

A Holistic Review of Systemic Lupus Erythematosus: From Inception to Intervention

Jakka Rohith Reddy¹, R. Anvesh², G. Anurudh Reddy³, P. Veeresh Babu⁴ and N. Sree Lakshmi⁵
^{1,2,3,4,5}Gokaraju Rangaraju College of Pharmacy, Hyderabad, Telangana – 500090, INDIA.

⁴Corresponding Author: pratap.veeresh@gmail.com

ORCID

<https://orcid.org/0000-0002-2135-3521>



www.jrasb.com || Vol. 4 No. 3 (2025): June Issue

Received: 10-06-2025

Revised: 15-06-2025

Accepted: 19-06-2025

ABSTRACT

SLE is a multi-system autoimmune disorder that primarily affects women of reproductive age. The specific etiology of SLE is unknown, however it is thought to be a mix of hereditary and environmental factors. The illness is defined by the development of auto-antibodies against nuclear and cytoplasmic antigens, which causes tissue and organ damage. The clinical symptoms of SLE can range from modest skin involvement to serious organ damage. SLE is diagnosed based on both clinical and laboratory data, with categorization criteria defined by EULAR and ACR being widely utilized. SLE treatment regimens vary depending on the severity of the disease and the organs involved, but constant monitoring and control are essential. Various environmental causes, including drugs, viral infections, and sun exposure, have been linked to SLE. Nail abnormalities and nail fold video capillaroscopy anomalies have been seen in SLE patients, suggesting possible links with illness severity. The therapeutic aims for SLE have evolved from decreasing side effects and organ damage to increasing health-related quality of life.

Keywords- Systemic Lupus Erythematosus (SLE), Autoimmune Disease, Lupus Nephritis, Neuropsychiatric Lupus, Antinuclear Antibodies (ANA), Genetic Predisposition.

I. INTRODUCTION

Systemic lupus erythematosus (SLE) is a intricate & multifaceted systemic autoimmune disorder which affects numerous systems within the body. It typically follows a pattern of recurring flare-ups and periods of improvement, and is frequently seen in women of childbearing age, with a female predominance of 9 to 1.^[1] This condition manifests in various phenotypes, each presenting with distinct clinical features that range from mild mucocutaneous manifestations to severe involvement of multiple organs, including the central nervous system, which can lead to dire consequences. In reality, whereas SLE can affect numerous organs and tissues, the pattern of clinical symptoms and autoimmune reactions varies by

patient and even evolves over time. The development of SLE involves the interplay of several immunopathogenic pathways, which contribute to the intricate pathophysiology of the disease.

It was in the year 1948 that Hargraves made a seminal discovery by describing the lupus erythematosus (LE cell), marking a significant milestone in the understanding of this complex condition. Subsequently, several pathogenic autoantibodies have been painstakingly identified, further elucidating the intricate web of dysregulated immune responses that underlie SLE. However, despite the considerable advances in technology and the expanding knowledge regarding the underlying causes and potential factors linked to SLE, as well as the precise mechanism of the condition of this disease

continues to remain elusive, lacking comprehensive understanding [2].

The exact cause of Systemic Lupus Erythematosus (SLE) is not fully understood, but it is believed to involve a combination of genetic predisposition, hormonal factors, and environmental triggers combine to elicit immunological responses. These reactions result in increased production of harmful auto-antibodies by B cells and regulation of cytokines, which cause damage to tissues and organs. SLE is identified by Abs to nuclear and intracellular Ags. Other auto-antibodies may also be identified in SLE patients, showing a link between SLE and other autoimmune illnesses. SLE clinical manifestations vary from mild skin symptoms to serious organ complications such as renal failure, hypertension of lungs, and cardiac issues. Not all indications occur concurrently; distinct symptoms may arise months or years apart.

Systemic Lupus Erythematosus (SLE) is diagnosed based on a combination of typical clinical manifestations and positive test results. The most advanced and precise classification criteria currently used are those developed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). Addressing SLE presents a significant challenge and requires an interdisciplinary approach. The treatment approach is decided by the disease's severity and the organs involved. Although SLE affects various systems, the disease's progression varies by individual, depending on the degree of symptoms, frequency of attacks, and periods of remission. Life expectancy may be shortened if major organs like the kidneys, lungs, or heart are heavily affected. However, with continuous monitoring and therapy, roughly 80-90% of those with SLE can have an minimal life expectancy [3,4,5].

The therapy aims for SLE patients have evolved during the last two decades. While patient survival was the primary goal in the early decades. In the modern management of SLE, there is a significant emphasis on reducing therapy-related side effects and organ damage while prioritizing the health-related quality of life. It is crucial to integrate comprehensive disease control with the effective use and safety of existing medications [7,8].

II. ETIOLOGY

Systemic Lupus Erythematosus is a complex disease involving multiple systems, and its cause is not fully understood. Nevertheless, various genetic, immunological, endocrine, and environmental factors contribute to the development of SLE. Familial separation and higher agreement rates in identical twins suggest a significant genomic component to Systemic Lupus Erythematosus (SLE), despite the lack of a clear legacy design. Similar incidences for identical twins

were reported as high as 50%. 100 gene regions with changes are linked to polygenic SLE (the majority of cases), whereas more than 30 genes have been found that cause monogenic SLE or SLE-like phenotypes. These genes are associated with immune system stimulation in response to external Ags, self-Ags production, and the trigiring of both the immune system's innate and adaptive functions.

The major histocompatibility (MHC) locus is where the most prevalent hereditary predisposition is found. The MHC includes genes encoding Ag-presenting compounds (group I antigens of human leukocytes [HLA-A, B, and C] and group II HLA molecules [HLADR, DQ, and DP]) [9]. Furthermore, women have a much greater chance of having SLE than males, with a 14-times increase in those with Klinefelter syndrome. This indicates a relationship among genes on the X chromosome. Following extensive investigations, the particular genes that are responsible yet to be identified.

The feminine gender and hormone impact are major risk factors for Systemic Lupus Erythematosus. The hormone estrogen activates CD8+ and CD4+ T lymphocytes, B lymphocytes, and macrophages, as well as the explosion of cytokines like IL-1, and the expression of Vascular Cell Adhesion Molecule (VCAM) and Intercellular Adhesion Molecule (ICAM). Moreover, estrogens and prolactin contribute to the development of autoimmunity, enhance the production of B-cell activation factor, and modulate the activation of lymphocytes and pDC. The use of contraceptives containing estrogen and hormone replacement therapy after menopause could exacerbate symptoms in individuals with SLE and has been associated with an increased prevalence of SLE. Additionally, patients with SLE often exhibit elevated levels of prolactin. Conversely, androgens have an immunosuppressive effect [10].

Several environmental factors for SLE are been discovered. Numerous drugs have been linked to lupus-like symptoms by triggering DNA demethylation and changing self-antigens. In contrast procainamide has greatest risk of leading drug-induced lupus, over hundred medications are linked to this illness. Furthermore, many medicines, such as sulfa-drugs, are generally acknowledged to lead exacerbations on SLE individuals.

UV radiation and sun exposure have been shown to cause higher cell apoptosis, making them important causes for SLE. Several viral infections were linked, and it is believed that the fundamental mechanism is molecular mimicry. Abs to the Epstein-Barr virus, most common in people with SLE, both in adolescents and adults, than in the rest of the individuals. Smoking is viewed as a hazardous element. Additional possible hazards include viral illnesses, vitamin D insufficiency, whaet sprout ingestion, and canavanine consisting foods [11].

III. EPIDEMIOLOGY

Worldwide, the occurrence and frequency of exhibit notable variations based on geographical factors, whereby Northern America demonstrates the most occurrence and prevalence, Africans reports the lowest incidence, and Australians reports the lest prevalence. The clinical outcome & management of the disease are significantly influenced by age, gender, and ethnicity [12,13,14].

The present rate of occurrence is 6.72 occurrences per hundred thousand individuals in the Caucasian community and 31.4 in the American-African community. The rise of infection among the negroid population in the USA is 517 per hundred thousand, compared to 134 per 100,000 among Caucasians and Europeans [15,16]. The Centers for Disease Control and Prevention have released a report stating that there is an approximate prevalence of around 3,22,000 instances of probable or definite Systemic Lupus Erythematosus. This prevalence is notably higher among individuals of African American, American Indian, and Alaska Native descent [16-20].

SLE mostly affects women in reproductive age, with a female-to-male frequency of 9:1. Nonetheless, the harm diminishes in women following menopause, although it remains twice as high as in males. According to research, lupus is worse in men, despite its rarity. Furthermore, males showcase a greater occurrence of skin manifestations, cytopenias, thrombosis, renal disease, cardiovascular disease, serositis, hypertension, neurological involvement and vasculitis in comparison to females. [21].

IV. HISTOPATHOLOGY

Tissue disease in SLE can be characterized by a various of abnormal immune pathways, even immunological complexes formation, Abs production, and immunological driven tissue destruction.

The presence of LE bodies, also known as hematoxylin bodies, is a distinguishing feature of SLE pathophysiology. These are identical globular masses of nuclear tissue that appear blue or purple when stained with hematoxylin. These entities can be found in a variety of organs, including the pulmonary system, urinary tract, the spleen, heart, lymphatic system, and the serous and synovial membranes. LE bodies include Igs and deoxy-NA, and their being engulfed by phagocytes results in the formation of the characteristic LE cell.

Pathological investigation of cutaneous lesions in SLE indicates immune complexes development, which causes damage in tissue, inflammation in vascular and perivascular, and persistent infiltration of mono-nuclear cells. Seviour lesions show necrosis of fibrinoid at the dermo-epidermal interface and in the dermis, as well as liquefaction epidermal degradation

and infiltration of inflammatory cells surrounding blood vessels, with a preponderance of T-cells. Frequent lesion might exhibit a high level of follicular clogging. In addition, all SLE lesions exhibit edema and red blood cell extravasation. The immunofluorescence study shows the accumulation of immunoglobulins (immunoglobulin A, B and G).

Vasculitis is a prevalent occurrence of Systemic Lupus Erythematosus, whereby vascular lesions can manifest in different pathologies. The most common lesion involves immune complex deposition accompanied by an inflammatory response, although it is possible to observe this phenomenon without a significant inflammatory response. Although less common, necrotizing vasculitis affecting both small and large vessels can be distinguished from other forms of vasculitis by the presence of immune complex deposition in the vessel wall [22].

Pathology of the neurological system in SLE includes tiny intracranial arteries with thrombotic lesions. These lesions may or may not be accompanied by inflammation around the blood vessels and the proliferation of endothelial cells. Necrotic vasculitis is extremely rare [23].

Lymphadenopathy is a prevalent occurrence in Systemic Lupus Erythematosus (SLE), and histological examination may reveal a upright in the no. of lymphoid follicles with the presence of giant cells, infiltration of plasma cells in the areas between the follicles, and necrosis in the Tcell zones surrounding the follicles. The observation of LE bodies is infrequent. The necrotic vessel wall exhibits the deposition of Ig and Complement C3. Splenomegaly was commonly observed in SLE, and pathological analysis shows the distinctive onionskin lesion characterized by multiple concentric rings of collagen surrounding the blood vessels. Follicular hyperplasia and the presence of fibrosis around the arteries are common findings.

Lupus pneumonitis may occur in as many as 10% of lupus patients. These individuals frequently exhibit interstitial lung disease (ILD), alveolitis, damage to the alveolar walls, edema, and bleeding. Immune globulin and the accumulation of complement can be seen in vessel walls. In some situations, recurrent interstitial pulmonary disease can develop in as many as 50% of these individuals. It is defined by the development of lymphoid aggregates and fibrosis within the lung interstitium, thickening of the septa, and an increase in the number of type-2 pneumocytes [24].

V. ENVIRONMENTAL FACTORS AND THEIR INFLUENCES

Epidemiological studies have conclusively demonstrated a link between the occurrence of systemic lupus erythematosus (SLE) and being exposed to silica, smoke from cigarettes, contraceptive pills, ultraviolet B radiation (UVB), some medications, and EBV. Potential

molecular processes supporting these correlations include higher stress caused by oxidation, cytokine inflammatory upregulation, system-wide inflammation, and epigenetic alteration [25].

Particulate Exposure:

Experimental investigations have shown evidence that crystallized silica causes cellular death and the discharge of cytoplasmic antigens. Additional disease processes involve increased inflammatory cytokine activity, a state of oxidative stress, & reduced regulatory T lymphocyte function. In mouse models, silica exposure has been linked to increased levels of plasma Abs and complex immune cells [26]. Harmful components in cigarette smoke, including a nicotine, can cause oxidative damage and harm naturally occurring compounds and genomic material. This damage may lead to genetic alterations that promote autoimmunity and increase the production of pro-inflammatory cytokines [27]. A comprehensive review of studies looking at the link between smoking and the risk of acquiring SLE found that smokers had a higher chance of having the disease than nonsmokers (OR 1.5; 95% CI 1.09, 2.08) [28].

Ultraviolet B exposure:

UVB light causes the evolution of reactive oxygen species (ROS) & increases the expression of cytokines that promote inflammation. In individuals with SLE, IFNs play a role in the development of UVB-induced inflammatory skin lesions. Furthermore, UVB radiation increases the expression of intracellular adhesion molecules that include ICAM-1 and LAF1, as well as the release of IL-8 & chemokine ligands. These chemicals attract immune component cells to place of irritation [25]. A different pathway for illness causing is UVB-induced methylation of the DNA within CD4⁺ T lymphocytes, which enhances auto-reactivity and the generation of autoantibodies. In addition, exposure to UVB impedes the removal of cells that are apoptotic [29,30].

Epstein-Barr Virus Infection:

SLE patients have higher EBV infection rates than controls with the same age [30]. One such cause is genetic defects, which cause in bad infestation management & increased recurrence of underlying EBV illness. In SLE patients, increased viral burdens, higher levels of EBV immunoglobulin A plus inadequate EBV-specific T lymphocytes indicate insufficient infection management [31,32]. Furthermore, the moreover prevalence of undetected infection and awakening causes an increase in the proportion of EBV-infected cells to engage in death, activating an innate as well as adaptive immune system reaction against both produced cellular proteins and EBV antigens. Inadequate management of infection with EBV could therefore lead to the onset of SLE. EBV may also contribute to the development of SLE via a process known as Molecular mimicry. Antibodies that target the EBV nuclear antigen (EBNA-1) react alongside

autoantigens related to SLE. In vulnerable people, the immunological response to EBNA-1 produces cross-reactive antibodies, which disseminate epitopes, eventually leading to an outbreak of SLE. Further viral links with SLE include CMV, parvovirus B19, and the hepatitis B virus vaccination [33].

Drug Exposure:

Drugs such as hydralazine, procainamide, isoniazid, minocycline, and TNF- α inhibitors may lead to the causing of SLE. Procainamide and hydralazine have the greatest risk of causing SLE, with rates of thirty percent & 5 to 10 percent, accordingly. Several suggested pathways for medication-induced lupus include familial susceptibility, epigenetic alterations within cells of the immune system, and drug bio-transformation. Procainamide is predominantly degraded by the process of acetylation which employs N-acetyltransferase enzymes. Individuals who are poor acetylators or have a hereditary N-acetyltransferase deficit may more likely to develop autoantibodies after being exposed to these medicines [34,35]. When neutrophils are stimulated, they discharge neutrophil extracellular traps (NETs), which include nuclear genetic material and cytosolic amino acids. Procainamide and hydralazine promote the development of NETs by activating receptors for muscarinic substances on neutrophils, resulting in an autoimmune response to auto-antigens [34].

Hormonal Influences:

Sex hormones have been shown to influence the way the immune system works, which means they may serve either sets off or defenders for onset of SLE. Research investigations proved that exposure to estrogen enhances the risk of SLE, but progesterone and testosterone provide protection by preventing the adverse impacts of estrogen. Furthermore, sex hormones can impact the progression of disease by increasing symptoms throughout adolescence, gestation, and following delivery. Estrogen function can has a role in the improving of the illness by boosting the generation of interferon type 1, improving the prognosis of self-reactive B cells that create anti-double stranded deoxy-NA antibodies, inducing dysfunction of T-reg cells, and altering TLR [36].

VI. PATHOGENESIS

The pathological process of SLE involves a delicate interplay between the exposome (environmental disturbance) and the genetic code, resulting in a genomic change that changes the functioning of a particular alleles which contributes to the disease's pathogenesis. Being exposed to outside variables such as ultraviolet B radiation, diseases, and chemicals causes a breakdown for immune tolerance in those with genetic predisposition, resulting in abnormal autoimmunity [37]. Self-antigen exposure to immune cells, maybe as a result of a higher apoptotic cell load,

sets off a self-perpetuating cycle including both adaptive and innate immune response [38].

Factors of pathogenesis are given below:

Genetic Susceptibility:

Over the last 10 years, a study of the entire genome, known as a genome-wide association study, has successfully identified more than 90 susceptibility regions for systemic lupus erythematosus. Many of these regions are influenced by single nucleotide polymorphisms that act in an additive manner. Furthermore, there have also been reports of rare forms of SLE caused by mutations in a single gene [39]. Out of the 730 polymorphisms associated with SLE, 21 result in changes to amino acids, 484 are located within coding regions of genes, and the remainder are found in intergenic regions. This suggests that these polymorphisms have a significant impact on the regulation of genes rather than the sequence of proteins [40]. The majority of the areas linked with an elevated risk of SLE are found inside or near genes that produce proteins involved in immune complex (IC) clearance, lymphocyte signaling, and signaling via the interferon type1 (IFN) pathway. In this review, we grouped the genes related with SLE risk based on their participation in key disease processes. However, because of their various roles, genes like these may contribute to the pathogenesis of disease via a variety of methods [25, 41].

T/B Cell Signaling:

Genes which confer susceptibility to SLE are responsible for aberrant signaling in T and B cells. These genes encode molecules known as adaptor molecules, kinases, and cytokines, which play a stand in regulating the causing, proliferation, and interaction of T and B cells [37,42]. When these molecules are expressed on the cell surface at higher levels, they lead to an overactive immune response. Another gene of interest is the protein tyrosine phosphatase non-receptor type 22 (PTPN22), which encodes an enzyme that modifies the signaling in receptors of T-cell lymphocyte (TCRs) and receptors of B-cell lymphocyte (BCRs), resulting in heightened autoreactivity of B lymphocytes in disease.

Role of T Cells:

T cell lymphocytes have a crucial role in the development of SLE. These is accomplished by producing cytokines that are pro-inflammatory, inducing B lymphocytes to make self-antibodies and maintaining the illness using a collection of autoreactive memory T lymphocytes populations. Yet, in individuals with SLE, the proportions of certain particular subsets of T cells and their roles are aberrant [44]. T follicular helper (Tfh) cells have critical roles in germinal center of induction process, development, isotype changing, and cellular hyper-mutation. These cells also generate a cytokine called IL-21. Tfh cells' abnormal proliferation in SLE is regulated by the way they communicate with OX40 ligand found on myeloid cells that present

antigen [45]. This enlargement is caused by TLR7 immune complexes of circulating-RNA. Individuals with SLE have an overabundance of the Tfh cell subgroup, which causes increased antibody production and the breakdown of tolerance [44-48].

Role of B lymphocyte Cells:

B lymphocytes lead to the development in SLE by responding to Agsthen producing autoantibodies. Aberrant induction of B lymphocyte is mediated by the TLR pathway, BAAF stimulation, then activation via the BCR [37,49]. Furthermore, the BCR regulates positively as well as negatively choosing, and continual BCR sensing is required to obtain B lymphocyte cell alive in healthy people. People with SLE having genetic polymorphic in the c-Src tyrosine kinase (Csk) allele demonstrate greater BCR-mediated induction of B lymphocytes & greater amounts of serum IgM [39,50]. BAFF's pro-survival signaling counters the BCR's pro-apoptotic signals. Nevertheless, a difference in these messages in SLE causes a breakdown in self-tolerance, which contributes to the generation of autoantibodies and the development of the illness [51].

Aberrant Apoptotic Cell Clearance:

The improper regulation of programmed cell death & the removal of cellular debris in the nucleus both contribute to increased exposure to self-antigens. Multiple routes have evolved to inhibit immune system activation in reaction to cell waste, but these systems are ineffective in SLE [52]. As a result, the prolonged living of effected cells is thought to be a component of the processes behind the onset of illness. Furthermore, poor elimination of immunological complexes comprising IgG2 and IgG3 due to defective apoptosis results in inefficient clearance. In rheumatological autoimmune disorders, macrophages, and Nk cells commonly express Tyro-3, Axl, and Mer (TAM) receptors [53]. TAM receptor activation enhances deadly cell engulfment and suppresses STAT1 and NF- κ B signaling pathways. In animal investigations, the lack of TAM receptors is linked to the existence of anti-double stranded DNA immunoglobulins, antiphospholipid immunoglobulins as well as SLE-like symptoms such as RA, and the buildup of immune globulin G [54].

Complement System role in SLE:

Complement deficiency has thought to speed up multiple phases within the pathogenic cycle in SLE. These phases include poor elimination of apoptotic waste & immunological complexes (IC), increased activity of auto-reactive CD+8 T cells, and damage to tissues brought about by the start of the pro-inflammatory response in regions with IC deposits [55]. Normally, C1q assists with the clearance of apoptotic debris and immunological complexes while also inhibiting CD8+ T cell responses to self-antigenic substances via altering the metabolism of mitochondria. Individuals with C1q homozygous deficit develop autoimmunity or a lupus-like condition as a result of

their apparent inability to eliminate cells that are dead [56].

Clearance of Apoptotic Cells and Immune Complexes:

An autoimmune response is triggered by exposure to own-antigens as a result of impaired apoptotic cell clearance. Furthermore, poor clearance of immune complexes generated when auto-antibodies attach to antigens might exacerbate the immune system's reaction [57]. This pathway's products are encoded by genes in the HLA class III area [58].

Role of Toll-Like Receptors:

The abnormal function of TLRs in SLE are being extensively reported. B-cell, which are linked to the mechanistic dysfunction of TLRs, have a significant impact on the pathogenesis of this condition [59]. TLRs are receptors that identify nucleic acids and cause a response of inflammation when triggered by antigens of nucleic acids contained in immune complexes or death waste. TLRs are embedded in the germline and are responsible for identifying certain bacteria, acting as the initial phase of protection towards them. They respond mostly to absorbed nucleic acids. TLRs activate two transcription factors: IRF3 and NF- κ B. This activation increases the production of IFN, which is critical to the disease's progression [39,46]. Overexpression of TLR7, has been linked to the development of RNA-reactive auto-antibodies and type I interferon. Similarly, overexpression of TLR9, a binding protein for DNA with unmethylated Central pattern generators sequence patterns, is linked to increased concentrations of autoantibodies against double-stranded DNA and a high incidence of illness [46].

Type 1 Interferon Signaling:

More than fifty percent of the known genes responsible for SLE contain molecules involved in the generation or response to type I interferons (IFN-1). Overexpression of the toll-like receptor 7 has been a well-known trigger for increased IFN-1 production and the development of SLE [60]. The lack of the type 1 interferon receptor protects mice from developing SLE. Further genes involved in this system are miR146a, RNASEH2C, SLC15A4, and IRAK1 [61].

VII. CLINICAL MANIFESTATIONS

Systemic Lupus Erythematosus (SLE) might show up as anything from minor symptoms to serious, potentially fatal illnesses. Before the age of fifty, cutaneous signs such as a malar rash and renal problems (lupus nephritis) are common presentations. When compared to individuals diagnosed beyond the age of 50, this group often has higher 10-year survival rates and uses immunosuppressive medication more frequently [63]. A number of variables, including age, race group, sex, genetic predisposition, and socioeconomic status, might affect when a patient presents and when therapy is started [64].

Pre-clinical lupus (PL) is a stage of SLE development in which a patient has a higher risk of developing the disease but does not show any symptoms at first. However, the majority of the antibodies found in their serum are autoantibodies [65]. As such, a more fraction of pre-clinical lupus (about 10- 20%) often advances to SLE. Patients with Parkinson's disease are mostly treated with corticosteroids, in addition to other immunosuppressive medications such as methotrexate and azathioprine.

Wide ranges of manifestations include:

Neuropsychiatric Manifestations:

SLE can impact the peripheral nervous system as well as the central nervous system, and it can also cause a variety of psychiatric symptoms, however diagnosis can be difficult. Over 50% of individuals have been observed to have chronic, severe headaches, which are the most common CNS manifestation. Even the prognosis for focal or generalized seizures is generally favorable, they can also be noticed and are associated with disease cause. Ischemic strokes are also more common in patients with SLE. Signs of SLE in the peripheral nervous system include cranial and peripheral neuropathies (sensorimotor and axonal) [66]. Significant factors influencing sleep quality included age, disease activity, anxiety, and depression. These factors were found to have a negative impact on SLE patients' health-related quality of life (HRQoL) [67].

Headaches, especially migraines, have been linked to decreased grey matter (GM) volume and increased white matter (WM) volume in SLE patients [68]. One unique clinical characteristic of NPSLE is post-steroid neuropsychiatric disorder (PSNP disease), which is efficiently treated with immunosuppressive medications [69].

Renal Manifestation:

One of the most serious effects of SLE is lupus nephritis (LN), which is also a strong indicator of a poor prognosis. One of the main factors contributing to the underlying mechanisms of LN is the participation of self-antibodies called anti-neutrophil cytoplasmic antibodies (ANCA), which target different cytoplasmic components. Compared to ANCA-negative individuals, ANCA-positive LN patients have a higher incidence of multi-system damage and a higher prevalence of antibodies against histones, nucleosomes, mitochondrial M2, and cardiolipin. Moreover, patients with LN who test positive for ANCA have higher pathological chronic renal index scores and worse renal outcomes [70]. LN was seen in 38.3% of cases in a worldwide multi-ethnic/racial observational cohort of people recently diagnosed with SLE; LN frequently manifests as the first symptom with a depressing prognosis in terms of ESRD [71].

Individuals with SLE have Antiphospholipid antibodies (aPL) and lupus anticoagulant (LA) which raise the risk of all-cause death in people with SLE who have end-stage renal disease. Patients with end-stage

renal illness who do not have SLE do not appear to be associated with this [72]. Tubulointerstitial (TIN) characteristics are commonly missed in cases with SLE. A study of renal samples from 142 individuals who had repeated biopsy found inflammatory interstitial infiltrates, fibrosis in intestines, and atrophy of the tubules. The first biopsy revealed a minimum of 1 TIN lesion for as many as 60% of individuals, however this figure jumped to 75% in patients who underwent a repeat biopsy. Tubular atrophy, which had a significant connection with interstitial fibrosis, had the greatest rate of deterioration between the first & second biopsies. In contrast, a substantial proportion of patients had a change from moderate-severe to mild signs, notably tubulitis and inflammatory penetration, with regression noted for nearly 70% of cases [73].

Gastrointestinal Manifestation:

Any portion of the gastrointestinal tract has the potential to be affected by Systemic Lupus Erythematosus (SLE). These clinical manifestations encompass various conditions such as impaired movement of the esophageal dysmotility, inflammation of the mesenteric blood vessels (mesenteric vasculitis), inflammation of the intestines (lupus enteritis), inflammation of the abdominal lining and accumulation of fluid (peritonitis and ascites), loss of protein through the intestines (protein-losing enteropathy), inflammation of the pancreas (pancreatitis), and inflammation of the liver resembling lupus (lupoid hepatitis) [74].

Initially, Intestinal Pseudo Obstruction was thought to be an uncommon consequence of SLE. However, it might be the initial sign of SLE, making diagnosis difficult and treatment delayed. IPO is invariably associated by pyeloureterectasis (dilation of the kidneys and ureters) or megacholedochus (enlargement of the bile duct owing to inflammation of the smooth muscles of the internal organs). This relationship indicates a bad outlook. In addition, the incidence of IPO correlates with the severity of SLE activity [75].

Pulmonary Manifestations:

Pleuritis is the most common respiratory symptom, albeit it is not necessarily associated with pleural effusion. Additional respiratory symptoms include diffuse alveolar haemorrhage associated with capillaritis, hypertension of pulmonary arterial, syndrome of shrinking lung [76].

An algorithm based on predictors including dyspnea, DLCO, and N-terminal pro-brain natriuretic peptide (NT-proBNP) was used to investigate pulmonary arterial hypertension (PAH) in a prospective research by Pérez-Peñate et al. These predictors were validated in the study as being associated with reduced prevalence of SLE-PAH, pulmonary hypertension (PH), and PAH [77]. Positive anti-RNP antibody and pericardial effusion are risk factors for PAH in SLE patients [78].

Nail & Nailfold manifestation:

People with SLE can lead a broad variety of nail abnormalities in addition to a wide range of abnormalities in nailfold videocapillaroscopy (NVC) that are similar to the early pattern of scleroderma. NVC anomalies were found by Higuera et al. in 13.8% of patients without nail dystrophy (ND) and 43.8% of patients with ND. They found that there was a relationship between anomalies in the NVC and an elevated damage index in cases of ND [79].

Haematological Manifestations:

More than half of SLE patients have anemia, with chronic illness anemia being the most common kind. Leukopenia is a common and severe condition that is frequently caused by neutropenia or lymphopenia. Thrombocytopenia varies in severity and can be linked to auto-abs against the thrombopoietin receptor, glycoprotein IIb/IIIa, or platelets, as well as antiphospholipid antibody syndrome [80].

Because antigens in the bloodstream cause the body to produce more antibodies, autoimmune cytopenia is a typical occurrence in SLE patients [81,82]. Pancytopenia is a frequent condition that is sometimes associated with myelofibrosis. Although SLE frequently results in soft, nontender lymphadenopathy, is referred to as Kikuchi-Fujimoto disease has been reported in a small number of instances.

Comorbidities:

The prognosis for people with SLE has indeed improved over the past four decades. This can be ascribed to improved treatment methods for the illness and any concomitant disorders, as well as to early and accurate diagnosis. Both the actual course of the illness and the side effects of immunosuppressant drugs can lead to SLE complications and comorbidities.

One of them, infections are the most common comorbidity in people with SLE and are frequently the main factor contributing to the disease's morbidity and death. When compared to healthy persons, SLE patients have a higher frequency of several infections. Urinary tract infections were the most prevalent infection among 144 SLE patients over a 5-year period, according to a retrospective study. Airway infections were linked to the use of steroids, mycophenolate mofetil (MMF), and cyclosporine, whereas urinary tract infections were linked to the use of CYC and steroids [83].

Infections can potentially affect the central nervous system in SLE. About 0.5% of SLE patients have been documented to have cryptococcal meningitis. A recent research of 108 female patients revealed that the use of steroids, immunosuppressive medications, and rheumatic illnesses were major risk factors for this infection. Nonetheless, it has been determined that SLE and other systemic immune disorders are separate risk factors for contracting this infection, highlighting the necessity of closely monitoring SLE patients undergoing immunosuppressive treatment [84]. Among

comparison to the general population, there were more hospitalizations from 2000 to 2011 for Herpes zoster as a result of infection-related problems among SLE patients. On the other hand, there was a declining trend in *Pneumocystis pneumonia* hospitalizations. Taking into account every reason for hospital admissions. The real causes of approximately 1600 SLE individuals those with SLE as in primary diagnosis excluded were cardiovascular symptoms and pregnancy-related issues. Compared to the general population, SLE patients had a greater rate of hospitalization for malignancies [85-88].

Cardiovascular Manifestations:

Two main factors that increase the risk of cardiovascular morbidity and mortality in patients with systemic lupus erythematosus are accelerated atherosclerosis and coronary heart disease. SLE patients were found to have a significantly higher incidence of coronary microvascular dysfunction (CMD) than the control group (67% & 26%, relatively), as assessed by transthoracic Doppler-derived echocardiography [89].

People with SLE also commonly develop valvular heart problems. In a research by Vivero et al., transthoracic echocardiograms were performed on 211 individuals with SLE, and the results showed that one in four of the patients had substantial valvulopathy. Notable discoveries revealed that valve thickening was more prevalent in SLE patients who tested positive for antiSm antibodies. Conversely, valvular dysfunction was found to be predicted by hypertension, the presence of both lupus anticoagulant (LA) and anticardiolipin antibodies (aCL). Moreover, thrombocytopenia, lymphopenia, age, length of illness, and the presence of aPL antibodies all showed significant correlations with both types of valvulopathy [90]. 5,018 SLE patients and 25,090 age and sex-matched controls participated in a retrospective case-control study that showed the percentage of aortic aneurysms was 4.5 times higher among SLE patients compared to the control group [91].

Carotid intima-media thickness and flow-mediated dilatation (FMD) were assessed in 100 individuals with SLE, 50 of them had been diagnosed with lupus nephritis (LN), in order to assess premature atherosclerosis. According to the study, FMD was significantly lower in LN patients but CMT values did not differ significantly between LN patients and SLE patients without nephritis [92-95].

Musculoskeletal Manifestations:

Musculoskeletal involvement occurs in 80–90% of people with SLE at some point under the disease's time; symptoms can range from moderate joint discomfort to severe arthritis that results in deformities. Any joint in the body may be impacted, however the lupus arthritis linked to SLE is usually non-destructive and defined by symmetrical inflammation affecting the tiny joints of the hands, knees, and wrists. [96].

Jaccoudarthropathy is an condition that results in non-destructive hand deformities, such as partial

dislocation of the joints of metacarpophalangeal and deviation of the fingers towards the ulnar side, which may resemble RA. The condition is caused by looseness in the joint capsule and ligaments. These abnormalities may usually be corrected, while they sporadically have the potential to become irreversible. Up to 10% of people with SLE may develop avascular necrosis, a condition in which bone tissue dies from insufficient blood flow. This disorder typically affects both hip joints [97].

Less than 10% of SLE cases have been shown to have inflammatory myopathy, which has similar but less prominent histological characteristics than polymyositis. Fibromyalgia is more common in patients with SLE; occurrences have been reported to reach 20%. Furthermore, it has been shown that individuals with SLE can develop rheumatoid nodules [98].

Pregnancy Manifestations:

Positive antiphospholipid antibody tests increase the risk of pre-eclampsia, thrombosis, spontaneous abortions, and loss of fetus in patients with SLE. Anti-Ro and Anti-La Abs have the potential to cross the placenta and get transferred, which can cause fetal heart block and newborn lupus, which is characterized by transaminitis, cytopenias, and a photosensitive rash. During the first pregnancy, the estimated risk of severe issues is 2%. It's crucial to remember that SLE usually gets worse during pregnancy, especially if treatment wasn't enough over the previous six months. Last but not least, it is critical to understand that pregnant women who experience more severe SLE symptoms, such as hypertension of pulmonary, serious heart illness, have an extraordinarily high rate of death [99].

Mucocutaneous Manifestations:

Mucocutaneous involvement is observed in over 80% of patients with SLE, and is considered as one of most notable and well-defined clinical characteristics of the disease. Skin lesions in SLE patients can be classified as nonspecific or lupus-specific. The three forms of lupus-specific lesions are:

- 1) Acute cutaneous lupus erythematosus (ACLE)
- 2) subacute cutaneous lupus erythematosus (SCLE) and
- 3) chronic cutaneous lupus erythematosus (CCLE).

Lesions associated with ACLE can be localized or widespread. The malar infection, also called as the butterfly rash, is the characteristic lead of ACLE. It appears as an elevated, itchy, erythematous rash that affects the nasal bridge and cheeks. The nasolabial folds, which are shielded from sunlight, are usually unaffected by this rash, which can present as either papular or macular. The malar rash usually appears suddenly, but it can linger for a few weeks before becoming indurated and scaling. Furthermore, the degree of the malar rash could vary in tandem with the activity of the underlying lupus. Rosacea, among other skin disorders, can also manifest in the same area and should be differentiated

from ACLE malar rash. When exposed to sunlight, a broad maculopapular or macular rash may develop as a result of generalized ACLE. Thankfully, ACLE lesions usually go away without leaving any scars.

The characteristics of the SCLE rash are its nonindurated form, extensive dispersion, lack of scarring, and photosensitivity. SCLE lesions usually heal without scarring, though they can last for several months. About 90% of SCLE cases have a positive Anti-Ro Ab, suggesting a correlation. In addition, some drugs, like hydrochlorothiazide, can also cause SCLE [10]. SCLE has occasionally been documented in people with RA and Sjogren syndrome [11].

The most common form of CLE, is called discoid lupus erythematosus. DLE can be localized (limited to the head and neck) or generalized (encompassing areas both above and below the neck), and it can occur with or without systemic lupus erythematosus (SLE). DLE frequently results in scarring after healing, particularly when it affects the scalp, where it may also be followed by irreversible hair loss. When DLE affects the mucosa, the oral cavity may experience painful, round, erythematous lesions. Histologically, enlarged DLE and cell carcinoma squamous may look same. Less frequently, lupus panniculitis which typically develops above the waist is linked to systemic lupus inflammation. When these lesions coexist with DLE lesions above them, they produce indentations on the skin's surface and are known as lupus profundus. On the fingers and toes, erythematous, painful plaques are the first sign of chilblains lupus. Conversely, lupus tumidus lesions are smooth, edematous plaques with erythematous coloration and no involvement of the epidermis.

People with SLE typically develop oral and nasal ulcers, which are frequently painless during the acute phase. These ulcers can appear as open sores that affect any part of the mouth, skin erosions, pinpoint hemorrhages (petechiae), flat patches (macule), or a gradual emergence of redness (erythema). The buccal mucosa, the hard part of the palate, and the vermilion border the line separating the lips from the surrounding skin are the regions most frequently impacted. More than 90% of SLE cases exhibit photosensitivity, or an enhanced sensitivity to light. The aberrant skin response to UVA/B and ultraviolet (UV) rays that characterizes this illness might last for weeks or months. Furthermore, some patients may report an aggravation of their overall symptoms when exposed to sunshine. Discoid Lupus Erythematosus (DLE), which causes scarring, or the existence of lupus hair, which is brittle and easily breakable and is mainly found in the temporal and parietal regions of the scalp, are the two main causes of hair loss (alopecia) in SLE.

Individuals with SLE can also exhibit a variety of additional cutaneous signs that are not unique to this disorder. These include cutaneous vasculitis, which is an inflammation of the blood vessels in the skin; blood

vessel disorders; sclerodactyly, which is a thickening and tightening of the skin; rheumatoid nodules, which are nodules typically associated with rheumatoid arthritis; calcinosis cutis, which is a skin deposit; blistering lesions, which are called bullous lesions; hives, which is a skin disorder characterized by target-shaped skin lesions; erythema multiforme, which is a skin disorder; acanthosis nigricans, which is a thickening and darkening of the skin; and ulcers on the legs, which are called leg ulcers [100].

VIII. DIAGNOSIS

The American College of Rheumatology (ACR) published the first version of the SLE categorization criteria in 1971. Two more updates were made in 1982 and 1997. The 1997 ACR criteria were updated in 2012 by the Systemic Lupus International Collaborating Clinics (SLICC) group. Four of the eleven criteria in the 1997 ACR criteria have to be met in order to classify an individual as having SLE. These included a range of symptoms.

Notable changes have been made to the 1997 ACR by the SLICC criteria to improve clinical significance. It needs that at least one of 4 clinical domain criteria and one of the immunologic domain area be met. Furthermore, new understandings of SLE immunology have been included into the neurologic and immunologic criteria. In addition, people with biopsy-confirmed nephritis who test positive for anti-double-stranded DNA or ANA can be categorized as having SLE without the need for any further criteria. The SLICC criteria are thought to be more legitimate and clinically relevant than the 1997 ACR criteria because of their increased sensitivity [101].

Biomarkers:

Systemic lupus erythematosus diagnosis, disease activity assessment, complication classification, and illness response to treatment interventions are all greatly aided by biomarkers. But because SLE has a complex pathophysiology and wide range of clinical manifestations, it is difficult for a single biomarker to adequately represent the disease's condition. Moreover, it has been shown that no single biomarker can accurately capture the specificity of disease; as a result, a various of bio-marker covering a range of illness symptoms may be more effective in detecting SLE [102].

Urinary Biomarkers:

Traditional urine indicators for Lupus Nephritis (LN) detection include the protein/creatinine ratio and the twenty-four-hour urine protein. Other urinary protein biomarkers that have been investigated as potential biomarkers for Systemic Lupus Erythematosus, specifically for LN, include chemokines (monocyte chemoattractant protein-1), cytokines (IL-17, IL-6), adhesion molecules, and growth factors. Only a small number of these biomarkers have undergone

independent validation, and none have been approved for use commercially in clinical practice [103].

Antinuclear Antibody:

ANA can be used for testing, and prognosis. It is frequently seen in SLE & other immune illnesses. ANA is a biomarker for SLE that has a low specificity of 20% but a high sensitivity of 95% to 97%. In addition to many other illnesses, elevated levels of ANA are found in a sizable segment of the healthy population. As a result, while a negative ANA test lessens the possibility of SLE, a positive ANA test by itself does not provide a definite diagnosis of SLE [104]. The most reliable test for ANA is the immunofluorescence assay (IF). Multiplex tests and ELISAs are also more available, however they have lower sensitivity and are thus not chosen over IF [105].

C3 & C4:

Since complement activation plays a main role in the etiology of SLE, measuring C3 & C4 levels in laboratory tests to gauge SLE patients' disease activity has become standard procedure. Individuals with reduced C-3 or C-4 levels and a +ANA test show a 92% specificity for the diagnosis of SLE [106]. However, C3 and C4's efficacy as SLE biomarkers may be limited due to their restricted specificity when used separately [107]. According to recent studies, elevated concentrations of cell-bound activation products and plasma complement products function as more important markers for diagnosis and have a good correlation with the activity of SLE [108].

Anti-dsDNA:

Anti-dsDNA antibodies are among the most unique kinds of antinuclear antibodies (ANA), and their 96% specificity for SLE is noteworthy. Their deposition in the glomeruli, basement membrane, and mesangium has been associated with renal involvement in SLE patients with active nephritis. As such, they are a useful marker for anticipating the onset of LN. It is important to remember that anti-dsDNA antibody levels can change over time and are a good indicator of disease activity. These levels may become undetectable during treatment, then rise during a flare-up, especially while nephritis is active. Anti-dsDNA antibodies have a relatively low diagnostic sensitivity, ranging from 52-70%, as a result of their ephemeral nature [1,109].

Anti-Smith Antibody:

A further important factor is immunological domain of the EULAR/ACR 2019 SLE pathology is anti-Smith Abs (anti-Sm). These antibodies show a high degree of specificity for SLE, with a 99% specificity [110]. Anti-Sm antibody expression in peripheral blood is more stable than anti-dsDNA antibody expression, making it a more reliable indicator of illness. However, anti-Sm Abs react very late to change in illness, suggesting that they could be used for biomarker to measure disease level in newly diagnosed cases of SLE. Moreover, it has been observed that these antibodies are

prognostic of silent LN and high disease activity, as demonstrated by lymphopenia, and have been linked to lupus nephritis [111-114].

IX. TREATMENT / MANAGEMENT FOR CLINICAL MANIFESTATIONS

Treatment for systemic lupus erythematosus aims to prevent damages to organ and achieve disease remission. Treatment options range from modest treatments like antimalarials and nonsteroidal anti-inflammatory medicines (NSAIDs) to more intense measures like corticosteroids and cytotoxic agents, depending on the afflicted organ system or systems and the severity of participation.

The treatment goals for lupus are as follows: (1) maintain the lowest possible level of activity by using immunomodulators and appropriate immunosuppressive measures, while also avoiding known triggers; (2) prevent organ damage from active lupus; (3) reduce any potential comorbidities from lupus and treatment, especially accelerated atherosclerosis, the main cause of death; and (4) address fatigue and pain, which are often unrelated to active lupus.

Physical and lifestyle therapies, emotional support, and patient education are essential components of managing systemic lupus erythematosus. Individuals identified as having SLE should be thoroughly educated on the disease's underlying pathology, the possibility of organ involvement, and the significance of taking prescribed drugs and staying under close observation. In addition, methods for lowering stress, enhancing sleep hygiene, exercising, and offering emotional support ought to be strongly promoted. Patients must be made aware of the negative impact smoking has on symptoms associated with SLE, as well as the importance of quitting smoking. Dietary suggestions have to include a diet rich in vitamin D and refrain from consuming echinacea and alfalfa sprouts. Sufficient protection from the sun is crucial, requiring all SLE patients to refrain from direct sun exposure by wearing light, loose-fitting dark clothing that covers a large amount of the body, scheduling activities appropriately, Ultraviolet-A and Ultraviolet-B sunscreens with an SPF of 30 or more are all recommended.

Cutaneous manifestations:

Corticosteroids or Calcineurin inhibitors, such as tacrolimus, are usually effective in treating mild cutaneous manifestations. For the majority of skin manifestations, hydroxychloroquine is the recommended medicine due to its excellent effectiveness. Quinacrine may be used in situations where hydroxychloroquine is intolerable or causes negative side effects. If methotrexate is not helpful, hydroxychloroquine might be tried. Systemic corticosteroids, belimumab (which provides dual advantages for underlying LN), and

mycophenolatemofetil may be considered in cases of severe or refractory illness [115].

Musculoskeletal manifestations:

The main medication recommended for the treatment of lupus arthritis is hydroxychloroquine. Leflunomide or methotrexate may be considered if the response is insufficient. It is acceptable to consider belimumab and rituximab in refractory situations [116].

Hematological manifestations:

Hematological problems caused by drugs need to be checked out. Most of the time, mild hematological abnormalities don't require therapy. Corticosteroids are the main treatment for hematological problems ranging from moderate to severe. Intravenous pulse dosage steroids, splenectomy may be required in cases of severe refractory hematological diseases [117].

Cardiopulmonary manifestations:

NSAIDs and high dosages of corticosteroids usually have an effect on serositis. Methotrexate and hydroxychloroquine could be used as corticosteroid substitutes. High doses of intravenous pulse corticosteroids are necessary for acute lupus pneumonitis, and in cases when diffuse alveolar bleeding is present, plasmapheresis and/or cyclophosphamide may also be necessary. Low to moderate dosages of corticosteroids combined with medications such as mycophenolatemofetil or azathioprine can be used to treat interstitial lung disease. Vasodilator therapy is necessary for pulmonary arterial hypertension, but anticoagulation is necessary for thrombotic consequences including pulmonary embolism. Consequently, the treatment of coronary arteritis and myocarditis requires substantial dosages of corticosteroids.

CNS/ Neuropsychiatric manifestations:

Getting a proper tests and rejecting out other possible causes is important before starting medication for SLE's CNS symptoms. When treating neuropsychiatric symptoms connected to inflammation, such as optic neuritis, and demyelinating illness, immunosuppressive medications like cyclophosphamide, or rituximab are used in combination with high-dose corticosteroids. For patients with thromboembolic central nervous system (CNS) events linked to antiphospholipid antibody syndrome, lifelong warfarin therapy is advised. For cognitive impairment, high-dose corticosteroids may be used, notwithstanding the paucity of strong evidence.

Renal manifestations:

The diagnosis of lupus nephritis will be made through biopsy, which will confirm the tests, eliminate other possible leadings, and help differentiate the illness. The Renin-Angiotensin Aldosterone System Blockade is the treatment for Class I and II liver disease. It is only necessary to undergo immunosuppression with high-dose corticosteroids and azathioprine when the daily proteinuria is greater than 1 gram.

The dosage of corticosteroids should be slowly reduced in time of therapy. Treatment for proliferative LN (Class III/IV) should be more aggressive. IV pulse dose methylprednisolone is the first step in induction therapy. High dose oral steroids are then administered together with IV cyclophosphamide. Maintenance therapy with either azathioprine or mycophenolatemofetil should be administered for a minimum of 3 years [118].

Manifestations during pregnancy:

Due to a higher risk of disease exacerbations, pregnancy may only be investigated if the condition was dormant at the time and six months earlier. Up until then, contraception should be used if necessary, with progesterone contraception only being preferred. Due to its link to a notable decrease in general disease activity and instances of worsened illness, hydroxychloroquine has been connected with significant benefits, it is considered safe to take during pregnancy and should be administered for the full course of the pregnancy. For modest illness symptoms, low-dose corticosteroids and azathioprine may be used. On the other hand, several immunosuppressive medications, including cyclophosphamide, leflunomide, are teratogenic and should not be used while pregnant. In the event of a first- or second-degree heart block, dexamethasone therapy should be started right away; however, prophylactic use of the medication is not recommended. A baby with an irreversible total heart block needs a permanent pacemaker.

X. CONCLUSION

Over the two decades there has been an advancement, in the treatment of lupus and its long term impacts. However numerous uncertainties still persist regarding this condition. The development of targeted therapies will necessitate randomized controlled trials in addition to the research efforts. Managing conditions, lupus requires exceptional commitment and care. Poor outcomes, relapses and instances of resistance often stem from non adherence to medication regimens, neglect and a lack of screening and reassessment of illness. To manage weight and levels of lipids effectively and prevent complications patients should receive counseling on disease pathology symptoms to watch for well as the importance of regular check ups, adherence to medications and defensive measures like dietary changes, consistent physical activity routines and lifestyle adjustments.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the support of Gokaraju Rangaraju College of Pharmacy for providing the necessary facilities and infrastructure to collect this information. Finally, we express our

profound gratitude to all colleagues and mentors whose insights and encouragement greatly contributed to the successful completion of this work.

CONFLICT OF INTEREST

None

REFERENCES

- [1] Justiz Vaillant. A.A. Goyal. A. Varacallo. M.A. (2025). Systemic Lupus Erythematosus. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
- [2] Molina-Rios. S. Rojas-Martinez. R. Estévez-Ramirez. G.M. Medina. Y.F. (2023). Systemic lupus erythematosus and antiphospholipid syndrome after COVID-19 vaccination. A case report. *Mod Rheumatol Case Re*, 7(1), 43-46.
- [3] Didier. K. Bolko. L. Giusti. D. Toquet. S. Robbins. A. Antonicelli. F. Servettaz. A. (2018) Autoantibodies associated with connective tissue diseases: what meaning for clinicians?. *Front Immunol*, 9, 541.
- [4] Aringer. M. Costenbader. K. Daikh. D. et al.: (2019) European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol*, 71, 1400- 12.
- [5] Stratta. P. Mesiano. P. Campo. A. et al. (2009). Life expectancy of women with lupus nephritis now approaches that of the general population. *Int J Immunopathol Pharmacol*, 22, 1135-41.
- [6] Morand. E.F. Mosca. M. (2017). Treat to target, remission and low disease activity in SLE. *Best Pract Res Clin Rheumatol*, 31, 342-50.
- [7] Franklyn. K. Lau. C.S. Navarra. S.V. et al. (2016). Definition and initial validation of a lupus low disease activity state (LLDAS). *Ann Rheum Dis*, 75, 1615-21.
- [8] Golder. V. Kandane-Rathnayake. R. Hoi. A.Y. et al. (2017). Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study. *Arthritis Res Ther*, 19, 62.
- [9] Selvaraja. M. Too. C.L. Tan. L.K. Koay. B.T. Abdullah. M. Shah. A.M. Arip. M. Amin-Nordin. S. (2022). *Lupus Sci Med*, 9(1).
- [10] Losada-García. A. Cortés-Ramírez. S.A. Cruz-Burgos. M. Morales-Pacheco. M. Cruz-Hernández. C.D. Gonzalez-Covarrubias. V. Perez-Plascencia. C. Cerbón. M.A. Rodríguez-Dorantes. M. (2021). Hormone related cancer and autoimmune diseases: A complex interplay to be discovered. *Front Genet*, 12, 673180.
- [11] Tayem. M.G. Shahin. L. Shook. J. Kesselman. M.M. (2022). A review of cardiac manifestations in patients with systemic lupus erythematosus and antiphospholipid syndrome with focus on endocarditis. *Cureus*, 14(1), e21698.
- [12] G.J. Pons-Estel. G.S. Alarcón. L. Scofield. L. Reinlib. G.S. Cooper. (2010). Understanding the epidemiology and progression of systemic lupus erythematosus, *Semin. Arthritis Rheum*, 39, 257-268.
- [13] E. Krishnan. H.B. Hubert. (2006). Ethnicity and mortality from systemic lupus erythematosus in the US. *Ann. Rheum. Dis*, 65, 1500-1505.
- [14] Rees. F. Doherty. M. Grainge. M.J. Lanyon. P. Zhang. W. (2017). The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. *Rheumatology (Oxford)*, 56, 1945-61.
- [15] Weckerle. C.E. Niewold. T.B. (2011). The unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. *Clin Rev Allergy Immunol*, 40, 42-9.
- [16] N. Danchenko. J. Satia. M. Anthony. (2006). Epidemiology of systematic lupus erythematosus: a comparison of worldwide disease burden. *Lupus*, 12, 308-318.
- [17] E.D. Ferucci. J.M. Johnston. J.R. Gaddy. L. Sumner. J.O. Posever. T.L. Choromanski. C. Gordon. S.S. Lim. C.G. Helmick. (2014). Prevalence and incidence of systemic lupus erythematosus in a population-based registry of American Indian and Alaska Native people. *Arthr. Rheumatol*. 66, 2494- 2502.
- [18] S.S. Lim. A.R. Bayakly. C.G. Helmick. C. Gordon. K.A. Easley. C. Drenkard. (2014). The incidence and prevalence of systemic lupus erythematosus, 2002-2004: the Georgia lupus registry. *Arthr. Rheumatol*, 66, 357-368.
- [19] E.C. Somers. W. Marder. P. Cagnoli. E.E. Lewis. P. De Guire. C. Gordon. C.G. Helmick. L. Wang. J.J. Wing. J.P. Dhar. J. Leisen. D. Shaltis. W.J. McCune. (2014). Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan lupus epidemiology and surveillance program. *Arthr. Rheumatol*, 66, 369-378.
- [20] C.G. Helmick. D.T. Felson. R.C. Lawrence. S. Gabriel. R. Hirsch. C.K. Kwoh. M.H. Liang. H.M. Kremers. M.D. Mayes. P.A. Merkel. S.R. Pillemer. J.D. Reveille. J.H. Stone. (2008). Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I, *Arthritis Rheum*, 58, 15-25.
- [21] Tsai. H.L. Chang. J.W. Lu. J.H. Liu. C.S. (2022). Epidemiology and risk factors associated with avascular necrosis in patients with autoimmune diseases: a nationwide study. *Korean J Intern Med*, 37(4), 864-876.

- [22] Hsu. T. Nguyen. P. Petronic-Rosic. V. (2022) A case of systemic lupus erythematosus with cutaneous granulomatous vasculitis. *JAAD Case Rep*, 21, 93-96.
- [23] Sinha. A. Rivera. A.S. Chadha. S.A. Prasada. S. Pawlowski. A.E. Thorp. E. DeBerge. M. Ramsey-Goldman. R. Lee. Y.C. Achenbach. C.J. Lloyd-Jones. D.M. Feinstein. M.J. (2021). Comparative Risk of Incident Coronary Heart Disease Across Chronic Inflammatory Diseases. *Front Cardiovasc Med*, 8, 757738.
- [24] Liu. T. Neuner. R. Thompson. A. Pottackal. G. Petullo. D. Liu. J. Nikolov. N. Sahajwalla. C. Doddapaneni. S. Chen. J. (2022) Clinical pharmacology considerations for the approval of belimumab for the treatment of adult patients with active lupus nephritis: A regulatory perspective. *Lupus*, 31(4), 424-432.
- [25] Pan. Q. Chen. J. Guo. L. et al. (2019) Mechanistic insights into environmental and genetic risk factors for systemic lupus erythematosus. *Am J Transl Res*, 11, 1241-54.
- [26] Brown. J.M. Archer. A.J. Pfau. J.C. Holian. (2003) A. Silica accelerated systemic autoimmune disease in lupusprone New Zealand mixed mice. *Clin Exp Immunol*, 131, 415-21.
- [27] Monteiro. B.G. Pizarro. C.B. (2022) Environmental and occupational exposures in the development of systemic lupus erythematosus in adults: a narrative review. *Rheumatology*, 61.
- [28] Costenbader. K.H. Kim. D.J. Peerzada. J. Lockman. S. Nobles-Knight. D. Petri. M. Karlson. E.W. (2004) Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. *Arthritis Rheum*, 50, 84957.
- [29] Achtman. J.C. Werth. V.P. (2015). Pathophysiology of cutaneous lupus erythematosus. *Arthritis Res Ther*, 17, 182.
- [30] Yu. C. Chang. C. Zhang. J. (2013) Immunologic and genetic considerations of cutaneous lupus erythematosus: a comprehensive review. *J Autoimmun*, 41, 34-45.
- [31] Berner. B.R. Tary-Lehmann. M. Yonkers. N.L. Askari. A.D. Lehmann. P.V. Anthony. D.D. (2005) Phenotypic and functional analysis of EBV-specific memory CD8 cells in SLE. *Cell Immunol*, 235, 29-38.
- [32] Su. R. Li. Z. Wang. Y. et al. (2020) Imbalance between Th17 and regulatory T cells in patients with systemic lupus erythematosus combined EBV/CMV viraemia. *Clin Exp Rheumatol*, 38, 864-73.
- [33] Poole. B.D. Scofield. R.H. Harley. J.B. James. J.A. (2006) Epstein-Barr virus and molecular mimicry in systemic lupus erythematosus. *Autoimmunity*, 39, 63-70.
- [34] Vaglio. A. Grayson. P.C. Fenaroli. P. Gianfreda. D. Boccaletti. V. Ghiggeri. G.M. Moroni. G. (2018) Drug-induced lupus: traditional and new concepts. *Autoimmun Rev*, 17, 912-8.
- [35] Rubin. R.L. (2005) Drug-induced lupus. Systemic Lupus Erythematosus (Second Edition). Tsokos GC (ed): Academic Press, 535-47.
- [36] Petri. M. (2008). Sex hormones and systemic lupus erythematosus. *Lupus*, 17, 412-5.
- [37] Karrar. S. Cunninghame Graham. D.S. (2018). Abnormal B cell development in systemic lupus erythematosus: what the genetics tell us. *Arthritis Rheumatol*, 70, 496-507.
- [38] JustizVaillant. A.A. Goyal. A. Varacallo. M. (2022) Systemic Lupus Erythematosus. StatPearls Publishing, Treasure Island.
- [39] Deng. Y. Tsao. BP. (2019). Genetics of human SLE. Dubois' Lupus Erythematosus and Related Syndromes (Ninth Edition). Wallace DJ, Hahn BH (ed): Elsevier, London, 54-68.
- [40] Laurynenka. V. Kottyan. L.C. Weirauch. M.T. Kaufman. K.M. Harley. J.B. (2021) Genetic predisposition to lupus across ancestries has >300 separable genetic contributions: what we know today. *Lupus Sci Med*.
- [41] Armstrong. D.L. Zidovetzki. R. Alarcón-Riquelme. M.E. et al. (2014). GWAS identifies novel SLE susceptibility genes and explains the association of the HLA region. *Genes Immun*, 15, 347-54.
- [42] Mak. A. Kow. N.Y. (2014). The pathology of T cells in systemic lupus erythematosus. *J Immunol Res*, 419029.
- [43] Al-Mayouf. S.M. Sunker. A. Abdwani. R. et al. (2011). Loss-of-function variant in DNASE1L3 causes a familial form of systemic lupus erythematosus. *Nat Genet*, 43, 1186-8.
- [44] Suárez-Fueyo. A. Bradley. S.J. Tsokos. G.C. (2016). T cells in systemic lupus erythematosus. *Curr Opin Immunol*, 43, 32-8.
- [45] Nakayamada. S. Tanaka. Y. (2021). Clinical relevance of T follicular helper cells in systemic lupus erythematosus. *Expert Rev Clin Immunol*, 17, 1143-50.
- [46] Tsokos. G.C. Lo. M.S. Costa Reis. P. Sullivan. K.E. (2016). New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat Rev Rheumatol*, 12, 716-30.
- [47] Giang. S. La Cava. A. (2016). Regulatory T cells in SLE: biology and use in treatment. *Curr Rheumatol Rep*, 18, 67.
- [48] Mellor-Pita. S. Citores. M.J. Castejon. R. Tutor-Ureta. P. Yebra-Bango. M. Andreu. J.L. Vargas. J.A. (2006). Decrease of regulatory T cells in patients with systemic lupus erythematosus. *Ann Rheum Dis*, 65, 553-4.
- [49] T. Katsuyama. G.C. Tsokos. V.R. Moulton. (2018). Aberrant T cell signaling and subsets in

- systemic lupus erythematosus. *Front. Immunol*, 9.
- [50] M.K. Crow. (2017). Etiology and Pathogenesis of Systemic Lupus Erythematosus, tenth ed., Elsevier Inc.
- [51] Jenks. S.A. Sanz. I. (2009). Altered B cell receptor signaling in human systemic lupus erythematosus. *Auto immun Rev*, 8, 209-13.
- [52] Möckel. T. Basta. F. Weinmann-Menke. J. Schwarting. A. (2021) B cell activating factor (BAFF): structure, functions, autoimmunity and clinical implications in systemic lupus erythematosus (SLE). *Autoimmun Rev*, 20, 102736.
- [53] Shao. W.H. Cohen. P.L. (2011). Disturbances of apoptotic cell clearance in systemic lupus erythematosus. *Arthritis Res Ther*, 13, 202.
- [54] Pagani. S. Bellan. M. Mauro. D. et al. (2020) New insights into the role of Tyro3, Axl, and Mer receptors in rheumatoid arthritis. *Dis Markers*, 2020, 1614627.
- [55] Jung. J.Y. Suh. C.H. (2015). Incomplete clearance of apoptotic cells in systemic lupus erythematosus: pathogenic role and potential biomarker. *Int J Rheum Dis*, 18, 294-303.
- [56] Cook. H.T. Botto. M. (2006). Mechanisms of disease: the complement system and the pathogenesis of systemic lupus erythematosus. *Nat Clin Pract Rheumatol*, 2, 330-7.
- [57] Leffler. J. Bengtsson. A.A. Blom. A.M. (2014). The complement system in systemic lupus erythematosus: an update. *Ann Rheum Dis*, 73, 1601-6.
- [58] Deng. Y. Tsao. B.P. (2010). Genetic susceptibility to systemic lupus erythematosus in the genomic era. *Nat Rev Rheumatol*, 6, 683-92.
- [59] Jorge. A.M. Means. T.K. (2019). Abnormalities in immune complex clearance and apoptotic cell clearance. *Dubois' Lupus Erythematosus and Related Syndromes* (Ninth Edition). Wallace DJ, Hahn BH (ed): Elsevier, London, 216-23.
- [60] Fillatreau. S. Manfroi. B. Dörner. T. (2021). Toll-like receptor signalling in B cells during systemic lupus erythematosus. *Nat Rev Rheumatol*, 17, 98-108.
- [61] Chyuan. I.T. Tzeng. H.T. Chen. J.Y. (2019). Signaling pathways of type I and type III interferons and targeted therapies in systemic lupus erythematosus. *Cells*.
- [62] Nacionales. D.C. Kelly-Scumpia. K.M. Lee. P.Y. et al. (2007). Deficiency of the type I interferon receptor protects mice from experimental lupus. *Arthritis Rheum*, 56, 3770-83.
- [63] Merola. J.F. Bermas. B. Lu. B. Karlson. E.W. Massarotti. E. Schur. P.H. Costenbader. K.H. (2014). Clinical manifestations and survival among adults with (SLE) according to age at diagnosis. *Lupus*, 23, 77884.
- [64] McCarty. D.J. Manzi. S. Medsger. T.A. Jr. Ramsey-Goldman. R. LaPorte. R.E. Kwok. C.K. (1995). Incidence of systemic lupus erythematosus. Race and gender differences. *Arthritis Rheum*, 38, 1260-70.
- [65] Gatto. M. Saccon. F. Zen. M. Iaccarino. L. Doria. A. (2019). Preclinical and early systemic lupus erythematosus. *Best Pract Res Clin Rheumatol*, 33, 101422.
- [66] Schwartz. N. Stock. A.D. Putterman. C. (2019). Neuropsychiatric lupus: new mechanistic insights and future treatment directions. *Nat Rev Rheumatol*, 15, 137-52.
- [67] BAI. R. LIU. S. ZHAO. Y. et al. (2016). Depressive and anxiety disorders in systemic lupus erythematosus patients without major neuropsychiatric manifestations. *J Immunol Res*, 2016: 2829018.
- [68] TJENSVOLLA. A.B. LAUVSNESB. M.B. HIROHATAC. S. et al. (2016). Migraine in patients with systemic lupus erythematosus is associated with reduced cerebral grey matter volume but not with measures of glial activation or anti-NR2 or anti-P antibodies. *Eur J Neurol*, 23, 780-6.
- [69] SHIMIZU. Y. YASUDA. S. KAKO. Y. et al. (2016). Poststeroid neuropsychiatric manifestations are significantly more frequent in SLE compared with other systemic autoimmune diseases and predict better prognosis compared with de novo neuropsychiatric SLE. *Autoimmun Rev*, 15, 786-94.
- [70] SHIMIZU. Y. YASUDA. S. KAKO. Y. et al. (2016). Poststeroid neuropsychiatric manifestations are significantly more frequent in SLE compared with other systemic autoimmune diseases and predict better prognosis compared with de novo neuropsychiatric SLE. *Autoimmun Rev*, 15, 786-94.
- [71] HANLY. G.J. O'KEEFFE. A.J. SU. L. et al. (2016). The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatology (Oxford)*, 55, 252-62.
- [72] BRODER. A. MOWREY. W.B. KIM. M. et al. (2016). Association between antiphospholipid antibodies and all-cause mortality among end-stage renal disease patients with and without SLE: a retrospective cohort study. *Rheumatology (Oxford)*, 55, 817-25.
- [73] PAGNI. F. GALIMBERTI. S. GALBIATI. E. et al. (2016). Tubulointerstitial lesions in lupus nephritis: International multicentre study in a large cohort of patients with repeat biopsy. *Nephrology (Carlton)*, 21, 35-45.
- [74] Fawzy. M. Edrees. A. Okasha. H. El Ashmaui. A. Ragab. G. (2016). Gastrointestinal

- manifestations in systemic lupus erythematosus. *Lupus*, 25, 1456-62.
- [75] ZHANG. L. XU. D. YANG. H. et al. (2016). Clinical features, morbidity, and risk factors of intestinal pseudoobstruction in systemic lupus erythematosus: a retrospective case-control. *Study J Rheumatol*, 43, 559-64
- [76] Medlin. J.L. Hansen. K.E. McCoy. S.S. Bartels. C.M. (2018). Pulmonary manifestations in late versus early systemic lupus erythematosus: a systematic review and meta-analysis. *Semin Arthritis Rheum*, 48, 198-204.
- [77] PÉREZ-PEÑATE. G.M. RÚA-FIGUEROA. I. JULIÁ-SERDÁ. G. et al. (2016). Pulmonary arterial hypertension in systemic lupus erythematosus: prevalence and predictors. *J Rheumatol*, 43, 323-9.
- [78] WANG. H. GUO. X. LAI. J. et al. (2016). Predictors of health-related quality of life in patients with systemic lupus erythematosus associated pulmonary arterial hypertension. *Clin Exp Rheumatol*, 34, 291-95.
- [79] HIGUERA. V. AMEZCUA-GUERRA. L.M. MONTAYA. H. et al. (2016). Association of nail dystrophy with accrued damage and capillaroscopic abnormalities in systemic lupus erythematosus. *J Clin Rheumatol*, 22, 13-8.
- [80] JUNG. J.H. SOH. M.S. AHN. Y.H. et al. (2016). Thrombocytopenia in systemic lupus erythematosus clinical manifestations, treatment, and prognosis in 230 patients. *Medicine (Baltimore)*, 95, e2818.
- [81] Keeling. D.M. Isenberg. D.A. (1993). Haematological manifestations of systemic lupus erythematosus. *Blood Rev*, 7, 199-207.
- [82] Bashal. F. (2013). Hematological disorders in patients with systemic lupus erythematosus. *Open Rheumatol J*, 7, 87-95.
- [83] SKARE. T.L. DAGOSTINI JS. ZANARDI. P.I. et al. (2016). Infections and systemic lupus erythematosus. *Einstein (Sao Paulo)*, 14, 47-51.
- [84] ZHENG. H. LI. M. WANG. D. et al. (2016). Genderspecific contributing risk factors and outcome of female cryptococcal meningoencephalitis patients. *BMC Infect Dis*, 16, 22.
- [85] PIGA. M. CASULA. L. PERRA. D. et al. (2016) Population-based analysis of hospitalizations in a West-European region revealed major changes in hospital utilization for patients with systemic lupus erythematosus over the period 2001-2012. *Lupus*, 25, 28-37.
- [86] YU. K.H. KUO. C.F. HUANG. L.H. et al. (2016). Cancer risk in patients with inflammatory systemic autoimmune rheumatic diseases: a nationwide population-based dynamic cohort study in Taiwan. *Medicine (Baltimore)*, 95, e3540.
- [87] KIM. T.H. BAE. S.C. LEE. S.H. et al. (2016). Association of complement receptor 2 gene polymorphisms with susceptibility to osteonecrosis of the femoral head in systemic lupus erythematosus. *Biomed Res Int*, 2016, 9208035.
- [88] SHOR. D.B. DAHAN. S. COMANESHTER. D. et al. (2016). Does inflammatory bowel disease coexist with systemic lupus erythematosus? *Autoimmun Rev*, 15, 1034-37.
- [89] KAKUTA. K. DOHI. K. SATO. Y. et al. (2016). Chronic inflammatory disease is an independent risk factor for coronary flow velocity reserve impairment unrelated to the processes of coronary artery calcium deposition. *J Am Soc Echocardiogr*, 29, 173-80.
- [90] VIVERO. F. GONZALEZ-ECHAVARRI. C. RUIZ. B. et al. (2016). Prevalence and predictors of valvular heart disease in patients with systemic lupus erythematosus. *Autoimm Rev*, 15, 1134-40.
- [91] GUY. A. TIOSANO. S. COMANESHTER. D. et al. (2016). Aortic aneurysm association with SLE – a case-control study. *Lupus*, 25: 959-63.
- [92] SHARMA. S.K. RATHI. M. SAHOO. S. et al. (2016). Assessment of premature atherosclerosis in systemic lupus erythematosus patients with and without nephritis. *Lupus*, 25, 525- 31.
- [93] SABIO. J.M. VARGAS-HITOS. J.A. MARTINEZBORDONADO. J. et al. (2016). Cumulated organ damage is associated with arterial stiffness in women with systemic lupus erythematosus irrespective of renal function. *Clin Exp Rheumatol*, 34, 53-7.
- [94] HINOJOSA-AZAOLA. A. ROMERO-DIAZ. J. VARGAS-RUIZ. A.G. et al. (2016). Venous and arterial thrombotic events in systemic lupus erythematosus venous and arterial thrombotic events in systemic lupus erythematosus. *J Rheumatol*, 43, 576-86.
- [95] MOYA. F.B. PINEDA GALINDO. L.F. GARCIA DE LA PENA. M. (2016). Impact of chronic glucocorticoid treatment on cardiovascular risk profile in patients with systemic lupus erythematosus. *J Clin Rheumatol*, 22, 8-12.
- [96] *Pract Res Clin Rheumatol*, 23, 495-506.
- [97] Mahmoud. K. Zayat. A. Vital. E.M. (2017). Musculoskeletal manifestations of systemic lupus erythmatosus. *Curr Opin Rheumatol*, 29, 486-92.
- [98] Mukkera. S. Mannem. M. Chamarti. K. Pillarisetty. L. Vulasala. S.S. Alahari. L. Ammu. A. Mukkera. A. Vadlapatla. R.K. (2022). Systemic Lupus Erythematosus-Associated Serositis Managed With Intravenous Belimumab: A Case Report. *Cureus*, 14(2), e22639.

- [99] Cavalli. S. Lonati. P.A. Gerosa. M. Caporali. R. Cimaz. R. Chighizola. C.B. (2022). Beyond Systemic Lupus Erythematosus and Anti-Phospholipid Syndrome: The Relevance of Complement From Pathogenesis to Pregnancy Outcome in Other Systemic Rheumatologic Diseases. *Front Pharmacol*, 13, 841785.
- [100] Emorinken. A. Dic-Ijiewere. M.O. Erameh. C.O. Ugheoke. A.J. Agbadaola. O.R. Agbebaku. F.O. (2021). Clinical and laboratory profile of systemic lupus erythematosus patients at a rural tertiary centre in South-South Nigeria: experience from a new rheumatology clinic. *Rheumatologia*, 59(6), 402-410.
- [101] Aringer. M. Costenbader. K. Johnson. S.R. (2022). Assessing the EULAR/ACR classification criteria for patients with systemic lupus erythematosus. *Expert Rev Clin Immunol*, 18(2), 135-144.
- [102] Liu. C.C. Kao. A.H. Manzi. S. Ahearn. J.M. (2013). Biomarkers in systemic lupus erythematosus: challenges and prospects for the future. *Ther Adv Musculoskelet Dis*, 5, 210-33.
- [103] Aragón. C.C. Tafúr. R.A. Suárez-Avellaneda. A. Martínez. M.T. Salas. A.L. Tobón. G.J. (2020). Urinary biomarkers in lupus nephritis. *J Transl Autoimmun*, 3, 100042.
- [104] Pisetsky. D.S. Bossuyt. X. Meroni. P.L. (2019). ANA as an entry criterion for the classification of SLE. *Autoimmun Rev*, 18, 102400.
- [105] Meroni. P.L. Bizzaro. N. Cavazzana. I. Borghi. M.O. Tincani. A. (2014). Automated tests of ANA immunofluorescence as throughput autoantibody detection technology: strengths and limitations. *BMC Med*, 12, 38.
- [106] Su. Y. Jia. R.L. Han. L. Li. (2007). Z.G. Role of anti-nucleosome antibody in the diagnosis of systemic lupus erythematosus. *Clin Immunol*, 122, 115-20.
- [107] Lim. K.L. Jones. A.C. Brown. N.S. Powell. R.J. (1993). Urine neopterin as a parameter of disease activity in patients with systemic lupus erythematosus: comparisons with serum sIL-2R and antibodies to dsDNA, erythrocyte sedimentation rate, and plasma C3, C4, and C3 degradation products. *Ann Rheum Dis*, 52, 429-35.
- [108] Weinstein. A. Alexander. R.V. Zack. D.J. (2021) A review of complement activation in SLE. *Curr Rheumatol Rep*, 23, 16.
- [109] Fu. S.M. Dai. C. Zhao. Z. Gaskin. F. (2015). Anti-dsDNA Antibodies are one of the many autoantibodies in systemic lupus erythematosus. *F1000Res*, 4, 939.
- [110] Flechsig. A. Rose. T. Barkhudarova. F. et al. (2017). What is the clinical significance of anti-Sm antibodies in systemic lupus erythematosus? A comparison with anti-dsDNA antibodies and C3. *Clin Exp Rheumatol*, 35, 598- 606.
- [111] Alba. P. Bento. L. Cuadrado. M.J. et al. (2003). Anti-dsDNA, anti-Sm antibodies, and the lupus anticoagulant: significant factors associated with lupus nephritis. *Ann Rheum Dis*, 62, 556-60.
- [112] Li. C. Mu. R. Lu. X.Y. He. J. Jia. R.L. Li. Z.G. (2014). Antilymphocyte antibodies in systemic lupus erythematosus: association with disease activity and lymphopenia. *J Immunol Res*, 2014, 672126.
- [113] Provost. T.T. Reichlin. M. (1981). Antinuclear antibody-negative systemic lupus erythematosus. I. Anti-Ro(SSA) and anti-La(SSB) antibodies. *J Am Acad Dermatol*, 4, 84-9.
- [114] Franceschini. F. Cavazzana. I. (2005). Anti-Ro/SSA and La/SSB antibodies. *Autoimmunity*, 38, 55-63.
- [115] Skudalski. L. Shahriari. N. Torre. K. Santiago. S. Bibb. L. Kodomudi. V. Grant-Kels. J.M. Lu. J. (2022). Emerging therapeutics in the management of connective tissue disease. Part I. Lupus erythematosus and Sjögren syndrome. *J Am Acad Dermatol*, 87(1), 1-18.
- [116] Dima. A. Jurcut. C. Chasset. F. Felten. R. Arnaud. L. (2022). Hydroxychloroquine in systemic lupus erythematosus: overview of current knowledge. *Ther Adv Musculoskelet Dis*, 14, 1759720X211073001.
- [117] Wafa. A. Hicham. H. Naoufal. R. Hajar. K. Rachid. R. Souad. B. Mouna. M. Zoubida. M.T. Mohamed. A. (2022). Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: a study of 20 Moroccan adult patients. *Clin Rheumatol*, 41(7), 2021-2033.
- [118] Scheen. M. Adedjouma. A. Esteve. E. Buob. D. Abisor. N. Planche. V. Fain. O. Boffa. J.J. De Seigneux. S. Mekinian. A. Haidar. F. (2022). Kidney disease in antiphospholipid antibody syndrome: Risk factors, pathophysiology and management. *Autoimmun Rev*, 21(5), 103072.