Clinical patterns of disease: From early systemic lupus erythematosus to late-onset disease

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex disease with an insidious clinical presentation. In up to half of the cases, SLE onset is characterized by clinical and serological manifestations that, although specific, are insufficient to fulfill the classification criteria. This condition, called incomplete SLE, could be as challenging as the definite and classifiable SLE and requires to be treated according to the severity of clinical manifestations. In addition, an early SLE diagnosis and therapeutic intervention can positively influence the disease outcome, including remission rate and damage accrual. After diagnosis, the disease course is relapsing-remitting for most patients. Time in remission and cumulative glucocorticoid exposure are the most important factors for prognosis. Therefore, timely identification of SLE clinical patterns may help tailor the therapeutic intervention to the disease course. Late-onset SLE is rare but more often associated with delayed diagnosis and a higher incidence of comorbidities, including Sjogren's syndrome. This review focuses on the SLE disease course, providing actionable strategies for early diagnosis, an overview of the possible clinical patterns of SLE, and the clinical variation associated with the different age-at-onset SLE groups.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex, multisystem chronic autoimmune disease predominantly affecting females in their childbearing years. A wide variability and combination of serologic abnormalities and clinical manifestations characterize SLE. The disease features may be influenced by several factors, including sex, age, and time elapsed since the onset of symptoms. The definite diagnosis and classification of SLE are preceded by preclinical and early clinical stages, which should be recognized to adopt preventive measures and ensure early diagnosis and therapeutic intervention aimed at preventing organ damage development that

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already begins to occur early in the clinical disease process. The clinical course is frequently subject to unpredictable flares of disease activity, progressive organ damage accrual, and reduced health-related quality of life. Therefore, understanding the disease course and clinical patterns is of the utmost importance to a timely diagnosis and proper management of SLE patients.

1.1. From preclinical to early systemic lupus erythematosus

1.1.1. Preclinical systemic lupus erythematosus

The current view of SLE pathogenesis is that environmental agents (e.g., infections, drugs, ultraviolet light) in a genetically susceptible individual trigger the activation of innate and adaptive immune responses, leading to the production of pathogenic autoantibodies. Positive feedback loops involving the innate and adaptive immune systems amplify autoimmune response during the preclinical stage of SLE [1]. As a result, there may be a prolonged preclinical phase characterized by accumulating an increasing number of autoantibody specificities. Anti-nuclear antibodies (ANAs) represent the immunologic hallmark of SLE, and they are typically present many years before the diagnosis while subjects are still asymptomatic. Although not currently part of the standard assessment for SLE, multiparametric predictive models based on genetic factors, transcriptomics (e.g., type I interferon signature), and soluble mediators (e.g., antibodies and pro-inflammatory cytokines) may be helpful for the identification of subjects at high risk of developing SLE clinical features [2,3]. Preventive measures in at-risk individuals include removing environmental modifiable risk factors claimed as potentially triggering SLE onset (Table 1) [4–18].

ANA-positive subjects who later develop SLE show progressive accumulation of a higher prevalence and higher titres of more specific autoantibodies, such as anti-dsDNA and anti-Sm, before the onset of SLE. Arbuckle et al. reported that anti-Ro/SSA antibodies were detected in sera of SLE patients on average 3.0 years before the clinical onset of SLE and up to 9.4 years (mean 3.7 years) before the definite diagnosis, while anti-dsDNA and anti-Sm were detected 1.2 and 0.5 years before clinical onset, respectively [19]. Isolated ANA positivity has low dependability for SLE diagnosis as it can be found in various systemic and organ-specific autoimmune diseases, viral infections, in subjects taking drugs known to induce ANA positivity (e.g., TNF-alpha inhibitors, isoniazid), even in healthy individuals and especially healthy relatives of SLE patients. Using indirect immunofluorescence (IIF) Hep-2 assay, the prevalence of low titers ANA (1:40) in the healthy population is estimated to be up to 30%, whereas it is less than 5% when higher titers of ANA (>1:160) are present [20]. A recent meta-regression analysis included 64 studies comprising 13,080 SLE patients and confirmed a reduced sensitivity and a greater specificity for increasing ANA titers using IIF-Hep2 [21]. Therefore, ANAs must be used as a sensitive screening test to narrow the population suspected of having SLE and should be combined with other autoantibodies serving as specific biomarkers (Table 2) [22–24]. There is no SLE diagnostic gold standard, so the diagnosis of the disease is still a clinical decision based on physician expertise and supported by biomarkers. The lag time between symptoms onset and diagnosis has progressively shortened since the implementation of autoantibody testing [25].

Table 1
Environmental factors, behaviours, or conditions associated with a risk of SLE development.

Factors associated with SLE development	Risk of SLE	Risk (95% CI)	References
Adherence to multiple healthy behaviors (healthy diet, regular exercise, no smoking, moderate alcohol consumption, maintaining a BMI <25 kg/m2)	Lower	HR: 0.42 (0.25–0.70)	[4]
Moderate alcohol intake	Lower	OR: 0.71 (0.55–0.93)	[5]
Sleep deprivation (<7 h per night)	Higher	OR: 2.9 (1.6–5.1)	[6]
UV radiation:			
- History of more than one severe sunburn before the age of 20 years	Higher	OR: 2.2 (1.2–4.1)	[7]
- Sunburn-susceptible skin type		OR 2.9 (1.6–5.1)	[7]
- Outdoor work in the 12 months preceding the SLE diagnosis		OR 2.0 (1.1–3.8)	[8]
- UV exposure		HR 1.28 (0.96–1.70)	[9]
Smoking:			
- Current smoking >10 pack-years	Higher	HR 1.60–1.86	[10]
- Current smokers		OR 1.56 (1.26–1.95)	[11]
- Ex-smokers		OR 1.23 (0.93–1.63)	[11]
Obesity (BMI≥30) at age 18	Higher	HR 2.38 (95% CI 1.26–4.51)	[12]
EBV reactivation (EBV DNA-positive rate)	Higher	OR: 3.86 (1.52–9.83)	[13]
Past use of oral contraceptives	Higher	RR: 1.4 (0.9–2.1)	[14]
Silica:			
- medium exposure	Higher	OR 2.1 (1.1–4.0)	[15]
- high exposure		OR 4.6 (1.4–15.4)	
Endometriosis	Higher	HR: 2.37 (1.35–4.14)	[16]
Agricultural pesticides exposure	Higher	OR 2.24 (1.28–3.93)	[17]
Black tea	Higher	OR 1.88 (1.03–3.41)	[18]
Caffeine rich beverages	Higher	OR 1.57 (0.95–2.61)	[18]

RR: Relative risk. OR: Odds ratio. HR: Hazard ratio. SLE: Systemic Lupus erythematosus. UV: ultraviolet. BMI Body Mass Index. EBV Epstein Barr Virus.

Table 2
Sensitivity, specificity, and predictive values of biomarkers used in the SLE diagnosis work-up.

Biomarker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	References
ANA	96.5–99.0	44.0–45.2	63.9	97.8	[22]
Anti-dsDNA	57.1–75.6	95.9–97.4	95.5	72.4	[22,23]
Anti-Sm	23.6–38.0	98.7–99.9	100	61.7	[22,23]
Anti-Ro/SSA	25.2	76.6	64.9	37.4	[24]
Antiphospholipid antibodies	26.3–53.6	86.0–87.7	70.5–72.7	51.6–72.8	[22,23]
Low C3 and/or C4	46.0–71.7	83.0–99.0	98.4	71.2	[22,23]

1.1.2. Incomplete systemic lupus erythematosus

SLE onset is often insidious, with the classifiable disease usually developing over years. At disease onset, in up to 50% of patients, clinical and serological manifestations are insufficient to meet the classification criteria of SLE [26]. Classification differs from diagnosis, as classification criteria are standardized definitions that help researchers identify a uniform group of patients for clinical research. They are traditionally not intended to capture all the possible patients but to create homogeneous cohorts for scientific purposes [27]. On the other hand, diagnostic criteria recognize the heterogeneity of the disease, intending to identify as many people with the condition as possible. Given the lack of diagnostic criteria, SLE diagnosis relies on the judgment of a trained physician, and it requires ruling out potential lupus mimickers, including other connective tissue disease (CTD), infections (e.g., Parvovirus B19, Epstein Barr virus, Leishmania), and malignancies (e.g., lymphoma). However, a set of classification criteria with a good combination of sensitivity and specificity may serve as a framework to aid clinicians in the diagnostic process (Table 3) [22,23].

The clinical condition of still-not-classifiable SLE has been defined in several ways, including borderline, latent, intermediate, probable, potential, possible, and, most frequently, incomplete SLE (iSLE). The term iSLE describes a condition characterized by clinical manifestations and serologic abnormalities specific to SLE (e.g., malar rash, hemolytic anemia, anti-dsDNA, anti-Sm) but insufficient for classification [28]. Patients with iSLE and classifiable SLE have comparable genetic loads of SLE risk loci, suggesting similar genetic susceptibility, while phenotypical differences may be influenced by gene-environment interactions [29]. iSLE does not

Table 3
Different set of classification criteria for SLE.

	ACR 1997	SLICC 2012	ACR/EULAR 2019
	4 of 11 criteria	4 of 17 criteria (at least one clinical and one immunological) OR biopsy-proven Lupus nephritis with ANA or anti-dsDNA	Entry criterion: ANA at least 1:80 on HEp-2 cells or equivalent. Total score ≥10 points (points)
Cutaneous	1. Malar rash 2. Photosensitivity 3. Discoid rash 4. Oral/nasopharyngeal ulcerations	1. Acute OR Subacute cutaneous lupus 2. Chronic cutaneous lupus 3. Oral OR nasal ulcers 4. Non scarring Alopecia	Acute cutaneous lupus (6) Subacute cutaneous OR discoid lupus (4) Oral ulcers (2) Non scarring alopecia (2)
Musculoskeletal	5. Non erosive arthritis (≥2 joints, with tenderness and swelling)	5. Synovitis: swelling or effusion (≥2 joints) OR tenderness (≥2 joints) and morning stiffness (≥30 min)	Synovitis: tenderness (≥2 joints) and morning stiffness (≥30 min) (6)
Serositis	6. Pleuritis OR Pericarditis	6. Serositis (pleurisy, pleural effusions, pleural rub, pericarditis, pericardial pain, pericardial effusion, pericardial rub)	Pleural OR Pericardial effusion (5) Acute pericarditis (6)
Renal	7 Persistent proteinuria >0.5 g/24 h OR cellular casts (RBC, granular, mixed)	7. Urine protein/creatinine (or 24 h urine protein) > 500 mg of protein/24 h OR Red blood cell casts	Proteinuria >0.5 mg/24 h (4) Class II or V LN (8) Class III or IV LN (10)
Neurologic	8. Seizures (excluding other causes or drugs) OR Psychosis (excluding other causes or drugs)	8. Seizures OR Psychosis OR Mononeuritis multiplex OR Myelitis OR Peripheral or cranial neuropathy OR Acute confusional state	Seizure (5) Psychosis (3) Delirium (2)
Hematologic	9 Hemolytic anemia - with reticulocytosis OR Leukopenia: <4000/mm3; OR Lymphopenia: <1500/mm3; OR Thrombocytopenia: <100,000/mm3	9. Hemolytic anemia 10. Leukopenia: <4000/mm3 OR Lymphopenia: <1000/mm3; 11. Thrombocytopenia: <100,000/mm3	Autoimmune Hemolysis (4) Leukopenia: <4000/mm3 (3) Thrombocytopenia: <100,000/mm3 (4)
Constitutional			Fever (2)
Immunologic	10. ANA 11. Anti-dsDNA OR Anti-Sm OR aPL (LAC, Anti-cardiolipin, false positive/positive syphilis for ≥6 months)	12. ANA 13. Anti-dsDNA 14. Anti-Sm 15. aPL (LAC, anticardiolipin medium/high titer, anti-β2-glycoprotein, false RPR) 16. Low complement (C3, C4, CH50) 17. Direct Coombs test	Anti-dsDNA (6) Anti-Sm (6) aPL (LAC, anticardiolipin IgG >40GPL, anti-β2-glycoprotein IgG > 40 units) (2) Low C3 AND low C4 (4) Low C3 OR Low C4 (3)
Sensitivity	82.8%	96.7%	96.1%
Specificity	93.4%	83.7%	93.4%

aPL: antiphospholipid antibodies.

identify a benign form of the disease in terms of severity or duration, or suggest an inevitable progression to classifiable SLE [27]. The definition of iSLE can partly overlap with that of undifferentiated CTD (UCTD), an entity characterized by serological and clinical features insufficient to meet the classification criteria of a specific CTD. According to Mosca et al. [30], there are two types of UCTD: a) stable UCTD, with signs and symptoms that remain stable over time (for at least three years); b) evolving UCTD, which evolves into a definite CTD including SLE in 20–60% of cases. Recognizing the UCTDs that correspond to iSLE and are at risk of evolving to classifiable SLE has clinical implications for treatment and follow-up [31].

About 10–50% of iSLE patients will progress to definite SLE, mostly within five years since onset, with iSLE patients usually being older at diagnosis than patients with definite SLE [31]. A recent meta-analysis helped to define further the clinical and serologic manifestations linked to progression to classifiable SLE (Table 4). [32]. A retrospective study reported that hydroxychloroquine (HCQ) treatment could delay the progression from iSLE to SLE and decrease the repertoire and expression levels of autoantibodies present at diagnosis [33]. New and more robust evidence is expected from the randomized, placebo-controlled, double-blind clinical trial SMILE (Study of Anti-Malarials in Incomplete Lupus Erythematosus) [34]. The SMILE trial enrolled patients with iSLE, defined by ANA (at least 1:80) and 1 or 2 additional SLICC criteria, to evaluate whether HCQ is effective in preventing or delaying the progression to SLE within 24 months and to provide further insights into the appropriate target population. Besides treating patients with HCQ, progression-preventive strategies should include lifestyle changes and removing modifiable environmental risk factors (Table 1), including smoking habits and unprotected sunlight exposure.

Although not classifiable as suffering from SLE using a set of validated criteria, patients with iSLE do not necessarily have a milder disease, and in many cases they are affected with an initial yet full-blown SLE and must be diagnosed and treated accordingly. Interestingly, the set of clinical and serologic features that would make a patient with UCTD or iSLE considered to be a full-blown SLE was sufficiently consistent across studies and included renal involvement, acute cutaneous manifestations, thrombocytopenia, autoimmune hemolytic anemia, seizure, anti-dsDNA, anti-Sm, and hypocomplementemia [32,35,36]. Moreover, a multicentre international study identified a set of clinical manifestations and serologic abnormalities helping to early distinguish SLE, irrespective of the fulfillment of classification criteria, from diseases mimicking SLE [24]. Besides mucocutaneous involvement with the typical malar rash (OR 15.0; 95%CI 8.4–26.6) and urine analysis abnormalities (e.g., proteinuria, haematuria, pyuria, and casts) due to kidney involvement (OR 17.0; 95%CI 4.1–70.4), also serositis (OR 6.6; 95%CI 3.5–12.3), synovitis (OR 3.8; 95%CI 2.6–5.4) and fever (OR 3.3; 95%CI 2.1–5.1) showed a statistically significant association with SLE diagnosis. Features less common in early SLE than in SLE mimickers included Raynaud's phenomenon, sicca symptoms, dysphagia, and fatigue [24]. These results provided information for the EULAR/ACR 2019 SLE classification criteria that achieved the highest combination of sensitivity (96.1%) and specificity (93.4%) compared to the ACR 1997 criteria (93.4% specificity and 82.8% sensitivity) and the SLICC 2012 criteria (96.7% sensitivity and 83.7% specificity) [23]. Several additional studies assessed the accuracy of the 2019 EULAR/ACR classification criteria, reporting both high sensitivity (87.3–97.4%) and high specificity (87.8–97.3%) [37–40]. Good receiver operating characteristics were confirmed in the sub-cohorts of early SLE (diagnosis less than 12–36 months) with 87.3–92.8% sensitivity and 87.8% specificity [35,38,40]. Notably, a recent single-center retrospective study suggested that 8.6–20.1% of patients diagnosed as having early SLE are not correctly classified using the EULAR/ACR 2019, SLICC 2012, and ACR 1997 criteria individually, while the combined use of all three sets of criteria ensured the classification of 97% of patients [39].

1.1.3. Early systemic lupus erythematosus

The term "early SLE" has been used as an alternative to iSLE to describe subjects with preclinical and clinical features consistent with SLE but not fulfilling classification criteria [41]. The meaning of the term early SLE is changing to denote a subject whose diagnosis of SLE was made recently with respect to the onset of symptoms, independently from classification (Fig. 1) [24,42]. This paradigm shift is driven by the growing awareness that early recognition of symptoms and subsequent early therapeutic intervention can prevent organ damage development and accrual. Nevertheless, the reported median lag between the onset of symptoms and diagnosis of SLE is still too long (≥2 years), mainly driven by the time between the first report of symptoms to a doctor and the assessment by a rheumatologist [43,44]. Some clinically actionable initiatives, such as developing red flags and implementing tools to screen patients for referral, may help reduce referral times from primary care providers or non-rheumatology specialties to rheumatologists (Table 5). For example, the SLE Risk Probability Index (SLERPI) is a clinician-friendly algorithm enabling risk prediction for diagnosis and exhibited high accuracy in early SLE subjects [42], even those not fulfilling any definite criteria set [45]. Pending

Table 4
Clinical and serological manifestations in UCTD significantly associated with progression to definite SLE and related grade evidence rating [32].

Grade evidence rating	Clinical manifestations	RR (95%CI)	Serological manifestations	RR (95%CI)
Moderate	Younger age	−6 years (−11.0; −0.9)	Anti-dsDNA	4.27 (1.92; 9.51)
	Serositis	2.69 (1.61; 4.51)		
Low	Renal disease	2.36 (1.32; 4.21)	ANA (Hom. pattern)	7.74 (1.53; 39.19)
	Malar rash	2.00 (1.48; 2.69)	Coombs test positive	3.82 (2.05; 7.15)
	Photosensitivity	1.78 (1.03; 3.08)	Anti-Sm	2.83 (1.22; 6.54)
	Alopecia	1.62 (1.01; 2.61)	Hypocomplementemia	2.17 (1.15; 4.12)
			Anti-cardiolipin	2.06 (1.36; 3.12)
			Anti-Ro/SSA	1.74 (1.11; 2.73)
Very Low	Thrombocytopenia	3.11 (1.38; 6.99)	False positive VDRL	1.79 (1.27; 2.51)

RR: relative risk. CI: confidence interval. Hom.: homogeneous.
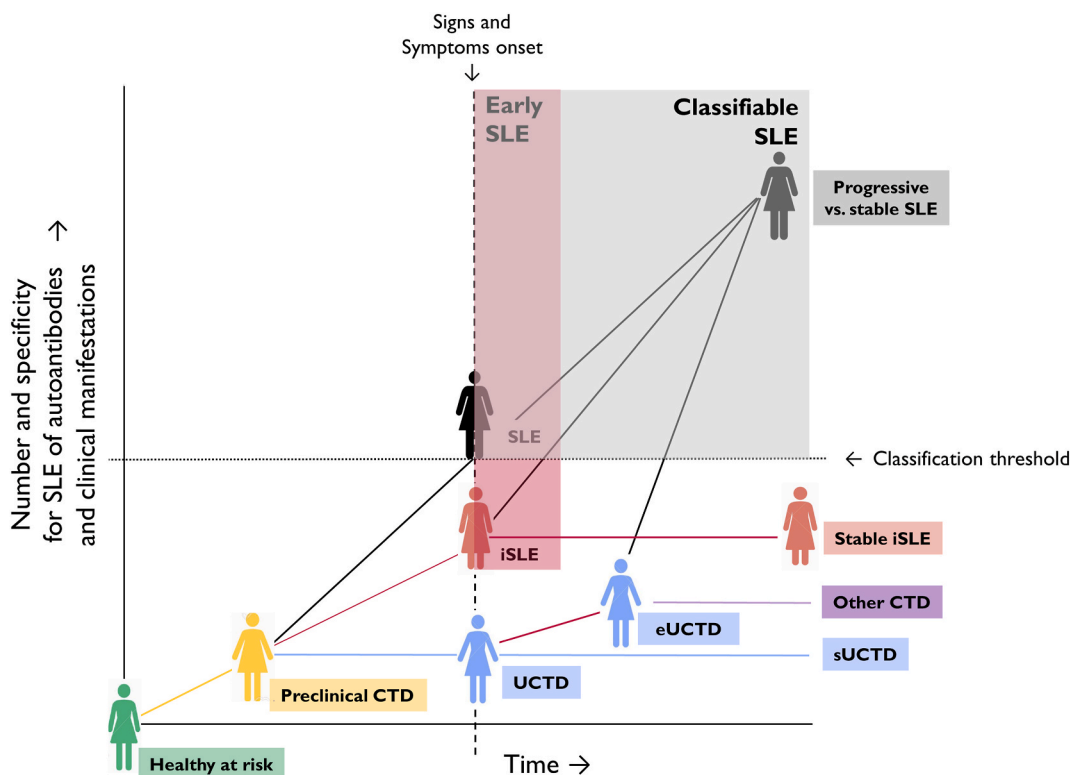
Fig. 1. Timeline of SLE development, clinical onset, diagnosis, and classification.

Healthy individuals with genetic susceptibility to autoimmunity *(green silhouette)* can be considered at risk of developing a CTD. Before the onset of clinical manifestations, there may be a preclinical phase *(yellow silhouette)* of variable and unpredictable duration characterized by accumulating an increasing number of autoantibodies with low (e.g., isolated ANA, anti-Ro/SSA) or high (e.g., anti-dsDNA, anti-Sm) specificity for SLE. If overt clinical signs or symptoms occur *(vertical dashed line)*, they can be aspecific for SLE (e.g., Raynaud phenomenon, arthralgia, sicca symptoms) and not enough to be classified with a defined CTD. These individuals *(blue silhouette)* might be described as having UCTD and can either stay stable over time (stable UCTD) or evolve to a defined CTD. If serological profiles and clinical manifestations are specific and suggestive of SLE (e.g., malar rash, seizures) but are not enough to be classified using validated criteria, individuals can be diagnosed with incomplete SLE *(red silhouette)*. Otherwise, if serological profiles and clinical manifestations are specific and sufficient, subjects can be diagnosed and classified as suffering from defined SLE *(black silhouette*, above the classification threshold, within the *dark grey window)*. When the diagnosis of SLE, including incomplete SLE, is made within a short time after symptom onset regardless of classification and severity it can be considered as early SLE *(pink window)* and has a higher chance of stable disease with better outcomes. CTD: connective tissue disease. UCTD: undifferentiated CTD, sUCTD: stable UCTD. eUCTD: evolving UCTD. SLE: systemic Lupus Eryhtematosus. iSLE: incomplete SLE.

further validation in different settings, the SLERPI may be helpful as a screening tool in subjects showing non-specific serological features (e.g., isolated ANA) with high-yield clinical manifestations (e.g., malar rash or proteinuria>500mg/24 h), in those suffering from multiple clinical manifestations but no immunological abnormalities or when specific autoantibodies (e.g., anti-dsDNA, anti-Sm) concur with a single clinical feature (e.g. thrombocytopenia or autoimmune hemolytic anemia).

Administrative database analysis showed that SLE patients diagnosed within six months of symptom onset had less severe disease,

Table 5

A list of possible causes of a delayed diagnosis and actionable solutions for decreasing referral times and enhancing early diagnosis strategies for SLE.

CHALLENGE	ACTIONS
SLE education/awareness	• Community awareness programme involving all the stakeholders
	• Education/training programme for primary care providers and non-rheumatology physicians
Tools for screening/referral	• Development and validation of local guidelines for screening and early referral, including "red flags" for SLE, or implementation of those already existing
	• Development of new SLE screening tools, including digital tools and AI application, or implementation of those already existing (e.g., SLERPI)
	• Screening programme in specific population (e.g., first degree relatives of SLE patients)
Timely access to specialist care	• Facilitated access to the clinic ("fast lupus track") or establishment of Early SLE Clinic
	• Increase in the number and strengthening of multidisciplinary referral centres ("lupus clinic")

SLERPI: SLE Risk Probability Index.

lower flare rates, and hospitalizations than those with a longer delay in the diagnosis [46]. In addition, observational studies showed that the achievement of remission or lupus low disease activity state (LLDAS) within six months since diagnosis, and their maintenance in the following 12 months, independently predicted lower damage development in newly diagnosed SLE patients [47,48]. Therefore, early therapeutic intervention is crucial when considering that organ damage develops from the very early stage of the disease, and up to 22% of SLE patients one year after diagnosis have at least one item of damage evaluated by the SLICC/ACR damage index [49,50]. Moreover, patients with early damage within one year since diagnosis have twice the risk of accruing damage, and the mortality rate is approximately three times higher than those without damage [50,51]. Implementing an integrated approach from the early stages of the disease by treating to target remission or LDA, adding HCQ as background treatment, addressing comorbidities, and minimizing prednisone use below 5 mg/day may help to reduce early damage development in newly diagnosed SLE patients [49,52].

Several definitions of early SLE have been proposed with respect to the time elapsed since symptom onset, ranging from <6 months to <36 months, with no general agreement [35,39,42,46,47]. Moreover, whether one of these timeframes represents a window of opportunity to increase the chance of achieving SLE remission and preventing damage development after treatment initiation has not been thoroughly investigated.

1.2. Clinical courses in systemic lupus erythematosus after inception

1.2.1. Patterns of SLE clinical course

The clinical course of SLE after diagnosis is generally characterized by periods of increased clinical disease activity (relapse or flare) alternating with periods of quiescence (remission) [53]. The duration of remission varies significantly among patients and depends on several factors, including compliance. Apart from this well recognized pattern of disease activity, early studies from the Johns Hopkins Lupus cohort also identified a "long quiescent" and a "chronically active" pattern [54]. That report was based on non-inception patients (not followed since diagnosis) and showed that the chronically active pattern was the most prominent with almost 40% of the cumulative patient years (mean follow-up of 4.5 years) [54]. About 20 years later, a study from the same center that included all patients with at least one year of follow-up concluded that only 19% will follow a chronically active disease pattern [55]. Relapsing-remitting disease was the most common pattern 50% of the patients whereas 31% followed a long quiescent course [55]. In these studies, disease activity was defined based on the Physician's Global Assessment (PGA) and the Mexican version of the SLEDAI (M-SLEDAI, excluding serology) while flares were defined as any increase in the M-SLEDAI score from the previous visit. In a study of 267 ethnically diverse inception patients (time from diagnosis to first clinic visit 3 months on average) from the Toronto Lupus Clinic who were followed for at least 10 years, approximately 70% of the patients demonstrated a relapsing-remitting pattern [53]. At baseline, these patients did not differ from individuals with prolonged remission or persistently active disease with regards to the demographic and clinical characteristics, serologic activity or initial therapeutic approach. During the first 10 years, these patients spent almost half the time in remission (mean 5.3 years) and they experienced 2–4 flares. Disease activity was defined on the basis of SLEDAI-2K; remission was defined as a clinical SLEDAI-2K = 0 and active disease as SLEDAI-2K $\geq$ 1.

Approximately 10% of the 267 patients ran a prolonged remission course. After the initial phase of disease activity (at diagnosis), these individuals achieved clinical remission (as defined by SLEDAI-2K) within two years from diagnosis and did not flare during the first decade of disease [53]. Most of these patients (74%) went on to demonstrate a monophasic disease course without any flare during follow-up of 18 years on average [56]. About 25% of them had severe manifestations at onset such as diffuse proliferative nephritis and neuropsychiatric lupus. Earlier reports on the patterns of disease activity in SLE failed to capture monophasic patients; the relatively
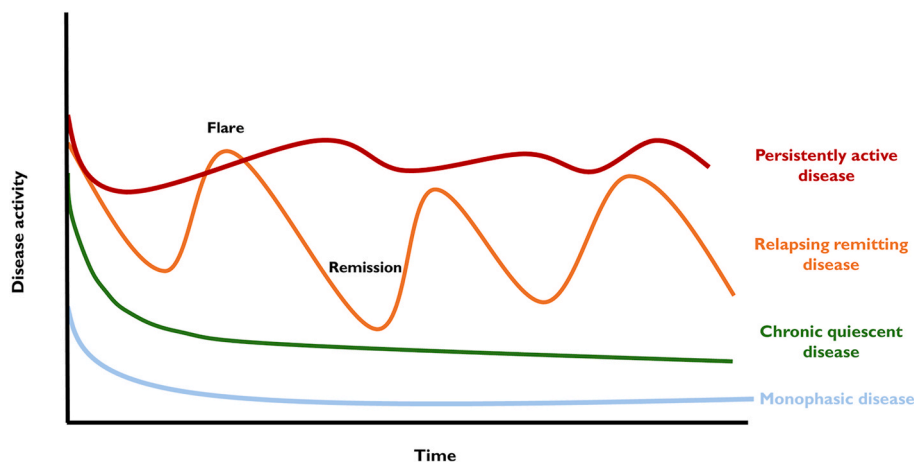

Fig. 2. Disease course patterns in SLE over time.
The majority (approximately 70%) of the patients will follow a relapsing-remitting course (orange line), while about 10% of them will display a persistently active (red line) or chronic quiescent pattern (green line). A few patients are following a monophasic pattern (blue line) with complete remission soon after diagnosis and no other episode of increased disease activity.

short follow up (1–5 years) may account for this [54,55,57,58]. In this context, severe clinical manifestations, such as lupus nephritis, may be resolved in several years after therapy initiation [59]. Thus, in the appropriate clinical setting (i.e. when signs of partial remission are evident), it seems reasonable to allow sufficient time for remission to occur.

Persistently active disease (never or only achieving short-lived remission, i.e. less than 6 months) was reported in approximately 10% [53]. Earlier studies reported a significantly higher percentage (up to 40%), albeit with a much shorter follow-up [54,60]. The factors which determine an unfavorable disease course have not been defined. However, it is believed that poor adherence to medications is a leading cause. About 43–75% of lupus patients were reported to have poor adherence in a systematic review, whereas about 33% arbitrarily discontinue their medications after 5 years [61]. Non-adherence has been linked to higher flare rate, morbidity and hospitalizations among lupus patients [62]. Other predictors include higher disease activity at onset, as well as musculoskeletal and skin involvement [60]. The different patterns of disease activity over time are displayed in Fig. 2.

In addition to the aforementioned well-defined patterns of disease activity, the remaining 10% of patients demonstrated an unusual course with one remission period that varied from 1 to 8 years during the first decade [53]. These "hybrid" patients demonstrated a global disease activity that fell between the relapsing-remitting and the persistently active patients. Their damage accrual at the end of 10 years was similar to the relapsing-remitting group.

1.2.2. Impact of clinical course on SLE prognosis

Disease course patterns greatly impact prognosis over time. There seems to be a linear relationship between disease activity and damage accrual over time with increasing irreversible damage in the persistently active and the relapsing-remitting patients. Even the patients who achieved prolonged remission developed some late damage [50,56,63]. Damage is related to disease activity and glucocorticoids; the latter becomes more prominent in later phases of the disease, most likely as a result of the prolonged exposure to glucocorticoids. Certain comorbidities that are directly or indirectly associated with glucocorticoids (osteoporosis, osteonecrosis and atherosclerotic cardiovascular events) are more frequently observed in the persistently active and relapsing-remitting pattern than in the patients who achieve prolonged remission [64,65]. In all relevant studies, damage was assessed with the SLICC/ACR Damage Index [66]. Disease patterns also affect mortality with persistently active disease being linked to higher mortality in the first five years after diagnosis [67].

Interestingly, the time in clinical remission was the most important predictor of damage accrual in most relevant studies [53,54, 68]. The relapsing-remitting patients who spent more than 50% of the first decade in remission had comparable damage accrual to the individuals who achieved prolonged remission (average time on remission 8.8 years) despite receiving higher cumulative glucocorticoid dose over the first 10 years [53]. Moreover, the "hybrid" patients were resembling all three groups according to their time in remission. Other investigators also showed that a 2-year remission is protective against damage in Caucasian lupus patients, whereas a sustained remission for 5 years was associated with 96% less risk of damage [68].

Since complete remission has not been strictly defined yet and is rare [69], LDA seems to be of value in daily practice and, also, in clinical trials for new medications in lupus. LDA captures a disease state that, although different than complete remission, leads to favorable long-term outcomes, such as reduced damage accrual and increased survival [70].

In this context, different definitions of low disease activity emerged during the last several years, namely minimal disease activity (MDA) [71], LDA [72] and lupus low disease activity state (LLDAS) [73]. The major differences (Table 6) consist of the level of acceptable disease activity as expressed by the SLEDAI-2K (from 1, 2 and 4, respectively) and the permissible treatment (prednisone up to 7.5 mg/day in LLDAS but not in MDA and LDA). All three definitions have been tested for their impact on long-term outcomes, such as damage accrual and mortality, and have shown that LDA status confers outcomes comparable to remission [70].

Duration and sustainability of LDA seems to be the most important factor for improved outcomes. Attainment of LDA for a short period (e.g. for a few months before the next disease flare) is not clinically meaningful in the long term. Relevant studies have shown that LDA duration of two years, at a minimum, will be translated to improved outcomes [74]. Interestingly, studies with prolonged follow-up reported that the LDA patients spent approximately 80% of the time in clinical remission [74,75]. Practically, this implies that patients had active disease in the beginning of the observation period and, then, achieved prolonged clinical remission with minor flares that could be managed with topical treatment.

The concept of LDA has not been applied to studies examining the disease activity patterns over time. It is possible that some flares of the relapsing-remitting patients will still fall into the definitions of LDA ("minor flares") while others will be more severe ("major flares"). If this is proven, it is reasonable that the outcomes of patients with minor flares only will be closer to the patients achieving prolonged remission. On the other hand, relapsing-remitting patients with major flares will develop outcomes closer to the persistently active ones. Such data may further improve the accuracy of predictive models and enhance the ability to apply early, patient-tailored

Table 6
Characteristics of the different definitions of low disease activity in SLE.

Criteria	Minimal Disease Activity (MDA)	Low Disease Activity (LDA)	Lupus Low Disease Activity State (LLDAS)
SLEDAI-2K	≤1 (clinical)	≤2 (clinical)	≤4
Serology (anti-dsDNA and C3/C4)	Excluded	Excluded	Included
Antimalarials	Accepted	Accepted	Accepted
Glucocorticoids (PDN equivalent)	≤5 mg/day	Not accepted	≤7.5 mg/day
Immunosuppressives	Accepted	Not accepted	Accepted

PDN: prednisone.

therapeutic approaches.

Of note, serology (anti-dsDNA antibodies and complement C3/C4) was not found to affect disease course patterns [53–55]. Serologically active clinically quiescent (SACQ) patients do not accrue more damage than patients in clinical and serological remission and, thus, do not warrant active treatment but close surveillance since they are occasionally linked to an increased flare risk [76]. Consequently, solely increased anti-dsDNA titers and/or decreased C3/C4 (without concomitant clinical activity) are accepted by most investigators for inclusion into the definition of remission [69,77]. Nevertheless, serology monitoring is indicated in periods with increased risk for disease relapse even in the absence of clinical activity.

SACQ patients are a particularly interesting subset of SLE. Initially identified in the late 1970s, such patients were intensively studied to understand the discrepancy between serological activity (increased anti-dsDNA titers and decreased levels of C3/C4) and disease activity [78]. Mechanistic studies on the nature of anti-dsDNA and anti-chromatin antibodies did not show any differences between SACQ and non-SACQ patients [79]. Moreover, the expression of interferon type I ("interferon signature") and pro-inflammatory cytokines/chemokines did not differ between SACQ and serologically and clinically quiescent patients, implying an "autoimmune remission" status [80]. Although many patients in a large cohort may exert a temporary SACQ status, only about 6% were demonstrated to maintain this status for 2 or more consecutive years [81]. About 60% of them flared in the next three years but fluctuations in the anti-dsDNA titers and/or complement levels were not reliable predictors. Compared to clinically active individuals, SACQ patients exhibited less damage accrual, less cardiovascular events and less renal damage over 10 years of follow-up [76].

The timely prediction of disease course holds the potential for a tailored treatment plan with early treatment de-escalation in the prolonged remission (or monophasic) patients or prolonged maintenance therapy in the case of relapsing-remitting or persistently active patients. Genetic factors that suppress the effector arm of the immune response or enhance immune regulation (or both) may be of importance [82] whereas epigenetic variables may also play a role in the attenuation of the pathogenetic process [83]. Several soluble mediators have been implicated in disease pathogenesis and their serum levels are altered before clinical flares [84]. Black race/ethnicity and increased disease activity over the first 2 years (as expressed by the adjusted mean SLEDAI-2K) were independently associated with disease course [53]. This implies that early response predicts better outcome over time and treat-to-target strategies should aim at remission or, if not possible, a LDA state.

1.3. Late-onset systemic lupus erythematosus

Although SLE may develop at any age, its peak incidence occurs during the reproductive age years [85]. There is no agreed definition of the age cut-off for late- or early-onset SLE [86]. Most studies define late-onset SLE (LSLE) as manifesting at or after 50 years of age [87,88]. A second definition of an age of 65 or more has also been proposed [89]. However, when comparing LSLE populations selected with these two different cut-off ages, no relevant differences were found [89]. There are fewer published data on LSLE in comparison to early-onset disease. However, differences in disease activity, clinical manifestations, comorbidities and morbidities have been demonstrated in diverse countries [86,90–94].

1.3.1. Epidemiology

In 2–20% of patients, SLE develops after the age of 50 [88,91,92]. Female predominance decreases with age, ranging from 7:1 to 18:1 in early-onset cases to 4:1 to 7:1 occurring after 50 [87,89,95]. This reduction has been linked to variations in estrogens levels [92,95]. Patients with LSLE are mainly Caucasian [89,92].

LSLE patients often take longer to diagnose. This delay could relate to LSLE being insidious in its onset with atypical clinical manifestations, comorbidities that may obscure key symptoms, and reluctance to consider SLE occurring in the elderly [88–90,92,96].

1.3.2. Clinical features

LSLE patients less frequently develop the characteristic manifestations of SLE of earlier onset, namely mucocutaneous, kidney and musculoskeletal disease [87,91–93,95] (Table 7). This is possibly due to immune senescence [92]. It has been widely accepted that

Table 7
Relative frequency of clinical features in adult SLE.

	Onset <45/50 years	Onset ≥45/50 years
Clinical features		
Arthritis [86–88,90–95,99,100]	45.0%–92.0%	21.9%–83.1%
Oral ulcers [86,87,90,92–95,99]	15.7%–47.2%	6.8%–40.3%
Malar rash [86–88,90–95,99]	36.0%–66.1%	18.2%–53.5%
Photosensitivity [86–88,90–95,99]	24.8%–73.5%	19.7%–64.4%
Discoid rash [86–88,90–95,99]	5.8%–21.5%	0.0–17.2%
Nephritis [86–88,90–95,97,99]	26.4%–56.9%	10.0%–49.3
Serositis [86–88,90,93–95]	19.1%–32.8%	17.7%–35.1
Pleuritis [91,92,99]	14.8%–22.9%	8.0%–23.8
Pericarditis [91,92,99]	9.4%–16.5%	4.0%–13.7
Interstitial lung disease [88]	3.3%	0.0
Neurologic disorder [86–88,90,91,93–95,100]	3.8%–27.2%	0.0–26.0%
Hematologic disorder [2,3,6,9,11,13]	60.5%–92.1%	50.0%–84.4%

The numbers in brackets refer to the relevant references.

LSLE presents with a more insidious disease onset, less organ involvement, and a more benign disease course [91,97]. Nevertheless, Alonso et al. [87] reported the most frequent clinical manifestation in both late- and early-onset SLE patients was arthritis, with no significant difference between groups, while some authors reported more frequent musculoskeletal involvement in LSLE [86,92,97]. Choi et al. [91] reported fever, anemia, and thrombocytopenia were less frequent in LSLE. Alonso et al. found a lower frequency of seizures and psychosis in older patients [87]. The most important age-related difference seems to be a notable decrease in the incidence and severity of renal disease in LSLE [87]. LSLE patients more often develop cardiopulmonary dysfunction, notably serositis and interstitial lung disease (ILD) [92,93,98]. Linked to advancing age, tobacco use and 'immune senescence', patients with SLE-Sjogren's syndrome (SS) overlap syndrome could be associated with a higher risk of ILD in LSLE [98].

Riveros Frutos et al. [92] reported LSLE patients more frequently had thromboembolism, deep vein thrombosis and lupus anti-coagulant positivity. However, no significant differences in thrombosis frequency between late- and young-onset SLE patients were found by Cartella et al. [99]. Furthermore, the incidence of antiphospholipid antibody syndrome does not differ significantly between late- and early-onset SLE patients [89,91,95].

Some studies found no significant difference in major organ involvement among different age of SLE onset groups [86,88,89,97]. The only significant difference reported by Padovan et al. [89] was in peripheral nervous system involvement, which was more frequent in the LSLE subgroup aged ≥65 years. The severity of SLE appears to decrease with age [88,91–93]. In contrast, Prevete et al. and Padovan et al. [86,89] found no difference between early- and late-onset SLE patients regarding disease activity. Organ damage seems to be more common in LSLE [89–91]. Although this increase is possibly due to iatrogenic effects such as osteoporosis and age-related morbidity, it challenges the interpretation of LSLE as a more benign disease [89,97].

1.3.3. Late-onset SLE comorbidities

LSLE patients had increased risks of multiple pre-existing comorbidities at diagnosis [86,92,95,97], including a higher incidence of hypertension, cerebro-vascular accidents, cardiovascular diseases, peripheral vascular diseases, cancer, osteoporosis, diabetes mellitus (DM), thyroid disease, higher body mass index, and depression [86,88,90–92,96]. For half of LSLE patients it only took less than one year to develop any increase in the burden of comorbidities, with a higher impact (33.3% cumulative incidence) to all-cause mortality [95].

LSLE patients more often have concomitant SS [87,91,92]. The subset of patients with LSLE and SS has a distinct clinical and laboratory phenotype, with a higher frequency of photosensitivity, oral ulcers, Raynaud's phenomenon, anti-Ro and anti-La anti-bodies. The relationship between LSLE and SS is debated, with autoimmune endocrinopathy being considered a manifestation of SLE and SS being claimed as a secondary manifestation of LSLE. Feng et al. [97] observed SS was the most common simultaneously occurring autoimmune disease, while hypertension and infection accounted for the most common non autoimmune disorders. In contrast, Choi et al. [91] found no significant difference in the prevalence of cancer, DM, thyroid disease. There was no significant difference when comparing the prevalence of hypertension in an age-matched general population. Thus, hypertension could be a consequence of the aging process instead of SLE itself [91].

1.3.4. Laboratory features

Patients with LSLE have a lower frequency of anti-dsDNA, anti-nucleosome, anti-Sm, anti-RNP antibodies and lupus anticoagulant positivity. Decreased complement levels, including C3, C4 and CH50, have also been reported to be less common in LSLE [86–89,91, 92,97] (Table 8). This serological profile could affect or reflect disease activity [91]. Some studies report an atypical immunological profile including higher frequencies of rheumatoid factor (RF), anti-Ro/SSA and anti-La/SSB antibodies [87,89,92]. The first could relate to RF occurring more frequently after age 65 [89]. In contrast, Padovan et al. reported significantly higher anti-dsDNA antibody levels in LSLE [89] and Wen et al. [93] significant differences in antibody profiles among SLE onset-age groups. Although SS was more

Table 8
Relative frequency of serological features in adult SLE.

	Onset <45/50 years	Onset ≥45/50 years
Serological features		
Autoantibodies*		
Anti-nuclear [86,87,90–94,97,99]	81.2%–100.0%	63.6%–100-0%
Anti-dsDNA [86–88,91–95,97,99]	42.9%–82.9%	28.0%–80.0%
Anti-Sm [86–88,91–95,97,99]	9.1%–33.9%	6.8%–26.9%
Anti-RNP [86–88,91,92,94,95,99]	13.2%–41.8%	10.0%–40.0%
Anti-Ro/SS-A [86–88,91,92,94,95,99]	31.9%–65.8%	23.7%–52.0%
Anti-La/SSS-B [86–88,91,92,94,95,99]	7.1%–27.5%	5.0%–24.0%
Lupus anticoagulant positive [86,91,92,94,95,99]	7.6%–34.8%	4.5%–33.3%
Rheumatoid factor [86,88,94,99]	7.9%–38.6%	12.5%–47.9%
Hypocomplementemia [87,88,90,94]	67.4%–92.4%	46.9%–75.0%
Low C3 [88,91,93,99]	67.0%–78.5%	15.0%–62.0%
Low C4 [88,91,93,99]	28.1%–87.9%	12.0%–64.4%
Low CH50 [91,99]	32.9%–37.0%	20.0%–27.5%

*The ratio of patients in each group with positive values for each autoantibody.

Abbreviations: dsDNA: double strand DNA; Anti-Sm: anti-Smith.

The numbers in brackets refer to the relevant references.

common in LSLE patients, there were no differences in the prevalence of anti-Ro/SS-A and anti-La/SS-B antibodies in a Korean cohort study. This study also found no relationship between autoantibody profiles and lupus nephritis in LSLE [91]. Elevation in inflammatory markers, namely the erythrocyte sedimentation rate and C-reactive protein does not appear to differ significantly among different age-groups [91].

1.3.5. Management

In some studies, the frequency of corticosteroid and hydroxychloroquine use did not differ significantly between age-at-onset groups [88–90]. In contrast, Feng et al. [97] found antimalarial drugs were less likely to be used in LSLE. Given the increased like-lihood of comorbidities in LSLE and their correlation with adverse outcomes, strategies for preventing or mitigating the impact of comorbidities should be enhanced, including minimizing the use of glucocorticoids and the related risk of osteoporosis, diabetes, hypertension, and mood disorders. Sohn et al. [88] reported that the frequency of immunosuppressive agent use was not different between late- and early-onset patients. In contrast, the frequency of cyclophosphamide and azathioprine use has been reported as significantly lower in LSLE [88,95,97], implying lower disease activity in this group compared to younger patients. Padovan et al. [89] reported that no immunosuppressive agents were used to treat a group of 30 LSLE patients aged ≥65 years.

1.3.6. Prognosis

In a cohort of hospitalized patients, the SLEDAI-2K scores in LSLE tended to decline more significantly than in younger patients at discharge, suggesting LSLE could be more sensitive to treatment [97]. Alonso et al. [87] found no significant difference in flare fre-quency between early and late-onset patients.

Although Sohn et al. [88] found standardized mortality ratio of LSLE was not higher than that of the general population, LSLE patients have a lower survival probability than early-onset SLE patients [87,91,92,96,97] because of their age. Feng et al. [97] observed nearly half of the mortality among LSLE patients was due to infections, particularly pulmonary, which were more frequent in comparison to early-onset patients. Vital organ damage/SLE-related mortality did not differ significantly. Although not independently associated with deaths in LSLE, anti-Sm antibody positivity and the use of antimalarial drugs, reported to be protective factors [100], were less frequent among these patients [97]. In contrast, Cartella et al. [99] reported cardiovascular disease as the main cause of mortality in LSLE. Overall higher mortality is possibly related to the higher comorbidity burden and organ damage due to aging and longer exposure to traditional cardiovascular risk factors in LSLE [91,96]. Long-term prospective studies are lacking to better un-derstand mortality in LSLE.

2. Conclusions

The diagnosis and classification of SLE may be preceded by preclinical and early clinical stages, which should be recognized to adopt preventive measures and ensure early diagnosis and timely therapeutic intervention. This can prevent damage development and accrual and positively influence SLE patients' prognosis. While uncommon, the possible diagnosis of SLE should not be discounted in older patients. Age at SLE onset may be one of the major disease prognosis factors. Younger SLE onset appears to correlate with a more active immunological profile, while late-onset SLE is insidious, with a higher incidence of comorbidities and more often associated with delayed diagnosis.

After diagnosis, the disease course is relapsing-remitting for most patients, while about 20% will follow a persistently active or prolonged remission course. Prolonged SACQ patients tend to accrue less damage compared to clinically active patients; only close surveillance and not active therapy are warranted. Time in remission and cumulative glucocorticoid exposure are the most important factors for prognosis. Management should aim at control of comorbidities especially in late-onset SLE. Multiparametric predictive models based on genetic factors, soluble mediators, and demographic/clinical characteristics may eventually help in the early determination of disease course and tailored therapeutic approaches. Awareness of the clinical variation associated with the different age-at-onset SLE groups is crucial to providing optimal medical care.

3. Practice points

3.1. Preclinical systemic lupus erythematosus

- SLE may be preceded by a prolonged preclinical phase characterized by accumulating autoantibodies, including ANA.
- Indirect immunofluorescence Hep-2 assay for ANA detection must be used as a sensitive screening test to narrow the population suspected of having SLE.
- Several environmental factors, behaviours, or conditions may increase SLE development risk; removing them represents a pre-ventive measure.

3.2. Incomplete systemic lupus erythematosus

- Classification criteria are standardized definitions not intended to make a diagnosis or to capture all the possible patients but to create homogeneous cohorts for scientific purposes.
- Diagnosis differs from classification because it relies on the judgment of a trained physician, and it requires ruling out potential diseases mimicking SLE.

- At onset, SLE is non-classifiable using a set of validated criteria in up to 50% of cases.
- iSLE denotes a condition of clinical diagnosis of SLE characterized by clinical and serological manifestations consistent with the disease but insufficient to meet the classification criteria.
- Using HCQ and removing modifiable environmental risk factors (e.g., smoking habits and unprotected sunlight exposure) can delay the evolution from UCTD or iSLE to classifiable SLE.

3.3. Early SLE

- Early SLE refers to a diagnosis made recently with respect to the clinical onset of the disease, including incomplete SLE and definite classifiable SLE, and may confer an increased chance of better outcomes.
- Developing red flags and implementing screening tools may help reduce referral times to rheumatologists and favor an early diagnosis.
- Implementing an integrated approach from the early stages of the disease by treating to target remission or LDA, adding HCQ, addressing comorbidities, and minimizing prednisone use below 5 mg/day may help to reduce early damage development in newly diagnosed SLE patients.

3.4. Patterns of SLE clinical course

- The clinical patterns of SLE course after diagnosis are relapsing-remitting course (50–70%), long quiescent course (10–31%), and chronically active (10–19%).
- Determining factors for persistently active disease are poor adherence to medications, higher disease activity at onset, as well as musculoskeletal and skin involvement.

3.5. Impact of clinical course on SLE diagnosis

- The duration of time in active disease predicts damage accrual and mortality.
- Compared to clinically active individuals, serologically active clinically quiescent patients exerted less damage accrual, fewer cardiovascular events, and less renal damage over 10 years of follow-up and, thus, do not warrant active treatment but close surveillance.
- Timely prediction of disease course can inform treatment approaches (e.g., early treatment withdrawal in the prolonged remission cohort or prolonged maintenance therapy in the relapsing-remitting course).

3.6. Epidemiology of late-onset SLE

- SLE can develop after age 50 (late-onset SLE) in 2–20% of patients.
- LSLE insidious onset with atypical clinical manifestations, comorbidities that may obscure key symptoms, and reluctance to consider SLE occurring in the elderly are responsible for delaying the diagnosis

3.7. Clinical features of late-onset SLE

- LSLE presents with a more insidious onset and lower disease activity but greater organ damage.
- Patients with LSLE less frequently develop mucocutaneous, kidney, and musculoskeletal disease.

3.8. Late-onset SLE comorbidities

- LSLE patients had increased risks of multiple pre-existing comorbidities at diagnosis.
- LSLE patients more often suffer from SS with a higher frequency of photosensitivity, oral ulcers, Raynaud's phenomenon, anti-Ro/SSA, and anti-La/SSB antibodies.

3.9. Laboratory features of late-onset SLE

- Patients with LSLE have a lower frequency of anti-dsDNA, anti-nucleosome, anti-Sm, anti-RNP antibodies and lupus anticoagulant positivity and higher frequency of rheumatoid factor, anti-Ro/SSA and anti-La/SSB antibodies.

3.10. Management of late-onset SLE

- The clinical management of SLE should focus on strategies for preventing or mitigating the impact of comorbidities, minimizing the use of glucocorticoids and the related risk of osteoporosis, diabetes, hypertension, and mood disorders.

3.11. Prognosis of late-onset SLE

- No significant difference was found in flare frequency between early and late-onset patients.
- LSLE patients have a lower survival probability than early-onset SLE patients, not only because of their age but also because of the higher comorbidity burden, organ damage, and more prolonged exposure to traditional cardiovascular risk factors.

4. Research agenda

- Further evidence is needed to prove the existence, define the time span, and maximize the exploitability of a window of opportunity in SLE.
- Predictive factors of disease course should be further investigated, including genetic, race/ethnicity factors, serologic markers, interferon type I ("interferon signature"), and pro-inflammatory cytokines/chemokines.
- Strategies for early diagnosis and treatment of late-onset SLE manifestations and comorbidities should be designed and implemented to decrease organ damage and mortality rates.

CRediT authorship contribution statement

Matteo Piga: Conceptualization, Writing – original draft, Writing – review & editing. **Kostantinos Tselios:** Writing – original draft, Writing – review & editing. **Luísa Viveiros:** Writing – original draft, Writing – review & editing. **Elisabetta Chessa:** Writing – original draft, Writing – review & editing. **Ana Neves:** Writing – original draft, Writing – review & editing. **Murray Barry Urowitz:** Conceptualization, Writing – original draft, Writing – review & editing. **David Isenberg:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

References

[1] Liu Z, Davidson A. Taming lupus-a new understanding of pathogenesis is leading to clinical advances. Nat Med 2012;18:871–82. https://doi.org/10.1038/nm.2752.

[2] Lu R, Munroe ME, Guthridge JM, et al. Dysregulation of innate and adaptive serum mediators precedes systemic lupus erythematosus classification and improves prognostic accuracy of autoantibodies. J Autoimmun 2016;74:182–93. https://doi.org/10.1016/j.jaut.2016.06.001.

[3] Munroe ME, Young KA, Kamen DL, et al. Discerning risk of disease transition in relatives of systemic lupus erythematosus patients utilizing soluble mediators and clinical features. Arthritis Rheumatol 2017;69(3):630–42.

[4] Choi MY, Hahn J, Malspeis S, et al. Association of a combination of healthy lifestyle behaviors with reduced risk of incident systemic lupus erythematosus. Arthritis Rheumatol 2022;74:274–83. https://doi.org/10.1002/art.41935.

[5] Chen J, Liao S, Pang W, et al. Life factors acting on systemic lupus erythematosus. Front Immunol 2022;13. https://www.frontiersin.org/articles/10.3389/fimmu.2022.986239. [Accessed 24 April 2023].

[6] Young KA, Munroe ME, Harley JB, et al. Less than 7 hours of sleep per night is associated with transitioning to systemic lupus erythematosus. Lupus 2018;27:1524–31. https://doi.org/10.1177/0961203318778368.

[7] Bengtsson AA, Rylander L, Hagmar L, et al. Risk factors for developing systemic lupus erythematosus: a case-control study in southern Sweden. Rheumatol Oxf Engl 2002;41:563–71. https://doi.org/10.1093/rheumatology/41.5.563.

[8] Cooper GS, Wither J, Bernatsky S, et al. Occupational and environmental exposures and risk of systemic lupus erythematosus: silica, sunlight, solvents. Rheumatol Oxf Engl 2010;49:2172–80. https://doi.org/10.1093/rheumatology/keq214.

[9] Barbhaiya M, Hart JE, Malspeis S, et al. Association of ultraviolet B radiation and risk of systemic lupus erythematosus among women in the nurses' health studies. Arthritis Care Res;n/a. doi:10.1002/acr.24974.

[10] Barbhaiya M, Tedeschi SK, Lu B, et al. Cigarette smoking and the risk of systemic lupus erythematosus, overall and by anti-double stranded DNA antibody subtype, in the Nurses' Health Study cohorts. Ann Rheum Dis 2018;77:196–202. https://doi.org/10.1136/annrheumdis-2017-211675.

[11] Jiang F, Li S, Jia C. Smoking and the risk of systemic lupus erythematosus: an updated systematic review and cumulative meta-analysis. Clin Rheumatol 2015;34:1885–92. https://doi.org/10.1007/s10067-015-3008-9.

[12] Cozier YC, Barbhaiya M, Castro-Webb N, et al. A prospective study of obesity and risk of systemic lupus erythematosus (SLE) among black women. Semin Arthritis Rheum 2019;48:1030–4. https://doi.org/10.1016/j.semarthrit.2018.10.004.

[13] Li Z-X, Zeng S, Wu H-X, et al. The risk of systemic lupus erythematosus associated with Epstein–Barr virus infection: a systematic review and meta-analysis. Clin Exp Med 2019;19:23–36. https://doi.org/10.1007/s10238-018-0535-0.

[14] Sanchez-Guerrero J, Karlson EW, Liang MH, et al. Past use of oral contraceptives and the risk of developing systemic lupus erythematosus. Arthritis Rheum 1997;40:804–8. https://doi.org/10.1002/art.1780400505.

[15] Parks CG, Cooper GS, Nylander-French LA, et al. Occupational exposure to crystalline silica and risk of systemic lupus erythematosus: a population-based, case-control study in the southeastern United States. Arthritis Rheum 2002;46:1840–50. https://doi.org/10.1002/art.10368.

[16] Fan Y-H, Leong P-Y, Chiou J-Y, et al. Association between endometriosis and risk of systemic lupus erythematosus. Sci Rep 2021;11:532. https://doi.org/10.1038/s41598-020-79954-z.

[17] Williams JN, Chang S-C, Sinnette C, et al. Pesticide exposure and risk of systemic lupus erythematosus in an urban population of predominantly African-American women. Lupus 2018;27:2129–34. https://doi.org/10.1177/0961203318805844.

[18] Kiyohara C, Washio M, Horiuchi T, et al. Modifying effect of N-acetyltransferase 2 genotype on the association between systemic lupus erythematosus and consumption of alcohol and caffeine-rich beverages. Arthritis Care Res 2014;66:1048–56. https://doi.org/10.1002/acr.22282.

[19] Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526–33. https://doi.org/10.1056/NEJMoa021933.

[20] Tan EM, Feltkamp TE, Smolen JS, et al. Range of anti-nuclear antibodies in "healthy" individuals. Arthritis Rheum 1997;40:1601–11. https://doi.org/10.1002/art.1780400909.

[21] Leuchten N, Hoyer A, Brinks R, et al. Performance of anti-nuclear antibodies for classifying systemic lupus erythematosus: a systematic literature review and meta-regression of diagnostic data. Arthritis Care Res 2018;70:428–38. https://doi.org/10.1002/acr.23292.

[22] Petri M, Orbai A-M, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86. https://doi.org/10.1002/art.34473.

[23] Aringer M, Costenbader K, Daikh D, et al. European league against rheumatism/American college of rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol 2019;71:1400–12. https://doi.org/10.1002/art.40930. 2019.

[24] Mosca M, Costenbader KH, Johnson SR, et al. Brief report: how do patients with newly diagnosed systemic lupus erythematosus present? A multicenter cohort of early systemic lupus erythematosus to inform the development of new classification criteria. Arthritis Rheumatol Hoboken NJ 2019;71:91–8. https://doi.org/10.1002/art.40674.

[25] Doria A, Zen M, Canova M, et al. SLE diagnosis and treatment: when early is early. Autoimmun Rev 2010;10:55–60. https://doi.org/10.1016/j.autrev.2010.08.014.

[26] Alarcón GS, Williams GV, Singer JZ, et al. Early undifferentiated connective tissue disease. I. Early clinical manifestation in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of well established connective tissue disease. J Rheumatol 1991;18:1332–9.

[27] Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res 2015;67:891–7. https://doi.org/10.1002/acr.22583.

[28] Lambers WM, Westra J, Jonkman MF, et al. Incomplete systemic lupus erythematosus: what remains after application of American college of rheumatology and systemic lupus international collaborating clinics criteria? Arthritis Care Res 2020;72:607–14. https://doi.org/10.1002/acr.23894.

[29] Slief M, Kheir JM, Smith M, et al. Genetic load in incomplete lupus erythematosus. Lupus Sci Med 2023;10:e000843. https://doi.org/10.1136/lupus-2022-000843.

[30] Mosca M, Tani C, Vagnani S, et al. The diagnosis and classification of undifferentiated connective tissue diseases. J Autoimmun 2014;48–49:50–2. https://doi.org/10.1016/j.jaut.2014.01.019.

[31] Sciascia S, Roccatello D, Radin M, et al. Differentiating between UCTD and early-stage SLE: from definitions to clinical approach. Nat Rev Rheumatol 2022;18:9–21. https://doi.org/10.1038/s41584-021-00710-2.

[32] Dyball S, Rodziewicz M, Mendoza-Pinto C, et al. Predicting progression from undifferentiated connective tissue disease to definite connective tissue disease: a systematic review and meta-analysis. Autoimmun Rev 2022;21:103184. https://doi.org/10.1016/j.autrev.2022.103184.

[33] James JA, Kim-Howard XR, Bruner BF, et al. Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus. Lupus 2007;16:401–9. https://doi.org/10.1177/0961203307078579.

[34] Olsen NJ, James JA, Arriens C, et al. Study of Anti-Malarials in Incomplete Lupus Erythematosus (SMILE): study protocol for a randomized controlled trial. Trials 2018;19:694. https://doi.org/10.1186/s13063-018-3076-7.

[35] Chung YK, Ho LY, Lee C, To CH, Mok CC. Validation of the 2019 EULAR/ACR classification criteria for systemic lupus erythematosus in ANA-positive Chinese patients. Ther Adv Musculoskelet Dis 2022;14. https://doi.org/10.1177/1759720X221100300.

[36] Aberle T, Bourn RL, Chen H, Roberts VC, Guthridge JM, Bean K, et al. Use of SLICC criteria in a large, diverse lupus registry enables SLE classification of a subset of ACR-designated subjects with incomplete lupus. Lupus science & medicine 2017;4(1):e000176.

[37] Tan BCH, Tang I, Bonin J, et al. The performance of different classification criteria for systemic lupus erythematosus in a real-world rheumatology department. Rheumatology 2022;61:4509–13. https://doi.org/10.1093/rheumatology/keac120.

[38] Pons-Estel GJ, Ugarte-Gil MF, Harvey GB, et al. Applying the 2019 EULAR/ACR lupus criteria to patients from an established cohort: a Latin American perspective. RMD Open 2020;6:e001097. https://doi.org/10.1136/rmdopen-2019-001097.

[39] Adamichou C, Nikolopoulos D, Genitsaridi I, et al. In an early SLE cohort the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria classify non-overlapping groups of patients: use of all three criteria ensures optimal capture for clinical studies while their modification earlier classification and treatment. Ann Rheum Dis 2020;79:232–41. https://doi.org/10.1136/annrheumdis-2019-216155.

[40] Lu W, Zhong Y, Weng C, et al. Utility of the ACR-1997, SLICC-2012 and EULAR/ACR-2019 classification criteria for systemic lupus erythematosus: a single-centre retrospective study. Lupus Sci Med 2022;9:e000718. https://doi.org/10.1136/lupus-2022-000718.

[41] Costenbader KH, Schur PH. We need better classification and terminology for "people at high risk of or in the process of developing lupus.". Arthritis Care Res 2015;67:593–6. https://doi.org/10.1002/acr.22484.

[42] Adamichou C, Genitsaridi I, Nikolopoulos D, et al. Lupus or not? SLE Risk Probability Index (SLERPI): a simple, clinician-friendly machine learning-based model to assist the diagnosis of systemic lupus erythematosus. Ann Rheum Dis 2021;80:758–66. https://doi.org/10.1136/annrheumdis-2020-219069.

[43] Kapsala NN, Nikolopoulos DS, Flouda SP, et al. From first symptoms to diagnosis of systemic lupus erythematosus: mapping the journey of patients in an observational study. Clin Exp Rheumatol 2023 Jan;41:74–81.

[44] Rees F, Doherty M, Davenport G, Riley RD, Zhang W, Grainge MJ. Early clinical features in systemic lupus erythematosus : can they Be used to achieve earlier diagnosis ? A risk prediction model. Arthritis Care Res 2017;69:833–41. https://doi.org/10.1002/acr.23021.

[45] Erden A, Apaydin H, Fanouriakis A, et al. Performance of the systemic lupus erythematosus risk probability index in a cohort of undifferentiated connective tissue disease. Rheumatology 2022;61:3606–13.

[46] Oglesby A, Korves C, Laliberté F, et al. Impact of early versus late systemic lupus erythematosus diagnosis on clinical and economic outcomes. Appl Health Econ Health Pol 2014;12:179–90. https://doi.org/10.1007/s40258-014-0085-x.

[47] Piga M, Floris A, Cappellazzo G, et al. Failure to achieve lupus low disease activity state (LLDAS) six months after diagnosis is associated with early damage accrual in Caucasian patients with systemic lupus erythematosus. Arthritis Res Ther 2017;19:247. https://doi.org/10.1186/s13075-017-1451-5.

[48] Floris A, Piga M, Perra D, et al. Treatment target in newly diagnosed systemic lupus erythematosus: the association of lupus low disease activity state and remission with lower accrual of early damage. Arthritis Care Res 2020;72:1794–9. https://doi.org/10.1002/acr.24086.

[49] Piga M, Floris A, Sebastiani GD, et al. Risk factors of damage in early diagnosed systemic lupus erythematosus: results of the Italian multicentre Early Lupus Project inception cohort. Rheumatol Oxf Engl 2020;59:2272–81. https://doi.org/10.1093/rheumatology/kez584.

[50] Bruce IN, O'Keeffe AG, Farewell V, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis 2015;74:1706–13. https://doi.org/10.1136/annrheumdis-2013-205171.

[51] Rahman P, Gladman DD, Urowitz MB, et al. Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. Lupus 2001;10:93–6. https://doi.org/10.1191/096120301670679959.

[52] Floris A, Chessa E, Sebastiani GD, et al. Glucocorticoid tapering and associated outcome in patients with newly diagnosed systemic lupus erythematosus: the real-world GULP prospective observational study. RMD Open 2022;8:e002701. https://doi.org/10.1136/rmdopen-2022-002701.

[53] Tselios K, Gladman DD, Touma Z, et al. Disease course patterns in systemic lupus erythematosus. Lupus 2019;28:114–22. https://doi.org/10.1177/0961203318817132.

[54] Barr SG, Zonana-Nacach A, Magder LS, et al. Patterns of disease activity in systemic lupus erythematosus. Arthritis Rheum 1999;42:2682–8. https://doi.org/10.1002/1529-0131(199912)42:12<2682::AID-ANR26>3.0.CO;2-2688.

[55] Györi N, Giannakou I, Chatzidionysiou K, et al. Disease activity patterns over time in patients with SLE: analysis of the Hopkins Lupus Cohort. Lupus Sci Med 2017;4:e000192. https://doi.org/10.1136/lupus-2016-000192.

[56] Tselios K, Gladman DD, Touma Z, et al. Monophasic disease course in systemic lupus erythematosus. J Rheumatol 2018;45:1131–5. https://doi.org/10.3899/jrheum.171319.

[57] Zen M, Bassi N, Nalotto L, et al. Disease activity patterns in a monocentric cohort of SLE patients: a seven-year follow-up study. Clin Exp Rheumatol 2012;30:856–63.

[58] Zen M, Iaccarino L, Gatto M, et al. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. Ann Rheum Dis 2015;74:2117–22. https://doi.org/10.1136/annrheumdis-2015-207347.

[59] Touma Z, Urowitz MB, Ibañez D, et al. Time to recovery from proteinuria in patients with lupus nephritis receiving standard treatment. J Rheumatol 2014;41:688–97. https://doi.org/10.3899/jrheum.130005.

[60] Nikpour M, Urowitz MB, Ibañez D, et al. Frequency and determinants of flare and persistently active disease in systemic lupus erythematosus. Arthritis Rheum 2009;61:1152–8. https://doi.org/10.1002/art.24741.

[61] Mehat P, Atiquzzaman M, Esdaile JM, et al. Medication nonadherence in systemic lupus erythematosus: a systematic review. Arthritis Care Res 2017;69: 1706–13. https://doi.org/10.1002/acr.23191.

[62] Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, et al. Adherence to treatment in systemic lupus erythematosus patients. Best Pract Res Clin Rheumatol 2013;27:329–40. https://doi.org/10.1016/j.berh.2013.07.001.

[63] Taraborelli M, Cavazzana I, Martinazzi N, et al. Organ damage accrual and distribution in systemic lupus erythematosus patients followed-up for more than 10 years. Lupus 2017;26:1197–204. https://doi.org/10.1177/0961203317693096.

[64] Nevskaya T, Gamble MP, Pope JE. A meta-analysis of avascular necrosis in systemic lupus erythematosus: prevalence and risk factors. Clin Exp Rheumatol 2017;35:700–10.

[65] Cramarossa G, Urowitz MB, Su J, et al. Prevalence and associated factors of low bone mass in adults with systemic lupus erythematosus. Lupus 2017;26: 365–72. https://doi.org/10.1177/0961203316664597.

[66] Gladman D, Ginzler E, Goldsmith C, et al. 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.

[67] Alarcón GS, McGwin G, Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups. VII [correction of VIII]. Predictors of early mortality in the LUMINA cohort. LUMINA Study Group. Arthritis Rheum 2001;45:191–202. https://doi.org/10.1002/1529-0131(200104)45:2<191::AID-ANR173>3.0.CO;2-2.

[68] Zen M, Iaccarino L, Gatto M, et al. The effect of different durations of remission on damage accrual: results from a prospective monocentric cohort of Caucasian patients. Ann Rheum Dis 2017;76:562–5. https://doi.org/10.1136/annrheumdis-2016-210154.

[69] van Vollenhoven R, Voskuyl A, Bertsias G, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). Ann Rheum Dis 2017;76:554–61. https://doi.org/10.1136/annrheumdis-2016-209519.

[70] Tselios K, Gladman D, Urowitz MB. How can we define low disease activity in systemic lupus erythematosus? Semin Arthritis Rheum 2019;48:1035–40. https://doi.org/10.1016/j.semarthrit.2018.10.013.

[71] Zen M, Bassi N, Nalotto L, et al. Disease activity patterns in a monocentric cohort of SLE patients: a seven-year follow-up study. Clin Exp Rheumatol 2012;30: 856–63.

[72] Polachek A, Gladman DD, Su J, et al. Defining low disease activity in systemic lupus erythematosus. Arthritis Care Res 2017;69:997–1003. https://doi.org/10.1002/acr.23109.

[73] Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a lupus low disease activity state (LLDAS). Ann Rheum Dis 2016;75:1615–21. https://doi.org/10.1136/annrheumdis-2015-207726.

[74] Zen M, Iaccarino L, Gatto M, et al. Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. Ann Rheum Dis 2018;77:104–10. https://doi.org/10.1136/annrheumdis-2017-211613.

[75] Tselios K, Gladman DD, Touma Z, et al. Clinical remission and low disease activity outcomes over 10 Years in systemic lupus erythematosus. Arthritis Care Res 2019;71:822–8. https://doi.org/10.1002/acr.23720.

[76] Steiman AJ, Gladman DD, Ibañez D, et al. Outcomes in patients with systemic lupus erythematosus with and without a prolonged serologically active clinically quiescent period. Arthritis Care Res 2012;64:511–8. https://doi.org/10.1002/acr.21568.

[77] Doria A, Gatto M, Zen M, et al. Optimizing outcome in SLE: treating-to-target and definition of treatment goals. Autoimmun Rev 2014;13:770–7. https://doi.org/10.1016/j.autrev.2014.01.055.

[78] Gladman DD, Urowitz MB, Keystone EC. Serologically active clinically quiescent systemic lupus erythematosus: a discordance between clinical and serologic features. Am J Med 1979;66:210–5. https://doi.org/10.1016/0002-9343(79)90529-1.

[79] Steiman AJ, Urowitz MB, Ibañez D, et al. Anti-dsDNA and antichromatin antibody isotypes in serologically active clinically quiescent systemic lupus erythematosus. J Rheumatol 2015;42:810–6. https://doi.org/10.3899/jrheum.140796.

[80] Steiman AJ, Gladman DD, Ibañez D, et al. Lack of interferon and pro-inflammatory cyto/chemokines in serologically active clinically quiescent systemic lupus erythematosus. J Rheumatol 2015;42:2318–26. https://doi.org/10.3899/jrheum.150040.

[81] Steiman AJ, Gladman DD, Ibañez D, et al. Prolonged serologically active clinically quiescent systemic lupus erythematosus: frequency and outcome. J Rheumatol 2010;37:1822–7. https://doi.org/10.3899/jrheum.100007.

[82] Sharabi A, Kasper IR, Tsokos GC. The serine/threonine protein phosphatase 2A controls autoimmunity. Clin Immunol Orlando Fla 2018;186:38–42. https://doi.org/10.1016/j.clim.2017.07.012.

[83] Stagakis E, Bertsias G, Verginis P, et al. Identification of novel microRNA signatures linked to human lupus disease activity and pathogenesis: miR-21 regulates aberrant T cell responses through regulation of PDCD4 expression. Ann Rheum Dis 2011;70:1496–506. https://doi.org/10.1136/ard.2010.139857.

[84] Thanou A, Jupe E, Purushothaman M, Niewold TB, Munroe ME. Clinical disease activity and flare in SLE: current concepts and novel biomarkers. J Autoimmun 2021;119. https://doi.org/10.1016/j.jaut.2021.102615.

[85] Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. Expet Rev Clin Immunol 2017;13:799–814. https://doi.org/10.1080/1744666X.2017.1327352.

[86] Prevete I, Iuliano A, Cauli A, et al. Similarities and differences between younger and older disease onset patients with newly diagnosed systemic lupus erythematosus. Clin Exp Rheumatol 2023;41:145–50. https://doi.org/10.55563/clinexprheumatol/oo5ymg.

[87] Alonso MD, Martinez-Vazquez F, de Teran TD, et al. Late-onset systemic lupus erythematosus in Northwestern Spain: differences with early-onset systemic lupus erythematosus and literature review. Lupus 2012;21:1135–48. https://doi.org/10.1177/0961203312450087.

[88] Sohn IW, Joo YB, Won S, et al. Late-onset systemic lupus erythematosus: is it "mild lupus"? Lupus 2018;27:235–42. https://doi.org/10.1177/0961203317716789.

[89] Padovan M, Govoni M, Castellino G, et al. Late onset systemic lupus erythematosus: no substantial differences using different cut-off ages. Rheumatol Int 2007; 27:735–41. https://doi.org/10.1007/s00296-006-0284-3.

[90] Sousa S, Gonçalves MJ, Inês LS, et al. Clinical features and long-term outcomes of systemic lupus erythematosus: comparative data of childhood, adult and late-onset disease in a national register. Rheumatol Int 2016;36:955–60. https://doi.org/10.1007/s00296-016-3450-2.

[91] Choi JH, Park DJ, Kang JH, et al. Comparison of clinical and serological differences among juvenile-, adult-, and late-onset systemic lupus erythematosus in Korean patients. Lupus 2015;24:1342–9. https://doi.org/10.1177/0961203315591024.

[92] Riveros Frutos A, Holgado S, Sanvisens Bergé A, et al. Late-onset versus early-onset systemic lupus: characteristics and outcome in a national multicentre register (RELESSER). Rheumatology Oxf Engl 2021;60:1793–803. https://doi.org/10.1093/rheumatology/keaa477.

[93] Wen L, Chen Z, Jin Z, et al. Clinical and laboratorial outcome of different age-onset systemic lupus erythematosus patients in Jiangsu, China: a multicentre retrospective study. Sci Rep 2022;12:10683. https://doi.org/10.1038/s41598-022-14840-4.

[94] Martínez-Barrio J, Ovalles-Bonilla JG, López-Longo FJ, et al. Juvenile, adult and late-onset systemic lupus erythematosus: a long term follow-up study from a geographic and ethnically homogeneous population. Clin Exp Rheumatol 2015;33:788–94.

[95] Sassi RH, Hendler JV, Piccoli GF, et al. Age of onset influences on clinical and laboratory profile of patients with systemic lupus erythematosus. Clin Rheumatol 2017;36:89–95. https://doi.org/10.1007/s10067-016-3478-4.

[96] Yu C-Y, Kuo C-F, Chou I-J, et al. Comorbidities of systemic lupus erythematosus prior to and following diagnosis in different age-at-onset groups. Lupus 2022; 31:963–73. https://doi.org/10.1177/09612033221100908.

[97] Feng X, Zou Y, Pan W, et al. Associations of clinical features and prognosis with age at disease onset in patients with systemic lupus erythematosus. Lupus 2014;23:327–34. https://doi.org/10.1177/0961203313513508.

[98] Medlin JL, Hansen KE, McCoy SS, et al. Pulmonary manifestations in late versus early systemic lupus erythematosus: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;48:198–204. https://doi.org/10.1016/j.semarthrit.2018.01.010.

[99] Cartella S, Cavazzana I, Ceribelli A, et al. Evaluation of mortality, disease activity, treatment, clinical and immunological features of adult and late onset systemic Lupus erythematosus. Autoimmunity 2013;46:363–8. https://doi.org/10.3109/08916934.2013.794793.

[100] Feng X, Zou Y, Pan W, et al. Prognostic indicators of hospitalized patients with systemic lupus erythematosus: a large retrospective multicenter study in China. J Rheumatol 2011;38:1289–95. https://doi.org/10.3899/jrheum.101088.