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Incidence of Systemic Lupus Erythematosus in a Population Based Cohort using Revised 1997 American College of Rheumatology and the 2012 Systemic Lupus International Collaborating Clinic Classification Criteria

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Abstract

In 2012, the Systemic Lupus International Collaborating Clinic (SLICC) group published a new set of classification criteria for systemic lupus erythematosus (SLE). Studies applying these criteria to real life scenarios have found either equal or greater sensitivity and equal or lower specificity to the 1997 ACR classification criteria (ACR 97). Nonetheless, there are no studies that have used the SLICC 12 criteria to investigate the incidence of lupus. We utilized the resource of the Rochester Epidemiology Project to identify incident cases of SLE in Olmsted County, Minnesota from 1993-2005 who fulfilled the ACR 97 or SLICC 12 criteria. A total of 58 patients met criteria by SLICC 12 and 44 patients met criteria by ACR 97. The adjusted incidence of 4.9 per 100,000 person-years by SLICC 12 was higher than that by ACR 97 (3.7 per 100,000 person-years, $p=0.04$). The median duration from the appearance of first criteria to fulfillment of the criteria was shorter for the SLICC 12 than for ACR 97 (3.9 months vs 8.1 months). The higher incidence by SLICC 12 criteria came primarily from the ability to classify patients with renal-limited disease, the expansion of the immunologic criteria and the expansion of neurologic criteria.

Keywords

Systemic lupus erythematosus; Epidemiology; Classification criteria

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with an estimated annual incidence of 1 to 10 per 100,000 and a prevalence of 5.8 to 130 per 100,000.¹⁻⁵ Disease manifestations are heterogeneous and many classification criteria have been proposed to identify patients for clinical research studies. The most widely used American College of Rheumatology (ACR) criteria were first published in 1971 and modified in 1982.^{6, 7} In 1997, Hochberg et al, in a letter to Arthritis and Rheumatism, suggested modernizing the criteria by removing the lupus erythematosus (LE) cell and replacing it with lupus anticoagulant and anticardiolipin antibodies which were first validated by the Systemic Lupus International Collaborating Clinic (SLICC) group in 2012.^{8, 9}

Although the ACR criteria are simple to use, there are many problems associated with them such as “double-counting” of photosensitivity and malar rash, exclusion of isolated lupus nephritis, omission of several immunologic tests including hypocomplementemia and anti-beta-2-glycoprotein (β -2-GP) I antibodies, and failure to capture a broad array of important neurological manifestations of lupus. Consequently, the patients recruited in clinical research studies according to the ACR criteria might not truly represent the complete spectrum of disease. Clough et al. proposed weighted criteria that were subsequently modified by Costenbader et al. as Boston Weighted criteria.^{10, 11} These criteria were more sensitive than the 1982 ACR classification criteria but had a lower specificity.¹² Because of the complexity of the calculation, the weighted criteria have not been used extensively.

In 2012, the SLICC group published a new set of classification criteria based on the study of 702 expert-rated patient scenarios.⁹ Eleven clinical and six immunologic criteria were identified and a patient had to meet at least four criteria with at least one clinical and one immunologic criteria. Some of the differences from the 1997 ACR (ACR 97) classification criteria included the addition of patients with isolated lupus nephritis as a stand-alone criterion, the expansion of cutaneous lupus manifestations, the addition of non-scarring alopecia and the inclusion of peripheral neuropathy, myelitis, mononeuritis multiplex and acute confusional state as neurologic criteria. The hematologic criteria were separated into individual parts and the arthritis and renal criteria were modified. The immunologic criteria that were combined together in the ACR 97 criteria were also separated. In the derivation set, the 2012 SLICC (SLICC 12) classification criteria had greater sensitivity but equal specificity to the ACR 97 criteria. However, in the validation set, the SLICC 12 criteria had a greater sensitivity (97% versus 83%; $P < 0.0001$) but a lower specificity (84% versus 96%; $P < 0.0001$) than the ACR 97 criteria. Studies applying these criteria to real life scenarios have found either equal or greater sensitivity and equal or lower specificity.¹³⁻¹⁸ Nonetheless, there are no studies that have used the SLICC 12 criteria to investigate the incidence of lupus.

The population of Olmsted County, Minnesota, provides a unique setting to address the epidemiology of SLE owing to resources of the Rochester Epidemiology Project (REP).^{19, 20} The REP provides access to the linked inpatient and outpatient medical records of Olmsted County residents for over five decades from all local providers (Mayo Clinic,

Olmsted medical center, local nursing homes and few private practitioners). Using the 1982 ACR classification criteria, we have previously reported the incidence of SLE at 3.1 per 100,000 from 1950 to 1992 and 2.9 per 100,000 from 1993 to 2005.^{21, 22} In this study, we compared the incidence of SLE from 1993-2005 using the ACR 97 criteria and the SLICC 12 criteria.

Material and Methods

Case definition

Cases were identified by searching medical records between January 1, 1993 and December 31, 2005 using the ICD-9 codes for SLE, lupus nephritis, central nervous system (CNS) lupus, cutaneous lupus and other medical index codes related to lupus. Medical records of these potential cases (n=438) were then comprehensively reviewed. A standardized data extraction form was utilized to record the following information: age at fulfillment of classification criteria, sex, race (White, Black, Native Hawaiian/other Pacific islander, Asian, native American and other), ethnicity (Hispanic and non-Hispanic), presence or absence of each of the ACR 97 criteria and the SLICC 12 criteria, date of the first appearance of each criteria, duration of follow up, status at last follow up (death or alive) and cause of death. An incident SLE case was defined as an individual age ≥ 18 years who had been a resident of Olmsted County, Minnesota for at least one year prior to diagnosis and who fulfilled either the ACR 97 criteria (at least four of eleven criteria) or the SLICC 12 criteria (at least four of the 17 criteria, with at least one clinical criteria and one laboratory criteria, or had biopsy-proven lupus nephritis with positive antinuclear antibody [ANA] or anti-double-stranded-deoxyribonucleic acid [ds-DNA]) between January 1, 1993 and December 31, 2005. The incidence date was the date of fulfillment of the fourth ACR or SLICC criteria. Pediatric patients with SLE, patients with drug-induced lupus, isolated cutaneous lupus, and overlap connective tissue diseases were excluded.

The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Statistical analyses

Descriptive statistics (means, percentages, etc.) were used to summarize the data. Comparisons of individual criteria between White and non-white groups were performed using Fisher's exact test. Age- and sex-specific incidence rates for SLE using either the ACR 97 criteria or the SLICC 12 criteria were estimated assuming the population of Olmsted County aged ≥ 18 years from 1993–2005 to be at risk. The age- and sex-specific denominators for each year were estimated from decennial census data. Incidence per 100,000 population was age and sex adjusted to the 2000 United States (US) white population. Poisson regression models adjusted for age and sex were used to examine potential calendar year trends in incidence rates over the time period of the study. Comparisons of incidence between cohorts were performed using Poisson methods. The comparison of time from first criteria to fulfillment of criteria among the patients who met both criteria was performed using a paired sign test. Analyses were performed using SAS

version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Our search strategy yielded 436 potential cases. The medical records of the 436 individuals were reviewed. 379 of these individuals were excluded for the following reasons: 17 denied authorization of their medical records for research, 105 cutaneous lupus erythematosus only, 2 drug induced lupus, 1 did not have sufficient details of cutaneous lesion, and 25 other rheumatic illnesses (5 undifferentiated connective tissue disease, 6 Sjögren's syndrome, 2 scleroderma, 1 overlap connective tissue disease, 6 mixed connective tissue disease, 1 polymyositis, 2 rheumatoid arthritis, 1 antiphospholipid antibody syndrome, and 1 psoriatic arthritis). 85 cases fulfilled the classification criteria for SLE but were not included as they were not Olmsted county residents (40) or they were prevalent cases (42) or they met criteria prior to 18 years of age (3). 143 cases had diagnostic codes related lupus but medical record review did not reveal any evidence of SLE or other rheumatic illnesses.

Therefore, there were 44 incident SLE cases (41 women, 3 men) who met the ACR 97 criteria and 58 incident cases (49 women, 9 men) who met the SLICC 12 criteria. All 44 cases who met ACR 97 criteria also met SLICC 12 criteria, while 14 cases met SLICC 12 criteria only. The cohort was predominantly white (84% white, 5% black, 5% Asian and 2% native American in the 58 incident cases who met the SLICC 12 criteria and 84% white, 7% black, 5% Asian and 2% native American in 44 incident cases who met the ACR 97 criteria). All patients were diagnosed as SLE or possible SLE by their treating medical providers. The mean ($\pm$ SD) age at SLE incidence date of 44.6 ± 17.8 years in the SLICC 12 cohort was not significantly different than 43.0 ± 16.8 years in the ACR 97 cohort ($p=0.21$). The overall adjusted incidence rate by the SLICC 12 criteria (4.9 per 100,000 person-years (p-y); 95% CI, 3.6 – 6.2 per 100,000 p-y) was significantly higher than that by the ACR 97 criteria (3.7 per 100,000 p-y; 95% CI 2.6 – 4.8 per 100,000 p-y; $p=0.044$). There was no evidence of a calendar year trend in incidence of SLE by either SLICC 12 ($p=0.34$) or ACR 1997 ($p=0.87$). Figure 1 shows the age and sex-adjusted incidence rates using the ACR 97 and the SLICC 12 criteria. Subgroup analysis according to sex showed that the adjusted incidence rates based on the SLICC 12 criteria were higher in both females and males compared with the ACR 97 criteria but this did not reach statistical significance ($p=0.06$ for females and $p=0.08$ for males). Female predominance was seen in both cohorts. However, the percentage of males was significantly higher in the SLICC 12 cohort compared with the ACR 97 cohort (16% versus 7%, respectively; $p=0.001$). The racial background of those who fulfilled only SLICC 12 criteria was similar to the complete SLICC 12 cohort (86% white and 7% black) even though the cohort was small and the comparison should be interpreted with caution.

Among the 44 incident SLE cases who met both ACR 97 and SLICC 12 criteria, the median duration from the appearance of the first criteria to fulfillment of SLE classification was shorter for the SLICC 12 criteria than the ACR 97 criteria (median 3.9 vs 8.1 months, respectively; range for both 0-302 months, $p=0.016$).

The median numbers of criteria present at time of incidence date were five in both ACR 97 (range 4-7) and the SLICC 12 group (range 2-8). Inflammatory synovitis (57%), followed by acute cutaneous lupus (52%), lymphopenia/leukopenia (36%) and thrombocytopenia (33%) were the most frequently observed SLICC clinical criteria while positive ANA (100%), followed by positive ds-DNA (61%) and hypocomplementemia (43% for C3, 51% for C4 and 30% for total complement) were the most common immunologic criteria. The frequency of individual criteria is shown in Table 1. Overall, the frequencies of individual criteria appeared to be similar between the white and non-white subgroups even though the renal criterion was relatively more frequent in the non-white subgroup ($p=0.11$ for SLICC and $p=0.025$ for ACR 97). Among the 14 SLE cases who fulfilled only the SLICC 12 criteria, three were classified based on renal biopsy and positive ANA or anti-ds-DNA while six cases did so based on the expansion of the immunologic criteria, particularly the inclusion of hypocomplementemia. Two cases were included on basis of neurologic involvement (peripheral neuropathy). The addition of non-scarring alopecia allowed two more cases to fulfill the SLICC 12, but not the ACR 97 criteria, while the revision of hematologic criteria, by decreasing the requirement of cytopenia from at least twice to once, led to the inclusion of one more case by SLICC 12 criteria. The clinical characteristics of these 14 SLE cases are described in Table 2.

Discussion

Our study demonstrated a higher incidence of SLE using the SLICC12 classification criteria compared to the ACR 97 classification criteria. The SLICC 12 criteria were useful in identifying patients with isolated renal or neurologic abnormalities who would not have otherwise been classified as lupus. The inclusion of serologic criteria, particularly hypocomplementemia, also helped in identifying additional cases. We also found an earlier date of fulfillment of classification criteria using SLICC criteria. It should be emphasized that these are classification criteria and are not intended to be used as diagnostic criteria in clinical practice. The incidence rates of SLE in this study are comparable to previously reported incidence rates in Caucasians that ranged from 0.7 to 5.0 per 100,000 p-y.²³

The strengths of this study include a comprehensive record-linkage system that allows capturing nearly all the cases of SLE in the community, unlike referral-based cohort study that could potentially capture only more severe cases. The majority of patients with suspected SLE in the community are assessed by a few rheumatologists and dermatologists specialized in lupus, which would make the clinical observations more uniform and would strengthen the accuracy of the fulfillment of cutaneous criteria, as some of the SLICC 12 cutaneous criteria require a dermatologist's interpretation. In addition, we manually reviewed the complete medical records (both inpatient and outpatient) from all medical providers in the community.

To date, four adult studies¹³⁻¹⁶ and two pediatric studies^{17, 18} from different regions (North America, Central America, South America and Europe) have validated the SLICC 12 criteria and are summarized in Table 3. Most of the studies found a higher sensitivity of the SLICC 12 criteria compared to the ACR 97 criteria.^{13, 16-18} The specificity was evaluated in four studies.¹⁵⁻¹⁸ The specificity of SLICC 12 criteria was similar to the ACR 97 criteria in two

studies^{15, 18} but was lower in the other two studies.^{16, 17} The expansion of immunologic criteria in the SLICC classification was responsible for the loss of specificity in the study by Ighe et al.¹⁶ For instance, patients with isolated antiphospholipid antibody syndrome (without SLE) were classified as SLE since these patients presented with thrombocytopenia, hypocomplementemia and other lupus associated antibodies. The main reason for loss of specificity in the pediatric study¹⁷ was the fulfillment of SLICC criteria by patients with hemolytic uremic syndrome and juvenile dermatomyositis.

Our study found that the SLICC 12 criteria allowed a shorter duration from the appearance of first criteria to fulfillment of the criteria requirement. This finding is different from a previous study by Pons-Estel et al.¹⁴ who found a higher percentage of patients who fulfilled the ACR 97 criteria before the SLICC 12 in GLADEL (Grupo Latino Americano De Estudio del Lupus) cohort than in LUMINA (LUPus in MINorities: NAture versus Nurture, 18.2% versus 12.5%). Nonetheless, it should be noted that fulfillment of the ACR 97 was a pre-requisite for inclusion to LUMINA cohort.

We acknowledge the limitations of this study including the small number of incident cases and the retrospective nature of data collection whereby all manifestations noted in the SLICC 12 criteria were not obtained systematically. However, the amount of missing data was relatively small with the exception of Coomb's test (in absence of hemolytic anemia), which was performed in only three patients, and lupus anticoagulant, which was performed in only seven patients. While obtaining these parameters in all patients could have theoretically increased the incidence of SLE by SLICC 12, it is not common in clinical practice to routinely obtain these tests for patients presenting predominantly with mucocutaneous manifestations and inflammatory arthritis. Our results might not be generalizable as SLE susceptibility and disease phenotypes are different across various racial and sociodemographic groups and the Olmsted County population is predominantly white. Therefore, the clinical spectrum of SLE may not be fully represented in this cohort. Moreover, the unique characteristics of the healthcare system in Olmsted County may result in more effective screening and diagnosis practices.

Conclusion

In conclusion, the incidence of SLE using the SLICC 12 criteria was higher than when using the ACR 97 criteria in identifying patients in our population. The SLICC 12 criteria also allowed a shorter duration of time from the appearance of the first criteria to SLE classification. Larger studies in a more diverse population are needed to validate our findings.

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Figure 1.

Incidence rate of SLE by age group; Solid line with square: incidence rate in male by SLICC; Solid line with circle: incidence rate in female by SLICC; Dotted line with square: incidence rate in male by ACR; Dotted line with circle: incidence rate in female by ACR 97

Table 1
Frequency of individual criteria

2012 SLICC criteria (n=57)		Revised 1997 ACR criteria (n=43)	
Clinical criteria	Numbers positive/ numbers total patients (%)	Clinical criteria	Numbers positive/ numbers total patients (%)
1. Acute cutaneous lupus	30/58 (52)	1. Malar rash	13/44 (30)
2. Chronic cutaneous lupus	5/58 (9)	2. Discoid rash	3/44 (7)
3. Oral or nasal ulcers	12/58 (21)	3. Photosensitivity rash	22/44 (50)
4. Non-scarring alopecia	7/58 (12)	4. Oral ulcer	12/44 (27)
5. Synovitis	33/58 (57)	5. Arthritis	30/44 (68)
6. Serositis	13/58 (22)	6. Serositis	13/44 (30)
7. Renal	17/58 (29)	7. Renal	14/44 (32)
8. Neurologic	5/58 (9)	8. Neurologic	2/44 (5)
a. Seizure	3/58 (5)	a. Seizure	2/44 (5)
b. Psychosis	1/58 (2)	b. Psychosis	0/44 (0)
c. Mononeuritis multiplex	0/58 (0)		
d. Myelitis	0/58 (0)		
e. Peripheral or cranial neuropathy	2/58 (3)		
f. Acute confusional state	0/58 (0)		
9. Hemolytic anemia	5/58 (9)	9. Hematologic	26/44 (59)
		a. Hemolytic anemia	4/44 (9)
		b. Leukopenia	18/44 (41)
		c. Lymphopenia	10/44 (23)
		d. Thrombocytopenia	15/44 (34)
10. Leukopenia or lymphopenia	21/58 (36)		
11. Thrombocytopenia	19/58 (33)		
Laboratory criteria	Numbers positive/ numbers tested (%)	Laboratory criteria	Numbers positive/ numbers tested (%)
12. ANA	58/58 (100)	10. ANA	44/44 (100)
13. Anti-dsDNA	35/57 (61)	11. Immunologic	33/44 (75)
		a. Anti-dsDNA	29/44 (66)
		b. Anti-Sm	5/30 (17)
		c. Antiphospholipid antibodies	10/29 (34)
14. Anti-Sm	7/39 (18)		

2012 SLICC criteria (n=57)		Revised 1997 ACR criteria (n=43)	
Clinical criteria	Numbers positive/ numbers total patients (%)	Clinical criteria	Numbers positive/ numbers total patients (%)
15. Antiphospholipid antibodies	10/33 (30)		
a. Lupus anticoagulant	1/7 (14)		
b. False positive RPR	2/13 (15)		
c. Anticardiolipin antibody	4/12 (33)		
d. Anti-beta 2-glycoprotein I	0/7 (0)		
16. Low complement	36/55 (65)		
a. Low C3	23/54 (43)		
b. Low C4	27/53 (51)		
c. Low CH50	14/46 (30)		
17. Direct Coombs' test in the absence of hemolytic anemia	2/2 (100)		

Table 2
Characteristics of 14 patients who fulfilled the 2012 SLICC criteria only

Case Number	Sex	Race	Age (years)	SLICC Criteria fulfilled
Case 1	M	African-American	32	Seizure, positive ANA, anti-Sm and low C3
Case 2	M	White	40	Hemolytic anemia, thrombocytopenia, positive ANA, anti-dsDNA and low C4
Case 3	M	White	46	Peripheral neuropathy, lymphopenia, leukopenia, positive ANA and low C3
Case 4	M	White	35	Biopsy-proven lupus nephritis and positive ANA
Case 5	M	White	85	Synovitis, lymphopenia, thrombocytopenia and positive ANA
Case 6	M	White	76	Synovitis, peripheral neuropathy, positive ANA and anti-dsDNA
Case 7	F	White	72	Biopsy-proven lupus nephritis, positive ANA, anti-dsDNA and low C4
Case 8	F	White	33	Biopsy-proven lupus nephritis, positive ANA, and anti-dsDNA
Case 9	F	White	21	Lymphopenia, leukopenia, positive ANA, anti-dsDNA, low C3 and low C4
Case 10	F	Information not available	27	Acute cutaneous lupus, positive ANA, anti-dsDNA, low C3 and low C4
Case 11	F	White	51	Acute cutaneous lupus, non-scarring alopecia, positive ANA and low C3
Case 12	F	White	66	Chronic cutaneous lupus, thrombocytopenia, positive ANA, anti-dsDNA, low C3 and low C4
Case 13	F	White	38	Acute cutaneous lupus, oral ulcers, non-scarring alopecia, positive ANA and low C4
Case 14	F	White	36	Chronic cutaneous lupus, non-scarring alopecia, positive ANA, anti-Sm and low C4

ANA indicates antinuclear antibody; Anti-Sm, Anti-Smith antibody; anti-dsDNA, anti-double-stranded deoxyribonucleic acid antibody; C3, complement component 3; C4, complement component 4; RPR, rapid plasma reagin

Table 3
Studies evaluating the performance of the SLICC 12 versus ACR and Boston Weighted Criteria

Study Number of patients	Study population	Sensitivity	Specificity (%)	Comments
Ines et al. [13] N= 2055	Patients of Portuguese and Spanish national registers who were recruited based on the clinical diagnosis of SLE.	SLICC 12: 93% ACR 97: 86%	N.A.	<ul style="list-style-type: none"> - Spanish registry - Excluded patients who had less than or equal to two ACR 97 criteria - Subgroup analysis found that the difference was largest in patients with disease duration of less than five years
Pons-Estel et al. [14] LUMINA, N=640 GLADEL, N=1480	LUMINA cohort were recruited based on the ACR 97 criteria while GLADEL cohort were recruited based on physician diagnosis. The LUMINA cohort was conducted in Alabama and Texas while GLADEL cohort was conducted in nine Latin American countries.	<p>LUMINA:</p> <ul style="list-style-type: none"> - 51.3 % same time - 12.5% SLICC 12 before ACR 97 - 36.2% ACR 97 before SLICC 12 <p>GLADEL:</p> <ul style="list-style-type: none"> - 60.8 % same time - 18.2% SLICC 12 before ACR 97 - 21.1% ACR 97 before 	N.A.	<ul style="list-style-type: none"> - LUMINA: 2.8% did not meet SLICC criteria despite mean of 1.2 years from the time when ACR criteria were met - SLICC 12 criteria components were not systematically collected / performed.

Study Number of patients	Study population	Sensitivity	Specificity (%)	Comments
		SLICC 12		
Amezcu-Guerra et al. [15] Cases, N=100, Controls, N=100	Retrospective chart review study form a university hospital in Mexico. Clinical diagnosis was used as gold standard for the diagnosis of SLE. Patients without clinical diagnosis of SLE were used as control.	SLICC 12: 92% ACR 97: 97%	SLICC 12: 99% ACR 97: 99%	- PPV: SLICC 12 98.8%, ACR 97 99.0 % - NPV: SLICC 12 92.5%, ACR 97 97.1%
Ighe et al. [16] Cases, N=243, Controls, N=55	Patients of Swedish KLURING register who were recruited based on the clinical diagnosis of SLE plus at least two organ involvements (Fries principle) and /or fulfillment of ACR 82. Patients without clinical diagnosis of SLE were used as control.	SLICC 12: 94% ACR 97: 90%	SLICC 12: 74% ACR 97: 92%	
Sag et al. [17] Cases (juvenile SLE), N=154 Controls, N=123	Retrospective chart review study form three pediatric lupus centers in United Kingdom, Italy and Turkey. Clinical diagnosis was used as gold standard for the diagnosis of SLE. Patients without clinical diagnosis of SLE were used as control.	SLICC 12: 99% ACR 97: 77%	SLICC 12: 85% ACR 97: 93%	
Fonseca et al. [18] Cases (juvenile SLE), N=81 Controls, N=92	Retrospective chart review study form a university hospital in Brazil. Clinical diagnosis was used as gold standard for the diagnosis of SLE. Patients without clinical diagnosis of SLE were used as control.	First Visit BW: 82% ACR 97: 58% SLICC 12: 82% First year BW: 91% ACR 97: 93% SLICC 12: 96%	First Visit BW: 83% ACR 97: 93% SLICC 12: 94% First year BW: 93% ACR 97: 91% SLICC 12: 88%	First Visit - PPV: BW 80.5%, ACR 97 88.5% and SLICC 12 91.8% - NPV: BW 83.5%, ACR 97 71.1% and SLICC 12 86.1%

LUMINA indicates Lupus in Minorities: NAture versus Nurture; GLADEL, Grupo Latino Americano De Estudio del Lupus or Latin American Group for the Study of Lupus; N.A., not available; SLICC, Systemic Lupus International Collaborating Clinics; ACR, American College of Rheumatology; BW, Boston weighted; PPV, positive predictive value; NPV, negative predictive value