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Brief overview about Systemic Lupus Erythematosus

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Abstract: Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease. The condition has several phenotypes, with varying clinical presentations from mild mucocutaneous manifestations to multiorgan and severe central nervous system involvement. Several immunopathogenic pathways play a role in the development of SLE. Several pathogenic autoantibodies have since been identified. Despite recent advances in technology and understanding of the pathological basis and risk factors for SLE, the exact pathogenesis is still not well known. Diagnosis of SLE can be challenging, and while several classification criteria have been posed, their utility in the clinical setting is still a matter of debate. SLE presents with a wide array of clinical manifestations and an expansive profile of autoantibodies. This clinical and serological heterogeneity makes it a great challenge to reach an accurate diagnosis. Therefore, physician acumen plays a pivotal role in diagnosing SLE since various clinical features, serological findings, imaging and histopathology must be considered simultaneously. Biomarkers play a vital role in diagnosing SLE, assessing disease activity, classifying complications and assessing disease response to therapeutic interventions. However, the clinical heterogeneity and the complex pathogenesis of SLE make it challenging for one biomarker to reflect the disease's state accurately. Additionally, no single biomarker has shown the ideal sensitivity and specificity for SLE; hence a combination of biomarkers reflecting different aspects of disease manifestations may be more effective in assessing SLE. Systemic lupus erythematosus is a disease of heterogenic manifestation involving multiple organs; therefore, the disease severity and organ involvement vary from patient to patient, thus posing a significant challenge in disease management and requiring an interdisciplinary approach. The treatment aims to prevent the flare-ups of the disease, promote remission and maintenance, besid preventing relapse at a minimum cost of side effects of the drugs used.

Keywords: Systemic Lupus Erythematosus

Introduction: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease. The condition has several phenotypes, with varying clinical presentations from mild mucocutaneous manifestations to multiorgan and severe central nervous system involvement. Several immunopathogenic pathways play a role in the development of SLE. Several pathogenic autoantibodies have since been identified. Despite recent advances in technology and understanding of the pathological basis and risk factors for SLE, the exact pathogenesis is still not well known. Diagnosis of SLE can be challenging, and while several classification criteria have been posed, their utility in the clinical setting is still a matter of debate. Management of SLE is dictated by organ system involvement. Despite several agents shown to be efficacious in treating SLE, the disease still poses significant morbidity and mortality risk in patients **(1)**.

Epidemiology

Globally, the reported incidence and prevalence of SLE differ significantly by geography with North America reporting the highest incidence and prevalence, Africa reporting the lowest incidence and Australia reporting the lowest prevalence. Age, gender and ethnicity play a significant role in determining the clinical outcome and management of the disease. SLE is more prevalent in the female population, but its course is more critical and expeditious in men, which culminates in a bad prognosis. This disparity can be attributed to the environmental surroundings and genomic differences **(2)**.

The current incidence rate is 6.73 cases per 100,000 per annum in the Caucasian population and 31.4 cases per 100,000 per annum in the African-American population. The prevalence rate among the U.S. black population is 517 per 100,000, while it is 134 per 100,000 among U.S. Caucasians and Europeans **(3)**.

SLE is seen mainly in women during the childbearing age between 15-44 years with a female predominance of 9:1, making SLE one of the most gender-differentiated autoimmune diseases. SLE, a common diagnosis during reproductive age, suggests hormonal influence in its pathogenesis, which also presents a host of medical and psychosocial challenges that affect family planning and pregnancy. **(4)**

Pathogenesis

The pathogenesis of SLE includes a complex interaction between the exposome (environmental influence) and genome to produce an epigenetic change that alters the expression of specific genes that contribute to disease development. Exposure to environmental factors as UVB radiation, infections and toxins triggers loss of immune tolerance in genetically susceptible individuals and leads to aberrant activation of

autoimmunity . Exposure of self-antigens to the immune cells, possibly from an increased apoptotic cell load, initiates a feed-forward loop between innate and adaptive immunity. The ensuing production of autoantibodies and immune complexes, autoreactive T cells and B cells, complement activation and cytokine release result in widespread tissue damage, manifesting as the clinical picture of SLE **(5)**.

- **Genetic susceptibility**

In the last decade, a genome-wide association study (GWAS) has mapped >90 SLE susceptibility loci, with many single nucleotide polymorphisms acting additively. In addition, rare monogenic forms of SLE have also been reported. Among the 730 SLE-associated polymorphisms, 21 lead to amino acid change, 484 exist within gene coding regions and the rest are intergenic, suggesting a significant effect on gene regulation instead of protein sequence. Most SLE risk loci are located within or near genes that encode products functioning in the clearance of immune complexes (IC), lymphocyte signaling and type I interferon (IFN-I) signaling **(6)**.

- **T/B Cell signaling**

The susceptibility genes involved in aberrant T/B cell signaling in SLE encode adaptor molecules, kinases and cytokines that regulate T/B-cell activation, proliferation and interaction. For example, the class II human leukocyte antigen region encodes molecules involved in antigen presentation. The upregulated surface expression of these molecules leads to a hyperactive immune response. HLA-DR2 and HLA-DR3 alleles are associated with SLE susceptibility and autoantibody production. Protein tyrosine phosphatase non-receptor type 22 (PTPN22) is another gene that encodes a tyrosine phosphatase that alters T-cell receptor (TCR) and B-cell receptor (BCR) signaling leading to enhanced B-cell autoreactivity in SLE. Similarly, C-terminal Src kinase (CSK) is another protein-encoding gene that encodes C-Src tyrosine kinase and BANK1, which encodes an adaptor/scaffold protein associated with altered B-cell activation **(6)**.

- **Role of T cells**

T cells play a significant role in SLE pathogenesis, driving inflammation by secretion of pro-inflammatory cytokines, inducing B cells to generate autoantibodies and maintaining disease via a pool of autoreactive memory T cells. However, the ratios of some T cell subsets and their function are abnormal in patients with SLE **(7)**.

T follicular helper (Tfh) cells are essential for germinal center induction, proliferation, isotype-switching and somatic hypermutation. In addition, these cells produce cytokine IL-21, which induces B cell differentiation into memory B cells and antibody-generating

plasmablasts. Pathologic expansion of the TFH cell subset contributes to enhanced antibody production and loss of tolerance in SLE patients **(8)**

Regulatory T (Treg) cells are a unique T cell subset population that suppresses the immune response and maintains self-tolerance, suppressing autoreactive lymphocytes in healthy individuals. The development of Treg cells is dependent on IL2 activity. In SLE, an imbalanced T cell cytokine profile characterized by decreased IL2 leads to impaired Treg cell development and function. Reduced expression of IL2 in T cells is caused by low levels of the transcription factor activator protein 1 (AP-1), which ultimately fuels SLE's development. IL2 also plays a role in restricting the expression of IL17, which is pro-inflammatory and its elevated levels in SLE contribute to local tissue damage **(9)**.

- **Role of B cells**

B cells contribute to the pathogenesis of SLE through their response to antigens and autoantibody production. The pathways implicated in the aberrant activation of B cells include the toll-like receptor (TLR) pathway, stimulation via beta cell-activating factor (BAAF) and B-cell receptor (BCR) mediated activation. The stimulation of B cells through the TLR pathway promotes loss of tolerance.SLE patients with high levels of BAFF exhibit significantly higher levels of anti-dsDNA, anti-histone, and anticardiolipin antibodies **(10)**.

SLE patients with polymorphisms of the c-Src tyrosine kinase (Csk) gene exhibit a higher level of BCR-mediated activation of B cells and a higher concentration of serum IgM levels. Imbalance of pro-survival BAFF signals in SLE leads to a loss of tolerance and autoantibody production eventually contributes to the disease pathogenesis **(11)**

- **Aberrant apoptotic cell clearance**

Dysregulation of apoptosis and nuclear debris clearance contributes to an increase in autoantigen exposure. Several pathways evolve to prevent immune activation in response to endogenous cellular debris, but these mechanisms are impaired in SLE . Hence, increased survival of defective lymphocytes is thought to be one of the mechanisms contributing to pathogenesis. Usually, Tyro-3, Axl and Mer (TAM) receptors are expressed by phagocytes, macrophages, and natural killer cells in rheumatological autoimmune diseases . The downstream activation of TAM receptors promotes the phagocytosis of apoptotic cells. In addition, it inhibits the signal transducer and activator of transcription 1 (STAT1) and the nuclear factor kappa-light-chain-enhancer of the activated B cell (NF-κB) pathway **(12)**.

- **Role of the complement system**

Complement dysfunction is proposed to accelerate several steps in the pathogenic pathways of SLE, such as impaired clearance of apoptotic debris and IC, increased autoreactive CD+8 T cell activity and tissue damage by activation of the inflammatory cascade in organs with IC deposition . C1q typically assists in the removal of apoptotic material and immune complexes and inhibits the CD8+ T cell response to self-antigens by modulating their mitochondrial metabolism. Patients with C1q homozygous deficiency develop autoantibodies and a lupus-like syndrome, evidently due to the inability to eliminate apoptotic cells **(13)**.

- **Clearance of apoptotic cells and immune complexes**

Exposure to self-antigens due to impaired clearance of apoptotic cells triggers the initiation of an autoimmune response. In addition, the impaired clearance of IC formed from autoantibodies bound to antigens can amplify the inflammatory response **(14)**.

- **Role of Toll-like receptors**

TLRs abnormality in SLE has been widely documented. B cell lymphocytes associated with TLRs' mechanistic dysfunction play a significant role in the pathogenesis of the disease . TLRs are nucleic acid recognition receptors that trigger an inflammatory response upon activation by nuclear antigens contained in IC or apoptotic debris. Downstream activation of TLRs leads to activation of two transcription factors, interferon regulatory factor 3 (IRF3) and nuclear factor-κB (NF-κB), which induces the expression of type I interferon (IFN), which plays a central role in disease pathogenesis **(15)**.

- **Type I Interferon signaling**

Over half of the identified SLE-susceptibility genes encode proteins linked to IFN-I production or response. Toll-like receptor 7 (TLR7) overexpression is a well-known driver of increased IFN-I production and pathogenesis of SLE **(16)**.

- **Environmental factors and their influence**

The association of SLE incidence with exposure to silica, cigarette smoke, oral contraceptives, ultraviolet B (UVB), certain drugs and Epstein-Barr virus (EBV) infection has been well established by epidemiological studies. Potential biologic mechanisms for these associations include increased oxidative stress, inflammatory cytokine upregulation, systemic inflammation, and epigenetic modifications **(17)**.

Clinical presentation

SLE exhibits a broad spectrum of presentations ranging from mild symptoms to severe, life-threatening conditions. Adults diagnosed before 50 years of age usually present with cutaneous symptoms (malar rash) and renal abnormalities (lupus nephritis), displayed higher 10-year survival and reported using more immunosuppressive therapy than patients getting diagnosed after 50 years of age . Various factors such as age, race, gender, genetic premise and socioeconomic status also influence the timeframe of presentation and therapy initiation. Hence the clinical presentation can vary drastically, and a high level of suspicion is needed for early diagnosis and treatment of these patients **(18)**.

Preclinical lupus (PL) is a phase in developing SLE when the patient is at higher risk of developing SLE but is found asymptomatic on presentation. However, autoantibodies are mostly detectable in these patients' serum . Antinuclear antibody (ANA), hematological and immunological disorders, arthritis and cutaneous manifestations were among the most presented symptoms of PL syndrome. Therefore, a significant proportion of preclinical lupus (approximately 10% to 20%) often transitions to SLE. Most PL patients are treated with steroids and other immunosuppressive therapies such as azathioprine and methotrexate. The most prevalent clinical presentations are summarized below **(19)**

Table (1): Most commonly encountered signs and symptoms in the patients of systemic lupus erythematosus**(20)**

System Involvement	Clinical presentation
Musculoskeletal	Jaccoud's arthropathy, arthralgia, arthritis, synovitis, tenosynovitis, myositis
Central and peripheral nervous system	Central Nervous system: Neuropsychiatric lupus, lupus cerebritis (seizure, headache), aseptic meningitis. Peripheral Nervous system: Transverse myelitis, mononeuritis multiplex, peripheral neuropathy, small fiber neuropathy, autonomic neuropathy. Additionally, delirium, and psychosis are also present
Gastrointestinal	Ascites, peritonitis, oral ulcers, esophageal dysmotility, protein-losing enteropathy
Hematological	Anemia, microangiopathic hemolytic anemia, thrombocytopenia
Pulmonary	Pleuritis, pulmonary arterial HTN, interstitial lung disease, pleural effusion
Cardiovascular	Libman-sacks-endocarditis, pericarditis, myocarditis

Renal	Proteinuria, hematuria, and glomerulonephritis

HTN: hypertension

- **Cardiovascular System**

All three layers of the heart, pericardium, myocardium, and endocardium, and often, coronary circulation, may be affected in SLE. The frequently seen manifestations include cardiomyopathy, valvular diseases, rhythm discrepancies, and heart failure. The most prevalent cardiac manifestation is pericarditis secondary to exudative pericardial effusions **(21)**.

- **Cutaneous Lupus**

Around 90% of patients develop skin manifestations during the SLE course. It has different types with distinct characteristics. It includes acute cutaneous lupus erythematosus, subcutaneous lupus erythematosus (SCLE) and chronic cutaneous lupus erythematosus.The most common cutaneous findings are photosensitivity, malar erythema, discoid LE lesions, nail fold telangiectasias and oral ulcers. Subacute cutaneous lupus is characterized by scaly erythematous lesions in sun-exposed area such as the back. Other findings include alopecia, livedo reticularis, Raynaud phenomenon and panniculitis. Extracutaneous features include fever, arthralgias, arthritis, fatigue, and CNS involvement**(22)**

Table (2): Common dermatologic manifestations of systemic lupus erythematosus((19)

Types	Clinical presentation
Acute Cutaneous Lupus Erythematosus	Hallmark: Malar or butterfly rash, erythematous raised pruritic rash, nasolabial folds are spared.
Subcutaneous Lupus Erythematosus (SCLE)	Photosensitive, widespread, non-indurated rash
Chronic cutaneous lupus erythematosus	Discoid lupus erythematosus (DLE) is the most common type

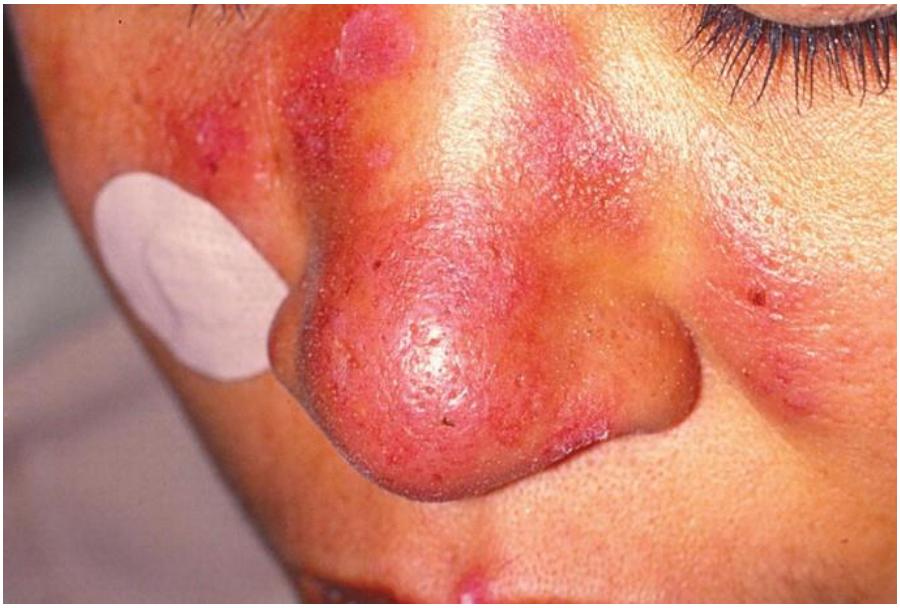

Fig. (1):SLE 3 Erythema of the malar areas and nose**(23)**

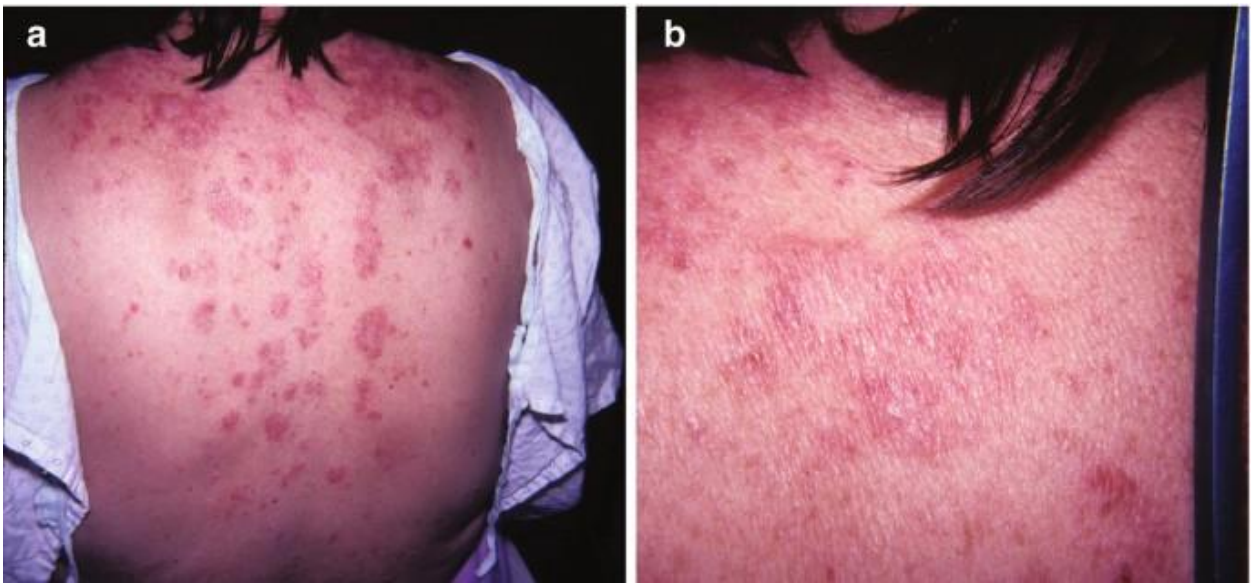

Fig. (2):(**a**) Scle Erythematous scaly patches of the back. (**b**) Scle2 Scaly patch in close up.**(23)**

- **Gastrointestinal system**

A vast array of gastrointestinal (GI) symptoms are also observed in SLE, including flatulence, diarrhea, abdominal cramps, hematemesis, gastric atony, duodenal and jejunal ileus, chronic

ulcerative colitis, oral ulcers, esophageal dysmotility issues, protein-losing enteropathy and lupus enteritis. Moreover, mesenteric vessel thrombosis, Budd-Chiari syndrome and hepatic veno-occlusive disease also occur secondary to SLE and anti-phospholipid antibody syndrome **(24)**.

- **Hematological system**

Around 18% to 80% of patients with SLE suffer from anemia. Anemia of chronic disease is the most prevalent type encountered in SLE. Microangiopathic hemolytic anemia, iron deficiency anemia, coomb's positive autoimmune hemolytic anemia, red blood cell aplasia, anemia secondary to chronic renal disease and pancytopenia are also seen in SLE. Autoimmune cytopenia is not infrequent in SLE owing to the presence of antigens in the blood vessel compartment, resulting in more production of antibodies **(25)**.

- **Musculoskeletal system**

Musculoskeletal manifestations such as arthralgia and arthritis are present in 80% to 90% of patients with SLE. Though any joint can be affected most commonly, there is symmetrical involvement of small joints such as hands, wrists, and knees. SLE arthritis might have a similar presentation to rheumatoid arthritis, including ulnar deviation and subluxation of the metacarpophalangeal joints and the term "ruphus" has been coined to represent this condition. Rarely, cases of avascular necrosis of the hip joint with bilateral involvement have also been reported **(26)**.

- **Nervous system**

The central and peripheral nervous system involvement and psychiatric symptoms are often seen in SLE. Often headache is the most frequently encountered symptom. Additionally, there is an increased risk for ischemic stroke in SLE patients compared to the general population. Cognitive dysfunction is another significant concern in SLE patients, as different studies showed a cognitive decline in these patients. Seizures, aseptic meningitis, demyelinating syndrome, and movement disorder are other CNS manifestations. Complications associated with the parasympathetic nervous system include autonomic neuropathies, mononeuritis multiplex , central and peripheral neuropathies. Psychiatric symptoms include anxiety, depression, and psychosis **(27)**.

- **Pulmonary system**

One of the most frequently seen pulmonary symptoms includes pleuritis, pleural effusion, acute reversible hypoxemia, pulmonary embolism, obstructive lung disease and upper airway disease. Pulmonary arterial hypertension is another grave complication of SLE. Other pulmonary conditions associated with SLE are lupus pneumonitis, interstitial lung disease, usual interstitial pneumonia , diffuse alveolar hemorrhage and pulmonary embolism **(28)**.

- **Renal system**

One of SLE's most prevalent and recognized clinical presentations is lupus nephritis. It is one of the earliest manifestations of SLE and occurs in around 50% of patients .Interstitial nephritis and thrombotic angiopathy are among the other renal manifestations which can be attributed to a surge of inflammatory cytokine profiles, for example, interleukins (IL-1, IL-6, IL-17, IL-18), tumor necrotic factor, Th1 and Th2 cytokines. Initially, proteinuria usually raises the suspicion of renal involvement. A wide range of manifestations (including mild presentation of sub-nephrotic proteinuria) may lead to diffuse involvement of renal structures, resulting in progressive glomerulonephritis and end-stage renal disease. Important signs and symptoms of renal involvement are lupus nephritis, including hematuria, raised creatinine, lower limb edema, anasarca and new onset of hypertension**(29)**.

Lupus nephritis (LN) is classified into six categories based on renal biopsy results. It includes glomerular immune complexes deposition, infiltration of renal parenchyma by T cells and macrophages and activation of toll-like receptors leading to elevated levels of antibodies and interferons **(30)**. Different stages of renal manifestations of SLE and their prognosis are listed below (**Table 3**).

Table (3):Classes of lupus nephritis and their prognosis(19)

Stages of Lupus Nephritis	Prognosis
Class I: Minimal mesangial lupus nephritis	Excellent prognosis
Class II: Mesangial proliferative lupus nephritis	Excellent prognosis
Class III: Focal lupus nephritis	Poor outcome
Class IV: Diffuse segmental nephritis	Poor outcome
Class V: Membranous lupus nephritis	Prognosis is favorable but with certain complications: Thromboembolism
Class VI: Advanced sclerosing lupus nephritis	Poor outcome as most symptoms are of irreversible injury

Diagnosis

SLE presents with a wide array of clinical manifestations and an expansive profile of autoantibodies. This clinical and serological heterogeneity makes it a great challenge to reach an accurate diagnosis. Therefore, physician acumen plays a pivotal role in diagnosing SLE since various clinical features, serological findings, imaging and histopathology must be considered simultaneously**(20)**.

Classification Criteria

Several classification criteria for SLE have been formulated with the primary goal of grouping individuals for clinical studies. Furthermore, these can provide a backbone for the diagnostic approach in an individual patient. The three most accepted classification criteria exist for SLE as follows: 1. the 1997 ACR (American College of Rheumatology), 2. the 2012 SLICC (Systemic Lupus International Collaborating Centers) and 3. the 2019 EULAR/ACR (European League Against Rheumatism/American College of Rheumatology).Each criterion is built on the previous sets by refining, adding, or new information. The major limitation of the 1997 ACR as diagnostic criteria was a low sensitivity of 83%. According to this classification, one in six patients of SLE would not be correctly classified, with sensitivity dropping to 66% early in the disease, because criteria items may need time to accumulate during disease, which was a further limitation to using 1997 ACR as a diagnostic criterion. To rectify this, the 2012 SLICC was introduced with improved sensitivity of 97% and an increase in sensitivity to 84% early in the disease. However, the specificity decreased to 84%, whereas ACR criteria specificity was 93% **(31)**.

The 2019 EULAR/ACR classification criteria for systemic lupus erythematosus (SLE) aim to maintain high specificity from ACR criteria and high sensitivity from SLICC criteria. They require a positive ANA test followed by weighted criteria grouped into clinical and immunological domains. Patients accumulating ≥10 points are classified as having SLE. This is a classification tool rather than a diagnostic criterion, but it's useful for suspecting SLE**(20)**.

Table (4): The 2019 EULAR/ACR classification criteria for systemic lupus erythematosus (SLE)**(20)**.

Domains	Criteria	Weight
Constitutional	Fever	2
Hematologic	Leukopenia	3

	Thrombocytopenia	4
	Autoimmune hemolysis	4
Neuropsychiatric	Delirium	2
	Psychosis	3
	Seizure	5
Mucocutaneous	Non-scarring alopecia	2
	Oral ulcers	2
	Subacute cutaneous or discoid lupus	4
	Acute cutaneous lupus	6
Serosal	Pleural or pericardial effusion	5
	Acute pericarditis	6
Musculoskeletal	Joint involvement	6
Renal	Proteinuria >0.5g/24h	4
	Renal biopsy class II or V lupus nephritis	8
	Renal biopsy class III or IV lupus nephritis	10
Immunological		
	Antiphospholipid antibodies (APA)	
	- Anti-cardiolipin antibodies OR	2
	- Anti-β2GPI antibodies OR	
	- Lupus anticoagulant	
	Complement proteins	
	- Low C3 OR	3
	- Low C4	
	- Low C3 AND low C4	4

	SLE-specific antibodies	
	- Anti-dsDNA antibody OR	6
	- Anti-Smith antibody	

Note: ANA must be present at a titer of ≥1:80 on HPe-2 cells or an equivalent positive test, and the presence of at least one clinical criterion and a total score of 10 is required for SLE classification. Within each domain, only the highest weighted criterion is counted toward the score.

Biomarkers

Biomarkers play a vital role in diagnosing SLE, assessing disease activity, classifying complications and assessing disease response to therapeutic interventions. However, the clinical heterogeneity and the complex pathogenesis of SLE make it challenging for one biomarker to reflect the disease's state accurately. Additionally, no single biomarker has shown the ideal sensitivity and specificity for SLE; hence a combination of biomarkers reflecting different aspects of disease manifestations may be more effective in assessing SLE **(32)**.

- **Antinuclear Antibody**

ANA is usually seen in SLE like other immunological diseases and can be used for screening, diagnosis and prognosis. As a biomarker of SLE, ANA has a high sensitivity ranging from 95% to 97% but low specificity of 20%. High levels of ANA can be seen in several other disorders, as well as a significant proportion of the healthy population; hence a positive ANA does not confirm the diagnosis of SLE, but a negative ANA makes it less likely .Immunofluorescence assay (IF) is the gold standard test for ANA; although enzyme-linked immunosorbent assays (ELISAs) and multiplex assays are widely available, they lack sensitivity and are, therefore, less preferred over IF **(33)**.

- **C3 and C4**

Complement activation is a critical component of SLE pathogenesis and measuring levels of C3 and C4 have been a standard component of laboratory evaluation to help assess disease activity in patients with SLE. Patients with low levels of C3 or C4, combined with a positive ANA test, have 94.3% specificity for an SLE diagnosis. In comparison, patients with simultaneously low C3 and C4 levels and a positive ANA test have 97.6% specificity for an SLE diagnosis . However, owing to the low specificity of C3 and C4 when used in isolation, their reliability as biomarkers for SLE can be limited .Recent studies suggest that elevated levels of plasma complement split products and cell-bound activation products are more useful diagnostic markers and closely correlate with SLE disease activity **(34)**.

- **Anti-dsDNA**

As one of the most distinct ANA types, anti-dsDNA antibodies have a high specificity (96%) for SLE and are the highest weighted criterion in the immunologic domain of the 2019 EULAR/ACR classification. The presence of anti-dsDNA antibodies has been correlated with renal involvement, as demonstrated by their deposition in glomeruli, basement membrane and mesangium in SLE patients with active nephritis, thus proving to be a valuable marker to predict the development of LN. Anti-dsDNA antibodies are closely correlated to disease activity, and their levels can fluctuate over time. Therefore, levels can be undetectable during treatment and increase during a flare, especially in active nephritis. Due to this transient appearance of anti-dsDNA antibodies, their diagnostic sensitivity is low (52% to 70%) **(35)**.

- **Anti-Smith Antibody**

The presence of anti-Smith antibodies (anti-Sm), like anti-dsDNA antibodies, is the highest weighted criterion in the immunological domain in EULAR/ACR 2019 classification for SLE. Anti-Sm antibodies are highly specific for SLE, with a specificity of 99% . Anti-Sm antibodies correlate with SLE disease activity and show a relatively static expression in peripheral blood, unlike anti-dsDNA antibodies, which show fluctuations in disease activity. Anti-Sm antibodies respond more slowly to changes in disease activity in SLE, implicating its use as a biomarker to assess disease activity in new-onset SLE. Moreover, anti-Sm antibodies are associated with lupus nephritis and have been identified as a predictor of silent LN and high disease activity, represented by lymphopenia and hypocomplementemia **(36)**.

- **Anti-Ro (SSA) and Anti-La (SSB) Antibodies**

Anti-Ro antibodies are seen in up to 50% of cases of SLE and anti-La antibodies in up to 20%. These antibodies are highly associated with Sjögren syndrome with 90% specificity and can be used to assess secondary Sjögren syndrome in patients with SLE as well as subacute cutaneous lupus, photosensitivity and neonatal lupus **(37)**.

- **Urinary Biomarkers**

Twenty-four-hour urine protein and protein/creatinine ratio are conventional urinary biomarkers for LN. Various urine protein biomarkers, including chemokines (monocyte chemoattractant protein-1, interferon-γ-inducible protein 10, and interleukin-8), cytokines (urinary tumor necrosis factor-like weak inducer of apoptosis, interleukin 17, interleukin-6, transforming growth factor-beta, adiponectin, and osteoprotegerin), adhesion molecules and growth factors have been evaluated as potential SLE biomarkers, particularly for LN. However, none have approval for commercial use in clinical practice.Despite the performance of the EULAR/ACR criteria, some patients with SLE can still be misdiagnosed. This gap can be attributed to the lack of reliable biomarkers with an ideal sensitivity and

specificity for SLE, the high level of physician skill and experience required to reach an accurate diagnosis and the fact that few patients with SLE show clinical symptoms in the early stages of the disease**(38)**.

Management

Systemic lupus erythematosus is a disease of heterogenic manifestation involving multiple organs; therefore, the disease severity and organ involvement vary from patient to patient, thus posing a significant challenge in disease management and requiring an interdisciplinary approach. The treatment aims to prevent the flare-ups of the disease, promote remission and maintenance, besid preventing relapse at a minimum cost of side effects of the drugs used **(39)**.

The choice of drugs used to treat the disease depends on the disease's activity. Since the EULAR guidelines for the management of SLE were published in 2008, there have been excellent advancements in managing the disease. Various scoring systems are used to assess the disease activity, among which the widely accepted are the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K), the Systemic Lupus Activity Questionnaire (SLAQ), Physician Global Assessment (PGA), the British Isles Lupus Assessment Group (BILAG 2004 index) and Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) **(39)**.In addition, since the damage done due to inflammation in SLE to various organs is irreversible, various indices are used to assess the damage, i.e., Systemic Lupus International Collaborating Clinics (SLICC), American College of Rheumatology Damage Index, and the Brief Index of Lupus Damage .These scoring systems play a significant role in determining the choice of drugs and their effectiveness in disease management as a SLEDAI score of zero indicates complete remission or absence of any active inflammation, a SLEDAI score of 1-5 indicates mild disease activity, and SLEDAI score of 6-10 indicates moderate disease activity, an increase of SLEDAI score of 3 or more than 3 indicates flare-up of disease and decrease of a score of 3 or more indicates a response to the treatment and improvement in the disease activity **(40)**.

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