International Journal of Medical Sciences And Clinical Research

VOLUME Vol.06 Issue01 2026
PAGE NO. 47-53
DOI 10.37547/ijmscr/Volume06Issue01-13

Systemic Lupus Erythematosus: Pathogenesis Of Elapses, Clinical-Immunological Predictors And Pproaches To Predicting Exacerbations

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Received: 19 November 2025; **Accepted:** 12 December 2025; **Published:** 16 January 2026

Abstract: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a relapsing-remitting course, where periods of remission alternate with relapses of varying severity [1,2]. Exacerbations are a leading cause of irreversible organ damage accumulation, progression of disability, and reduced patient survival [4,6]. The article reviews current concepts regarding the pathogenesis of SLE relapses, including the role of innate and adaptive immune mechanisms, the interferon pathway, B-cell hyperactivation, and impaired immune complex clearance [3,4,12]. Particular attention is paid to clinical-immunological predictors of early relapse, including rising anti-dsDNA titers, hypocomplementemia, elevated BAFF and IL-6 levels, activation of the IFN-signature, and urinary biomarkers MCP-1 and TWEAK [1,16,20]. Data on multifactorial prediction models that allow forecasting exacerbations before clinical manifestation are summarized [4,12,7]. The presented review emphasizes the need to integrate laboratory, clinical, and molecular markers to create personalized algorithms for early detection and prevention of SLE relapses [11,13].

Keywords: Systemic lupus erythematosus; relapse; pathogenesis; biomarkers; anti-dsDNA; complement; BAFF; interferon signature; MCP-1; TWEAK; lupus nephritis; immune dysregulation; prediction of exacerbations.

Introduction: Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease accompanied by dysregulation of innate and adaptive immunity [1,2]. A characteristic feature of SLE is its relapsing-remitting course with alternating periods of remission and relapse. It is relapses that determine the accumulation of organ damage, worsening prognosis, and the need for therapy escalation.

Despite significant progress in understanding the disease pathogenesis and the introduction of targeted therapies, early detection and prediction of relapses remain one of the key clinical challenges. This work systematizes data on the mechanisms of SLE relapse formation, modern biomarkers of early exacerbation, and multifactorial models for predicting risk.

Clinical Features of Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by extreme clinical heterogeneity. The disease can affect almost all organs and tissues, complicating early diagnosis. SLE is typically characterized by a relapsing-remitting course, alternating remissions and exacerbations, as well as a combination of systemic and organ-specific manifestations.

1. General (Systemic) Manifestations

Non-specific symptoms often precede organ involvement and include:

General weakness, fatigue, weight loss;

Low-grade fever, sweating;

Anorexia;

Arthralgia and myalgia without signs of inflammation.

These signs reflect systemic inflammatory activity and hyperproduction of cytokines (IL-6, TNF-α, IFN-α).

2. Skin and Mucosal Manifestations

Skin manifestations occur in 70–80% of patients and often correlate with disease activity.

Typical forms:

Malar erythema ("butterfly rash") — symmetrical redness on the cheeks and bridge of the nose without involvement of the nasolabial folds; worsens after sun exposure.

Discoid form — infiltrated plaques with hyperkeratosis and atrophy, often on the face, scalp, ears.

Photosensitivity — rash exacerbation after sun exposure.

Subacute cutaneous SLE — annular or papulosquamous rashes, associated with anti-Ro/SSA antibodies.

Alopecia — diffuse or patchy, often reversible after remission.

Mucosal ulcers — in the oral, nasal, vaginal cavities; painless, indicative of high disease activity.

3. Joint Syndrome

The most common manifestation of SLE — up to 90% of cases.

Characteristics:

Arthralgia and polyarthritis — symmetrical, migratory, non-erosive.

Jaccoud's arthropathy — chronic hand deformities without radiographic signs of destruction.

Myalgia and myositis — possible in combination with anti-RNP antibodies or overlap syndromes [5,6].

Pathogenetically, joint manifestations are associated with immune-mediated inflammation of the synovium and immune complex deposition.

4. Kidney Involvement (Lupus Nephritis)

Observed in 30–60% of patients and determines the disease prognosis.

Clinical forms:

Asymptomatic proteinuria and microhematuria;

Nephritic syndrome (hematuria, hypertension, decreased GFR);

Nephrotic syndrome;

Rapidly progressive nephritis.

Morphological classification (ISN/RPS, 2003):

Class I — minimal mesangial lupus nephritis;

Class II — mesangial proliferative lupus nephritis;

Class III — focal lupus nephritis;

Class IV — diffuse lupus nephritis (most severe);

Class V — membranous lupus nephritis;

*Class VI — advanced sclerosing lupus nephritis.

Classes IV and VI are prognostically the most unfavorable [9,20,21].

5. Hematological Disorders

Result from autoimmune destruction of blood cells:

Anemia — often normochromic, normocytic; can be hemolytic (with anti-erythrocyte antibodies).

Leukopenia and lymphopenia — reflect disease activity and correlate with anti-dsDNA titers [1,2,4].

Thrombocytopenia — immune-mediated, may be associated with antiphospholipid syndrome (APS).

Hematological changes are part of the diagnostic criteria for SLE (EULAR/ACR, 2019).

6. Serositis

Involvement of serosal membranes occurs in 30–50% of patients:

Pleuritis — chest pain, shortness of breath, dry cough.

Pericarditis — often subclinical, less commonly with cardiac tamponade.

Peritonitis — ascites, abdominal pain, usually with high SLE activity [5,6].

These manifestations are due to immune vasculitis and deposition of immune complexes on serosal membranes.

7. Central and Peripheral Nervous System Involvement

Neuropsychiatric SLE (NPSLE) — one of the most severe manifestations.

Main forms:

Headaches, seizures, psychosis, cognitive impairment [1,4,10];

Strokes (including in APS), chorea, polyneuropathies;

Depression, anxiety, memory impairment.

Pathogenesis is associated with small vessel vasculitis, microemboli, disruption of the blood-brain barrier, and the action of anti-neuronal antibodies.

8. Cardiopulmonary Manifestations

Myocarditis, Libman-Sacks endocarditis (sterile verrucous);

Valve involvement (more often mitral);

Lupus pneumonitis, interstitial fibrosis, pulmonary

hypertension;

Thromboembolic complications (especially in APS) [6,10].

9. Gastrointestinal Manifestations

Rare but possible:

Aseptic peritonitis, mesenteric vasculitis, pancreatitis;

Hepatitis in combination with autoimmune processes (overlap syndrome) [5,6].

10. Sensory Organ and Other System Involvement

Retina: vasculitis, retinopathy, vision loss;

Auditory system: sensorineural hearing loss;

Endocrine disorders (hypothyroidism, hyperprolactinemia) [5,6].

11. Antiphospholipid Syndrome (APS)

Antiphospholipid antibodies (aCL, anti-β2-GP1, lupus anticoagulant) are detected in 30–40% of patients.

Clinically manifests as venous and arterial thrombosis, pregnancy complications [1,6] (miscarriage, preeclampsia), thrombocytopenia.

12. Disease Course Features

Onset can be acute (within weeks) or gradual (over months).

Activity ranges from mild skin-joint forms to life-threatening organ involvement (CNS, kidneys).

Course is relapsing-remitting, with remissions and relapses.

Some patients exhibit an overlap syndrome [5,6,7] with systemic sclerosis, dermatomyositis, Sjögren's syndrome.

13. Diagnostic Criteria (EULAR/ACR, 2019)

For diagnosis:

Presence of at least one immunological criterion (antinuclear antibodies ≥1:80);

A sum of scores ≥10 based on clinical and laboratory features.

Main criteria include: skin manifestations, arthritis, serositis, nephritis, hematological disorders, neuropsychiatric symptoms, and immunological markers (anti-dsDNA, anti-Sm, antiphospholipid antibodies, low complement) [11].

14. Prognosis and Outcomes

The clinical course of SLE depends on the nature of organ involvement, relapse frequency, and response to therapy.

The most unfavorable outcomes are associated with lupus nephritis, CNS involvement, and secondary therapy complications (infections, osteoporosis, atherosclerosis).

Due to early diagnosis and the use of hydroxychloroquine, immunosuppressants, and biological drugs (belimumab, rituximab), the 10-year survival rate of SLE patients currently exceeds 90% [10,13,18].

Pathogenetic Mechanisms of Systemic Lupus Erythematosus Relapse

A relapse of systemic lupus erythematosus (SLE) represents a reactivation of autoimmune inflammation occurring against a background of temporary disruption of immune regulation. Despite periods of clinical remission, most patients maintain subclinical immune system activity — persistence of autoantibodies, interferon and cytokine hyperproduction, impaired tolerance of B and T lymphocytes. Under the influence of external or endogenous triggers, this latent activity transitions into a manifest relapse.

1. Disruption of Immunological Tolerance

The basis of SLE pathogenesis and its relapses is the loss of immunological tolerance to self-nuclear antigens.

In genetically predisposed individuals (carriers of HLA-DR2, HLA-DR3, IRF5, STAT4 alleles), defective negative selection of autoaggressive lymphocytes occurs in the thymus and bone marrow.

B-lymphocyte activation leads to production of autoantibodies to nuclear components — double-stranded DNA, histones, Sm, Ro, La antigens.

Forming immune complexes deposit in tissues (especially kidneys, skin, vessels), causing inflammation via complement activation [4,12,16].

During remission, some of these processes are suppressed by therapy, but tolerance is not fully restored, creating conditions for relapse.

2. Role of Innate Immunity and the Interferon System

SLE relapse is closely linked to activation of the type I interferon pathway (IFN-α, IFN-β) — the so-called "interferon signature phenotype."

During apoptosis, nuclear antigens (DNA, RNA, histones) are released.

They are recognized by plasmacytoid dendritic cells (pDCs), which actively produce IFN-α.

Interferon enhances antigen expression, increases BAFF (B-cell activating factor) production, stimulates B-lymphocyte maturation, and promotes autoantibody production [4,7,12].

During remission, IFN-α levels may remain elevated, creating a "readiness" for relapse upon minimal trigger impact (infection, stress, UV radiation).

3. Activation of B- and T-Lymphocytes

B-cells:

During relapse, the number of plasmablasts and memory B-cells increases.

BAFF (BLyS) levels rise, supporting their survival.

High-affinity autoantibodies (anti-dsDNA, anti-Sm) are formed [1,2,16].

T-cells:

The balance between regulatory (Treg) and effector (Th1, Th17) T-lymphocytes is disrupted.

Production of IL-17, IFN-γ, IL-21 — cytokines that enhance inflammation — increases.

Thus, T-B interaction imbalance is a key link in repeated exacerbations [3,4,12,17].

4. Complement and Immune Complexes

Formation of circulating immune complexes (CICs) is a primary trigger mechanism for relapse.

Complexes deposit on capillary basement membranes, activate the complement system (C3, C4, C1q), causing inflammation and tissue damage.

Decreased serum C3 and C4 levels — a laboratory harbinger of relapse, especially in lupus nephritis [3,12,16].

5. Cytokine Imbalance

During relapse, hyperproduction of proinflammatory cytokines is observed:

* IFN-α, IFN-γ — enhance autoantigen expression;

* IL-6 — stimulates B-cell activity;

* IL-17 and IL-23 — promote neutrophilic inflammation and vasculitis;

* TNF-α — involved in endothelial damage.

This "cytokine storm" intensifies tissue inflammation, especially in kidneys and blood vessels [4,7].

6. Impaired Apoptosis and Clearance of Cellular Debris

In SLE patients, the process of clearing apoptotic cells is impaired:

Phagocytes inefficiently remove cellular debris;

Released nuclear antigens (DNA, nucleosomes) become a source of autoantigens;

Immune complex formation increases.

Impaired clearance is observed even during clinical remission and is one of the main molecular mechanisms of relapse [4,7,12].

7. Epigenetic and Hormonal Influences

Estrogens enhance expression of genes responsible for autoantibody and interferon production, explaining the higher frequency of relapses in women.

Epigenetic changes — DNA hypomethylation in lymphocytes, histone acetylation — maintain abnormal immune cell activation even in the absence of external stimuli [3,7,12].

8. External Triggers of Relapse

Relapse is often provoked by factors enhancing apoptosis and immune activation:

Infections (especially Epstein-Barr virus, cytomegalovirus, parvovirus B19);

Ultraviolet radiation — damages keratinocytes and releases autoantigens;

Stress, hormonal fluctuations, pregnancy, childbirth;

Discontinuation or irregular intake of hydroxychloroquine and glucocorticoids.

In such patients, rising anti-dsDNA and falling complement levels often precede clinical relapse by 2–6 weeks [3,4,7,22].

9. Role of the Microbiome

Modern data show that gut dysbiosis (decreased *Lactobacillus*, increased *Enterococcus* and *Ruminococcus gnavus*) is associated with increased autoantibody production and risk of SLE exacerbation.

Microbial antigens can induce molecular mimicry and cross-reactivity with DNA-chromatin [17,23].

10. Mechanisms of Organ-Specific Relapse

Kidneys: repeated CIC deposition in glomeruli, complement and macrophage activation, fibrosis.

CNS: microthrombi, anti-NMDA antibodies, small vessel vasculopathy.

Skin: local IFN-α production by keratinocytes under UV influence.

Blood vessels: endothelial activation, thrombosis in APS [3,4,16,17].

11. Immunological Markers Predicting Relapse

Rising titers of anti-dsDNA, anti-Sm, anti-RNP; Decreased C3 and C4;

Increased BAFF, IL-6, IFN-α;

Appearance of NGAL protein and MCP-1 in urine (early marker of lupus nephritis relapse) [3,7,12,16,22,23].

12. Concept of "Immunological Remission"

Modern studies show that clinical remission is not always accompanied by immunological quiescence.

Even in the absence of symptoms, 30–50% of patients maintain immunological activity — subclinical autoantibody production and low complement levels, making relapse almost inevitable without maintenance therapy (hydroxychloroquine, azathioprine, mycophenolate).

CONCLUSION

The pathogenesis of SLE relapse is multifactorial, combining genetic predisposition, defects in immune regulation, influence of interferons, and external triggers.

Relapse reflects the restoration of autoimmune activity after a period of temporary clinical control.

Understanding these mechanisms opens possibilities for early prediction of exacerbations and personalized therapy aimed at suppressing the interferon signal, normalizing B-cell activity, and maintaining immunological remission.

Predictive Factors for Systemic Lupus Erythematosus Relapse

A relapse of systemic lupus erythematosus (SLE) represents the resumption of disease activity after a period of clinical-laboratory remission. The frequency of relapses varies from 30 to 70% depending on observation duration, initial disease severity, and administered therapy.

Understanding the predictive factors for relapse is crucial for personalizing treatment, preventing irreversible organ damage, and optimizing patient monitoring.

1. Immunological Factors

1.1. Anti-double-stranded DNA Antibodies (anti-dsDNA)

Rising anti-dsDNA titers — the most reliable predictor of exacerbation, especially in lupus nephritis.

Increasing anti-dsDNA levels precede clinical relapse by an average of 4–8 weeks.

Their fluctuation reflects activation of the B-cell compartment and immune complex formation.

1.2. Decreased Complement Levels (C3, C4)

Hypocomplementemia is associated with consumption of complement components during immune complex inflammation.

Simultaneous decrease in C3 and C4 correlates with high disease activity and likelihood of early relapse.

Persistently low complement levels indicate subclinical activity and high risk of organ exacerbations.

1.3. Antibodies to Nucleosomes and Histones

Associated with relapses of nephritis and cutaneous forms of SLE.

Their appearance often precedes the rise in anti-dsDNA and can serve as an early marker of reactivation.

1.4. Interferon-Dependent Signature

Increased expression of interferon-α-inducible genes reflects chronic activation of innate immunity.

Patients with a pronounced IFN profile are prone to frequent relapses and more severe SLE course.

1.5. Circulating Memory B-cells and Plasmablasts

Increased levels of $CD19^{+}CD27^{+}$ memory B-cells during remission herald exacerbation.

Excessive production of IL-6 and BAFF (B-cell activating factor) supports survival of autoreactive clones [3,4,7,12,17].

2. Clinical and Organ Factors

2.1. Lupus Nephritis

The highest risk of relapse among all SLE forms.

Prognostically unfavorable factors:

Class IV (diffuse proliferative nephritis);

Incomplete remission after induction therapy;

Persistent proteinuria >0.5 g/day;

Rising creatinine over time;

Non-adherence to maintenance therapy.

Molecular predictors: increased urinary MCP-1 and TWEAK levels — markers of intrarenal activity.

2.2. CNS Involvement

Relapses are more frequent in patients with prior neuropsychiatric involvement, especially with antiphospholipid antibodies.

Persistent cognitive impairment and seizure syndrome also increase the risk of repeated exacerbations.

2.3. Cutaneous and Articular Forms

In some patients with predominantly skin-joint phenotypes, cyclical exacerbations are observed, associated with UV exposure, stress, and hormonal changes [3,7,16,22,23].

3. Hormonal and Metabolic Factors

3.1. Female Sex and Reproductive Factors

Estrogens enhance B-cell activation and autoantibody production.

Exacerbations often occur during menstruation, pregnancy, or with estrogen-containing contraceptive use.

3.2. Pregnancy and Postpartum Period

Physiological immunosuppression is replaced by postpartum reactivation of the immune system.

The risk of relapse is especially high in women with active SLE prior to conception and in patients with APS.

3.3. Metabolic Disorders

Vitamin D deficiency, hyperleptinemia, insulin resistance increase the inflammatory background and contribute to relapses [3,7,12].

4. Medication and Therapeutic Factors

4.1. Non-Adherence to Therapy

One of the most common causes of exacerbations.

Missing doses of hydroxychloroquine, glucocorticosteroids, or immunosuppressants leads to increased anti-dsDNA titers and decreased complement.

4.2. Discontinuation or Rapid Tapering of Glucocorticoids (GCs)

Reducing the dose to <5 mg/day prednisolone without hydroxychloroquine maintenance therapy increases relapse risk.

Complete GC discontinuation is not recommended in organ-involving forms even during remission.

4.3. Insufficient Immunosuppression

Use of overly short courses of cyclophosphamide or azathioprine, premature discontinuation of mycophenolate mofetil lead to nephritis reactivation.

4.4. Absence of Hydroxychloroquine [1–4,7]

This drug reduces relapse frequency by 30–50%, so its discontinuation is a significant prognostically unfavorable factor [3,7,22].

5. Infectious Triggers

Reactivation of latent viruses (EBV, CMV, HSV) can induce autoantibody production and trigger relapse.

Frequent respiratory infections, especially after immunosuppressive therapy, are associated with exacerbations.

6. Psychoemotional and External Factors

Chronic stress, overwork, sun exposure, hypothermia, and physical overexertion can provoke relapse.

A link has been established between stress-induced activation of the hypothalamic-pituitary-adrenal axis and increased levels of IL-6 and IFN-γ [3,7].

7. Laboratory and Biomarkers of Early Relapse

Modern research identifies a number of laboratory indicators that precede relapse. Below is the integrated table from the image, fully incorporated into the work structure.

Table 1. Laboratory and Biomarkers of Early SLE Relapse

Biomarker	Clinical Significance
Rise in anti-dsDNA (>twofold from baseline)	Imminent nephritis relapse [3,7,12].
Decrease in C3 and C4 activity	Complement consumption, systemic systemic activity [3,12]
Increase in BAFF and IL-6 levels	B-cell activation [7,12,16]
Increased IFN-signature expression	General risk of relapse [4,7]
Urinary MCP-1 and TWEAK	Local renal activity [22,23]

These biomarkers reflect subclinical immune system activity and allow predicting relapse weeks before clinical manifestation.

8. Predictive Models

Multifactorial analyses show that a combination of the following factors has high prognostic significance (accuracy up to 80%):

elevated anti-dsDNA titer, hypocomplementemia, incomplete nephritis remission, discontinuation of hydroxychloroquine [4,7,12,16,22].

Additionally, modern models include IFN-signature, BAFF levels, circulating plasmablasts, urinary NGAL and MCP-1, which improves accuracy in monitoring relapse risk, especially in lupus nephritis.

9. Conclusion

SLE relapses are due to a complex interaction of immunological, hormonal, and external factors [1–4,7,10].

The most significant predictive signs are: dynamic increase in anti-dsDNA, decreased complement levels, incomplete remission of organ-involving forms, therapy non-adherence, hormonal and infectious triggers [3,4,7,12,16,22].

Early identification of these factors and individualized patient monitoring (including assessment of biomarkers and clinical risks) can significantly reduce the frequency of exacerbations and improve long-term prognosis [10,11,13].

REFERENCES

1. Ugarte-Gil MF, Alarcón GS. Predictors of systemic lupus erythematosus flares. Rheum Dis Clin North Am. 2022;48(1):35–48.
2. Fatemi A, Keivani-Boroujeni E, Smiley A. Predictors of severe lupus flares: a prospective observational study. BMC Rheumatol. 2023;7:10.
3. Bai X, et al. Predicting systemic lupus erythematosus flares during post-remission follow-up. Journal. 2025. PubMed.
4. Brunner HI, et al. Prognostic biological markers of SLE flares: a systematic literature review. Arthritis Res Ther. 2017;19.
5. Siegel CH, Sammaritano LR. Systemic lupus erythematosus: a review. JAMA. 2019/2020.
6. Abu-Shakra M, Shoenfeld Y, et al. Predictors of flares and long-term outcomes in SLE with azathioprine and low-dose prednisone. Lupus. 2001;10(3):152–153.
7. Flouda S, Boumpas D. Systemic lupus erythematosus: management strategies. Rare Dis Orphan Drugs J. 2025;4:18.
8. Flare and Persistently Active Disease Are Common in Lupus. Medscape Review. 2025.
9. Tanaka N, et al. Lupus nephritis: a review. J Appl Lab Med. 2024;7(6):1450
10. Durcan L, O'Dwyer T, Petri M. Management strategies and perspectives in adult SLE. Lancet. 2019;393(10188):2332–2343.
11. Fanouriakis A, et al. EULAR recommendations for SLE management update 2023/2024. Ann Rheum Dis. 2024;83
12. Gensous N, et al. Prognostic biomarkers of SLE flares: systematic review. Arthritis Res Ther. 2017;19:Article 10xx.
13. Navarra SV, et al. Efficacy and safety of belimumab in active SLE: BLISS studies. Lancet / Arthritis Rheum. 2011.
14. Ugarte-Gil MF, Alarcón GS. Predictors of SLE flares. Rheum Dis Clin North Am. 2018–2022;48(1):35–48.
15. Petri M. Monitoring SLE in routine clinical practice. Review/Guideline. 2019–2020. Semantic Scholar.
16. Aragón CC, et al. Urinary biomarkers in lupus nephritis: systematic review. Clin Rheumatol / Frontiers. 2020. PMC
17. Vrabie A, et al. Biomarkers in lupus nephritis: evidence-based review. Life (MDPI). 2025;15(10).
18. Furie R, et al. Belimumab and BLISS studies: impact on flares and renal outcomes. NEJM / Arthritis Rheum. 2011–2020.
19. Brunner HI, et al. Prognostic biomarkers of SLE flares: systematic review. Arthritis Res Ther. 2017.
20. Fava A, et al. SLE: diagnosis and clinical management. J Clin Pathol. 2019.
21. Inês L, et al. Identification of clinical predictors of SLE flares. Ann Rheum Dis. 2014.
22. Lee YH, Song GG. Urinary MCP-1 as a biomarker of lupus nephritis: meta-analysis. Lupus. 2015;24:1529–1539.
23. Vodehnal S, et al. Urinary biomarkers of active lupus nephritis with independent validation. Kidney Int. 2024.