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UP TO DATE IN INTERNAL MEDICINE: FROM OLDER TO THE NEW 2019 SYSTEMIC LUPUS ERYTHEMATOSUS CLASSIFICATION CRITERIA

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Abstract

Systemic lupus erythematosus (SLE) is considered the prototype of autoimmune diseases, the most complex autoimmune pathology and it is characterized by a wide range of immune processes, important antibodies production as well as an impressive spectrum of clinical manifestations. The great variety of lupus signs and symptoms caused difficulties in establishing well-defined classification criteria, as well as sustaining the clinical diagnosis.

In 2019, a joint initiative of European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) released a new set of classification criteria for SLE, worldwide SLE experts were involved, this being the largest SLE classification effort up to date.

Keywords: *systemic lupus erythematosus, classification criteria.*

Rezumat

Lupusul eritematos sistemic (LES) este considerat prototipul bolilor autoimune, reprezentând cea mai complexă patologie autoimună și fiind caracterizat printr-o gamă largă de procese imune, producție importantă de anticorpi, precum și un spectru impresionant de manifestări clinice. Marea varietate a semnelor și simptomelor de lupus a pus dificultăți în stabilirea unor criterii de clasificare bine definite, precum și în susținerea diagnosticului clinic.

În 2019, o inițiativă comună a European League Against Reheumatism (EULAR) și American College of Reumatology (ACR) a condus la lansarea unui nou set de criterii de clasificare pentru LES, fiind implicați experți LES la nivel mondial, în cel mai mare efort de clasificare a LES până în prezent.

Cuvinte cheie: *lupus eritematos sistemic, criterii de* clasificare.

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Systemic lupus erythematosus (SLE) is considered the prototype of autoimmune diseases, the most complex autoimmune pathology and it is characterized by a wide range of immune processes, important antibodies production as well as an impressive spectrum of clinical manifestations. The great variety of lupus signs and symptoms as well as the successive, additive, sometimes over many years' occurrence of these aspects might bring difficulties in establishing well-defined classification criteria, as well as sustaining the clinical diagnosis. One review of literature showed that twenty five lupus guidelines were published between 2014 and 2018"[1]. However, important aspects of SLE disease are still incomplete acknowledged, like photosensitivity and vasculitis definition or optimal immunosuppression duration"[1].

In 1962, American Rheumatism Association (ARA) Committee on Diagnosis and Therapeutic Criteria defined the first set of SLE classification criteria in 1971 and then published the status of the Criteria for the Classification of SLE[2]. According to this criteria, the pathology was classified as SLE when any or more than four out of fourteen lupus manifestations were present simultaneously or successively, during any interval of follow-up[2].

The SLE criteria were revised in 1982, incorporating the preliminary SLE classification set in order to increase both sensitivity and specificity of the used items and the cutoff value used to define the disease. Therefore, important immunological parameters were included in the 1982 revised criteria for the classification of SLE, namely the antinuclear antibodies (ANAs), assessed by indirect immunofluorescence (IFI), as well as the antibodies to double-stranded DNA (anti-dsDNA) and anti-Sm antibodies. Some of the items referring to similar organ involvement were arranged in the same domain and also less specific characteristics were not included, like Raynaud phenomenon or alopecia[3]. The 1982 revised SLE classification criteria were tested in patients from 18 clinics and proved 96% for both sensitivity and specificity[3].

The next criteria set, the 1997 Update of the 1982 American College of Rheumatology (ACR) Revised Criteria for Classification of SLE, was probably the most frequently used classification criteria in research works. This criteria set was more reliable for clinical studies having a greater specificity. In the 1997 update ACR criteria, for the immunological items, the positive lupus cell preparation was removed and for the antiphospholipid antibodies assessment the false syphilis positivity was completed with lupus anticoagulant and anticardiolipin (IgM and IgG serotypes) antibodies tests[4]. At least four serially or simultaneous criteria

sustained the classification of the clinical case as SLE. Clinician experts observed that there still are SLE cases, especially in early disease that however cannot meet the 1997 SLE ACR criteria. Thus, a new project of classification criteria was initiated in order to obtain an improved classification set that includes new immune markers and has better sensitivity and clinical relevance for the SLE diagnosis[5].

Altogether, it is important to stress that classification criteria are not designed for diagnosis or treatment decisions and so, they should never be used to exclude patients who do not fully meet these criteria from receiving appropriate therapies.

The Systemic Lupus International Collaborating Clinics (SLICC) group revised and validated the ACR SLE classification criteria. They were derived from a set of 702 expert-rated lupus patient scenarios. The items were split into clinical criteria and immunological criteria and so, the lupus disease was sustained when at least four out of seventeen criteria (including at least one clinical and one immunologic criterion) or lupus nephritis on renal biopsy in patients with either positive ANAs or anti-dsDNA[5]. The 2012 SLICC classification criteria reflect the disease specific heterogeneity, having a high sensitivity that allows the SLE diagnosis even in early stages. As expected, the other aspects are related to the risk of “false” SLE classification (due to occurrence of non-specific features like arthritis, alopecia, leukopenia etc.). SLICC criteria added histology-proven nephritis compatible with SLE as sufficient for classification, if ANA or anti-dsDNA present. While achieving their goal of increasing sensitivity, the SLICC criteria have lower specificity than the 1997 ACR criteria. In their cohort of the 2012 SLICC criteria validation, the specificity was lower (84% vs. 96%) while the sensitivity was higher (97% vs. 83%) than the ACR criteria[5], but further one meta-analysis found similar specificity (96% vs. 98%), but higher sensitivity (95% vs. 90%) when comparing the 2012 SLICC criteria with the 1997 ACR in adult patients[6], difference that was than show in other research to be more evident in early disease patients[7].

In 2019, a joint initiative of European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) released a new set of classification criteria for SLE, validated using lupus patients' data sets. For defining the new criteria, worldwide SLE experts were involved, this being the largest SLE classification effort up to date[8].

The experts highlight again the fact that this new criteria set was particularly designed for research purpose and not for clinical diagnosis. Therefore, considering the disease heterogeneity, in daily clinical practice, SLE cases not fulfilling the current classification criteria are encountered and so, they must never be used to exclude these patients from receiving appropriate therapies.

The general structure of previous classifications sets was mainly similar and the new task tried in 2019 to change the general paradigm in order to obtain both higher sensitivity and specificity. Thus, the new 2019 EULAR/ACR criteria are designed differently regarding previous lupus criteria sets, namely they can be applied mainly in patients under suspicion of SLE especially in early disease. Moreover, similarly to the new gout or polymyalgia rheumatica criteria, the structure of the new 2019 SLE criteria was changed by introducing an obligatory entry criterion: the positivity of ANA (anytime) by immunofluorescence (IFI) on HEp-2 cells ≥1:80 or a solid phase ANA screening immunoassay with at least equivalent performance. Therefore, the ANA positivity is

now mandatory in establishing the SLE classification[8].

Furthermore, in order to sustain a diagnosis at least one clinical criterion must be found. When compared to previous criteria sets, the new set is fulfilled at a cut off of 10 points from different domains, but a different "power" was attributed for each parameter and only the highest weighted criterion is counted for each domain. Thus, the criteria are not simply counted out of the full number of the criteria comprised in the classification set.

The criteria are divided into ten domains: fever, renal (class II to IV nephritis and proteinuria more than 0.5g per day), serositis (pleural or pericardial), muco-cutaneous (acute, subacute, oral ulcers, alopecia), central nervous system (seizure, psychosis, and delirium), joint involvement (arthritis), hematological (autoimmune hemolysis, thrombocytopenia, leukopenia, complement), SLE-specific antibodies and antiphospholipid (APS) antibodies, respectively. Each criterion is counted when no other present pathology can explain its occurrence. Only the item weighted highest in the respective domain is counted for the final score. There is need of a total score equal or more than 10 points (out of a theoretical maximum 51 points) in order to fulfill the classification criteria (see Table 1). The current system changed therefore the yes/no decision for clinical involvement to a point system in which only one manifestation for each domain, the one that is higher weighted, is counted[8].

A literature review as well as a meta-regression evaluation of the available diagnosis data was realized in order to test de performance of ANA to sustain the SLE diagnosis. The review showed that ANA at 1:80 titer has a negative likelihood ratio (LR) of 0.03 (CI 0.02 -0.04) for the SLE diagnosis, better results than that of compression ultrasound use in ruling out deep vein thrombosis[9]. Even if the ANA is basically the SLE immunological marker, regarding the entry criteria formulated, it is important to mention that up to 5% of the SLE patients appear to be ANA negative. In this clinical situation the current classification criteria could not be applied[9], and this is only one of the reasons why the classification criteria are proposed for research and not for clinical diagnosis and so, the 2019 SLE criteria do not necessary exclude the SLE diagnosis in ANA seronegative cases.

The IFI is a complex method that is difficult to be standardized, therefore false-negative cases might also be assumed. The ANA titers are also fluctuating over time, the history of ANA positivity, regardless the ANA status in the moment of the classification criteria use, could be noted as valid entry criterion. Another issue is related to ANA positivity in IFI due to anti-DSF70 antibodies, serological markers that are supposed to rule out a

Cut-off ≥10 points additive criteria (not simultaneously), occurrence on one occasion is enough, at least one clinical criterion, only the highest weighted criterion is counted for each domain		
Entry criterion : ANA - IIF ≥ 1: 80 (Hep-2 cells or equivalent)		
Additive criteria Domain		Points
Constitutional - Fever	> 38.3 º	2
Renal	Class III/ IV Nephritis	10
	Class II/ V Nephritis	8
	Proteinuria > 0.5g/ day	4
Serositis	Acute pericarditis	6
	Effusion (pleural/ pericardial)	5
Mucocutaneous	Acute cutaneous lupus	6
	Subacute or discoid cutaneous lupus	4
	Oral ulcers	2
	Non-scarring alopecia	2
Neuropsyhiatric	Seizure	5
	Psychosis	3
	Delirium	2
Joint involvement	Arthritis	6
Hematologic	Autoimmune hemolysis (reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH and positive Coombs test)	4
	Thrombocytopenia < 100000/dL	4
	Leukopenia < 4000/dL	3
Complement	C3 and C4 low	4
	C3 or C4 low	3
SLE-specific antibodies	Anti-Sm or anti-DNA antibodies	6
APS-specific antibodies	Anti-cardiolipin IgA, IgM, or IgG or Anti-beta 2 glycoprotein I IgA, IgM, or IgG or Lupus anticoagulant	2
ANA - IIF – Antinuclear antibodies by indirect immunofluorescence; APS – antiphospholipid syndrome; LDH – lactate dehydrogenase ; SCLE – subacute cutaneous lupus erythematosus		

***Table 1**. The 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria for Systemic Lupus Erythematosus(8)*

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systemic immune involvement, SLE included [9]. Therefore, such cases should be analyzed separately in clinical practice and the criteria should only be apply when there is clinical SLE suspicion.

The ANA evaluation was the first step in defining the new criteria set[8 9]. This step was followed by literature review made to identify 21 candidate criteria[10], criteria reduction, criteria definition and weighing based on their performance and, finally, analysis compared to already available SLE classification criteria, using a validation cohort including 696 SLE patients and 574 controls[8]. In order to determine what clinical manifestations are related to the SLE diagnosis, the data of a multicenter cohort of 389 patients with early SLE were compared to those of 227 with SLE-mimicking conditions. In this cohort, of early SLE disease, the patients' diagnosis was sustained based on the clinical experience and judgement of experienced rheumatologists[11]. The lupus symptoms already included and counted for classification in ACR 1997 or SLICC 2012 proved to be significantly more encountered in the study SLE cohort. Symptoms that are not included in previous criteria sets (fever and weight loss) were associated with the SLE diagnosis, but only fever was classified as possible criterion. The new 2019 SLE classification set includes for the first time the fever of unknown origin as clinical criterion counted with 2 points, fever being more common in SLE patients vs mimicking conditions (34.5% vs 13.7%, $p<0.001$)[11]. However, it is of utmost importance to stress that fever, like all other criteria manifestations, should only be counted if no better explanation exists and that infections have been suspected first in any patient with (potential) SLE, particularly when CRP is elevated. Some other symptoms considered but found to be less common in early SLE were Raynaud's phenomenon, sicca symptoms, dysphagia and fatigue[11].

For this step of the development of new classification criteria when patients with newly diagnosed SLE were analyzed for better identification of these patients as the inclusion of these patients in studies will allow identifying therapies designed to stop the disease progression.

However, the patients' inclusion was done from rheumatology centers and this might be a bias of selection as patients presenting initially to other specialties might have different disease patterns[11]. For example, arthritis might be more frequent in these patients than in those presenting in other specialties than rheumatology (pediatric SLE or dermatology with skin dominant disease)

In clinical practice, the classification criteria will perform differently in SLE population and moreover, each clinical case should be regarded upon all its aspects, remembering

that available tools are proposed for classification, for use in research studies and not directly for patients' diagnosis. One recent analysis showed that for childhood-onset SLE, the specificity of 2012 SLICC criteria was better than that of the 2019 EULAR/ ACR at the first visit as well at one year (80.9% vs 67.4%, p=0.008 and 76.4% vs 58.4%, p=0.001, respectively), but similar sensitivities. When the cut-off for defining the classification was moved from 10 to 13 points, the 2019 EULAR/ ACR criteria scored better [12]. Future studies will further test the usefulness of the new SLE classification criteria in routine clinical practice.

Points to remember

- The new SLE 2019 EULAR/ACR criteria are classification criteria (design mainly for research purpose) and not diagnosis criteria.
- The ANA positivity is now mandatory, marked as entry criteria.
- Similar to previous SLE classifications sets, the criteria are additive and not necessarily simultaneous.
- A minimum of 10 points should be obtained in order to sustain the SLE diagnosis.
- For each domain (7 clinical and 3 immunological domains), only the feature with the highest score is counted.
- There are ten domains (constitutional, renal, serositis, mucocutaneous, neuropsyhiatric, joint, hematologic, complement, SLE antibodies, APS antibodies).

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