This article has been accepted for publication in ARD following peer review.
The definitive copyedited, typeset version is available online at 10.1136/annrheumdis

Performance of the 2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus in Early Disease, Across Sexes and Ethnicities

Sindhu R. Johnson, Ralph Brinks, Karen H. Costenbader, David I. Daikh, Marta Mosca, Rosalind Ramsey-Goldman, Josef S. Smolen, David Wofsy, Dimitrios Boumpas, Diane L. Kamen, David Jayne, Ricard Cervera, Nathalie Costedoat-Chalumeau, Betty Diamond, Dafna D. Gladman, Bevra H. Hahn, Falk Hiepe, Søren Jacobsen, Dinesh Khanna, Kirsten Lerstrøm, Elena Massarotti, W. Joseph McCune, Guillermo Ruiz-Irastorza, Jorge Sanchez-Guerrero, Matthias Schneider, Murray B. Urowitz, George Bertsias, Bimba F. Hoyer, Nicolai Leuchten, Chiara Tani, Sara K. Tedeschi, Zahi Touma, Gabriela Schmajuk, Branimir Anic, Florence Assan, Tak Mao Chan, Ann E. Clarke, Mary K. Crow, László Czirják, Andrea Doria, Winfried B. Graninger, Bernadett Halda-Kiss, Sarfaraz Hasni, Peter Izmirly, Michelle Jung, Gábor Kumánovics, Xavier Mariette, Ivan Padjen, José M. Pego-Reigosa, Juanita Romero-Díaz, Iñigo Rúa-Figueroa Fernández, Raphaèle Seror, Georg Stummvoll, Yoshiya Tanaka, Maria G. Tektonidou, Carlos Vasconcelos, Edward M. Vital, Daniel Wallace, Sule Yavuz, Pier Luigi Meroni, Marvin J Fritzler, Ray P. Naden, Thomas Dörner, Martin Aringer.

Sindhu R. Johnson MD PhD FRCPC, Division of Rheumatology, Department of Medicine, Toronto Western Hospital, Mount Sinai Hospital; Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

Ralph Brinks PhD, Policlinic and Hiller Research Unit for Rheumatology, Medical Faculty, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany

Karen H. Costenbader MD MPH, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

David I. Daikh MD, University of California at San Francisco and VA Medical Center, San Francisco, CA, USA

Marta Mosca MD PhD, Rheumatology Unit, Azienda Ospedaliero Universitaria Pisana, University of Pisa, Pisa, Italy

Rosalind Ramsey-Goldman MD DrPH, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Josef S. Smolen MD, Medical University of Vienna, Austria

David Wofsy MD, Russell/Engleman Rheumatology Research Center, University of California at San Francisco, San Francisco, USA

Dimitrios Boumpas MD, Medical School, National and Kapodestrian University of Athens, and Biomedical Research Foundation of the Athens Academy, Athens, Greece; Medical School, University of Cyprus, Nicosia, Cyprus.

Diane L. Kamen MD MSCR, Medical University of South Carolina, Charleston, SC, USA

David Jayne MD FRCP FRCPE FMedSci, Department of Medicine, University of Cambridge, United Kingdom

Ricard Cervera MD PhD FRCP, Department of Autoimmune Diseases, Hospital Clínic, University of Barcelona, Barcelona, Catalonia, Spain

Nathalie Costedoat-Chalumeau, MD PhD AP-HP, Cochin Hospital, Internal Medicine Department, Centre de référence maladies auto-immunes et systémiques rares d'île de France, Paris, France ; Université Paris Descartes-Sorbonne Paris Cité, Paris, France ; INSERM U 1153, Center for Epidemiology and Statistics Sorbonne Paris Cité (CRESS), Paris, France

Betty Diamond MD, Feinstein Institute, Manhasset, NY, United States

Dafna D. Gladman, MD FRCPC, Division of Rheumatology, Department of Medicine, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada

Bevra H Hahn MD, University of California at Los Angeles, Los Angeles, CA, USA

Falk Hiepe MD, Charité – Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Rheumatology and Clinical Immunology, Berlin, Germany

Søren Jacobsen MD DMSc, Copenhagen Lupus and Vasculitis Clinic, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Dinesh Khanna MD MS, University of Michigan, Ann Arbor, MI, USA

Kirsten Lerstrøm, Lupus Europe, co-opted trustee for research, Essex, UK

Elena Massarotti MD, Brigham and Women's Hospital, Boston MA; Harvard Medical School, Boston, USA

W. Joseph McCune MD, University of Michigan, Ann Arbor, MI, USA

Guillermo Ruiz-Irastorza MD PhD, Autoimmune Diseases Research Unit, Department of Internal Medicine, Biocruces Bizkaia Health Research Institute, Hospital Universitario Cruces, UPV/EHU, Bizkaia, The Basque Country, Spain

Jorge Sanchez-Guerrero MD MSc, Division of Rheumatology, Department of Medicine Mount Sinai Hospital/University Health Network, University of Toronto, Toronto, Ontario, Canada; and Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Matthias Schneider MD, Policlinic and Hiller Research Unit for Rheumatology, Medical Faculty,Heinrich-Heine-University, Düsseldorf, Germany

Murray B. Urowitz MD, Division of Rheumatology, Department of Medicine, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada

George Bertsias MD, Rheumatology, Clinical Immunology and Allergy, University of Crete Medical School, Heraklion, Greece; and Institute of Molecular Biology-Biotechnology, Foundation for Research and Technology - Hellas (FORTH), Heraklion, Greece

Bimba F. Hoyer MD, Department of Rheumatology and Clinical Immunology, University Hospital of Schleswig-Holstein at Kiel, Kiel, Germany

Nicolai Leuchten MD, University Medical Center and Faculty of Medicine Carl Gustav Carus, TU Dresden, Dresden, Germany

Chiara Tani MD, Rheumatology Unit, Azienda Ospedaliero Universitaria Pisana, University of Pisa, Pisa, Italy

Sara K. Tedeschi MD MPH, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Zahi Touma, MD PhD, Division of Rheumatology, Department of Medicine, Toronto Western Hospital, Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

Gabriela Schmajuk MD MS, University of California at San Francisco and the VA Medical Center, San Francisco, USA

Branimir Anic MD, Division of Clinical Immunology and Rheumatology, University of Zagreb School of Medicine and University Hospital Centre Zagreb, Zagreb, Croatia

Florence Assan MD, Université Paris-Saclay, INSERM, CEA, Centre de recherche en Immunologie des infections virales et des maladies auto-immunes ; AP-HP. Université Paris Saclay, Hôpital Bicêtre, Rheumatology ; 94270, Le Kremlin Bicêtre, France.

Tak Mao Chan MD, University of Hong Kong, Hong Kong
Ann E. Clarke MD MSc, Division of Rheumatology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

Mary K. Crow MD, Hospital for Special Surgery, New York, NY, USA

László Czirják MD, University of Pécs, Medical School, Pécs, Hungary

Andrea Doria MD, Rheumatology Unit, Department of Medicine (DIMED),
University of Padova, Padova, Italy

Winfried B. Graninger MD, Medical University of Graz, Graz, Austria

Bernadett Halda-Kiss MD, University of Pécs, Medical School, Pécs, Hungary

Sarfaraz Hasni MD, NIAMS, NIH, Bethesda, MD

Peter Izmirly MD, New York University School of Medicine, New York, New York, USA

Michelle Jung, University of Calgary, Calgary, Alberta, Canada

Gábor Kumánovics MD, University of Pécs Medical School, Pécs, Hungary

Xavier Mariette MD PhD, Université Paris-Saclay, INSERM, CEA, Centre de recherche en Immunologie des infections virales et des maladies auto-immunes ; AP-HP.Université Paris Saclay, Hôpital Bicêtre, Rheumatology ; 94270, Le Kremlin Bicêtre, France

Ivan Padjen MD, Division of Clinical Immunology and Rheumatology, University of Zagreb School of Medicine and University Hospital Centre Zagreb, Zagreb, Croatia

José M. Pego-Reigosa MD PhD, Department of Rheumatology, University Hospital of Vigo, IRIDIS Group, Instituto de Investigación Sanitaria Galicia Sur (IISGS), Vigo, Spain

Juanita Romero-Díaz MD, , MSc, Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Iñigo Rúa-Figueroa Fernández MD, Hospital Dr Negrin, Las Palmas, Spain

Raphaèle Seror MD, PhD, Université Paris-Saclay, INSERM, CEA, Centre de recherche en Immunologie des infections virales et des maladies auto-immunes ; AP-HP.Université Paris Saclay, Hôpital Bicêtre, Rheumatology ; 94270, Le Kremlin Bicêtre, France.

Georg Stummvoll MD, Medical University of Vienna, Vienna, Austria

Yoshiya Tanaka MD PhD, University of Occupational & Environmental Health, Kitakyushu, Japan

Maria G. Tektonidou MD PhD, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Carlos Vasconcelos MD PhD, Centro Hospitalar do Porto, ICBAS, UMIB, University of Porto, Porto, Portugal

Edward M Vital MRCP PhD, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds; NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Daniel J. Wallace MD, Cedars-Sinai, Los Angeles, CA, USA

Sule Yavuz MD, Istanbul Bilim University, Istanbul Florence Nightingale Hospital, Istanbul, Turkey

Pier Luigi Meroni MD, Clinical Immunology and Rheumatology Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy

Marvin J Fritzler PhD MD, Faculty of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
Ray P. Naden MB ChB FRACP, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Thomas Dörner MD, Charité – Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Rheumatology and Clinical Immunology, Berlin, Germany

Martin Aringer MD, University Medical Center and Faculty of Medicine Carl Gustav Carus, TU Dresden, Dresden, Germany

Corresponding Authors
Sindhu R. Johnson MD PhD, Division of Rheumatology, Ground Floor, East Wing, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, Canada, M5T 2S8. Phone 1-416-603-6417 Fax.1-416-603-4348. Email: Sindhu.Johnson@uhn.ca

Martin Aringer MD, Division of Rheumatology, Department of Medicine III, University Medical Center TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany. Phone +49 351 458 4422 Fax +49 351 458 5801 E-mail martin.aringer@uniklinikum-dresden.de

Word Count 2110

Funding information. This body of work was jointly supported by the European League Against Rheumatism and the American College of Rheumatology. This research was supported [in part] by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health.

Key words. Systemic lupus erythematosus, lupus, classification criteria, validation

Competing Interests. No potential conflicts of interest relevant to this article were reported.

Data availability. Data are available upon reasonable request

Contributorship. All authors contributed to the study design, data collection and/or evaluation and critical review of the final manuscript.

Patient involvement. Patients were involved in the cross-sectional survey for item generation, involved in the steering committee meeting for item reduction phases, drafting and review of the final manuscript.

Abstract

Objectives. The EULAR/ACR 2019 Classification Criteria for systemic lupus erythematosus (SLE) have been validated with high sensitivity and specificity. We evaluated the performance of the new criteria with regard to disease duration, sex, and race/ethnicity, and compared its performance against the SLICC 2012 and ACR 1982/1997 criteria.

Methods. Twenty-one SLE centers from 16 countries submitted SLE cases and mimicking controls to form the validation cohort. The sensitivity and specificity of the EULAR/ACR 2019, SLICC 2012 and ACR 1982/1997 criteria were evaluated.

Results. The cohort consisted of female (n=1098), male (n=172), Asian (n=118), Black (n=68), Hispanic (n=124) and White (n=941) patients; with an SLE duration of 1-<3 years (n=196) and 5 years (n=879). Among patients with 1-<3 years disease duration, the EULAR/ACR criteria had better sensitivity than the ACR criteria (97% versus 81%). The EULAR/ACR criteria performed well in men (sensitivity 93%, specificity 96%) and women (sensitivity 97%, specificity 94%). Among women, the EULAR/ACR criteria had better sensitivity than the ACR criteria (97% versus 83%) and better specificity than the SLICC criteria (94% versus 82%). Among White patients, the EULAR/ACR criteria had better sensitivity than the ACR criteria (95% versus 83%) and better specificity than the SLICC criteria (94% versus 83%). The EULAR/ACR criteria performed well among Black patients (sensitivity of 98%, specificity 100%), and had better sensitivity than the ACR criteria among Hispanic patients (100% versus 86%) and Asian patients (97% versus 77%).

Conclusions. The EULAR/ACR 2019 criteria perform well among patients with early disease, men, women, White, Black, Hispanic and Asian patients. These criteria have superior sensitivity than the ACR criteria and/or superior specificity than the SLICC criteria across many subgroups.

INTRODUCTION

Classification criteria constitute a cornerstone of clinical research in Rheumatology as they facilitate identification of homogeneous groups of patients for inclusion into observational studies and clinical trials.[1] The European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) 2019 classification criteria for SLE were developed through an international collaboration using both data-driven and expert-based consensus-finding methods.[2-10] The new criteria define the presence of one or more results for antinuclear antibody (ANA) tests at a titer of ≥1:80 (or an equivalent positive test) as an entry requirement. The subsequent criteria are grouped into seven clinical domains (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal and renal) and 3 immunologic domains (antiphospholipid antibodies, hypocomplementemia, SLE-specific antibodies). Related organ system criteria are clustered hierarchically and numerically weighted to form an additive point system. A patient can be classified as having SLE if the ANA entry criterion is fulfilled, at least one clinical criterion is present, and the accumulated points of all domains total 10 or more. One attribution rule for all items replaced exclusion criteria, stating that items should only be counted if there was no explanation more likely than SLE. Novel features of the classification system are the inclusion of fever, in the absence of infection or other causes, as a criterion to assist in classification of earlier disease; and separation of class II and V from class III and IV lupus nephritis as distinct criteria. Class III or IV lupus nephritis was found to be more influential in the classification of an ANA positive individual and given 10 points, thereby forming the only singular sufficient criterion for classification of SLE in the presence of ANA.

In the validation cohort, the new criteria had a sensitivity of 96% and a specificity of 93%. This led to the endorsement of the new criteria by both EULAR and ACR.[11, 12] Through the criteria development and review processes, investigators and reviewers questioned the operating characteristics of the new criteria in subsets of SLE patients.[13] Indeed, there is a need for criteria that perform well in early disease for more timely inclusion in clinical trials and research studies.[14] Furthermore, differences in SLE disease expression have been described between sexes and across ethnicities which may impact the performance of classification criteria in these

groups of patients.[15-17] Therefore, the objectives of this study were to evaluate the sensitivity and specificity of the EULAR/ACR 2019 classification criteria in early disease, across sexes and ethnicities.[11, 12] We also comparatively evaluated the operating characteristics of the EULAR/ACR 2019 classification criteria against the ACR 1982/1997[18, 19] and the Systemic Lupus International Collaborating Clinics (SLICC) 2012[20] classification criteria for SLE.

METHODS

SLE cases and controls. Twenty-one SLE expert centers from 16 countries submitted between 20 and 100 SLE cases and the same number of SLE mimicking controls each to form the validation cohort for the EULAR/ACR 2019 classification criteria. The investigators from these centers had not been part of the steering committee, the nominal group technique[7] nor the multicriteria decision analysis[10] of the project and were thus unaware of the new criteria form or content. The 100 case and control limit per center was used to preclude any one center from dominating the cohort. Data on all cases and controls, including demographic data and SLE duration, were collected using a standardized form.

Data administration. Cases and control diagnoses (SLE or not SLE) were made by the submitting investigator and were independently verified by 3 SLE experts. Previous sets of classification criteria were not considered when selecting cases nor controls. Data were double entered into a computerized database. Data quality was maintained using logic and range checks. Data queries were reconciled by interrogation of the submitting investigator. Research ethics board approval and patient consent was obtained by the data coordinating center and all submitting centers, as required locally.

SLE subsets. Disease duration was calculated from date of physician diagnosis to date of data submission. Data on sex were self-reported as male or female. Data on gender were not collected. Data on ethnicity, self-reported and verified by the investigators, were collected from the medical records, and categorized as White, Black, Hispanic (Latin American heritage) and Asian.

Statistical analysis. Sensitivity and specificity for each of the classification criteria sets among subsets of SLE patients were estimated with their corresponding 95% confidence intervals (CI). Non-overlapping confidence intervals denotes statistically significant differences. Statistical analyses were performed using R, version 3.4.0 (The R Foundation of Statistical Computing).

RESULTS

Cohort. Cases and controls were submitted from centers in Austria, Canada, Croatia, France, Germany, Greece, Hong Kong, Hungary, Japan, Italy, Mexico, Portugal, Spain, Turkey, United Kingdom, and United States of America. The validation cohort (n=1270) consisted of female (n=1,098 (86%)) and male (n=172 (14%)) patients; Asian (n=118 (9%)), Black (n=68 (5%)), Hispanic (n=124 (10%)) and White (n=941 (74%)) patients; and patients with an SLE duration of less than 1 year (n=34 (3%)), 1 to less than 3 years (n=196 (16%)), 3 to less than 5 years (n=157 (12%)), and 5 or more years (n=879 (69%)). The 5 subjects who were Arab and 13 subjects who had an ethnicity categorized as 'Other' were excluded from the ethnicity analyses as their numbers were so small. Four subjects had missing disease duration data.

Operating characteristics. As shown in Table 1, which includes 95% CIs, the EULAR/ACR 2019 criteria performed well among patients with early disease defined as 1 to less than 3 years of disease duration (sensitivity 97%, specificity 96%) and among patients with 3 to less than 5 years disease duration (sensitivity 96%, specificity 99%). The EULAR/ACR 2019 criteria also performed well among patients with established disease defined as 5 or more years disease duration (sensitivity 96%, specificity 93%). They also perform well in men (sensitivity 93%, specificity 96%), women (sensitivity 97%, specificity 94%), and in all the race/ethnicity groups examined. Table 1.

Among women, the EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria (97% (95%CI 95-98%) versus 83% (95%CI 80-86%) and better specificity than the SLICC criteria (94% (95%CI 91-96%) versus 82% (95%CI 79-86%). (Figure 1.)

Among White patients, the EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria (95% (95%CI 93-97%) versus 83% (95%CI 79-86%) and better specificity than the SLICC criteria (94% (95%CI 91-96%) versus 83% (95%CI 80-87%). (Figure 2.) The EULAR/ACR 2019 criteria performed well among Black patients with a sensitivity of 98% (95%CI 90-100%) and specificity 100% (95%CI 74-100%). The 95% confidence intervals around these estimates are larger due to the smaller sample size. The EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria among Hispanic patients (100% % (95%CI 95-100%) versus 86% (95%CI 76-93%) and Asian patients (97% (95%CI 91-100%) versus 77% (95%CI 65-86%).

In patients with 1 to less than 3 years disease duration, the EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria (97% (95%CI 92-99%) versus 81% (95%CI 72-88%). Among patients with 5 or more years disease duration, the EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria (96% (95%CI 94-98%) versus 84% (95%CI 80-87%) and better specificity than the SLICC criteria (93% (95%CI 89-95%) versus 81% (95%CI 76-85%). Among SLE patients with less than 3 years disease duration (early disease), oral ulceration, non-scaring alopecia and pleural/pericardial effusions occurred more frequently. Among SLE patients with a disease duration of 5 or more years, acute cutaneous lupus, arthritis, seizures, pericarditis, leukopenia and class III or IV nephritis occurred more frequently. Table 3.

The operating characteristics of the ACR 1982/1997 and SLICC 2012 reported in other studies are summarized in Table 2 and are generally consistent with their performance in the present study.

DISCUSSION

The EULAR/ACR 2019 criteria have strong operating characteristics (sensitivity and specificity) across subsets of SLE patients, specifically among male and female, White, Black, Hispanic and Asian patients. Importantly, the new criteria perform well among patients with early disease. Indeed, this was one of the reasons to develop new classification criteria. Furthermore, the new criteria confer improved performance compared to previous sets of SLE classification criteria, retaining their superior sensitivity compared to the ACR criteria, as well as their superior specificity compared to the SLICC criteria in many of these groups. There was no subset of patients identified in which the new criteria performed substantially worse than previous criteria. The EULAR/ACR 2019 SLE criteria reflect the current thinking of the international SLE community about how SLE is to be classified and reduce the potential risk of misclassification of ANA positive patients.

Our demonstration that the EULAR/ACR 2019 SLE criteria perform well in early disease is an important contribution to the field. We tested different definitions of early disease (less than 1 year, 1 to less than 3 years, 3 to less than 5 years disease duration), and in all of our definitions, the new criteria performed well. The validity of classification criteria for early disease allows for more timely inclusion in clinical trials and observational studies. It is hoped that intervention in those early in their disease course may prevent complications and irreversible damage.[14] Identifying when the disease started can be challenging as a patients may have symptoms or even full SLE for a period of time before being diagnosed. We note that there is no standardized definition of 'early' SLE. However, other definitions of early, very early, latent or incomplete disease (i.e. other terms used to describe patients with some symptoms and signs of SLE) have been proposed.[14, 21] In this study, disease duration was calculated from the date of physician diagnosis to date of data submission. While such data are not available from the EULAR/ACR patient data set, another very important stage of the disease is from first sign or symptom to diagnosis. We encourage investigators to test the performance of the new classification criteria using these alternative definitions of 'early' disease. It should be noted, that in our study, the diagnosis of all cases and controls was verified by 3 independent reviewers from different centers, thereby reducing potential bias of a submitting center. If investigators test alternative

definitions of early disease, we encourage investigators to submit cases and controls for independent verification.

The operating characteristics of the ACR 1982/1997 and SLICC 2012 criteria in this study were similar to those reported by others.[22, 23] Among Asian patients, Oku et al reported sensitivity and specificity of the ACR criteria (88% and 85%, respectively) and the SLICC criteria (99% and 80%, respectively).[24] Among patients with less than 5 years disease duration in the Portuguese and Spanish National Registries (Reuma.pt and RELESSER cohorts, respectively), Ines et al reported a sensitivity of 76% for the ACR criteria and 89% for the SLICC criteria.[23] Similarly among patients with >5 years disease duration, they reported a sensitivity of 89% for the ACR criteria and 90% for the SLICC criteria.[23] In an international early SLE cohort, Mosca et al reported similar sensitivity and specificity as Ines et al for the ACR criteria (66% and 97%, respectively) and the SLICC criteria (84% and 82%, respectively).[5] Thus, the performance characteristics of previous iterations of SLE classification criteria in our study are similar to those in other cohorts and therefore further support the generalizability of our conclusions.

One potential limitation of this study is the numbers of patients from non-White ethnicities. Although we had sufficient numbers of patients to estimate performance in multiple subgroups, larger numbers of patients would improve the precision of our estimates. This is particularly true of the Black patient subset. The underrepresentation of Black patients in this cohort may be partially explained by a low number of Black patients in European cohorts. It may also reflect a sampling bias that occurred by chance in the North American cohorts. There is a need for more Black patients with SLE and control group diseases to refine the precision of our estimates evaluating the operating characteristics of the new criteria in this group. Moreover, there were only three centers from Asia and none from Africa or South America contributing patients to this analysis. Future collaborative studies by EULAR and ACR should consider recruiting a broader spectrum of referral centers from these regions to avoid similar

limitations. Investigators are encouraged to test these new criteria in larger numbers of Black patients and other race/ethnic groups as well as SLE centers worldwide.

Secondly, these subgroup analyses were conducted using the same cohort to validate the new criteria. The observed excellent operating characteristics across subgroups is similar in magnitude to the operating characteristics observed in the whole cohort. Others are encouraged to test the performance characteristics in independent cohorts.[25] Two cautionary notes are made to investigators who embark on comparative evaluation of the new criteria to previous classification criteria. The new classification criteria are not diagnostic criteria. Neither EULAR nor ACR endorse the development or validation of diagnostic criteria. [26] It is therefore inappropriate to evaluate these criteria as diagnostic criteria.[26] These criteria have been endorsed for identifying SLE patients for research studies and will facilitate comparisons across studies. The diagnosis of SLE remains in the domain of the appropriately trained physician. These criteria should have no treatment implications for patients.[26] Most importantly, failure to fulfil these criteria should not be used by payers to deny appropriate therapy to patients, which in the case of the EULAR/ACR criteria prominently applies to patients who never had positive ANA.

A critical feature of the reliable application of these classification criteria is appropriate attribution. A criterion should not be counted if there is a more likely explanation than SLE. The requirements to use the precise definition of criteria and ascertain correct attribution for each criterion may reduce the opportunity of testing the criteria performance in pre-existing databases. These requirements are necessary for achieving specificity and facilitating reliable application of the criteria between sites and between studies.

In conclusion, the EULAR/ACR 2019 SLE classification criteria perform well among patients with early disease. The new SLE classification criteria also perform well in both sexes, and among White, Black, Hispanic and Asian patients. More work is needed to improve the precision of the estimates among Black and evaluate criteria performance in other race/ethnicities. Overall, the

new criteria provide added value compared to previous versions of SLE classification. The EULAR/ACR 2019 SLE criteria provide early and accurate classification of SLE across various SLE patient subpopulations.

Acknowledgements.
The authors wish to acknowledge Banita Aggarwal and Keshini Devakandan for data entry, data cleaning, queries to submitting investigators, data cutting and maintenance of the validation cohort and the important role of all participants in the expert Delphi exercise who were not involved in later phases of the project (supplementary material).

REFERENCES

1. Johnson SR, Goek ON, Singh-Grewal D et al. Classification criteria in rheumatic diseases: a review of methodologic properties. *Arthritis Rheum* 2007;57:1119-33.

2. Aringer M, Dorner T, Leuchten N et al. Toward new criteria for systemic lupus erythematosus-a standpoint. *Lupus* 2016;25:805-11.

3. Leuchten N, Hoyer A, Brinks R et al. Performance of Antinuclear Antibodies for Classifying Systemic Lupus Erythematosus: A Systematic Literature Review and Meta-Regression of Diagnostic Data. *Arthritis Care Res (Hoboken)* 2018;70:428-38.

4. Schmajuk G, Hoyer BF, Aringer M et al. Multicenter Delphi Exercise to Identify Important Key Items for Classifying Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)* 2018;70:1488-94.

5. Mosca M, Costenbader KH, Johnson SR et al. Brief Report: How Do Patients With Newly Diagnosed Systemic Lupus Erythematosus Present? A Multicenter Cohort of Early Systemic Lupus Erythematosus to Inform the Development of New Classification Criteria. *Arthritis Rheumatol* 2019;71:91-8.

6. Leuchten N, Milke B, Winkler-Rohlfing B et al. Early symptoms of systemic lupus erythematosus (SLE) recalled by 339 SLE patients. *Lupus* 2018;27:1431-6.

7. Johnson SR, Khanna D, Daikh D et al. Use of Consensus Methodology to Determine Candidate Items for Systemic Lupus Erythematosus Classification Criteria. *J Rheumatol* 2019;46:721-6.

8. Tedeschi SK, Johnson SR, Boumpas D et al. Developing and Refining New Candidate Criteria for Systemic Lupus Erythematosus Classification: An International Collaboration. *Arthritis Care Res (Hoboken)* 2018;70:571-81.

9. Touma Z, Cervera R, Brinks R et al. Associations among classification criteria items within systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2019.

10. Tedeschi SK, Johnson SR, Boumpas DT et al. Multicriteria decision analysis process to develop new classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:634-40.

11. Aringer M, Costenbader K, Daikh D et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:1151-9.

12. Aringer M, Costenbader K, Daikh D et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2019;71:1400-12.

13. Chi H, Teng J, Wang Z et al. Do the 2019 EULAR/ACR SLE classification criteria close the door on certain groups of SLE patients? *Ann Rheum Dis* 2019.

14. Costenbader KH, Schur PH. We need better classification and terminology for "people at high risk of or in the process of developing lupus". *Arthritis Care Res (Hoboken)* 2015;67:593-6.

15. Johnson SR, Urowitz MB, Ibanez D et al. Ethnic variation in disease patterns and health outcomes in systemic lupus erythematosus. *J Rheumatol* 2006;33:1990-5.

16. Cervera R, Doria A, Amoura Z et al. Patterns of systemic lupus erythematosus expression in Europe. *Autoimmunity Reviews* 2014;13:621-9.

17. Low ESH, Krishnaswamy G, Thumboo J. Comparing the 1997 update of the 1982 American College of Rheumatology (ACR-97) and the 2012 Systemic Lupus International Collaborating Clinics (SLICC-12) criteria for systemic lupus erythematosus (SLE) classification: which enables earlier classification of SLE in an urban Asian population? *Lupus* 2019;28:11-8.

18. Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.

19. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.

20. Petri M, Orbai AM, Alarcon GS et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677-86.

21. Ganczarczyk L, Urowitz MB, Gladman DD. "Latent lupus". *J Rheumatol* 1989;16:475-8.

22. Ighe A, Dahlström Ö, Skogh T et al. Application of the 2012 Systemic Lupus International Collaborating Clinics classification criteria to patients in a regional Swedish systemic lupus erythematosus register. *Arthritis Research & Therapy* 2015;17:3.

23. Ines L, Silva C, Galindo M et al. Classification of Systemic Lupus Erythematosus: Systemic Lupus International Collaborating Clinics Versus American College of Rheumatology Criteria. A Comparative Study of 2,055 Patients From a Real-Life, International Systemic Lupus Erythematosus Cohort. *Arthritis Care & Research* 2015;67:1180-5.

24. Oku K, Atsumi T, Akiyama Y et al. Evaluation of the alternative classification criteria of systemic lupus erythematosus established by Systemic Lupus International Collaborating Clinics (SLICC). *Mod Rheumatol* 2018;28:642-8.

25. Adamichou C, Nikolopoulos D, Genitsaridi I et al. In an early SLE cohort the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria classify non-overlapping groups of patients: use of all three criteria ensures optimal capture for clinical studies while their modification earlier classification and treatment. *Ann Rheum Dis* 2020;79:232-41.

26. Dahlstrom O, Sjowall C. The diagnostic accuracies of the 2012 SLICC criteria and the proposed EULAR/ACR criteria for systemic lupus erythematosus classification are comparable. *Lupus* 2019;28:778-82.

Table 1. Sensitivity and Specificity of SLE Classification Criteria Across Sexes, Ethnicities and Disease Duration

	Sensitivity 95% CI			Specificity 95% CI		
	ACR 1982/1997 Criteria	**SLICC 2012 Criteria**	**EULAR/ACR 2019 Criteria**	**ACR 1982/1997 Criteria**	**SLICC 2012 Criteria**	**EULAR/ACR 2019 Criteria**
Sex						
Women	**0.83**	**0.97**	**0.97**	**0.93**	**0.82**	**0.94**
n=1,098	0.80-0.86	0.95-0.98	0.95-0.98	0.91-0.95	0.79-0.86	0.91-0.96
Men	**0.78**	**0.94**	**0.93**	**0.94**	**0.9**	**0.96**
n=172	0.68-0.87	0.87-0.98	0.86-0.98	0.87-0.98	0.82-0.96	0.90-0.99
Disease Duration						
< 1 year	**0.56**	**0.89**	**0.89**	**0.92**	**0.92**	**0.92**
n=34	0.21-0.86	0.52-0.99	0.52-1.00	0.74-0.99	0.74-0.99	0.74-0.99
1 to <3 years	**0.81**	**0.98**	**0.97**	**0.95**	**0.88**	**0.96**
n=196	0.72-0.88	0.93-1.00	0.92-0.99	0.88-0.98	0.80-0.94	0.90-0.99
3 to <5 years	**0.81**	**0.91**	**0.96**	**0.94**	**0.89**	**0.99**
n=157	0.70-0.90	0.82-0.97	0.88-0.99	0.87-0.98	0.80-0.94	0.94-1.00
≥5 years	**0.84**	**0.97**	**0.96**	**0.93**	**0.81**	**0.93**
n=879	0.80-0.87	0.96-0.99	0.94-0.98	0.90-0.95	0.76-0.85	0.89-0.95
Ethnicity						
White	**0.83**	**0.96**	**0.95**	**0.93**	**0.83**	**0.94**
n=941	0.79-0.86	0.94-0.97	0.93-0.97	0.90-0.95	0.80-0.87	0.91-0.96
Black	**0.82**	**0.98**	**0.98**	**1**	**0.92**	**1**
n=68	0.70-0.91	0.90-1.00	0.90-1.00	0.74-1.00	0.62-1.0	0.74-1.00
Hispanic	**0.86**	**1**	**1**	**0.96**	**0.78**	**0.96**
n=124	0.76-0.93	0.95-1.00	0.95-1.00	0.87-1.00	0.65-0.89	0.87-1.00
Asian	**0.77**	**0.99**	**0.97**	**0.93**	**0.91**	**0.91**
n=118	0.65-0.86	0.93-1.00	0.91-1.00	0.82-0.99	0.79-0.98	0.79-0.98

ACR American College of Rheumatology, SLICC Systemic Lupus International Collaborating Clinics, EULAR European League Against Rheumatism

Non-overlapping confidence intervals indicates statistical significance

Table 2. Summary of previously published operating characteristics of SLE classification criteria among patient subsets

Reference	Subset	ACR Criteria		SLICC Criteria	
		Sensitivity % (95%CI)	Specificity % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)
Ethnicity					
Oku et al. 2018	Asian	88% (83 - 92%)	85% (80 - 89%)	99% (96 - 100%)	80% (75 - 85%)
Disease duration					
Ighe et al. 2015	0 – 4 years	ACR 1982 60% (44 - 75%)	NR	89% (73- 97%)	NR
	5 – 9 years	89% (77 - 96%)	NR	89% (77 - 96%)	NR
	10 – 14 years	76% (62 - 86%)	NR	88 % (75 - 95%)	NR
	15 – 19 years	69% (54 - 81%)	NR	84% (71 - 93%)	NR
	≥20 years	86% (75 - 92%)	NR	97% (89 - 100%)	NR
Ighe et al. 2015	0 – 4 years	ACR 1997 82% (65 - 92%)	NR	SLICC* 80% (64 - 91%)	NR
	5 – 9 years	94% (84 - 99%)	NR	84% (71 - 92%)	NR
	10 – 14 years	91% (79 - 98%)	NR	84% (70 - 92%)	NR
	15 – 19 years	86% (72 - 94%)	NR	80% (66 - 90%)	NR
	≥20 years	91 % (82 - 97%)	NR	94% (85 - 98%)	NR
Ines et al. 2015	Any duration	ACR 1997 86%	NR	93%	NR
	≤5 years	76%	NR	89%	NR
	>5 to ≤10 years	82%	NR	90%	NR
	>10 to ≤15 years	88%	NR	95%	NR
	>20 years	94%	NR	97%	NR
Mosca et al. 2019	Early cohort, At diagnosis	66%	92%	84%	82%

*SLICC-12 with a requirement for involvement of at least two organ systems for SLE diagnosis
NR Not reported

Table 3. Frequency of criteria in early and established SLE

Criteria	**Early Disease** <3 years duration	**Established disease** >5 years duration
Constitutional		
Fever	12.6%	15.1%

Mucocutaneous		
Non-scarring alopecia	29.4%	26.4%
Oral ulcers	25.2%	17.9%
Subacute cutaneous or discoid lupus	11.1%	11.3%
Acute cutaneous lupus	34.2%	44.5%
Arthritis	28.7%	69.3%
Neurologic		
Delirium	0%	0.6%
Psychosis	2.1%	1.4%
Seizure	2.1%	5.6%
Serositis		
Pleural or pericardial effusion	18.9%	10.5%
Acute pericarditis	3.5%	6.8%
Hematologic		
Leukopenia	39.9%	44.5%
Thrombocytopenia	41.3%	35.9%
Autoimmune hemolysis	18.9%	19.6%
Renal		
Proteinuria >0.5g/24h	9.8%	7.2%
Renal biopsy Class II or V lupus nephritis	7.0%	8.9%
Renal biopsy Class III or IV lupus nephritis	16.1%	24.7%
Antiphospholipid antibodies		
Anti-cardiolipin antibodies or Anti-β2GP1 antibodies or Lupus anticoagulant	26.6%	28.0%
Complement proteins		
Low C3 or low C4	21.7%	24.7%
Low C3 and low C4	49.7%	46.2%
Highly specific antibodies		
Anti-dsDNA antibody or Anti-Smith antibody	83.2%	78.3%

Figure 1. Forest plot comparing the sensitivity and specificity of SLE classification criteria in Women.

Footnote. Cl 95% confidence interval. All women (n=1098) were included in this analysis

Figure 2. Forest plot comparing the sensitivity and specificity of SLE classification criteria in White subjects

Footnote. Cl 95% confidence interval. All White subjects (n=941) were included in this analysis.

Key Messages

What is already known about this subject?
Classification criteria are needed to identify homogeneous groups of patients for inclusion into clinical trials and observational studies. The 2019 EULAR/ACR Classification Criteria have excellent sensitivity and specificity.

What does this study add?
The 2019 EULAR/ACR criteria perform well among patients with early disease, men, women, White, Black, Hispanic and Asian patients.

How might this impact on clinical practice?
These criteria have superior sensitivity than the ACR criteria and/or superior specificity than the SLICC criteria across many subgroups. They can be used as inclusion criteria for study of novel treatments in systemic lupus erythematosus.