Dermatology Practical & Conceptual

Increased Neutrophil-to-Lymphocyte Ratio as a Marker of Systemic Immunity in Lichen Sclerosus

Alessia Paganelli[1,2], Alessandra Corrente[3], Roberta Priori[4], Giovanni Di Zenzo[5], Francesco Moro[1], Laura Colonna[1], Emanuele Scala[6], Giovanni Pellacani[7], Dario Didona[8]

1. Center for Regenerative and Immunological Dermatology (CEDRI), IDI-IRCCS Istituto Dermopatico Dell'Immacolata, Rome, Italy
2. Department of Life Sciences, Health and Health Professions, Link Campus University, Rome, Italy
3. Cell and Molecular Biology Lab, IDI-IRCCS Istituto Dermopatico Dell'Immacolata, Rome, Italy
4. Rheumatology Unit, Department of Internal Medicine and Medical Specialties, AOU Policlinico Umberto I, Rome, Italy
5. Cellular and Molecular Biology Lab, IDI-IRCCS Istituto Dermopatico Dell'Immacolata, Rome, Italy
6. Laboratory of Experimental Immunology, IDI-IRCCS Istituto Dermopatico Dell'Immacolata, Rome, Italy
7. Dermatology Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Science, University of La Sapienza, Rome, Italy
8. Rare Diseases Unit, IDI-IRCCS Istituto Dermopatico Dell'Immacolata, Rome, Italy

Key words: NLR, Neutrophil-to-lymphocyte ratio, Lichen sclerosus, Autoimmunity, Chronic inflammatory skin diseases

Citation: Paganelli A, Corrente A, Priori R, et al. Increased Neutrophil-to-Lymphocyte Ratio as a Marker of Systemic Immunity in Lichen Sclerosus. *Dermatol Pract Concept*. 2026;16(2):7184. DOI: https://doi.org/10.5826/dpc.1602a7184

Accepted: January 29, 2025; **Published:** April 2026

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Alessia Paganelli, Professor, MD, PHD; IDI-IRCCS Istituto Dermopatico Dell'Immacolata; via dei Monti di Creta 104, 00199, Rome, Italy; Department of Life Sciences, Health and Health Professions, Link Campus University, Rome, Italy. ORCID ID: 0000-0002-0916-7769. E-mail: a.paganelli@idi.it

ABSTRACT

Introduction: Lichen sclerosus (LS) is a chronic inflammatory dermatosis traditionally considered a localized condition, yet associations with autoimmune comorbidities and circulating autoantibodies suggest possible systemic immune involvement. The neutrophil-to-lymphocyte ratio (NLR) is an inexpensive biomarker of systemic inflammation and frailty, but its role in LS has not been investigated.

Aims: To evaluate NLR values in patients with LS and assess whether LS is associated with systemic inflammatory changes.

Methods: This single-center retrospective observational study analyzed anonymized laboratory data from patients diagnosed with LS at IDI-IRCCS (Rome, Italy) between January 2020 and January 2025. Full blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), age, and sex were collected. Patients were subdivided into three age groups (<65, 65–74, ≥75 years). Welch's ANOVA and t-tests assessed group differences; chi-square tests examined NLR frailty-range distribution; Pearson correlations evaluated associations with CRP and ESR.

Results: A total of 631 samples were included. Mean NLR was 2.34 ±1.36, increasing significantly with age (P=0.02). Approximately one third of patients fell within frailty-associated NLR ranges. Among adults <65 years, mean NLR (2.17 ±1.00) was significantly higher than in two healthy control cohorts (1.85 ± 0.64 and 1.65 ± 1.96; both P<0.01). NLR correlated moderately with ESR (r=0.47) and modestly with CRP (r=0.36).

Conclusions: LS is associated with higher NLR values than those observed in healthy controls, indicating mild systemic inflammation. These findings support the concept that LS may not be exclusively localized but may involve broader immune dysregulation. NLR may help identify LS patients with potential systemic involvement, although prospective validation is required.

Introduction

Lichen sclerosus (LS) is a chronic inflammatory, scarring dermatosis typically involving the anogenital region. Local itching and pain lead to sexual and urinary dysfunction, deeply impacting patients' quality of life [1,2]. Due to the nonspecific nature of the initial clinical manifestations, LS remains an overlooked condition, and the diagnosis is often delayed [3,4].

Estimates on disease epidemiology are highly variable, depending upon sex and age [5]. A recent study on 2,525,340 subjects demonstrated a prevalence of 0.7% in females aged 65 or older [6]. However, overall LS prevalence is probably still underestimated, possibly due to LS underdiagnosis [4,7].

Immune system dysregulation plays a central role in the pathogenesis of LS, with both humoral and T cell-mediated mechanisms implicated [8,9]. A significant proportion of LS patients exhibit one or more autoimmune-related conditions, a family history of autoimmune diseases, or the presence of autoantibodies [10]. Common comorbidities include thyroiditis, alopecia areata, vitiligo, and pernicious anemia, while rarer associations include bowel disease, localized scleroderma/morphea, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis [11].

Pathogenically, LS is characterized by a predominant Th1 immune response, leading to the overproduction of pro-inflammatory cytokines and mediators such as IL-1, IL-15, IFN-γ, and TNF-α [12-14]. However, the positive response of extragenital LS to dupilumab suggests that IL-4/IL-13 signaling may also play a role in LS, particularly in cases characterized by pruritus and lichenification [15].

Not surprisingly, the exaggerated inflammatory response in LS is also attributed to a reduction in regulatory T cell (Treg) activity. This is further accompanied by lower levels of IL-10, without a parallel decrease in TGF-β levels [8,14]. IL-10, a critical anti-inflammatory mediator, plays a vital role in modulating immune responses, whereas TGF-β is essential to Treg differentiation and function [16,17]. The diminished Treg activity in LS has been linked to overexpression of microRNA-155 (miR-155) and reduced Foxp3+ Treg levels in LS lesions [18,19]. In a mouse model, artificially increasing miR-155 expression led to an altered Treg cell phenotype, impairing Treg suppressive function [20]. Similarly, another study showed that elevated miR-155 levels in CD4+ T cells compromised Treg-mediated suppression [21]. Collectively, these immune alterations not only sustain inflammation but also foster a persistent autoimmune environment, driving autoantibody production, which exacerbates tissue damage and perpetuates the cycle of disease progression.

However, it is not clear whether immunological changes in LS are limited to lesional sites or whether cutaneous manifestations are the epiphenomenon of systemic autoimmunity. Oyama and collaborators in 2003 demonstrated the presence of anti-ECM1 (extracellular matrix protein 1) autoantibodies in 75% of patients affected by vulvar LS [22]. Subsequent studies confirmed these findings in male genital LS [23]. The lack of such autoantibodies in other immune-mediated skin diseases (e.g., lupus, systemic sclerosis, bullous pemphigoid) suggests anti-ECM1 antibodies to be LS-specific, despite not present in 100% of patients. Nonetheless, these discoveries provided the first evidence of systemic immune alterations in LS.

While it is well recognized that inflammatory skin diseases such as psoriasis are linked to systemic immune alterations, data on lichen sclerosus are limited. As a result, no clear guidelines exist on laboratory evaluations at diagnosis, and biomarker research is virtually absent, partly because it is still uncertain whether the condition reflects systemic or purely local immune dysregulation.

In recent years, there has been a marked increase in publications exploring the neutrophil-to-lymphocyte ratio (NLR) across various branches of medicine (Figure 1) This parameter has attracted significant attention primarily because it is inexpensive and easily accessible as it can be derived directly from a routine complete blood count. The NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count (typically expressed per μL of blood). It is considered a biomarker that represents the interplay between systemic inflammation and the immune response. Numerous

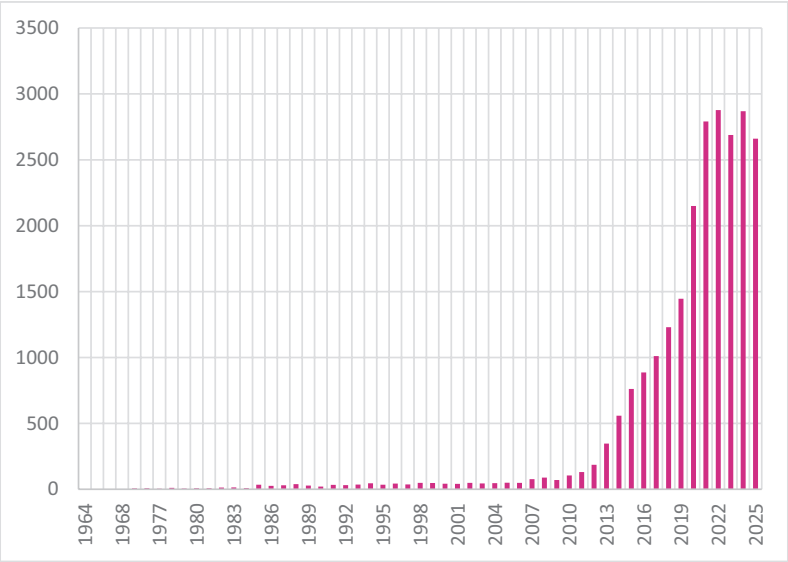

Figure 1. Timeline of published papers available on PubMed focusing on NLR (last updated October 2025).

studies have investigated its role (Figure 1), highlighting its value in both diagnostic and prognostic contexts.

Research shows that healthy adults typically have NLR values around 1.6–1.9 [24,25]. Studies also indicate that NLR rises with age, in parallel transition from robustness to pre-frailty and frailty, as well as to increased mortality risk [26,27]. Proposed thresholds are <1.19 for robust health, >2.44 for frailty transition, and >3.53 for elevated mortality risk. Prefrail individuals, including those with chronic immune-mediated diseases, tend to show intermediate values. Not surprisingly, increased NLR is also observed in several immune-mediated skin diseases, including lupus erythematosus, psoriasis, vitiligo, and atopic dermatitis [27-29].

LS is often referred to as a localized mucocutaneous disorder [12]. However, the presence of circulating autoantibodies has been described in subjects suffering from LS [30-32]. Moreover, a higher incidence of both immune-mediated and metabolic comorbidities has been documented in LS patients. However, current recommendations do not indicate any systematic screening of systemic conditions being required as a routine workup in LS patients.

Objectives

The aim of the present study was to investigate potential changes in the NLR among patients affected by lichen sclerosus, shedding light on potential systemic involvement in such condition.

Materials and Methods

We performed a single-center retrospective observational study. All the study procedures were conducted at IDI-IRCCS Istituto Dermopatico dell'Immacolata (IDI-IRCCS Rome, Italy). We retrospectively collected anonymized blood results from patients with a diagnosis of lichen sclerosus (ICD9 701.0) according to institutional CRF. Database search was limited to the last five years (Jan 2020–Jan 2025). Only cases with availability of full blood count were taken into consideration. Other collected data included age, sex, and serum inflammation markers such as CRP (C-reactive protein) and/or ESR (erythrocyte sedimentation rate). Our local lab for normal values for ESR and CRP were set as cutoffs. Published datasets were used as controls [24,25]. All the study procedures were performed in accordance with the principles of Helsinki declaration (Protocol LS-ASM661/23).

Results were stratified according to different age groups: A) young adults: aged <65; B) older adults: between 65-74 years of age; C) aged subjects: ≥75. Other variables used for patient subclassification included sex (M/F), NLR frailty ranges (≤2.44, 2.44–3.55; ≥3.55), and inflammation markers (normal Vs increased CRP/ESR).

Statistical Analysis

Measures of central tendency and dispersion (for quantitative variables) or percentages (for yes/no and qualitative variables) were used to describe univariate distribution characteristics. Measures of central tendency and percentages were accompanied by appropriate two-tailed 95% confidence intervals. For comparisons between two groups, the Student t-test was used; p-values ≤ 0.05 were considered significant. NLR values are summarized as mean ± standard deviation (SD). Between-group comparisons (lichen sclerosus vs. two healthy control datasets) were conducted using **Welch's t-test** to account for unequal variances. The magnitude of difference was quantified using **Cohen's** *d*.

Ninety-five percent confidence intervals (95% CIs) were calculated for all means. In sensitivity analyses, non-parametric comparisons (Mann-Whitney U) were also performed to confirm the robustness of results. Statistical significance was defined as $P<0.05$ (two-tailed).

Differences in mean NLR among the groups were evaluated using **Welch's analysis of variance** (**ANOVA**). When the overall test was significant, **pairwise post-hoc comparisons** were performed using **Welch's t-tests** with **Bonferroni correction** for multiple testing. Effect sizes were expressed as **Cohen's** *d*. A two-tailed *p*-value of <0.05 was considered statistically significant. Associations between age subclasses and NLR frailty group distribution were assessed using the **chi-square test of independence**. Expected frequencies were checked to confirm test validity. When significant, standardized residuals were examined to identify which cells contributed most to the association. Statistical significance was set at $P<0.05$ (two-tailed).

The relationship between NLR and ESR or between NLR and CRP was assessed using Pearson's correlation analysis. Both variables were continuous and approximately normally distributed. The Pearson correlation coefficient (r) was calculated to evaluate the strength and direction of the linear association between NLR and ESR/CRP. A 95% confidence interval (CI) was computed for the correlation coefficient, and statistical significance was tested using a two-tailed p-value. An alpha level (α) of 0.05 was used to determine statistical significance.

All statistical analyses were conducted using standard statistical software (SPSS v29 and R v4.3).

Results

In total, 631 blood samples from LS patients were included in the present study. Mean NLR was found to be 2.34 ±1.36 (Table 1). An increasing trend could be appreciated in NLR according to patient age, in line with previously published data. Mean NLR differed significantly among the three age groups (Welch's ANOVA, $P=0.02$). Post-hoc tests indicated that only group C (2.50 ±1.82) had a significantly higher NLR compared with group A (2.17 ± 1.00; $P=0.048$, Cohen's d=0.24), while differences between other groups were not significant. No statistically significant difference was detected between the age groups except for aged subjects, who showed a modestly higher NLR than did adults (mean 2.50 Vs 2.17), with a small effect size (Cohen's d≈0.24).

Based on previously published cutoffs [33], approximately one third of the LS cohort could be categorized as frail (Figure 2). Of note, only 54/631 (8.6%) samples had NLR values indicative of an extremely robust health status (<1.19).

The distribution of patients across NLR groups differed significantly by age subclass ($\chi^2(4) = 12.1$, $P=0.017$). Not surprisingly, patients <65 years showed a higher proportion in the "robust" subgroup, whereas those aged 65–75 years more frequently displayed NLR belonging to the "frail" category. The oldest subgroup (>75 years) demonstrated a modest relative increase in "extremely frail" membership. Full data on sample categorization according to NLR and age subgroups are shown in Table S1.

Further insights into the role of NLR in the setting of LS are provided by comparison with two healthy control datasets (Table 2) [24,25]. Mean NLR was higher in patients with lichen sclerosus than in healthy controls (2.17 ±1.00 vs 1.85 ±0.64; mean difference 0.32, 95% CI for patient mean: 2.03–2.31; Welch t-test $P=0.001$, Cohen's d=0.35), although the effect size was small. Results persisted when compared with an additional control cohort (mean 1.65 ±1.96; $P<0.0001$).

Lastly, we assessed possible correlations between NLR and other systemic inflammation markers (ESR, CRP) in our cohort (Figure 3). A moderate positive correlation was found between NLR and ESR (r=0.4672; 95% CI: 0.3121–0.5980) in 117 samples, indicating that higher NLR values were associated with higher ESR levels ($P<0.0001$). However, NLR explains only about 22% of the variation in ESR, suggesting other factors also influence ESR levels ($R^2=0.2183$). Likewise, data from 135 paired observations of NLR and CRP demonstrated a positive correlation between NLR and CRP (r=0.3584; 95% CI: 0.2017–0.4973; $P<0.0001$). Nonetheless, our findings only indicate a modest positive linear association between NLR and CRP, with less than 13% variability

Table 1. NLR values of enrolled patients. Data are indicated as mean ± SD. For each category, the total number (N) of analyzed samples and relative percentages (%) are also shown.

	Adult 18-65 Yo	Older Adults 65-75 Yo	Aged ≥ 75 Yo	Tot (N=631)
M	2.14 ± 1.1 (N=123; 19.5%)	2.61 ± 0.88 (N=64; 10.14%)	2.45 ± 1.65 (N=217; 34.39%)	2.38 ± 1.4 (N=404; 64.03%)
F	2.23 ± 0.8 (N=74; 11.73%)	2.08 ± 0.7 (N=94; 14.9%)	2.62 ± 2.36 (N=59; 9.35%)	2.27 ± 1.37 (N=227; 35.97%)
Total	2.17 ± 1 (N=197; 31.22%)	2.3 ± 0.82 (N=158; 25%)	2.5 ± 1.82 (N=276; 43.74%)	2.34 ±1.36 (N=631; 100%)

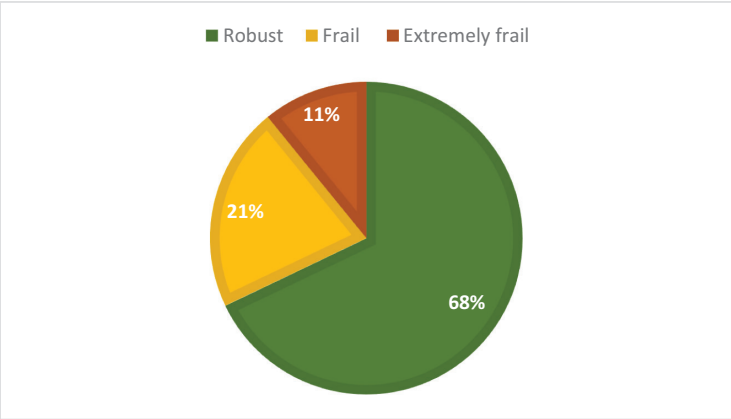

Figure 2. Pie chart graphically representing patient distribution according to previously established thresholds of NLR for frailty. Proportions are indicated as %. As shown in figure, approximately one third of the LS cohort falls within the frail category, regardless of age.

Table 2. Comparison of mean NLR values in the LS cohort and other publicly-available datasets of healthy controls (HC).

Group	n	Mean ± SD	95% CI of mean	Welch's t vs LS	p-value	Cohen's d
LS	197	2.17 ± 1.00	2.03 – 2.31	–	–	–
HC (Accardi et al.)	91	1.85 ± 0.64	1.72 – 1.98	3.27	0.0011	0.35
HC (Forget et al.)	413	1.65 ± 1.96	1.46 – 1.84	4.34	<0.0001	0.30

Note: only adult patients aged <65 yr were taken into consideration in order to avoid possible biases in NLR variations due to intrinsic aging. The mean NLR among patients with lichen sclerosus (2.17 ±1.00) was significantly higher than in both healthy control cohorts (1.85 ±0.64 and 1.65 ±1.96; P<0.01 for both comparisons). Effect sizes were small (Cohen's d≈0.3–0.35).

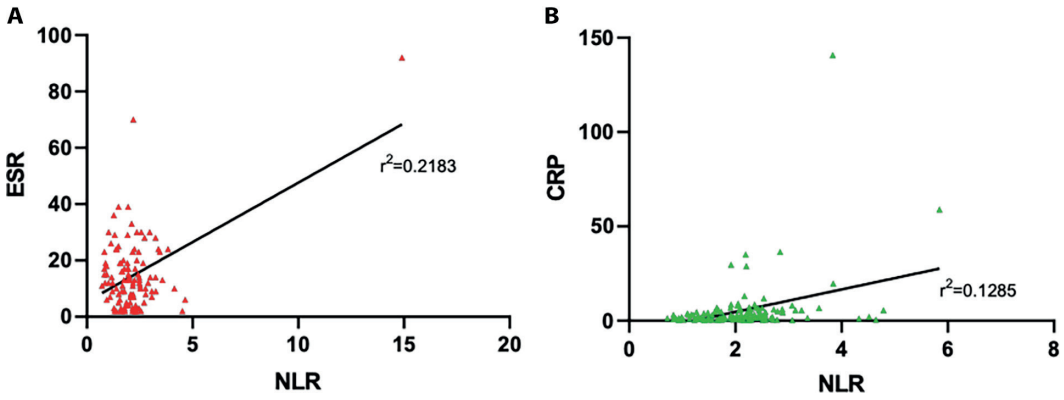

Figure 3. Correlation between NLR and inflammation markers. A positive correlation was found between NLR and both ESR (A) and CRP (B). However, NLR explains only a small proportion of the variability in ESR/CRP levels, suggesting these markers to be complementary rather than surrogates.

in CRP values possibly being explained by NLR (R^2=0.1285). Detailed results on serum inflammatory markers are shown in Table S2 and Table S3.

Discussion

Recent studies have investigated normal NLR values and their significance in healthy aging as well as NLR's predictive role in human disease. In a study by Forget et al aimed at determining the normal value of NLR in healthy subjects, 413 routine blood samples from workers involved in a healthcare prevention program (median age 38, range: 21–66 years) were analyzed. Mean NLR in this cohort was found to be 1.65 (±1.96, SD:0.78-3.53; 95% CI: 0.75–0.81; and 3.40-3.66) [24].

Another study by Accardi et al. on 249 subjects found mean NLR in adults aged <65 years was found to be 1.85 ±0.64 (range: 19.5–64.7 years; N=91; 45 M, 46 F) (25).

The current literature suggests NLR is increased in aging as well as in chronic inflammatory conditions, suggesting this parameter is highly indicative of the so called "inflammaging" process [34,35]. Interestingly, data from the InCHIANTI study helped summarize the relationship between NLR and aging, focusing on the progression from a robust state to pre-frailty, frailty, and ultimately death [26,33]. Not only were individuals with elevated NLR levels found to have a higher likelihood of transitioning from a robust condition to pre-frail or frail states, but NLR also emerged as a strong independent predictor of mortality, regardless of other inflammatory or aging-related biomarkers.

The NLR thresholds identified by the aforementioned study were <1.19 for extremely robust subjects, >2.44 for transition from pre-frail to frail, and >3.53 being indicative of an increased risk of death. The same data also showed females to be more likely to progress to frailty [33]. As such, it is plausible that pre-frail subjects, including individuals affected by chronic immune-mediated disorders, have intermediate values.

Our findings demonstrate that mean NLR values in LS patients were significantly higher than those observed in two independent healthy control datasets, although the magnitude of this difference was modest. Moreover, nearly one third of the overall cohort fell within frailty-associated NLR thresholds independently of age range, suggesting that LS may be accompanied by a low-grade systemic inflammatory state both in young and in older individuals. However, the small effect size and only moderate correlation between NLR and other systemic inflammatory markers such as ESR and CRP indicate that LS-related systemic inflammation is mild and heterogeneous.

These data add to the growing body of evidence supporting a peculiar immunological background in LS, with previous studies indicating LS to be largely driven by pro-inflammatory cytokines (such as IL-1, IL-15, IFN-γ, and TNF-α), alongside reduced IL-10 levels. The observation of elevated NLR values in our cohort is therefore in line with these mechanistic insights and mirrors findings in other immune-mediated dermatoses such as psoriasis, vitiligo, atopic dermatitis, and lupus erythematosus, in which NLR has been shown to reflect the balance between pro-inflammatory and immunoregulatory pathways [36,37]. From a clinical perspective, our results support the hypothesis that LS may extend beyond a purely cutaneous disorder, at least in a subset of patients [30,38]. As such, NLR could help stratify patients who may benefit from closer monitoring or adjunctive systemic evaluation.

Evidence from other chronic inflammatory and autoimmune conditions indicates that NLR is not only a reliable indicator of disease activity but may also decrease following effective anti-inflammatory or immunomodulatory interventions [39,40]. This raises the possibility that NLR could serve not only as a baseline indicator of systemic inflammatory burden but also as a dynamic marker to monitor treatment response or disease evolution. However, our study design did not allow an assessment of NLR changes over time or in response to treatment. Prospective longitudinal studies evaluating NLR before and after topical or systemic therapies as well as during long-term follow-up are therefore warranted to clarify whether modulation of cutaneous inflammation translates into measurable systemic immune changes.

The use of NLR, an inexpensive and routinely available parameter, could help clinicians identify LS patients at risk of systemic inflammatory involvement or frailty, either among older individuals or those with concomitant autoimmune or metabolic diseases [41]. This approach could encourage a more holistic evaluation of LS patients, potentially guiding multidisciplinary care and prompting future studies exploring therapeutic interventions aimed at systemic inflammation.

However, we also acknowledge some limitations of our study. The retrospective single-center design may restrict generalizability, and the absence of clinical data such as disease duration, activity, or treatment exposure prevented us from evaluating NLR as a prognostic marker. Moreover, no information was available on disease severity, comorbid conditions, or concurrent medications that could influence NLR values. The cross-sectional nature of our dataset limits causal inference, and the lack of cytokine or autoantibody profiling precludes a deeper understanding of the immunological pathways underlying the observed associations. Future prospective and multicenter studies incorporating clinical, serological, and molecular parameters are warranted to confirm these findings and clarify the relationship between systemic and cutaneous inflammation in LS.

Conclusion

In conclusion, our study demonstrates that patients with lichen sclerosus exhibit higher NLR values compared with healthy individuals, suggesting a mild but measurable degree of systemic immune activation. This finding supports the concept that LS may not be confined to local tissue pathology, but rather, that it forms part of a broader inflammatory and potentially autoimmune spectrum. NLR represents a simple, cost-effective tool that could be further explored as a biomarker of systemic involvement and frailty risk in LS, although longitudinal validation studies are required to establish its clinical relevance.

Acknowledgments: The authors sincerely thank the Lichen Sclerosus Patient Association (LISCLEA) for their support.

References

1. Jerkovic Gulin S, Liljeberg L, Seifert O. The Impact of Genital Lichen Sclerosus in Men and Women on Quality of Life: A Prospective Cohort Study. *Int J Womens Dermatol* 2024, *10*, e131, DOI:10.1097/JW9.0000000000000131.
2. Kirtschig G, Becker K, Günthert A, et al. Evidence-Based (S3) Guideline on (Anogenital) Lichen Sclerosus. *J Eur Acad Dermatol Venereol* 2015, *29*, e1-43, DOI:10.1111/jdv.13136.
3. Fistarol SK, Itin PH. Diagnosis and Treatment of Lichen Sclerosus: An Update. *Am J Clin Dermatol* 2013, *14*, 27–47, DOI:10.1007/s40257-012-0006-4.
4. Kirtschig G. Lichen Sclerosus-Presentation, Diagnosis and Management. *Dtsch Arztebl Int* 2016, *113*, 337–343, DOI:10.3238/arztebl.2016.0337.
5. Halonen P, Jakobsson M, Heikinheimo O, Gissler M, Pukkala E. Incidence of Lichen Sclerosus and Subsequent Causes of Death: A Nationwide Finnish Register Study. *BJOG* 2020, *127*, 814–819, DOI:10.1111/1471-0528.16175.
6. Veerabagu SA, Li Y, Grinsfelder M, Little AJ, Srivastava D, Wehner MR. Lichen Sclerosus Prevalence and Squamous Cell Carcinoma Development in Female Medicare Beneficiaries. *JAMA Dermatol* 2025, *161*, 978–980, DOI:10.1001/jamadermatol.2025.2257.
7. Paganelli A, Fabbri PV, Ghidini F, Bigi L, Lasagni C, Ceccarelli PL. Treatment and Follow-up of Genital Lichen Sclerosus in Male Children: Multidisciplinary Management at a Tertiary Care Center. *Dermatol Reports* 2023, DOI:10.4081/dr.2023.9774.
8. Gambichler T, Belz D, Terras S, Kreuter A. Humoral and Cell-Mediated Autoimmunity in Lichen Sclerosus. *Br J Dermatol* 2013, *169*, 183–184, DOI:10.1111/bjd.12220.
9. Paganelli A, Didona D, Scala E. Cytokine Networks in Lichen Sclerosus: A Roadmap for Diagnosis and Treatment? *Int J Mol Sci* 2025, *26*, 4315, DOI:10.3390/ijms26094315.
10. Corazza M, Schettini N, Zedde P, Borghi A. Vulvar Lichen Sclerosus from Pathophysiology to Therapeutic Approaches: Evidence and Prospects. *Biomedicines* 2021, *9*, 950, DOI:10.3390/biomedicines9080950.
11. Paganelli A, Contu L, Ficarelli E, Garbarino F, Motolese A. Management of Lichen Sclerosus and Related Comorbidities at a Tertiary Referral Center: Beyond Topical Steroids. *Dermatol Pract Concept* 2024, *14*, e2024262, DOI:10.5826/dpc.1404a262.
12. De Luca DA, Papara C, Vorobyev A, et al. Lichen Sclerosus: The 2023 Update. *Front Med (Lausanne)* 2023, *10*, 1106318, DOI:10.3389/fmed.2023.1106318.
13. Farrell AM, Dean D, Millard PR, Charnock FM, Wojnarowska F. Cytokine Alterations in Lichen Sclerosus: An Immunohistochemical Study. *Br J Dermatol* 2006, *155*, 931–940, DOI:10.1111/j.1365-2133.2006.07414.x.
14. Tchórzewski H, Rotsztejn H, Banasik M, Lewkowicz P, Głowacka E. The Involvement of Immunoregulatory T Cells in the Pathogenesis of Lichen Sclerosus. *Med Sci Monit* 2005, *11*, CR39-43.
15. Peterson DM, Damsky WE, Vesely MD. Treatment of Lichen Sclerosus and Hypertrophic Scars with Dupilumab. *JAAD Case Rep* 2022, *23*, 76–78, DOI:10.1016/j.jdcr.2022.03.002.
16. Moreau JM, Velegraki M, Bolyard C, Rosenblum MD, Li Z. Transforming Growth Factor-B1 in Regulatory T Cell Biology. *Sci Immunol* 2022, *7*, eabi4613, DOI:10.1126/sciimmunol.abi4613.
17. Iyer SS, Cheng G. Role of Interleukin 10 Transcriptional Regulation in Inflammation and Autoimmune Disease. *Crit Rev Immunol* 2012, *32*, 23–63, DOI:10.1615/critrevimmunol.v32.i1.30.
18. Terlou A, Santegoets LAM, van der Meijden, et al. An Autoimmune Phenotype in Vulvar Lichen Sclerosus and Lichen Planus: A Th1 Response and High Levels of microRNA-155. *J Invest Dermatol* 2012, *132*, 658–666, DOI:10.1038/jid.2011.369.
19. Soltanzadeh-Yamchi M, Shahbazi M, Aslani S, Mohammadnia-Afrouzi M. MicroRNA Signature of Regulatory T Cells in Health and Autoimmunity. *Biomed Pharmacother* 2018, *100*, 316–323, DOI:10.1016/j.biopha.2018.02.030.
20. Divekar AA, Dubey S, Gangalum PR, Singh RR. Dicer Insufficiency and microRNA-155 Overexpression in Lupus Regulatory T Cells: An Apparent Paradox in the Setting of an Inflammatory Milieu. *J Immunol* 2011, *186*, 924–930, DOI:10.4049/jimmunol.1002218.
21. Stahl HF, Fauti T, Ullrich N, et al. miR-155 Inhibition Sensitizes CD4+ Th Cells for TREG Mediated Suppression. *PLoS One* 2009, *4*, e7158, DOI:10.1371/journal.pone.0007158.
22. Oyama N, Chan I, Neill SM, et al. Autoantibodies to Extracellular Matrix Protein 1 in Lichen Sclerosus. *Lancet* 2003, *362*, 118–123, DOI:10.1016/S0140-6736(03)13863-9.
23. Edmonds EVJ, Oyama N, Chan I, Francis N, McGrath JA, Bunker CB. Extracellular Matrix Protein 1 Autoantibodies in Male Genital Lichen Sclerosus: Correspondence. *British Journal of Dermatology* 2011, *165*, 218–219, DOI:10.1111/j.1365-2133.2011.10326.x.
24. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What Is the Normal Value of the Neutrophil-to-Lymphocyte Ratio? *BMC Res Notes* 2017, *10*, 12, DOI:10.1186/s13104-016-2335-5.
25. Accardi G, Calabrò A, Caldarella R, et al. Immune-Inflammatory Response in Lifespan—What Role Does It Play in Extreme Longevity? A Sicilian Semi- and Supercentenarians Study. *Biology* 2024, *13*, 1010, DOI:10.3390/biology13121010.
26. Pellegrino R, Paganelli R, Di Iorio A, et al. Temporal Trends, Sex Differences, and Age-Related Disease Influence in Neutrophil, Lymphocyte Count and Neutrophil to Lymphocyte-Ratio: Results from InCHIANTI Follow-up Study. *Immun Ageing* 2023, *20*, 46, DOI:10.1186/s12979-023-00370-8.
27. Pellegrino R, Paganelli R, Di Iorio A, et al. Lack of Immune Resilience Negatively Affects Physical Resilience: Results From the InCHIANTI Follow-Up Study. *J Gerontol A Biol Sci Med Sci* 2024, *79*, glae076, DOI:10.1093/gerona/glae076.
28. Solak B, Dikicier BS, Cosansu NC, Erdem T. Neutrophil to Lymphocyte Ratio in Patients with Vitiligo. *Postepy Dermatol Alergol* 2017, *34*, 468–470, DOI:10.5114/ada.2017.71114.
29. Chen X, Yang X, Zhang M, Zhao Y, Guo S. Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios as Systemic Inflammatory Biomarkers for Atopic Dermatitis in US Adults: A Cross-Sectional NHANES Study Revealing Subgroup Heterogeneity. *Front Immunol* 2025, *16*, 1585451, DOI:10.3389/fimmu.2025.1585451.
30. Oyama N, Chan I, Neill et al. Autoantibodies to Extracellular Matrix Protein 1 in Lichen Sclerosus. *Lancet* 2003, *362*, 118–123, DOI:10.1016/S0140-6736(03)13863-9.
31. Goolamali SK, Barnes EW, Irvine WJ, Shuster S. Organ-Specific Antibodies in Patients with Lichen Sclerosus. *Br Med J* 1974, *4*, 78–79, DOI:10.1136/bmj.4.5936.78.
32. Howard A, Dean D, Cooper S, Kirtshig G, Wojnarowska F. Circulating Basement Membrane Zone Antibodies Are Found in Lichen Sclerosus of the Vulva. *Australas J Dermatol* 2004, *45*, 12–15, DOI:10.1111/j.1440-0960.2004.00026.x.
33. Paganelli R, Di Iorio A. The Neutrophil-to-Lymphocyte Ratio in Aging and Immunosenescence. *Explor Immunol* 2025, *5*, 1003200, DOI:10.37349/ei.2025.1003200.

34. Pellegrino R, Paganelli R, Di Iorio A, et al. Neutrophil, Lymphocyte Count, and Neutrophil to Lymphocyte Ratio Predict Multimorbidity and Mortality-Results from the Baltimore Longitudinal Study on Aging Follow-up Study. *Geroscience* 2024, *46*, 3047–3059, DOI:10.1007/s11357-023-01034-7.
35. Tap L, Corsonello A, Di Rosa M, et al. Inflammaging and Blood Pressure Profiles in Late Life: The Screening for CKD among Older People across Europe (SCOPE) Study. *J Clin Med* 2022, *11*, 7311, DOI:10.3390/jcm11247311.
36. Ye JH, Zhang Y, Naidoo K, Ye S. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Psoriasis: A Systematic Review and Meta-Analysis. *Arch Dermatol Res* 2024, *316*, 85, DOI:10.1007/s00403-024-02823-6.
37. Ma L, Zeng A, Chen B, Chen Y, Zhou R. Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Patients with Systemic Lupus Erythematosus and Their Correlation with Activity: A Meta-Analysis. *Int Immunopharmacol* 2019, *76*, 105949, DOI:10.1016/j.intimp.2019.105949.
38. Hofer MD, Meeks JJ, Mehdiratta N, Granieri MA, Cashy J, Gonzalez CM. Lichen Sclerosus in Men Is Associated with Elevated Body Mass Index, Diabetes Mellitus, Coronary Artery Disease and Smoking. *World J Urol* 2014, *32*, 105–108, DOI:10.1007/s00345-013-1090-7.
39. Zheng Z, Liu J, He T, Liu C. The Predictive Value of NLR, SII, and Complement 3 in Treatment Response for Systemic Lupus Erythematosus with Immune Thrombocytopenia. *Front Immunol* 2025, *16*, 1606510, DOI:10.3389/fimmu.2025.1606510.
40. Ali NT, Ali GS, Mohsen Ali H. NLR Outperforms PLR in SLE Diagnosis and Prognosis: An AI-Enhanced Meta-Analysis of 12 850 Patients with Ethnicity-Specific Cut-Offs. *Lupus Sci Med* 2025, *12*, e001696, DOI:10.1136/lupus-2025-001696.
41. Yoon D, Yun C, Beerman I, Beydoun MA, Launer LJ, Song M. Elevated Neutrophil-to-Lymphocyte Ratio and the Incidence of Autoimmune Diseases: Evidence from a Large Prospective Cohort Study. *Sci Rep* 2026, *16*, 667, DOI:10.1038/s41598-025-21188-y.