It also collects the ACR-1997 classification criteria for SLE at baseline and annually. Disaggregated pBILAG scores and ACR-1997 classification criteria data were used to calculate the ACR/EULAR-2019 scores (first and last study visit). ANA positivity was defined as a titre of ≥1:80. Renal biopsy data were also obtained where available.

***ANA positive patients presenting over a 12-month period (“unselected ANA positive control Cohort”) –*** Clinical and laboratory data were collected from electronic patient charts of 129 CYP who, as part of an investigative work-up, were found to be ANA positive (titre of ≥1:80, between 01/2018-01/2019) and therefore fulfilled the ACR/EULAR-2019 entry criterion for SLE. Data were used to calculate ACR-1997, SLICC-2012 and ACR/EULAR-2019 scores. The electronic records of these patients were re-checked 18 months after the initial positive ANA measurement, to check if the patients diagnosis had changed over time.

***Statistical analysis --*** Data from the UK JSLE Cohort Study were used to assess the performance of the ACR/EULAR-2019 classification criteria for SLE, primarily against the ACR-1997 criteria (“the reference criteria”), but also against the SLICC-2012 criteria. Data are primarily expressed descriptively (median, range, percentages and inter-quartile ranges). The differences between age groups, classification criteria and demographic details were compared using Chi-square tests. Where comparisons were made between three different groups (e.g. age groups) and a significant difference was detected, further Chi-square tests were used to determine exactly where the significant difference lay, with a Bonferroni correction applied for multiple testing.

Sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated to assess the performance of SLICC-2012 and ACR/EULAR-2019 classification criteria against the ACR-1997 criteria (reference criteria). In these analyses, the UK JSLE Cohort group of patients (n=482) were combined with the unselected ANA positive patients (n=129), with the later acting as a control group (total n=611). Chi squared test were used to calculate p-values for the sensitivities and specificities, and binomial exact test was used to calculate p-values for the positive and negative predictive values. McNemar’s test was used to assess for a difference between ACR-1997 and ACR/EULAR2019, ACR-1997 and SLICC-2012 and SLICC-2012 and ACR/EULAR-2019, in the number of patients classified as having jSLE at first and last visit.

In the absence of a definitive “gold standard”, the level of agreement between the different criteria was also assessed using receiver operator curves (ROC). In these analyses the area under the curve (AUC) was calculated for the following comparisons: ACR-1997 vs ACR/EULAR-2019, ACR-1997 vs SLICC-2012 and SLICC-2012 vs ACR/EULAR-2019. AUC values of 1.0–0.9, 0.9–0.8, 0.8–0.7, 0.7–0.6 and 0.6–0.5 were considered to be excellent, good, fair, poor and fail, respectively (13). Kappa coefficients were calculated to assess inter-rater agreement between the criteria. A kappa coefficient value of more than 0.4 is considered acceptable (15,16). Absolute values and CIs for the AUC and kappa coefficient are reported. All statistics were calculated using STATA 14 (StataCorp LLC, USA) and Excel (Microsoft, USA). Results were considered significant if the p-value was <0.05.

**Results**

***UK JSLE Cohort study participants’ clinical and demographic features –*** From inception to date, the UK JSLE Cohort Study has recruited 760 patients. 482 patients met this study’s inclusion criteria. The median age at diagnosis was 12.8 years [IQR 10.4 – 17.9], with a male to female ratio of 1:5. Data on age of onset were missing for 5 patients, therefore of the 477 jSLE patients where age of onset was available, 50 (10%) were classified as having jSLE with disease onset at <8 years of age (pre-pubertal), 268 (56%) between 8-13 years (peri-pubertal), and 159 (33%) >14 years of age (adolescent). Median follow-up was 39 months [IQR 18 – 195]. Ethnicity data were missing for 10 patients, of the 472 where ethnicity was known, 242 (50%) of patients were White Caucasian, 140 (29%) were South Asian (30%), 73 (15%) were Black African/Caribbean and 17 (4%) were of a mixed ethnic background. ANA positivity at first visit was highest in patients presenting between 14-16 years (95%) compared with other age groups (<8 years: 88%; 8-14 years: 93%). Demographic and clinical information is summarised in Table 1.

***Participants fulfilling*** ***SLE classification criteria at first and last visit -*** The number of UK JSLE Cohort Study participants fulfilling ACR-1997, SLICC-2012 and ACR/EULAR-2019 classification criteria at the time of their “first” and “last” visit are displayed in Figure 1. At first visit, 385/482 (80%) patients fulfilled ACR-1997 criteria for SLE, 402/482 (83%) ACR/EULAR-2019 criteria and 443/482 (92%) fulfilled SLICC-2012 criteria. By the last visit, 427/482 (89%) patients fulfilled the ACR-1997 criteria, and 434/482 (90%) ACR/EULAR-2019 criteria and 463/482 (96%) fulfilled SLICC-2012 criteria. There was a significant increase in the number of patients classified as SLE between first and last visit by all classification criteria (all p<0.001). At both first and last visit, the number of patients fulfilling the different classification criteria (ACR-1997, SLICC-2012 and ACR/EULAR-2019) varied significantly (p<0.001 at both first/last visit).

At first visit, 30 (6%) patients who would otherwise have scored ≥10 using the ACR/EULAR-2019 criteria for SLE were ANA negative and therefore did not fulfil the ACR/EULAR-2019 entry criterion for SLE (despite 18/30 (60%) fulfilling either ACR-1997 or SLICC-2012 criteria). 15/30 (50%) of these patients subsequently developed ANA positivity, and therefore met the ACR/EULAR-2019 criteria by their last visit. Further information on the individual criteria fulfilled by patients who met the classification criteria threshold for one set of criteria, but not the others, at their first visit is shown in Supplementary Table S1.

***Clinical and laboratory criteria fulfilled --*** Individual clinical and immunological items fulfilled from the three different classification criteria at first and last presentation are displayed in Supplementary Table S2. Of note, across the UK JSLE Cohort Study, the proportion of ANA positive individuals increased from first (448/482, 93%) to last visit (463/482, 96%; p<0.001), increasing the number of individuals fulfilling the entry criterion of ACR/EULAR-2019. At first visit, 10 patients exhibited grade III or IV nephritis on biopsy whilst testing negative for ANA at inclusion/first visit. Three patients continued to be ANA negative at the time of their last visit. A negative ANA would exclude these 10 patients at first visit and 3 patients at last visit from classification of SLE using ACR/EULAR-2019 criteria.

***SLE classification criteria in relation to age at diagnosis within the full UK JSLE Study Cohort (n=482) --*** Age specific differences in clinical presentation and laboratory findings have previously been demonstrated in CYP with jSLE(17). To address the question of whether the number of classification variables differed according to age, jSLE patients were sub-divided into the following groups: pre-pubertal (<8 years), peri-pubertal (8-13 years) and adolescent/post-pubertal (≥14 years) (Table 2). For ACR/EULAR-2019 criteria, a significant difference was seen in the proportion of patients fulfilling criteria according to age, at both first (p=0.02) and last visit (p=0.001). At first visit, a lower proportion of pre-pubertal patients (32/50, 64%) fulfilled the ACR/EULAR-2019 criteria as compared to both peri-pubertal (219/268, 81%, p=0.04) and adolescent patients (126/159, 79%; p=0.002, Table 2). This likely relates to the observation that ANA positivity was numerically highest at diagnosis in adolescent patients (14-16 years: 151/159, 95%) when compared with other age groups (<8 years: 44/50, 88%; 8-14 years: 249/268, 93%) (Table 1). This difference was not seen using either ACR-1997 or SLICC-2012 criteria (p-values >0.05).

***Performance of SLE classification criteria in an “unselected” paediatric population testing positive for ANA and the full UK JSLE Study Cohort combined –*** To test sensitivity, specificity, positive and negative predictive values of classification criteria in ANA positive CYP independent of their final diagnosis, ACR-1997 criteria were used as reference criteria in an unselected population of CYP who tested positive for ANA at Alder Hey Children’s Hospital over a 12 month period (n=129), combined with 482 CYP from the UK JSLE Cohort Study (n= 611 total). The unselected ANA positive CYP cohort consisted of 92 females and 37 males, with a median age 11 years [IQR 7-14].

At both first and last visit, sensitivity of SLICC-2012 (both 98%) was comparable to ACR-1997 criteria, and higher when compared to ACR/EULAR-2019 criteria (first visit: 94%, last visit: 96%, both p<0.001). Conversely, specificity of SLICC-2012 was significantly lower compared to ACR/EULAR-2019 criteria at both first (SLICC-2012: 67% vs ACR/EULAR-2019: 77%, p<0.001) and last visit (SLICC-2012: 71% vs ACR/EULAR-2019: 81%, p<0.001).

The proportion of CYP fulfilling classification criteria who were correctly identified as jSLE (PPV, based on the ACR-1997 reference criteria) was higher using ACR/EULAR-2019 compared to SLICC-2012 criteria at both first and last visit (88% at first and 93% at last visit for ACR/EULAR-2019, vs 84% at first and 89% at last visit for SLICC-2012, Table 3). Conversely, the proportion of CYP not fulfilling criteria and correctly identified as not having jSLE (negative predictive value) was lower for ACR/EULAR-2019 compared to SLICC-2012 criteria (87% at first and 89% at last visit for ACR/EULAR-2019, vs 95% at both first and last visit for SLICC-2012).

***Level of agreement between classification criteria --*** In the absence of a “gold standard” test for jSLE, ROC curves and kappa coefficient analysis were used to assess levels of agreement between ACR/EULAR-2019 and the previous criteria (Table 4). When ACR-1997 criteria were used as the reference criteria to classify patients as having jSLE, the AUC for ACR/EULAR-2019 was 0.78 (confidence interval (CI 0.73–0.83). The kappa coefficient for inter-rater agreement between ACR-1997 and ACR/EULAR-2019 criteria was 0.58 (CI 0.53–0.63). When SLICC-2012 criteria were used as the reference criteria to classify CYP as having jSLE, the AUC for ACR/EULAR-2019 criteria was 0.89 (CI 0.75–0.90) and the kappa coefficient for inter-rater agreement between the two criteria was 0.76 (CI 0.69–0.78). This demonstrates variable agreement between the different criteria, with the strongest agreement being between ACR/EULAR-2019 and SLICC-2012.

***False positive classification of CYP using ACR/EULAR-2019 in an “unselected” CYP cohort testing positive for ANA --*** A total of 6/129 (5%) individuals in the aforementioned ohort tested positive for ANA, despite having an alternative diagnosis (false positives).Of these, 5/6 met ACR/EULAR-2019 criteria, 4/6 met SLICC-2012 criteria, and 2/6 met ACR-1997 criteria for SLE (Table 5). Two patients fulfilled all three SLE classification criteria, including one patient with RNP (ribonucleoprotein)-positive mixed connective tissue disease and one patient with biopsy proven renal dysplasia. Two patients exclusively fulfilled ACR/EULAR-2019 criteria, including one patient diagnosed with Cornelia de Lange syndrome and one with IgA Vasculitis. One patient diagnosed with Juvenile Dermatomyositis met both ACR/EULAR-2019 and SLICC-2012 criteria, and one patient with LPS-responsive beige-like anchor protein (*LRBA*) gene mutation with idiopathic thrombocytopenic purpura and hypogammaglobulinaemia met SLICC-2012 classification criteria.

**Discussion**

Classification criteria are important and accepted tools to allow selection of homogenous patient cohorts for clinical trials. By definition, classification criteria therefore aim for high specificity whilst allowing reduced sensitivity(3,4,18,19). This discriminates classification from diagnostic criteria, which aim for high sensitivity while accepting reduced specificity to not miss patients in the diagnostic process(18). Recently published ACR/EULAR-2019 criteria for SLE were the result of a consensus process of adult rheumatologists, aiming at a homogenous case definition of SLE patients, not primarily considering potential differences between jSLE and adult-onset disease. Paediatric rheumatologists were not involved in the process and jSLE cohorts were also not included in performance testing. Therefore to date, it remains largely unclear whether these “new” criteria perform sufficiently well in CYP with jSLE (9,20).

Two recent studies have assessed the performance of ACR/EULAR-2019 criteria in jSLE(10,11). The first study included 122 jSLE patients and 89 controls (ANA positive with other rheumatic diseases). Using an ACR/EULAR-2019 criteria cut off score of ≥10, the new criteria were less specific at the time of the first visit (67.4%) than both the ACR-1997 (83.2%) and SLICC criteria (80.9%). For sensitivity, the new ACR/EULAR-2019 criteria scored better than ACR 1997 (87.7% vs 70.5%) and worse than the SLICC-2012 criteria (89.3%). The authors assessed additional cut-off points for the new ACR/EULAR-2019 score, showing a score of ≥13 to result in increased specificity, improved PPV, and cut-off point accuracy (11).

The second study included 112 SLE patients aged 2-21 years (jSLE and adult-onset SLE) and 105 controls aged 1-19 years with other rheumatic diseases. The rheumatologist’s diagnosis of SLE served as the reference standard criterion. Authors showed the ACR/EULAR-2019 criteria to have higher sensitivity (85% vs 72%; p=0.023) and similar specificity (83% vs 87%; p=0.456) when compared to 1997-ACR criteria. Examining ACR/EULAR-2019 classification summary scores according to ethnicity, the absolute scores were higher in non-White than White patients (22+10 vs. 17+9; p<0.01). Sub-analysis showed sensitivity of the criteria was not influenced by patient ethnicity, age or gender(10).

In this present study including a markedly larger national study population (UK JSLE Cohort Study), differences between ACR-1997 and SLICC-2019 vs. ACR/EULAR-2019 criteria were mainly caused by the absence of the entry criterion, ANA positivity, affecting a total of 30 CYP (6%). Indeed, higher frequencies of ANA negative patients diagnosed and/or classified as having jSLE have been reported previously, and are therefore a concern in relation to ACR/EULAR-2019 criteria(17). ANA negativity, especially in young jSLE patients, may be associated with a strong genetic contribution to disease pathology (e.g. monogenic causes or increased number of risk alleles), which may cause systemic inflammation and tissue damage (initially) in the absence of autoantibodies. Indeed, over time, 50% of initially ANA negative jSLE patients developed ANA positivity, and therefore at last visit, also met ACR/EULAR-2019 criteria. While one could argue that this is of benefit when selecting homogenous populations for clinical trials, it creates problems for jSLE patients in whom their condition is evolving and who develop autoantibody positivity over time (17).

Another concern is that in the in absence of widely agreed diagnostic criteria for SLE, many healthcare professionals use classification criteria to aid diagnosis. Using the ACR/EULAR-2019 criteria to do this would result in a significant proportion of jSLE patients (especially ANA negative patients) that may be missed. Unfortunately, this will mostly affect young jSLE patients, in who diagnosis can already be delayed(21). Particularly among pre-pubertal jSLE patients (pre-pubertal, <8 years), fewer individuals fulfilled ACR/EULAR-2019 criteria when compared to ACR-1997 and SLICC-2012(17).

Using a combined cohort including UK JSLE Cohort Study participants and “unselected” ANA positive CYP to calculate specificity, sensitivity and predictive values, based on ACR-1997 criteria as reference criteria, reduced sensitivity was calculated for ACR/EULAR-2019 criteria compared to SLICC-2012, while specificity was higher in ACR/EULAR-2019 compared to SLICC-2012 criteria. This confirms findings from above in a larger cohort including additional differential diagnoses, and indicates that inclusion of ANA as an entry criterion may reduce sensitivity, while potentially increasing specificity. Thus, if (incorrectly) used to diagnose patients, ACR/EULAR-2019 criteria may miss individuals and/or delay diagnosis in CYP who develop autoantibodies later in disease, including those as a result of monogenic disease causes (17).

As classification criteria aim at high specificity while potentially accepting slightly reduced sensitivity, we investigated a “unselected” cohort of ANA positive CYP. Five patients were falsely classified as having jSLE using ACR/EULAR-2019 criteria, while this was the case in four patients using SLICC-2012 and in two individuals using ACR-1987 criteria. Thus, specificity of EULAR/ACR-2019 criteria may indeed be limited when compared to other sets of criteria, resulting in false positive results. Other immune complex mediated conditions with ANA positivity and renal involvement are of particular concern (e.g. IgA Vasculitis) (22). Additional studies, further investigating the performance of ACR/EULAR-2019 classification criteria in multi-ethnic cohorts, across ages, and at different disease stages are warranted. Inclusion of sub-cohorts of CYP with different systemic inflammatory disease will be critical to reliably evaluate specificity and sensitivity.

The absence of widely accepted diagnostic tools for jSLE meant that ACR-1997 criteria needed to be used as “reference standard”. Particular strengths of this cohort are the availability of longitudinal data in this national cohort, allowing assessment of classification criteria performance at different disease stages (first vs. last visit). This, and the significantly larger sample size, are key enhancements when compared to the two previous studies comparing ACR/EULAR-2019 to ACR-1997 and SLICC-2012 criteria in jSLE cohorts. Future assessment of how these criteria perform in an international cohort of jSLE patients is also warranted.

**Conclusions**

Based on observations in a large national jSLE cohort (the UK JSLE Cohort Study), ACR/EULAR-2019 criteria miss a significant proportion of pre-pubertal jSLE patients, mostly because of the absence of ANA positivity. Performance improves with age, and sensitivity (initially reduced) is comparable to SLICC-2012 criteria at last visit. Overall, specificity is higher when compared to SLICC-2012. However, concerns remain due to more false positives being seen using ACR/EULAR-2019 criteria. Given the rarity of jSLE, some clinicians will have limited experience in making the diagnosis of jSLE and may rely on classification criteria to aid diagnosis. Doing this with the ACR/EULAR-2019 criteria, a significant proportion of jSLE patients (especially ANA negative patients), may be initially missed, leading to diagnostic delay, morbidity and potentially mortality. If classification criteria are designed to include paediatric and adult populations, paediatric specialists should be consulted and included in the consensus and evaluation process, as seemingly minor differences can affect outcomes.

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**Authors’ contributions:**

SR, EMDS, LM, and CMH led on the conception and design of the study. SR and EMDS performed the statistical analysis. All authors participated in the acquisition of and interpretation of the data. MWB is Chief Investigator of the UK JSLE Cohort Study. All authors were involved in drafting the manuscript and revising it critically for important intellectual content. They have also all read and given final approval of the version to be published.

**Availability of data and material**

The data underlying this article will be shared on reasonable request to the corresponding author.

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**Table 1: Demographic details of the full UK jSLE Study Cohort, and those scoring ≥4 ACR-1997 criteria.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Demographics** | **Full UK jSLE Study Cohort\***  **n=482 (%)** | **ACR-1997 ≥ 4** | |
| **First visit, n=385 (%)\*\*** | **Last visit, n=427 (%)\*\*\*** |
| **Ethnicity** | | | |
| **White Caucasian** | 242 (51%) | 180 (47%) | 209 (49%) |
| **Black African/ Caribbean** | 73 (15%) | 58 (15%) | 66 (15%) |
| **South Asian** | 140 (30%) | 119 (31%) | 128 (30%) |
| **Other** | 17 (4%) | 14 (4%) | 15 (4%) |
| **Gender\*** | | | |
| **Female** | 402 (83%) | 318 (83%) | 357 (93%) |
| **Male** | 74 (15%) | 61 (16%) | 64 (17%) |
| **Age** | | | |
| **Age at diagnosis** | 12.8 [10.4 – 17.9] | 12.9 [10.7-17.9] | 12.8 [10.5-18.0] |
| **Numbers of patients in different age groups** | | | |
| **< 8 years** | 50 (10%) | 37 (10%) | 43 (10%) |
| **8-14 years** | 268 (56%) | 218 (57%) | 242 (57%) |
| **>14 years** | 159 (33%) | 127 (33%) | 138 (32%) |
| **ANA positivity according to age group** | | | |
| **< 8 years** | 44 (88%) | 34 (92%) | 42 (98%) |
| **8-14 years** | 249 (93%) | 205 (94%) | 233 (96%) |
| **>14 years** | 151 (95%) | 125 (98%) | 135 (98%) |

Full UK JSLE Study Cohort includes patients fulfilling ≥4 ACR-1997 criteria **and** those fulfilling 2-3 ACR-1997 criteria. Numbers of patients and percentages shown. Median age and interquartile range in square brackets. \*Data missing for full jSLE Study Cohort patients is as follows: a) 5 patients for age, b) 10 patients for ethnicity, c) 38 patients for ANA, d) 6 patients for gender. \*\*Data missing for ACR-1997 ≥4 cohort patients at first visit is as follows: a) 3 patients for age, b) 14 patients for ethnicity, c) 21 patients for ANA and d) 6 patients for gender in the sub-group of patients ACR-1997 ≥4. Data is missing for ACR-1997 ≥4 cohort patients at last visit is as follows: a) 4 patients for age, b) 9 patients for ethnicity, c) 17 patients for ANA and d) 5 patients for gender in the sub-group of patients ACR-1997 ≥4. P-values for comparisons made between each demographic category within full cohort (n=482) are <0.001 for ethnicity, <0.001 for gender, <0.001 for age groups at diagnosis and 0.24 for ANA positivity according to age. P-values for differences between first and last groups were not calculated as the patients form the same overall group and are therefore not independent. Statistical analyses comparing the demographic details between the full jSLE Study Cohort vs. those fulfilling ≥4 ACR-1997 criteria at the first and last visit are not undertaken as there is overlap in the patients included in the different sub-groups. ANA = Antinuclear antibody, ACR-1997 = American College of Rheumatology 1997 revised version of criteria.

**Table 2: Number of UK JSLE Cohort patients fulfilling the different classification criteria for SLE (by age)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Number of patients fulfilling the ACR-1997 criteria\*** | | **Number of patients fulfilling the ACR/EULAR-2019 criteria \*** | | **Number of patients fulfilling the SLICC-2012 criteria \*** | |
| **First visit**  **n (%)** | **Last visit**  **n (%)** | **First visit**  **n (%)** | **Last visit**  **n (%)** | **First visit**  **n (%)** | **Last visit**  **n (%)** |
|
| **Pre-pubertal**  <8 years (n=50) | 37  (74%) | 43  (86%) | 32  (64%) | 35  (70%) | 44  (88%) | 48  (96%) |
| **Peri-pubertal**  8-13 years (n=268) | 218  (81%) | 242  (90%) | 219  (81%) | 239  (89%) | 249  (93%) | 256  (96%) |
| **Adolescent**  >14 years (n=159) | 127  (80%) | 138  (87%) | 126  (79%) | 133  (84%) | 144  (91%) | 155  (97%) |
| **P-value** | **0.5** | **0.4** | **0.02\*** | **0.001\*\*** | **0.2** | **0.7** |

Numbers displayed are those patients fulfilling the different classification criteria, with percentages in brackets. Overall, patient age was not available for 5/482 UK JSLE Cohort Study patients. \*Of the patients fulfilling≥4 ACR-1997 criteria for Lupus (n=385 at first visit and n=427 at last visit), age was unknown in 3 patients at first visit and 4 patients at last visit. Of patients scoring≥10 using ACR/EULAR-2019 criteria (n=402 at first visit and n=434 at last visit), age was unknown in 4 patients at first visit and 4 patients at last visit. Of the patients fulfilling≥4 SLICC-2012 criteria (n=441 at first visit and n=463 at last visit), age was unknown in 4 patients at first visit and 4 patients at last visit. ACR-1997 = American College of Rheumatology 1997 revised version, ACR/EULAR-2019 = American College of Rheumatology/ European League Against Rheumatism 2019, SLICC-2012 = Systemic Lupus International Collaborating Clinics 2012. Chi-squared tests used to calculate p-values when comparing the proportion of patients fulfilling different criteria, for individual age groups at an individual visit (either first or last visit). Post hoc analysis showed \*Significance lies between the pre-pubertal and peri-pubertal age group (p=0.04), and the pre-pubertal and adolescent age group (p=0.002). \*\* Significance lies between the pre-pubertal and peri-pubertal age group (p=0.05) and the pre-pubertal and adolescent age group (p=0.05).

**Table 3: Sensitivity, specificity and positive and negative predictive values** **of ACR/EULAR-2019 and SLICC-2012 criteria**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Classification Criteria** | **Sensitivity** | | **Specificity** | | **Positive predictive value** | | **Negative predictive value** | |
| **First**  **visit (%)** | **Last**  **visit (%)** | **First**  **visit (%)** | **Last**  **visit (%)** | **First visit (%)** | **Last**  **visit (%)** | **First**  **visit (%)** | **Last**  **visit (%)** |
| **ACR/EULAR-2019** | 94 | 96 | 77 | 81 | 88 | 93 | 87 | 89 |
| **SLICC-2012** | 98 | 98 | 67 | 71 | 84 | 89 | 94 | 94 |
| **P-values** | **<0.001**  **\*** | **<0.001**  **\*** | **<0.001**  **\*** | **<0.001**  **\*** | **<0.001**  **\*\*** | **<0.001**  **\*\*** | **<0.001**  **\*\*** | **<0.001**  **\*\*** |

The ACR-1997 criteria were used as reference criteria for calculation of sensitivities, specificities, positive and negative predictive values. \*P-values calculated using Chi-squared test, comparing the sensitivities or specificities obtained by the different classification criteria (ACR/EULAR-2019 vs SLICC-2012) at each timepoint. \*\*P-values calculated using a binomial exact test, and relates to positive predictive value and negative predictive value for each set of criteria. ACR/EULAR-2019 = American College of Rheumatology/ European League Against Rheumatism 2019, SLICC-2012 = Systemic Lupus International Collaborating Clinics 2012.

**Table 4: Level of agreement between classification criteria**

|  |  |  |  |
| --- | --- | --- | --- |
| **Reference criteria** | **Comparator criteria** | **AUC**  **(CI)** | **Kappa co-efficient (CI)** |
| **ACR-1997** | **ACR/EULAR-2019** | 0.78 (0.73 – 0.83) | 0.58 (0.53 – 0.63) |
| **SLICC-2012** | 0.63 (0.54 – 0.67) | 0.37 (0.27 – 0.41) |
| **SLICC-2012** | **ACR/EULAR-2019** | 0.89 (0.75 – 0.90) | 0.76 (0.69 – 0.78) |

ACR-1997 = American College of Rheumatology 1997 revised version, ACR/EULAR-2019 = American College of Rheumatology/ European League Against Rheumatism 2019, SLICC-2012 = Systemic Lupus International Collaborating Clinics 2012 AUC = Area Under the Curve, CI = 95% confidence interval. AUC from ROC curves generated using data from the full UK jSLE Study Cohort, n = 482.

**Table 5: False positive classification of SLE in unselected ANA positive control Cohort.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Individual patients and diagnosis at the time of analysis** | **Clinical features** | **Classification criteria scores** | | |
| **ACR/EULAR-2019 score**  **(n = 5)** | **SLICC-2012 score**  **(n = 4)** | **ACR-1997 score**  **(n = 2)** |
| 1 | MCTD (RNP +ve) | Anti-dsDNA positivity, low complement, lymphopenia and pericardial effusion | 21 | 6 | 4 |
| 2 | Renal Dysplasia\* | Mouth ulcers, urine albumin creatinine ratio of >300 mg/mmol, leukopenia and low complement | 13 | 4 | 4 |
| 3 | Cornelia de Lange syndrome with osteoarthritis | ANA positive, osteoarthritis and low complement | 10 | N/A | N/A |
| 4 | IgA Vasculitis | ANA positive, arthritis and proteinuria | 10 | N/A | N/A |
| 5 | Juvenile dermatomyositis | ANA positive, malar rash, arthritis and low C4) | 10 | 4 | N/A |
| 6 | LRBA gene mutation with ITP and hypo-gammaglobulinaemia | ANA positive, alopecia, thrombocytopenia, Direct antiglobulin test (DAT) positivity | N/A | 5 | N/A |

ACR-1997 = American College of Rheumatology 1997 revised version, classified as SLE if score ≥ 4 points. ACR/EULAR-2019 = American College of Rheumatology/ European League Against Rheumatism 2019, classified as SLE if score ≥ 10 points. SLICC-2012 = Systemic Lupus International Collaborating Clinics 2012, classified as SLE if score ≥ 4 points. MCTD = mixed connective tissue disease. RNP +ve = ribonucleoprotein antibody positive. LRBA = LPS responsive beige-like anchor protein. ITP = idiopathic thrombocytopenia purpura. N/A = non-applicable (criteria threshold not met). \*Renal dysplasia was demonstrated on biopsy, with no inflammation demonstrated and negative immunofluorescence. The electronic records of these patients were re-checked 18-24 months after the initial positive ANA measurement, confirming that none of the initial diagnoses had changed over this time period.

**Figure 1: Patients classified as having JSLE at first and last visit using three sets of criteria**

Figure 1 footnote

Full UK jSLE Study Cohort: 482 patients. \*Chi squared test used to calculate p-values for differences in the numbers classified using each set of criteria p-value at first (p=0.007) and last visit (p<0.001). \*\* McNemar’s test used to calculate the p-values for differences in the number classified at first and last by individual classification criteria, ACR-1997 p<0.001, ACR/EULAR-2019 p 0.0003, SLICC p=0.0001.

**Supplementary Table S1: JSLE patients meeting one set of classification criteria at first visit, but not another set**

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical/laboratory features** | **ACR-1997 criteria met (but not SLICC-2012 or ACR/EULAR-2019)¶** | **ACR/EULAR-2019 criteria met (but not SLICC-2012 or ACR-1997)ƚ** | **SLICC-2012 criteria met (but not ACR-1997 or ACR/EULAR-2019)β** |
| **Malar Rash** | 9/19 (47%) | 2/11 (18%) | 5/21 (24%) |
| **Discoid Lupus** | 1/19 (5%) | 0 | 2/21 (10%) |
| **Photosensitivity** | 10/19 (53%) | 0 | 5/21 (24%) |
| **Oral/nasal ulcer** | 11/19 (58%) | 0 | 3/21 (14%) |
| **Non-erosive arthritis** | 5/19 (26%) | 5/11 (45%) | 5/21 (24%) |
| **Serositis** | 0 | 0 | 0 |
| **Nephritis** | 0 | 3/11 (27%) | 0 |
| **Neurological disorder** | 0 | 0 | 1/21 (5%) |
| **Haematologic disorder** | 5/19 (26%) | 4/11 (36%) | 10/21 (48%) |
| **Anti-dsDNA** | 2/19 (11%) | 5/11 (45%) | 4/21 (19%) |
| **Anti-smith** | 1/19 (5%) | 3/11 (27%) | 0 |
| **Anti-Phospholipid antibodies** | 4/19 (21%) | 0 | 5/21 (24%) |
| **Low complement** | 10/19 (53%) | 2/11 (18%) | 16/21 (76%) |

¶Total number of patients fulfilling ACR-1997, but not SLICC-2012 or ACR/EULAR criteria = 19; ƚTotal number of patients fulfilling ACR/EULAR-2019 but not SLICC-2012 or ACR-1997 = 11. βTotal number of patients fulfilling SLICC-2012 but not ACR-1997 or ACR/EULAR-2019 criteria = 21. ACR-1997 = American College of Rheumatology 1997 revised version, ACR/EULAR-2019 = American College of Rheumatology/ European League Against Rheumatism 2019, SLICC-2012 = Systemic Lupus International Collaborating Clinics 2012.

**Supplementary Table S2: Clinical and immunological criteria fulfilled by full UK JSLE Cohort Study participants.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Clinical characteristics** | **ACR 1997**  **(score ≥ 4)** | | **ACR/EULAR-2019 (score ≥10)** | | **SLICC-2012**  **(score ≥ 4)** | | **P-value**  **first visit\*** | **P-value last visit\*\*** |
| **First visit n=385 (%)** | **Last visit n=427 (%)** | **First**  **visit n=402**  **(%)** | **Last**  **visit**  **n=434 (%)** | **First visit**  **n=441 (%)** | **Last**  **visit**  **n= 463 (%)** |
| **Malar rash** | 238 (62%) | 301 (70%) | 228  (57%) | 245 (56%) | 246 (56%) | 303 (65%) | 0.18 | **<0.001** |
| **Discoid lupus** | 38 (10%) | 65  (15%) | 37  (9%) | 58 (13%) | 39  (9%) | 65 (14%) | 0.88 | 0.48 |
| **Photosensitivity** | 97 (25%) | 160 (37%) | 86  (21%) | 125 (29%) | 103 (23%) | 160 (35%) | 0.44 | **0.02** |
| **Oral/nasal ulcer** | 134 (35%) | 188 (44%) | 109  (27%) | 129 (30%) | 138 (31%) | 190  (41%) | 0.06 | **<0.001** |
| **Non-erosive arthritis** | 244 (63%) | 287 (67%) | 239  (59%) | 262 (60%) | 266 (60%) | 292 (63%) | 0.29 | **<0.001** |
| **Serositis (pericarditis and/or pleural effusion)** | 64 (17%) | 91 (21%) | 65  (16%) | 86 (20%) | 66 (15%) | 91 (20%) | 0.33 | 0.80 |
| **Nephritis** | 138 (36%) | 166 (39%) | 137  (34%) | 170 (39%) | 136 (31%) | 167 (36%) | 0.30 | 0.28 |
| **Neurologic disorder** | 24  (6%) | 37  (9%) | 23  (6%) | 34  (8%) | 22  (5%) | 39  (8%) | 0.73 | **0.03** |
| **Haematological**  **Haemolytic anaemia**  **Leukopenia**  **Lymphopenia**  **Thrombocytopenia** | 92  (24%)  99 (26%)  180 (47%)  54 (14%) | 110 (26%)  132 (31%)  226 (53%)  83 (19%) | 93  (23%)  102  (25%)  166  (41%)  78  (19%) | 111 (26%)  120 (28%)  194 (45%)  96 (22%) | 97 (22%)  112 (25%)  196 (44%)  86 (20%) | 108 (23%)  143 (31%)  239 (52%)  94 (20%) | 0.07  0.99  0.30  **0.02** | 0.64  0.78  **0.03**  0.61 |
| **Immunological characteristics** | | | | | | | | |
| **ANA positive** | 367 (95%) | 414 (97%) | 402  (100%) | 434  (100%) | 421  (95%) | 453  (98%) | **0.02** | **0.002** |
| **Anti – dsDNA** | 266 (69%) | 313 (73%) | 264  (66%) | 306 (71%) | 294 (67%) | 330 (71%) | 0.58 | 0.64 |
| **Anti – Smith** | 80 (21%) | 107 (25%) | 78  (19%) | 108 (25%) | 95 (22%) | 117 (25%) | 0.74 | 0.97 |
| **Anti-Phospholipid antibodies** | 83 (22%) | 113 (26%) | 76  (19%) | 117 (27%) | 97 (22%) | 130 (28%) | 0.45 | 0.85 |
| **Low Complement**  **C3**  **C4**  **Both** | 163 (42%)  80 (21%)  156 (41%) | 278 (65%)  169 (40%)  267 (63%) | 163  (41%)  90  (22%)  157  (39%) | 284 (65%)  121 (28%)  272 (63%) | 175 (40%)  103 (23%)  166 (38%) | 288 (62%)  122 (26%)  274 (59%) | 0.73  0.67  0.70 | 0.54  **<0.001**  0.47 |

Numbers of patients fulfilling the different criteria at first and last visit are presented throughout the table, with the percentage of patients in brackets. \*Comparison of the proportion of patients presenting with each clinical or immunological criterion considered by ACR-1997, ACR/EULAR-2019 and SLICC-2012 at first visit. \*\*Comparison of the proportion of patients presenting with each clinical or immunological criterion considered by ACR-1997, ACR/EULAR-2019 and SLICC-2012 at last visit. The criteria fulfilled are cumulative (at any point in time). dsDNA = double stranded DNA, ANA = anti-nuclear antibody, ACR-1997 = American College of Rheumatology 1997 revised version, ACR/EULAR-2019 = American College of Rheumatology/ European League Against Rheumatism 2019, SLICC-2012 = Systemic Lupus International Collaborating Clinics 2012. P-values calculated using chi-squared test for differences in scores at either first and last visit when comparing between all three sets of criteria.