



DR. MASSIMO RADIN (Orcid ID : 0000-0003-1941-2606)

DR. ALESSANDRA BORTOLUZZI (Orcid ID : 0000-0003-2416-8134)

DR. LAURA ANDREOLI (Orcid ID : 0000-0002-9107-3218)

DR. SAVINO SCIASCIA (Orcid ID : 0000-0003-1266-9441)

Article type : Brief Report

Impact of the new 2019 EULAR/ACR classification criteria for Systemic Lupus Erythematosus in a multicenter cohort study of 133 women with undifferentiated connective tissue disease

Massimo Radin-MD¹, Karen Schreiber-MD^{2,3}, Irene Cecchi-MD¹, Alessandra Bortoluzzi-MD⁴, Francesca Crisafulli-MD⁵, Cristiano M. de Freitas-MD⁶, Beatrice Bacco-MD⁷, Elena Rubini-MD¹, Silvia G. Foddai-MD¹, Melissa Padovan-MD⁴, Silvia Gallo Cassarino-MD⁷, Franco Franceschini-MD⁵, Danieli Andrade-MD-PhD⁶, Chiara Benedetto-MD-PhD⁸, Marcello Govoni-MD⁴, Tiziana Bertero-MD⁷, Luca Marozio-MD-PhD⁸, Dario Roccatello-MD¹, Laura Andreoli-MD-PhD⁵ and Savino Sciascia-MD-PhD¹

¹Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, Department of Clinical and Biological Sciences, and SCU Nephrology and Dialysis, S. Giovanni Bosco Hospital, Turin, Italy.

²Department of Thrombosis and Haemophilia, Guy's and St Thomas' Hospital, London, United Kingdom.

³Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

⁴Department of Medical Sciences, University of Ferrara and Azienda Ospedaliero-Universitaria Sant'Anna, Cona (Ferrara), Italy

⁵Department of Clinical and Experimental Sciences, University of Brescia, and Unit of Rheumatology and Clinical Immunology, ASST Spedali Civili, Brescia, Italy

⁶Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

⁷Clinical Immunology Department, AO Mauriziano, Umberto I, University of Turin, Italy

⁸Department of Surgical Sciences, Obstetrics and Gynecology, Sant'Anna University Hospital, University of Turin, Italy

Corresponding Author: Massimo Radin, MD

Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, Department of Clinical and Biological Sciences University of Turin and SCU Nephrology and Dialysis, S. Giovanni Bosco Hospital, Piazza del Donatore di Sangue 3, 10154, Turin, Italy.

Email massimo.radin@unito.it Tel +390112402056

Fax +390112402052

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/ACR.24391](https://doi.org/10.1002/ACR.24391)

This article is protected by copyright. All rights reserved

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Total word count: 1473

Short Title: Application of the 2019 EULAR/ACR classification for SLE to a large cohort of UCTD patients

Key words: Undifferentiated Connective Tissue Disease; Systemic Lupus Erythematosus; Connective tissue disease; Classification Criteria

Acknowledgments: None **Disclosure of Conflicts of Interest:** None declared **Funding:** None declared

Abstract

Objective

We aimed to investigate the impact of applying the 2019 EULAR/ACR classification criteria for systemic lupus erythematosus (SLE) in a previously described cohort of women with undifferentiated connective tissue disease (UCTD).

Methods

This study included 133 women with UCTD. At the time of inclusion into the study, none of the patients meet any classification criteria for other defined systemic connective tissue disease.

Results

When applying the 2019 EULAR/ACR classification criteria to the cohort, 22 patients (17%) fulfilled the classification criteria of SLE. Patients classified as SLE had significantly higher frequency of mucocutaneous manifestations (23%vs.5%; $p=0.007$), arthritis (59%vs.17%; $p<0.001$), isolated urine abnormalities (18%vs.1%; $p<0.001$) and highly specific antibodies (50%vs.15%; $p<0.001$). At follow-up, these patients were statistically significantly more likely to fit also the ACR 1997 and SLICC criteria (18.2%vs. 1.8%; $p<0.001$).

Patients who were diagnosed as SLE per the ACR 1997 and SLICC criteria during the follow-up scored significantly more points in the new 2019 EULAR/ACR classification criteria when compared to the other UCTD patients (mean score 8.3 ± 3.7 vs. 4.5 ± 4 ; $p<0.05$).

Conclusion

When applying the 2019 EULAR/ACR criteria for SLE in a cohort of patient with UCTD, we observed that in up to 17% of cases the original classification could be challenged. New implementation will help to early identify patients at higher risk of developing more severe CTD manifestations.

Significance and Innovations

- When applying the new 2019 EULAR/ACR classification criteria, up to 17% of UCTD patients of our cohort of 133 patients meet the classification criteria for SLE
- Patients meeting the 2019 EULAR/ACR classification criteria for SLE had higher frequency of mucocutaneous manifestations, arthritis, isolated urine abnormalities and highly specific antibodies to SLE.
- This study supports the need of classification criteria for UCTD, especially to identify patients at higher risk of developing more severe CTD manifestations.

1.0 Introduction

Classification criteria for any given disease may provide some framework to help in diagnosis and are frequently used this way for teaching purposes. They traditionally have a high specificity, which generally is counterbalanced by a lower sensitivity. Consequently, few individuals are incorrectly labeled as having a disease (false positives), but a proportion of those with the disease diagnosis may be “missed,” i.e., labeled as not having the disease based on the classification criteria (false negatives). This may make classification criteria inappropriate for use in routine clinical care (1).

The case of undifferentiated connective tissue disease (UCTD) is emblematic. UCTD is an umbrella term describing a condition characterized by clinical and laboratory findings suggestive for connective tissue disease (CTD) but not fulfilling the current classification criteria for any definite CTD (2–4). In September 2019 a new set of classification criteria for systemic lupus erythematosus (SLE) have been proposed (5). As a main difference from previous SLE classification criteria the presence of antinuclear antibodies (ANA) are required as entry criterion, showing a sensitivity of 96.1% and specificity of 93.4%. Several studies applied the new 2019 EULAR/ACR classification criteria for SLE to different cohorts and compared them with the previous classification criteria (6,7). However, it is unknown if the new classifications criteria for SLE might impact on the categorization of patients previously diagnosed with UCTD. Far from being only an academic question, being classified or not as having SLE may pose clinical and logistic consequences, as patients with a diagnosis of ‘SLE’ might be followed-up according to a specific local protocol and have in-label access to certain medications (such as biologics) or may be eligible for the participation in clinical trials.

Herein, we applied the 2019 EULAR/ACR classification criteria for SLE (5) in a previously described cohort of 133 women with UCTD and ANA positivity (8).

2.0 Methods

2.1 Patients

The multicenter retrospective study (8) described the foetal/perinatal and maternal outcomes of a cohort of UCTD patients ever pregnant from 2010 to 2019.

All patients were diagnosed with UCTD according to the established consensus (4,9,10) and were ANA positive. ANA positivity was confirmed and tested as previously described (8).

At the time of pregnancy none of the patients fulfilled the ACR 1997 criteria (11), the SLICC criteria (12) for SLE or other any other defined systemic CTD.

2.2 Statistics:

Categorical variables are presented as number (%) and continuous variables are presented as mean (S.D.). The significance of baseline differences was determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as appropriate. A two-sided P-value <0.05 was statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

3.0 Results

3.1 Patients characteristics of our multicenter cohort

The analysis included 133 women (mean age at data collection 38.3 ± 6.8 years old; mean disease duration at data collection 10.2 ± 5.1 years; mean follow-up at data collection 9.2 ± 4.7 years).

Clinical and laboratory characteristics of the cohort have been previously described elsewhere (8). Briefly, the most common clinical manifestations were joint involvement (57.9%), followed by Raynaud's phenomenon (40.6%), photosensitivity (32.3%) and haematological manifestations (27.1%). Thirty-three patients (24.8%) tested persistently positive for aPL (13) and forty-eight patients (36.1%) were also found to be positive for anti-ENA, being anti-Ro/SSA positivity the most common (45 patients; 33.8%).

3.2 Disease Evolution at Follow-up

Patients had a mean follow-up at data collection of 9.2 ± 4.7 years and during the follow-up, 16 patients (12%) developed novel clinical and/or laboratory features, and their diagnosis was changed in definite CTD. Mean time of follow-up before the diagnosis of definite CTD was achieved was 5.3 ± 2.8 years. Seven patients (5.3%) were later classified according to ACR 1997 criteria (11) and SLICC criteria (12) as SLE, seven

patients (5.3%) as mixed CTD, one patient (0.75%) as systemic sclerosis and one patient as Sjögren's syndrome.

3.3 Application of the 2019 EULAR/ACR classification criteria for SLE

When applying the 2019 EULAR/ACR classification criteria to the cohort, 22 patients (17%) at the time of their first pregnancy scored ≥ 10 points and meet the classification criteria of SLE (5).

Table 1 and Figure 1 summarize the positive clinical and immunological domains when considering all the UCTD patients and the patients that meet the 2019 EULAR/ACR classification criteria for SLE at study entry.

When considering the most frequent positive domains, patients that scored ≥ 10 points, and were therefore classifiable at study entry as SLE by 2019 EULAR/ACR classification criteria, had significantly higher frequency of mucocutaneous manifestations (23% vs. 5%; $p=0.007$), arthritis (59% vs. 17%; $p<0.001$), isolated urine abnormalities [isolated proteinuria ≥ 0.5 g/24h (defined as presence of proteinuria without other urine abnormalities); 18% vs. 1%; $p<0.001$] and highly specific antibodies (50% vs. 15%; $p<0.001$) when compared to patients with UCTD who scored <10 points.

When considering patients who met the 2019 EULAR/ACR SLE criteria, those patients at follow-up were statistically significantly more likely to be classified as having SLE according to the ACR 1997 (11) and SLICC criteria (12) compared to the other UCTD patients (18.2% vs. 1.8%; $p<0.001$), had also fewer years of disease duration (8.23 vs. 10.7; $p<0.05$) and were more likely to develop pre-eclampsia in pregnancy (18% vs. 0%; $p<0.001$).

Patients who were diagnosed as SLE according to the ACR 1997 and SLICC criteria scored significantly higher when applying the 2019 EULAR/ACR classification criteria when compared to the other UCTD patients (mean score 8.3 ± 3.7 vs. 4.5 ± 4 ; $p<0.05$).

Table 2 summarizes the clinical and immunological characteristics of the patients that at the follow-up fulfilled the ACR 1997 and SLICC criteria for SLE.

4.0 Discussion

UCTD is a heterogeneous nosologic entity which includes various clinical scenarios, encompassing from mild symptoms, such as arthralgia, to more severe manifestations

including severe organ involvement such as non-specific interstitial pneumonia. Since the 1980s many studies were carried out to analyze all the aspects of UCTD, from incidence, prevalence, clinical and serological profile to possible evolution over time to a defined CTD. It is now fully accepted that UCTD represents a separate clinical entity and that only up to 30% of UCTD patients will develop a defined CTD in a five years period time (9,10).

To date, UCTD has been reported as one of the most common rheumatic diseases (14), however, there are no validated classification criteria for UCTD patients.

In our previous experience (8), we demonstrated that at follow-up, up to 12% of patients evolved from UCTD to definite CTD(5.3% towards SLE), rates in line with previous experiences reported in the current literature (15). When applying the new 2019 EULAR/ACR classification criteria (5), up to 17% of patients would have been classified as SLE patients before their pregnancy. This has some important implications, as, to date, there are no well-defined recommendations for the diagnosis and, more importantly, the management UCTD patients.

These patients, with higher scores, according to the new 2019 EULAR/ACR classification criteria (5), had higher rates of pre-eclampsia during pregnancy, which suggests that were at higher risk of pregnancy complications.

Taken the above together, this study carries some important messages. One could speculate that an early identification as SLE of patients with a previous diagnosis of UCTD might impact of their clinical management, leading for instance to a closer follow-up. Similarly, it might lead to an in-label access to specific treatment (e.g. belimumab), eligibly to enter a clinical trial or the patients may be eligible to different forms of monetary reimbursement.

Finally, the lack of tailored classification criteria in UCTD might result in underestimating or neglecting patients that fall under the umbrella term UCTD. For the patient this may result in lack of timely follow up, lack of 'awareness'/education of their underlying condition (as they are not classified as having a disease *per se*) with an exhaustive list of possible consequences related to their non-classification.

Some limitations should be acknowledged. First the retrospective nature of the study could potentially affect the reproducibility of the results. Second, since this study carries

an intrinsic gender bias, results might not be consistent when applied to a male population.

In conclusion, when applying the 2019 EULAR/ACR criteria for SLE in a cohort of women with UCTD, we observed that in up to 17% of cases the original classification could be challenged, advocating the need of updated classification criteria for UCTD. This study further supports the concept that in selected cases classification and diagnostic criteria represent a continuum. When discriminating between conditions with a marked overlap, such as SLE and UCTD, the proposal of new classification criteria should balance specificity and sensitivity. When developing new classification criteria, one approach is to select patients and the control groups as representative as possible of the settings (the medical practices) in which these criteria will be used.

5. References

1. Aggarwal R, Ringold S, Khanna D, Neogi T, Johnson SR, Miller A, et al. Distinctions between diagnostic and classification criteria? *Arthritis Care Res (Hoboken)* 2015;67:891–7.
2. LeRoy EC, Maricq HR, Kahaleh MB. Undifferentiated connective tissue syndromes. *Arthritis Rheum* 1980;23:341–3. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7362686>. Accessed March 11, 2019.
3. Alarcón GS, Williams G V, Singer JZ, Steen VD, Clegg DO, Paulus HE, et al. Early undifferentiated connective tissue disease. I. Early clinical manifestation in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of well established connective tissue disease. *J Rheumatol* 1991;18:1332–9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1757934>. Accessed March 13, 2019.
4. Doria A, Mosca M, Gambari PF, Bombardieri S. Defining unclassifiable connective tissue diseases: incomplete, undifferentiated, or both? *J Rheumatol* 2005;32:213–5. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15693073>. Accessed March 13, 2019.
5. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:1151–1159.
6. Carneiro AC, Ruiz MM, Freitas S, Isenberg D. A comparison of three classification criteria sets for Systemic Lupus Erythematosus – a study looking at links to outcome and mortality. *Arthritis Care Res (Hoboken)* 2019.
7. Adamichou C, Nikolopoulos D, Genitsaridi I, Bortoluzzi A, Fanouriakis A, Papastefanakis E, 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* 2019:annrheumdis-2019-216155. Available at: <http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2019-216155>. Accessed November 12, 2019.
8. Radin M, Schreiber K, Cecchi I, Bortoluzzi A, Crisafulli F, De Freitas C, Bacco B, Rubini E, Foddai SG, Padovan M, Gallo Cassarino S, Franceschini F, Andrade D, Benedetto C, Govoni M, Bertero T, Marozio L, Roccatello D AL and SS. A multicentre study of 244 pregnancies in undifferentiated connective tissue disease: maternal/foetal outcomes and disease evolution. *Rheumatology (Oxford)* 2019;Accepted f.
9. Mosca M, Tani C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a new frontier for rheumatology. *Best Pract Res Clin Rheumatol* 2007;21:1011–1023. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18068858>. Accessed March 11, 2019.
10. Mosca M, Tani C, Neri C, Baldini C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD). *Autoimmun Rev* 2006;6:1–4. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17110308>. Accessed March 11, 2019.
11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.

12. Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–2686. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22553077>.

Accessed January 2, 2019.

13. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16420554>. Accessed July 4, 2016.

14. Bourn R, James JA. Preclinical lupus. *Curr Opin Rheumatol* 2015;27:433–439. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26125103>. Accessed March 13, 2019.

15. Bortoluzzi A, Furini F, Campanaro F, Govoni M. Application of SLICC classification criteria in undifferentiated connective tissue disease and evolution in systemic lupus erythematosus: Analysis of a large monocentric cohort with a long-term follow-up. *Lupus* 2017;26:616–622.

Legends of Figures and Tables

Table 1. Positive Domains in All patients and in patients with Systemic Lupus Erythematosus

Table 2. Clinical and immunological characteristic of the patients that at the follow-up fulfilled the ACR 1997 and SLICC criteria for Systemic Lupus Erythematosus

Figure 1. Clinical and Immunological Domains Positive in All patients and Systemic Lupus Erythematosus

| | ALL (n=133) | UCTD (n=111) | SLE* (n=22) | p |
|--------------------------------------|------------------------|-------------------------|------------------------|-----------------|
| Mucocutaneous | 11 | 6 | 5 | .007 |
| Arthritis | 32 | 19 | 13 | <.001 |
| Serositis | 7 | 4 | 3 | .054 |
| Hematologic | 25 | 21 | 4 | .94 |
| Renal** | 5 | 1 | 4 | <.001 |
| Antiphospholipid Antibodies | 28 | 26 | 2 | .131 |
| Complement | 21 | 16 | 5 | .954 |
| Highly Specific Antibodies*** | 28 | 17 | 11 | <.001 |

*Table 1. Positive Domains in All patients and in patients with Systemic Lupus Erythematosus**

All the reported number are percentage; SLE – Systemic Lupus Erythematosus; UCTD – Undifferentiated Connective Tissue Disease;

**As per new classification criteria (5)*

*** Isolated proteinuria $\geq 0.5\text{g}/24\text{h}$ without other urinary anomalies*

**** Highly specific antibodies stand for anti-dsDNA and/or anti-Sm antibodies*

| | Clinical manifestations at study inclusion, prior SLE Diagnosis (ACR1997, SLICC) | Clinical manifestations at follow-up and subsequent SLE Diagnosis (ACR1997, SLICC) |
|------------------|---|---|
| Patient 1 | Thrombocytopenia and Arthritis | After 1 year: LN class IV and acute cutaneous lupus |
| Patient 2 | Acute Cutaneous Lupus and Arthritis | After 9 years: LN class IV |
| Patient 3 | Hypo C3 and Hypo C4 and Arthritis | After 8 years: Discoid Lupus and anti-dsDNA positivity |
| Patient 4 | Thrombocytopenia and anti-dsDNA positivity | After 5 years: Arthritis and leucopenia |
| Patient 5 | Antiphospholipid antibody positivity | After 3 years: LN class IV and anti-dsDNA positivity |
| Patient 6 | Isolated proteinuria(>0.5g/24h) and anti-dsDNA positivity | After 3 years: LN class IV and anti-dsDNA positivity |
| Patient 7 | Arthritis | After 1 year: Acute cutaneous lupus and HypoC3 and HypoC4 |

Table 2. Clinical and immunological characteristic of the patients that at the follow-up presented new clinical manifestations and/or laboratory features, fulfilling the ACR 1997 and SLICC criteria for Systemic Lupus Erythematosus.

Patients that evolved towards a diagnosis of SLE, after a mean follow-up of 4.3 years (S.D. ± 3.2), they met the ACR 1997 and SLICC criteria on follow up.

SLE – Systemic Lupus Erythematosus; LN – Lupus Nephritis

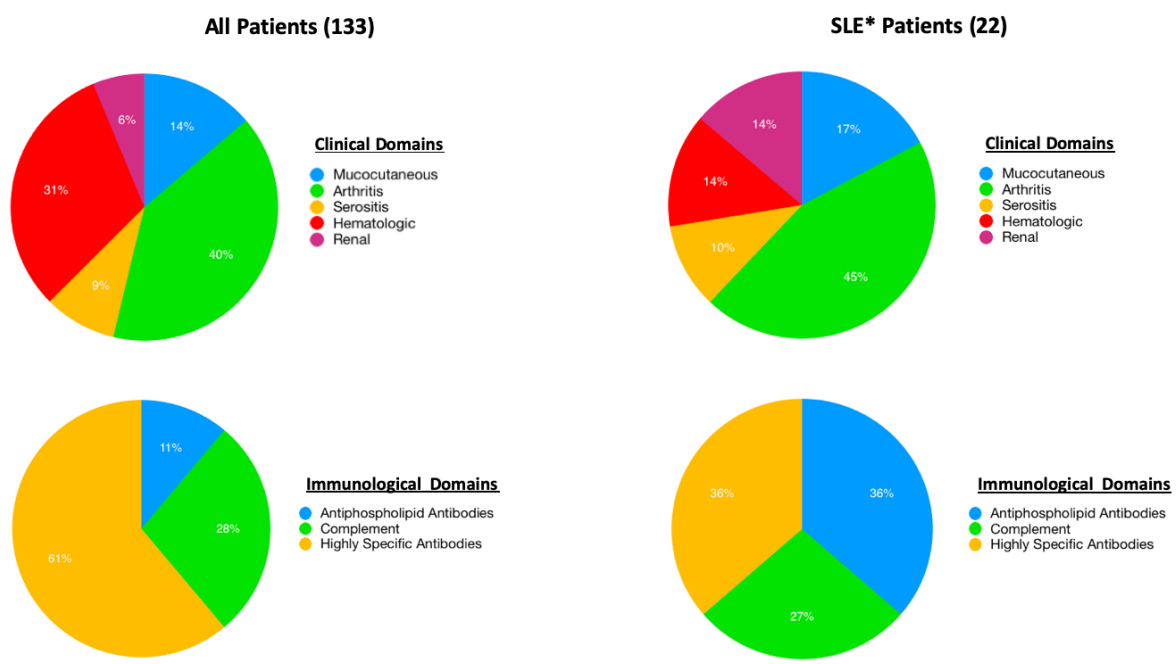


Figure 1. Clinical and Immunological Domains Positive in All patients and Systemic Lupus Erythematosus*

*As per new classification criteria (5)