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Use of SLICC criteria in a large, diverse lupus registry enables SLE classification of a subset of ACR-designated subjects with incomplete lupus

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ABSTRACT

Objective: SLE is traditionally classified using the American College of Rheumatology (ACR) criteria. The Systemic Lupus International Collaborating Clinics (SLICC) recently validated an alternative system. This study examined large cohorts of subjects with SLE and incomplete lupus erythematosus (ILE) to compare the impact of ACR and SLICC criteria.

Methods: Medical records of subjects in the Lupus Family Registry and Repository were reviewed for documentation of 1997 ACR classification criteria, SLICC classification criteria and medication usage. Autoantibodies were assessed by indirect immunofluorescence (ANA, antidouble-stranded DNA), precipitin (Sm) and ELISA (anticardiolipin). Other relevant autoantibodies were detected by precipitin and with a bead-based multiplex assay.

Results: Of 3575 subjects classified with SLE under at least one system, 3312 (92.6%) were classified as SLE by both systems (SLE^{both}), 85 only by ACR criteria ($SLE^{ACR\text{-}only}$) and 178 only by SLICC criteria ($SLE^{SLICC\text{-}only}$). Of 440 subjects meeting 3 ACR criteria, 33.9% (149/440) were $SLE^{SLICC\text{-}only}$, while 66.1% (n=291, designated ILE) did not meet the SLICC classification criteria. Under the SLICC system, the complement criterion and the individual autoantibody criteria enabled SLE classification of $SLE^{SLICC\text{-}only}$ subjects, while $SLE^{ACR\text{-}only}$ subjects failed to meet SLICC classification due to the combined acute/subacute cutaneous criterion. The SLICC criteria classified more African-American subjects by the leucopenia/lymphopenia criterion than did ACR criteria. Compared with $SLE^{ACR\text{-}only}$ subjects, $SLE^{SLICC\text{-}only}$ subjects exhibited similar numbers of affected organ systems, rates of major organ system involvement (~30%: pulmonary, cardiovascular, renal, neurological) and medication history.

Conclusions: The SLICC criteria classify more subjects with SLE than ACR criteria; however, individuals with incomplete lupus still exist under SLICC criteria. Subjects who gain SLE classification through SLICC criteria exhibit heterogeneous disease, including potential major organ involvement. These results provide supportive evidence that SLICC criteria may be more inclusive of SLE subjects for clinical studies.

INTRODUCTION

The clinical and immunological heterogeneity of patients with SLE hinders timely diagnosis, effective management and treatment development. Clinical trials of SLE typically select subjects based on the American College of Rheumatology (ACR) classification criteria,[1] which require meeting ≥4 of 11 clinical and/or serological criteria. Although the ACR criteria remain a historical standard for identifying patients with SLE, individuals diagnosed with lupus by expert rheumatologists may not meet these criteria, while some who do meet the criteria have minimal disease. Therefore, ongoing efforts have sought more sensitive and specific criteria to identify patients with significant lupus.[2]

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) validated new SLE classification criteria through a series of consensus exercises using symptomatology and laboratory results drawn from real rheumatologic cases.[3] SLE classification using SLICC criteria requires either meeting ≥4 of 17 criteria, including at least one clinical and one immunological criterion, or demonstrating biopsy-proven lupus nephritis with positive ANA or antidouble-stranded (ds)DNA.[3]

Because SLICC criteria emphasise immunological and haematological lupus manifestations, it has been proposed that subjects who gain SLE classification through SLICC criteria may be less likely to exhibit clinically significant organ involvement compared with subjects classified through ACR criteria.[4] To address this question, the current study compared subjects who were classified by SLICC criteria with other subjects with SLE and incomplete lupus erythematosus (ILE) in a large, well-characterised, racially and geographically diverse cohort.

METHODS

Study subjects

This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Oklahoma Medical Research Foundation (OMRF) Institutional Review Board. Study participants were previously enrolled to the Lupus Family Registry and Repository (LFRR)[5] and provided written informed consent, detailed clinical questionnaire information, connective tissue disease screening questionnaire responses,[6] demographic information, blood samples and medical records, which were reviewed for ACR[1] and SLICC[3] criteria and for medication history (see online supplementary methods, supplementary figure 1).

Autoantibody detection

Autoantibodies were analysed by the College of American Pathologists-certified OMRF Clinical Immunology Laboratory. ANA and anti-dsDNA were analysed by indirect immunofluorescence, extractable nuclear antibodies by immunodiffusion and anticardiolipin by ELISA.[7]

Autoantibody specificities were compared using a multiplexed, bead-based assay (BioPlex 2200, Bio-Rad, Hercules, California, USA) that simultaneously detects dsDNA, chromatin, ribosomal P, Ro/SSA (60 and 52 kDa), La/SSB, Sm, SmRNP complex, RNP, centromere B, Scl-70 and Jo-1 autoantibodies.[8] Anti-dsDNA is reported in IU/mL with a manufacturer-specified positive cut-off of 10.0 IU/mL, and other specificities as an Antibody Index (AI) value (range 0–8) based on the fluorescence intensity of each of the other autoantibody specificities, with a manufacturer-recommended positive cut-off of AI=1.0.[8]

Statistical analyses

In R V.3.3.0 (R Foundation, https://www.r-project.org/), we compared means by unpaired t-test, medians by Mann-Whitney U test and proportions by either logistic regression using $SLE^{SLICC\text{-}only}$ as the reference group or Fisher's exact test for comparisons with an observed value of 0. Two-sided $p<0.05$ was considered to be statistically significant.

RESULTS

Approximately one-third of subjects with 3 ACR criteria are classified with SLE by SLICC criteria

Medical record review of subjects in the LFRR identified 3397 subjects with SLE classified using ACR criteria. Of these, 3312 (97.5%) also reached SLICC classification (SLE^{both}), while 85 reached only ACR classification ($SLE^{ACR\text{-}only}$). An additional 178 reached only SLICC classification, but not ACR classification ($SLE^{SLICC\text{-}only}$). Approximately one-third of subjects with only three ACR criteria (149/440; 33.9%) met SLE classification by

Table 1 Demographics of subjects with SLE and ILE based on 2012 SLICC and 1997 ACR criteria

	$SLE^{SLICC\text{-}only}$* (n=178)	$SLE^{ACR\text{-}only}$† (n=85)	SLE^{both}‡ (n=3312)	ILE§ (n=291)
Sex				
Female, n (%)	160 (89.9)	74 (87.0)	2976 (89.9)	255 (87.6)
		p=0.494	p=0.989	p=0.458
Age, years				
Average (range)	43.7 (10–81)	45.4 (12–79)	42.0 (8–82)	47.5 (9–80)
		p=0.345	p=0.118	**p=0.002**
Race, n (%)				
European American	89 (50.0)	52 (61.2)	1466 (44.3)	165 (56.7)
		p=0.090	p=0.134	p=0.158
African-American	44 (24.7)	14 (16.5)	1079 (32.6)	69 (23.7)
		p=0.133	**p=0.030**	p=0.804
Hispanic	12 (6.7)	5 (5.9)	239 (7.2)	12 (4.1)
		p=0.791	p=0.811	p=0.216
Asian	10 (5.6)	2 (2.4)	128 (3.9)	10 (3.4)
		p=0.250	p=0.245	p=0.261
American Indian	2 (1.1)	5 (5.9)	99 (3.0)	10 (3.4)
		p=0.044	p=0.165	p=0.144
Mixed	21 (11.8)	7 (8.2)	276 (8.3)	22 (7.6)
		p=0.383	p=0.109	p=0.126
Other¶	0 (0.0)	0 (0.0)	25 (0.8)	3 (1.0)
		p=1.000	p=0.985	p=0.985

Bold p values are significant ($p<0.05$) for comparison with $SLE^{SLICC\text{-}only}$.
*$SLE^{SLICC\text{-}only}$ were classified with SLE by SLICC criteria, but not ACR criteria.
†$SLE^{ACR\text{-}only}$ were classified with SLE by ACR criteria, but not SLICC criteria.
‡SLE^{both} were classified with SLE by both SLICC and ACR criteria.
§Patients with ILE met three ACR criteria and were not classified with SLE by SLICC standards.
¶Other includes Pacific Islander and unknown.
ACR, American College of Rheumatology; ILE, incomplete lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics.

SLICC criteria. The other 291 subjects with three ACR criteria were not classified by SLICC criteria. These subjects, designated ILE, served as a comparison group expected to have more limited disease. Demographics were similar across the three SLE groups, while subjects with ILE were slightly older (table 1).

Subjects who do not meet ACR classification criteria gain SLE classification through SLICC haematological, immunological and alopecia criteria

Two SLE$^{\text{SLICC-only}}$ subjects (1.1%) were classified by SLICC criteria through biopsy-proven lupus nephritis with positive ANA or anti-dsDNA (figure 1A, bottom). The remaining 176 (98.9%) had one to four more SLICC criteria than ACR criteria. SLE$^{\text{SLICC-only}}$ subjects gained criteria through low complement levels (81/178, 45.5%) and the separation of ACR immunological subcriteria into separate SLICC criteria (69/178, 38.8%), but African-American SLE$^{\text{SLICC-only}}$ subjects most often gained criteria through the less stringent definition of leucopenia/lymphopenia (16/44, 36%) (figure 1D–E). Other than maculopapular rash, leading to a new criterion in 38 SLE$^{\text{SLICC-only}}$ subjects (21.3%), and sensory neuropathy (14 SLE$^{\text{SLICC-only}}$ subjects; 7.9%), new SLICC subcriteria made little contribution to additional individuals reaching SLE classification (see online supplementary figure 3).

Of the 85 SLE$^{\text{ACR-only}}$ subjects, 76 (89.4%) met <4 SLICC criteria (figure 1A, top). Nine (10.6%) met ≥4 SLICC clinical criteria, but were excluded by SLICC criteria due to an absence of immunological criteria. Loss of SLE classification by SLICC criteria was primarily due to the combination of malar rash and photosensitivity into a single SLICC criterion (53/85; 62.4% of SLE$^{\text{ACR-only}}$; figure 1B, see online supplementary figure 1). However, among African-American SLE$^{\text{ACR-only}}$ subjects, the majority lost a criterion due to the stricter threshold for anticardiolipin positivity (figure 1C).

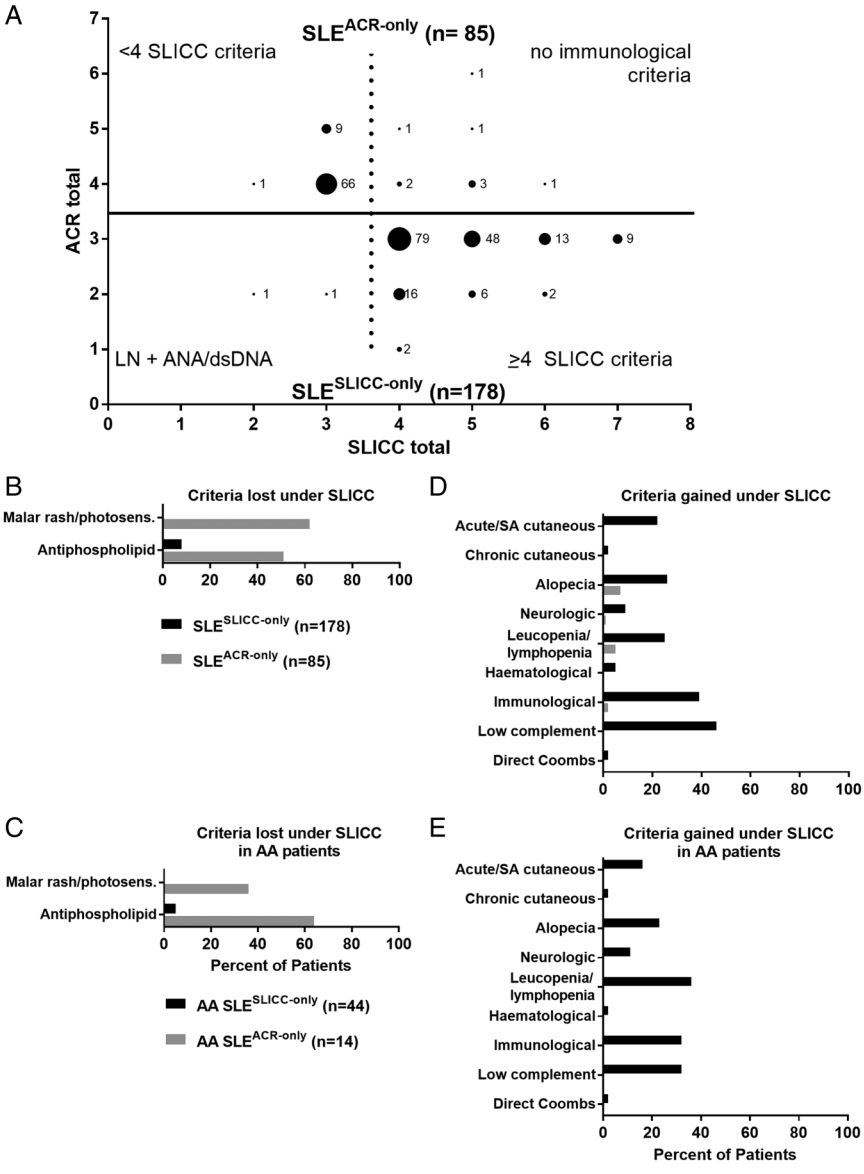

Figure 1 Subjects gain SLE classification through Systemic Lupus International Collaborating Clinics (SLICC) criteria of low complement, immunological manifestations and leucopenia/lymphopenia. (A) Medical record review identified subjects classified with SLE by American College of Rheumatology (ACR) criteria only (n=85; top, grey) or by SLICC criteria only (n=178; bottom, black). Labelled dots indicate the number of subjects who satisfied a given number of ACR criteria (y-axis) and SLICC criteria (x-axis). Criteria lost (B, C) or gained (D, E) under the SLICC system compared with the ACR system were evaluated in all SLE$^{\text{SLICC-only}}$ (black) and SLE$^{\text{ACR-only}}$ (grey) subjects (B, D) or in subjects self-reporting African-American race (C, E). See online supplementary figure 2 for criteria gained and lost in European American and other subjects. AA, African American; dsDNA, anti-double-stranded DNA; LN, lupus nephritis; SA, subacute.

Table 2 SLICC criteria, autoantibody specificities and medication history in patients with SLE and ILE based on SLICC and 1997 ACR criteria

	SLE$^{SLICC\text{-}only}$† (n=178)	SLE$^{ACR\text{-}only}$‡ (n=85)	SLE^{both}§ (n=3312)	ILE¶ (n=291)
SLICC clinical criteria				
Number positive, mean	2.06	2.27 p=0.244	4.15 **p<0.0001**	1.45 **p<0.0001**
Acute/subacute cutaneous rashes, n (%)	76 (42.7)	71 (83.5) **p<0.0001**	2514 (75.9) **p<0.0001**	124 (42.6) p=0.986
Chronic cutaneous rashes, n (%)	10 (5.6)	6 (7.1) p=0.648	562 (17.0) **p<0.001**	26 (8.9) p=0.194
Oral/nasal ulcers, n (%)	11 (6.2)	13 (15.3) **p=0.020**	934 (28.2) **p<0.0001**	31 (10.6) p=0.104
Alopecia, n (%)	46 (25.8)	6 (7.1) **p=0.001**	1248 (37.7) **p=0.002**	2 (0.7) **p<0.0001**
Arthritis, n (%)	67 (37.6)	46 (54.1) **p=0.012**	2344 (70.8) **p<0.0001**	131 (45.0) p=0.117
Serositis, n (%)	10 (5.6)	9 (10.6) p=0.152	1198 (36.2) **p<0.0001**	17 (5.8) p=0.920
Renal, n (%)	23 (12.9)	9 (10.6) p=0.589	1262 (38.1) **p<0.0001**	13 (4.5) **p=0.001**
Neurological, n (%)	22 (12.4)	5 (5.9) p=0.113	585 (17.7) p=0.071	4 (1.4) **p<0.001**
Anaemia, n (%)*	3 (1.7)	0 (0.0) p=0.553	253 (7.6) **p=0.007**	1 (0.3) p=0.166
Leucopenia/lymphopenia, n (%)	83 (46.6)	26 (30.6) **p=0.014**	2339 (70.6) **p<0.0001**	67 (23.0) **p<0.0001**
Thrombocytopenia, n (%)	16 (9.0)	2 (2.4) p=0.064	498 (15.0) **p=0.029**	5 (1.7) **p=0.001**
SLICC immunological criteria				
Number positive, mean	2.54	0.90 **p<0.0001**	2.86 **p<0.001**	1.25 **p<0.0001**
ANA, n (%)	176 (98.9)	74 (87.1) **p=0.001**	3299 (99.6) p=0.165	280 (96.2) p=0.109
Anti-dsDNA, n (%)	93 (52.2)	2 (2.4) **p<0.0001**	2128 (64.3) **p=0.001**	34 (11.7) **p<0.0001**
Anti-Sm, n (%)	32 (18.0)	1 (1.2) **p=0.004**	807 (24.4) p=0.053	8 (2.8) **p<0.0001**
Antiphospholipid, n (%)*	67 (37.6)	0 (0.0) **p<0.0001**	1016 (30.7) p=0.051	39 (13.4) **p<0.0001**
Complement, n (%)*	81 (45.5)	0 (0.0) **p<0.0001**	1884 (56.9) **p=0.003**	3 (1.0) **p<0.0001**
Coombs, n (%)*	3 (1.7)	0 (0.0) p=0.553	323 (9.8) **p=0.002**	0 (0.0) p=0.054
Autoantibody specificities**				
Number positive, median	1	0 **p=0.004**	2 **p<0.0001**	1 **p<0.0001**
dsDNA, n (%)	37 (22.7)	1 (1.6) **p=0.005**	803 (30.2) **p=0.043**	13 (4.5) **p<0.0001**
Chromatin, n (%)	62 (38.0)	12 (19.0) **p=0008**	1433 (53.9) **p=0.0001**	47 (16.4) **p<0.0001**
Ribosomal P, n (%)	9 (5.5)	2 (3.2) p=0.468	355 (13.4) **p=0.005**	3 (1.0) **p=0.011**
Ro/SSA, n (%)	48 (29.4)	16 (25.4) p=0.545	1049 (39.5) **p=0.011**	64 (22.4) p=0.097
La/SSB, n (%)	17 (10.4)	4 (6.3) p=0.348	388 (14.6) p=0.142	24 (8.4) p=0.472

Continued

Table 2 Continued

	SLE$^{SLICC\text{-}only}$† (n=178)	SLE$^{ACR\text{-}only}$‡ (n=85)	SLE^{both}§ (n=3312)	ILE¶ (n=291)
Sm, n (%)	24 (14.7)	4 (6.3) p=0.096	726 (27.3) **p=0.0005**	17 (5.9) **p=0.003**
SmRNP, n (%)	45 (27.6)	11 (17.5) p=0.116	1056 (39.7) **p=0.002**	35 (12.2) **p<0.0001**
RNP, n (%)	44 (27.0)	12 (19.0) p=0.217	954 (35.9) **p=0.022**	45 (15.7) **p=0.004**
Centromere B, n (%)	6 (3.7)	2 (3.2) p=0.853	100 (3.8) p=0.957	19 (6.6) p=0.194
Scl-70, n (%)	6 (3.7)	2 (3.2) p=0.854	72 (2.7) p=0.465	6 (2.1) p=0.323
Jo-1, n (%)*	0 (0.0)	0 (0.0) p=1.000	8 (0.3) p=1.000	2 (0.7) p=0.537
Medications used				
Number, median	2	2 p=0.212	3 **p<0.0001**	2 **p<0.0001**
None, n (%)	12 (6.7)	4 (4.7) p=0.052	34 (1.0) **p<0.0001**	45 (15.5) **p=0.006**
Hydroxychloroquine, n (%)	133 (74.7)	66 (77.6) p=0.605	2755 (83.2) **p=0.004**	173 (59.4) **p<0.0001**
Steroids, n (%)	147 (82.6)	67 (78.8) p=0.464	3105 (93.8) **p<0.0001**	187 (64.3) **p<0.0001**
Immunosuppressants, n (%)	60 (33.7)	25 (29.4) p=0.486	1683 (50.8) **p<0.0001**	80 (27.5) p=0.154
Major immunosuppressants, n (%)	41 (23.0)	11 (12.9) p=0.058	1309 (39.5) **p<0.0001**	30 (10.3) **p<0.001**

Bold p values are significant (p<0.05) for comparison with SLE$^{SLICC\text{-}only}$ by logistic regression or by Fisher's exact test where indicated (*) due to a 0 value. Note that power may be inadequate to detect differences when events are rare, particularly when the total n is also low, as for SLE$^{ACR\text{-}only}$.
†SLE$^{SLICC\text{-}only}$ were classified with SLE by SLICC criteria, but not ACR criteria.
‡SLE$^{ACR\text{-}only}$ were classified with SLE by ACR criteria, but not SLICC criteria.
§SLE^{both} were classified with SLE by both SLICC and ACR criteria.
¶Patients with ILE met three ACR criteria and were not classified with SLE by SLICC criteria.
**Determined by in-house, multiplex, bead-based assay.
ACR, American College of Rheumatology; ILE, incomplete lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics.

Subjects classified with SLE only by SLICC criteria share clinical and immunological features with other subjects with SLE, including major organ involvement

Acute/subacute cutaneous rashes, arthritis and leucopenia/lymphopenia were the most common SLICC clinical criteria in all groups (table 2). SLE$^{SLICC\text{-}only}$ subjects exhibited relatively low prevalence of acute/subacute cutaneous rashes and arthritis, but higher prevalence of alopecia, leucopenia/lymphopenia and thrombocytopenia. SLE$^{SLICC\text{-}only}$ and SLE^{both} subjects exhibited similar prevalence of multiple SLICC immunological criteria and had more SLICC immunological criteria than SLE$^{ACR\text{-}only}$ or ILE (table 2). SLE$^{SLICC\text{-}only}$ sera displayed significantly more autoantibody specificities and higher prevalence of lupus-associated specificities than SLE$^{ACR\text{-}only}$ or ILE. SLE^{both} displayed the highest number and prevalence of lupus-associated specificities. Autoantibodies not specifically associated with lupus (anticentromere B, anti Scl-70 and anti Jo-1), were observed at low frequencies in all groups. The rate of major clinical involvement (serositis, renal or neurological) did not differ between SLE$^{SLICC\text{-}only}$ and SLE$^{ACR\text{-}only}$ (48/178, 27.0% vs 19/85, 22.4%; p=0.422), but was significantly lower in SLE$^{SLICC\text{-}only}$ compared with SLE^{both} (2098/3312, 63.3%; p<0.0001) and higher compared with ILE (38/291, 11.3%; p<0.0001; see online supplementary table S1).

Subjects classified with SLE by only SLICC or only ACR criteria demonstrate similar medication histories

Nearly all subjects had used at least one lupus-related medication type, including hydroxychloroquine, steroids, immunosuppressants (methotrexate, azathioprine and sulfasalazine) and/or major immunosuppressants (mycophenolate mofetil, cyclophosphamide) (table 2). Neither the number of medication types used nor the use of each medication type differed significantly between SLE$^{SLICC\text{-}only}$ and SLE$^{ACR\text{-}only}$. Major immunosuppressant use was slightly more common among SLE$^{SLICC\text{-}only}$ subjects compared with SLE$^{ACR\text{-}only}$ subjects, but this difference was non-significant. Medication use was greatest in SLE^{both} and lowest in ILE.

DISCUSSION

In a heterogeneous disease, optimised classification criteria would maximise inclusion of patients with clinically significant disease and exclude those without it. Although classification criteria are in many ways more restrictive than diagnostic criteria, classification criteria may directly impact patient access to new biologics; belimumab was approved only for patients meeting SLE classification criteria, since the trials excluded all others. While limited by retrospective design using community-based medical records from clinical care, lack of follow-up data and relatively small number of $SLE^{ACR\text{-}only}$ subjects, this study provides new insights to patients identified by ACR and SLICC classification criteria.

The most ill patients with obvious, multiple-organ SLE are classified by both ACR and SLICC criteria. Therefore, we compared these criteria in a large collection of patients with partial lupus syndromes. Twice as many subjects met only SLICC criteria ($SLE^{SLICC\text{-}only}$) as met only ACR criteria ($SLE^{ACR\text{-}only}$), consistent with previous reports suggesting increased sensitivity of SLICC compared with ACR criteria.[3 9–13] However, SLICC criteria did exclude many subjects with clinically suggestive features of lupus. Despite a relatively low prevalence of acute/subacute cutaneous rashes and arthritis, $SLE^{SLICC\text{-}only}$ subjects displayed a phenotypic range similar to other patients with SLE and distinct from ILE, including haematological, immunological and major organ system (serositis, renal or neurological) involvement. They were also younger than subjects with ILE, supporting the probability of a defined connective tissue disease.[14]

Consistent with previous studies,[11 12] $SLE^{ACR\text{-}only}$ subjects primarily lost SLE classification under SLICC criteria due to the combination of malar rash and photosensitivity; $SLE^{SLICC\text{-}only}$ subjects primarily gained a criterion through low complement. African-Americans comprised >30% of our registry and primarily gained classification through the SLICC leucopenia/lymphopenia criterion or lost classification due to the stricter SLICC antiphospholipid criterion. In the absence of racially informed reference values, the leucopenia/lymphopenia criterion may lead to misclassification of patients with benign leucopenia of ethnicity; this highlights the need to consider racial diversity when developing and applying SLE classification criteria.[15]

Disease severity did not differ between $SLE^{SLICC\text{-}only}$ and $SLE^{ACR\text{-}only}$ subjects, based on major organ system involvement and medication history. Along with a trend for increased major immunosuppressant use, $SLE^{SLICC\text{-}only}$ subjects presented several features associated with increased risk for morbidity and mortality, including a marginally higher proportion of minority subjects and increased prevalence of thrombocytopenia, anti-dsDNA and anticardiolipin responses compared with $SLE^{ACR\text{-}only}$.[16 17] Therefore, although they lack ACR classification, patients who gain classification under SLICC criteria appear to have significant disease, and prospective study is warranted. Additionally, immunological and haematological similarities between $SLE^{SLICC\text{-}only}$ and SLE^{both} subjects suggest that these patients might benefit from the same mechanistically targeted treatments and could be included in the same trials.

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