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RELATIONSHIP BETWEEN NEUTROPHIL-TO-LYMPHOCYTE RATIO AND SERUM ZINC LEVELS WITH THE SEVERITY OF ATOPIC DERMATITIS

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ABSTRACT
Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease with varying disease severity, commonly assessed using the Scoring Atopic Dermatitis (SCORAD) index. Based on the pathogenesis of AD, the neutrophil-to-lymphocyte ratio (NLR) and serum zinc are potential biomarkers that may reflect inflammation and skin barrier integrity. Evidence regarding their association with AD severity is still limited, particularly in Indonesia. To analyze the association between NLR and serum zinc levels with the severity of AD based on SCORAD. This analytic observational study with a cross-sectional design included 30 adult patients with AD. Diagnosis was established based on clinical history, dermatological examination, and Hanifin–Rajka criteria. Disease severity was assessed using SCORAD. NLR was obtained from routine blood tests, and serum zinc levels were measured using enzyme-linked immunosorbent assay (ELISA). Associations between variables were analyzed using Spearman correlation. There was a significant positive correlation between NLR and SCORAD ($r=0.567$; $p=0.001$) and a significant negative correlation between serum zinc levels and SCORAD ($r=-0.414$; $p=0.023$). Most subjects had mild disease (50%), followed by moderate (40%) and severe (10%). Higher NLR values and lower serum zinc levels were observed in subjects with more severe AD. NLR and serum zinc levels are associated with AD severity and have potential to be additional indicators of disease activity.

Keywords: atopic dermatitis; NLR; SCORAD; serum zinc

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INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, relapsing inflammatory skin disease associated with atopy. Disease severity is influenced by genetic, immunologic, and environmental factors and is commonly assessed using the Scoring Atopic Dermatitis (SCORAD) index (Kolb et al., 2026; Maintz et al., 2023; Nemeth et al., 2024). The prevalence of AD has increased globally over recent decades, affecting up to 20% of children and approximately 10% of adults worldwide (Silverberg & Simpson, 2023; Tian et al., 2023). In Indonesia, AD remains a common dermatological problem, with several regional studies reporting variable prevalence rates, including 11.3% in Kalimantan and 2.57% in West Sulawesi, with a predominance among children (Aurellya & Santoso, 2023; Putri et al., 2024).

One biomarker that may reflect this immunological imbalance is the neutrophil-to-lymphocyte ratio (NLR) (Hagino et al., 2023; Maharani et al., 2023). Previous studies have demonstrated that NLR is elevated in various chronic inflammatory conditions and may serve as a potential indicator of disease severity (Buonacera et al., 2022). Recent studies in patients with AD have also shown that increased NLR values are significantly associated with higher disease severity and elevated

SCORAD scores, suggesting that NLR may be a useful additional biomarker of disease activity in AD (Chen et al., 2025; Kim et al., 2023).
The role of nutritional factors in the pathogenesis of AD has also gained increasing attention (Kolb et al., 2026; Nemeth et al., 2024). Zinc is an essential micronutrient that plays a crucial role in maintaining skin barrier integrity and regulating inflammatory and immune responses. Zinc is involved in several biological mechanisms, including regulation of filaggrin expression, cytokine modulation, and inflammatory signaling pathways. Zinc deficiency can impair immune function by reducing lymphocyte activity and enhancing inflammatory responses, thereby potentially worsening the severity of AD (Mathpal et al., 2022; Zou et al., 2023).

Zinc levels can be measured using various biological samples; however, serum zinc measurement is the most practical and commonly used method for assessing zinc status (Shahzad et al., 2023; Zou et al., 2023). Several studies have demonstrated that lower serum zinc levels are associated with increased severity of AD and impaired skin barrier function (Abdallah et al., 2024; Kilic et al., 2023). Variations in findings among studies indicate that the relationship between zinc levels and AD severity remains inconclusive and requires further investigation. Therefore, this study was conducted to analyze the relationship between NLR and serum zinc levels and the severity of atopic dermatitis as measured by the SCORAD index.

METHOD

This study is an observational analytical study with a cross-sectional approach conducted from January 2025 to March 2026. The study will be conducted at the dermatology and venereology outpatient clinic of Prof. Dr. Chairuddin Panusunan Lubis Hospital, Universitas Sumatera Utara. Blood sample examinations were conducted at Integrated Laboratory of Faculty of Medicine Universitas Sumatera Utara. This study was conducted after obtaining ethical clearance from Health Research Ethics Committee of Universitas Sumatera Utara with letter number 1388/KEPK/USU/2024 issued on December 4, 2024 and letter number 73/KEPK/USU/2026 issued on January 28, 2026. This study has also obtained an implementation permit from Prof. dr. Chairuddin Panusunan Lubis Hospital, Universitas Sumatera Utara with letter number 5999/UN5.5.6.D2/PT.01.04/2024.

Sampling was conducted using a consecutive sampling technique until the minimum required sample size of 30 adult patients aged >18 years who were diagnosed with AD according to Hanifin-Rajka criteria based on anamnesis and physical examination findings and treated at the dermatology and venereology outpatient clinic of Prof. dr. Chairuddin Panusunan Lubis Hospital, Universitas Sumatera Utara from January 2025 until the required sample size was achieved and were willing to follow the research flow by signing a written informed consent form. Patients with other skin infections that can affect NLR value; with chronic inflammatory diseases which includes severe infections (Systemic Inflammatory Response Syndrome [SIRS]/sepsis), Human immunodeficiency viruses/Acquired Immunodeficiency Syndrome (HIV/AIDS), cancer, diabetes mellitus, cardiovascular disease, hepatitis and kidney disorders based on anamnesis; receiving antibiotic and corticosteroid therapy in the last 1 week or zinc supplementation for any reason in the last 1 month; pregnant and breastfeeding patients were excluded from this study.

Blood samples were taken from median cubital vein, collected in a 5 ml serum separator vacutainer tube, and then centrifuged at 3600 rpm for 10 minutes to separate the plasma. The plasma obtained was taken using aliquot method into a plastic tube that had been labeled according to patient's identity. The NLR value was obtained from blood tests results using a hematology analyzer. Serum zinc levels were examined using Enzyme-Linked Immunosorbent Assay (ELISA) method with a spectrophotometer according to standard laboratory procedures. The results will appear on the monitor screen and click print. The collected data was statistically processed using statistical software. The data were analyzed univariately to identify frequency distribution of research

subjects' characteristics. Data normality was tested using Shapiro-Wilk test. The results indicated that data were not normally distributed, therefore bivariate analysis was performed using Spearman correlation test.

RESULT

This study was conducted from January 2025 to March 2026, involving 30 patients diagnosed with AD based on clinical history and physical examination who met inclusion and exclusion criteria. Most participants were female (76.7%), indicating a higher proportion of AD cases among women in this cohort. The majority of subjects were aged 36–45 years (33.3%), suggesting that AD was more commonly observed in young to middle-aged adults. Regarding disease severity, most patients presented with mild (50%) to moderate (40%) AD, while only a small proportion (10%) had severe disease. The majority of patients had NLR values within the normal range (1.0–2.3), which reflects a relative balance between innate and adaptive immune components, while some subjects were in high category (>2.3) indicating increased systemic inflammatory activity in AD. Serum zinc levels were generally within the normal range (≥70 µg/dl) with total of 27 patients (90%), while only 3 patients (10%) with zinc deficiency (<70 µg/dl) were observed (Table 1).

Table 1.
Characteristics of subjects (n=30)

Characteristics	f	Percentage (%)
Gender		
Male	7	23.3
Female	23	76.7
Age		
18-25 years old	5	16.7
26-35 years old	5	16.7
36-45 years old	10	33.3
46-55 years old	5	16.7
56-65 years old	5	16.7
>65 years old	0	0
AD Severity		
0-25 (Mild)	15	50
26-50 (Moderate)	12	40
50-103 (Severe)	3	10
NLR Values		
<1.0	0	0
1.0-2.3	20	66.7
>2.3	10	33.3
Serum Zinc Levels		
<70 µg/dL	3	10
≥70 µg/dL	27	90

Bivariate analysis using Spearman correlation was applied due to the non-normal distribution of SCORAD scores. The results demonstrated a statistically significant positive correlation between NLR and SCORAD scores ($r = 0.567$, $p = 0.001$), indicating that higher NLR values are associated with greater disease severity. In contrast, serum zinc levels showed a significant negative correlation with SCORAD scores ($r = -0.414$, $p = 0.023$), indicating that lower zinc levels are associated with increased disease severity. These findings indicate that higher NLR values and lower serum zinc levels were associated with greater disease severity in patients with AD (table 2).

Table 2.
Spearman correlation test result

		NLR	Serum Zinc Levels
SCORAD	Correlation coefficient (r)	0,567	- 0,414
	Sig. (2-tailed) (p)	0,001	0,023
	Total samples (n)	30	30

DISCUSSION

The findings of this study showed that most patients had mild to moderate AD severity. This result is consistent with previous studies by Barbarot et al. and Kleyn et al. report, which reported that AD severity in adults is predominantly mild to moderate, whereas severe cases occur less frequently. This condition is thought to be related to variations in immune responses and differences in genetic factors that influence skin barrier integrity, therefore not all individuals with a predisposition to AD develop severe disease (Barbarot et al., 2022; Kleyn et al., 2022).

Similar findings were also reported in global epidemiological studies by Tian et al. and Silverberg et al., which showed a similar distribution pattern of severity, with most cases being mild to moderate, reflecting the heterogeneous nature of the disease and variability in host immune responses (Tian et al., 2023; Silverberg & Simpson, 2023). This pattern may be explained by the pathophysiology of AD, in which skin barrier dysfunction and immune dysregulation, particularly activation of the T-helper-2 (Th2) inflammatory pathway, contribute to disease development. Reduced filaggrin expression increases transepidermal water loss (TEWL) and facilitates allergen penetration, leading to increased production of cytokines interleukin (IL)-4, IL-13, and IL-31, which contribute to inflammation and pruritus. In most patients, these processes are not extensive enough to produce severe manifestations, whereas severe AD is more commonly associated with stronger genetic predisposition, more pronounced barrier dysfunction, and persistent environmental exposure (Patrick et al., 2021; Sroka-Tomaszewska & Trzeciak, 2021; Zou et al., 2023).

The predominance of female patients in this study may be influenced by both biological and environmental factors. Sex hormones, particularly estrogen, are known to modulate immune responses by enhancing Th2 pathway activation, which plays an important role in AD pathogenesis through increased production of IL-4, IL-5, and IL-13 (Niu et al., 2023). In addition, females are generally more frequently exposed to cosmetic products, skincare products, and household chemicals that may act as irritants or allergens on sensitive skin. These findings are consistent with previous epidemiological studies reporting a slightly higher prevalence and greater disease burden of AD among adult females compared to males (Marani et al., 2024; Tian et al., 2023).

Most subjects in this study were adults of productive age. This finding is consistent with recent studies demonstrating that AD commonly persists into adulthood or may present as adult-onset AD (Nur et al., 2025; Silverberg & Simpson, 2023). Increased exposure to environmental irritants, occupational factors, and psychological stress during adulthood may contribute to disease persistence and exacerbation. Similar findings were also reported in Indonesia by Nur et al., who observed that the majority of AD patients were adults (Nur et al., 2025).

This study demonstrated that most patients had NLR values within the normal range (1.0–2.3), although a significant positive correlation between NLR and SCORAD scores was observed. This finding suggests that even within normal range, variations in NLR values may reflect changes in systemic inflammatory response. This relates to the use of continuous data analysis, meaning that differences within normal range can potentially reflect variations inflammation degree. The positive correlation between NLR and SCORAD scores indicates that increased systemic inflammatory response are associated with greater AD severity. NLR reflects the balance between innate inflammatory responses represented by neutrophils and adaptive immune responses represented by lymphocytes. In chronic inflammatory conditions such as AD, increased production of pro-inflammatory mediators may elevate neutrophil counts, while lymphocyte counts may relatively decrease due to migration of immune cells into inflamed skin tissue. These changes increase the neutrophil-to-lymphocyte ratio and reflect the intensity of systemic inflammation associated with disease severity (Chen et al., 2025; Kim et al., 2023; Tian et al., 2023).

The findings of this study are consistent with previous studies reporting that NLR may serve as an additional inflammatory marker in AD. Djuanda et al. reported that most AD patients had normal to mildly elevated NLR values, reflecting the chronic inflammation nature of the disease (Djuanda et al., 2021). Hagino et al. also demonstrated that peripheral leukocyte ratios, including NLR, can be used as indicators of inflammation in AD and are associated with disease activity (Hagino et al., 2023). The increased NLR values (>2.3) in some patients in this study likely reflect higher inflammatory activity, which is associated with increased immune response and inflammatory mediators in skin (Chen et al., 2025). Zhang et al. also reported that patients with more severe AD had significantly higher NLR values compared to those with milder disease, therefore parameter can be used as an additional indicator to assess inflammatory activity in AD (Zhang et al., 2021). Kim et al. further explained that elevated NLR in AD is associated with activation of type 2 immune responses and increased production of inflammatory cytokines such as IL-6 and Tumor Necrosis Factor (TNF)-α, contributing to greater inflammatory cell infiltration, higher IgE levels, more severe pruritus, and wider skin involvement (Kim et al., 2023).

The characteristics of subjects in this study showed that most patients had serum zinc levels within normal range. This condition may be influenced by relatively adequate nutritional status and variations in dietary zinc intake, as serum zinc levels are highly dependent on daily nutritional consumption. A significant negative correlation between serum zinc levels and SCORAD scores was observed, although not all patients experienced clinical deficiency. Zinc deficiency in this study was more commonly found in patients with higher SCORAD scores. Similar findings were reported by Abdallah et al., who demonstrated that serum zinc levels decreased with increasing AD severity in a study involving 45 AD patients and 45 healthy controls, although not all patients developed clinical zinc deficiency (Abdallah et al., 2024). This finding is also consistent with a study by Kilic et al. in 2023, which reported that not all patients with AD experience zinc deficiency, resulting in variations in serum zinc levels among individuals (Kilic et al., 2023). In contrast, studies by Kim et al. and Park et al. reported generally lower serum zinc levels in AD patients compared to healthy controls and emphasized the role of zinc deficiency in exacerbating inflammatory skin diseases (Kim et al., 2021; Park et al., 2022).

The negative correlation between serum zinc levels and SCORAD scores indicates that lower zinc levels are associated with increased inflammatory activity and impaired skin barrier function in AD patients. Zinc plays an essential role in immune regulation and maintenance of skin barrier integrity. As an important cofactor for various enzymes, zinc contributes to keratinocyte proliferation, differentiation, and epidermal structural protein synthesis. Zinc deficiency may enhance inflammatory responses through activation of inflammatory signaling pathways, leading to increased production of pro-inflammatory cytokines such as IL-6 and TNF-α. In addition, zinc deficiency may worsen epidermal barrier dysfunction, resulting in increased TEWL and enhanced penetration of allergens and microorganisms that trigger skin inflammation (Shahzad et al., 2023; Wei et al., 2024; Zou et al., 2023). Luong et al. also demonstrated that lower serum zinc levels were associated with higher SCORAD scores, increased pruritus, and poorer quality of life among AD patients (Luong et al., 2024).

Several studies have further demonstrated the therapeutic benefits of zinc supplementation in AD. Kim et al. reported that oral zinc supplementation improved serum zinc levels, reduced Eczema Area and Severity Index (EASI) scores, decreased TEWL, and improved pruritus symptoms in adult AD patients with low zinc levels (Kim et al., 2021). Similarly, Lee et al. demonstrated that zinc supplementation as an adjunctive therapy improved skin barrier function and reduced AD severity (Lee et al., 2024). Experimental studies by Wei et al. further explained that zinc may suppress the release of C-X-C motif chemokine ligand-10 (CXCL10) from keratinocytes through activation of peroxisome proliferator-activated receptor alpha (PPAR-α) and inhibition of the signal transducer

and activator of transcription (STAT) pathway, thereby reducing T-cell recruitment and skin inflammation (Wei et al., 2024).

The findings of this study demonstrate that NLR and serum zinc levels are associated with AD severity as measured by SCORAD score. NLR showed a significant positive correlation with SCORAD scores, whereas serum zinc levels demonstrated a significant negative correlation. These findings suggest that increased systemic inflammatory responses and lower zinc levels contribute to worsening disease activity in AD. NLR may reflect the intensity of systemic inflammation associated with disease severity, while zinc plays an important role in immune modulation and maintenance of skin barrier function, even when serum levels remain within the normal range. NLR and serum zinc levels can be used as simple, accessible, and useful additional parameters for evaluating inflammatory activity and disease severity in AD alongside the SCORAD index.

CONCLUSION

NLR values and serum zinc levels showed a significant association with AD severity based on SCORAD score and have the potential to serve as additional indicators of disease activity. NLR values tended to be higher and serum zinc levels lower in patients with more severe AD severity.

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