https://doi.org/10.37939/jrmc.v28i1.2550

Varied Presentations Of Patients With Systemic Lupus Erythematosus – What Makes Pakistani Lupus Patients Different

Muhammad Shahzad Manzoor[1], Shamaila Mumtaz[2], Faran Maqbool[3], Darakhshaan Samar[4], Muhammad Hammas Adil[5], Javaria Malik[6]

Abstract

Objective: This study was conducted to characterize the clinical presentation, results of serological and immunological tests and sociodemographic factors in the Pakistani Lupus population.

Methods: This prospective, cross-sectional study was undertaken at the Clinic for Arthritis and Rheumatic Diseases, Rawalpindi Teaching Hospital, Rawalpindi, Pakistan between January 2020 and June 2023, involving adult patients with SLE (classified based on 1997 revised ACR criteria). Demographic data, clinical and laboratory features, auto-antibody profile, disease duration, treatment history and organ damage (calculated by SLICC/ACR-DI) were recorded for all patients. Descriptive statistics and logistic regression analysis were performed for statistical assessment.

Results: A total of 98 patients (94.9% females and 5.1% males) were enrolled in the study. The mean age of patients was 30.93±11.09 years while the mean duration of illness was 3.27±3.01years. The most commonly observed clinical manifestations were neuropsychiatric systemic lupus erythematosus in 84% of patients and mucocutaneous involvement (photosensitivity, mucosal ulcers, facial rash, alopecia and discoid lupus in 63.92%, 56.70%, 48.45%, 37.11% and 13.40% patients respectively). They were followed by serositis, arthralgias and renal involvement in 60.42%, 33.67% and 25% of patients respectively. Anti-nuclear antibody by indirect immunofluorescence was positive in all while anti-dsDNA was positive in 50% of patients.

Conclusions: Fatigue was the most commonly recorded symptom while Neuropsychiatric SLE was the most commonly observed systemic manifestation in the Pakistani population followed by mucocutaneous involvement, serositis, arthralgias and renal involvement. Reasons for serious manifestations at initial presentation include deficiency of healthcare professionals trained in the field of Rheumatology and lack of awareness among patients.

Keywords: Clinical profile, Systemic Lupus Erythematosus, Clinical and laboratory features, Organ damage, Pakistan.

[1] Associate Professor, Rawalpindi Medical University; [2] Senior Registrar, Rawalpindi Medical University; [3] Assistant Professor, Rawalpindi Medical University; [4] Post Graduate Trainee, Rawalpindi Medical University; [5] Consultant Rheumatologist, FGPGMI; [6] Senior Registrar, Rawalpindi Medical University.
Correspondence: Dr. Shamaila Mumtaz, Senior Registrar (Medicine), Rawalpindi Medical University, Taxila. **Email:** shumaila.daud81@yahoo.com
Cite this Article: Manzoor M.S. ., Mumtaz, S. ., Faran, M., Samar, D.,Adil, H. ., & Malik, J. (2024). Varied Presentations Of Patients With Systemic Lupus Erythematosus – What Makes Pakistani Lupus Patients Different. *Journal of Rawalpindi Medical College*, *28*(1). https://doi.org/10.37939/jrmc.v28i1.2550.
Received February 19, 2023; accepted March 08, 2024; published online March 16, 2024

1. Introduction

Systemic Lupus Erythematosus (SLE) is a prototypic autoimmune disease with multi-system involvement.[1] Auto-antibodies are produced against components of the nuclear/cytoplasmic complexes, cell surface antigens and clinical manifestations that are highly variable.[2,3] The auto-antibodies mainly include anti-nuclear antibodies, anti-dsDNA and anti-Smith antibodies, which were also included in the 1997 American College of Rheumatology diagnostic criteria for SLE. Clinically the disease has a relapsing and remitting course which has an incapacitating effect on the psychological and physical health of an individual. The symptomatology of the disease is characterized mainly by cutaneous, musculoskeletal, haematological and sicca symptoms along with involvement of neurological and renal tissue. The clincal features however vary to a great extent.[7]

Multiple theories have been put forward to understand the underlying mechanism of the disease. Numerous pathophysiological mechanisms have been highlighted that lead to immune dysregulation leading to alterations in immune tolerance, hyperactivity of B and T-cells, defective clearance of immune complexes and apoptotic cells. Despite the ongoing extensive scientific work, the exact mechanism of the disease remains unknown. [8,10] However, scientific evidence exists to suggest that a variety of etiological factors such as genetic, hormonal, environmental and sociodemographic, have a role to play in the occurrence and progression of disease. This multiplicity of etiological factors may explain the great degree of variability in clinical and immunological presentations of the disease.[5] The variability, however, is seen to depend significantly on ethnicities and geographical locations of populations.[3] As pointed out in the Hopkins Lupus Cohort Study, ethnicity/race is a major determinant of clinical

manifestations and laboratory and immunological test results.[6] The disease also shows a prominent gender bias, affecting females more than males. However, in males, the symptoms are seen to be more severe and have a worse prognosis.[4]

SLE has a debilitating effect on an individual with the majority of patients having irreversible organ damage at the time of diagnosis of disease.[11] In the early 1950s, it was thought to be a rare disease predominantly affecting females. As awareness spread and research was undertaken the burden of disease in different populations was highlighted.[12] Multiple researchers have revealed the incidence, prevalence and socioeconomic burden of disease in various populations. Multiple studies were also conducted to understand the clinical features and immunological variations seen in various ethnicities. The data for incidence and prevalence of SLE in Asia is limited. However, few studies have shown increased severity of clinical manifestations in Asians with a preponderance of renal symptoms.[16] The probability of long-term survival also appears to be lower in the Asian population when compared to American and European populations.[13-15] Pakistan being one of the most densely populated countries in the world suffers from a health care system paralyzed by a lack of resources and an ever-increasing burden of population which is estimated to be over 190 million by the year 2020.[9]

As vast literature is available on clinical and immunological findings of SLE patients in different populations of the world, literature on the Pakistani population is still scarce. Thus, the present study was conducted to better understand and characterize the clinical presentations, results of serological and immunological tests and sociodemographic factors in a population of Pakistan.

2. Materials & Methods

This prospective, cross-sectional study was undertaken at the Clinic for Arthritis and Rheumatic Diseases, Rawalpindi Teaching Hospital, Rawalpindi, Pakistan from January 2020 to June 2023, after seeking approval from the Hospital Ethics Review Board. After informed consent, adult patients (above 16 years of age) of both genders, fulfilling the 1997 ACR revised classification criteria for SLE were enrolled in the study. Exclusion criteria included the presence of any coexisting rheumatic disease or overlap syndrome (e.g. rheumatoid arthritis, Sjogren's syndrome, systemic sclerosis, polymyositis) or any systemic illness leading to dysfunction of internal organs (e.g. diabetes mellitus, chronic liver disease or renal failure). All patients were assessed by a rheumatologist by taking standard medical history and conducting a physical examination.

A specifically designed proforma was used to record information for all patients. Demographic data was recorded which included age, gender, area of residence and level of education. Clinical data as per the ACR criteria (appendix 1) were recorded.

Disease duration and treatment history of all patients were recorded and organ damage in each patient was calculated by using SLICC/ACR-DI.

Descriptive statistics and logistic regression analysis were performed for statistical assessment. All descriptive statistics were presented as means and standard deviations (SD) for quantitative variables and as relative frequencies and percentages for categorical variables. The relationship of the presence of individual manifestations to disease duration in years and organ damage using SLICC/ACR-DI was studied by logistic regression. The odds ratio and 95% confidence interval were used to present the strength of the association. The level of significance was taken as ≤ 0.05. All recorded data was entered into Statistical Package for the Social Sciences (SPSS) version 18 for analysis.

3. Results

A total of 98 patients were enrolled in the study. 93 patients (94.9%) were females while only 5 patients (5.1%) were males. 23 (23.5%) patients were uneducated, 9 (9.2%) had been to elementary school, 14 (14.3%) to middle school, 33 (33.6%) to high school, and only 19 (19.4%) were graduates.

The mean age of patients at the time of enrollment in the study was 30.93±11.09 years (30.60±9.32 years in male and 30.95±11.22 years in female patients). 33 (33.7%) patients were married while 65 (66.3%) patients were unmarried. The mean duration of illness was 3.27±3.01 years. Duration of illness was less than 2 years in 50.6% of patients and less than 5 years in 85.4% of patients.

Most commonly observed clinical manifestations were constitutional features (fatigue in 87% and fever in 55% of patients), NPSLE (neuropsychiatric systemic lupus erythematosus in 84% of patients) and mucocutaneous involvement (photosensitivity, oral ulcers, malar rash,

alopecia and discoid rash in 63.92%, 56.70%, 48.45%, 37.11% and 13.40% patients respectively). Among patients with neuro-psychiatric manifestations, 23.8% had major neurological involvement including generalized tonic-clonic fits (13 patients), altered mentation (10 patients) and ischemic CVA (5 patients) while 8.3% of patients had major psychiatric involvement which included psychosis (5 patients) and depressive illness with suicidal ideation (2 patients).

Other commonly observed clinical manifestations included serositis, arthralgias and renal involvement in 60.42%, 33.67% and 25% of patients respectively, as shown in Table 1.

Table 1:

Clinical Features	Patients (Percentage)
Constitutional features	87% (fatigue)
Neuropsychiatric	84% (23.8%- major)
Malar rash	47(48.45%)
Discoid rash	13(13.40%)
Oral ulcers	55(56.70%)
Alopecia	36(37.11%)
Photosensitivity	62(63.92%)
Serositis	58(60.42%)
Arthralgia	33(33.67%)
Renal involvement	25(25.51%)

Laboratory findings including those suggestive of cytopenias, auto-immune hemolytic anemia and auto-antibody profile are stated in Table 2.

Table 2:

Laboratory parameter	Patients (Percentage)
Leucopenia	11(11.22%)
Lymphopenia	4(4.08%)
Thrombocytopenia	13(13.26%)
Direct Coomb's test positive	3(3.06%)
Lupus anti-coagulant	5 patients (NA in 88 patients)
Anti-cardiolipin antibody	7 patients (NA in 88 patients)
Beta 2 Glycoprotein I	3 patients (NA in 88 patients)
ANA	98(100%)
Anti-dsDNA	49(50%)

Among auto-antibody profiles, ANA (anti-nuclear antibody by indirect immunofluorescence) was positive in all patients while anti-dsDNA was positive in 50% of patients. Due to a lack of resources workup for anti-phospholipid antibody syndrome could be done only in 10 patients (shown as missing completely at random data in the remaining 88 patients) as shown in Table 2. 4 out of 10 (40% of patients with secondary anti-phospholipid antibody syndrome) had history of seizures.

SLICC/ACR-DI score was 2.1(mean) in patients with neuro-psychiatric SLE and 0.7(mean) in patients with non-neuropsychiatric SLE (p-value less than 0.001). This SLICC/ACR-DI score was similar in the two groups when neurologic involvement was excluded (p=0.10).

4. Discussion

Systemic Lupus Erythematosus (SLE) is a chronic illness with multisystem involvement that needs early recognition, diagnosis, monitoring and therapy to improve life expectancy. Incidence, clinical manifestations and severity of illness differ in different parts of the world due to ethnic differences as well as environmental factors.

The average diagnostic delay from the onset of initial clinical manifestation was more than 3 years in our patients. A study conducted on Lupus patients from the Punjab province in Pakistan reported an average diagnostic delay of 3.42±1.34 years which is almost similar to our results. This diagnostic delay is even more common in children, the male population and those with elderly onset disease (patients with initial manifestation of SLE over the age of 50 years) as the suspicion is less than in females of reproductive age group.[17,18] Damage can occur during the early years of disease and is directly proportional to disease duration.

In a study conducted in the UK in a primary care setting involving more than 1000 lupus patients, 75% of patients had mild-to-moderate disease while only 25% of patients had severe disease at baseline with a mean duration between first clinical manifestation and diagnosis of 26 months.[19] In our study, there was an average diagnostic delay of 30 months with 84% of patients having NPSLE (with 23.8% having major neuropsychiatric manifestations). These differences between the Western population and our study are understandable as the Pakistani population has a low literacy rate as well as a lack of access to healthcare facilities. Another contributing factor is a shortage of specialized rheumatology departments even in urban areas and teaching hospitals.

Southeast Asian individuals have a two to three times higher prevalence of SLE than Caucasians.[20] SLE patients have higher morbidity and mortality when they develop internal organ involvement especially renal,

neuro-psychiatric, cardiac and pulmonary. In our study, one-fourth of patients had severe neuropsychiatric involvement like seizures, altered mentation, cerebrovascular accidents, psychosis or severe depression with suicidal ideation. Previous studies from Pakistan have also reported similar figures.[21] These figures are much higher than the western population.[8]

Other commonly observed systemic manifestations in our patients were mucocutaneous involvement, serositis and musculoskeletal manifestations with prevalence matching other studies from the same region. However, renal involvement in our patients was less than previously reported.[16]

Causes of much higher neurological involvement and more evidence of organ damage (as shown by SLICC/ACR-DI score) at initial presentation need to be probed. Ethnic differences and late presentation are possible explanations.

Our study has some limitations that should be considered. Our centre is the only public sector rheumatology centre in the district that provides specialized care for patients with rheumatic diseases. As a result, we receive patients with more severe disease. Secondly, secondary anti-phospholipid syndrome is associated with serious manifestations especially neurological involvement in patients with SLE. However, its assessment could not be done in all of our patients due to financial constraints.

Further research is warranted to analyze potential risk factors contributing to the presence and severity of individual clinical manifestations of SLE as well as their relationship with specific auto-antibodies.

5. Conclusion

Fatigue is the most commonly observed constitutional feature while Neuropsychiatric SLE is the most commonly observed clinical manifestation in the Pakistani population followed by mucocutaneous involvement, serositis, arthralgias and renal involvement. Reasons for serious manifestations at the initial presentation include a deficiency of healthcare professionals trained in the field of Rheumatology and a lack of awareness among patients, which should be dealt with at the national level. Further studies regarding secondary anti-phospholipid antibody syndrome in Pakistani lupus patients are warranted.

CONFLICTS OF INTEREST- None

Financial support: None to report.
Potential competing interests: None to report

Contributions:

M.S.M, S.M, F.M, D.S, M.H.A, J.M - Conception of study
M.S.M, S.M, F.M, D.S, M.H.A, J.M - Experimentation/Study Conduction
M.S.M, S.M, F.M, D.S, M.H.A, J.M - Analysis/Interpretation/Discussion
M.S.M, S.M, F.M, D.S, M.H.A, J.M - Manuscript Writing
M.S.M, S.M, F.M, D.S, M.H.A, J.M - Critical Review
M.S.M, S.M, F.M, D.S, M.H.A, J.M - Facilitation and Material analysis

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

References

1. Suda M, Kishimoto M, Ohde S, Okada M. 2020. Validation of the 2019 ACR/EULAR classification criteria of systemic lupus erythematosus in 100 Japanese patients: a real-world setting analysis. Clin. Rheumatol. 39:1823–27
2. Sternhagen E, Bettendorf B, Lenert A, Lenert PS. The Role of Clinical Features and Serum Biomarkers in Identifying Patients with Incomplete Lupus Erythematosus at Higher Risk of Transitioning to Systemic Lupus Erythematosus: Current Perspectives. J Inflamm Res. 2022;15:1133-1145.
3. Sahoo RR, Wakhlu A, Agarwal V. Neglected tropical rheumatic diseases. Clin Rheumatol. 2022 May;41(5):1293-1304.
4. Skudalski L, Shahriari N, Torre K, Santiago S, Bibb L, Kodomudi V,et al. Emerging therapeutics in the management of connective tissue disease. Part I. Lupus erythematosus and Sjögren syndrome. J Am Acad Dermatol. 2022 Jul;87(1):1-18.
5. Emorinken A, Dic-Ijiewere MO, Erameh CO, Ugheoke AJ, Agbadaola OR, Agbebaku FO. Clinical and laboratory profile of systemic lupus erythematosus patients at a rural tertiary centre in South-South Nigeria: experience from a new rheumatology clinic. Reumatologia. 2021;59(6):402-410.
6. Kayser C, Dutra LA, Dos Reis-Neto ET, Castro CHM, Fritzler MJ, Andrade LEC. The Role of Autoantibody Testing in Modern Personalized Medicine. Clin Rev Allergy Immunol. 2022 Oct;63(2):251-288.
7. Wafa A, Hicham H, Naoufal R, Hajar K, Rachid R, Souad B,et al. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: a study of 20 Moroccan adult patients. Clin Rheumatol. 2022 Jul;41(7):2021-2033.
8. Scheen M, Adedjouma A, Esteve E, Buob D, Abisror N, Planche V,et al. Kidney disease in antiphospholipid antibody syndrome: Risk factors, pathophysiology and management. Autoimmun Rev. 2022 May;21(5):103072.
9. Khan A, Haroon M, Lashari N, Khan S, Khanum A, Asif S. Inflammatory arthritis and younger age of lupus onset are

associated with the development of neuropsychiatric lupus: experience from a single centre in Pakistan. Acta Rheumatol. (2021) 8:1–7

10. Takeshima Y, Iwasaki Y, Nakano M, Narushima Y, Ota M, Nagafuchi Y,et al. Immune cell multi-omics analysis reveals contribution of oxidative phosphorylation to B-cell functions and organ damage of lupus. Ann Rheum Dis. 2022 Jun;81(6):845-853.
11. Aringer M, Costenbader K, Johnson SR. Assessing the EULAR/ACR classification criteria for patients with systemic lupus erythematosus. Expert Rev Clin Immunol. 2022 Feb;18(2):135-144.
12. Durcan L, O'Dwyer T, Petri M. Management strategies and future directions for systemic lupus erythematosus in adults. Lancet. (2019) 393:2332–43.
13. Shamim R, Farman S, Batool S, Khan S, Raja M. Association of systemic lupus erythematosus disease activity index score with clinical and laboratory parameters in pediatric onset systemic lupus erythematosus. Pak J Med Sci. (2020) 36:467
14. Bingham K, DiazMartinez J, Green R, Tartaglia M, Ruttan L, Su J, et al. Longitudinal relationships between cognitive domains and Depression and anxiety symptoms in systemic lupus erythematosus. Semin Arthritis Rheum. (2021) 51:1186–92.
15. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions. Hoboken, NJ: John Wiley & Sons; (2019). 10.1002/9781119536604
16. Meier A, Bodmer N, Wirth C, Bachmann L, Ribi C, Pröbstel A, et al. Neuro-psychiatric manifestations in patients with systemic lupus erythematosus: a systematic review and results from the Swiss lupus cohort study. Lupus. (2021) 30:1565–76.
17. Ragab S, Ibrahim A. Neuropsychiatric lupus erythematosus in a cohort of Egyptian patients. Egypt J Neurol Psychiatry Neurosurg. (2022) 58:1–7.
18. Meier A, Bodmer N, Wirth C, Bachmann L, Ribi C, Pröbstel A, et al. Neuro-psychiatric manifestations in patients with systemic lupus erythematosus: a systematic review and results from the Swiss lupus cohort study. Lupus. (2021) 30:1565–76.
19. Dima A, Jurcut C, Chasset F, Felten R, Arnaud L. Hydroxychloroquine in systemic lupus erythematosus: overview of current knowledge. Ther Adv Musculoskelet Dis. 2022;14:1759720X211073001.
20. Mukkera S, Mannem M, Chamarti K, Pillarisetty L, Vulasala SS, Alahari L,et al. Systemic Lupus Erythematosus-Associated Serositis Managed With Intravenous Belimumab: A Case Report. Cureus. 2022 Feb;14(2):e22639.
21. Baranyi G, Scholl C, Fazel S, Patel V, Priebe S, Mundt A. Severe mental illness and substance use disorders in prisoners in low-income and middle-income countries: a systematic review and meta-analysis of prevalence studies. Lancet Glob Health. (2019) 7:e461–71.