The Multiple Faces of Systemic Lupus Erythematosus: Pearls and Pitfalls for Diagnosis

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ABSTRACT
Systemic lupus erythematosus is the prototype multisystem autoimmune disorder characterised by a broad spectrum of organ involvement and a multitude of laboratory abnormalities. Clinical heterogeneity, unpredictable course and lack of pathognomonic clinical and serological features pose a considerable challenge in the diagnosis of SLE. The latter remains largely clinical, typically accompanied however by features of serologic autoimmunity, which are characteristic for the disease. Despite significant improvements in treatment strategies, an early diagnosis often continues to be an unmet need, as the median reported delay from symptom onset to SLE diagnosis is approximately 2 years. Classification criteria are usually used to support the diagnosis, yet with significant caveats. In this article, we provide an updated review of the clinical presentation of lupus and give clues for an accurate diagnosis.

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INTRODUCTION
Systemic lupus erythematosus (SLE) is a complex autoimmune disease with a broad spectrum of clinical manifestations and accompanying laboratory abnormalities. Its onset is often insidious, with clinically evident disease developing over years, following a period of preclinical evidence of autoimmunity. Early in the disease course, many patients present with only a few features of the disease, that can resemble other autoimmune, infectious, or haematological diseases. This paucity of specific manifestations, its insidious onset and the wide range of potential organ involvement often pose considerable challenges in the diagnosis of SLE.

Although increasing awareness, mainly due to advances in autoantibodies and understanding of the disease presentation, has reduced the diagnostic delay from approximately 50 months before 1980 to approximately 24 months in current times, the time lag is still long. According to recent studies, the mean time between onset of symptoms and SLE diagnosis is approximately 2 years, although a longer time has been reported for males, childhood-onset, and late-onset SLE, probably due to the lower index of suspicion in these patients. The delay in SLE diagnosis may lead to respective delay in treatment initiation, thus increase the risk of organ damage and affect short- and long-term outcomes. Importantly, for patients with major organ involvement, such as nephritis or neuropsychiatric lupus, this delay in diagnosis and treatment initiation has been associated...
with adverse outcomes. Also, there is evidence to support that early initiation of glucocorticoids and immunosuppressive agents may lead to earlier disease remission, thus improving long-term prognosis. Although a universally accepted definition of what constitutes “early” diagnosis is lacking, and a window of opportunity for timely treatment has not been clearly defined, some studies suggest that patients diagnosed within 6 months from symptom onset experience lower rates of flares, hospitalisations, healthcare utilisation costs, and disease-related damage.

SLE CLASSIFICATION CRITERIA: CHRONICLE AND NEW DIAGNOSTIC TOOLS

The diagnosis of SLE remains clinical, typically supported by laboratory abnormalities indicative of autoimmune reactivity. In practice, since diagnostic criteria for the disease have not been developed, diagnosis is usually made in a patient who presents with a combination of specific clinical and immunologic features, following the exclusion of other diagnoses which can mimic SLE. The various sets of classification criteria of SLE reflect the multifaceted nature of the disease and they have been primarily developed to ensure the inclusion of homogeneous groups of patients in clinical and epidemiological studies. Although they are often used as a diagnostic aid in routine clinical practice, they cannot be applied in every individual case, since misclassification may occur due to their sensitivity and specificity (which are both less than 100%). Classification criteria with a high sensitivity may be used informally to support a clinical diagnosis, however, the possibility of ‘overdiagnosis’ is well recognised and should not be overlooked. Following the first classification criteria from the American College of Rheumatology (ACR), the SLICC criteria, published in 2012, aimed for earlier diagnosis and higher sensitivity, by necessitating the patient to satisfy ≥4 criteria (at least one clinical and one immunologic), or to have biopsy-proven lupus nephritis in the presence of antinuclear antibodies (ANA) or anti-double-stranded DNA antibodies. As compared with ACR-1997 criteria, the SLICC-2012 criteria demonstrated better sensitivity (94.6% vs 89.6%) with a similar or slightly lower specificity (95.5% vs 98.1%), ensuring classification of more patients at a population level. The most recent set of classification criteria have been published in 2019 following a combined effort from the European League Against Rheumatism (EULAR)/ACR, and requiring a positive ANA test at least once as entry criterion, combined with at least 10 additional points derived from weighted criteria, grouped in 7 clinical and 3 immunologic domains. Data from the validation cohort suggested that the EULAR/ACR-2019 criteria achieved a higher and similar sensitivity as compared with ACR 1997 (96.1% vs 82.8%) and SLICC 2012 (96.1% vs 96.7%), respectively. Accordingly, the specificity was similar to ACR 1997 criteria (93.4% vs 93.4%), but higher than SLICC 2012 (93.4% vs 83.7%). Following their publication, data from recent cohort studies and a meta-analysis showed that both the SLICC-2012 and EULAR/ACR-2019 have a higher sensitivity as compared with ACR-1997 criteria, and thus are more suitable for the identification of patients with early disease. The performance of existing sets of SLE classification criteria in several real-life patient cohorts is shown in Table 1. A diagnosis is often most challenging in the early stages of the disease, when the latter may manifest only a few or even a single clinical manifestation (organ-dominant lupus). In such settings, application of existing sets

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<th>ACR 97 Sensitivity</th>
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<th>EULAR/ACR 19 Sensitivity</th>
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SLE: Systemic Lupus Erythematosus; ACR: American College of Rheumatology; SLICC: Systemic Lupus International Collaborating Clinics; EULAR: European Alliance of Associations for Rheumatology; ACR: American College of Rheumatology; N/A: not applicable.
of classification criteria may assist diagnosis; in fact, the combination of all three sets ensures the highest sensitivity.\textsuperscript{25,27,41} Importantly, a recent retrospective study showed that different sets of criteria still fail to classify a significant proportion of cases at the time of diagnosis by an expert, and thus some patients with potentially high disease burden may be “missed”.\textsuperscript{41} This study proposed that modifications of classification criteria, such as the use of an alternative entry criterion in ANA-negative patients or the classification of patients with fewer criteria from multiple domains, may enhance their diagnostic accuracy, enabling an earlier diagnosis and timely treatment of more patients.\textsuperscript{41}

Recently, Adamichou et al. introduced a clinically applicable model to assist SLE diagnosis, by the use of machine learning.\textsuperscript{32} The SLE Risk Probability Index (SLERPI) consists of 14 variably weighted clinical and serological SLE features, that can produce individualised risk probabilities for clinical SLE against competing rheumatologic diseases (i.e., “definite”, “likely/possible”, “possible”, “unlikely”), alike clinical diagnostic reasoning. In the binary model, a threshold >7 can be used as a dichotomous algorithm (i.e., SLE or not) with high accuracy (94.2%) for SLE diagnosis, including early and severe disease.\textsuperscript{52} By operating the full probabilistic model, the algorithm can be used to exclude SLE (risk probability <14%), confirm SLE (risk probability >96%), or suggest identification and monitoring of patients with intermediate probabilities (15-85%).\textsuperscript{52} Recent studies on SLERPI performance showed a similar or higher sensitivity [98.5% (95% CI; 96.7%-99.4%)] compared to the classification criteria sets, albeit with lower specificity [84.6% (95% CI; 76.9%-90.4%)].\textsuperscript{53,54} Interestingly, SLERPI showed a good diagnostic performance for the earlier identification of SLE, comparable with EULAR/ACR-2019 criteria, especially among patients with undifferentiated connective tissue disease and those with severe organ involvement, in an ambulatory basis, as well as in the hospital setting.\textsuperscript{54-56} Further research in cohorts with larger samples and diverse ethnic racial characteristics, is needed to further establish the clinical utility and diagnostic value of this tool.

**CLINICAL PRESENTATION OF SLE**

*How does lupus present?*

A typical pattern of presenting clinical picture for lupus does not exist. Moreover, what makes the diagnosis often challenging, is the fact that the diverse array of manifestations often do not appear simultaneously but rather accumulate gradually over the disease course, occasionally with a time interval of several months or even years between them.\textsuperscript{16,24,32} Additionally, a considerable proportion of patients present with non-specific manifestations, such as arthritis, fever or fatigue, or with rare and atypical features, such as unusual rashes, neuropsychiatric manifestations, or abdominal vasculitis, among others. A small but challenging group of patients might present with single-organ involvement, the so called ‘organ-dominant lupus’.\textsuperscript{4,25} Sex, age and ethnicity may also influence the expression of SLE, as people of white race tend to develop milder phenotypes compared to Blacks or Asians.\textsuperscript{4,12,16,57}

Mucocutaneous lesions and musculoskeletal involvement are almost universal in SLE, occurring in about 90% of SLE patients. Arthralgias and true synovitis are very common manifestations, with the majority of patients manifesting a symmetric non-erosive polyarthritis, usually early in the disease course.\textsuperscript{4,32,57}

Lupus nephritis (LN) represents one of the most characteristic manifestations and usually, although not exclusively, occurs early in the disease course. Renal involvement presents in about 25-50% of patients, with higher percentages in certain ethnic groups, such as African-Americans.\textsuperscript{32,57-62} Hematologic involvement is also a frequent manifestation and can be a presenting manifestation of SLE. Its clinical presentation is highly variable, including the possible involvement of all three blood cell lines, while occasionally can be associated with severe lupus disease.\textsuperscript{32,57,62} Notably, severe organ involvement in lupus has been associated with haematological abnormalities, with thrombocytopenia representing an independent risk factor of death and being associated with higher disease activity and greater damage in different SLE cohorts.\textsuperscript{54-67}

Neuropsychiatric lupus (NPSLE) prevalence varies widely among different cohorts, owing to differences in definition and attribution to the disease per se. Importantly, most severe neuropsychiatric syndromes tend to manifest more frequently around the onset of SLE and are significantly more frequent as presenting manifestations in childhood-onset lupus.\textsuperscript{68-72} Importantly, non-infectious fever, recently included as a criterion in the 2019 EULAR/ACR criteria, with data from different early SLE cohorts, suggest the importance of this manifestation as an early feature, despite its obviously low specificity.\textsuperscript{8,10}

**MULTISYSTEM VERSUS ORGAN-DOMINANT DISEASE**

A minority of SLE patients may present with organ-dominant disease, often with a severe clinical manifestation.\textsuperscript{25} The diagnosis of organ-dominant disease is challenging, because these patients typically do not fulfill classification criteria; in these circumstances, judgment of a physician experienced in SLE may result in a diagnosis of ‘possible SLE’, only after rigorous exclusion of alternative causes for the patient’s symptoms. In such clinical scenarios, the diagnosis can be substantiated in patients displaying manifestations with a high specificity for SLE (e.g., malar rash, positivity for SLE-specific autoantibodies, such as anti-dsDNA or anti-Smith), or when there is histologic
suspicions or confirmation of lupus, particularly in cases of nephritis and cutaneous lupus. In patients not falling into one of these categories, the diagnosis of SLE may be delayed until additional clinical or serological features accumulate, potentially affecting the long-term prognosis. For patients presenting with mild-moderate single-organ symptoms, a strategy of ‘watchful waiting’ or a therapeutic trial with low to moderate dose of glucocorticoids might be beneficial. By contrast, prompt interventions are needed for patients presenting with severe or life-threatening manifestations. In such situations, an aggressive work-up is warranted to rule out other life-threatening conditions, particularly those that can be exacerbated by immunosuppressive treatments like infections. Following this, with a possible diagnosis of SLE, immunosuppressive treatment is justified, under the supervision of an experienced SLE physician and multidisciplinary evaluation. Revisiting the accuracy of the diagnosis after a period of time in doubtful cases is of utmost importance. Contrary to organ-dominant presentation, diagnosing SLE in patients with multisystem involvement is generally considered as more straightforward, because these individuals usually have a more familiar clinical picture for physicians with less experience in the disease. Nonetheless, it is still important to consider various conditions that mimic SLE in the differential diagnosis, especially when specific features are absent. In cases with more benign clinical presentations, an optimal evaluation should rule out other connective tissue diseases and chronic infections, in the presence of suggestive symptoms. In patients with severe multi-system SLE requiring hospitalisation, it’s essential to consider viral infections, sepsis and full-blown vasculitis as potential alternative diagnoses that should be part of the corresponding diagnostic work-up. In this regard, the diagnosis of SLE always demands a holistic assessment that should be adapted to each individual case based on disease severity and available clinical and laboratory findings.

SEX-AGE DIFFERENCES AND THE ROLE OF ETHNICITY

The incidence of childhood-onset SLE (cSLE, diagnosis in patients < 16 years old) among all SLE cases may account for up to 20% in different cohorts, while a similar incidence at 10-20% has been reported for SLE patients with late-onset disease (i.e. diagnosis after 50 years). Of note, most recent cohorts have reported a notable increase in the proportion of SLE patients with late-diagnosis, and a higher average age at SLE diagnosis when compared to studies conducted prior to 2000. Traditionally, cSLE is considered a more severe form of lupus characterised by high disease activity, early accumulation of damage and increased need for potent immunosuppressive therapy. In a large cohort from the UK including patients with different ethnic backgrounds, cSLE was associated with a higher frequency of lupus nephritis, mucocutaneous manifestations, thrombocytopenia, haemolytic anaemia, seropositivity for SLE-specific antibodies, and with increased mortality rates, while adult-onset SLE patients were more likely to exhibit arthritis and leukopenia. On the other hand, patients with late-onset SLE exhibit more frequently serositis and pulmonary involvement. Two recent studies comparing cSLE with late-onset disease showed that cSLE tends to manifest more frequently lupus nephritis, acute cutaneous lupus, alopecia, oral ulcers, and fever, while late-onset-SLE was linked to increased incidence of pleuritis and pericarditis. The characteristic 9-10:1 female-to-male ratio in SLE seems to diminish with increasing age at diagnosis, reaching as low as 2.6:1 for patients with late-onset disease and indicating that male patients tend to develop SLE at an older age. In a recent cohort study, male SLE patients had a higher mean age at disease onset and frequency of late-onset SLE. Numerous studies have sought to discern disparities between male and female SLE phenotypes, yielding conflicting findings. Nevertheless, a common trend in these studies suggests that male patients are more inclined to experience serositis, thrombosis, and late-onset disease. While earlier cohort studies reported a higher prevalence of renal involvement in males, recent reports do not confirm this observation; still, LN in men is associated with worse outcomes. Male SLE patients accumulate irreversible damage earlier in the disease course and have significantly higher SLICC damage index scores within the 5 first years of the disease, suggesting a more aggressive phenotype. Racial and ethnic background is an additional major determinant of the lupus phenotype. Collectively, most studies suggest a more severe disease in black, Hispanic, and Asian patients. Multi-ethnic cohort studies demonstrated that white patients exhibited the lowest prevalence of LN, while Asians are less likely to manifest neuropsychiatric events. Musculoskeletal and skin manifestations are commonly observed among white individuals, while chronic cutaneous lupus is more frequent among black SLE patients. Immune-mediated cytopenias are typical manifestations among patients of Asian origin, while serositis appears to be more prevalent in Hispanics. With respect to antibodies, Black and Asian individuals are more commonly positive for anti-Smith and anti-dsDNA, while antiphospholipid antibodies are more often positive in white SLE patients compared to other ethnicities. Based on all of the above, it becomes evident that physicians of multiple disciplines need to be well-informed about the varying SLE presenting pictures based on a patient’s sex, age and racial/ethnic background, in order to be able to tailor the diagnostic work-up for each individual patient.
DIAGNOSIS OF LUPUS IN THE HOSPITAL SETTING

Although the majority of lupus patients are usually diagnosed in an outpatient setting, SLE can occasionally first present with severe or critical disease necessitating hospitalisation. Previous studies have reported significant variations in rates of hospitalisation and reasons of admission, mainly reflecting underlying socioeconomic and ethnic differences. Approximately 10-20% of SLE patients are hospitalised annually, the most common causes of admission being active disease (11%-80.8%) and infections (10.9%-37%). Among hospitalised SLE patients, about 20-30% are new cases diagnosed during hospitalisation. The clinical presentation of lupus flare in hospital setting varies among different studies and usually reflect severe forms of the disease. Lupus nephritis and haematological disorders are identified as the most frequent flare manifestations in most studies, accounting for 17.2%-63.4% and 17%-58%, respectively. We recently studied the clinical phenotypes of SLE patients diagnosed during hospitalisation and found that neuropsychiatric syndromes were the most common ones leading to admission, comprising 21% of patients (a generally higher proportion compared with previous literature, 1.6%-24.8%). Thus, NPSLE is an emerging severe lupus phenotype, given also the fact that most NPSLE events (30-40%) occur at disease onset or early in the disease course (within the first year). Thromboembolic events, serositis and musculoskeletal or constitutional manifestations were less common in hospitalised patients, possibly implying an outpatient management for these disease phenotypes. Importantly, while patients with SLE have an increased risk for cardiovascular events compared with the general population, these are less frequent reported flares, and mostly reflect lupus hospitalisations related to disease damage or comorbidities, rather than SLE itself.

PRECLINICAL SLE, INCOMPLETE SLE AND UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE

The period preceding a formal diagnosis of SLE has been referred to as “preclinical lupus”, “lupus-like disease” or “incomplete lupus” (ILE). Although there are no universally accepted definitions for these entities, in older literature ILE typically pertained to patients who had one or more, but fewer than four, ACR SLE classification criteria. Undifferentiated connective tissue disease (UCTD) is a broader term used for individuals who exhibit symptoms suggestive of a CTD but do not meet specific classification criteria for any. Among patients with UCTD, a small proportion (10-20%) will eventually develop SLE. To date, no single biomarker has been shown to predict the progression of these patients to definite SLE, thus, only close follow-up will promptly capture those individuals who transition to SLE. Female sex, younger age, malar rash, oral ulcers, and thrombocytopenia have been associated with transition from ILE to SLE in these studies, while ILE patients who remained stable over time were more likely to manifest arthritis and leukopenia. Importantly, ILE patients who transition to SLE during follow-up tend to exhibit a more benign disease course, characterised by a lower incidence of major organ involvement. Independent risk factors for transition from UCTD to SLE include fever, discoid lesions, serositis, anti-dsDNA and anti-Sm. Importantly, patients with either ILE or UCTD tend to progress to SLE within the first years following diagnosis, signifying the need for more tight monitoring during this early period.

In contrast to incomplete/undifferentiated forms of lupus, preclinical SLE typically refers to individuals with serological evidence of autoimmunity (e.g., positivity for ANA and/or other autoantibodies), without any evident clinical symptoms. Several studies have been conducted to identify risk factors associated with the transition from the pre-clinical stage to definitive SLE, with the primary objective to minimise diagnostic delay. Approximately 90% of patients with SLE develop autoantibodies prior to diagnosis. Notably, non-specific antibodies including ANA, anti-phospholipid, anti-Ro, and anti-La, were detected at an earlier pre-clinical stage compared to SLE-specific antibodies, such as anti-Sm and anti-dsDNA antibodies. A Swedish SLE cohort study showed that 63% of SLE patients develop ANA approximately 5 years prior to the diagnosis, whereas anti-Sm antibodies become detectable closer to the time of diagnosis. Nevertheless, only a minority of SLE patients carry SLE-specific antibodies during the pre-clinical phase. Furthermore, non-specific antibodies, particularly ANA, are prevalent in a range of autoimmune disorders and can also be found in individuals without autoimmune conditions, rendering them unsuitable for diagnostic purposes. Results from the same Swedish cohort indicated that increased levels of IP-10 (interferon gamma induced protein 10) and interferon-a (IFN-a) are evident in SLE patients at pre-clinical stage. Indeed, recent evidence demonstrate that IFN-a might potentially serve as a surrogate marker for the transition from the pre-clinical stage to established SLE, and validation studies are currently in progress. In this regard, a higher IFN score along with family history could help to identify ANA-positive individuals who will progress to definitive connective tissue disease, including SLE, although IFN upregulation (albeit lower) was evident even in ANA-positive individuals who did not ultimately progress to SLE. Ongoing research in the field of preclinical disease is of utmost importance for uncovering diagnostic biomarkers.
to identify individuals at high-risk for closer monitoring and intervention, ideally aiming at preventing the transition to full-blown disease.

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The authors declare no conflict of interest.

**AUTHOR CONTRIBUTIONS**
NK and DS drafted the manuscript. AF supervised the writing and edited the manuscript. All authors approve the final form.

**REFERENCES**


