Performance of the new SLICC classification criteria in childhood systemic lupus erythematosus: a multicentre study

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Abstract

Objective

The Systemic Lupus International Collaborating Clinics (SLICC) group has recently proposed a new set of criteria for the classification of systemic lupus erythematosus (SLE). We aimed to compare the sensitivity and specificity of the new SLICC criteria with those of the American College of Rheumatology (ACR) criteria in our childhood-onset SLE patients.

Methods

Three main paediatric lupus centres from Europe participated in this study. Of these centres, one was predominantly a paediatric nephrology centre (Great Ormond Street Hospital, London, UK), one was predominantly a paediatric rheumatology centre (Istituto Giannina Gaslini, Genoa, Italy), and one was a combined centre taking care of both group of patients (Hacettepe University, Ankara, Turkey). The features present at disease onset in patients with childhood-onset SLE, younger than 18 years of age, seen between January 2000 and December 2012 were retrospectively reviewed. For the evaluation of specificity, patients admitted to each centre between May and December 2012 for conditions other than SLE, in whom ANA was deemed necessary within the diagnostic work-up were included as controls. PASW 18.0 for Windows was used for statistical analyses.

Results

Both sets of classification criteria were analysed in 154 childhood SLE patients with a mean age at disease onset of 12.7 years and in 123 controls with a mean age of 8.9 years. The sensitivity and specificity of the ACR criteria were 76.6% and 93.4%, respectively, whereas those of the SLICC criteria were 98.7% and 85.3%, respectively. Four patients out of 5 with haemolytic uraemic syndrome (HUS) and 4 patients out of 8 with juvenile dermatomyositis (JDM) met four of the SLICC criteria, whereas 22 lupus nephritis patients failed to meet four of the ACR criteria.

Conclusions

In our paediatric series, the SLICC criteria showed better sensitivity ($p<0.001$) and led to fewer misclassifications, but were less specific ($p<0.001$) than the ACR criteria.

Key words

SLICC criteria, childhood SLE, ACR criteria, systemic lupus erythematosus, nephrology, rheumatology

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with variable organ involvement. Reliable classification criteria are needed to conduct collaborative clinical and basic research in this disease. Furthermore, it should be taken into account that classification criteria are often used as diagnostic criteria in routine clinical practice. The most widely used classification criteria for SLE are the American College of Rheumatology (ACR) criteria published in 1982 (1). These criteria were revised in 1997 (2) by deleting the LE cell criterion and by modifying the immunologic criterion with the inclusion of antiphospholipid antibodies.

Recently the Systemic Lupus International Collaborating Clinics (SLICC) group undertook a revision of the ACR classification criteria to address multiple concerns that have arisen since the development of the 1982 criteria (3). In patients with adult-onset disease, the SLICC Classification Criteria resulted in fewer misclassifications (62 *vs*. 74, p=0.24) and had greater sensitivity (97% *vs*. 83%, p<0.0001) but were less specific (84% *vs*. 96%, p<0.0001) than the ACR criteria. The SLICC criteria have not yet been tested in childhood SLE, we decided to compare their sensitivity and specificity with those of the 1997 ACR criteria in our SLE patients with a childhood onset. Thus we aimed to analyse whether this new criteria were to be more valuable in our daily practice in paediatrics.

Patients and methods

Three centers were invited to participate in the study and to provide data from patients with childhood SLE seen in the last 10 years. All patients were younger than 18 years of age at onset. Fifty-five patients were enrolled at the Rheumatology unit of the Instituto Giannina Gaslini (IGG) of Genoa, Italy, 44 patients were enrolled at the Nephrology unit of the Great Ormond Street Hospital (GOSH) of London, UK, and 55 patients were enrolled at the Nephrology-Rheumatology unit of the Hacettepe University (HU) of Ankara, Turkey. The control group consisted of a total of 123 patients, admitted to the same centres in the same period, in whom ANA determination was deemed necessary by the attending physician within the diagnostic work-up. They were patients with the following diagnoses: 16 juvenile idiopathic arthritis, 8 juvenile dermatomyositis, 5 unclassified vasculitidis, + other vasculitidis: 5 Takayasu arteritis, 8 polyarteritis nodosa, 7 Granulomatous polyangitis/Wegener Granulomatosis, 10 Behçet's disease, 6 HSP/IgA Vasculitis, 3 Eosinophilic polyangitis/Churg-Strauss syndrome, 4 Kawasaki disease; 3 undifferentiated connective tissue disease, 1 mixed connective tissue disease, 6 acute idiopathic thrombocytopenic purpura, 4 septic arthritis, 5 haemolytic uraemic syndrome, 2 acute lymphoproliferative syndrome, 1 familial Mediterranean fever, 1 autoimmune haemolytic anaemia, 2 Muckle-Wells syndrome, 1 autoimmune encephalitis, 8 systemic sclerosis, 2 acute post-streptococcal glomerulonephritis, 5 rheumatic fever, and 10 patients with undifferentiated diagnosis. Of the JIA patients, 6 had oligoarticular, 5 had polyarticular and 5 had systemic onset disease.

Patient and control data were collected on standardised case report forms. The gold standard for the diagnosis of SLE was based on the lupus expert opinion at each centre (SO, AR, and SM). Demographic features, laboratory data, including serum complement levels and autoantibody titers, and specific items included in the ACR criteria and SLICC criteria were included. Renal biopsy specimens were evaluated at the pathology department of each centre.

The sensitivity of ACR and SLICC criteria was evaluated on the features recorded at disease diagnosis. The specificity of each criterion set was tested against control patients.

Statistical analysis

Statistical analyses were performed using PASW 18.0. Descriptive statistics included percentages for sex, age, and each SLICC criterion. The Chi-square test or Fisher's exact test, where appropriate, was used to compare these percentages in different groups. A p-value of 0.05 was considered to show a statistically significant result.

Results

One hundred and fifty-four childhood SLE patients and 123 control patients were included in the study. The mean age at disease onset of childhood SLE patients was 12.7 years (range 4–19 years) and that of control patients was 8.9 years (range 0–18 years). Among childhood SLE patients, 83.1% were female.

The results of assessment of sensitivity of each classification criterion in childhood SLE and control patients are shown in Supplementary Table. Overall, the SLICC criteria resulted in fewer misclassifications (20 *vs*. 44) and showed greater sensitivity (98.7% *vs*. 76.6% $p<0.001$) than ACR criteria, but were less specific (85.3% *vs*. 93.4% $p<0.001$) (Table I). Four patients out of 5 with haemolytic uraemic syndrome (HUS) and 4 patients out of 8 with juvenile dermatomyositis (JDM) met four of the SLICC criteria, hence constituting false positives.

Twenty-two childhood SLE patients had biopsy-confirmed lupus nephritis and were ANA-positive, but failed to fulfill four of the ACR criteria at disease onset. They met the SLICC criteria, however.

When we compared the results between the 3 centres, acute cutaneous lupus, arthritis and antiphospholipid antibodies were less common and renal involvement was more common among patients seen at the nephrology centre (GOSH, London, UK). However, haemolytic anaemia, leucopenia, anti dsDNA, anti Sm and direct coombs were recorded more frequently at the rheumatology centre (IGG, Genoa, Italy) (Fig. 1) (Suppl. Table). The sensitivity of the new criteria was lowest (95.5%), whereas the specificity was best among patients seen in the nephrology centre (96.4%) (Table I).

Table I. Performances of SLICC and ACR (1997) classification criteria

		"Sensitivity"	"Specificity"	Misclassified cases (number)
Combined nephrology-rheumatology centre	1997 ACR criteria	39/55 (70.9%)	37/40 (92.5%)	19
	SLICC criteria	55/55 (100%)	32/40 (80%)	8
Nephrology centre	1997 ACR criteria	27/44 (61.4%)	28/28 (100%)	17
	SLICC criteria	42/44 (95.5%)	27/28 (96.4%)	3
Rheumatology centre	1997 ACR criteria	52/55 (94.5%)	50/55 (90.9%)	8
	SLICC criteria	55/55 (100%)	46/55 (83.6%)	9
Overall study	1997 ACR criteria	118/154 (76.6%)	115/123 (93.4%)	44
	SLICC criteria	152/154 (98.7%)	105/123 (85.3%)	20

When we compared our findings in childhood SLE patients with the prevalence of the criteria in adult patients with SLE reported by Petri *et al*. (3), renal involvement, neurologic findings, haemolytic anaemia, low complement levels, positive titers of anti-dsDNA antibodies were more frequent in children than in adults ($p<0.001$). Chronic cutaneous lupus, oral ulcer, alopecia, arthritis, serositis, leukopenia and positive titers for antiphospholipid antibodies were more common in adults ($p<0.05$) (Fig. 2) (Suppl. Table).

Discussion

Overall, the new SLICC criteria performed better, were more sensitive, and resulted in fewer misclassifications than the ACR criteria, but were less specific, especially among childhood SLE patients from the combined nephrology rheumatology centre (80%).

When each criterion was assessed individually, a number of issues became apparent. In the SLICC criteria, malar rash and photosensitivity are parts of the same criterion, along with other acute cutaneous manifestations of lupus. Such grouping probably increases

Supplementary Table. Sensitivity of each SLICC criterion at our study and prevalence of each criteria in adult patients.

Criteria	Sensitivity (n=55) combined centre	Sensitivity (n=44) nephrology centre	Sensitivity (n=55) rheumatology centre	*p*-value between centres	Reported prevalance of criterion in adults** (n=310)	Overall sensitivity (n=154)	*p*-value between adult and childhood cases
Acute cutaneous lupus	60	43.2	72.7	**0.012***	65.2	59.7	0.155
Chronic cutaneous lupus	7.3	0	7.3	0.185	**19.7**	**5.2**	<0.001*
Oral ulcers	14.5	11.4	14.5	0.874	**44.2**	**13.6**	**<0.001***
Non-scarring alopecia	10	13.6	7.3	0.580	**31.9**	**10.4**	**<0.001***
Arthritis	61.8	4.5	63.6	**<0.001***	**79.0**	**46.1**	**<0.001***
Serositis	10.9	0	7.3	0.087	**35.2**	**6.5**	**<0.001***
Renal	43.6	68.2	41.8	**0.017***	**32.9**	**50.0**	**<0.001***
Neurologic	18.2	31.8	14.5	0.092	**5.5**	**20.8**	**<0.001***
Haemolytic anaemia	9.1	13.6	36.4	**0.001***	**7.1**	**20.1**	**<<0.001***
Leukopenia	29.1	13.6	60	**<0.001***	**46.4**	**35.7**	**0.010***
Thrombocytopenia	16.4	15.9	16.4	0.995	13.5	16.2	0.304
ANA	96.4	93.2	98.2	0.165	96.5	96.1	0.789
Anti-dsDNA	74.5	75.0	83.6	**0.015***	**57.1**	**77.9**	**<0.001***
Antiphospholipid antibody	40	11.4	47.3	**<0.001***	**53.6**	**34.4**	**<0.001***
Low complement	85.5	68.2	76.4	0.114	**59.0**	**77.3**	**<0.001***
Direct Coombs	27.3	15.9	45.5	**<0.001***	–	**30.5**	–

*$p<0.05$ statistically significant
**Based on Petri M. *et al*., 2012 (3)

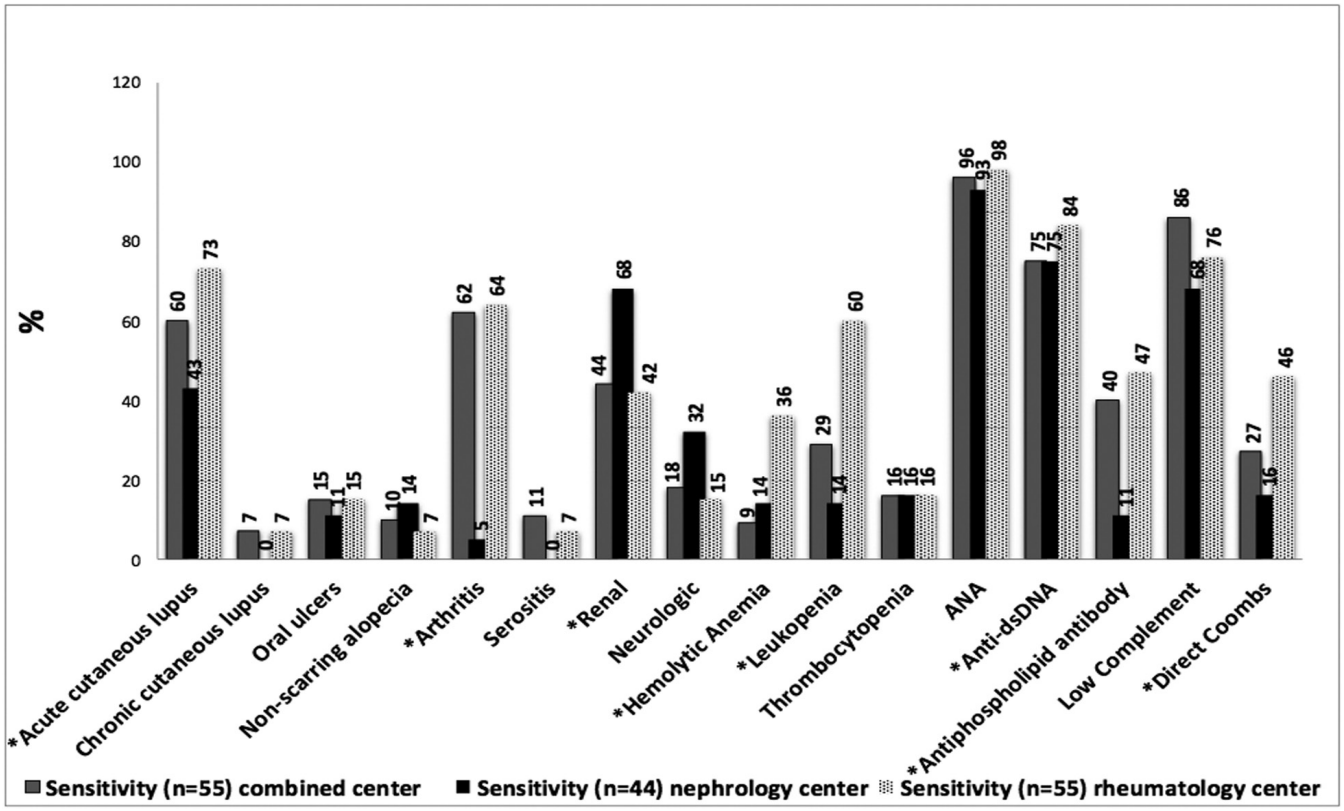

Fig. 1. Prevalence of each criterion between centres. *$p<0.05$.

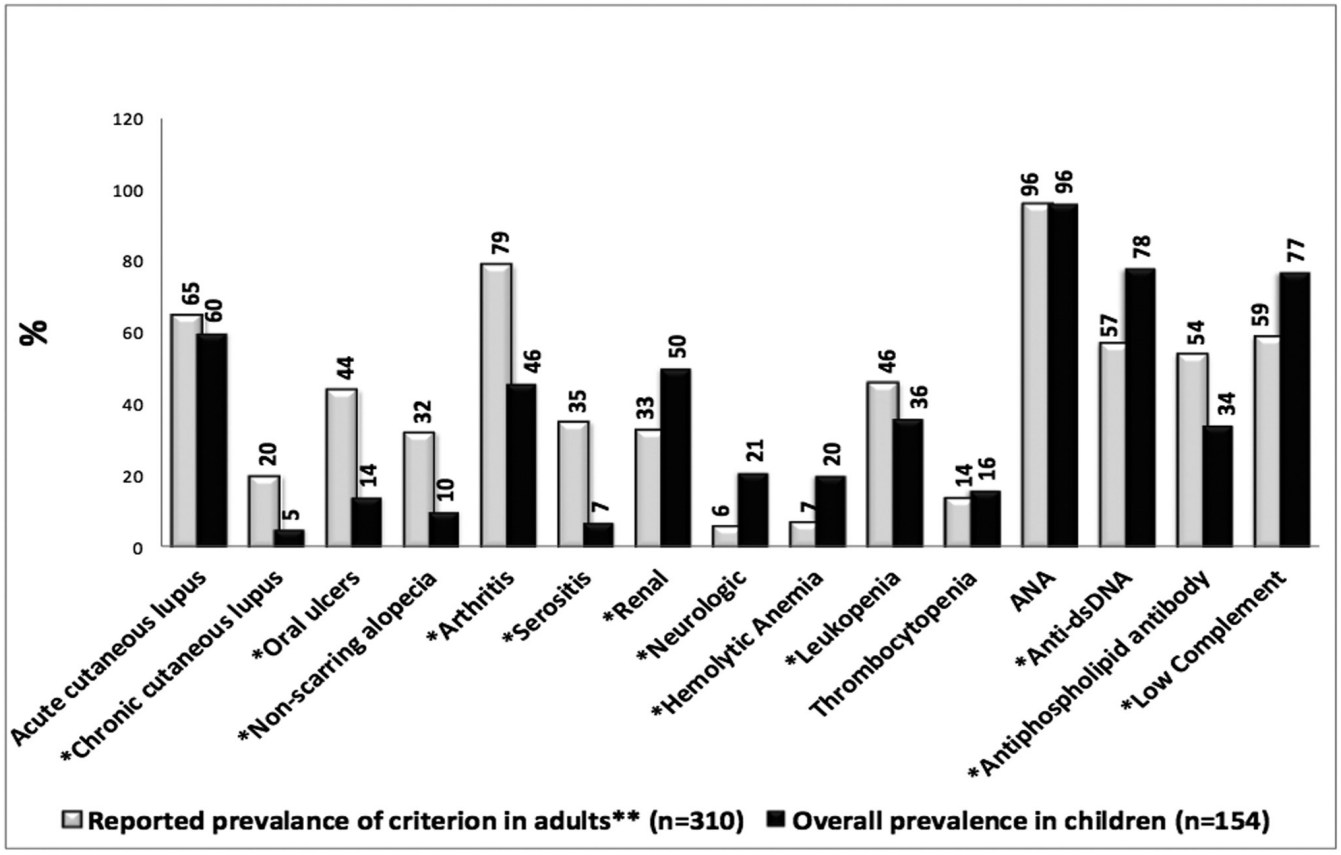

Fig. 2. Prevalence of each SLICC criterion at our study and in adult patients. *$p<0.05$. Petri M. *et al*. 2012 (3).

the performance regarding skin features in children. Discoid rash is rare in children; however, they may present with skin features described in the new SLICC criteria such as hypertrophic (verrucous) lupus, chillblains lupus, mucosal lupus – included among the chronic cutaneous changes. On the other hand, the expanded spectrum jeopardises the specificity, since JDM patients may fit in the description.

In the SLICC criteria, oral ulcers definition was changed to "in the absence of other causes, such as vasculitis, Behçet's disease, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods". The ACR criteria do not incorporate this restriction, which led to the misclassification of one of our Behçet patients as SLE. Furthermore, in the SLICC criteria "arthritis" is defined as "tenderness in 2 or more joints and thirty minutes or more of morning stiffness", which may increase the sensitivity of the arthritis criterion.

In the ACR criteria, "serositis (especially pleural effusion)" has low specificity because there are many causes for this feature. Pleural effusion may accompany several non-lupus renal diseases (including HUS), which occurred in some patients in our cohort. The SLICC group has revised the "serositis" item as "in the absence of other causes, such as infection, uraemia, and Dressler's pericarditis", in the hope of achieving a better performance.

In the SLICC criteria, the haematologic criterion is split into three items: haemolytic anaemia, leukopenia and thrombocytopenia. Thus any HUS patient automatically has 2 of these clinical features. In fact, 4 of our 5 HUS patients with haemolytic anaemia, thrombocytopenia, low C3 or C4, and proteinuria were falsely classified as SLE with the new SLICC criteria. In practice this weakness of the criteria may pose a problem in the differentiation of a patient with HUS *versus* renal microangiopathy related to antiphospholipid syndrome in lupus.

The SLICC group has revised the immunologic criteria as well. ANA, anti dsDNA, anti Sm, antiphospholipid antibody, low complement and direct Coombs test all account for an individual criterion. The low complement level may lead to loss of specificity in diseases such as HUS or acute post streptococcal GN.

One of the major changes in SLICC criteria is that "Biopsy confirmed nephritis compatible with SLE according to the International Society of Nephrology/ Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis in the presence of ANA or anti-dsDNA antibodies" is classified as definite SLE. As a result of this change, patients with renal involvement consistent with SLE nephritis and positive autoantibodies who lack 4 criteria can be classified as SLE. Some of our lupus patients with nephritis who did not meet the ACR criteria fulfilled the SLICC criteria.

Our study has certain limitations. It was a retrospective study and therefore the data was obtained from the patient charts. There is a possible referral bias especially for the controls in especially the pure rheumatology and nephrology centres. We have tried to overcome this by also analysing the combined results. Recently, Livingston *et al*. compared the features of patients with childhood-onset and adult-onset SLE in 2 metaanalyses. The first one (4) compared the clinical manifestations and found that fever, some hematological abnormalities (such as haemolytic anaemia and thrombocytopenia), lymphadenopathy, CNS and renal disease were more common in childhood SLE, whereas Raynaud's phenomenon, pleuritis, and sicca syndrome were more common in adult SLE. Since renal and CNS involvements are regarded as severe manifestations of SLE, this finding supports the notion that this disease has a more severe course in children (5, 6). In the second meta-analysis (5), antibody profiles, disease activity and damage scores were compared. Positive anti-dsDNA antibody and IgG/IgM anticardiolipin antibody and higher disease activity scores were more common in childhood SLE, whereas disease damage and the frequency of rheumatoid factor positivity were greater in adult SLE. When we compared the results obtained in our sample of childhood SLE patients with those reported by Petri et al in patients with adult-onset SLE, findings were similar, although not all differences were statistically significant (Fig. 2) (Suppl. Table).

In summary, in our patients with childhood SLE the SLICC criteria showed better sensitivity and led to fewer misclassifications, but were less specific than the ACR criteria. Our results underscore the need for an adaptation of existing classification criteria to increase their performance in children and adolescents with SLE.

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