BJMS BATNA JOURNAL OF MEDICAL SCIENCES
www.batnajms.net

BATNA JOURNAL OF MEDICAL SCIENCES
2024, VOL. 11, NO. 4, 501–509
DOI: 10.48087/BJMSra.2024.11417

REVIEW ARTICLE

OPEN ACCESS

Incomplete lupus in adults. who, when, and how to treat?

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ABSTRACT

Systemic lupus erythematosus (SLE) often evolves from a preclinical phase, characterized by immune dysregulation and incomplete clinical manifestations that do not meet classification criteria. This article explores the spectrum of incomplete lupus erythematosus (ILE) and its potential transition to classified SLE. Notably, a significant proportion of ILE patients exhibit various clinical manifestations, including autoimmune abnormalities and organ damage, despite not fulfilling formal SLE criteria. Recent studies suggest that 10–50% of ILE cases may progress to SLE within five years, often presenting a milder form without severe organ involvement. The article highlights the need for improved screening and monitoring strategies for people with a high risk of SLE, particularly those with risk factors or serological abnormalities. Current guidelines lack comprehensive management approaches for ILE patients either symptomatic or asymptomatic, emphasizing the necessity for further research into preventive therapies, such as hydroxychloroquine, to mitigate disease progression. Ultimately, understanding the pathogenesis and clinical management of incomplete forms of SLE is crucial for early intervention and improved patient outcomes.

ARTICLE HISTORY

Received 22 Nov 2024
Accepted 10 Dec 2024

KEYWORDS

Systemic Lupus Erythematosus, Incomplete Lupus Erythematosus, Biomarkers, Hydroxychloroquine

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1. INTRODUCTION

SLE is a multisystemic disease of unknown aetiology, with multiple clinical presentations. (1) Its female-to male ratio is 9:1 in adults. (2) In 65% of patients , its onset is between the age of 16 and 55. (3) Apart from the rare TREX1 mutation or deficiencies in early complement components, the development of SLE likely requires a combination of factors that contribute to genetic susceptibility. (4,5) One study found that the cumulative number of genetic risk variants was higher among patients with childhood-onset SLE compared to those whose disease onset occurred in adulthood.(6) The diagnosis of SLE is not always straightforward, it could be a big challenge , especially in patients with isolated serological abnormalities in the absence of clinical manifestations , or in contrast, clinical manifestations suggestive of SLE without serological biomarkers. Moreover, asymptomatic patients with weakly positive SLE biomarkers pose significant diagnostic and management challenges, which become even more complex when there is a high-risk factor of SLE. Patients generally fall into two categories: (1) those with preclinical, asymptomatic stages often with minor lab abnormalities or high-risk factors, and (2) those with clinical manifestations (symptomatic) that do not meet full SLE criteria. We will try through this article to address the questions posed in the title: which patient should be treated, when and how?

2. IMMUNOLOGICAL TESTS POSITIVITY AND THEIR MEANING

SLE is characterized by a diverse array of autoantibodies, targeting both intracellular and extracellular components. These autoantibodies play distinct roles in the pathogenesis, prediction, prognosis, and protection of the disease. (7)

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In this article, we will delve into the most significant autoantibodies associated with SLE, exploring their roles and implications for diagnosis and management.

Table 1. Risk factors for Systemic Lupus Erythematosus.

Risk factors for SLE	
Gender	Woman
Race and ethnicity	African Americans
	Hispanics
Genetics	Family history of SLE
Diseases	Endometriosis
	Celiac Disease
	Periodontal Inflammation
	Atopic dermatitis
	allergic rhinitis
Lifestyle	Smoking
Elements deficiency	vitamin D
	Selenium
	Iron
	growth differentiation factor 15

3. ANTI-NUCLEAR ANTIBODIES (ANA)

The detection of ANA by indirect immunofluorescence (IIF) is a vital immunological biomarker in serum for classifying patients with SLE. (8) According to the EULAR/ACR-2019 criteria, a titer of 1:80 or more is considered a crucial entry criterion for SLE. (9) Although ANA sensitivity in SLE is high (90-95%), its specificity is relatively low, with ANA found in 5-20% of healthy individuals—a rate that rises with age. This highlights that ANA alone is not diagnostic for SLE or any other autoimmune condition (10), and it is also observed in various autoimmune, malignant, or infectious diseases (11). Importantly, a negative ANA test does not exclude SLE (12). Differences in IIF-ANA test results may be due to the use of HEp-2 cells, testing protocols, or lab-specific criteria for positivity (13). Additionally, the DFS70 antibody in ANA-positive individuals is often a marker for patients unlikely to develop SLE, though it does not exclude the disease. (14) However, this is not an exclusion criterion for SLE.

4. ANTI-DOUBLE-STRANDED DNA (ANTI-DSDNA)

Anti-dsDNA antibodies play a crucial role in the diagnosis and monitoring of SLE. (15). Although enzyme-linked immunosorbent assay (ELISA) is a sensitive method for anti-dsDNA detection, the assay's low specificity often requires confirmation with a more specific test, such as the Farr assay. It is also valuable for tracking disease activity. Anti-dsDNA is more sensitive for predicting exacerbations than C3 or C4 levels. (16) It is essential to acknowledge that not all anti-dsDNA antibodies are pathogenic. While these antibodies are a hallmark of SLE, their presence does not always indicate disease activity or progression. Several key points support this theory and warrant further discussion. Firstly, the presence of anti-dsDNA antibodies predicts the presence of a spectrum of other antibodies specific for chromatin ligands and structures, although only the Z-DNA structure has been shown to be immunogenic by itself. (17) Secondly, there are different types of anti-dsDNA antibodies. The IgM type and non-complement-fixing IgG subtype are linked to low disease activity and remission, while the IgG type and complement-fixing IgG subtype are associated with high disease activity and kidney involvement. This emphasizes that not all anti-dsDNA antibodies have the same effect on the disease. (18-19) Thirdly, the primary response to DNA may be oligo-specific, but the secondary response is directed towards non-DNA immunogens, which may affect specificity. (20) Fourthly, anti-dsDNA antibodies can have two origins, infectious (usually temporary and of low level/avidity) or autologous (sustained and of high level/avidity), and they can complement each other, as viral infections can trigger flares of SLE. (21) Finally, studies have shown that the complex of mitochondrial DNA and anti-mitochondrial DNA antibody is known to induce plasmacytoid dendritic cell IFN-α production and is found in lupus nephritis renal biopsy, correlating better with LN than anti-dsDNA. (22-23) Understanding the complexity of anti-dsDNA antibodies is essential for accurate SLE diagnosis and monitoring.

5. COMPLEMENT

Decreased levels of complement components C3, C4, and CH50 can serve as indicators of disease activity and glomerulonephritis in SLE patients . (24) However, it is essential to perform serial and comparative measurements, due to potential fluctuations unrelated to disease state in some patients. Additionally, it is not uncommon for patients to have a C4 null allele, which can affect the interpretation of complement levels . (25)

6. ANTI-SM

Anti-Sm antibodies are known for their high specificity and low sensitivity, making them a valuable diagnostic criterion for SLE. (26) However, research has also revealed that anti-Sm antibodies possess neural toxicity, which can have significant implications for patients with SLE. (27) Interestingly, there is a hypothesis that an infection with Epstein Barr virus (EBV) in predisposed individuals may trigger the development of lupus. This theory is based on the discovery that the proline-rich sequence PPPGMRPP of the Sm core is similar to the sequence PPPGRRP found in EBV. This similarity suggests that cross reacting epitopes may play a role in the induction of lupus in susceptible individuals. (28)

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Photoprotection
- Sun light and indoor fluorescent lighting.

Smoking cessation

Diet and nutrition
- Vitamin D, Omega-3 , Selenium.
- well-balanced diet. (Mediterranean-style diet)

Exercise
- aerobic, aquatic, resistance-based, and mind-body-based (e.g. yoga).

Weight loss

Avoiding drugs lupus-like effect
- Hydralazine, Procainamide, Quinidine, Isoniazide, Diltiazem...etc.

Avoiding extreme stress and fatigue
- Psychosocial interventions should be considered

Avoiding infections

Figure 1. Life style management of SLE

7. ANTI-PHOSPHOLIPID ANTIBODIES

Antiphospholipid antibodies are a family of autoantibodies that can interact with negatively charged phospholipids and phospholipid-binding proteins. The testing involves three primary antibody categories: Lupus anticoagulants (IgG, IgM), Anticardiolipin antibodies (IgA, IgG, and IgM), and Anti-β2-glycoprotein Ib (anti-β2GPIb) antibodies (IgA, IgG, and IgM). Despite being a component of the criteria for SLE classification, anti-phospholipid antibodies are non-specific and can be detected in various conditions beyond SLE like other autoimmune disease , infection, drug induced disorders, and healthy patient . (29)

8. ANTI-RNP ANTIBODIES

Anti-RNP antibodies target small nuclear ribonucleoproteins (snRNPs), which are RNA-protein complexes involved in pre-mRNA processing. However, these antibodies are not specific for SLE and can be found in various other autoimmune diseases, including mixed connective tissue disease (MCTD) especially in high titers, Sjögren's syndrome , rheumatoid arthritis , systemic sclerosis, and inflammatory myositis . (30)

9. ANTI-SSA/RO AND ANTI-SSB/LA ANTIBODIES

Anti-SSA/Ro and anti-SSB/La antibodies can be present in SLE and are significant due to their ability to cross the maternal placenta, potentially inducing neonatal lupus and congenital heart block . (31) Recent studies in French and Greek populations have highlighted the importance of measuring both Ro specificities (Ro52/TRIM and SSA60/Ro) separately. The findings suggest that: Positive SSA60/Ro and negative Ro52/TRIM : Is commonly found in SLE patients, particularly when antiphospholipid antibodies are present. Isolated positive Ro52/TRIM : Is associated with a variety of diseases. Positivity of both Ro52/TRIM and SSA60/Ro: Is strongly associated with Sjögren's syndrome , emphasizing the need for careful interpretation of test results . (32- 33)

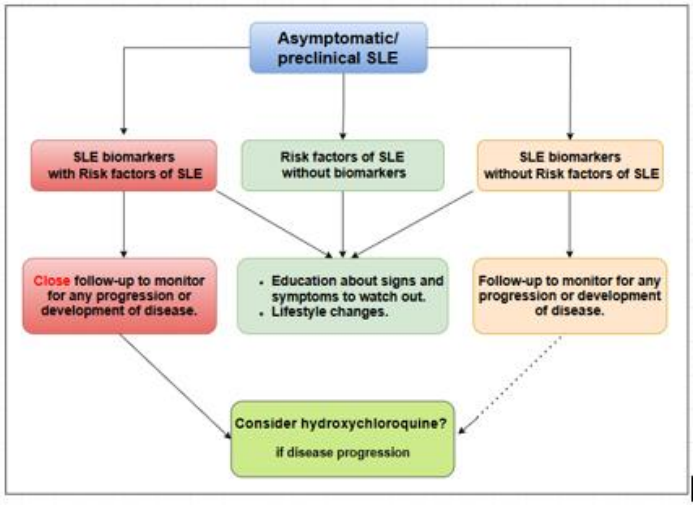

Figure 2. Management algorithm for asymptomatic/preclinical SLE

10. RISK FACTORS FOR SLE

A large number of systematic reviews have studied the risk factors of SLE (TABLE 1). It predominantly affects women, with the gender disparity being particularly pronounced among younger patients, notably those in their twenties. (34) Additionally, certain racial and ethnic groups are more frequently and severely affected by SLE, with African Americans and Hispanics experiencing higher incidences than Caucasians, a difference likely due to genetic predispositions and socioeconomic factors.(34)

Research also indicates potential links between SLE and conditions like endometriosis, which may exacerbate SLE by modulating immune responses and promoting autoantibody production due to oestrogen's effects on cellular immunity. (35) Likewise, a potential link between SLE and celiac disease has been suggested, albeit with moderate evidence. Periodontal inflammation may also relate to SLE, though evidence for this link remains weak. (36)

Conditions such as atopic dermatitis and allergic rhinitis share immunological similarities with SLE, including immune dysregulation and heightened inflammatory mediators. Elevated

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IgE and IL-2 levels, commonly seen in these conditions, may act as triggers for SLE onset by disrupting immune balance. (37) Detecting antibodies in individuals with these associated diseases could aid in early identification of those at risk, potentially preventing SLE progression.

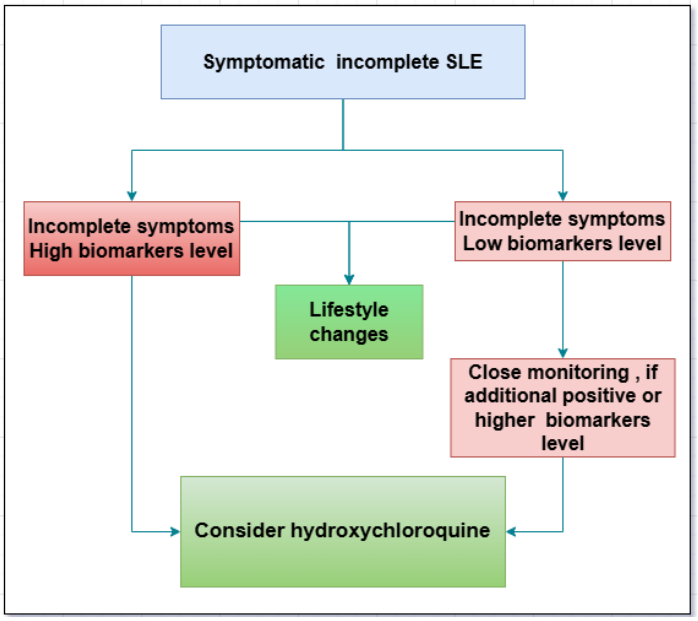

Figure 3. Management algorithm for symptomatic incomplete SLE.

Certain lifestyle factors are known to influence SLE risk. Studies show a significant relationship between low vitamin D levels and SLE incidence or worsening. Vitamin D, particularly 1,25-dihydroxyvitamin D3, has been found to modulate immunity by suppressing B cell proliferation, reducing memory B cells, and decreasing immunoglobulin production. It also impacts dendritic cell activity, IFN-α production, and T cell responses, creating a more balanced immune environment that may protect against SLE. Further investigation is required to clarify vitamin D's precise role in SLE. (38)

Smoking, particularly current smoking, is linked to an increased SLE risk, while former smoking shows no significant effect (35). Smoking is also associated with various SLE clinical manifestations and may reduce treatment efficacy. (39) Smoking is hypothesized to impact SLE risk by interacting with specific gene polymorphisms and influencing DNA methylation. Notably, these methylation changes may be reversible after smoking cessation, although further research is necessary to understand these complex interactions. (40)

Table 2. SLICC and EULAR/AC criteria for Systemic Lupus Erythematosus.

2012 SLICC criteria	2019 EULAR/ACR criteria
Clinical Criteria: 1. Acute cutaneous lupus 2. Chronic cutaneous lupus 3. Oral ulcers 4. Nonscarring alopecia 5. Synovitis involving two or more joints or tenderness in two or more joints 6. Serositis 7. Renal disorder 8. Neurologic disorder 9. Hemolytic anemia 10. Leukopenia (<4000/mm3 at least once) 11. Thrombocytopenia (<100,000/mm3) Immunological Criteria: 1. ANA above laboratory reference range 2. Anti-dsDNA above laboratory reference range 3. Anti-Sm 4. Antiphospholipid antibodies 5. Low complement 6. Direct Coombs test SLE classification requires: Either biopsy-proven lupus nephritis in the presence of ANA or anti-dsDNA as a 'standalone' criterion, or four criteria with at least one of the clinical and one of the immunological/ANA criteria	Obligatory Entry criterion: Antinuclear antibodies 1.Constituional fever 2.Acute cutaneous lupus 3.Subacute cutaneous OR Discoid lupus 4.Oral ulcers 5.Non-scaring alopecia. 6. Joint involvement 7. Pleural or pericardial effusion 8. Acute pericarditis 9. Proteinuria > 0.5g/24h 10. Renal biopsy class II OR V lupus nephritis 11. Renal biopsy class III OR IV lupus nephritis 12. Delirium 13.Seizure 14.Psychosis/delirium 15.Autoimmune hemolysis 16.Leukopenia 17.Thrombocyopenia 18.Anti-dsDNA antibodies 19.Anti-Sm antibodies 20.Anti-Cardiolipin OR Anti-B2GP1 OR Lupus anticoagulant 21.Low C3 OR low C4 OR Low C3 and C4 SLE classification requires: (a) fulfilled entry criterion (b) at least one clinical criterion (c) total score ≥ 10 points

A family history of SLE remains one of the strongest risk factors, warranting discussion in greater depth in the chapter on transition risk. Some studies also suggest protective factors against SLE, including serum selenium, iron, and growth differentiation factor 15, which may have implications for disease prevention and management. (41)

11. DIAGNOSIS OF SLE

Diagnosing SLE can be a daunting task, it involves a combination of clinical evaluation and laboratory tests, with the exclusion of alternative diagnoses. In the absence of definitive diagnostic criteria, clinicians often rely on SLE classification criteria to identify key clinical features that support a diagnosis of SLE.

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Key serologic markers, such as anti-dsDNA and anti-Sm antibodies, are strongly associated with SLE and play a significant role in its diagnosis. Various classification criteria exist for research and epidemiological purposes. These include the 1971 preliminary classification with 14 clinical and lab features (42), the 1982/1997 ACR criteria requiring four out of eleven features (43), the 2012 SLICC criteria (44), and the 2019 EULAR/ACR criteria (45). The SLICC criteria (Table 2) are widely used due to their high sensitivity, especially in early-stage SLE. The 2019 EULAR/ACR criteria introduced an updated structure, requiring a positive ANA test as an entry criterion and incorporating weighted criteria within defined domains. These criteria achieved high specificity (93%) while improving sensitivity to 96%, comparable to the SLICC criteria (97%) (46,47). These updated criteria are intended to apply across diverse ethnicities and early-stage disease, although further validation is ongoing. The 2019 EULAR/ACR classification criteria introduce a revised structure that emphasizes a positive antinuclear antibody (ANA) test as a mandatory entry criterion. This update reflects the foundational role of ANA in systemic lupus erythematosus (SLE). The criteria include weighted items categorized within specific domains, paired with a common attribution rule that ensures each criterion is applied to SLE only when no alternative diagnosis is more plausible. Key updates include the incorporation of fever as a criterion and refinements to other individual criteria. The revised criteria achieve high specificity (93%), consistent with the ACR standards, while enhancing sensitivity to 96%, which is comparable to the 2012 SLICC criteria (97%). (46,47) Additionally, the 2019 criteria have demonstrated applicability across diverse ethnic populations and early-stage disease, although further external validation is necessary. It is crucial to highlight two enduring principles, unchanged since the original 1982 ACR criteria. Classification vs. Diagnosis: Classification criteria are not synonymous with diagnosis. A diagnosis is made by a trained clinician based on a comprehensive assessment, which may include but is not limited to classification criteria. Meeting classification criteria is not a prerequisite for initiating treatment and withholding treatment solely because a patient does not meet these criteria can be inappropriate and potentially harmful (48,49,50). Limited Role in Screening: Classification criteria are not intended for screening purposes. They should only be applied in scenarios where there is a clinical suspicion of SLE to guide categorization for research or clinical purposes (46,47).

12. INCOMPLETE SLE AND TRANSITION RISK TO SLE

SLE is frequently preceded by immune dysregulation and/or clinical symptoms that do

not yet fulfil the criteria for SLE classification. Over time, these patients might alternatively progress to classified SLE by meeting additional criteria, or they may experience a milder and consistent disease course that never worsens. (51) In a Spanish study it was found that the predominant symptoms in patients with ILE were positive ANA in (94.7%), immunological abnormalities (55.1%), and arthritis in (44.2) , and haematological disorder (43.5%). Less frequent were cardiac, neuropsychiatric manifestations and lupus nephritis. (52) Although ILE is often regarded as a milder form of lupus, organ damage is commonly observed. In a Chinese retrospective study, authors identified various types of organ involvement in ILE patients. Pulmonary arterial hypertension was the most frequent, affecting 22.1% of cases, followed by kidney (11.7%), neurological in (10.4%), and peripheral vasculopathy in (9.1%). (53) It is estimated that 10–50% of ILE patients will develop SLE, with most transitions occurring within five years of ILE onset, indicating that many patients in these studies may not develop SLE. Nevertheless, the severity of their clinical symptoms and the buildup of organ damage highlight the importance of careful monitoring and treatment of incomplete lupus, even without a formal SLE diagnosis. (52,53) Several studies have found that individuals with ILE who transitioned to an SLE generally experienced a milder form of SLE, without significant organ involvement, particularly the absence of nephritis, vasculitis, or major central nervous system involvement. (54) Previous research has indicated that the progression of SLE autoantibodies occurs in three distinct stages. The first stage, termed the "normal" phase, involves asymptomatic individuals without detectable SLE autoantibodies. The second stage, known as "benign autoimmunity," is marked by the presence of autoantibodies, such as antinuclear, anti-Ro, anti-La, or antiphospholipid antibodies, with no clinical symptoms at this point. In the final stage, referred to as "pathogenic autoimmunity," more significant autoantibodies, like anti–double-stranded DNA, anti-Sm, and anti–nuclear ribonucleoprotein, emerge. This stage also sees the onset of clinical symptoms, which ultimately lead to an SLE diagnosis. (55) It seems then, autoimmune abnormalities start as simple or isolated events, and that spread and multiply until they are manifested as a potentially devastating clinical condition. (56) Currently, there is no established consensus on how to identify individuals at high risk for SLE or at which preclinical phase of the disease a patient should be referred to a rheumatologist. (57) Population research has employed a Connective Tissue Disease Screening Questionnaire (CSQ) to assess for SLE and various other connective tissue diseases. It has demonstrated high sensitivity for SLE (96%), but moderate specificity (86%, 95%). It works best as part of a two-step screening process, followed by a review of medical records or an in-person evaluation, and should not be relied on as the sole method of diagnosis. (58) Numerous biomarkers have shown potential in identifying at-risk patients during the early phases ILE. While certain exams are easily obtainable and within reach, several questions regarding their utility for screening purposes require further clarification. These include autoantibodies such as ANA and anti-SSA/Ro60,

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genetic susceptibility loci, and elevated levels of cytokines and chemokines, which often appear alongside the initial emergence of autoantibodies. Additionally, markers of complement activation have also been observed during these early stages. (57) SLE likely develops and progresses due to a complex interaction of genetic predisposition, lifestyle, environmental risk factors, and immune dysregulation. In individuals carrying genetic risk alleles for SLE, exposure to environmental risk factors throughout life may trigger synergistic interactions that accelerate the onset of autoimmunity and inflammation. Approximately 5-12% of individuals with a first-degree relative who has SLE will develop the disease, while those with a congenital deficiency in the complement component C4 face an increased risk of up to 90%. (59) . Therefore, family history of SLE is a significant risk factor for the eventual development of SLE and other autoimmune diseases, with the risk varying based on the degree of relatedness. However, absolute risk remains low. According to a Danish national cohort study only around 2% of individuals with an SLE-affected non-twin first-degree relative developed SLE during an average of 22 years of follow-up. (60) In a follow-up study, it was observed that women have a much higher rate of transition to SLE compared to their male family members. (61) Additional research has also indicated an increased likelihood of developing SLE when a combination of genetic and environmental factors are present, such as low levels of vitamin D in individuals with certain CYP24A1 alleles, (62), as well as smoking and a high genetic risk score (GRS). (63) Environmental factors include current cigarette smoking, obesity (especially at younger ages), childhood and adult trauma, stress, post-traumatic stress disorder, depression, environmental air pollution, exposure to silica, as well as hormonal exposures and reproductive factors in women. (64,65)

13. MANAGEMENT OF INCOMPLETE FORMS OF SLE

Unfortunately, the management of asymptomatic and ILE is not addressed in current guideline recommendations for SLE, which primarily focus on well-defined disease states (66). As a result, the approach to managing these patients remains unclear.

When considering management, two distinct subsets of patients must be considered: the first includes individuals in preclinical or asymptomatic stages (Figure 2) , with or without serological and minor laboratory abnormalities and/or high-risk factors of SLE. This subset can be further divided into three categories: (1) high risk factors without biomarkers, (2) serological abnormalities without high risk factors, and (3) high risk factors with biomarkers positivity. The second subset includes patients who present with clinical manifestations but do not yet meet the ACR or SLICC criteria for SLE. (Figure 3)

14. ASYMPTOMATIC /PRECLINICAL SLE

-Patients with high risk factors of SLE without biomarkers: We suggest reassurance regarding the very low absolute risk to have an SLE, education about signs and symptoms to watch out and lifestyle changes. (Figure 1)

-Patients with serological abnormalities without high risk factors: Patients who are 'incidentally' found to have a clearly positive ANA (titer >1:80) should undergo a thorough history and physical examination to assess for signs and symptoms of disease. In addition, routine testing should be conducted, including a complete blood count, serum creatinine, liver enzymes, urinalysis, C3 and C4 complement levels, an ENA panel, anti-dsDNA, and anti-phospholipid antibody screening. (67) The same management steps will be provided to the patient, additionally, the patient will undergo regular follow-up to monitor for any progression or development of disease.

-Patients with high risk factors and positive biomarkers: A more rigorous follow-up protocol should be established. If additional preclinical features are identified, such as further positive serology or a persistently low white blood cell count, the patient should undergo more frequent clinical follow-up (e.g., every 6–12 months) to monitor for disease progression. This is especially important, as disease progression typically occurs early, with a median time of 5.3 years. (68) Further research is needed to determine whether additional preventive strategies, such as the use of hydroxychloroquine, are safe and cost-effective in this population, (69,70) along with education and lifestyle measures.

Symptomatic / ILE patient not fulfilling SLE criteria

In addition to lifestyle modification and vitamin D supplementation, some authors provide evidence suggesting that HCQ may impact the development of SLE. It seems that in patients with ILE, HCQ has been shown to delay the transition to classifiable SLE. Additionally, HCQ reduces the repertoire and expression levels of autoantibodies present once the full diagnostic criteria for SLE are met. (71) The SMILE trial is a multicentre, NIH-funded, randomized, placebo-controlled, double-blind study investigating the role of hydroxychloroquine (HCQ) in patients with ILE. It is designed to determine whether HCQ can prevent ILE patients from accumulating additional SLE criteria and developing progressive disease. The study is generating a valuable biobank of samples for future mechanistic research. The final participant is expected to complete the trial in mid-2024. (72) It will offer important information to clinicians on the potential use of HCQ in preventing the development of SLE, as well as help determine the viability of prevention studies in. However, we believe that patients at high risk of transition to SLE, particularly those with very high biomarker levels, may benefit from preventive therapy with HCQ. Although the approaches outlined above are clinically reasonable, the optimal follow-up strategy and potential preventive interventions for these patients have not yet been clearly established. Further evaluation and validation of these proposed clinical pathways are needed to determine their effectiveness.

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15. CONCLUSION

In conclusion, the management of incomplete and asymptomatic forms of systemic lupus erythematosus remains a significant challenge in rheumatology. As emerging evidence indicates the risk of progression from incomplete lupus erythematosus to classified SLE, it is imperative to adopt a proactive approach that includes careful monitoring and tailored interventions. Screening tools and biomarkers show promise in identifying high-risk patients, yet more research is needed to establish standardized protocols for their management. Hydroxychloroquine may offer a preventive strategy for selected individuals at high risk of developing SLE, but further studies are essential to validate its effectiveness and safety. By enhancing our understanding of the transitional phases of lupus and refining our management strategies, we can potentially mitigate the impact of this complex autoimmune disease and improve the quality of life for affected individuals.

Competing interests: The authors declare that they have no competing interest.

Highlights

- Diagnosing SLE is challenging, as it requires a mix of clinical evaluations, lab tests, and the exclusion of other diagnoses.

-Meeting classification criteria are not synonymous with an official diagnosis; treatment should not be withheld from those who don't meet the classification criteria but may still benefit from intervention.

-ILE, a pre-SLE phase, often includes symptoms like ANA positivity, arthritis, and blood disorders, though some cases involve organ damage. About 10-50% of ILE cases progress to full SLE within five years.

-Patients with ILE may develop organ damage (e.g., pulmonary hypertension) even without a full SLE diagnosis. Those who progress to SLE generally have milder cases without major organ involvement.

-Genetic predispositions, environmental factors (e.g., smoking, pollution), and immune dysregulation play a role in SLE progression. Screening tools like the Connective Tissue Disease Screening Questionnaire (CSQ) show potential but need further study for routine screening use.

-For individuals at high risk but asymptomatic, management involves lifestyle changes, monitoring, and sometimes biomarker testing. Those with family history and positive biomarkers require closer follow-up.

-HCQ shows potential to delay ILE progression to SLE. The SMILE trial is currently investigating HCQ's role in preventing SLE progression in ILE patients.

-More research is essential to establish effective management protocols for asymptomatic and incomplete lupus. Preventive strategies like HCQ could be beneficial, but further validation is needed to confirm safety and efficacy.

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