Reumatizam 2021;68(Supl 1/Suppl 1):1–14
https://doi.org/10.33004/reumatizam-supp-68-1-1

KLASIFIKACIJSKI KRITERIJI ZA SISTEMSKI ERITEMSKI LUPUS

CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Višnja Prus[1]

[1]Zavod za reumatologiju, kliničku imunologiju i alergologiju,
Klinika za unutarnje bolesti Medicinskog fakulteta Sveučilišta J. J. Strossmayera u Osijeku,
Klinički bolnički centar Osijek, Osijek / Division of Rheumatology, Clinical Immunology and Allergology,
Department of Internal Medicine of the Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek,
University Hospital Centre Osijek, Osijek

Adresa autora za dopisivanje / Corresponding author's address:
Doc. dr. sc. Višnja Prus, dr. med.
Zavod za reumatologiju, kliničku imunologiju i alergologiju
/ Division of Rheumatology, Clinical Immunology and Allergology
Klinika za unutarnje bolesti / Department of Internal Medicine
Medicinski fakultet Osijek / Faculty of Medicine Osijek
Klinički bolnički centar Osijek / University Hospital Centre Osijek
J. Huttlera 4
31 000 Osijek
Hrvatska / Croatia
e-pošta: prus1@net.hr

Primljeno / Received: 13. 9. 2021. / 13 September 2021
Prihvaćeno / Accepted: 23. 9. 2021. / 23 September 2021

Sažetak

Sistemski eritemski lupus (SLE) jest sustavna autoimunosna upalna bolest izrazito heterogene kliničke slike, nepoznate etiologije. Zbog potrebe za homogeniziranjem različitih fenotipa (kliničkih i laboratorijskih) te provođenja kliničkih studija s ciljem boljeg razumijevanja i liječenja ove kompleksne bolesti, tijekom desetljeća formirani su i korišteni različiti klasifikacijski alati – kriteriji temeljeni na zastupljenosti pojedinih očitovanja bolesti i laboratorijskih pokazatelja. Nerijetko su korišteni kao pomoćni dijagnostički kriteriji, što nije opravdano s obzirom na njihovu visoku specifičnost, a nisku osjetljvost. Tijekom vremena kriteriji su se mijenjali, nadopunjavali i korigirali, što je rezultiralo većom specifičnošću i osjetljivošću. I dalje je mišljenje iskusnog kliničara temelj dijagnoze SLE-a, dok je namjena klasifikacijskih kriterija formiranje dobro definirane homogene kohorte za klinička istraživanja.

Ključne riječi: Sistemski eritemski lupus – dijagnoza, klasifikacija

Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune inflammatory disease with highly heterogeneous clinical manifestations and of unknown etiology. Due to the need to homogenise different phenotypes (clinical and laboratory) and conduct various clinical studies, in order to better understand and treat this complex disease, different classification tools have been developed and used over the decades – criteria based on the presence of individual disease manifestations and quality indicators in laboratory medicine. Classification tools were often used as auxiliary diagnostic criteria, which is not justified due to their high specificity and low sensitivity. The criteria have changed, they were supplemented and corrected over time, which resulted in a higher level of specificity and sensitivity. The opinion of an expert clinician is still the basis for the diagnosis of SLE, while the purpose of the classification criteria is to form well-defined homogeneous cohorts for further clinical research.

Keywords: Lupus erythematosus, systemic – classification, diagnosis

UVOD

Sistemski eritemski lupus (SLE – prema engl. *Systemic Lupus Erythematosus*) jest kronična upalna autoimunosna bolest koja zahvaća različite organe i organske sustave (1,2,3). SLE je „klasična" autoimunosna bolest čije je obilježje stvaranje autoantitijela i imunokompleksa te njihovo odlaganje u tkiva.

Izrazito je heterogene kliničke slike („bolest sa sto lica") koja uz imunološku heterogenost otežava postavljenje dijagnoze, posebice u ranoj fazi. Tijekom vremena izmjenjuju se faze remisije, niske aktivnosti i relapsa bolesti. Oštećenja organa ne javljaju se istovremeno, s vremenom se nakupljaju, što dodatno otežava ranu dijagnozu bolesti.

Fenotip bolesti, odnosno skup svih njezinih kliničkih i laboratorijskih očitovanja, može se opisati na nekoliko razina i stupnjeva složenosti (5). Zadnjih desetljeća razvijeno je više različitih instrumenata kojima se opisuje fenotip bolesti: 1. klasifikacijski kriteriji, kojima se opisuju najvažniji simptomi, znakovi i dijagnostičke pretrage karakteristične za SLE (6– 9), 2. indeksi aktivnosti bolesti (10), 3. indeksi oštećenja (11).

Instrumenti su razvijeni kako bi se omogućilo ujednačeno praćenje bolesnika te usporedba rezultata različitih istraživanja.

KLASIFIKACIJSKI KRITERIJI

Klasifikacijske kriterije za određenu bolest čine standardizirane definicije uz formiranje dobro definirane i relativno homogene kohorte s ciljem usporedbe i interpretacije rezultata različitih studija (12). Značajka klasifikacijskih kriterija jest visoka specifičnost, što znači da će vrlo malo bolesnika koji ne boluju od određene bolesti biti obuhvaćeno kriterijima (tzv. lažno pozitivni), dok će zbog niže osjetljivosti dio oboljelih biti proglašen „zdravima" (tzv. lažno negativni). Dijagnoza SLE-a postavlja se kombiniranjem kliničkih znakova, laboratorijskih, imunoloških nalaza i pretraga, uz poznavanje epidemiološke situacije. Zbog niske osjetljivosti klasifikacijski kriteriji nisu dobar dijagnostički alat u rutinskoj kliničkoj praksi; koriste se samo kao pomoćno sredstvo.

Kriteriji Američkoga reumatološkog društva (engl. American College of Rheumatology, *ACR)*

Prvo izdanje klasifikacijskih kriterija SLE-a Cohena i sur. objavljeno je 1971. godine. Prvi, preliminarni kriteriji za SLE sadržavali su 14 elemenata i bili visoko osjetljivi, no samo za bolesnike s dugotrajnom bolesti (7,13–15). Zbog nedovoljno visoke specifičnosti preliminarnih kriterija u kojima su kožne manifestacije bile suviše zastupljene, dok istovremeno nisu bili uključeni ostali organi u dovoljnoj mjeri, ACR je 1982.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory autoimmune disease that affects various organs and organ systems (1,2,3). SLE is a "classic" autoimmune disease characterised by the production of autoantibodies, immunocomplexes and their deposition in tissues.

This disease has highly heterogeneous clinical manifestations (it is commonly known as "the disease with a thousand faces") which, in addition to its immunological heterogeneity, make it difficult to diagnose, especially at an early stage. Phases of remission, low activity, and relapse of the disease alternate over time. Organ damage does not occur simultaneously, it accumulates over time, which further complicates the early diagnosis of the disease.

The phenotype of the disease, that is, the set of all its clinical and laboratory manifestations, can be described at several levels and degrees of complexity (5). In recent decades, several different tools have been developed in order to describe the disease phenotype: 1. classification criteria, which describe the most important symptoms, signs and diagnostic tests characteristic of SLE (6–9), 2. disease activity indices (10), 3. damage indices (11).

These tools have been developed to allow uniform patient monitoring and comparison of different studies' results.

CLASSIFICATION CRITERIA

Classification criteria for a particular disease consist of standardised definitions in addition to the formation of a well-defined and relatively homogeneous cohort with the aim of comparing and interpreting the results of different studies (12). One of the features of the classification criteria is high specificity, which means that very few patients who do not suffer from a particular disease will be covered by the criteria (the so-called "false-positive" outcome), while, due to lower sensitivity, some patients will be declared "healthy" (the so-called "false-negative" outcome). The diagnosis of SLE is made by combining clinical signs, laboratory, immunological findings and tests, in addition to the knowledge of the epidemiological situation. Due to their low sensitivity feature, classification criteria are not a good diagnostic tool in routine clinical practice; they are used only as an auxiliary tool.

The American College of Rheumatology (ACR) Classification Criteria

The first edition of the classification criteria for SLE, prepared by Cohen et al., was published in 1971. The first, preliminary criteria for SLE included 14 elements and they were highly sensitive, but only for patients

objavio njihovu reviziju (ACR-1982). Izostavljen je Raynaudov fenomen i alopecija iz kožnih kriterija, izdvojena su ANA (antinuklearna protutijela) kao poseban kriterij, a prag proteinurije snižen je s 3,5 g/dan na 0,5 g/dan te je dodana i prisutnost staničnih cilindara u urinu uz radiološki potvrđen neerozivni artritis. Dopunjeni klasifikacijski kriteriji Tana iz 1982. godine (8) validirani su i ustanovljena je viša osjetljivost i specifičnost od preliminarne verzije iz 1971. godine (17,18). Uvjet za uključivanje bolesnika u studiju bilo je ispunjenje ukupno četiriju kriterija, neovisno o kojim kriterijima se radi.

Somogy je 1993. godine validirao ACR-kriterije na populaciji od 100 bolesnika koji boluju od SLE te 100 bolesnika koji boluju od drugih reumatskih bolesti liječenih u Zavodu za kliničku imunologiju i reumatologiju KBC-a Zagreb. Rezultati su pokazali velike razlike u doprinosu određenog kriterija za SLE (19).

Daljnjim napretkom u dijagnostici i razumijevanju patogeneze bolesti ustanovljena je povezanost SLE i antifosfolipidnog sindroma (engl. APS) te je 1997. godine predloženo kriterijima dodati i antifosfolipidna protutijela (21). Ujedno je dogovoreno da se kriterij pozitivnih LE stanica izbaci. Hochbergovu reviziju tih kriterija iz 1997. godine prihvatilo je Američko društvo za reumatologiju (ACR) (9,20).

Navedeni su kriteriji od svoje objave u širokoj upotrebi. Služe za opis kliničke slike bolesti u bolesnika s već postavljenom dijagnozom SLE-a, dok nepotpuni lupus (NLE) koji ne zadovoljava kriterije, a klinički i imunološki ukazuje na mogući razvoj lupusa, u ranoj fazi može ostati neprepoznat. Riječ je o 11 očitovanja bolesti (od kojih neka imaju podskupine ili potkriterije) koja uključuju simptome, znakove i nalaze dijagnostičke obrade karakteristične za SLE. Za klasifikaciju bolesnika potrebno je ispuniti 4 od ukupno 11 kriterija. Kriteriji su kumulativni, pribrajaju se tijekom vremena – jedanput ispunjen kriterij prema definiciji kriterija ispunjen je trajno (tablica 1) (8,9).

Klasifikacijski kriteriji često se koriste kao pomoćna mjera u postavljanju kliničke dijagnoze bolesti, s obzirom na to da do danas nisu razvijeni dijagnostički kriteriji za SLE. Kriteriji nisu dovoljno osjetljivi za bolesnike u ranoj fazi bolesti unatoč njihovoj visokoj osjetljivosti (>85%) i specifičnosti (>95%). U pacijenata s dugotrajnom bolesti, njihova osjetljivost na početku bolesti može biti značajno niža.

Striktno pridržavanje navedenih kriterija u dijagnostičke svrhe može odgoditi postavljanje dijagnoze, budući da su klasifikacijski kriteriji razvijeni s ciljem da budu u prvom redu specifični, a tek potom osjetljivi i namijenjeni su homogeniziranju skupina pri kliničkim istraživanjima (10,21,22).

Postoje bolesnici s jasno dijagnosticiranim SLE-om koji ne zadovoljavaju četiri klasifikacijska kriterija, who suffered from a long-term, that is, chronic disease (7, 13–15). Due to the insufficiently high specificity of the preliminary criteria in which cutaneous manifestations were overrepresented, while other organs were not sufficiently represented, the ACR published the revised classification criteria in 1982 (ACR-1982). Raynaud's phenomenon and alopecia were omitted from the criteria related to cutaneous manifestations, ANAs (antinuclear antibodies) were singled out as a special criterion, and the proteinuria threshold was lowered from 3.5 g / day to 0.5 g / day, and the presence of cellular casts in urine was added along with radiologically confirmed non-erosive arthritis. Tan's updated classification criteria from 1982 (8) were validated, and a higher sensitivity and specificity were established in comparison with the preliminary version from 1971 (17,18). The condition for inclusion of patients in the study was the fulfilment of a total of four criteria, regardless of the criteria involved.

In 1993, Somogy validated the ACR criteria on a population of 100 patients who suffered from SLE and 100 patients who suffered from other rheumatic diseases treated at the Division of Clinical Immunology and Rheumatology, University Hospital Centre Zagreb. The results showed large differences in the contribution of a particular criterion for SLE (19).

Further advances in the diagnosis and understanding of the disease pathogenesis have established a connection between SLE and antiphospholipid syndrome (APS), and in 1997, a proposition was made for the addition of antiphospholipid antibodies to the criteria (21). It was also agreed that the criterion of positive LE cells be omitted from the criteria. Hochberg's 1997 revision of these criteria was accepted by the American College of Rheumatology (ACR) (9,20).

The aforementioned criteria have been widely used ever since the date of their publication. They are used to describe the clinical features of the disease in patients who are already diagnosed with SLE, while incomplete lupus erythematosus (ILE), which does not meet the criteria but clinically and immunologically indicates the possible development of lupus, may remain unrecognised at an early stage. These are 11 disease manifestations (some of which have subgroups or subcriteria) that include symptoms, signs, and diagnostic processing findings characteristic of SLE. In order to classify patients according to the aforementioned criteria, 4 out of a total of 11 criteria must be met. The criteria are cumulative, they are added over time – once the criterion is met according to the definition of the criterion, it is met permanently (Table 1) (8,9).

Classification criteria are often used as an auxiliary measure in making a clinical diagnosis of the disease, as no diagnostic criteria for SLE have been developed to date. The criteria are not sensitive enough for pa-

Tablica 1. Klasifikacijski kriteriji Američkoga reumatološkog društva (engl. kr. ACR) – revizija iz 1997. godine (prema referenciji br. 9)

Table 1 Classification criteria of the American College of Rheumatology (ACR) – the 1997 revision (according to reference No 9)

Kriterij ACR-a / ACR Criterion	Definicija / Definition
Leptirasti eritem / Malar Rash	Fiksni eritem, u razini ili iznad razine kože obraza, sklon poštedi nazolabijalnih brazda / Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Diskoidni osip / Discoid rash	Crveni uzdignuti kožni plakovi prekriveni keratotičnim ljuskama i folikularnim čepovima; atrofično ožiljkavanje može nastupiti u starijim lezijama / Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Fotosenzitivnost / Photosensitivity	Kožni osip kao rezultat neuobičajene reakcije na Sunčevu svjetlost, prema anamnezi ili opservaciji liječnika / Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oralne ulceracije / Oral ulcers	Oralne ili nazofaringealne ulceracije, obično bezbolne, uočio ih liječnik / Oral or nasopharyngeal ulceration, usually painless, observed by physician
Artritis / Arthritis	Neerozivni artritis koji zahvaća ≥2 periferna zgloba, karakteriziran osjetljivošću na dodir, oteklinom ili izljevom / Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Serozitis / Serositis	a) pleuritis – uvjerljiva anamneza pleuritične boli ili trenje koje je čuo liječnik ili dokaz pleuralnog izljeva / pleuritis – convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion b) perikarditis – dokumentiran EKG-om, trenjem ili dokazom perikardijalnog izljeva / pericarditis – documented by electrocardiogram or rub or evidence of pericardial effusion
Bubrežni poremećaj / Renal Disorder	a) perzistentna proteinurija >0,5 grama na dan ili više od 3+ / persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed b) stanični cilindri – eritrocitni, hemoglobinski, granularni, tubularni ili miješani / cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed
Neuropsihijatrijski poremećaj / Neurologic Disorder	a) epilepsija / seizures b) psihoza / psychosis (obje u izostanku podražajnih lijekova ili poznatoga metaboličkog poremećaja kao što su uremija, ketoacidoza ili elektrolitni disbalans / both in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance)
Hematološki poremećaj / Hematologic Disorder	a) hemolitička anemija – s retikulocitozom / hemolytic anemia – with reticulocytosis b) leukopenija – < 4000/mm^3 u barem dva navrata / leukopenia – < 4,000/mm^3 on ≥ 2 occasions c) limfopenija – < 1500/mm3 u barem dva navrata / lymphopenia – < 1,500/ mm^3 on ≥ 2 occasions d) trombocitopenija < 100.000/mm^3 bez podražajnih lijekova / thrombocytopenia – <100,000/ mm^3 in the absence of offending drugs
Imunosni poremećaj / Immunologic Disorder	a) anti-dsDNK-protutijela u abnormalnom titru / anti-DNA: antibody to native DNA in abnormal titer b) prisutnost protutijela protiv Sm-nuklearnog antigena / anti-Sm: presence of antibody to Sm nuclear antigen c) pozitivan nalaz antifosfolipidnih protutijela / positive finding of antiphospholipid antibodies on: – abnormalna razina antikardiolipinskih protutijela IgM ili IgG u serumu ili / an abnormal serum level of IgG or IgM anticardiolipin antibodies – pozitivan rezultat testa za lupusni antikoagulans dobiven standardnom metodom ili / a positive test result for lupus anticoagulant using a standard method or – lažno pozitivan test na sifilis / a false-positive test on syphilis
Antinuklearna protutijela / Positive Antinuclear Antibody	Abnormalni titar antinuklearnih protutijela određen imunofluorescencijom ili ekvivalentnim esejom / An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time

odnosno postoje bolesnici s jasno definiranim drugim sistemskim bolestima veziva koji zadovoljavaju četiri ili više klasifikacijskih kriterija. Također, s vremenom se uočilo da neki parametri koji su važni u svakodnevnom kliničkom radu nisu uključeni u klasifikacijske kriterije (10,11).

S obzirom na to da je tijek bolesti obilježen periodičkom afekcijom jednoga organskog sustava za drugim, pacijenti mogu bolovati godinama kako bi ispunili klasifikacijske kriterije. Upravo ova činjenica osnovni je problem postojeće klasifikacije i postavljanja pravodobne dijagnoze.

tients in the early stages of the disease despite their high sensitivity (> 85%) and specificity (> 95%). Patients who suffer from a chronic, that is, long-term disease, may have a significantly lower sensitivity at the onset of the disease.

Strict adherence to these criteria for diagnostic purposes may delay diagnosis, as classification criteria have been developed to be primarily specific and secondarily sensitive and intended to homogenise groups in clinical trials (10,21,22).

There are patients with clearly diagnosed SLE who do not meet the four classification criteria, and there

Unatoč dugotrajnoj primjeni klasifikacijskih kriterija ACR-a još nije potpuno odgovoreno na pitanje u kojoj je mjeri ukupan broj kriterija pokazatelj težine bolesti (23).

Tijekom vremena učinjene su dodatne statističke obrade u svrhu unaprjeđivanja postojećih kriterija. Kalibrirani kriteriji Klinike u Clevelandu (*Cleveland Clinic weighted criteria*) te Bostonski kalibrirani kriteriji (*Boston weighted criteria*, BW) dobiveni su korištenjem Bayesovog teorema. BW-klasifikacija boduje svaki kriterij posebno (24–26). Posljedično, neke su definicije kriterija revidirane. Nakon usporedbe, ustanovljeno je da na ovaj način modificirani kriteriji imaju veću osjetljivost, ali manju specifičnost od aktualnih ACR-kriterija. Edworthy i sur., koristeći statističku metodu rekurzivnog particioniranja, pokušali su ustanoviti važnost pojedinog kriterija u klasifikaciji SLE-a. Koristeći podatke iz ACR-1982 klasifikacije, autori su uvrstili dvije derivirane varijable: standardiziranu ANA (antinuklearna protutijela) i vrijednosti komplementa (C), dok su imunološki i hematološki kriteriji zastupljeni svaki zasebno. Ovom je metodom postignuta visoka specifičnost i osjetljivost te je većina ispitanika pravilno klasificirana u skupine bolesnih i zdravih (27).

U Hrvatskoj se dosadašnja saznanja o obilježjima bolesnika sa SLE-om temelje na rezultatima istraživanja iz baza podataka triju sveučilišnih centara (Zagreb, Osijek, Rijeka). Prus je ispitivala epidemiološke značajke SLE-a u Istočnoj Hrvatskoj (28), Cerovec je 2012. ispitivao prevalenciju ACR-kriterija u pacijenata oboljelih od lupusa liječenih u Zavodu KBC-a Zagreb (29, 30), M. Majer model praćenja SLE u RH (31), Padjen analizu uzroka smrti oboljelih od SLE-a i kvantifikaciju fenotipa (6,32), F. Anić povezanost težine bolesti i aktivnosti bolesti s novim kriterijima (33), Bakula vrjednovanje kvalifikacijskih kriterija u SLE (34). Postoji potreba za objedinjavanjem podataka uz daljnju širu suradnju.

Usporedbe rezultata različitih istraživanja i dalje su otežane zbog metodoloških razlika. Studije se međusobno razlikuju po tome jesu li prospektivne ili retrospektivne, prema razdoblju provođenja, demografskim karakteristikama bolesnika, broju uključenih bolesnika, prema izvorima podataka i opsegu prikupljenih podataka te prema tomu jesu li rezultati studije uspoređeni sa sličnim parametrima dobivenima analizom opće populacije (33,34). Razlikuju se također prema načinu definiranja početka bolesti – radi li se o prvom postavljanju kliničke dijagnoze SLE-a ili trenutku ispunjavanja četiriju ili više klasifikacijskih kriterija ACR-a (35,36).

Iako kriteriji iz 1997. godine (ACR-1997) nikada nisu validirani, do danas se koriste u svrhu istraživanja, ali i kao i pomagalo u kliničkoj praksi za postavljanje dijagnoze SLE-a.

are patients with clearly defined other systemic connective tissue diseases who meet four or more classification criteria. In addition to that, over time, it has been observed that some parameters that are important in everyday clinical work are not included in the classification criteria (10,11).

Since the course of the disease is marked by periodic activity of one organ system after another, patients may be ill for years in order to meet the classification criteria. It is this fact that is the basic problem of the existing classification and timely diagnosis of the disease.

Despite the long-term application of the ACR classification criteria, the question of the extent to which the total number of criteria is an indicator of disease severity has not yet been fully answered (23).

Over time, additional statistical processing has been performed in order to improve the existing criteria. The Cleveland Clinic weighted criteria and the Boston weighted (BW) criteria were established through the application of Bayes' theorem. BW classification evaluates each criterion separately (24–26). Consequently, some definitions of the criteria have been revised. After their comparison, it was found that the criteria modified in this way have a higher sensitivity, but lower specificity than the current ACR criteria. Edworthy et al., have attempted to establish the importance of a particular criterion in the SLE classification by using a statistical method of recursive partitioning. Using data from the ACR-1982 classification, the authors included two derived variables: standardised ANAs (antinuclear antibodies) and complement values (C), while immunological and haematological criteria were represented separately. Through the use of this method, high specificity and sensitivity were achieved, and most subjects were correctly classified into groups of ill and healthy patients (27).

In Croatia, the current knowledge about the characteristics of patients suffering from SLE is based on the results of research from the databases of three university centres (Zagreb, Osijek and Rijeka). Prus examined the epidemiological features of SLE in Eastern Croatia (28), in 2012 Cerovec researched the prevalence of ACR criteria in patients suffering from lupus who were treated at the University Hospital Centre Zagreb (29, 30), M. Majer investigated models of SLE monitoring in the Republic of Croatia (31), Padjen explored the analysis of causes of death in patients suffering from SLE and quantification of disease phenotypes (6,32), F. Anić analysed the connection of disease severity and disease activity with new criteria (33), and Bakula explored the validation of qualification criteria in SLE (34). There is a need to consolidate data with further collaboration on a broader scale.

Comparisons of the results of different studies are still difficult to make due to methodological differences. The studies can be different from each other in

Klasifikacijski kriteriji Međunarodnih suradnih ustanova za sistemski lupus i Američkog reumatološkog društva (engl. Systemic Lupus International Collaborating Clinics / American College of Rheumatolgy – *SLICC/ACR)*

Međunarodna grupa autora posvećena istraživanju sistemskoga eritemskog lupusa učinila je reviziju i modifikaciju klasifikacijskih kriterija. Godine 2003. na sastanku grupe SLICC u Lundu (Švedska) započeto je stvaranje klasifikacijskih kriterija SLICC za SLE. Preliminarni klasifikacijski kriteriji SLICC doneseni su 2008. godine, a objavljeni tek 2012. godine. Sadrže 17 kriterija (11 kliničkih i 6 imunoloških). Uvedeni su brojni novi klinički (kožni, zglobni, neurološki) i laboratorijski (hematološki, bubrežni, imunološki) kriteriji (tablica 2).

Za klasifikaciju SLE-a, prema novim kriterijima, također je potrebno četiri ili više klasifikacijskih kriterija, s time da obvezatno moraju biti prisutni i klinički i serološki kriteriji (barem jedan klinički i jedan laboratorijski) ili ako ima biopsijom dokazan lupusni nefritis s pozitivnom ANA i/ili ADNA. Stoga, bolesnici bez pozitivnih autoprotutijela ili niskog komplementa, što predstavlja osnovu SLE-a, ne mogu biti klasificirani kao oboljeli od SLE-a (10).

Višegodišnja revizija klasifikacije SLE-a koju je proveo SLICC bila je proces u dva koraka koji se sastojao od izvođenja kriterija i potvrđivanja kriterija u dvjema velikim skupinama pacijenata. U skupini derivacija, klasifikacija SLICC-12 pokazala je veću osjetljivost od kriterija ACR-97, gotovo jednaku specifičnost i imala je znatno manje pogrešnih klasifikacija. U koraku validacije nije bilo statističke razlike između dviju klasifikacija. Klasifikacijski kriteriji SLICC-a iz 2012. godine kompleksniji su od kriterija ACR-a te u odnosu prema njima imaju nešto višu osjetljivost (97% : 83%), a nižu specifičnost (84% : 96%) (10). Viša osjetljivost novoga klasifikacijskog pravila SLICC-a posljedica je ponajprije odvajanja i preciznijeg definiranja pojedinih obilježja koja pripadaju određenom klasifikacijskom kriteriju (tablice 3 i 4).

Odabir ovih kriterija ima prednost u studijama u kojima je potrebna viša osjetljivost s obzirom na to da smanjuju broj bolesnika s „nekompletnim" lupusom (NLE) (38,39), za razliku od potrebe za višom specifičnošću, kada su kriteriji ACR-a ipak povoljniji izbor (39).

Još uvijek su revidirani kriteriji ACR-a „zlatni standard" za klasifikaciju SLE-a, dok klasifikacijski kriteriji SLICC-a predstavljaju alternativne kriterije koji se koriste u svakodnevnom kliničkom radu i kliničkim istraživanjima.

Potrebna je daljnja validacija kriterija SLICC-a na novim skupinama bolesnika zbog procjene njihove

terms of various aspects: they can be either prospective or retrospective, they can differ in terms of their period of implementation, demographic characteristics of patients, number of patients included in the study, data sources and scope of data collected, and they can differ from each other in whether the study results were compared with similar parameters obtained by general population analysis or not (33,34). They also differ in the way they define the onset of the disease – whether it is the first time a clinical diagnosis of SLE is made or the moment when four or more ACR classification criteria are met (35,36).

Although the 1997 criteria (ACR-1997) were never validated, they have been used for research purposes but also as an auxiliary tool in clinical practice for SLE diagnosis to date.

The Systemic Lupus International Collaborating Clinics / American College of Rheumatology (SLICC/ACR) Classification Criteria

An international group of authors dedicated to the study of systemic lupus erythematosus has revised and modified the classification criteria. In 2003, at the meeting of the SLICC group in Lund (Sweden), the establishment of SLICC classification criteria for SLE was initiated. The preliminary SLICC classification criteria were adopted in 2008 and published in 2012. They include 17 criteria (11 clinical and 6 immunological). Numerous new clinical (cutaneous, articular, neurological) and laboratory (haematological, renal, immunological) criteria have been introduced (Table 2).

For the classification of SLE, according to the new criteria, four or more classification criteria are also required, provided that both clinical and serological criteria (at least one clinical and one laboratory) or biopsy-proven lupus nephritis with positive antinuclear antibodies (ANAs) and / or anti-double stranded DNA antibodies (Anti-dsDNA) are present. Therefore, patients without positive autoantibodies or a low complement, which is the basis of SLE, cannot be classified as suffering from SLE (10).

The perennial revision of the SLE classification conducted by SLICC was a two-step process consisting of deriving and validating criteria in two large groups of patients. In the derivation group, the SLICC-12 classification showed a higher sensitivity than the ACR-97 criterion, an almost equal specificity, and it had significantly fewer misclassifications. In the validation step, there was no statistical difference between the two classifications. The 2012 SLICC classification criteria are more complex than the ACR criteria and have a slightly higher sensitivity (97%:83%), and lower specificity (84%:96%) in relation to them (10). The higher sensitivity of the new SLICC classification rule is primarily due to the separation and more precise definition of

Tablica 2. Klasifikacijski kriteriji *Systemic Lupus International Collaboration Clinics* (engl. kr. SLICC) (prema referenciji br. 10)
Table 2 The Systemic Lupus International Collaboration Clinics (SLICC) classification criteria (according to reference No 10)

Klinički kriterij / Criterion	Definicija / Definition
Akutni kožni lupus / Acute Cutaneous Lupus	Leptirasti eritem, bulozni lupus, toksična epidermalna nekroliza, makulopapulozni osip, fotosenzitivni osip u odsutnosti dermatomiozitisa ili subakutni kožni lupus / Lupus malar rash, bullous lupus, toxic epidermal necrolysis, maculopapular lupus rash, photosensitive lupus rash in the absence of dermatomyositis or Subacute Cutaneous Lupus
Kronični kožni lupus / Chronic Cutaneous Lupus	Klasični diskoidni osip, hipertrofični (verukozni) lupus, lupusni panikulitis (profundus), mukozni lupus, lupus tumidus, *chillblains* lupus, preklapanje diskoidnog lupusa i lichena planusa / Classic discoid rash, hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap
Oralne ili nazalne ulceracije / Oral or nasal ulcers	U odsutnosti drugih uzroka / In the absence of other causes
Neožiljna alopecija / Non-scarring alopecia	Difuzno stanjivanje vlasišta uz fragilnost kose te vidljive otkrhnute vlasi, u odsutnosti drugih uzroka / Diffuse thinning or hair fragility with visible broken hairs, in the absence of other causes
Artritis / Arthritis	Sinovitis koji zahvaća ≥2 zgloba, karakteriziran oteklinom ili izljevom; ili osjetljivost ≥2 zgloba uz jutarnju zakočenost dulju od 30 minuta / Synovitis involving 2 or more joints, characterized by swelling or effusion; or tenderness in 2 or more joints and at least 30 minutes of morning stiffness
Serozitis / Serositis	Tipična pleuralna bol dulja od jednog dana ili pleuralni izljevi ili pleuralno trenje; tipična perikardijalna bol dulja od jednog dana ili perikardijalni izljev ili perikardijalno trenje ili perikarditis dokazan ultrazvukom, u odsutnosti drugih uzroka / Typical pleurisy for more than 1 day or pleural effusions or pleural rub; typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day or pericardial effusion or pericardial rub or pericarditis by electrocardiography in the absence of other causes
Bubrežni poremećaj / Renal disorder	Proteinurija >500 mg/24 sata ili eritrocitni cilindri / Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours or red blood cell casts
Neurološki poremećaj / Neurologic disorder	Epilepsija, psihoza, mononeuritis multipleks u odsutnosti drugih uzroka, mijelitis, periferna ili kranijalna neuropatija u odsutnosti drugih uzroka, akutno smeteno stanje, u odsutnosti drugih uzroka / Seizures, psychosis, mononeuritis multiplex in the absence of other known causes, myelitis, peripheral or cranial neuropathy in the absence of other known, acute confusional state, in the absence of other causes
Hemolitička anemija / Hemolytic anemia	Prisutnost hemolitičke anemije / Presence of hemolytic anemia
Leukopenija / Leucopenia	Leukopenija <4000/mm^3 ili limfopenija <1000/mm^3 barem jedanput, u odsutnosti drugog uzroka / Leukopenia (<4000/mm^3) or Lymphopenia (<1000/mm^3) at least once: In the absence of other known causes
Trombocitopenija / Thrombocytopenia	<100.000/mm^3 barem jedanput, u odsutnosti drugih uzroka / <100,000/mm^3 at least once, in the absence of other known causes
Imunološki kriterij / Immunologic criteria	Definicija / Definition
Antinuklearna protutijela / Antinuclear antibody	Iznad gornje granice referentnih vrijednosti za laboratorij / Level above laboratory reference range
Anti-dsDNK-protutijela / Anti-dsDNA antibody	Kao za ANA (ili >2 puta iznad gornje granice referentnih vrijednosti ako se mjere metodom ELISA) / Level above laboratory reference range (or >2-fold the reference range if tested by ELISA)
Anti-Sm-protutijela / Anti-Sm-antibody	Prisutnost protutijela protiv Sm-nuklearnog antigena / Presence of antibody to Sm nuclear antigen
Pozitivnost antifosfolipidnih protutijela / Antiphospholipid antibody positivity	Pozitivni test lupusnog antikoagulansa, lažno pozitivan test rapidnog reagina plazme, srednji ili visoki titar antikardiolipinskih protutijela (IgG, IgA, IgM), prisutnost protutijela protiv β_2-glikoproteina I (IgG, IgA, IgM) / Positive test for lupus anticoagulant, false-positive test result for rapid plasma reagin, medium-or high-titer anticardiolipin antibody level (IgA, IgG, or IgM), positive test result for anti-2-glycoprotein I (IgA, IgG, or IgM)
Snižen komplement / Low complement	Snižen C3, C4 ili CH50 / Low C3, C4, or CH50
Izravni Coombsov test / Direct Coombs' test	Pozitivan test u odsutnosti hemolitičke anemije / Positive test in the absence of hemolytic anemia

Tablica 3. Razlike između klasifikacija SLICC-12 i ACR-97 (prema ref. 39)
Table 3 Differences between SLICC-12 and ACR-97 classifications (according to ref No 39)

Klinički kriteriji / Clinical criterion ACR 1997	Klinički kriteriji / Clinical criterion SLICC 2012
1. Leptirasti osip / Malar rash	Akutni kožni lupus (makulopapulozni, psoriaziformni, bulozni, toksična epidermalna nekroliza) / Acute Cutaneous Lupus (maculopapular lupus rash, psoriasiform lupus rash, bullous lupus, toxic epidermal necrolysis)
2. Diskoidni osip / Discoid rash	Kronični kožni lupus (hipertrofični, sluznički, panikulitis, *chillblain*, lupus tumidus, diskoid/lichen planus overlap) / Chronic cutaneous lupus (hypertrophic, mucosal, panniculitis, chilblains, lupus erythematosus tumidus, discoid lupus/lichen planus overlap)
3. Fotosenzitivnost / Photosensitivity	Alopecija bez stvaranja ožiljaka / Nonscarring alopecia
4. Oralne ulc. / Oral ulcer	*Vrijedi i anamnestički podatak / The anamnestic data is also valid*
5. Artritis / Arthritis	Bol duž zglobne linije, jutarnja zakočenost, *može biti i erozivni* / Pain along the joint line, morning stiffness, *it can also be erosive*
6. Serozitis / Serositis	Pleuritis >1 dan/pl. izljev ili pl. trenje. Perikarditis (klinička slika, perikard. izljev ili trenje, EKG) / Pleurisy for >1 day/pleural effusions, or pleural rub. Pericarditis (clinical picture, pericardial effusion or pericardial rub, EKG)
7. Bubrežno oštećenje / Renal disease	Prihvatljiv i jednokratni uzorak urina, eritrocitni cilindri / Single urine sample, red blood cell casts
8. NPSLE (grand mal epi/psihoza) / Neurologic disorders (grand mal epi/psychosis)	M. multiplex, mijelitis, periferna/kranijalna neuropatija, akutno konfuzno stanje / Mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state
9. Hematološki poremećaj / Hematologic disorders	Hemolitička anemija / Hemolytic anemia Leukopenija (<4000) / Limfopenija (<1000) – 1x / Leukopenia (<4,000/mm^3)/Lymphopenia (<1,000/mm^3) – 1x Trombocitopenija – 1x / Thrombocytopenia (<100,000/mm^3) – 1x

Tablica 4. Razlike između klasifikacija SLICC-12 i ACR-97 (prema ref. 39)
Table 4 Differences between SLICC-12 and ACR-97 classifications (according to ref No 39)

Imunološki kriteriji / Immunologic criteria ACR 1997	Imunološki kriteriji / Immunologic criteria SLICC 2012
10. Anti-dsDNA positive ili/or Anti-Sm positive ili/or aCL IgG/IgM, LAC, RPR	12. Anti-dsDNA 13. Anti-Sm 14. aCL IgA/IgM/IgG, LAC, RPR, anti-β_2 GPI (IgA, IgG, or IgM) 15. Utrošak / Low complement (C3/ C4/CH50) 16. Direktni Coombs+ (u odsutnosti HA) / Positive direct Coombs test (in the absence of hemolytic anemia) 17. ANA
11. ANA	

eventualne superiornosti u odnosu na ACR-97 (40,41). M. Bakula provela je istraživanje u Referentnom centru MZ za SLE (KBC Zagreb) s ciljem potvrde novih kriterija klasifikacije SLICC-12 u skupini pacijenata u stvarnom okruženju, usporedbe kriterija ACR-97 i SLICC-12 i procjene kriterija SLICC-12 u ranim fazama SLE-a (<5 godina) u odnosu na kriterije ACR-97 (33).

Klasifikacijski kriteriji Europskog društva za reumatologiju i Američkog reumatološkog društva (EULAR/ACR) iz 2019. godine

U rujnu 2019. Europska liga protiv reumatizma (EULAR) i Američko društvo za reumatologiju (ACR) objavili su nove kriterije za klasifikaciju SLE-a (42–44).

individual characteristics that belong to a particular classification criterion (Tables 3 and 4).

The choice of these criteria is preferred in studies in which higher sensitivity is required as they reduce the number of patients with "incomplete" lupus erythematosus (ILE) (38,39), as opposed to the need for higher specificity, which is the case where the ACR criteria are the more favourable choice (39).

The ACR "gold standard" criteria for SLE classification are still being revised, while the SLICC classification criteria are alternative criteria used in day-to-day clinical work and clinical research.

Further validation of the SLICC criteria in new patient groups is required in order to assess their even-

EULAR/ACR kriteriji imaju osjetljivost od 96,1% i specifičnost od 93,4% u etabliranoj bolesti.

Iako su kriteriji SLICC-a iz 2012. uklonili neke nedostatke prethodnih ACR-ovih kriterija (npr. dodavanjem mukokutanih i neuropsihijatrijskih manifestacija, hipokomplementemije i antinuklearnih protutijela – ANA) i ponudili preciznije definicije kriterija, njihova specifičnost bila je niža od kriterija ACR-a iz 1997. godine. Iako klasifikacijski kriteriji ACR-a iz 1997. imaju istu specifičnost kao i novi EULAR/ACR od 93,4%, imaju osjetljivost od samo 82,8%. Kriteriji SLICC-a imaju nešto veću osjetljivost od navedenih, odnosno 96,7%, ali im je specifičnost samo 83,7%.

U najvećoj do sada međunarodnoj inicijativi za donošenjem novih kriterija za SLE sudjelovalo je 200 stručnjaka iz različitih neovisnih centara (među kojima B. Anić i I. Padjen iz Referentnog centra MZ za SLE u RH), analizirano je 4.000 pacijenata.

Pregledom literature sintetizirane su karakteristike ispitivanih kriterija bolesnika koje su razmatrane za klasifikaciju SLE-a. Zatim su poboljšane definicije kriterija, čime je poboljšana valjanost i pouzdanost konačnoga klasifikacijskog sustava. Uvažena je preporuka stručnjaka za SLE glede grupiranja kriterija u domene, stvarajući hijerarhijsku organizaciju kriterija unutar domena. (43,44) EULAR i ACR podržali su višefazni razvoj klasifikacijskih kriterija za SLE temeljen na rigoroznoj metodologiji.

Korištenjem metodološkog pristupa koji se temelji na mjernoj znanosti kriteriji su razvijeni u četiri faze: 1. generiranje kriterija, 2. smanjenje kriterija, 3. definiranje i ponderiranje kriterija i 4. pročišćavanje i validacija. Pri validacijskom postupku najvažnije je odrediti osjetljivost i specifičnost pojedinog kriterija i cijelog klasifikacijskog pravila (slika 1) (44,45).

Posljednja EULAR/ACR klasifikacija zahtijeva kao ulazni kriterij titar ANA koji je prepoznat kao važan kriterij za klasifikaciju lupusa, ali i kao test probira u kliničkoj praksi, od najmanje 1:80 na HEp-2 stanicama ili ekvivalent pozitivnog testa barem jednom; u suprotnom, smatra se da pacijent nema SLE. Ako je prisutan, razmatraju se 22 „aditivno ponderirana" klasifikacijska kriterija, koji obuhvaćaju sedam kliničkih domena (konstitucionalne, hematološke, neuropsihijatrijske, mukokutane, serozne, mišićno-koštane, bubrežne) i tri imunološke domene (antifosfolipidna protutijela, komponente komplementa, SLE-specifična protutijela). Kriteriji se ne moraju javljati istodobno, ali se svaki morao dogoditi bar jednom da bi se uvrstio. Svakom se kriteriju dodjeljuju bodovi u rasponu od 2 do 10. Pacijenti s najmanje jednim kliničkim kriterijem i 10 ili više bodova klasificirani su kao SLE (slika 2) (43,44).

tual superiority over ACR-97 (40,41). M. Bakula conducted research at the National Referral Centre for SLE of the Ministry of Health of the Republic of Croatia (UHC Zagreb) with the aim of confirming the new SLICC-12 classification criteria in the group of patients in the real environment, comparing the ACR-97 and SLICC-12 criteria and evaluating the SLICC-12 criteria at the early stages of SLE (<5 years) in relation to the ACR-97 criteria (33).

The 2019 European Alliance of Associations for Rheumatology (EULAR) / American College of Rheumatology (ACR) SLE Classification Criteria

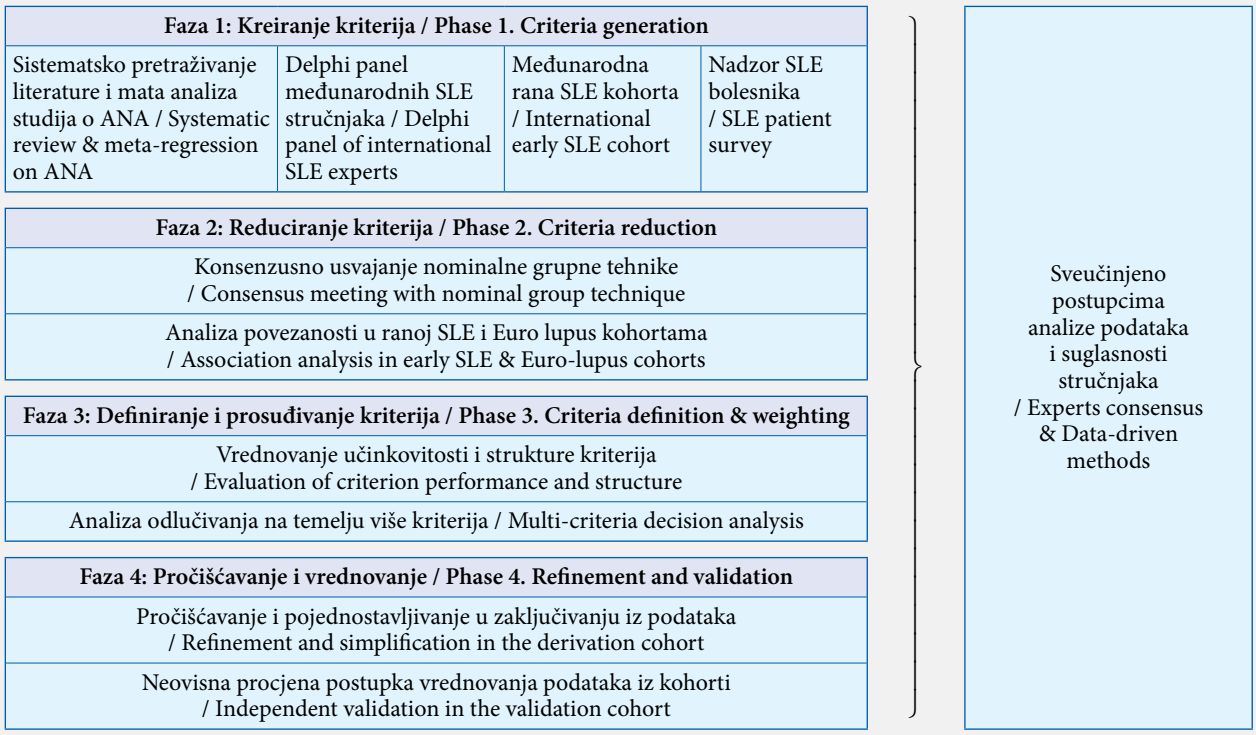
In September 2019, the European Alliance of Associations for Rheumatology (EULAR), formerly known as the European League Against Rheumatism, and the American Society of Rheumatology (ACR) published new criteria for SLE classification (42–44). EULAR / ACR criteria have a sensitivity of 96.1% and a specificity of 93.4% in the established disease.

Although the 2012 SLICC criteria removed some of the shortcomings of the previously used ACR criteria (e.g., by adding mucocutaneous and neuropsychiatric manifestations, hypocomplementemia and antinuclear antibodies – ANAs) and offered more precise definitions of the criteria, their specificity was lower than the specificity of the 1997 ACR criteria. Although the 1997 ACR classification criteria have the same specificity as the new EULAR / ACR criteria, that is, a specificity of 93.4%, they have a sensitivity of only 82.8%. The SLICC criteria have a slightly higher sensitivity than the above-mentioned ones, i.e., a sensitivity of 96.7%, but they have a specificity of only 83.7%.

200 experts from different independent centres participated in the largest international initiative for the adoption of new SLE criteria (including experts such as B. Anić and I. Padjen from the National Referral Centre for SLE of the Ministry of Health of the Republic of Croatia) in which 4,000 patients were analysed.

In the literature review, the characteristics of the examined patient criteria that were considered for the SLE classification were synthesised. The definitions of the criteria were then improved, thus improving the validity and reliability of the final classification system. The recommendation of SLE experts regarding the grouping of criteria into domains has been taken into account, thus creating a hierarchical organisation of criteria within domains. (43,44) EULAR and ACR have spoken in favour of the multi-stage development of SLE classification criteria based on a rigorous methodology.

By using a methodological approach based on metrology, the criteria were developed in four phases: 1. criteria generation, 2. criteria reduction, 3. criteria



Slika 1. Europska liga za borbu protiv reumatizma 2019. / Američki koledž za reumatologiju: klasifikacijski kriteriji za sistemski eritemski lupus (prema ref. 45)

Figure 1 2019 European League Against Rheumatism / American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus (according to ref No 45)

USPOREDBA KLASIFIKACIJSKIH KRITERIJA EULAR/ACR-A ZA SLE S KRITERIJIMA SLICC-12 I RANIJIM KRITERIJIMA ACR-97

Iako su kriteriji SLICC-a iz 2012. uklonili neke nedostatke prethodnih ACR-ovih kriterija i ponudili preciznije definicije kriterija, njihova specifičnost bila je niža od kriterija ACR-a iz 1997. godine. Iako klasifikacijski kriteriji ACR-a iz 1997. imaju istu specifičnost kao i novi EULAR/ACR iz 2019. od 93,4%, imaju osjetljivost od samo 82,8%. Kriteriji SLICC-a imaju nešto veću osjetljivost od navedenih, odnosno 96,7%, ali im je specifičnost je samo 83,7%. Kriteriji SLICC-a zadržali su opću strukturu poznatu iz kriterija ACR-a. EULAR/ACR kriteriji koriste antinuklearna protutijela (ANA) kao obvezni ulazni kriterij, imaju ponderirane kriterije i grupiraju ih u domene. Ondje gdje su kriteriji SLICC-a značajno povećali osjetljivost, izgubivši određenu specifičnost, kriteriji EULAR/ACR ponovno su povećali specifičnost (46).

Novi sustav klasifikacije SLE-a otvara nove mogućnosti istraživanja za rani ili latentni lupus. Sustav aditivnih bodova i relativna vjerojatnost klasifikacije omogućili bi sustavno praćenje pojedinih bolesnika koji su ispod praga klasifikacije. To bi olakšalo proučavanje evolucije bolesti i ranu intervenciju (48).

definition and weighting, and 4. refinement and validation. In the validation procedure, the most important thing is to determine the sensitivity and specificity of each criterion and the entire classification rule (Figure 1) (44,45).

As an entry criterion, the latest EULAR / ACR classification requires the ANA titre, which is recognised as an important criterion for lupus classification, but also as a screening test in clinical practice, of at least 1:80 titre on HEp-2 cells or an equivalent positive test obtained at least once; otherwise, the patient is considered as not suffering from SLE. If the titre is present, 22 "additive-weighted" classification criteria are considered, comprising seven clinical domains (constitutional, haematological, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and three immunological domains (antiphospholipid antibodies, complement components, SLE-specific antibodies). The criteria do not have to occur at the same time, but each criterion had to happen at least once to be included in the study. Each criterion is awarded points ranging from 2 to 10. Patients with at least one clinical criterion and 10 or more points were classified as patients suffering from SLE (Figure 2) (43,44).

Ulazni kriteriji: Antinuklearna protutijela (ANA) u titru > 1:80 na HEp-2 stanicama ili ekvivalentni pozitivni
/ **Entry criterion:** Antinuclear antibodies (ANA) at a titer of ≥ 1:80 on HEp-2 cells or an equivalent positive test

↓

Ukoliko nisu ispunjeni ne klasificiraj kao SLE, ukoliko jesu primjeni dodatne kriterije.
/ If absent, do not classify as SLE, if present, apply additive criteria.

↓

Dodatni kriteriji

Ne primjenjuj ukoliko postoji vjerojatnija dijagnoza od SLE, dovoljno je samo jedno opažanje/ispunjenje kriterija, za klasifikaciju SLE potreban je barem jedan klinički kriterij i > od 10 bodova, kriteriji ne moraju biti opaženi/ispunjeni istovremeno, unutar svake domene samo ispunjeni kriterij s najvećom vrijednosti se računa u ukupnom zbroju bodova.
/ **Additive criteria**
Do not count a criterion if there is a more likely explanation than SLE. Occurrence of a criterion on at least one occasion is sufficient. SLE classification requires at least one clinical criterion and ≥ 10 points. Criteria need not occur simultaneously. Within each domain, only the highest weighted criterion is counted toward the total scores.

Klinička domena i kriteriji: Težina: **Clinical domains and criteria: Weight:**	**Imunološka domena i kriteriji: Težina:** **Immunology domains and criteria: Weight:**
Konstitucionalni: / Constitutional: vrućica / fever 2 boda/points	***Antifosfolipidna protutijela: / Antiphospholipid antibodies:*** anti-kardiolipinska protutijela ili / anti-cardiolipin antibodies or anti-beta 2 GP1 protutijela ili / anti-β2GP1 antibodies or lupus antikagulant / lupus anticoagulant 2 boda/points
Hematološki: / Hematologic: leukopenija / leukopenia 3 boda/points trombocitopenija / thrombocytopenia 4 boda/points autoimuna hemoliza / autoimmune hemolysis 4 boda/points	***Proteini komplementa: / Complement proteins:*** sniženi C3 ili C4 / low C3 or low C4 3 boda/points sniženi C3 i C4 / low C3 and low C4 4 boda/points
Neuropsihijatrijski: / Neuropsychiatric delirij / delirium 2 boda/points psihoza / psychosis 3 bodova/points paroksizmalne atake /seizure 5 boda/points	***SLE specifična protutijela: / SLE-specific antibodies*** anti dsDNA protutijela* ili / anti-dsDNA antibody* or anti Smith protutijela/ anti-Smith antibody / anti-Smith antibody 6 bodova/points
Koža i sluznice: / Mucocutaneous: alopecija bez ožiljaka / non-scarring alopecia 2 boda/points oralne ulceracije / oral ulcers 2 boda/points subakutni kožni ili diskoidni lupus / subacute cutaneous OR discoid lupus 4 boda/points akutni kožni lupus / acute cutaneous lupus 6 bodova/points	
Serozne ovojnice: / Serosal: pleuralni ili perikardijalni izljev / pleural or pericardial effusion 4 boda/points akutni perikarditis / acute pericarditis 6 bodova/points	
Koštano-mišićni sustav: / Musculoskeletal: zahvaćenost zglobova / joint involvement 6 bodova/points	
Bubrezi: / Renal: proteinurija > 0,5 g/24 sata / proteinuria > 0.5 g/24 h 4 boda/points biopsija bubrega – tip II ili V lupusni nefritis / renal biopsy Class II or V lupus nephritis 8 bodova/points tip III i IV lupusni nefritis / renal biopsy Class III or IV lupus nephritis 10 bodova/points	
RAČUNANJE UKUPNOG ZBROJA: / TOTAL SCORE:	

↓

Klasificirati kao sistemski lupus ako je rezultat ≥ 10 te ako su ulazni kriteriji ispunjeni.
/ Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Slika 2. Klasifikacijski kriteriji za sistemski eritemski lupus. § Dodatne stavke kriterija unutar iste domene neće se računati. *Napomena: U testu s najmanje 90% specifičnosti prema relevantnim kontrolama (prema referencama 44,45)

*Figure 2 Classification criteria for systemic lupus erythematosus. §Additional criteria items within the same domain will not be counted. *Note: In an assay with at least 90% specificity against relevant disease controls (according to ref No 44,45)*

Uporaba dodatnog sustava bodovanja omogućila bi uvid u tijek i težinu bolesti, odnosno potencijalni utjecaj vrlo visokih ocjena na težinu bolesti i kasniju prognozu. Tijekom daljnje primjene novih klasifikacijskih kriterija potrebno je preispitivati relativni doprinos pojedinih kriterija (pondera) i eventualne dodatne kriterije koji bi potencijalno mogli imati prognostički značaj, a time i primjenu u kliničkoj praksi (47,48).

ZAKLJUČAK

Klasifikacijski kriteriji za SLE prošli su kroz mnoge revizije od prve verzije iz 1971. godine. Korisni su u definiranju homogenih skupina bolesnika s etabliranom bolesti. Definiranje i obuhvaćanje svih oboljelih izuzetno je zahtjevno kada je riječ o heterogenoj bolesti kao što je SLE. Do sada je kroz brojne studije i statističke analize uložen velik napor kako bi se poboljšala njihova specifičnost i osjetljivost. Napredak u razumijevanju etiopatogeneze bolesti, kao i nove mogućnosti dijagnostike, doveli su do preispitivanja postojećih kriterija i potrebe za njihovim osuvremenjivanjem.

Novi klasifikacijski kriteriji EULAR/ACR-a iz 2019. razvijeni su primjenom rigorozne metodologije s multidisciplinarnim i međunarodnim sudjelovanjem te imaju izvrsnu osjetljivost i specifičnost. Korištenje ANA kao ulaznog kriterija, hijerarhijski grupirani i ponderirani kriteriji odražavaju trenutno razmišljanje o SLE-u. Poboljšani klasifikacijski kriteriji zasigurno će pridonijeti točnijem definiranju raznolikih kliničkih očitovanja u sklopu SLE-a. Iako su klasifikacija i dijagnoza različiti pojmovi koji moraju ostati jasno odvojeni, informacije izvedene iz procesa razvrstavanja prema kriterijima također su korisne u dijagnostičke svrhe (47).

Kliničko iskustvo i procjena reumatologa ostaju i dalje uporišna točka u postavljanju dijagnoze i planiranju liječenja SLE-a, dok su klasifikacijski kriteriji namijenjeni stvaranju homogenizirane kohorte za klinička istraživanja.

Zbog svega navedenog, postoji jasna potreba za izradom kriterija koji će se koristiti i u kliničkoj praksi i u istraživanjima.

Zahvala:

Zahvaljujem Ani Mariji Masle, dr. med. i Draženu Bedekoviću, dr. med. na svesrdnoj pomoći pri izradi rada.

Izjava o sukobu interesa: Autorica izjavljuje da nije u sukobu interesa.

COMPARISON OF THE EULAR / ACR CLASSIFICATION SLE CRITERIA WITH THE SLICC-12 CRITERIA AND PREVIOUSLY USED ACR-97 CRITERIA

Although the 2012 SLICC criteria removed some of the shortcomings of the previously used ACR criteria and offered more precise definitions of the criteria, their specificity was lower than the specificity of the 1997 ACR criteria. Although the 1997 ACR classification criteria have the same specificity as the new 2019 EULAR / ACR criteria, that is, the specificity of 93.4%, they have a sensitivity of only 82.8%. The SLICC criteria have a slightly higher sensitivity than the abovementioned ones, i.e., a sensitivity of 96.7%, but they have a specificity of only 83.7%. The SLICC criteria retained the general structure known from the ACR criteria. The EULAR / ACR criteria use antinuclear antibodies (ANAs) as a mandatory inclusion criterion, they have weighted criteria and they group them into domains. In cases in which the SLICC criteria have significantly increased sensitivity, thus losing some specificity, the EULAR / ACR criteria have increased specificity once again (46).

The new SLE classification system opens up new research possibilities for early-stage or latent lupus. A system of additive points and the relative probability of classification would allow systematic monitoring of individual patients who are below the classification threshold. This would facilitate the study of disease evolution and early intervention (48). The use of an additional scoring system would provide insight into the course and severity of the disease, i.e., the potential impact of very high scores on the severity of the disease and the subsequent prognosis. During the further application of the new classification criteria, it is necessary to review the relative contribution of individual criteria (weights) and possible additional criteria that could potentially have prognostic significance, and thus could be applied in clinical practice (47,48).

CONCLUSION

The SLE classification criteria have undergone many revisions since their first version published in 1971. They are useful in defining homogeneous groups of patients with established disease. The process of definition and inclusion of all patients is extremely demanding when it comes to a heterogeneous disease such as SLE. So far, a great deal of effort has been made through numerous studies and statistical analyses in order to improve their specificity and sensitivity. Advances in understanding the etiopathogenesis of the disease, as well as new diagnostic possibilities, have led to a re-examination of existing criteria and the need for their modernisation.

LITERATURA / REFERENCES

1. Lahita RG. Introduction. U: Lahita RG, ur. Systemic Lupus Erythematosus. New York: John Willey and Sons; 2004, 29–32.
2. Tassiulas O, Boumpas DT. Clinical features and treatment of systemic lupus erythematosus. U: Firestein GS, Budd RC, Harris ED i sur, ur. Kelley's Textbook of Rheumatology. 8th ed. Philadelphia: W. B. Saunders Company; 2009, 1263–300.
3. Anić B, Bosnić D. Sustavni eritemski lupus. U: Vrhovac B, Jakšić B, Reiner Ž, Vucelić B, ur. Interna medicina. Zagreb: Naklada Ljevak; 2008, str. 1386–90.
4. Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. Lancet. 2014;384:1878–88.
5. Bosnić D. Povijest sistemskog eritemskog lupusa. Reumatizam. 2009;56:9–13.
6. Padjen I, Cerovec M, Mayer M, Anić B. Sistemski eritemski lupus: opis i kvantifikacija fenotipa bolesti. Reumatizam. 2017; 64:1–9.
7. Cohen AS, Reynolds WE, Franklin EC i sur. Preliminary criteria for the classification of systemic lupus erythematosus. Bull Rheum Dis. 1971;21:643–8.
8. Tan EM, Cohen AS, Fries JF i sur. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271–7.
9. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40:1725–34.
10. Petri M, Orbai AM, Alarcón GS i sur. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64:2677–86.
11. Mikdashi J, Nived O. Measuring disease activity in adults with systemic lupus erythematosus: the challenges of administrative burden and responsiveness to patient concerns in clinical research. Arthritis Res Ther. 2015;17:183.
12. Gladman D, Ginzler E, Goldsmith C i sur. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum. 1996;39:363–9.
13. Bourn R, James JA. Pre-clinical lupus. Curr Opin Rheumatol. 2015;27:433–9.
14. Aggarwal R, Ringold S, Khanna D i sur. Distinctions between diagnostic and clasification criteria. Arthritis Care Res (Hoboken). 2015;67:891–7.
15. Fries JF, Siegel RC. Testing the „preliminary criteria for classification of SLE". Ann Rheum Dis. 1973;32:171–7.
16. Fries JF, Siegel RC. Testing the „preliminary criteria for classification of SLE". Ann Rheum Dis. 1973;32:171–7.
17. Wolf L, Sheahan M, McCormick J, Michel B, Moskowitz RW. Classification criteria for systemic lupus erythematosus. Frequency in normal patients. J AM Med Assoc. 1976;236:1497–9.
18. Passas CM, Wong RL, Peterson M, Testa MA, Rothfield NF. A comparison of the specificity of the 1971 and 1982 American Rheumatism Association criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1985;28:620–3.
19. Levin RE, Weinstein A, Peterson M, Testa MA, Rothfield NF. A comparison of the sensitivity of the 1971 and 1982 American Rheumatism Association criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1984;27:530–8.

The new 2019 EULAR / ACR classification criteria have been developed using a rigorous methodology with multidisciplinary and international participation and they have produced excellent results in terms of sensitivity and specificity. The use of ANA as an entry criterion and hierarchically grouped and weighted criteria reflects the current opinion in relation to SLE. The improved classification criteria will certainly contribute to a more accurate definition of the various clinical manifestations within the scope of SLE. Although classification and diagnosis are different terms that must remain clearly separated, information derived from the criteria classification process is also useful for diagnostic purposes (47).

The rheumatologists clinical experience and assessment continue to be a cornerstone in SLE diagnosis and SLE treatment planning, while the classification criteria are intended to create a homogenised cohort for clinical trials.

Due to all of the aforementioned facts, there is a clear need to develop criteria that will be used in both clinical practice and research.

Acknowledgment:

I would like to thank Ana Marija Masle, MD and Dražen Bedeković, MD for their wholehearted support in the preparation of this paper.

Conflict of interest statement: The author declares no conflict of interest.

20. Somogy L, Čikeš N, Marušić M. Evaluation of criteria contributions for the classification of systemic lupus erythematosus. Scand J Rheumatol. 1993;22:58–62.
21. Piette JC, Wechsler B, Francis C, Godeau P. Systemic lupus erythematosus and the antiphospholipid syndrome: reflections about the prevalence of ARA criteria. J Rheumatol. 1992;19: 1835–7.
22. Bertsias GK, Pamfil C, Fanouriakis A i sur. Diagnostic criteria for systemic lupus erythematosus: has the time come? Nat Rev Rheumatol. 2013;9:687–94.
23. Petri M. Review of classification criteria for systemic lupus erythematosus. Rheum Dis Clin North Am. 2005;3:245–54.
24. Cervera R, Khamashta MA, Font J i sur. Systemic lupus erythematosus: Clinical and Rheumatolmmunological patterns of disease in a cohort of 1000 patients. Medicine (Baltimore). 1993;72.113–24.
25. Clough JD, Elrazak M, Calabrese LH, Valenzuela R, Braun WB, Williams GW. Weighted criteria for the diagnosis of systemic lupus erythematosus. Arch Intern Med. 1984; 144:281–5.
26. Costenbader KH, Karlson EW, Mandl LA. Defining lupus cases for clinical studies: the Boston weighted criteria for the classification of systemic lupus erythematosus. J Rheumatol. 2002; 29:2545–50.
27. Edworthy SM, Zatarain E, McShane DJ, Bloch DA. Analysis of the 1982 ARA lupus criteria dana set by recursive partitioning methodology: new insights to the relative merit of individual criteria. J Rheumatol. 1988;15:1493–8.
28. Prus V. Epidemiologija SLE u istočnoj Hrvatskoj. Disertacija, Medicinski fakultet Sveučilišta J. J. Strossmayera u Osijeku, 2011.
29. Cerovec M. Klinička i epidemiološka obilježja bolesnika oboljelih od SLE u RH. Disertacija, Medicinski fakultet Sveučilišta u Zagrebu, 2012.
30. Cerovec M, Anić B, Padjen I, Čikeš N. Prevalence of the American College of Rheumatology classification criteria in a group of 162 systemic lupus erythematosus patients from Croatia. Croat Med J. 2012;53:149–54.
31. Mayer M. Model praćenja sustavnog eritemskog lupusa analizom bolničkog morbiditeta te specifičnog mortaliteta mapiranjem. Disertacija, Medicinski fakultet Sveučilišta u Zagrebu, 2012.
32. Padjen I. Analiza uzroka smrti u bolesnika sa SLE praćenih u tercijarnom bolničkom centru tijekom 10-godišnjega razdoblja od 2002.–2011. Disertacija, Medicinski fakultet Sveučilišta u Zagrebu, 2016.
33. Bakula M. Validation of the new classification criteria for systemic lupus erythematosus on a patient cohort from a national referral center: a retrospective study. Dissertation, School of Medicine, University of Zagreb, 2019.
34. Anić F, Zuvić-Butorac M, Štimac D, Novak S. New classification criteria for systemic lupus erythematosus correlate with disease activity. Croat Med J. 2014;55:14–9.
35. Thumboo J, Lee HY, Fong KY I sur. Accuracy of medical record scoring of the SLICC/ACR damage index for systemic lupus erythematosus. Lupus. 2000;9:358–62.
36. Borchers AT, Keen CL, Shoenfeld Y, Gershwin ME. Surviving the butterfly and the wolf: mortality trends in systemic lupus erythematosus. Autoimmun Rev. 2004;3:423–5.
37. Ugarte-Gil MF, Alarcón GS. Incomplete systemic lupus erythematosus: Early diagnosis or over diagnosis? Arthritis Care Res (Hoboken). 2016;68:285–7.
38. Aberle T, Bourn RL, Chen H i sur. Use of SLICC criteria in a large, diverse lupus registry enables SLE classification of a subset of ACR-designated subjects with incomplete lupus. Lupus Sci Med. 2017;4:176.
39. Ines L, Silva C, Galindo M i sur. Classification of systemic lupus erythematosus: Systemic Lupus International Collaborating Clinics versus American College of Rheumatology criteria. A comparative study of 2055 patients from a real-life, International systemic lupus erythematosus cohort. Arthritis Care Res (Hoboken). 2015;67:1180–5.
40. Touma Z, Costenbader KH, Johnson SR i sur. Do patients with SLE at onset differ from mimickers? A comparison of clinical and serological manifestations in a multicenter cohort to inform the development of new classification criteria for SLE Ann Rheum Dis. 2016;75:558.
41. Martinez Muñoz A, Chaparro Del Moral R, Papasideroet SB i sur. Diagnostic value of the new classification criteria for systemic lupus erythematosus (SLE) developed by the Systemic lupus international collaborating clinics (SLICC) group in an Argentinian cohort of patients with SLE (abstract). Lupus. 2013;22:62–6.
42. Aringer M, Dorner T, Leuchten N, Johnson SR. Toward new criteria for systemic lupus erythematosus – A standpoint. Lupus. 2016;25:805–11.
43. Aringer M, Costenbader K, Daikh D i sur. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78:1151–9.
44. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus // Arthritis Rheumat. 2019;9:1400–14.
45. Tedeschi SK, Johnson SR, Boumpas DT i sur. Multicriteria decision analysis process to develop new classification criteria for systemic lupus erythematosus Ann Rheum Dis. 2019;78: 634–40.
46. Aringer M, Petri M. New classification criteria for systemic lupus erythematosus. Curr Opin Rheumatol. 2020;32:590–6.
47. Petri M, Goldman DW, Alarcón GS i sur. A Comparison of 2019 EULAR/ACR SLE classification criteria with two sets of earlier SLE classification criteria. Arthritis Care Res (Hoboken). 2020;48:1231–5.