Performance of the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus in Asian patients: a single-centre retrospective cohort study in Korea

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Abstract

Objective

To evaluate the performance of the 2019 European League against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for systemic lupus erythematosus (SLE) in Asian patients.

Methods

We conducted an electronic medical chart review of patients with SLE and defined rheumatic diseases. Classification criteria of the 1997 ACR, 2012 Systemic Lupus International Collaborating Clinics (SLICC), and 2019 EULAR/ACR were examined based on sensitivity, specificity, positive predictive value, negative predicted value, and accuracy using clinical diagnosis as the gold standard.

Results

A total of 335 SLE patients and 337 non-SLE patients were analysed. Non-SLE patients included rheumatoid arthritis (RA) (n=92), anti-phospholipid syndrome (APS) (n=57), mixed connective tissue disease (n=52), systemic sclerosis (n=43), primary Sjögren's syndrome (SS) (n=39), undifferentiated connective tissue disease (n=28), RA with secondary SS (n=24), dermatomyositis (n=1), and spondyloarthropathy (n=1). The sensitivity was 97.6% (95% confidence interval (CI): 0.954–0.989) for the 2019 EULAR/ACR criteria, 98.5% (95% CI: 0.966–0.995) for the 2012 SLICC criteria and 95.5% (95% CI: 0.927–0.975) for the 1997 ACR criteria. The specificity was 91.4% (95% CI: 0.879–0.942) for the 2019 EULAR/ACR criteria, 92.6% (95% CI: 0.892–0.951) for the 2012 SLICC criteria 93.8% (95% CI: 0.906–0.961) for the 1997 ACR criteria.

Conclusion

The 2019 EULAR/ACR criteria for SLE had comparable performance to the 2012 SLICC criteria regarding diagnostic sensitivity and specificity in Korean population of SLE and other rheumatic diseases. However, the new criteria could not reach higher specificity than the 2012 SLICC criteria.

Key words

classification criteria, diagnosis, sensitivity, specificity, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease affecting multiple organs and systems. The presentation of the disease ranges from subtle manifestations to lethal events affecting major organs. These manifestations can evolve from time to time and the underlying pathogenesis is complex. Consequently, such complexity and heterogeneity of the disease makes the classification of SLE difficult. Classification criteria have evolved since the American College of Rheumatology (ACR) first published the criteria in 1971 (1). These criteria were modified into 11 categories with the addition of new immunologic tests in 1982 (2). They were then updated in 1997 (3), with a few modifications in immunologic criterion. The ACR classification criteria have been widely used in clinical trial and real-world practice for almost 50 years. In 2012, Systemic Lupus International Collaborating Clinics (SLICC) proposed new classification criteria which introduced new clinical items and required both clinical and immunological items for SLE classification (4). This criteria also accepted biopsy proven lupus nephritis as the sole criterion for classification of SLE in the presence of antinuclear antibodies (ANAs) or antibodies to double-stranded DNA (dsDNA). Subsequent studies have indicated that the SLICC criteria have higher sensitivity than other classification criteria, particularly for recent-onset SLE (5-7). However, the SLICC criteria had lower specificity than the 1997 ACR criteria (4, 8). In 2017, EULAR and ACR proposed new SLE classification criteria for SLE which included positive ANA as obligatory entry criterion and additive weighted grouped criteria. Such new criteria were further validated and endorsed by EULAR and ACR and published in September 2019 (9). However, there are no reports evaluating the performance of the new criteria in Asian population. The aim of the present study was to evaluate the performance of the 2019 EULAR/ACR criteria in comparison with the 2012 SLICC and the 1997 ACR criteria in Korean patients with SLE.

Methods

Patients

We conducted electronic medical chart review of patients with SLE or defined rheumatic diseases as control group. For SLE group, we reviewed all SLE patients followed at our rheumatology clinic in Seoul National University Hospital. For non-SLE control group, patients with a well-established clinical diagnosis of other rheumatic disease were randomly selected. Patients should have been followed up by rheumatologist in our hospital for more than 2 years. Patients with overlapping syndromes, uncertain diagnosis, or incomplete medical record were excluded. Items in the classification criteria were counted if they were thought to be caused by SLE and not counted if there were more likely explanation other than SLE. We did not count items related to infection, drugs or metabolic derangements.

Laboratory analysis

ANA was detected by indirect immunofluorescence using HEp-2 cells (Bio-Rad, USA). Anti-dsDNA antibodies were detected by radioimmunoassay (reference range 0–7 IU/ml) (DIA-Source, Belgium). Anti-Sm antibodies were tested by fluorescence enzyme immunoassay. Anti-cardiolipin antibodies and anti-β2 glycoprotein I antibodies were measured by chemiluminesent assay (Werfen, USA). Lupus anticoagulant was tested according to the International Society on Thrombosis and Haemostasis guidelines (10). Complement C3 and C4 measurements were performed by immunoturbidimetry (Abbott, USA).

Statistical analysis

Using clinical diagnosis as gold standard, the 2019 EULAR/ACR classification criteria, the 1997 ACR criteria, and the 2012 SLICC criteria were examined for sensitivity (proportion SLE cases correctly classified), specificity (proportion of non-SLE cases correctly classified), positive predictive value (PPV, proportion of SLE-classified cases that were true SLE cases), negative predicted value (NPV, proportions of non-SLE-classified cases that were true non-SLE cases), and accuracy (propor-

tions of cases correctly classified) with 95% confidence intervals (CIs). Concordance was evaluated by Cohen's unweighted kappa test with 95% CIs. This study was approved by the Institutional Review Board of Seoul National University Hospital. The requirement of obtaining informed consent was waived as this retrospective study involved a minimum risk to enrolled patients and no identifiable information was used.

Results

A total of 382 SLE patients and 2775 non-SLE patients were reviewed retrospectively. After excluding 47 SLE patients with incomplete medical records, a total of 335 SLE patients and 337 non-SLE patients were included in the analysis (Table I). Non-SLE included rheumatoid arthritis (RA) (n=92), antiphospholipid syndrome (APS) (n=57), mixed connective tissue disease (n=52), systemic sclerosis (n=43), primary Sjögren's syndrome (SS) (n=39), undifferentiated connective tissue disease (n=28), RA with secondary SS (n=24), dermatomyositis (n=1), and spondyloarthropathy (n=1). All patients with mixed connective tissue disease and undifferentiated connective tissue disease in the centre were included and patients with other diseases were randomly selected to balance the number with SLE group. The median age was 32.0 [interquartile range (IQR): 24.0 to 43.0] years in the SLE group and 48.0 [IQR: 33.0 to 57.0] years in the non-SLE group. Most patients (90.1% in SLE group and 86.6% in control group) were females. In the SLE group, 320 (95.5%), 330 (95.8%), and 327 (97.6%) patients fulfilled the 1997 ACR criteria, the 2012 SLICC criteria, and the 2019 EULAR/ACR criteria, respectively. Among SLE patients, 4 patients were ANA negative. All clinical manifestations included in the SLE classification criteria were more common in the SLE group compared to those in the non-SLE group. Among immunological criteria, anti-β2 glycoprotein-I antibodies tended to be more common in the non-SLE group without statistical significance (5.3% *vs*. 4.5%, p=0.734).

Ninety-four percent of SLE patients fulfilled all three classification criteria (1997 ACR, 2012 SLICC, and 2019 EULAR/ACR criteria). Sensitivity, specificity, predictive values, and accuracies of these classification criteria are shown in Table II. The sensitivity was 97.6% (95% CI: 0.954–0.989) for the 2019 EULAR/ACR criteria, 98.5% (95% CI: 0.966–0.995) for the 2012 SLICC criteria and 95.5% (95% CI: 0.927–0.975) for the 1997 ACR criteria. The specificity was 91.4% (95% CI: 0.879–0.942) for the 2019 EULAR/ACR criteria, 92.6% (95% CI: 0.892–0.951) for the 2012 SLICC criteria and 93.8% (95% CI: 0.906–0.961) for the 1997 ACR criteria. Among SLE patients who were classified as SLE with the 2012 SLICC criteria, five patients did not meet the new criteria: 3 patients had sum of weighted score ≥10 but were ANA negative; 2 patients had lymphopenia (<1000/mm^3) which was counted as a criterion in the 2012 SLICC criteria but not in the new crite-

Table I. Clinical and immunological characteristics of SLE and non-SLE patients included in the analysis.

	SLE group (n=335)	Non-SLE group (n=337)	p-value
Age (years)	32.0 [24.0;43.0]	48.0 [33.0;57.0]	<0.001
Female, n (%)	302 (90.1)	292 (86.6)	0.195
Clinical manifestations, n (%)			
Acute cutaneous lupus	212 (63.3%)	12 (3.6%)	<0.001
Chronic cutaneous lupus	25 (7.5%)	0 (0.0%)	<0.001
Photosensitivity	87 (26.0)	12 (3.6)	<0.001
Non-scarring alopecia	143 (42.7)	9 (2.7)	<0.001
Oronasal ulcers	121 (36.1)	15 (4.5)	<0.001
Arthritis	220 (65.7)	105 (31.2)	<0.001
Serositis	95 (28.4)	6 (1.8)	<0.001
Proteinuria	204 (60.9)	7 (2.1)	<0.001
Biopsy proven lupus nephritis	112 (33.4)	1 (0.3)	<0.001
Neurologic disorder*	51 (15.2)	13 (3.9)	<0.001
Haemolytic anaemia	115 (34.3)	4 (1.2)	<0.001
Leukopenia (<4000/mm^3)	215 (64.2)	60 (17.9)	<0.001
Lymphopenia (<1000/mm^3)	190 (56.7)	33 (10.0)	<0.001
Thrombocytopenia (<100,000/mm^3)	132 (39.4)	22 (6.6)	<0.001
Unexplained fever >38.3°C	105 (31.3)	6 (1.8)	<0.001
Immunologic criteria, n (%)			
ANA	331 (98.8)	244 (72.4)	<0.001
Anti-dsDNA	299 (89.3)	32 (9.5)	<0.001
Anti-Sm	87 (26.0)	7 (2.1)	<0.001
Lupus anticoagulant	84 (25.1)	52 (15.4)	0.003
Anti-cardiolipin antibody	49 (14.6)	35 (10.4)	0.122
Anti-β2 glycoprotein-I antibody	15 (4.5)	18 (5.3)	0.734
Low C3 or low C4	284 (84.7)	10 (3.0)	<0.001
Low C3 and low C4	246 (73.4)	5 (1.5)	<0.001

Values are presented as number (%) or median [interquartile range]. *Neurologic criteria according to 2012 SLICC criteria. ANA: anti-nuclear antibodies; dsDNA: double stranded DNA; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics.

Table II. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy including 95% confidence intervals (in parentheses) of each classification criteria

	1997 ACR	2012 SLICC	2019 EULAR/ACR
Sensitivity	0.955 (0.927-0.975)	0.985 (0.966-0.995)	0.976 (0.954-0.989)
Specificity	0.938 (0.906-0.961)	0.926 (0.892-0.951)	0.914 (0.879-0.942)
PPV	0.938 (0.910-0.958)	0.929 (0.901-0.951)	0.919 (0.888-0.941)
NPV	0.955 (0.928-0.971)	0.984 (0.963-0.993)	0.975 (0.951-0.987)
Accuracy	0.946 (0.925-0.962)	0.955 (0.937-0.969)	0.945 (0.925-0.961)

ACR: American College of Rheumatology; EULAR: European League against Rheumatism; NPV, negative predictive value; PPV: positive predictive value; SLICC: Systemic Lupus International Collaborating Clinics.

ria. Two SLE patients who had positive ANA, cutaneous lupus, and arthritis did not fulfill the 1997 ACR or 2012 SLICC criteria, but fulfilled the new criteria because of the weighted score system.

Among non-SLE patients, 25 patients met the 2012 SLICC criteria. Among these patients, 21 patients met the new criteria as well. However, 4 patients did not meet the new criteria: 1 patient was anti-phospholipid syndrome (APS) with ANA negative; 1 ANA positive patient had leukopenia, alopecia and acute cutaneous lupus which was counted separately in the 2012 SLICC criteria; 1 ANA positive patient was APS with positive anti-cardiolipin antibody and lupus anticoagulant and had thrombocytopenia and haemolytic anaemia which was counted separately in the 2012 SLICC criteria; and 1 ANA positive patient with arthritis and leukopenia met 2012 SLICC criteria because of cranial neuropathy which was included in the 2012 SLICC criteria but not in the new criteria. The 2019 EULAR/ACR score ≥12 rather than a score ≥ 10 resulted in higher specificity (94.7%), positive predictive value (94.8%), and accuracy (96.0%) with similar sensitivity (97.3%).

The 2019 EULAR/ACR criteria showed high concordance with clinical diagnosis, showing kappa index of 0.890 (95% CI: 0.855–0.925). Similarly, the 1997 ACR and the 2012 SLICC criteria had kappa indices of 0.893 (95% CI: 0.860–0.926) and 0.911 (95% CI: 0.88–0.942), respectively. Kappa index between the 2019 EULAR/ACR criteria and the 1997 ACR or 2012 SLICC criteria was 0.890 (95% CI: 0.855–0.925) or 0.943 (95% CI: 0.918–0.968), respectively.

Discussion

Recently, many data regarding the pathogenesis, biomarkers and treatment strategy of SLE emerged and the new classification criteria were published (9, 11). The development of a new classification system raises the question of whether it can be applied to various ethnic populations. In this study of 672 Koran patients with SLE or non-SLE control disease, the 2019 EULAR/ACR criteria showed comparable performance in sensitivity and specificity compared to the 1997 ACR and the 2012 SLICC criteria. However, it failed to achieve higher specificity.

The biggest change of the new criteria is the use of positive ANA as an entry criterion. This change was based on the high sensitivity of ANA tests and the consensus of excluding ANA negative patients form clinical trials despite the existence of a small group of SLE patients who are ANA negative (9). This entry criterion may lower the sensitivity of the classification criteria, although it will provide higher specificity. In the control cohort of our study, one APS patient who met the SLICC criteria was not classified as SLE by the new criteria because of the ANA entry criterion.

Another change about the new criteria is the introduction of domain system with hierarchically clustered and differentially weighted criteria. Under this system, patients with multiple manifestations in one domain such as leukopenia and thrombocytopenia or alopecia and oral ulcers who could be classified as SLE based on the 2012 SLICC criteria did not fulfill the new classification criteria. This system has an advantage of excluding purely mucocutaneous lupus from SLE and allowing highly specific selection of subjects for clinical trials targeting SLE with vital organ involvement. However, this classification may not be suitable for trials targeting mainly mucocuatenous symptoms.

In the validation study by the SLICC group, the 2012 SLICC criteria had much lower specificity (84%) than the 1997 ACR criteria (96%) (4). The primary goal of the new classification criteria was to increase specificity similar to the 1997 ACR criteria while maintaining the high sensitivity of 2012 SLICC criteria (9). In the present study, the new criteria reached higher sensitivity than the 1997 ACR (97.6% *vs*. 95.5%). However, its specificity was numerically lower than the 1997 ACR or the 2012 SLICC criteria (91.4% *vs*. 93.8% or 92.6%). When the cut-off score for SLE classification in the 2019 EULAR/ACR was set as ≥12 rather than ≥10, higher specificity (94.7%) was achieved while sensitivity (97.3%) maintained. In a previous study of paediatric SLE, the 2017 weighted criteria (12) showed higher sensitivity than the 1997 ACR criteria (97.4% *vs*. 87.2%) and similar specificity with the 2012 SLICC criteria (98.4% *vs*. 99.7%) (13). In another study, the new criteria reached specificity of 73% which was comparable to but still lower than that of the 2012 SLICC criteria (75%) and clearly lower than that of the 1982 ACR criteria (94%) (14). In a study that compared the performance of classification criteria in childhood-onset SLE, the sensitivity of the new EULAR/ACR criteria was similar to that of 2012 SLICC criteria (89.3% *vs*. 89.3%) but the specificity was higher for 2012 SLICC criteria at first visit compared to the new criteria (80.9% *vs*. 67.4%) (15). In a study regarding neuropsychiatric SLE, the sensitivity was 87% for the proposed criteria, 85% for the 2012 SLICC criteria and 89% for the 1997 ACR criteria. The specificity was 74% for the proposed criteria, 76% for the 2012 SLICC criteria and 89% for the 1997 ACR (16). These trends were similar to our study. In addition, in a retrospective study including SLE and primary SS patients, the new criteria were met in 97.9% of SLE patients and in only 4.2% of primary SS patients, suggesting the utility of the new criteria differentiating SLE and primary SS in clinical practice (17).

This study has some limitations. First, it was a retrospective study involving patients from a single centre in Korea. A selection bias cannot be excluded and clinical manifestations are not likely to be fully assessed in a retrospective study. In addition, in the non-SLE group, anti-dsDNA and anti-Sm antibody showed higher false positivity than expected (9.5% and 2.1%, respectively). Although this cannot be fully explained, it was reported that 14.5% and 5.5% of the control patients had positive anti-dsDNA and anti-Sm, respectively in previous studies (14, 18). Lastly, although we made a great effort to count the criteria only when the manifestation was not better explained by another condition, this attribution rule could be applied partly because of the retrospective nature of the study. However, this SLE and non-SLE cohort reflects patients from tertiary referral

centre and provides additional external validation data in Asian patients.

In conclusion, the 2019 EULAR/ACR criteria for SLE had comparable performance to the 2012 SLICC criteria in diagnostic accuracy, sensitivity, and specificity in Korean population of SLE and other rheumatic diseases, although the new criteria could not reach higher specificity than the 2012 SLICC criteria.

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