

Review

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Early diagnosis of systemic lupus erythematosus

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How to cite this article: Aringer M, Bertsias G. Early diagnosis of systemic lupus erythematosus. *Rare Dis Orphan Drugs J.* 2025;4:13. <https://dx.doi.org/10.20517/rdodj.2024.59>

Received: 23 Dec 2024 **First Decision:** 5 Mar 2025 **Revised:** 18 Apr 2025 **Accepted:** 20 May 2025 **Published:** 28 May 2025

Academic Editor: Daniel Scherman **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Systemic lupus erythematosus (SLE) poses significant diagnostic challenges. First, it is characterized by a highly variable combination of autoantibodies and a wide range of possible organ involvement and symptoms. Second, no single laboratory test can definitively confirm or exclude the diagnosis. Third, due to the low incidence of SLE, clinicians must carefully balance considering SLE as a potential diagnosis against more common causes of similar symptoms. The joint European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria provide a helpful framework for thinking about SLE diagnosis, although they are not intended for diagnostic use. Nevertheless, several elements of the criteria - such as the requirement for anti-nuclear antibodies (ANA) positivity as an entry point (similar to a screening test), the weighted scoring of clinical and immunological features, and the attribution of findings to SLE only when no more likely alternative explanation exists - highlight principles that are also useful in the diagnostic process. Conceptionally, diagnosing SLE can be seen as a three-step process: (1) considering the possibility of SLE; (2) systematically collecting evidence for or against the diagnosis; and (3) making a diagnostic decision based on whether the accumulated evidence sufficiently supports or refutes the diagnosis. This review follows the three-step framework in discussing the clinical diagnosis of SLE clinical diagnosis.

Keywords: Lupus, arthritis, fever, hematology, mucocutaneous manifestations, nephritis, serositis



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INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can affect virtually every organ system. Its wide range of manifestations can be immunologically explained by common mechanisms, including the generation of autoantibodies, deposition of immune complexes, and subsequent cytokine production - particularly type I interferons - as illustrated by the Erlangen anti-CD19 CAR T cell experience^[1,2]. Lupus is highly variable in its presentation and may initially involve only one or a few symptoms^[3-6], making early diagnosis challenging. However, prompt identification of SLE is crucial due to the risk of irreversible organ damage^[7,8].

SLE is a relatively rare condition. While prevalence varies significantly across ethnical and regional populations, it affects approximately one in 1,000 women and one in 10,000 men - reflecting an overall prevalence of 1:2,000 and a tenfold higher risk in women^[9-15]. This means that isolated symptoms such as fatigue or joint pain are unlikely to indicate SLE. Even when joint symptoms are more pronounced, more common rheumatic disorders, such as rheumatoid arthritis, are typically considered first. As a result, many physicians, particularly general practitioners, may have limited or no firsthand experience with early-stage SLE^[2,16].

Although some SLE-related autoantibodies can be detected via immunological testing, such evaluations usually require prior clinical suspicion. Cases of SLE with minimal organ involvement may go unnoticed unless symptoms affecting the skin, joints, or kidneys prompt further investigation. In contrast, when the disease presents with a full spectrum of manifestations, such as mucocutaneous lesions, serositis, or hematological abnormalities, diagnosis is generally more straightforward.

Conceptually, the diagnostic process can be divided into three steps [Table 1], although in practice these often run in parallel. The first step is consideration of SLE, which is prompted by clinical patterns that raise suspicion. The second step involves gathering evidence for or against the disease by systematically evaluating possible manifestations and relevant biomarkers. The third step is the diagnostic decision, where the clinician determines whether the accumulated data support a diagnosis of SLE or an alternative explanation. This review will follow this three-step framework.

REASONS FOR SUSPECTING SLE

Although it may initially seem counterintuitive, the specificity of clinical signs, symptoms, and laboratory findings is crucial from the very beginning of the diagnostic process - particularly in a rare disease like SLE. For example, fatigue is one of the most frequently reported and distressing symptoms among SLE patients, with a high prevalence rate^[17-21]. Based on this, one might expect fatigue to be a strong indicator for suspecting SLE. However, data from the early SLE cohort - an essential component in the development of the EULAR/ACR criteria - showed that fatigue was actually more prevalent among individuals with conditions that mimic SLE^[4]. Given that fatigue is widespread in the general population and linked to numerous autoimmune and non-autoimmune diseases, it should not, in isolation, trigger an investigation for lupus.

In contrast, many items listed in the EULAR/ACR classification criteria^[22-24] can meaningfully raise suspicion of SLE. These include joint involvement (inflammatory arthritis), mucocutaneous manifestations such as oral ulcers and non-scarring alopecia, serositis, hematological cytopenias, and immune complex-mediated nephritis. Additional signs such as unexplained fever and seizures - once other more common differential diagnoses have been excluded - can also be indicative^[22,25]. Other relevant symptoms include photosensitive rashes, scarring alopecia, various forms of vasculitis, severe pneumonitis (with or without

Table 1. Three steps toward a diagnosis of SLE

Step	Main focus	Relevant aspects
1	Consideration of SLE	Organ involvement patterns, relatively specific manifestations
2	Gathering evidence for SLE	Spectrum of clinical features, SLE autoantibodies, complement levels
3	Diagnostic decision (SLE or not)	Individual risk profile, alternative diagnoses explaining objective findings

alveolar hemorrhage), and features suggestive of antiphospholipid syndrome^[26,27]. In all cases, a thorough diagnostic workup is necessary to exclude alternative causes, including infections, drug reactions, other autoimmune diseases, malignancies, or thrombotic events. Table 2 lists symptoms that significantly increase the likelihood of SLE being the underlying condition. Of note, some of these features are not part of the EULAR/ACR criteria, primarily due to their relatively low incidence worldwide.

Importantly, SLE symptoms often appear in combination^[28]. This is especially true for symptoms affecting multiple organ systems. In contrast, signs confined to a single organ system may have other explanations, such as hematological diseases causing multiple cytopenias. Consequently, the likelihood of SLE increases when multiple suggestive features are present simultaneously. Conversely, diagnosing mono-symptomatic SLE remains particularly challenging^[3].

GATHERING EVIDENCE

Once there is a reasonable initial suspicion of SLE, the next logical steps are: (i) an assessment of additional potential SLE symptoms that may not yet be apparent; and (ii) serological testing. The former includes taking a comprehensive medical history and conducting a thorough physical examination. This process may be supported by classification criteria checklists and/or SLE activity scoring systems. Basic laboratory investigations - such as a complete blood count with differential and a urinalysis (especially to detect proteinuria) - are also essential^[29]. As a general rule, subtle or asymptomatic SLE manifestations commonly include cytopenias and lupus nephritis.

It is also advisable to order tests for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), kidney and liver function, and creatinine kinase (CK). A completely normal ESR makes active SLE less likely, while CRP levels tend to remain relatively low even during active SLE. Notable exceptions include lupus arthritis and serositis, where CRP levels may be elevated^[30].

The extent of serological testing should correspond to the level of clinical suspicion, which is influenced by both clinical and laboratory findings as well as background risk factors. These risk factors include ethnicity, a family history of autoimmune diseases, sex, and age. Although SLE can affect individuals of any sex or age, it is most prevalent among women of reproductive age.

If the clinical risk is low, testing for anti-nuclear antibodies (ANA) alone often provides sufficient sensitivity to exclude SLE if the result is negative. Data derived from the EULAR/ACR classification criteria project and external validation studies suggest that correctly performed ANA tests have a sensitivity of 97% to 99.5%^[24,31,32]. Despite substrate-related variability^[33], a meta-analysis involving 2,839 SLE patients reported a 95% sensitivity for ANA^[34]. Another meta-analysis found no significant difference in ANA sensitivity between adult and juvenile SLE cases^[35].

When the diagnosis remains uncertain, additional testing for autoantibodies - such as those against double-stranded DNA (dsDNA) and the extractable nuclear antigens (ENA) Sm, U1-RNP, Ro, and La - is

Table 2. Symptoms and findings relevant to early SLE (Percentages from Mosca et al.^[43])

Symptom or finding	%	Definition	Remarks
SLE criteria items			
Arthritis	58	Inflammatory arthritis, anti-CCP-negative	Arthralgias alone are insufficient
Malar rash	50		Rosacea is an important DD
Subacute cutaneous LE	9		
Discoid LE	9	Scarring, discoid lesions	Primarily limited to cutaneous LE
Oral ulcers	22	Recurrent, large, painful	DD include Behçet's GPA
Non-scarring alopecia	31		DD includes alopecia areata
Pleuritis	22	Pain + objective findings	Infection and PE are more common
Pericarditis	19	Pain + objective findings	Infection is much more common; DD includes other rheumatic diseases
Proteinuria	13	Persistent, in the absence of infection	Kidney biopsy is often warranted
Hemolytic anemia	5	Coombs test required	
Thrombocytopenia	7	Platelets < 50,000 (ITP-like)	Mild thrombocytopenia may occur in APS
Leukopenia	16		Many causes (infection, drugs, etc.)
Fever	35	Unexplained, persistent, > 38.3 °C	Rule out common causes
Seizures	3		
Non-criteria items			
Autoimmune hepatitis		May require histological confirmation	
Ascites	3	Due to sterile peritonitis or hepatitis	May also result indirectly via APS
Photosensitive rash	32	Skin rash appearing days after UV exposure	
Pneumonitis	1	Severe, acute, often hemorrhagic	DD includes AAVs and infections
Prolonged APTT	13	Persistent despite 1:1 mixing with healthy plasma	May indicate APS
Thrombosis	4	Venous or arterial	May suggest APS
Valvular lesions	1	Libman-Sacks endocarditis	Often associated with APS
Scarring alopecia		Due to discoid LE	Primarily cutaneous LE
Leukocytoclastic vasculitis		Confirmed by histology; immune complex-mediated	Often limited to skin; many DDs
Urticaria vasculitis		Confirmed by histology; immune complex-mediated	

AAV: ANCA (Anti-neutrophil cytoplasmic antibodies)-associated vasculitides; APS: antiphospholipid syndrome; APTT: activated partial thromboplastin time; DD: differential diagnosis; GPA: granulomatosis with polyangiitis (Wegener's); ITP: idiopathic thrombocytopenic purpura; PE: pulmonary embolism; UV: ultraviolet light.

recommended. Approximately 2% of ANA-negative SLE patients may still test positive for one or more of these specific autoantibodies, particularly anti-Ro^[36]. In patients who are ANA-positive and have undergone only minimal testing, these additional antibodies become essential in the diagnostic workup.

It is crucial to understand the characteristics of dsDNA antibody tests. ELISA-based tests are generally more sensitive but have lower specificity. The Crithidia luciliae immunofluorescence test (CLIFT), on the other hand, is more specific but less sensitive. Radioimmune assays such as the Farr test are largely unavailable today^[37-41]. While anti-histone antibodies are common in drug-induced lupus, they are also frequently seen in SLE. Anti-nucleosome (or anti-chromatin) antibodies, typically measured by ELISA, exhibit relatively high sensitivity but reduced specificity.

As part of the diagnostic process, testing for lupus anticoagulant and antibodies to cardiolipin and β_2 -glycoprotein I is also important. Additionally, serum levels of complement proteins C3 and C4 should be measured. Where available, tests for cell-bound complement split products can improve the sensitivity for

detecting immune-complex-mediated complement activation^[42].

Subject to local laws and regulations, it may also be beneficial to consider experimental tests, provided their performance characteristics are sufficiently understood. For example, evidence of a type I interferon signature can support an SLE diagnosis. However, not all patients with SLE exhibit this signature, and it can also be present in other diseases, such as dermatomyositis or viral infections^[43].

DIAGNOSTIC DECISIONS

When making a decision, findings must be carefully scrutinized for face validity, both individually and in combination. One must ask: is there a more likely explanation than lupus? For example, could anti-CCP-positive joint disease suggest rheumatoid arthritis instead, or could combined cytopenias indicate a hematological disorder? Any items for which a more plausible alternative diagnosis exists should be put aside. If considered at all, they should be used with great caution. This process will help generate a consolidated list of findings that support a diagnosis of SLE.

If the combined findings lack a common explanation other than SLE, the likelihood of an SLE diagnosis increases. At this stage, it is also important to consider whether the clinical picture can plausibly be attributed to immune complex deposition or direct autoantibody effects - both of which are key effector mechanisms in SLE. As shown in [Figure 1](#), the diagnostic process typically starts with one symptom that has at least some specificity for SLE. This is followed by immunological testing and a comprehensive evaluation for additional SLE manifestations, ensuring that alternative explanations are ruled out. Ultimately, confirmation of autoantibody involvement, alongside either one highly specific clinical item or a combination of less specific but unrelated findings, will often tip the diagnostic balance. In many cases, a single compelling and specific item can drive the diagnosis.

To some extent, the EULAR/ACR classification criteria represent a condensed version of this approach. These criteria were primarily designed to define patient cohorts with high specificity for clinical trials and scientific research^[44,45], and are not meant to replace clinical diagnosis. In fact, the criteria's publication explicitly states that diagnosing SLE remains the responsibility of a qualified physician assessing an individual patient^[22]. Classification criteria are necessarily limited to a feasible, and thus relatively short, list of features.

[Figure 2](#) presents the specific items included in the EULAR/ACR classification criteria, along with their assigned weights (represented by column heights). This figure illustrates that classification is typically achieved through a combination of items that collectively reach the threshold of ≥ 10 points. Rarely is classification based solely on a single finding, such as proliferative lupus nephritis, unless accompanied by a history of positive ANA. In general, the lower the specificity of a criterion for SLE, the more items will be required to reach the classification threshold.

It is also important to emphasize that: (i) Unlike classification, which determines eligibility for a clinical trial and is irreversible, a diagnosis can be revised if subsequent disease course suggests an error; (ii) Following an SLE diagnosis, the initial management steps typically include hydroxychloroquine, vitamin D supplementation, counseling on UV exposure, and risk factor control. The diagnosis itself does not automatically warrant immunosuppressive therapy. Instead, treatment decisions are driven by organ-specific manifestations. Conversely, significant organ involvement may justify an SLE diagnosis even when classification criteria are not fully met^[46]. Therefore, the diagnostic process tends to be more inclusive than the classification framework.

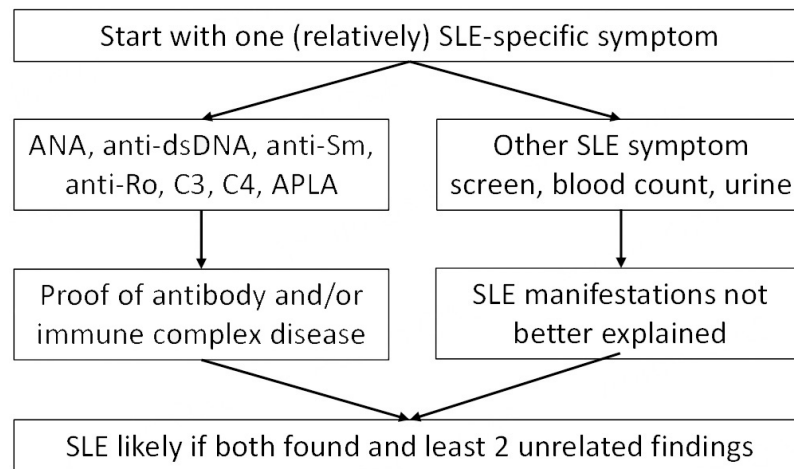


Figure 1. A simplified depiction of the typical path to an SLE diagnosis.

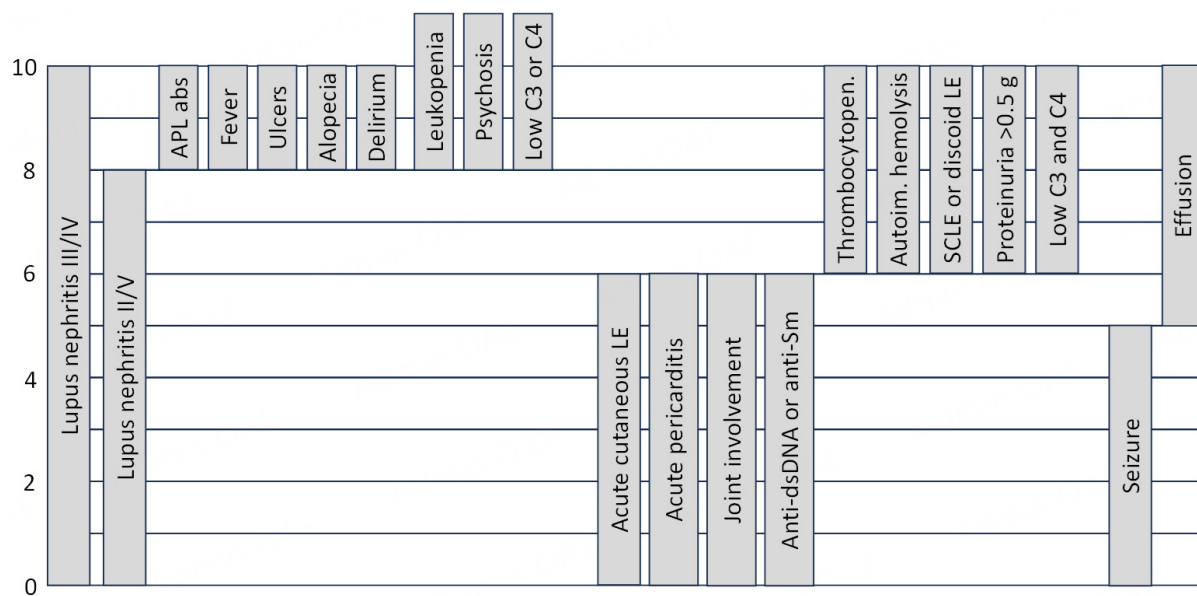


Figure 2. Example combinations of items meeting the EULAR/ACR classification threshold (≥ 10 points) for ANA-positive individuals. Note: Items with the same weight can be combined, but only the highest-ranking item from each organ domain (e.g., mucocutaneous or hematological) is counted.

Diagnostic reasoning also considers underlying risk factors. Women of childbearing age face more than a tenfold higher risk of SLE than men of the same age, while the sex difference is smaller in older adults^[47-49]. A family history of autoimmune disease and certain high-risk ethnic backgrounds also weigh in favor of an SLE diagnosis. In the future, genetic risk may become accessible through comprehensive profiling of individual risk variants, but such capabilities are not yet available.

TOOLS FOR DIAGNOSING SLE

To assist in diagnosing SLE, particularly for physicians with limited experience in managing the disease, an electronic diagnostic tool has been developed. The SLE Risk Probability Index (SLERPI) was created using Random Forests and Least Absolute Shrinkage and Selection Operator-logistic regression (LASSO-LR)

based on a discovery cohort of 802 adults with either SLE or other rheumatic diseases^[50]. By analyzing the accuracy of various features from existing SLE classification criteria, the developers created a simplified scoring system. In this system, a diagnosis of SLE is considered likely if the cumulative score exceeds 7. Individual feature scores range from 1 (e.g., mucosal ulcers) to 4.5 (e.g., proteinuria, thrombocytopenia, or autoimmune hemolytic anemia), with a deduction of 1 point for the presence of interstitial lung disease [Table 3].

SLERPI demonstrated high sensitivity in initial validation studies, ranging from 91.8% to 98.6% across different cohorts, and has since been validated by multiple research groups^[51-53]. However, its specificity is generally lower than that of the EULAR/ACR 2019 classification criteria. This may be partly because ANA is included in the SLERPI scoring rather than used as a mandatory entry criterion. Although clinical expertise remains superior, especially in cases where patients present with manifestations not covered by the SLERPI scoring system^[54], SLERPI provides a valuable aid in standard diagnostic scenarios. In addition to SLERPI, several other machine learning-based predictive models for SLE have also been developed^[55].

PRE-SLE

Progression rates from unspecific ANA-positive states are relatively low, and such patients are typically identified using the EULAR/ACR criteria^[56]. Ideally, however, interventions aimed at controlling - and if possible, completely suppressing - SLE should begin even before the onset of overt disease. Encouragingly, efforts toward developing such preemptive strategies are already underway. These strategies will need to carefully consider an individual's background risk and are likely to incorporate immunological markers, nonspecific symptoms, and possibly isolated organ manifestations. Understanding the transition from preclinical SLE to fully developed disease is a critical area of research^[57]. Emerging data from cohorts with incomplete SLE are beginning to shed light on this transition^[58]. Ultimately, the most effective approach will likely involve a large-scale, global initiative.

Several factors must be taken into account. As previously mentioned, genetic predisposition plays a significant role^[6,59-62]. For example, the concordance rate of SLE in monozygotic twins, i.e., the likelihood that the second twin will develop SLE once the first is diagnosed, is approximately 25%^[63]. Individuals with certain complement deficiencies face even higher risks^[64,65]. Similarly, those with type I interferonopathies - genetic conditions that lead to excessive production of type I interferons - also have an elevated risk^[66].

Notably, specific SLE-related autoantibodies can be detected years before clinical onset^[67]. This is particularly true for autoantibodies clinical RNA-binding proteins, such as Ro and La. Importantly, these antibodies have also been linked to a positive type I interferon signature^[68,69], presumably due to the formation of RNA-containing immune complexes. This raises the possibility that, either through interferons-mediated mechanisms or other immune complex-driven processes, patients may experience symptoms such as myalgias and fatigue even at this very early stage.

CONCLUSION

Achieving an early and accurate diagnosis of SLE is a critical goal. Due to the disease's heterogeneity and relatively low incidence and prevalence, it is important that all physicians are familiar with its characteristic features. The identification of a single clinical or laboratory finding suggestive of SLE - one that is not attributable to another condition - should prompt a comprehensive evaluation for additional signs and relevant laboratory markers. These include urine analysis for proteinuria, complete and differential blood counts, complement levels (C3 and C4), ANA, and antibodies to Sm, dsDNA, Ro, La, U1-RNP, and phospholipids. Although features within diagnostic domains often cluster together, the presence of two

Table 3. Features and corresponding scores in SLERPI

Score	Feature
+4.5	Proteinuria > 500 mg/24 h
+4.5	Thrombocytopenia or autoimmune hemolytic anemia
+3	Malar rash or maculopapular rash
+3	ANA
+2.5	Immunological disorder (any of: anti-DNA, anti-Sm, antiphospholipid antibodies)
+2	Subacute cutaneous or discoid lupus erythematosus
+2	Arthritis
+2	Low complement (C3 and C4)
+1.5	Serositis
+1.5	Alopecia
+1.5	Neurological disorder (per SLICC criteria ^[27])
+1.5	Leucopenia
+1	Mucosal ulcers
-1	Interstitial lung disease

independent criteria - explained by other conditions or medications - is typically sufficient to support a likely diagnosis of SLE. In routine clinical settings, the SLERPI may be a useful tool to enhance diagnostic confidence. Looking ahead, the ability to intervene in the very early, subclinical stages of SLE will depend on the development and implementation of additional diagnostic strategies.

DECLARATIONS

Authors' contributions

Conceptualization, visualization, and writing - review & editing of the manuscript: Aringer M, Bertsias G

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Both authors have worked on the EULAR/ACR classification criteria for SLE and Dr. Bertsias also on the SLERPI. The authors declared that there are no commercial interests in relation to this manuscript.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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