

Diagnostic performance of classification criteria for systemic lupus erythematosus: A validation study from Singapore

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ABSTRACT

Introduction: Classification criteria for systemic lupus erythematosus (SLE) include American College of Rheumatology (ACR) 1997, Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) 2012 and European Alliance of Associations for Rheumatology (EULAR)/ACR 2019 criteria. Their performance in an Asian childhood-onset SLE (cSLE) population remains unclear as the clinical manifestations differ. We aim to evaluate the diagnostic performance in a cSLE cohort in Singapore.

Method: Cases were physician-diagnosed cSLE, while controls were children with mixed and undifferentiated connective tissue disease that posed an initial diagnostic challenge. Data were retrospectively reviewed to establish the 3 criteria fulfilled at diagnosis and over time.

Results: The study population included 120 cSLE cases and 36 controls. At diagnosis, 102 (85%) patients fulfilled all criteria. SLICC-2012 had the highest sensitivity (97.5%, 95% confidence interval [CI] 92.3–99.5), while ACR-1997 had the highest specificity (91.7%, 95% CI 77.5–98.3). All criteria had diagnostic accuracies at more than 85%. Over time, 113 (94%) fulfilled all criteria. SLICC-2012 remained the criteria with the highest sensitivity (99.2%, 95% CI 95.4–99.9), while ACR-1997 had the highest specificity (75.0%, 95% CI 57.8–87.9). Only SLICC-2012 and ACR-1997 had more than 85% diagnostic accuracy over time. Using a cutoff score of ≥ 13 for EULAR/ACR-2019 criteria resulted in improved diagnostic performance.

Conclusion: SLICC-2012 criteria had the highest sensitivity early in the disease course in this first study evaluating the SLE classification criteria performance in a Southeast Asian cSLE cohort, while the ACR-1997 criteria had the highest specificity. Using a cutoff score of ≥ 13 for EULAR/ACR-2019 improved the diagnostic performance.

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CLINICAL IMPACT

What is New

- To the authors' knowledge, this is the first study to evaluate systemic lupus erythematosus (SLE) classification criteria in an East Asian childhood-onset SLE (cSLE) cohort.
- The results concurred that the SLICC-2012 criteria had the highest sensitivity, and the ACR-1997 criteria had the highest specificity. We also demonstrated that a cutoff score ≥ 13 is more suitable for the EULAR/ACR-2019 criteria.

Clinical Implications

- Local and regional medical professionals can be informed about the better sensitivity of the SLICC-2012 classification criteria and the common clinical manifestations, leading to an earlier diagnosis of cSLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a broad spectrum of clinical presentation.¹ Clinical diagnosis by rheumatologists remains the gold standard, but the diagnosis is often challenging due to variability in disease expression mimicking other conditions.

As such, classification criteria have been developed to establish homogeneous groups of patients to include in clinical trials and epidemiological studies. In 1971, the American College of Rheumatology (ACR) developed the first set of classification criteria consisting of 11 clinical and laboratory features, which was later modified in 1997.²⁻⁴ The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) group subsequently developed a new set of criteria, and patients must meet at least 4 of 17 criteria, including

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at least 1 clinical and 1 immunological criterion or have documented lupus nephritis (LN) with positive autoantibodies.⁵ More recently, the European Alliance of Associations for Rheumatology (EULAR)/ACR-2019 criteria were developed, with a positive level for antinuclear antibody (ANA) at a serum dilution of 1:80 as a required entry criterion followed by weighted items including 7 clinical domains and 3 immunological domains.⁶

These classification criteria were initially developed and validated in adult SLE cohorts. Childhood-onset SLE (cSLE) represents 20% of the total SLE patient.⁷ Compared to the adult population, there is more haematological and renal involvement with lesser arthritis and serositis in cSLE.⁸ Even among the paediatric population, there is variation in clinical manifestation frequencies.⁹ Several studies have thus attempted to validate the classification criteria in cSLE cohorts. A recent meta-analysis showed that SLICC-2012 had the highest sensitivity while the ACR-1997 had the highest specificity.¹⁰ In that meta-analysis, only one predominant East Asian cohort was included.¹¹

Southeast Asia comprises 11 countries with diverse histories, religions and cultures. There is a paucity of studies evaluating the performance of SLE classification criteria in cSLE cohorts in this region. The primary aim of this study is to assess and compare the performance of ACR-1997, SLICC-2012 and EULAR/ACR-2019 classification criteria in a cSLE cohort in Singapore both at diagnosis and over time.

METHOD

Patient selection

We included all patients with cSLE diagnosed in KK Women's and Children's Hospital, Singapore, from August 2002 to December 2022. All patients were younger than 16 years at onset and were diagnosed by trained paediatric rheumatologists. The control group consisted of patients with well-established diagnoses of mixed connective tissue disease (MCTD) and undifferentiated connective tissue disease (UCTD) who posed an initial diagnostic challenge. Positive antinuclear antibodies (ANA) was not a mandatory criterion in the control group, as the diagnosis of cSLE is also considered in patients with negative ANA, especially in the early stages of the disease. Patients were excluded if they were followed up for less than a year.

Data collection

Patients were recruited from our web-based prospective and ongoing registry (RECORD, or Registry for Childhood Onset Rheumatic Diseases).¹² Demographic, clinical and laboratory

data were recorded. Definitions of cutaneous manifestations, oral ulcers, arthritis, serositis, cytopenia, and renal and neurological involvement were those provided by the respective criteria.⁴⁻⁶ ANA was determined by indirect immunofluorescence on human cell epithelioma (HEp-2) cells substrate and defined as positive if staining reactivity at $\geq 1:80$. Anti-double stranded DNA (dsDNA) test was determined by enzyme-linked immunosorbent assay (ELISA) and/or indirect immunofluorescence on *Crithidia lucilae* substrate. The anti-extractable nuclear antigen (anti-ENA) profile, including Ro, La, Smith, and ribonuclear proteins, were measured qualitatively using the ELISA technique and were considered positive if the values were above the laboratory reference range. Lupus anticoagulant was determined by the dilute Russell's viper venom time with confirmatory testing. Both anti-cardiolipin antibody and anti- β_2 -glycoprotein antibody isotypes Immunoglobulin M (IgM) and Immunoglobulin G (IgG) were determined by ELISA with a cut-off value of 20 IgM phospholipid (MPL) or IgG phospholipid (GPL) units, respectively, for ACR-1997 and SLICC-2012 criteria; and a cut-off value of 40 MPL or GPL for EULAR/ACR criteria set.

Statistical analyses

Non-parametric analyses were used to describe data and were shown as median (interquartile range [IQR]) for continuous variables and percentages for categorical variables. Sensitivity, specificity, predictive values and diagnostic accuracies were estimated for each of the classification criteria. We also calculated the diagnostic performance of EULAR/ACR-2019 criteria using a separate cutoff score of 13 to compare our results to similar studies. Chi-squared or Fisher's exact, Mann Whitney U or Kruskal Wallis tests were applied to compare differences between groups where appropriate. McNemar's test was performed to assess differences in sensitivity and specificity between the criteria. The diagnostic performances were also evaluated for patients with specific organ involvement in subgroup analyses. All analyses were performed using SPSS, version 23.0 (IBM Corp, NY, US) and GraphPad Prism V.7 (GraphPad Software, Inc, CA, US) with statistical significance set at $P < 0.05$.

Ethics

This study was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The SingHealth Centralised Institutional Review Board (CIRB) approved this study and waived the need for informed consent for this database study (CIRB: 2019/2961 and 2019/2192).

RESULTS

Sample demographics

The demographic characteristics of our study cohort are presented in Table 1. A total of 120 cSLE patients were included (83% females, 52% Chinese). The median age at onset was 12.1 years (10.0–14.0), and the median age at diagnosis was 12.9 years (10.6–14.4). The median duration of follow-up was 5.7 years (3.0–8.4). Controls consisted of 32 patients with UCTD and 4 with MCTD (total 36 patients, 89% females, 64% Chinese). Patients with cSLE had a younger age at disease onset ($P=0.022$), younger age at diagnosis ($P=0.004$), shorter duration of follow-up ($P=0.004$) and a shorter duration from disease onset to diagnosis ($P=0.022$).

Clinical characteristics

The clinical characteristics of our study cohort are presented in Table 2. The most common clinical manifestations at diagnosis were haematologic involvement (83%), fever (60%) and arthritis (51%). Renal involvement was present in 37% of the cSLE patients at diagnosis and 47% over time. In the control group, only haematologic involvement had a prevalence of more than 50% at diagnosis and over time.

Immunologic characteristics

ANA was positive in 98% of the cSLE cohort and 94% of the control at diagnosis. One control patient only developed positive ANA later, while all cSLE patients who were ANA positive were already noted to have positive ANA at diagnosis. Anti-

dsDNA antibody was present in 88% of the cSLE patients compared to 33% in the control group. The most common anti-ENA antibody in the cSLE cohort was anti-Ro/SSA (58%), while anti-U1RNP was the most common in the control group (39%).

Performance of the criteria at diagnosis

At diagnosis, 102 patients (85%) fulfilled all 3 criteria, 1 patient only fulfilled SLICC-2012 criteria, 2 patients only fulfilled EULAR/ACR-2019 criteria, and none fulfilled only ACR-1997 criteria (Fig. 1). One patient did not fulfil any of the criteria as there was only biopsy-proven lupus nephritis without positive ANA. SLICC-2012 criteria had the highest sensitivity (97.5%, 95% CI 92.3–99.5), followed by the EULAR/ACR-2019 criteria (96.7%, 95% CI 91.7–99.1), both of which were higher than the ACR-1997 criteria (86.7%, 95% CI 79.3–92.2, $P<0.001$ and $P=0.004$, respectively; see Table 3 and Fig. 2). ACR-1997 criteria had the highest specificity (91.7%, 95% CI 77.5–98.3%) compared to SLICC-2012 (69.4%, 95% CI 51.2–83.7%, $P=0.008$) and EULAR/ACR-2019 (50.0%, 95% CI 32.9–67.1%, $P<0.001$) criteria. When a cutoff score of ≥ 13 was used for the EULAR/ACR-2019 criteria, the sensitivity remained similar to the original score of ≥ 10 (95.8%, 95% CI 90.5–98.6% $P=0.999$), but the specificity increased significantly (75.0%, 95% CI 57.8–87.9%, $P=0.031$). SLICC-2012 criteria had the highest diagnostic accuracy (91%, 95% CI 85.4–95.0%), but a cutoff score of ≥ 13 for EULAR/ACR-2019 criteria resulted in similar diagnostic accuracy to SLICC-2012.

Table 1. Demographic characteristics of the study cohort.

Characteristics	SLE ^a (n=120)	Controls ^b (n=36)	P value
Female, no. (%)	99 (83)	32 (89)	0.445
Ethnicity, no. (%)			0.270
Chinese	62 (52)	23 (64)	
Malay	33 (27)	10 (27)	
Indian	8 (7)	2 (6)	
Others	17 (14)	1 (3)	
Age at disease onset, years*	12.1 (10.0–14.0)	13.4 (11.2–15.1)	0.022
Age at diagnosis, years*	12.9 (10.6–14.4)	14.4 (11.9–16.0)	0.004
Duration from onset to diagnosis, months*	1.2 (0.5–3.1)	2.9 (1.0–20.9)	0.022
Duration for follow-up, years*	5.7 (3.0–8.4)	2.9 (1.2–5.4)	0.004
Positive ANA, no. (%)	118 (98)	34 (94)	0.228

ANA: antinuclear antibody; SLE: systemic lupus erythematosus
* Median (interquartile range)
^a According to certified paediatric rheumatologists' diagnosis.
^b Controls are 4 patients with mixed connective tissue disease and 32 patients with undifferentiated connective tissue disease.

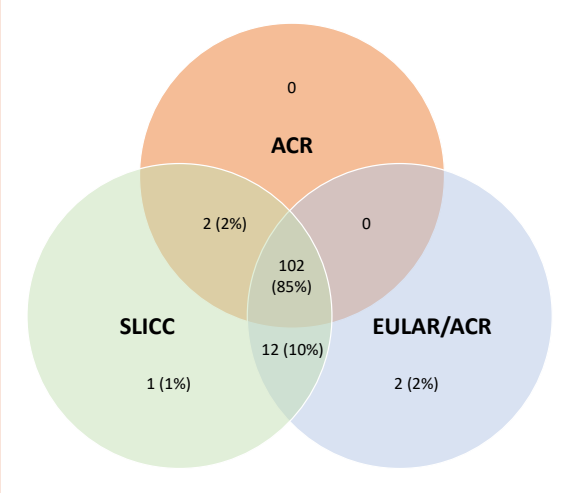
Table 2. Clinical characteristics of cases and controls at diagnosis.

Clinical characteristics	At diagnosis		Over time	
	Cases, n=120	Controls, n=36	Cases, n=120	Controls, n=36
Fever	72 (60.0)	9 (25.0)	74 (61.7)	9 (25.0)
Malar rash	53 (44.2)	1 (2.8)	58 (48.3)	1 (2.8)
Discoid rash	14 (11.7)	0 (0)	22 (18.3)	0 (0)
Photosensitivity	17 (14.2)	2 (5.6)	19 (15.8)	2 (5.6)
Oral ulcer	39 (32.5)	1 (2.8)	43 (35.8)	1 (2.8)
Alopecia	37 (30.8)	3 (8.3)	54 (45.0)	3 (8.3)
Haematologic involvement	100 (83.3)	19 (52.8)	108 (90.0)	21 (58.3)
Renal involvement	44 (36.7)	1 (2.8)	56 (46.7)	1 (2.8)
Neurological involvement	6 (5.0)	0 (0)	9 (7.5)	0 (0)
Arthritis	61 (50.8)	16 (44.4)	73 (60.8)	17 (47.2)
Serositis	11 (9.2)	1 (2.8)	16 (13.3)	1 (2.8)
Low complements	97 (80.8)	13 (36.1)	113 (94.2)	18 (50.0)
ANA	118 (98.3)	34 (94.4)	118 (98.3)	35 (97.2)
Anti-dsDNA	105 (87.5)	12 (33.3)	106 (88.3)	13 (36.1)
Anti-Smith	46 (38.3)	5 (13.9)	48 (40.0)	7 (19.4)
Anti-Ro/SSA	66 (55.0)	13 (36.1)	70 (58.3)	13 (36.1)
Anti-La/SSB	29 (24.2)	8 (22.2)	29 (24.2)	8 (22.2)
Anti-U1RNP	56 (46.7)	12 (33.3)	60 (50.0)	14 (38.9)
Antiphospholipid antibodies	31 (25.8)	3 (8.3)	36 (30.0)	3 (8.3)

ANA: antinuclear antibody; dsDNA: double-stranded DNA; La/SSB: Sjögren’s syndrome B; Ro/SSA: Sjögren’s syndrome A; U1RNP: U1-ribonucleoprotein

Data presented in median (interquartile range) and number (%). Features with more than 50% are highlighted in bold.

Fig. 1. cSLE (n=120) patients classified according to ACR 1997, SLICC-2012, EULAR/ACR 2019 classification criteria.



ACR: American College of Rheumatology 1997 criteria; EULAR/ACR: European Alliance of Associations for Rheumatology 2019 criteria; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics 2012 criteria.

Table 3. Performance measures for the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria.

	ACR 1997	SLICC	EULAR/ACR	EULAR/ACR*
At diagnosis				
Sensitivity	86.7 (79.3 – 92.2)	97.5 (92.3 – 99.5)	96.7 (91.7 – 99.1)	95.8 (90.5 – 98.6)
Specificity	91.7 (77.5 – 98.3)	69.4 (51.2 – 83.7)	50.0 (32.9 – 67.1)	75.0 (57.8 – 87.9)
PPV	97.2 (92.1 – 99.0)	91.4 (86.7 – 94.6)	86.6 (61.9 – 92.6)	92.7 (87.9 – 95.8)
NPV	67.3 (56.4 – 76.7)	89.3 (72.3 – 96.3)	81.8 (61.9 – 92.6)	84.4 (69.2 – 92.9)
Positive LR	10.4 (3.51 – 30.8)	3.19 (1.95 – 5.23)	1.93 (1.39 – 2.65)	3.83 (2.17 – 6.76)
Negative LR	0.15 (0.09 – 0.23)	0.04 (0.01 – 0.11)	0.07 (0.02 – 0.18)	0.06 (0.02 – 0.13)
Accuracy	87.8 (81.6 – 92.5)	91.0 (85.4 – 95.0)	85.9 (79.4 – 91.0)	91.0 (85.4 – 95.0)
Over time				
Sensitivity	95.0 (89.4 – 98.1)	99.2 (95.4 – 99.9)	98.3 (94.1 – 99.8)	96.7 (91.7 – 99.1)
Specificity	75.0 (57.8 – 87.9)	50.0 (32.9 – 67.1)	36.1 (20.8 – 53.8)	69.4 (51.9 – 83.7)
PPV	92.7 (87.8 – 95.7)	86.9 (82.7 – 90.2)	83.7 (80.0 – 86.8)	91.3 (86.6 – 94.5)
NPV	81.8 (66.9 – 90.9)	94.7 (71.3 – 99.2)	86.7 (60.6 – 96.5)	86.2 (70.0 – 94.4)
Positive LR	3.80 (2.15 – 6.70)	1.98 (1.43 – 2.75)	1.54 (1.20 – 1.97)	3.16 (1.93 – 5.18)
Negative LR	0.07 (0.03 – 0.15)	0.02 (0.01 – 0.12)	0.05 (0.01 – 0.20)	0.05 (0.02 – 0.13)
Accuracy	90.4 (84.6 – 94.5)	87.8 (81.6 – 92.5)	84.0 (77.3 – 89.4)	90.4 (84.6 – 94.5)

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics
 *ACR/EULAR using a score ≥ 13 instead of ≥ 10 .
 Data presented in % or ratio (95% CI).

Performance of the criteria over time

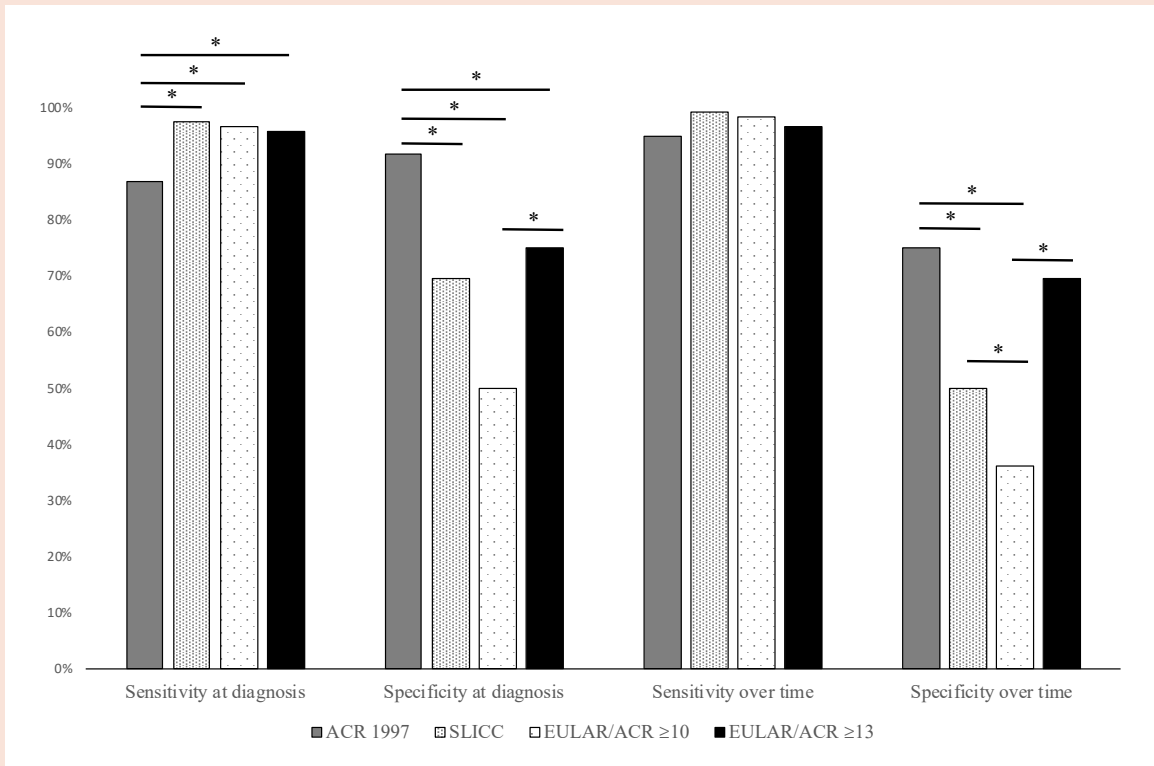
Over time, SLICC-2012 criteria had the highest sensitivity (99.2%, 95% CI 95.4–99.9), but all 3 criteria sensitivities were no longer significantly different (Table 3, Fig. 2). The specificities of all 3 criteria decreased over time. ACR-1997 criteria retained the highest specificity (75.0%, 95% CI 57.8–87.9) compared to SLICC-2012 (50.0%, 95% CI 32.9–67.1, $P=0.004$) and EULAR/ACR-2019 (36.1%, 95% CI 20.8–53.8, $P<0.001$) criteria. When a cutoff score of ≥ 13 was used for the EULAR/ACR-2019 criteria, the sensitivity remained similar to the original score of ≥ 10 (96.7%, 95% CI 91.7–99.1, $P=0.500$). However, the specificity increased significantly and no longer differed from the ACR-1997 criteria (69.4%, 95% CI 51.9–83.7, $P=0.687$). Over time, both ACR-1997 and EULAR/ACR-2019 criteria using a cutoff score of ≥ 13 had the highest diagnostic accuracy (90.4%, 95% CI 84.6–94.5).

Performance of the criteria at diagnosis for patients with specific organ involvement

We studied the diagnostic performance of the criteria at diagnosis according to specific organ involvement. The sensitivities of SLICC-2012 and EULAR/ACR-2019 criteria remained similar for patients with renal involvement, arthritis, haematologic involvement, hypocomplementemia and positive ANA (Fig. 3). The sensitivity of ACR-1997 criteria improved slightly for patients with renal involvement and arthritis (86.7% versus [vs] 95.5% and 98.4%, respectively).

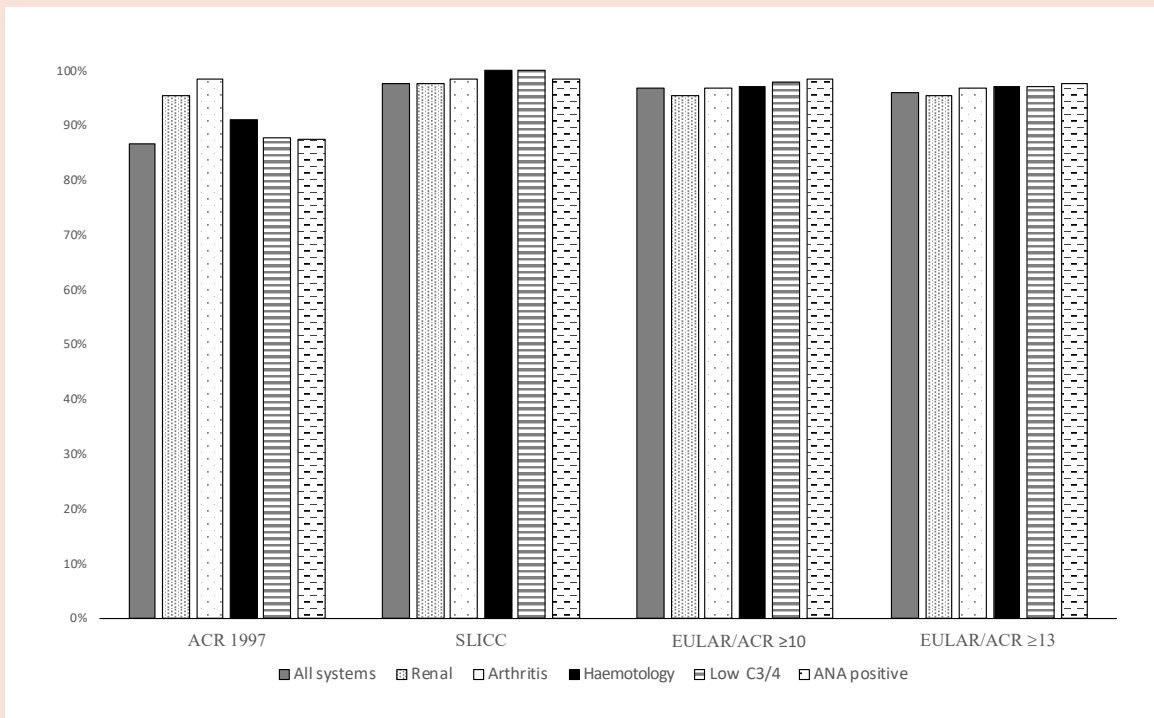
All 3 criteria had 100% specificities for patients with renal involvement at diagnosis, while specificities were the same for patients with positive ANA. All 3 criteria had decreased specificities in patients with hypocomplementemia (ACR-1997: 91.7% vs 76.9%, SLICC-2012: 69.4% vs 38.5%, EULAR/ACR-2019: 50.0% vs 23.1%). SLICC-2012 criteria specificity decreased for patients with

Fig. 2. Comparison of sensitivity and specificity of the classification criteria at diagnosis and over time (* denotes $P<0.05$).



ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics

Fig. 3. Comparison of the sensitivity of the classification criteria at diagnosis for patients with various system involvement.



ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics

haematologic involvement (69.4% vs 52.6%) but increased for patients with arthritis (69.4% vs 75.0%). EULAR/ACR-2019 criteria had decreased specificity for patients with arthritis (50.0% vs 37.5%), but the decrease in specificity is lesser when a cutoff score of ≥ 13 is used (75.0% vs 68.8%).

DISCUSSION

Owing to different frequencies of clinical manifestations and immunological markers in cSLE patients, studies have attempted to examine the diagnostic performance of existing SLE classification criteria. A recent meta-analysis of predominant Western cSLE studies showed that the SLICC-2012 criteria had the highest sensitivity, while the ACR-1997 criteria had the highest specificity.¹⁰ In the present study comprising a Southeast Asian cSLE cohort, our findings concurred that the SLICC-2012 criteria had the highest sensitivity, and the ACR-1997 criteria had the highest specificity, both at diagnosis and over time.

The clinical presentation of SLE is highly diverse. cSLE patients have more renal, haematological and neurological involvement and less arthritis and cutaneous manifestations.^{7,8} In addition to differences across age groups, genetics and ethnicity also influence SLE phenotypic expression resulting in clinical heterogeneity among cSLE patients. In an analysis of the Southeast Asian cSLE cohorts, renal and haematological manifestations featured prominently compared to Western and East Asian cSLE cohorts, while discoid rash was comparatively less common in this region except for the Philippines.⁹ There was also a more significant proportion of patients with positive anti-dsDNA antibodies. In our cohort, haematological abnormalities were the most common manifestations at diagnosis, followed by fever and arthritis. Cutaneous manifestations were less common, and even the prevalence of malar rash was less than that of a Western cSLE cohort (48% vs 63%).¹³ Regarding immunological markers, almost all our cSLE patients had a positive ANA. Our cohort had a high proportion of positive anti-dsDNA antibodies and hypocomplementemia, and more than half of the patients also had positive anti-Ro and anti-U1RNP antibodies.

Given that the diagnostic performance of SLE classification criteria in different cohorts varies according to disease phenotypic expression, this study observed several similarities and differences in our cohort. At diagnosis, all 3 classification criteria demonstrated good sensitivity. Still, the exclusion of hypocomplementemia, a common manifestation, along with the combination of haematologic

abnormalities into a singular feature, resulted in an inferior sensitivity of the ACR-1997 criteria compared to that of the SLICC-2012 and EULAR/ACR-2019 criteria. This finding is concordant with the results of the meta-analysis by Chang et al., albeit the ACR-1997 criteria sensitivity in our cohort was higher than that of the meta-analysis.¹⁰ As a more stringent criterion, all patients who fulfilled the ACR-1997 criteria also fulfilled the SLICC-2012 and EULAR/ACR-2019 criteria, but the converse was invalid. The highest sensitivity was found with the SLICC-2012 criteria, similar to the meta-analysis result. However, this differs from a later Chinese study that demonstrated the highest sensitivity with the EULAR/ACR-2019 criteria.¹⁴ As classification criteria are often used in clinical practice to guide diagnosis, the SLICC-2012 criteria and EULAR/ACR-2019 criteria, both with high sensitivities and diagnostic accuracies, minimise the chance of physicians missing out on potential cSLE patients, especially early on in the disease. Overall, the SLICC-2012 criteria are more practical for clinical use without the need of a weighted score as well as positive ANA as an entry criterion.

At diagnosis, the ACR-1997 criteria had the highest specificity. Notably, the specificities across all 3 criteria in our study were significantly lower than that reported in the current literature. We attribute this to selecting patients with UCTD and MCTD as the control group, compared to other studies that commonly recruited patients with positive ANA or other distinct rheumatic diseases as controls. The latter groups of patients either lack multisystem involvement or display distinct clinical manifestations specific to other rheumatic diseases, making it easier for the criteria to classify patients who do not have cSLE correctly. Patients with UCTD and MCTD often present overlapping features with SLE, and it is of interest if the classification criteria can accurately distinguish cSLE patients in the face of diagnostic dilemmas at initial presentation. The specificities of SLICC-2012 and EULAR/ACR-2019 criteria were dismal, while the ACR-1997 criteria retained relatively high specificity. Ohara et al. also demonstrated more misclassification of cSLE when they analysed the subgroup of patients with MCTD using the EULAR/ACR-2019 and SLICC-2012 criteria.¹⁵ As classification criteria require high specificity, the performance of SLICC-2012 and EULAR/ACR-2019 remains debatable in cSLE patients.

The effect of time on the diagnostic performance of the 3 classification criteria was assessed in this study, given the cumulative characteristics of these 3 classification systems. While the SLICC-2012 and EULAR/ACR-2019 criteria could classify patients

earlier than the ACR-1997 criteria, the latter's sensitivity increased and caught up over time. Fonseca et al. reported similar findings in their Brazilian cSLE cohort.¹⁶ However, another study conducted in Oman showed that the sensitivity of ACR-1997 criteria remained inferior to the other 2 classification criteria despite increasing over time.¹⁷ On the other hand, the specificities of all 3 classification criteria decreased substantially over time. Contrary to our results, both Fonseca et al. and Levinsky et al. reported no significant differences in the ACR-1997 and SLICC-2012 criteria specificities at first-year visits in their respective cSLE cohorts.^{18,19} We attributed this difference to our selection of the control cohort and cautioned the use of SLICC-2012 and EULAR/ACR-2019 criteria in cSLE clinical trials, which may falsely include patients with MCTD and UCTD.

The EULAR/ACR-2019 criteria were developed through a collaborative effort to create a single, internationally accepted set of classification criteria for SLE.⁶ In our study, the EULAR/ACR-2019 criteria did not confer additional benefits in terms of sensitivity or specificity compared to the earlier ACR-1997 and SLICC-2012 criteria, similar to the findings in the meta-analysis.¹⁰ Furthermore, cSLE patients with a negative ANA will be missed out. Suda and colleagues suggested an ANA titre of $\geq 1:40$ as the entry criterion to achieve better sensitivity.²⁰ Cheng et al. also pointed out that patients with UCTD and MCTD in a Chinese cSLE cohort were most likely to be misclassified as having SLE by the EULAR/ACR-2019 criteria due to high weightage of arthritis and mucocutaneous manifestation.¹⁴ Despite having an entry criterion, the specificity of the EULAR/ACR-2019 criteria did not surpass that of the ACR-1997 and SLICC-2012 criteria in our study. However, a EULAR/ACR-2019 score ≥ 13 significantly improved the specificity without compromising the sensitivity, along with improved positive predictive value and diagnostic accuracy, making it comparative to the earlier 2 criteria. This finding echoed previous studies' results.^{14,17} Over time, both sensitivity and specificity of the EULAR/ACR-2019 criteria, using a cutoff score of ≥ 13 , were also similar to the ACR-1997 and SLICC-2012 criteria, with superior specificity compared to the SLICC-2012 criteria. This new cutoff score appears to be more appropriate in cSLE cohorts.

SLE patients with major organ involvement have a poorer prognosis, and prompt diagnosis is essential to improve patient outcomes. Cheng and colleagues demonstrated higher sensitivity of

the SLICC-2012 and EULAR/ACR-2019 criteria in patients with renal involvement compared to ACR-1997 criteria.¹⁴ This difference in sensitivities was not appreciated in our study, presumably due to a ceiling effect as all 3 criteria had high sensitivities in patients with renal involvement. On the other hand, all 3 criteria had 100% specificity for patients with renal involvement. Therefore, renal involvement is particular to cSLE patients compared to MCTD and UCTD, concurring with a high weightage assigned to biopsy-proven lupus nephritis in both the SLICC-2012 and EULAR/ACR-2019 criteria. We also analysed the diagnostic performance of these classification criteria in patients with haematologic involvement and hypocomplementemia, given the high prevalence of these features in our cSLE cohort. Unsurprisingly, there was a substantial decrease in the specificity of SLICC-2012 criteria given that haemolytic anaemia, leukopenia or lymphopenia, and thrombocytopenia all represent individual features and, therefore, a disproportionate weightage in patients with Evans syndrome. Remarkably, the specificities across all 3 criteria decreased when analysing only patients with hypocomplementemia, as our control patients with MCTD and UCTD also had relatively high rates of hypocomplementemia.

This study presents several unique findings in the diagnostic performance of existing SLE classification criteria in a Southeast Asian cSLE cohort, but it is not without limitations. First, the data for patients diagnosed before 2009, before the setup of our registry, were retrieved retrospectively from medical records. However, this number represents the minority ($n=15$, 10%). Second, our control cohort is small. We selected only patients with MCTD and UCTD who posed an initial diagnostic challenge to test the diagnostic performance of the 3 criteria, simulating daily clinical practice, as the inclusion of healthy controls or patients with distinct rheumatic diseases often resulted in the overly optimal diagnostic performance of the classification criteria. Third, there is an inherent lack of an objective diagnosis as the standard of reference other than the treating physician's diagnosis, which could lead to inconsistency. Yet, this allowed the evaluation of classification criteria in a real-world setting. Lastly, our cSLE cohort is a heterogeneous cohort of mixed races. As the sample size was small, we could not examine the diagnostic performance in subgroups of patients according to race. We hope that with more data from the region, the diagnostic performance of these classification criteria in cSLE can be further validated.

CONCLUSION

The SLICC-2012 criteria had the highest sensitivity in this first study evaluating the SLE classification criteria performance in a Southeast Asian cohort, especially early in the disease course, while the ACR-1997 had the highest specificity both at diagnosis and over time. The low specificities of the SLICC-2012 and EULAR/ACR-2019 criteria in our study cautioned using these classification criteria in cSLE cohorts. Although the EULAR/ACR-2019 criteria did not confer additional benefits compared to the earlier two, adopting a cutoff score ≥ 13 instead of 10 further improved the diagnostic performance of the EULAR/ACR-2019 criteria in cSLE, making it comparative to the earlier 2 criteria.

Authors' contributions

All authors contributed to the study's conception and design. Kai Liang Teh (KLT), Yun Xin Book (YXB), and Thaschawee Arkachaisri (TA) performed data collection and interpretation. KLT and TA did the data analysis. KLT and TA wrote the first draft of the manuscript authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration

The authors have declared no conflicts of interest.

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