American College of Rheumatology Criteria at Inception, and Accrual over 5 Years in the SLICC Inception Cohort

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ABSTRACT. ***Objective.*** To determine the frequency of each American College of Rheumatology (ACR) criterion met at time of enrollment, and the increase in each of the criteria over 5 years.

Methods. In 2000 the Systemic Lupus International Collaborating Clinics (SLICC) recruited an international inception cohort of patients with systemic lupus erythematosus (SLE; ≥ 4 ACR criteria) who were followed at yearly intervals according to a standard protocol. Descriptive statistics were used to assess the total and cumulative number of ACR criteria met at each visit. Regression models were done to compare the increase of individual and cumulative criteria as a function of race/ethnicity group, and sex.

Results. In all, 768 patients have been followed for a minimum of 5 years. Overall, 59.1% of the patients had an increase in the number of ACR criteria they met over the 5-year period. The mean number of ACR criteria met at enrollment was 5.04 ± 1.13 and at year 5 was 6.03 ± 1.42. At enrollment, nonwhite patients had a higher number of ACR criteria (5.19 ± 1.23) than white patients. The total number of criteria increased in both white and nonwhite ethnicities, but increased more among whites. Males had a slightly lower number of criteria at enrollment compared to females and males accrued fewer criteria at 5 years.

Conclusion. In this international inception cohort of SLE patients with at least 4 ACR criteria at entry, there was an accumulation of ACR criteria over the following 5 years. The distribution of criteria both at inception and over 5 years is affected by sex and ethnicity. (First Release April 1 2014; J Rheumatol 2014;41:875–80; doi:10.3899/jrheum.130704)

Key Indexing Terms:
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In longterm observational studies and in therapeutic trials, patients with systemic lupus erythematosus (SLE) are often recruited if they have 4 or more classification criteria[1]. Heinlen, *et al*[2] have shown that symptoms associated with the revised American College of Rheumatology (ACR) criteria for the classifications of SLE are commonly present before the diagnosis of SLE. Alarcon, *et al*[3] examined the accrual of SLE criteria in a multiethnic cohort, prior to the accrual of 4 criteria. They found through a Cox-regression multivariable model that Hispanic ethnicity (from Texas) and HLA-DRB1*0301 were predictors of shorter time to criteria accrual, whereas older age and married/living together were associated with longer time to criteria accrual. However, the rate of accrual of additional revised ACR criteria after the diagnosis of SLE is unknown. To address this question in an optimal manner requires a group of patients with 4 ACR criteria followed at intervals from inception. The aims of our study were to determine the frequency of occurrence of each ACR criterion at enrollment, the mean number of criteria in each of the first 5 years of disease, and the increase in the number of each of the criteria over 5 years.

MATERIALS AND METHODS

Setting and patient selection. The Systemic Lupus International Collaborating Clinics (SLICC) group assembled in 1991 and consists of investigators interested in the study of outcomes in SLE[4]. In 2000, the SLICC group developed an international inception cohort of patients with SLE recruited within 15 months of diagnosis (presence of at least 4 ACR criteria) and followed at yearly intervals according to a standard protocol. For this study, 24 SLICC centers from 10 countries in North America, Europe, and Asia were included.

Patient assessment. A standard protocol, which includes demographics and clinical and laboratory features of SLE, was used at recruitment and at yearly intervals. Each ACR criterion was ascertained at each visit except for the antinuclear antibody test, which was often not done annually because of its limited usefulness once the diagnosis of SLE was established.

Statistical analysis. Time 0 was considered the time of enrollment into the cohort. For each of the yearly visits, the cumulative percentage of patients who have ever had each of the ACR criteria was evaluated, as well as the total number of ACR criteria ever present. Descriptive statistics were used to assess the cumulative and total number of ACR criteria at each visit. A comparison between patients who had an increased number of ACR criteria to those who did not was performed; comparatives included demographics and disease-related and therapy variables. A multivariate analysis was then performed including all 11 individual ACR criteria at enrollment to determine which criteria were more likely to be associated with a further increase in total number of ACR criteria by the 5-year timepoint. The accumulation of ACR criteria was evaluated and plotted against year since entry into the SLICC Registry for Atherosclerosis cohort. Logistic regression adjusting for repeated measures and using autoregressive correlation matrix (generalized estimating equation) were done to compare the increase, over the 5 years of followup, in the cumulative presence of ACR criteria. This was done separately for each individual criterion. Regression models were done for sex and then for ethnicity with no other variable included in the model. Then, regression models were done to compare the increase as a function of race/ethnicity group and sex correcting for disease activity and treatment as well as marital status and education level. The same approach was used to compare the total number of ACR criteria using linear regression models adjusting for repeated measures.

RESULTS

Between 2000 and 2012, 1845 patients with SLE were recruited. By definition all patients had 4 or more ACR classification criteria at entry into the cohort. There were 993 patients who had not reached a 5-year followup, and 84 missed their fifth-year appointment. This study population comprised 768 patients who had been followed for a minimum of 5 years. The patient population was 681 females (88.7%); 387 were white (50.4%), 110 African (14.3%), 119 Asian (15.5%), 128 Hispanic (16.7%), and 24 other race/ethnicities (3.1%). The mean (± SD) age at inclusion into the SLICC cohort was 35.0 ± 13.3 years, and the mean disease duration was 5.4 ± 4.1 months. The mean Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) was 5.6 ± 5.6. Three hundred nine patients had disease duration of ≥ 6 months at the time of study enrollment. A comparison to the 768 included in the study to those not included in the study revealed that there was a lower frequency of discoid rash (10.8% vs 14.1%, respectively, $p = 0.04$), and a higher frequency of hematologic disorder (66.8% vs 60.4%, $p = 0.006$) at enrollment. Of the 768 patients, 349 were married (45.4%) or in common-law relationships, and 453 had postsecondary education (59.2%; Table 1).

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Table 1. Comparison at enrollment of patients who increased their total number of American College of Rheumatology (ACR) criteria to those who did not. Except for p values, data are n (%) unless otherwise indicated.

At Enrollment	Total Group, n = 768	Patients Who Increased Total No. ACR Criteria in 1st 5 yrs, n = 454	Patients Who Did Not Increase Total No. ACR Criteria in 1st 5 yrs, n = 314	p
Female	681 (88.7)	412 (90.8)	269 (85.7)	0.03
Marital status (married/common law)	349 (45.4)	203 (44.7)	146 (46.5)	0.66
Ethnicity				
Asian	119 (15.5)	69 (15.2)	50 (15.9)	
Black	110 (14.3)	69 (15.2)	41 (13.1)	
White	387 (50.4)	243 (53.5)	144 (45.9)	0.04*
Hispanic	128 (16.7)	57 (12.6)	71 (22.6)	
Other	24 (2.1)	16 (3.5)	8 (2.6)	
Education > high school	453 (59.2)	272 (60.0)	181 (58.0)	0.57
SLEDAI-2K, mean ± SD	5.6 ± 5.6	5.63 ± 5.62	5.50 ± 5.46	0.76
Age, yrs, mean ± SD	35.0 ± 13.3	34.2 ± 13.0	36.1 ± 13.7	0.05
Disease duration, mos	5.4 ± 4.1	5.2 ± 4.0	5.8 ± 4.3	0.07
Taking steroids at enrollment	531 (69.1)	306 (67.4)	225 (71.7)	0.21
Taking antimalarials at enrollment	486 (63.3)	282 (62.1)	204 (65.2)	0.39
Taking immunosuppressives at enrollment	308 (40.1)	171 (37.7)	137 (43.6)	0.1
Malar rash	276 (35.9)	162 (35.7)	114 (36.3)	0.86
Discoid rash	83 (10.8)	50 (11.0)	33 (10.5)	0.83
Oral ulcers	294 (38.3)	172 (37.9)	122 (38.9)	0.77
Serositis	217 (28.3)	128 (28.2)	89 (28.3)	0.96
Arthritis	583 (75.9)	330 (72.7)	253 (80.6)	0.01
Photosensitivity	276 (35.9)	176 (38.8)	100 (31.9)	0.05
Renal disease	236 (30.7)	123 (27.1)	113 (36.0)	0.009
Neurological disorder	47 (6.1)	32 (7.1)	15 (4.8)	0.2
Hematological disorder	513 (66.8)	269 (59.3)	244 (77.7)	< 0.0001
Immunological disorder	610 (79.4)	353 (77.8)	257 (81.9)	0.17
Antinuclear antibodies	734 (95.6)	434 (95.6)	300 (95.5)	0.97
Total no. ACR criteria	5.04 ± 1.13	4.91 ± 1.03	5.22 ± 1.25	0.0003

* Comparing whites to all other ethnicities combined. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

ACR criteria at enrollment. The most frequent clinical criteria at enrollment were arthritis (75.9%), oral ulcers (38.3%), and malar rash and photosensitivity (each at 35.9%; Table 1). At enrollment only 30.7% met the renal disorder criterion (cellular casts or proteinuria > 0.5 g/dl) while only 6.1% met the neurologic disorder criterion (seizures or psychosis). The laboratory criteria were more prevalent, with antinuclear antibodies occurring in 95.6%, immunologic disorder (anti-dsDNA antibodies, anti-Smith antibodies, anticardiolipin antibodies, or positive lupus anticoagulant) in 79.4%, and hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia) in 66.8%. The mean number of ACR criteria at enrollment was 5.04 ± 1.13.

Accrual of ACR criteria over 5-year followup. Overall, 59.1% of the patients had an increase in the number of ACR criteria over the 5-year period, with an average increase of 1 criterion per patient.

A comparison of patients who had an increased number of ACR criteria to those who did not is presented in Table 1. Among the 454 patients who did have an increase, the mean increase was 1.7 ± 0.9 criteria per patient. A multivariate analysis was run comparing patients who accrued ACR criteria to those who did not, modeling for the 11 individual ACR criteria at enrollment. It revealed that patients with arthritis, renal disorder, and hematological disorder were less likely to increase the total number of ACR criteria over the 5 years [OR (95% CI) 0.57 (0.40, 0.82) for arthritis; 0.65 (0.47, 0.89) for renal disorder; 0.41 (0.30, 0.57) for hematologic disorder]. The yearly increase in ACR criteria accumulation is shown in Table 2. At 5 years the percentage of occurrence of each criterion increased, and the 3 most common clinical criteria at enrollment (arthritis, oral ulcers, and malar rash) continued to be the most prevalent. However, renal disorder increased to 43.5% and neurologic disorder to 10.2%. The mean number of criteria per patient increased over the 5 years to 6.03 ± 1.42.

Effect of sex. Analysis of the relationship between sex and each individual criterion revealed that males had a lower frequency of malar rash, oral ulcers, arthritis, and photosensitivity, and a higher incidence of renal and immunologic disorders. Males had a slightly lower number of criteria compared to females (Figure 1A).

Effect of race/ethnicity. At enrollment, nonwhite patients

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Table 2. Accumulation of American College of Rheumatology (ACR) criteria. In 454 (59.1%) patients, the total number of criteria increased in 5 years.

ACR Criteria	At Inception, n (%)	At 1 yr, n (%)	At 2 yrs, n (%)	At 3 yrs, n (%)	At 4 yrs, n (%)	At 5 yrs, n (%)
Malar rash	276 (35.9)	310 (40.4)	333 (43.4)	349 (45.4)	361 (47.0)	372 (48.4)
Discoid rash	83 (10.8)	94 (12.2)	105 (13.7)	123 (16.0)	130 (16.9)	137 (17.8)
Oral ulcers	294 (38.3)	328 (42.7)	367 (47.8)	384 (50.0)	397 (51.7)	412 (53.7)
Serositis	217 (28.3)	231 (30.1)	243 (31.6)	250 (32.6)	254 (33.1)	261 (34.0)
Arthritis	583 (75.9)	608 (79.2)	621 (80.9)	628 (81.7)	643 (83.7)	649 (84.5)
Photosensitivity	276 (35.9)	308 (40.1)	324 (42.2)	334 (43.5)	340 (44.3)	346 (45.1)
Renal disorder	236 (30.7)	266 (34.6)	294 (38.3)	311 (40.5)	322 (41.9)	334 (43.5)
Neurologic disorder	47 (6.1)	58 (7.6)	66 (8.6)	71 (9.2)	77 (10.0)	78 (10.2)
Hematologic disorder	513 (66.8)	566 (73.7)	599 (78.0)	610 (79.4)	621 (80.9)	630 (82.0)
Immunologic disorder	610 (79.4)	637 (82.9)	646 (84.1)	653 (85.0)	657 (85.6)	662 (86.2)
Antinuclear antibody	734 (95.6)	741 (96.5)	743 (96.7)	746 (97.1)	748 (97.4)	750 (97.7)
Total no. criteria, mean ± SD	5.04 ± 1.13	5.40 ± 1.26	5.65 ± 1.34	5.81 ± 1.37	5.92 ± 1.39	6.03 ± 1.42

had a higher number of ACR criteria (5.19 ± 1.23) than white patients (4.88 ± 1.02, p = 0.0001). The total number of criteria increased in both white and nonwhite ethnicities, but increased more among whites. However, at 5 years there was no statistically significant difference (5.95 ± 1.42, vs 6.11 ± 1.43, Figure 1B). At each annual assessment in nonwhite patients, renal disease, hematologic disorder, and immunologic disorder were more frequent, and photosensitivity was less frequent than in whites (data not shown). When individual ethnicities were considered, both white and black had 4.88 criteria at inception while Asians had 5.07 and Hispanics had 5.71. Hispanics had a significantly higher number of ACR criteria over the entire 5 years of followup compared to whites (p < 0.0001, Figure 1C).

Table 3 summarizes the relationship between race/ethnicity and the accrual of each criterion. Whites were used as the comparator group in the statistical tests. The analysis was adjusted for sex, age, SLEDAI-2K, steroids, antimalarials, and immunosuppressives. Asians had a lower frequency of accrual of arthritis, photosensitivity, and neurologic disorder, and were more likely to accrue hematologic and immunologic disorders. Blacks were found to have decreased accrual of malar rash, oral ulcers, and photosensitivity and increased accrual of discoid rash. Hispanics had increased accrual of arthritis and malar rash and lower frequency of photosensitivity and neurologic disorder.

DISCUSSION

The classification criteria for SLE were derived to ensure confidence that patients included in studies could be considered to have SLE by accepted standards[1]. Most therapeutic trials and longitudinal observational cohort and registry studies require the presence of 4 or more criteria for inclusion. Recently the SLICC group has developed an alternative set of classification criteria for SLE[5]. Unfortunately, appropriate information for applying these criteria in this cohort was not collected in a systematic fashion and therefore these criteria could not be tested in the current study.

Previous studies have addressed the accrual of ACR criteria prior to the diagnosis of SLE[2,3]. In our study we examined the accrual of criteria beyond 4 in a multinational multicenter inception cohort of patients already diagnosed with SLE. In the first 5 years after diagnosis, there is accumulation of each of the criteria in a small number of patients varying from 2.1% for antinuclear antibody to 12.5% for malar rash, 12.8% for renal disorder, and 15.2% for hematologic disorder. In a single-center inception cohort, 28% of the patients who did not have renal disorder at inception developed it over followup, the majority within the first 5 years[6]. This should alert the clinician to look for further manifestations of SLE beyond 4, particularly over the first 5 years. Patients who accrued additional criteria in the first 5 years were less likely to have arthritis, renal, or hematological criteria at inception, and were more likely to be older and receiving antimalarial therapy. These clinical criteria are among the most commonly present at inception. Older-age SLE has been shown to have a lower frequency of malar rash, arthritis, and nephropathy; and accrued those manifestations at followup less frequently compared to younger patients[7]. That antimalarials are protective against the accrual of manifestations is in keeping with the current concept that they are protective for mortality and morbidity in SLE[8,9].

Sex differences were observed in our study. While males had a lower number of criteria at inception, they did demonstrate more renal disorder, hematologic disorder, and immunologic disorder. Similar observations were recently reported for a Chinese cohort[10], the Hopkins' cohort, and the LUMINA cohort[11,12]. In a large sample of patients with SLE from the Dallas Fort Worth Metropolitan Area, males were also found to have more severe disease[13]. Thus, although SLE is more common among females, its expression may be more severe in males.

Different race/ethnicity groups present with different criteria. Although nonwhite ethnicities each had more renal, hematologic, and immunologic disorders than whites, whereas whites had higher frequency of photosensitivity when adjusted for sex, age, disease activity, and therapies,

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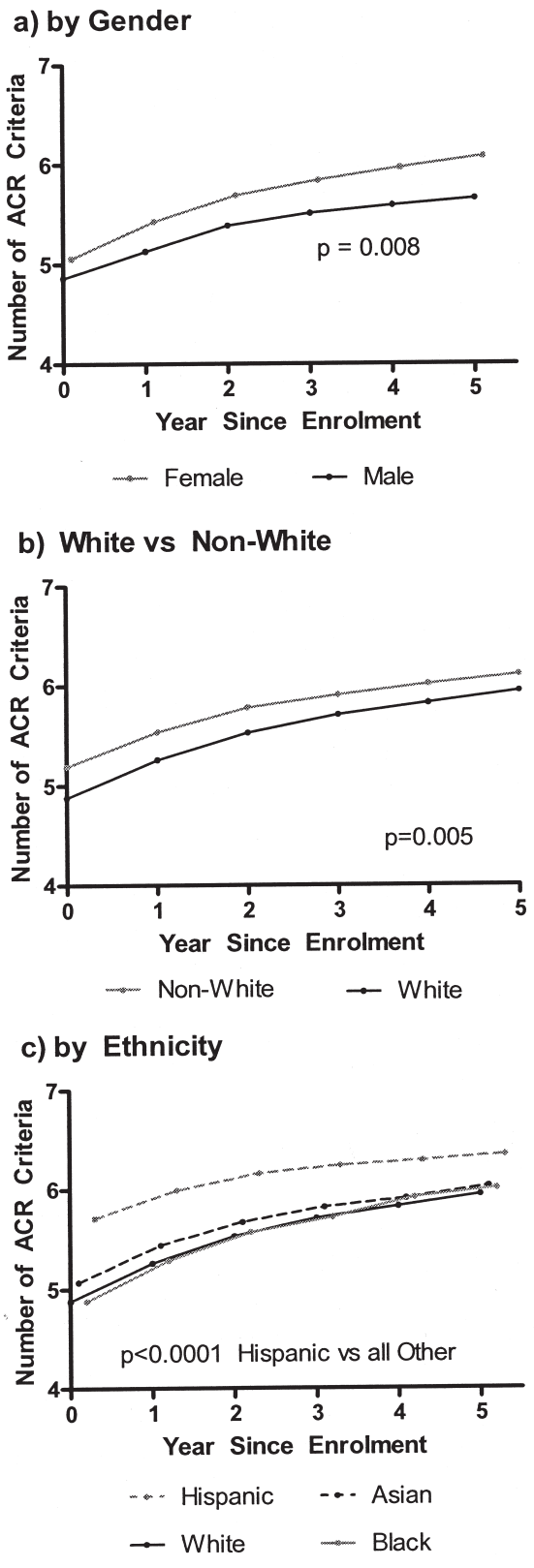

Figure 1. Effect of sex, race, and ethnicity on the number of American College of Rheumatology (ACR) criteria accrual.

Table 3. American College of Rheumatology (ACR) criteria accumulation by ethnicity and sex after adjusting for age, SLE Disease Activity Index-2K, steroids, antimalarials, and immunosuppressives.

ACR Criteria	OR	95% CI	p*
Malar rash			
Male	0.53	(0.33, 0.87)	0.01
White	1		
Asian	1.25	(0.82, 1.92)	0.3
Black	0.57	(0.36, 0.91)	0.02
Hispanic	1.56	(1.05, 2.42)	0.05
Discoid rash			
Male	0.85	(0.44, 1.63)	0.62
White	1		
Asian	0.72	(0.38, 1.35)	0.3
Black	2.26	(1.38, 3.72)	0.001
Hispanic	0.76	(0.38, 1.54)	0.45
Oral ulcers			
Male	0.52	(0.33, 0.82)	0.005
White	1		
Asian	0.88	(0.58, 1.33)	0.53
Black	0.61	(0.40, 0.93)	0.02
Hispanic	1.21	(0.78, 1.89)	0.407
Serositis			
Male	0.92	(0.56, 1.49)	0.72
White	1		
Asian	0.81	(0.50, 1.33)	0.41
Black	1.14	(0.73, 1.81)	0.56
Hispanic	1.21	(0.76, 1.92)	0.42
Arthritis			
Male	0.49	(0.30, 0.82)	0.006
White	1		
Asian	0.46	(0.28, 0.75)	0.002
Black	1.04	(0.62, 1.72)	0.89
Hispanic	2.28	(1.20, 4.33)	0.01
Photosensitivity			
Male	0.43	(0.26, 0.72)	0.001
White	1		
Asian	0.54	(0.34, 0.84)	0.006
Black	0.3	(0.18, 0.49)	<0.0001
Hispanic	0.55	(0.35, 0.87)	0.01
Renal disorder			
Male	1.73	(1.07, 2.80)	0.03
White	1		
Asian	1.19	(0.73, 1.93)	0.49
Black	1.6	(1.00, 2.56)	0.05
Hispanic	1.64	(1.02, 2.64)	0.04
Neurologic disorder			
Male	1.05	(0.50, 2.19)	0.89
White	1		
Asian	0.25	(0.09, 0.70)	0.008
Black	0.89	(0.46, 1.72)	0.72
Hispanic	0.38	(0.17, 0.87)	0.02
Hematologic disorder			
Male	1.27	(0.75, 2.17)	0.38
White	1		
Asian	2.1	(1.25, 3.52)	0.005
Black	1.2	(0.74, 1.94)	0.45
Hispanic	1.04	(0.63, 1.71)	0.88
Immunologic disorder			
Male	2.2	(1.01, 4.77)	0.05
White	1		
Asian	2.19	(1.17, 4.11)	0.01
Black	1.81	(0.97, 3.37)	0.06
Hispanic	1.68	(0.89, 3.19)	0.11

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Table 3. Continued.

ACR Criteria	OR	95% CI	p*
Antinuclear antibody			
Male	3.52	(0.44, 28.4)	0.24
White	1		
Asian	1.23	(0.38, 3.97)	0.72
Black	1.53	(0.43, 5.43)	0.51
Hispanic	0.54	(0.22, 1.29)	0.16
	Variable Estimate	95% CI	p vs White
Total no. ACR criteria			
Male	–0.38	(–0.61, –0.15)	0.001
White	0		
Asian	–0.15	(–0.41, 0.10)	0.23
Black	–0.11	(–0.36, 0.13)	0.35
Hispanic	0.23	(–0.05, 0.50)	0.1

*p value for individual ethnicity compared to white. SLE: systemic lupus erythematosus.

only immunologic disorder remained significantly higher, whereas photosensitivity remained significantly lower in all ethnicities. Although renal disorder was higher among nonwhites, this difference remained significant only for Hispanics. These observations are consistent with a previous report from the SLICC cohort that demonstrated that nonwhites had a higher disease burden in terms of active disease than whites at presentation and over the first 5 years[14]. A study from the Toronto Cohort found that black Canadians also had more renal disease than whites[15]. Ethnic differences in SLE manifestations have also been observed in the LUMINA cohort, where Texan Hispanics as well as black American patients fared worse than whites and Puerto Rican Hispanics[16,17]. Thus ethnicity has an effect on disease expression in SLE, although it is unclear to what extent these less favorable outcomes relate to differences in ancestral genes and socioeconomic status[18].

In this international inception cohort of SLE patients with at least 4 ACR criteria at entry, there was an accumulation of ACR criteria over the following 5 years. The distribution of criteria both at inception and over 5 years is affected by sex and ethnicity.

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