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Original Research Article

Systemic Lupus Erythematosus: A Narrative Review of Disease

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Abstract: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by several clinical and immunological manifestations, lacking accurate methods of diagnosis and treatment. This article focuses on the latest research in SLE's epidemiology, diagnosis methods, and treatment strategies. SLE has a gender-based and ethnicity- based prevalence, with more cases observed in females than males and African population than Caucasians. The diagnosis of SLE is also challenging due to the multifactorial nature of the disease. The diagnosis is generally based on classification rather than diagnostic criteria. Several classification criteria have been proposed, with the most important being ACR-1997, SLICC-2012, and EULAR/ACR-2019. The latest criteria suggested the use of weights linked to different clinical and immunological manifestations. Moreover, several treatment therapies have also been proposed to treat SLE. Anti-malarial drugs are generally regarded as suitable in the earlier stages of SLE. The standard therapy against SLE is mycophenolate mofetil, except for ongoing pregnancy, where azathioprine is used. Currently, different immunosuppressants and immunomodulators are being evaluated in clinical studies against SLE. Anyways, a combination of different therapies might be a holistic approach to the disease, but the heterogenicity of SLE still remains a challenge.

Keywords: Systemic Lupus Erythematosus, Epidemiology, Diagnosis, Treatment.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disease leading to inflammation and tissue damage in the affected areas. SLE up regulates the production of several auto-antibodies, leading to micro-vascular inflammations. SLE is characterized by heterogeneous nature, making its diagnosis and treatment quite challenging [1]. SLE has several disease phenotypes, from mild mucocutaneous appearance to organ and central nervous system (CNS) damage. Metry, Al Salmi [2] have reported photosensitivity, malar rash, hair loss, and discoid lupus as some of the cutaneous manifestations of SLE. Musculoskeletal manifestations involve myalgia, arthralgia, and arthritis. Moreover, studies have shown that more than 60 genetic regions are associated directly or indirectly with the development of SLE [3]. These genetic regions are also associated with key innate and adaptive immune system pathways.

The groundbreaking research of Dr. Hargraves in 1948 on LE cells determined the autoimmune nature of SLE [4]. LE cell was first discovered as a neutrophil or macrophage located in the bone marrow after phagocyting nuclear debris. LE cell assay has long served as a biomarker for SLE, which was later replaced by serum antinuclear antibody (ANA) assay. Zharkova, Celhar [4] have also indicated some factors that add to the initiation and progression of SLE. The factors involve a decrease in tolerance and production of auto B and T effector lymphocytes, production of ANAs; perturbations in necrosis and phagocytosis; production of self-antigens; tissue inflammation, and perturbation in immune regulation.

SLE is a multifactorial disease with many symptoms similar to other disorders, making the diagnosis difficult. The treatment options are also limited and mostly rely on immunosuppression therapy, further increasing the chances of reappearance of the disease. Hence, a detailed overview summarizing the latest trends in SLE research is essential. Therefore, this article summarizes the latest findings in the disease's

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epidemiology, diagnosis, and treatment, focusing on recent studies.

METHODOLOGY

Different keywords and terminologies were used to retrieve relevant studies from PubMed and Google Scholar. The keywords included Systemic Lupus Erythematosus, SLE, epidemiology of SLE, diagnosis of SLE, treatments, advancements in SLE, the role of the immune system in SLE, etc. Further, the role of specific therapies against SLE was searched using terms like "*Therapy name*" in SLE". Only recent research and review articles from the year 2012 onwards were included in this article. Moreover, short communications, conference abstracts, and incomplete studies were omitted in this article.

Fig. 1 represents the number of results found on different databases and the total number of selected studies for this review.

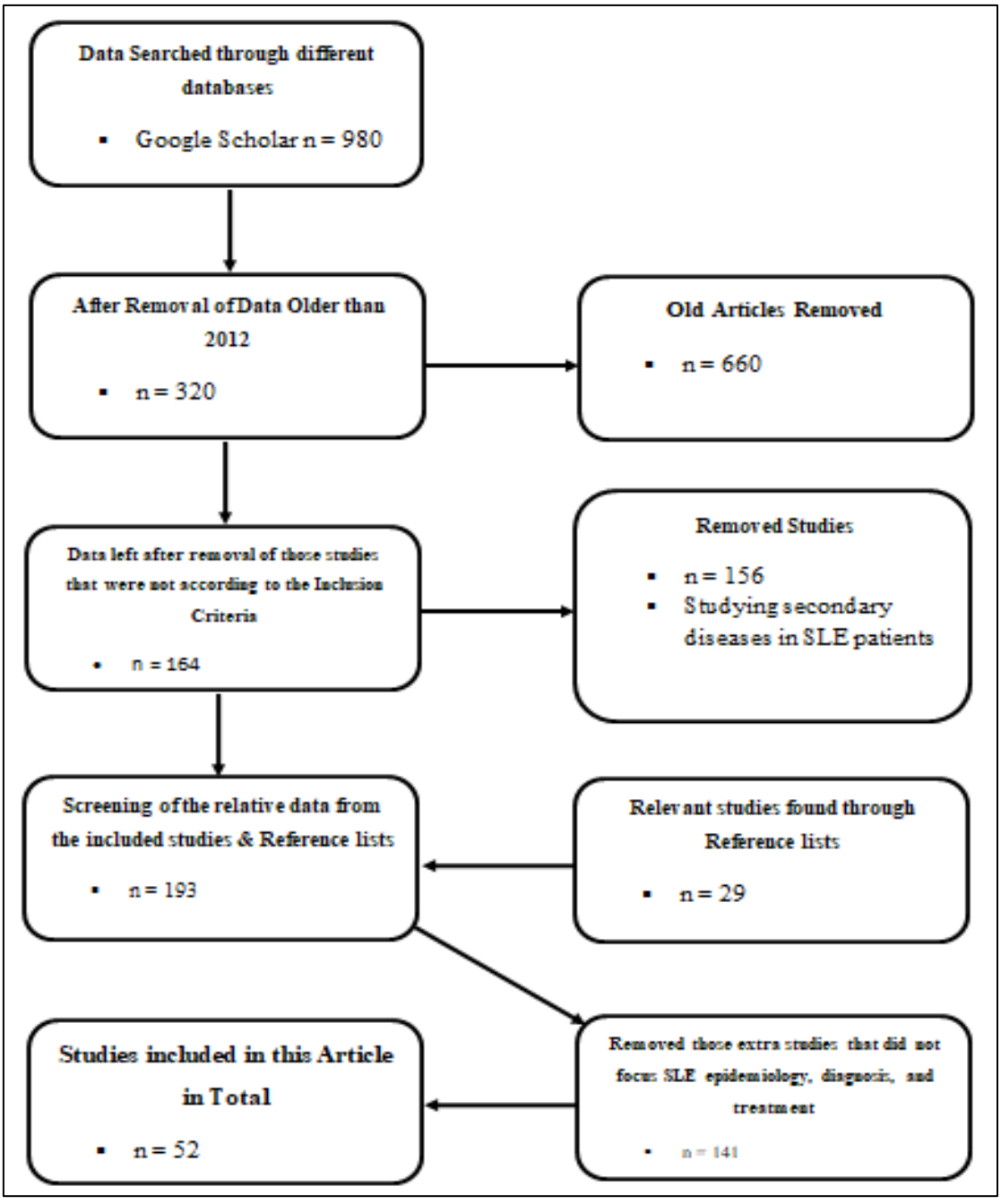

Fig. 1: Summary of the data searched, and the method opted for data selection

EPIDEMIOLOGY

SLE is present worldwide in a gender-biased nature. SLE impacts females more than males, with a ratio of 13:1 between the two in the age group 14 to 44 years old. However, the ratio drops to 2:1 in children and the elderly [5]. Even though SLE is found in all

ethnic groups, its prevalence is higher in African populations of America and Europe, but not in Africa itself. Studies have shown that African-American females are at three time's higher risk compared to Caucasian females. Rees, Doherty [6] reported SLE's incidence and prevalence as of 2016. The results indicated an incidence rate of 23.2/100,000 and a prevalence of 241/100,000 persons in North America. However, the incidence was as low as 0.3/100,000 in Africa and Ukraine. The prevalence was the lowest in Northern Australia (0/847 persons). Rees, Doherty [6] also observed gender-based trends in the incidence and prevalence of SLE. The incidence rate was 7.89/100,000 for female individuals compared to 1.53/100,000 for male individuals in the UK. Moreover, ethnicity-based trends were also observed. In North America, the incidence was the highest in African and Native American populations. The incidence rate of 31.2/100,000 in African Americans, 30.0/100,000 in Native Americans, 18.0/100,000 in white Americans, and 16.7/100,000 in Asian Americans were reported. In addition, Smith, Lythgoe [7] have outlined the epidemiology and clinical aspects of juvenile SLE. The results indicate a peak onset age of 12.7, while the prevalence ranges between 1.89 to 34.1/100,000 children depending on age, gender, and ethnicity. Even though the prevalence is higher in female children than male children, the trend is still not as strong as observed in adults. Further, the prevalence was higher in African-American children than in white American children. SLE can also be fatal due to severe tissue and organ damage. Leading causes of death due to SLE include vascular disease, malignancy, renal failure, and infections. Moreover, atherosclerosis is also higher in juvenile SLE [7].

Leuchten, Milke [8] studied the prevalence of different antibodies and infected organs resulting from SLE in a group of 339 patients. The antibodies against dsDNA, Ro/SSA, La/SSB were found in 53.4%, 22.4%, and 13.0% of patients, respectively. Moreover, joints, skin, and kidneys were the most infected organ system reported in 81.7%, 66.1%, and 33.0% of patients, respectively. Photosensitivity was prevalent in at least 74% of the patients, which is a reason why skin was affected in 66.1 of patients. Most of the participants had a long history of SLE, averaging 17 years. During this time, a lot of symptoms, like joint pain, skin rashes, and alopecia, decreased for several patients due to different therapies. However, the episodes of different infections were also prevalent as most patients relied on immunosuppressants as a therapy, which allows opportunistic pathogens to cause infections. Despite the difficult diagnosis and multifactorial nature of SLE, its incidence is decreasing as Rees, Doherty [9] have observed a 1.2% annual decline in the incidence rate from 1999 to 2012 in the UK. However, SLE still remains a challenge, and improved methodologies are required for its diagnosis and treatment.

Diagnosis

Given the multifactorial nature of SLE, its diagnosis is based on multiple clinical manifestations and serological assays. Mostly, ANA assays are used in the diagnosis; however, a negative test cannot rule out the possibility of SLE, as more than 20% of patients gave negative results despite SLE. Researchers have developed several diagnostic assays over time to incorporate newer aspects of SLE. Majorly, the diagnosis follows classification criteria, given the lack of diagnostic criteria [10]. A recent update to the classification system in 2019 by the European League against Rheumatism (EULAR) and the American College of Rheumatology has enabled clinicians to perform a more accurate diagnosis of SLE.

ACR developed criteria for SLE classification in 1982 (updated in 1997) and was used for almost three decades. Afterward, Systemic Lupus International Collaborating Clinics (SLICC) gave criteria to classify SLE based on at least one clinical manifestation and one immunological property [5]. The clinical manifestations in SLICC criteria included chronic or acute cutaneous lupus, synovitis, nasal or oral ulcers, serositis, neurological manifestations, thrombocytopenia, haemolytic anaemia, and lymphopenia. In comparison, the immunological criterion included ANA, anti-dsDNA, direct Coombs test, anti-smith, hypocomplementemia, and antiphospholipid antibodies. Both SLICC and EULAR/ACR-2019 criteria require immunological assays, unlike ACR-1997, where only clinical manifestation was needed. EULAR/ACR- 2019 criteria reduce the chances of including false positive cases by making ANA assay a compulsory entry point of SLE. Aringer [11] has outlined the EULAR/ACR criteria in detail. EULAR/ACR-2019 criteria have introduced the concept of weighted criteria, where different clinical and immunological manifestations are given certain weights. When a certain threshold is crossed, the criteria suggest a patient suffers from SLE. For example, fever and ulcers have a weight of 2 each, while anti-sm and anti-dsDNA have a weight of 6 each. A patient with weighted manifestations of 10 or more can be regarded as SLE positive. Moreover, the International Society of Nephrology / Renal Pathology Society (ISN/RPS) class III and IV nephritis each has a weight of 10, which alone is sufficient to diagnose a patient with SLE. A concise example adopted from Aringer [11] regarding the classification of weights of different clinical and immunological manifestations are given in table 1.

Table 1: EULAR/ACR 2019 Classification Criteria Domains and Weights [11].

Manifestation										**Weight**
Constitutional	**Hematological**	**Neuropsychiatric**	**Mucocutaneous**	**Serosal**	**Musculoskeletal**	**Renal**	**Antiphospholipid**	**Low complements**	**SLE antibodies**	
						GN III/IV				10
										9
						GN II/V				8
										7
			ACLE	Pericarditis	Joint Involvement				Anti-sm/dsDNA	6
		Seizure		Effusion		U-Prot>0.5g/d				5
	PLT < 100,000 / Hemolysis		DLE / SCLE					C3 and C4 Low		4
	Leuko < 4000	Psychosis						C3 or C4 Low		3
Fever		Delirium	Alopecia/ Ulcers				APL Abs			2

GN III/IV: International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III or IV lupus glomerulonephritis, GN II/V: ISN/RPS class II and V lupus glomerulonephritis, ACLE: Acute cutaneous lupus erythematosus, U-prot: Urinary protein, PLT: Platelets, DLE: Discoid lupus erythematosus, SCLE: Subacute cutaneous lupus erythematosus, APL Abs: Antiphospholipid antibodies.

Batu, Kaya [12] has drawn a comparison between ACR-1997, SLICC-2012, and EULAR/ACR-2019 in terms of sensitivities and specificities. Sensitivities observed for the three criteria were 68.7%, 95.4%, and 91.6%, respectively. While the specificity scores were 94.8%, 89.7%, and 88.5%, respectively, for the three criteria. The results indicated that the SLICC-2012 criteria were the best in terms of sensitivity and specificity. It was also suggested that the probable cause of EULAR/ACR-2019 criteria lagging behind SLICC-2012 could be the strict definition of the inclusion criteria in the former. For example, pleural effusion is during pneumonia is most likely due to the infection and not PLE itself. Hence, further research and updates are still required to improve the diagnosis of SLE.

Treatment Strategies

The basic purpose of SLE treatment is to attain remission with minimum organ damage. The treatment therapy depends on the type of organ damage and the extent of severity of the disease. Such antimalarial drugs are used for the mild type of disease while for severe type of disease cytotoxic and corticosteroids are commonly used. Some drugs exhibit certain side effects however, for a decade, substantial efforts have been made to advance the treatment regimens and increase the survival rate of an affected person.

Antimalarial drugs are one of the earliest therapeutic agents used for SLE treatment. They still are legitimately regarded as the foundation of SLE treatment. These drugs are highly useful for the treatment of dermatological manifestations and arthritis. However, they could be included in all treatment

approaches for SLE, except if a definite adverse reaction appears. Hydroxychloroquine has been shown to be the only medication that increases survival in lupus patients [13]. It has been reported to minimize cardiovascular incidents. Serena *et al.,* [14] demonstrated in a recent study that Long-term usage of hydroxychloroquine in combination with aspirin shows thromboprotective effects in SLE and adds more rationale for its sustained use in SLE patients. In addition, studies have demonstrated that Hydroxychloroquine has a positive impact on pregnancy outcomes such as the protection from the atrioventricular block, prevention of infection, and osteoporosis incidence, and might even potentially have an impact on the prevention of neoplasia [15]. The key concern in using hydroxychloroquine is poor adherence or taking an insufficient dose, which is frequently prompted by problems concerning retinal toxic effects, an uncommon consequence that only manifests after prolonged usage.

The administration of high-dose or "pulsed" glucocorticoids to promptly abolish the autoimmune response in organ-threatening symptoms is a crucial part of SLE therapeutic interventions due to the well-established effectiveness of glucocorticoids in the acute management of SLE. Unfortunately, shortly after the initial use of glucocorticosteroids, it became apparent that individuals taking glucocorticosteroid medication might experience dose-dependent adverse effects, and a number of research studies later showed that their prolonged usage could have detrimental ramifications. According to the findings of a recent review study, the use of glucocorticosteroids increases the risk of organ damage by up to 50% [16]. Even lower dosages, over time, lead to increased risk for blindness, bone weakness, bone breakage, and cardiovascular disease. The majority of research studies have demonstrated the average 5-7.5 mg/day use of glucocorticosteroids, beyond which the risk for damage accretion is greatly enhanced [17].

Preliminary randomized clinical studies showed that glucocorticosteroids and cyclophosphamide combination treatment resulted in improved renal performance and a greater incidence of remission in lupus nephritis patients in contrast to only glucocorticosteroids use. However, this combination therapy showed adverse effects including a greater incidence of infections and ovarian dysfunction [16]. In order to reduce the rate of complications related to the therapeutic approach, some other strategies have been employed including the use of immunosuppressive medications (azathioprine, methotrexate, cyclosporine A, and mycophenolate mofetil). Recently, induction treatment for lupus nephritis has been suggested by adopting multi-target intervention [18]. According to a research study, when the renal response was assessed after 6 months of treatment instead of 18 months, combined use of tacrolimus with mycophenolate mofetil and prednisolone showed greater positive effects as compared to a combination of cyclophosphamide and prednisolone [19]. According to a phase II trial conducted by Rovin *et al.,* it has been shown that the use of mycophenolate mofetil supplemented with low dose voclosporin, a novel calcineurin inhibitor having resilient absorption and bioavailability, improved renal responsiveness. However, a positive result was accompanied by increased levels of side effects, notably death [20].

The preferable medicine for standard therapy is mycophenolate mofetil, except for ongoing pregnancy. In case of pregnancy, azathioprine is an alternative option. In addition to tacrolimus, calcineurin inhibitors are also effective supplementary treatments for lupus nephritis [18]. The selection of an immunosuppressive medication for non-renal disorder patients is mainly based on a clinical assessment like methotrexate is suggested when skin involvement and joint problems are the main symptoms, azathioprine or cyclosporine A are prescribed in case of hematological disease event or when pregnancy is being deemed. Cyclophosphamide is a preferable drug in case of SLE-related severe neuropsychological dysfunction and also for any life-threatening organ damage symptoms of the disease [21]. Recently, a novel treatment option for people with severe symptoms of SLE has surfaced i.e., sirolimus. This drug inhibits the mammalian target of rapamycin, a serine-threonine kinase important for the proliferation of T cells [22, 23]. Increased organ damage and death rates may result from immunosuppressive medications due to adverse effects like serious infections, cancer, teratogeny, and fertility problems.

Several biologics that directly target the pathological pathways governing the onset and progression of lupus have recently been introduced as a result of advancements in our knowledge of the etiology and pathogenesis of SLE. Rituximab and belimumab are two such therapeutic agents that are now available for patient use, while some are under investigation in preclinical and clinical studies. Due to the failure of two significant phase III randomized placebo- controlled studies in non-renal lupus (EXPLORER) and renal lupus (LUNAR) rituximab is still not approved [16, 24]. However, observational studies suggested the effective use of rituximab for refractory lupus nephritis and severe non- renal SLE treatment [25-27]. Belimumab (Benlysta®; GlaxoSmithKline), a completely humanized monoclonal antibody that blocks B lymphocyte stimulator (BlyS), is the only specialized biologic drug approved for the treatment of lupus now. The effectiveness of intravenous belimumab on clinically active SLE was investigated in two phases III trials, BLISS-52 and BLISS-76. The results of these trials demonstrated improved disease response in the treatment group relative to the placebo group. Additionally, the need for steroids and flares

decreased with belimumab use, and the level of health-related quality of life (HRQoL) and tiredness improved significantly [28]. Another clinical trial reported the safe and effective use of belimumab via the subcutaneous route [29]. However, some side effects of belimumab use have been reported such as the onset of lupus nephritis [30, 31]. One recent therapeutic option that can be used for those patients who face complications of infections along SLE and those who do not respond well to other conventional treatment regimens, is the use of intravenous immunoglobulins. They are used as first-line treatment for those SLE patients who have serious neuropsychological manifestations [32]. Therapeutic plasma exchange (TPE) is a viable therapeutic option for those patients who suffered from leucopenia and psychosis in SLE and are not responsive to other drugs. TPE is regarded as an effective treatment, particularly for SLE patients having thrombotic thrombocytopenic purpura and catastrophic antiphospholipid syndrome [33].

Recently, several studies reported the effective use of anti-IFNα receptor antibody anifrolumab for SLE complete remission and minimal side effects [34, 35]. Due to its promising effects, this drug has been approved by Food and Drug Administration (FDA) in 2020 after the TULIP Phase III trials and the MUSE Phase II trial [34-36]. Clinical trials have reported a decrease in overall SLE disease activity, organ damage, and consistently reduced use of oral corticosteroids in anifrolumab-treated groups as compared to the placebo group. This drug obtained approval in Europe in December 2021.

Some other emerging targeted drugs some of which undergo clinical trials for their effective use in SLE treatment, reduced use of corticosteroids with minimum to no organ damage and side effects have been summarized in table 2.

Table 2: Emerging targeted therapies for controlling pathogenesis of SLE

Targeted Drug	Target	Effects	References
Tabalumab	Target BAFF (B-cell activating factor)	Did not show any promising results and effectiveness against SLE	[37]
Blisibimod			[38]
Atacicept			[39]
Epratuzumab	Target B-cell receptor signaling	Negative results, as there was no difference in response rate in the treatment group and placebo group from a phase III clinical trial observed	[40]
Abatacept	Target T-/B-cell costimulatory pathway	Did not meet the primary endpoints	[41]
Bortezomib	Blocks Proteasome	Improves disease activity with some side effects	[42, 43]
Baricitinib	Target Janus kinase/signal transducer and activator of transcription (JAK/STAT)	Administration of 4mg/day of it in clinically active SLE patients with skin and joint manifestations from a phase IIb showed positive results in improving disease symptoms along occurrence of some infections	[44]
N-acetylcysteine	Blocks mammalian target of rapamycin (mTOR) in T cells	Improvement in disease activity	[45]
Idebenone	Mitochondria	Improves SLE-related organ damage	[46]
Interleukin-2 (IL-2)	Target T cells	Complete remission of lupus nephritis was shown in 53% treated group as compared to 16-67% of the placebo group with no serious side effects in a randomized controlled clinical trial	[47]

In the context of a holistic approach, recent research studies have also greatly emphasized the improvement in the lifestyle of lupus patients. Special attention should be governed to habits like ceasing smoking, modifications in inactive lifestyle, and intake of supplements and foods rich in Vitamin D [48]. Recently, a metanalysis revealed that tobacco smoking is very harmful to overall health, additionally; it decreases the effectiveness of SLE treatments including hydroxychloroquine and belimumab in cutaneous lesions and systemic manifestations of SLE. The smoke of a cigarette is also a risk factor for developing SLE [49]. Physical exercise is becoming increasingly important for decreasing SLE-related cardiovascular risks and has been demonstrated to improve physical and psychological well- being [50]. Several studies have reported deficiency of Vitamin D as a common source of SLE, and its impact on disease severity. On the other hand, several recent studies have shown the positive impact of Vitamin D supplementation in the improvement of SLE management [51].

DISCUSSION AND CONCLUSION

The current narrative review of the literature showed that SLE is widespread and has a gender-biased tendency. The data illustrates that females are more susciptible to SLE compared to males. Moreover, SLE affects people of many ethnicities; however, it is more common among African Americans and Europeans than it is among Africans themselves. African-American women are three times more at risk than women of other races, according to studies [5-7, 9]. Studies have also reported that SLE has several manifestations such as skin, joint pain, renal dysfunction, alopecia, fatigue, etc. [8, 9]. As SLE has multifactorial nature, its diagnosis is based on multiple clinical manifestations and serological assays. Mostly, ANA assays are used in

the diagnosis. ANA, anti-dsDNA, direct Coombs test, anti-smith, hypocomplementemia, and antiphospholipid antibodies are commonly used immunological tests for the diagnosis of SLE. However, ACR-1997 needs only the presence of clinical manifestation as a diagnosis of SLE; it also has more chances of false positive results. While EULAR/ACR-2019 criteria reduce the chances of including false positive cases. In a recent study, Batu, Kaya [12] compared the sensitivities and specificities of ACR-1997, SLICC-2012, and EULAR/ACR-2019. In terms of sensitivities, SLICC-2012 was found to be the most sensitive (95.4%) as compared to the other two. While ACR-1997 was observed to be the most specific with 94.8% scores, then SLICC-2012 with 89.7%, and EULAR/ACR-2019 with 88.5% scores. Overall results indicated that the SLICC-2012 criteria are one of the best criteria in terms of sensitivity and specificity for SLE diagnosis [10-12]. Several treatment approaches have been reported in previous literature with positive effects. Choice of treatment depends on the type of SLE manifestation, severity of organ damage, accompanied infections etc. Several drugs including antimalarial, immunosuppressive agents, corticosteroids and biologics are the most important class of drugs extensively being studies for the treatment of SLE and increasing the survival rate of patients [13, 15, 22, 25].

In conclusion, the present study indicated that due to the multifactorial nature of the disease, more specified diagnostic approaches should be investigated which will be helpful in accurately diagnosing disease severity. Moreover, in the last 3 decades, several improvements in SLE treatment strategies have been reported which ultimately increase the survival rate and overall quality of life of SLE patients. However, still there is a need to discover new treatment approaches. Although significant attempts have been in progress from the scientific community and related sectors, the authorization of novel medicines has been hampered by the heterogeneity of SLE, distinct progression pathways, and concurrent medicines. It is anticipated that a more accurate classification of pathophysiological processes based on genetic and clinical characteristics would lead to the design of efficient and less harmful SLE therapeutic approaches.

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