

Antinuclear Antibody Immunofluorescence Patterns and Their Clinical Correlations in Patients with Systemic Lupus Erythematosus: A Study from a Tertiary Center in Nepal

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ABSTRACT:

Introduction: Antinuclear antibodies (ANAs) detected by indirect immunofluorescence (IIF) on HEp-2 cells are a diagnostic hallmark of systemic lupus erythematosus (SLE). Specific patterns are linked to clinical manifestations. Data on ANA patterns and their clinical correlations in South Asian populations, particularly Nepal, remain limited. **Methods:** This hospital-based cross-sectional study included 167 SLE patients (≥ 16 years) diagnosed by 2019 EULAR/ACR criteria. ANA testing was performed using IIF on HEp-2 cells, with patterns classified according to ICAP. Clinical data and immunological markers (anti-dsDNA, ENAs) were collected. Statistical analysis used Chi-square tests, with $p < 0.05$ considered significant. **Results:** Among 167 patients (82% female, median age 39 years), the most prevalent patterns were nuclear homogeneous (NH; 45.5%), nuclear fine speckled (NFS; 25.7%), and nuclear coarse speckled (NCS; 16.8%). NH significantly associated with arthritis ($p = 0.02$), non-scarring alopecia ($p = 0.03$), lupus nephritis ($p = 0.02$), thrombocytopenia ($p = 0.02$), direct Coombs test ($p = 0.04$), anti-dsDNA ($p < 0.001$), anticardiolipin IgG ($p = 0.03$), lupus anticoagulant ($p = 0.01$), anti-histone ($p = 0.01$), and anti-nucleosome antibodies ($p < 0.001$). NFS associated with malar rash ($p = 0.01$). Anti-Sm/RNP and anti-RNP 68 strongly associated with NCS ($p < 0.001$ for both). **Conclusions:** This study reveals specific ANA patterns and their significant clinical and immunological associations in Nepalese SLE patients. The NH pattern correlates strongly with severe manifestations such as lupus nephritis and with multiple autoantibodies, highlighting the importance of ANA pattern analysis for diagnosis and risk stratification.

Keywords: ANA pattern; Antinuclear antibodies; Rheumatology; Systemic lupus erythematosus.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by the production of autoantibodies directed against nuclear, cytoplasmic, and cell surface antigens. Among these, antinuclear antibodies (ANAs) are the most commonly detected and serve as a hallmark of the disease, present in over 95% of patients with SLE.^{1,2} The detection and interpretation of ANAs play a central role in the diagnosis and management of autoimmune diseases. Indirect immunofluorescence (IIF) on HEp-2 cells remains the gold standard method for ANA testing due to its high sensitivity and its ability to produce distinct fluorescence patterns that help identify specific autoantibodies.^{3,4}



The immunofluorescence patterns (homogeneous, speckled, nucleolar, and centromere) are associated with different disease phenotypes and clinical manifestations. In SLE, specific ANA patterns correlate with distinct clinical features and disease severity. The homogeneous pattern is often associated with anti-double-stranded DNA (anti-dsDNA) antibodies and lupus nephritis, whereas the speckled pattern is commonly linked with anti-Sm or anti-RNP antibodies and mucocutaneous or musculoskeletal involvement.^{5,6}

Data on ANA patterns and their clinical correlations remain limited in South Asian populations, particularly in Nepal, where unique genetic and environmental factors may influence autoimmune disease expression. This study aims to evaluate the distribution of ANA immunofluorescence patterns and their associations with clinical manifestations in patients with SLE at a tertiary care center in Nepal.

METHODS:

A hospital-based cross-sectional observational study was conducted in the Department of Internal Medicine at Kathmandu Medical College and Teaching Hospital (KMC), Sinamangal, Kathmandu, Nepal, from August 2025 to July 2026. Ethical approval was obtained from the Institutional Review Committee (IRC) of Kathmandu Medical College (Ref. 21072025/25). The study adhered to the principles outlined in the Declaration of Helsinki and local regulatory guidelines.

Patients aged 16 years or older who were classified with SLE according to the 2019 EULAR/ACR classification criteria were eligible for inclusion.⁷ Both outpatients and inpatients were included. All participants had undergone ANA testing by IIF on HEp-2 cells and had complete clinical and laboratory data available for review. Written informed consent was obtained from all participants.

Patients were excluded if they had overlap syndromes or other autoimmune rheumatological disorders, including mixed connective tissue disease, scleroderma, or rheumatoid arthritis. Additional exclusion criteria included: (a) absence of IIF-ANA testing or incomplete ANA pattern results; (b) incomplete clinical records or missing essential laboratory investigations; and (c) refusal to provide informed consent.

The sample size was calculated using the formula for an infinite population: $n = Z^2pq/d^2$.

Assuming a 95% confidence interval ($Z = 1.96$), a prevalence of 6.6% based on Jaffri et al.⁸ ($p = 0.066$), a complementary probability of 93.4% ($q = 0.934$), and a precision of 5% ($d = 0.05$), the calculated sample size was 94.72. This was rounded up to a minimum of 95 participants.

A consecutive sampling technique was employed. All patients who fulfilled the inclusion criteria and presented to the Department of Internal Medicine during the study period were enrolled consecutively until the required sample size was achieved.

ANA testing was performed using indirect immunofluorescence (IIF) microscopy on HEp-2 cell substrate slides. The cutoff for ANA positivity was defined as a titer $\geq 1:80$. Positive samples were classified according to immunofluorescence staining patterns using the International Consensus on ANA Patterns (ICAP), categorized from AC-1 to AC-31, with unclassified patterns reported as AC-XX.⁹

Extractable nuclear antigen (ENA) profile testing was performed using a line immunoassay (line blot) on nitrocellulose strips coated with purified or recombinant antigens, including Sm, Sm/RNP, SSA/Ro, SSB/La, Jo-1, Scl-70, anti-histone, anti-nucleosome, anti-centromere, anti-RNP 68, anti- $\beta 2$ GP1, and anti-cardiolipin, according to the manufacturer's instructions.

Antibodies against double-stranded DNA (dsDNA) were detected using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Orgentec, Germany). Microwells were pre-coated with calf thymus dsDNA antigen. Calibrators, controls, and appropriately diluted patient sera were added to the wells. After incubation and washing, results were developed using an enzyme-conjugated detection system according to the manufacturer's instructions, and optical density was measured for interpretation.

Clinical data were collected from patient records, including demographic characteristics and disease manifestations across multiple organ systems. These included constitutional symptoms (fever, fatigue); musculoskeletal manifestations (arthralgia, arthritis); hematological involvement (leukopenia, thrombocytopenia, autoimmune hemolytic anemia); mucocutaneous features (non-scarring alopecia, oral ulcers, cutaneous lupus); neuropsychiatric manifestations (seizures, psychosis); cardiovascular involvement (myocarditis); serositis (pleuritis, pericarditis); and renal manifestations (proteinuria, lupus nephritis).

Data entry was performed using Microsoft Excel. Statistical analysis was conducted using the SPSS 21.1. Continuous variables were presented as mean $\pm$ standard deviation (SD). Categorical variables were expressed as frequency and percentage. The Chi-square test was used to assess the significance of associations between categorical variables. A p -value < 0.05 was considered statistically significant.

RESULTS

Over the 12-month study period, 176 patients with SLE presented to our center. Of these, 167 patients met the eligibility criteria and were included in the study. All included patients tested positive for ANA, and all positive samples demonstrated a classifiable ICAP pattern. The study population was predominantly female, with 137 (82%) females and 30 (18%) males. The median age was 39 (IQR: 30-50) years and median duration of illness was 23 (IQR: 12-48) weeks.

The distribution of ANA immunofluorescence patterns is presented in **Table 1**. Nuclear homogeneous (NH) was the most common pattern (45.51%), followed by nuclear fine speckled (NFS; 25.75%), nuclear coarse speckled (NCS; 16.77%), cytoplasmic dense fine speckled (CFDS; 5.39%), and Others (6.59%).

Summary of significant clinical and immunological associations by ANA Pattern Group is presented in **Table 2**. Overall, the groups demonstrated limited divergence in most clinical domains. However, several immunological

markers exhibited statistically significant between-group differences, suggesting that serological heterogeneity, rather than overt clinical phenotype, primarily distinguishes these categories.

Constitutional symptoms were the most common clinical domain, present in 66.47% ($n = 111$) of patients. Fever was the most frequent constitutional symptom ($n = 67$, 40.12%), followed by fatigue ($n = 58$, 34.73%). Both symptoms were distributed across all groups, with the highest frequencies observed in the NH group. However, these differences did not reach statistical significance (fever: $\chi^2 = 5.28$, $p = 0.25$; fatigue: $\chi^2 = 2.91$, $p = 0.57$).

Musculoskeletal symptoms (arthralgia/arthritis) were present in 57.49% ($n = 96$) of patients. Arthralgia without arthritis was observed in 35.33% ($n = 59$), while arthritis was present in 22.16% ($n = 37$). Both manifestations were distributed across all groups, with the highest absolute frequencies in the NH category. A statistically significant association was observed between arthritis and the NH pattern ($\chi^2 = 5.32$, $p = 0.02$, Cramer's $V = 0.18$).

Hematological involvement (AIHA, leukopenia, and thrombocytopenia) was present in 50.30% ($n = 84$) of patients. Among these, AIHA was the most common ($n = 19$, 11.38%), followed by thrombocytopenia ($n = 14$, 8.38%) and leukopenia ($n = 12$, 7.19%). AIHA and leukopenia did not show statistically significant between-group differences (AIHA: $\chi^2 = 2.41$, $p = 0.66$; leukopenia: $\chi^2 = 3.27$, $p = 0.51$). In contrast, thrombocytopenia demonstrated a significant association with the NH pattern ($\chi^2 = 9.96$, $p = 0.02$, Cramer's $V = 0.24$).

Mucocutaneous manifestations showed variable distribution across groups. Mucosal involvement (oral ulcers) was present across all groups, with no statistically significant between-group differences ($\chi^2 = 1.25$, $p = 0.86$). Non-scarring alopecia was significantly associated with the NH pattern ($\chi^2 = 4.34$, $p = 0.03$, Cramer's $V = 0.17$), while malar rash was significantly more frequent in the NFS group ($\chi^2 = 7.37$, $p = 0.01$, Cramer's $V = 0.21$).

Renal involvement (proteinuria >0.5 g/day and biopsy-proven lupus nephritis) was observed across all groups. Proteinuria was numerically more prevalent in the NH group ($n = 37$, 48.68%), followed by NFS ($n = 14$, 32.56%) and NCS ($n = 9$, 32.14%). Biopsy-proven lupus nephritis showed a similar distribution and was significantly associated with the NH pattern ($\chi^2 = 6.33$, $p = 0.01$, Cramer's $V = 0.20$).

Serosal involvement, neuropsychiatric

Table 1. Distribution of ANA Immunofluorescence Patterns ($n=167$)*

ANA Pattern	ICAP Code	n	%
Nuclear Homogeneous	AC-1	76	45.51
Nuclear Fine Speckled	AC-4	43	25.75
Nuclear Coarse Speckled	AC-5	28	16.77
Cytoplasmic Dense Fine Speckled	AC-19	9	5.39
Cytoplasmic Reticular	AC-21	3	1.80
Cytoplasmic Fine Speckled	AC-20	2	1.20
Centromere	AC-3	2	1.20
Multiple Nuclear Dots	AC-6	1	0.60
Smooth Nuclear Envelope	AC-11	1	0.60
Punctate Nucleolar	AC-10	1	0.60
NuMa-like	AC-26	1	0.60

*percentages may not sum to 100% due to rounding. The "Others" category in subsequent analyses includes the six patterns with frequencies ≤ 3 (AC-3, AC-6, AC-10, AC-11, AC-20, AC-21, AC-26).

Table 2: Summary of Significant Clinical and Immunological Associations by ANA Pattern Group*

Domain / Marker	Overall Prevalence	Significant Association	χ^2	p-value	Cramer's V
Clinical					
Arthritis	22.16%	NH	5.32	0.02	0.18
Non-scarring alopecia	12.57%	NH	4.34	0.03	0.17
Malar rash	28.14%	NFS	7.37	0.01	0.21
Thrombocytopenia	8.38%	NH	9.96	0.02	0.24
Lupus nephritis	17.37%	NH	6.33	0.01	0.20
Immunological					
Direct Coombs test	12.57%	NH	10.35	0.04	0.25
Lupus anticoagulant	26.35%	NH	13.79	0.01	0.29
Anti-dsDNA	41.92%	NH, NFS	42.45	<0.01	0.50
Anti-histone	23.35%	NH	11.85	0.01	0.32
Anti-nucleosome	40.12%	NH	30.15	<0.01	0.43
Anti-Sm/RNP	31.14%	NCS	28.65	<0.01	0.32
Anti-RNP 68	17.96%	NCS	34.20	<0.01	0.41
Anticardiolipin IgG	17.96%	NH	11.15	0.03	0.26

*Full data for all clinical features and immunological markers are available in Supplementary Tables S1 and S2, respectively. #For domain/ marker with expected cell frequencies <5 in some comparisons, Chi-square test results may be less reliable. These associations should be interpreted with caution and validated in larger cohorts.

manifestations, and myocarditis were infrequent across all groups, with no statistically significant between-group differences. The details are presented in **Supplementary Table S1** available online.

The immunological domain exhibited the most pronounced group differences. A summary of significant associations is presented in **Table 2**, with the full dataset available in **Supplementary Table S2**, which is available online.

Direct Coombs test (DCT) positivity showed a statistically significant association with the NH pattern ($\chi^2 = 9.11$, $p = 0.01$, Cramer's V = 0.23), with overall between-group differences also significant ($\chi^2 = 10.35$, $p = 0.04$, Cramer's V = 0.25).

Anti-dsDNA antibodies demonstrated one of the strongest associations, with marked between-group heterogeneity ($\chi^2 = 42.45$, $p < 0.01$, Cramer's V = 0.50). Anti-dsDNA positivity was significantly associated with both the NH pattern ($\chi^2 = 40.20$, $p < 0.01$, Cramer's V = 0.49) and the NFS pattern ($\chi^2 = 10.40$, $p < 0.01$, Cramer's V = 0.25).

Anti-nucleosome and anti-histone antibodies demonstrated a highly significant between-group difference ($\chi^2 = 32.42$, $p < 0.01$, Cramer's V = 0.44), with both antibodies showing significant association with the NH pattern (anti-nucleosome: $\chi^2 = 30.15$, $p < 0.01$, Cramer's V = 0.43; anti-histone: $\chi^2 = 11.85$, $p = 0.01$, Cramer's V = 0.32).

Anti-Sm/RNP and anti-RNP 68 antibodies

each exhibited highly significant between-group differences (anti-Sm/RNP: $\chi^2 = 28.65$, $p < 0.01$; anti-RNP 68: $\chi^2 = 34.20$, $p < 0.01$) and were strongly associated with the NCS pattern (Cramer's V = 0.32 and 0.41, respectively).

Among antiphospholipid antibodies, lupus anticoagulant ($\chi^2 = 13.79$, $p = 0.01$, Cramer's V = 0.29) and anticardiolipin IgG ($\chi^2 = 11.15$, $p = 0.03$, Cramer's V = 0.26) showed significant between-group differences, both associated with the NH pattern.

In contrast, anti-Smith (Sm), anti-centromere, anti-Ro, anti-La/SSB, anticardiolipin IgM, and anti- β 2GPI (IgG and IgM) antibodies did not differ significantly across groups. The details are presented in **Supplementary Table S2**.

DISCUSSION

This cross-sectional study of 167 Nepalese SLE patients found the nuclear homogeneous (NH) pattern most prevalent (45.5%), followed by NFS (25.7%) and NCS (16.8%). The NH pattern significantly associated with lupus nephritis, arthritis, thrombocytopenia, and multiple autoantibodies. Serological heterogeneity, rather than clinical phenotype, primarily distinguishes ANA pattern categories.

Females were predominantly affected (82% vs 18%), consistent with the well-established higher

prevalence of SLE in women.¹⁰ The peak diagnosis age (30–50 years) aligns with findings from Barber et al., confirming that SLE predominantly affects young to middle-aged adults.¹⁰

Among 167 patients, we identified 11 distinct ANA patterns out of 31 defined by ICAP. The NH pattern was most prevalent (46%), followed by NFS (25.7%), NCS (16.8%), CFDS (5.4%), cytoplasmic reticular (1.8%), and cytoplasmic fine speckled and centromere patterns (1.2% each). This predominance of NH pattern aligns with Taiwanese and Swedish cohorts.^{11,12} However, studies from Saudi Arabia reported the nuclear speckled pattern as most frequent (79.5%),¹³ and a South Indian study reported homogeneous pattern in 31% and speckled in 17%.¹⁴ These regional variations likely reflect genetic differences, environmental factors, disease activity, or concurrent steroid therapy.¹⁵⁻¹⁷

We grouped less frequently observed patterns into an "other" category due to their low frequency. This category included cytoplasmic reticular, cytoplasmic fine speckled, centromere, multiple nuclear dots, smooth nuclear envelope, punctate nucleolar, and NuMA-like patterns. Among these, the NuMA-like pattern is particularly rare, and only a single case was identified in our study. The NuMA-like pattern is an uncommon mitotic ANA pattern and is rarely encountered in routine clinical practice. Several studies evaluating ANA pattern distribution have not reported the presence of a NuMA-like pattern, likely reflecting its extremely low prevalence and the requirement for expert-level recognition.^{11,12} Studies focusing on rare ANA patterns, particularly mitotic spindle apparatus antibodies, have reported the presence of the NuMA-like pattern. For example, Betancur et al. demonstrated that the NuMA pattern was the most frequent among rare ANA patterns, highlighting its clinical relevance despite its overall low prevalence.¹⁸

Fever (40.1%) was the most prevalent constitutional symptom, followed by fatigue (34.7%). Although both were most frequent in the NH group, these differences were not significant ($p = 0.25$ and $p = 0.57$, respectively), suggesting constitutional symptoms are broadly distributed across ANA patterns and lack pattern-specific predictive value.

Arthritis (22.2%) showed a significant association with the NH pattern ($p = 0.02$, $V = 0.18$). This association may reflect the high prevalence of anti-dsDNA antibodies in NH patients, as anti-dsDNA has been linked to inflammatory arthritis

in SLE. However, previous cohort studies have not consistently demonstrated this association,¹² possibly because ANA patterns primarily reflect autoantibody specificity rather than directly predicting clinical phenotypes like arthritis.

Lupus nephritis was significantly associated with the NH pattern ($p = 0.01$, $V = 0.20$), consistent with a recent study.¹⁹ This association is biologically plausible, as the NH pattern is commonly produced by anti-dsDNA antibodies, which are pathogenic in lupus nephritis. Non-scarring alopecia (NH; $p = 0.03$, $V = 0.17$) and malar rash (NFS; $p = 0.01$, $V = 0.21$) also showed significant associations, consistent with an Indonesian study.²⁰

Thrombocytopenia ($p = 0.02$, $V = 0.24$) was significantly associated with the NH pattern. This may be mediated by anti-dsDNA antibodies or other autoantibodies cross-reacting with platelet antigens, though further mechanistic studies are needed.

Serositis, neuropsychiatric manifestations, and myocarditis were infrequent, with no significant between-group differences. Their low event rates precluded meaningful statistical analysis, consistent with their relatively lower prevalence in SLE cohorts.¹²

The immunological domain exhibited the most pronounced between-group differences. Direct Coombs test (DCT) positivity was significantly associated with the NH pattern ($p = 0.035$, $V = 0.25$), consistent with Ramachandran et al.²¹ The presence of anti-dsDNA might be associated with a positive DCT, especially among patients with a homogeneous nucleus pattern. Anti-dsDNA antibodies demonstrated marked heterogeneity ($p < 0.001$, $V = 0.50$) and were significantly associated with both NH ($p < 0.001$, $V = 0.49$) and NFS ($p = 0.001$, $V = 0.25$) patterns. This is expected, as anti-dsDNA antibodies typically produce a homogeneous or peripheral pattern on HEp-2 cells.

Anticardiolipin IgG ($p = 0.025$, $V = 0.26$) and lupus anticoagulant ($p = 0.008$, $V = 0.29$) were significantly associated with the NH pattern. However, Ramachandran et al. reported aCL IgG in 13% of patients with nuclear speckled pattern, 7.1% with mixed pattern, and 0% with NH pattern, suggesting population-specific variations in these associations.²¹

Anti-nucleosome and anti-histone antibodies showed highly significant associations with the NH pattern ($p < 0.001$, $V = 0.44$ and $p = 0.01$, $V = 0.32$, respectively), consistent with their known coexistence with anti-dsDNA antibodies.

Anti-Sm/RNP and anti-RNP 68 antibodies exhibited highly significant associations with the NCS pattern ($p < 0.001$ for both; $V = 0.32$ and 0.41 , respectively). This is biologically plausible, as anti-Sm and anti-RNP antibodies typically produce a coarse speckled pattern on IIF. Ramachandran et al. similarly reported the nuclear speckled pattern as most prevalent among patients with anti-Sm and anti-RNP antibodies.²¹

In contrast, anti-Smith, anticentromere, anti-Ro, anti-La/SSB, anticardiolipin IgM, and anti- β 2GP1 antibodies did not show significant differences across groups. These markers were either uncommon or evenly distributed, suggesting they do not strongly contribute to group stratification.

This study has several limitations. The single-center, cross-sectional design limits generalizability and precludes causal inference. The sample size, calculated using general population prevalence (6.6%), may underpower detection of associations with rare patterns. Disease activity was not quantified using validated instruments. Despite these limitations, this study provides valuable baseline data on ANA patterns in Nepalese SLE patients.

Our findings have several practical implications for clinicians in Nepal and similar resource-limited settings. The NH pattern's association with lupus nephritis and thrombocytopenia suggests closer renal and hematological monitoring for these patients. The NCS pattern may guide targeted anti-Sm/RNP testing in resource-limited settings. ANA-IIF patterns should complement, not replace, broader clinical and serological assessment. Rare pattern recognition requires ongoing training and expert-level interpretation.

Future multi-center, longitudinal studies with larger sample sizes and validated disease activity measures are needed to validate our findings and assess prognostic value. Integration of genetic and environmental factors, along with cost-effectiveness analyses, would further inform region-specific clinical guidelines.

CONCLUSIONS:

The nuclear homogeneous (NH) pattern is the most prevalent ANA-IIF pattern in Nepalese SLE patients, followed by nuclear fine speckled (NFS) and nuclear coarse speckled (NCS). The NH pattern is significantly associated with lupus nephritis, arthritis, thrombocytopenia, and multiple immunological markers, including anti-dsDNA, anti-nucleosome, and anti-histone antibodies. The NCS pattern is strongly associated with anti-Sm/RNP and anti-RNP 68 antibodies. Serological heterogeneity, rather than clinical phenotype, primarily distinguishes ANA pattern categories. These findings provide baseline data for ANA pattern interpretation in Nepalese SLE patients and highlight the NH pattern as a potential marker for renal and hematological risk stratification.

Conflict of Interest: None.

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Authors' Contribution:

Prabin Khatri: Conceptualization, methodology, research design, definition of intellectual content, investigation, data curation, writing-original draft, writing- review and editing, supervision. **Ravi Shukla:** Literature search, methodology, data analysis, statistical analysis and interpretation, writing-review and editing. **Raj Adhikari:** Validation, resources, investigation, data curation, writing, review, and editing. **Aabishkar Subedi:** Data acquisition, manuscript preparation, manuscript editing, and manuscript review. **Puja Shrestha:** Data analysis and interpretation, manuscript editing, and manuscript review. **Mamata Bhattarai Khatri:** Resources, manuscript editing, and manuscript review.

Data Availability Statement:

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Consideration:

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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