



# Evaluation of the systemic immune-inflammatory index and its relationship with disease severity in patients with alopecia areata

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## Abstract

**Aim:** Systemic Immune-Inflammatory Index (SII) is an index that assesses the systemic inflammatory response and has been increasingly used in recent times. The objective of this study is to evaluate the role of systemic inflammation in alopecia areata (AA) by examining the SII and to investigate its relationship with disease severity.

**Materials and Methods:** This is a retrospective study in which SALT (Severity of Alopecia Tool) scores, SII values, and neutrophil-to-lymphocyte ratios (NLR) of patients diagnosed with AA and followed up at our clinic between January 2023 and March 2024 were evaluated.

**Results:** The study included a total of 153 patients with AA (99 males and 54 females) and 91 healthy controls. NLR in the patient group ( $2.24 \pm 0.64$ ) was significantly higher than in the control group ( $2.04 \pm 0.54$ ) ( $p = 0.013$ ). SII in the patient group ( $593.38 \pm 214.25$ ) was also significantly higher than in the control group ( $497.26 \pm 154.72$ ) ( $p = 0.001$ ). There was a significant positive correlation between the SALT score and the NLR ( $p = 0.001$ ). Similarly, there was a significant positive correlation between the SALT score and the SII ( $p = 0.001$ ). The SII for the group with alopecia universalis was significantly higher than for other patient groups ( $p = 0.001$ ). There was a positive, statistically significant relationship between disease duration and both the NLR and SII ( $p = 0.001$  and  $p = 0.001$ ).

**Conclusion:** We observed elevated inflammatory parameters suggesting systemic inflammation in patients with AA. The NLR and SII were both higher in the patient group compared to the control group. Additionally, as the SALT score increased, so did the levels of NLR and SII. We concluded that in addition to its diagnostic utility in AA, SII also serves as a biomarker that correlates with disease severity.



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## Introduction

Alopecia areata (AA) is a condition characterized by inflammation, resulting in hair loss without leaving permanent scars on the scalp [1]. A meta-analysis has reported that it affects about 2% of the global population [2]. The clinical presentation of AA varies significantly, ranging from small, well-defined patches of hair loss to complete loss of hair from the scalp and body. Alopecia universalis (AU) is the most severe form of the disease, marked by the loss of all body hair [1]. Although the exact cause of AA is not fully understood, it is believed to stem from the loss of immune privilege in hair follicles, autoimmune-induced destruction of the follicles, and an

increase in inflammatory pathways [1,3]. The anagen hair follicle is considered as an area with immune privilege, but this immune-protective environment is compromised in alopecia areata (AA). Inflammatory immune cells contribute to the dystrophic hair follicle cycle, leading to enter the telogen phase prematurely. According to the autoimmune hypothesis, autoreactive T cells infiltrate the hair follicle while preserving the stem cell compartment. There is a correlation between the density of CD8<sup>+</sup> T cells and the severity of the disease. Autoantigens derived from the hair follicle might also play a role [3]. Various genetic and environmental factors play a role in the development and progression of alopecia areata (AA) [1]. In 2004, Olsen et al. published a tool for assessing the severity of AA based on the percentage of hair loss in the scalp regions at the top, back, and both sides of the head. These per-

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centages are then multiplied by the weighting factor for the scalp area they represent, and the resulting values for each region are summed to obtain a total score. This tool is called the Severity of Alopecia Tool (SALT) score [4]. According to this tool, a SALT score of 0 indicates no hair loss, while a score of 100 signifies complete hair loss [4]. The Systemic Immune-Inflammatory Index (SII) was first described by Hu et al. as an index for assessing systemic inflammatory response [5]. They explored the prognostic value of this index in hepatocellular carcinoma (HCC). The authors concluded that SII is a strong prognostic indicator of poor outcomes in patients with HCC and is a promising tool for guiding HCC treatment strategies [5]. SII is calculated using a formula that considers specific immune system markers in the bloodstream. The calculation formula is as follows:  $\text{platelets} \times \text{neutrophils} \div \text{lymphocytes}$  [5]. SII is frequently used to predict mortality in cancer patients, as it has been shown that elevated SII values are linked to a higher likelihood of death [6]. This may be due to an imbalance between factors that promote tumor growth and those that fight tumors in the body. When this imbalance happens, the number of neutrophils and platelets tends to increase, while lymphocytes decrease, leading to a higher SII [7]. In recent years, the range of applications for the SII has been widening, with an increasing number of studies suggesting that it can be used to predict the severity of certain diseases and track the outcomes of treatment [7,8].

The aim of this study is to assess the role of systemic inflammation in AA by evaluating SII and to explore the correlation between SII and the severity of the disease.

## Materials and Methods

Our study is a retrospective analysis evaluating the demographic data, SALT scores, and complete blood counts of patients diagnosed with AA and followed up at our clinic from January 2023 to March 2024. Prior to the study, ethical approval was obtained from Ankara Bilkent City Hospital with approval number TABED-2-24-127, dated 17.04.2024.

In patients with AA, the expected average SII is 590 (SD = 210), while in the control group, the expected average SII is 512 (SD = 200). To achieve an effect size of 0.38, a total of 174 participants (87 patients and 87 controls) is required, with a power of 80% and a Type I error rate of 5%. The sample size calculation was performed using G\*Power.

All AA patients over 18 years old who had no other systemic diseases, were not receiving systemic therapy, had no active infections, and had complete data were included in our study. The Neutrophil-to-Lymphocyte Ratio (NLR) represents the ratio of neutrophils to lymphocytes. SII was calculated using the following formula:  $\text{SII} = \text{Neutrophil count} \times \text{Platelet count} \div \text{Lymphocyte count}$ .

The data obtained were compared with those of a healthy control group consisting of individuals who visited our clinic for general check-ups and had complete blood counts available in the hospital system within the same time-frame. The first 100 healthy individuals over 18 years old who met these criteria and were followed up at our clinic

from January 2023 to March 2024 were included as the control group.

## Statistical analysis

To analyze the findings from this study, statistical analyses were conducted using IBM SPSS Statistics 22 software. The Kolmogorov-Smirnov test was used to evaluate the normality of distribution for the parameters. When evaluating the study data, descriptive statistical methods (mean, standard deviation, frequency) were used alongside inferential statistics. The Student's t-test was applied to compare quantitative data between two groups. Pearson correlation analysis was used to examine relationships between parameters that followed a normal distribution. The Chi-squared test was employed to compare categorical parameters. The optimal cut-off points were determined based on the Receiver Operating Characteristic (ROC) curve analysis. Statistical significance was set at a level of  $p < 0.05$ .

## Results

A total of 153 patients with alopecia areata (99 males and 54 females) and 91 healthy controls (59 males and 32 females) were included in the study. The mean age in the patient group was  $31.08 \pm 8.88$  years (range: 18-57), while the mean age in the control group was  $29.76 \pm 8.74$  years (range: 18-55).

In the patient group, the duration of the disease ranged from 0.01 months to 312 months, with a mean duration of  $37.40 \pm 72.62$  months and a median of 5 months. The SALT score ranged from 1 to 100, with a mean of  $24.33 \pm 35.06$  and a median of 6. In the patient group, 31 cases (20.3%) were categorized as alopecia universalis, the most severe form of the disease. Evaluations regarding demographic and clinical characteristics are shown in Table 1.

The differences in mean age and gender distribution between the groups were not statistically significant ( $p > 0.05$ ).

The mean platelet count in the patient group was significantly higher than that in the control group ( $p = 0.003$ ).

**Table 1.** Evaluations regarding patient and control groups.

	Patient Mean±SD	Control Mean±SD	P
Age (year)	31.08±8.88	29.76±8.74	0.260
Sex N (%)			
Male	99 (64.7%)	59 (64.8%)	+ 0.984
Female	54 (35.3%)	32 (35.2%)	
Platelet Count ( $10^3$ )	263.56±55.55	244.25±43.22	0.003*
Neutrophil Count ( $10^3$ )	4.50±1.10	4.15±0.90	0.010*
Lymphocyte Count ( $10^3$ )	2.12±0.61	2.11±0.52	0.895
NLR	2.24±0.64	2.04±0.54	0.013*
SII	593.38±214.25	497.26±154.72	0.001*

Student t test. +Chi-square test \* $p < 0.05$ . SD: standart deviation NLR: Neutrophil/lymphocyte ratio SII: Systemic immune-inflammation index.

**Table 2.** Correlation between the SALT score and inflammatory parameters (NLR, SII).

	SALT score	
	R	p
NLR	0.410	0.001*
SII	0.393	0.001*

Pearson correlation analysis \*p<0.05. NLR: Neutrophil/lymphocyte ratio; SII: Systemic immune-inflammation index.

**Table 3.** Correlation between Disease Duration and Inflammatory Parameters (NLR, SII).

	Disease Duration (months)	
	R	p
NLR	0.331	0.001*
SII	0.368	0.001*

Pearson correlation analysis \*p<0.05. NLR: Neutrophil/lymphocyte ratio; SII: Systemic immune-inflammation index.

**Table 4.** Comparison of SII and NLR Values Between the Alopecia Universalis Group and the Non-Alopecia Universalis Group.

	Alopecia Universalis		p
	Present Mean±SD	Absent Mean±SD	
NLR	2.75±0.80	2.12±0.52	0.001*
SII	760.12±238	551.02±186.23	0.001*

Student's t test \*p<0.05. SD: standart deviation; NLR: Neutrophil/lymphocyte ratio; SII: Systemic immune-inflammation index.

The mean neutrophil count in the patient group was significantly higher than that in the control group (p=0.010). There was no statistically significant difference in lymphocyte levels between the groups (p>0.05).

The Neutrophil-to-Lymphocyte Ratio (NLR) in the patient group (2.24±0.64) was significantly higher than that in the control group (2.04±0.54) (p=0.013) (Table 1).

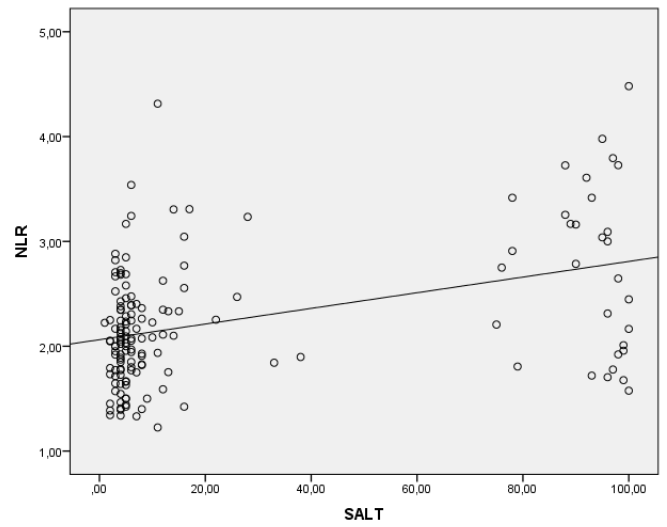
The level of the Systemic Immune-Inflammatory Index (SII) in the patient group (593.38±214.25) was significantly higher than that in the control group (497.26±154.72) (p=0.001) (Table 1).

*Correlation between SALT score and inflammatory parameters (NLR, SII)*

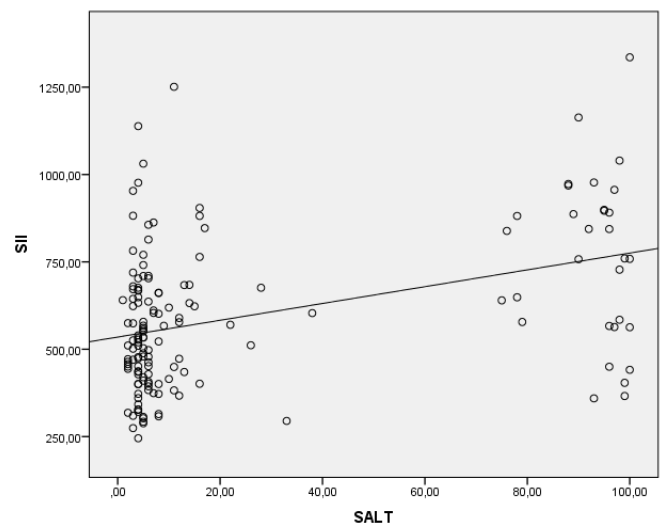
There was a statistically significant positive correlation of moderate strength (41%) between the SALT score and NLR (p=0.001). A statistically significant positive correlation of moderate strength (39.3%) was observed between the SALT score and SII (p=0.001) (Table 2, Figures 1,2).

*Correlation between disease duration and inflammatory parameters (NLR, SII)*

A statistically significant positive correlation of moderate strength (33.1%) was found between the duration of the



**Figure 1.** Relationship between the SALT Score and NLR There was a positive, moderate (41%), and statistically significant relationship between the SALT Score and NLR (p:0.001).

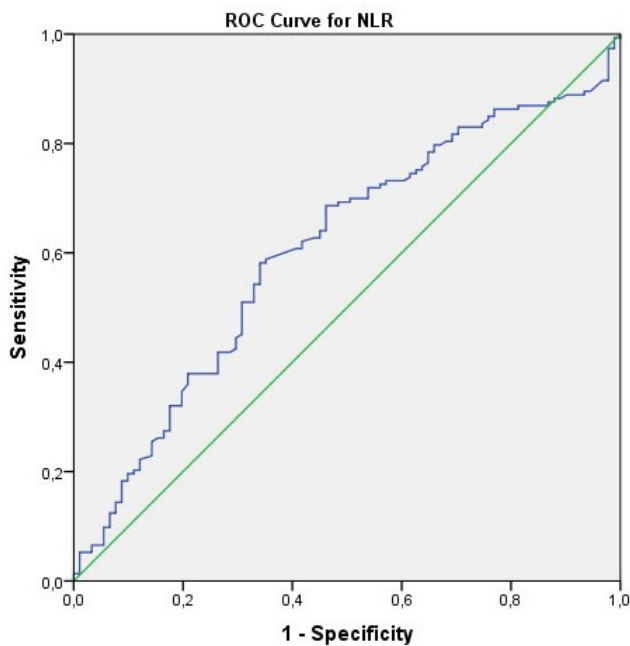


**Figure 2.** Relationship between the SALT Score and SII There was a positive, moderate (39.3%), and statistically significant relationship between the SALT Score and SII (p:0.001).

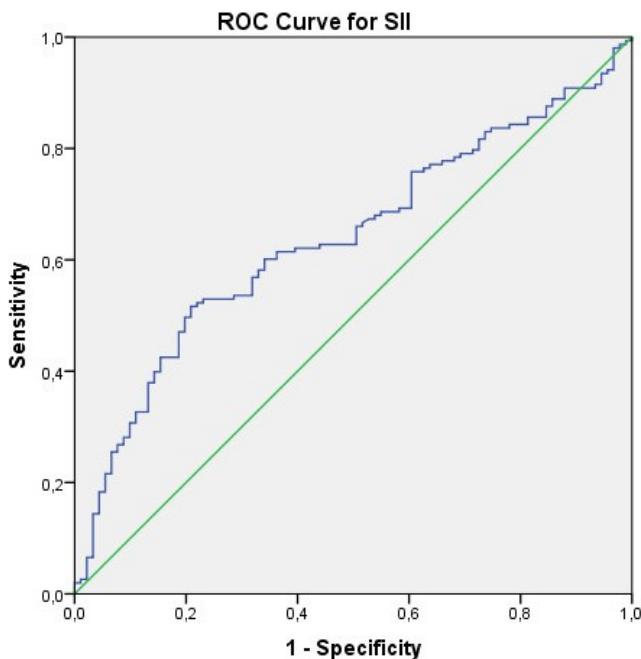
disease and the NLR (p=0.001). A statistically significant positive correlation of moderate strength (36.8%) was observed between the duration of the disease and the SII (p=0.001) (Table 3).

*Comparison of SII and NLR values between the alopecia universalis group and the non-alopecia universalis group*

The group with alopecia universalis had a significantly higher average of NLR (p=0.001). The group with alopecia universalis also had a significantly higher average of SII (p=0.001) (Table 4).



**Figure 3.** ROC Curve for NLR in alopecia areata diagnosis.



**Figure 4.** ROC Curve for SII in alopecia areata diagnosis.

#### *The ROC curve for NLR in disease diagnosis*

A ROC curve was plotted for the NLR in the diagnosis of the disease. The area under the curve (AUC) was 0.607 (95% CI: 0.543-0.679), with a standard error of 0.037. This was found to be significantly higher than 0.5 ( $p=0.005$ ), indicating that the NLR has diagnostic value in identifying the disease.

The cut-off point for the NLR in diagnosing AA was determined to be  $>2$ . At this cut-off point, the sensitivity

was 58.8% and the specificity was 64.8%. This suggests that an NLR above 2 could serve as an indicator for diagnosing the condition, albeit with moderate sensitivity and specificity (Figure 3).

#### *The ROC curve for SII in disease diagnosis*

A ROC curve was plotted for the SII in disease diagnosis. The AUC was 0.638 (95% CI: 0.568-0.707), with a standard error of 0.035. This was significantly higher than 0.5 ( $p=0.001$ ), indicating the ROC curve's diagnostic utility for SII.

The cut-off point for SII in disease diagnosis was determined to be  $>560$ . At this cut-off, the sensitivity was 51.6% and the specificity was 79.1%. This suggests that an SII above 560 could be used as an indicator for diagnosis, with moderate sensitivity but relatively high specificity (Figure 4).

## Discussion

SII, derived from the counts of lymphocytes, neutrophils, and platelets in peripheral blood, is considered as a reliable indicator of inflammation levels and immune system activity [9]. SII has been previously investigated in various dermatological conditions [8-18]. One of the dermatological diseases in which SII is most frequently assessed is psoriasis [8-13]. Psoriasis is known to share a common chronic inflammatory origin with other conditions like metabolic syndrome and cardiovascular disease [8,9]. In a national study conducted by Zhao et al., involving 17,913 participants, a significant and positive correlation was found between the SII and psoriasis, as determined by multivariable linear regression analysis [9]. Increased levels of various inflammation- and immunity-based indices such as the NLR, Platelet-to-Lymphocyte Ratio (PLR), and Monocyte-to-Lymphocyte Ratio (MLR) were observed and were associated with Psoriasis Area and Severity Index (PASI) scores, indicating disease severity in individuals with psoriasis [9]. In a study by Yorulmaz et al., it was shown that the SII was significantly higher in patients with psoriasis compared to the control group, and that patients with moderate-to-severe psoriasis had higher SII values than those with mild psoriasis [8]. In a study conducted by Dinçer Rota et al., the relationship between SII and disease activity in psoriasis was evaluated. The study included 71 patients with psoriasis and 70 healthy controls. According to PASI scores, two subgroups were created: (1) the group with PASI  $< 4.5$  ( $n = 36$ ) and (2) the group with PASI  $\geq 4.5$  ( $n = 35$ ). Clinical features and SII values were examined to identify differences between these two subgroups. Additionally, SII values were compared based on whether there was involvement of the scalp, joints, nails, or genital area. SII values were found to be significantly higher in patients with psoriasis. Additionally, the subgroup with a PASI score of 4.5 or higher, along with patients who had nail and genital involvement, also showed statistically significantly higher SII values [10]. Tamer et al. evaluated the impact of biological agent therapy on the SII and the Systemic Inflammation Response Index (SIRI) in patients with psoriasis. They calculated these indices in 220 psoriasis patients before and 3 months after biological agent therapy. It was found that Both

SII and SIRI experienced substantial reductions following treatment with adalimumab, infliximab, ixekizumab, secukinumab, ustekinumab, or risankizumab. Additionally, the study suggested that SII might be related to comorbidities associated with systemic inflammation in psoriasis, such as psoriatic arthritis, hypertension, hepatic steatosis, and coronary artery disease. Based on these findings, they concluded that SII and SIRI could serve as useful indicators for treatment selection and monitoring in psoriasis patients undergoing therapy with biological agents [11]. The reduction of the SII following biological therapies, particularly TNF-alpha blockers, and its potential use in monitoring these treatments has been supported by another study [12]. Recently, Sugimoto and colleagues demonstrated a positive correlation between SII and PASI scores, finding that patients with higher SII scores were less likely to continue treatment with conventional systemic drugs [13]. These studies have further clarified the role of SII in psoriasis. SII may represent a valuable biomarker for assessing disease activity, treatment response, and the risk of developing comorbidities in psoriasis. This suggests that SII could guide more personalized and effective treatment approaches for patients with psoriasis. In Utlu's study, the relationship between hidradenitis suppurativa (HS) and complete blood count (CBC) parameters, as well as new inflammatory indicators like the SII and the SIRI, was investigated. It was reported that SII and SIRI are more reliable biomarkers for HS patients compared to other inflammation parameters, suggesting that they could be used as new indicators for assessing treatment response and monitoring in HS [14].

In a study by Hayran et al., SII was evaluated in HS patients, and it was found to be statistically higher in HS patients compared to healthy controls. A statistically significant positive correlation was also noted between SII and disease severity in HS patients [15]. These studies suggest that SII, similar to its role in psoriasis, may indicate systemic inflammation in HS and could be used as a biomarker for monitoring disease severity and treatment response, holding potential as a valuable tool for disease management.

The SII has also been evaluated in other dermatological diseases [16-18]. In their study, Karaosmanoğlu et al. examined complete blood count parameters and SII to explore the role of systemic inflammation in rosacea. They found that monocyte and platelet counts, the SII, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were significantly higher in rosacea patients compared to the control group. However, there was no significant correlation between disease severity and ESR, CRP, or the SII index. The results of this study suggest that, in addition to inflammation occurring at the skin level, there may be a broader inflammatory response in the blood of rosacea patients [16]. In a study by Tanaçan et al., the correlation of the SII, NLR, derived Neutrophil-to-Lymphocyte Ratio (dNLR), and Platelet-to-Lymphocyte Ratio (PLR) with disease severity in patients with recurrent aphthous stomatitis (RAS) was evaluated, and it was reported that higher values of these inflammatory parameters were correlated with disease severity [17]. In another study by Tanaçan et al. aimed at assessing the ef-

fectiveness of SII in determining Behçet's disease activity, higher counts of white blood cells, platelets, and neutrophils, along with greater red cell distribution width, elevated ESR, CRP, and ferritin levels, and increased SII were observed in the active disease group. They suggested that SII could be used as an additional indicator for evaluating Behçet's disease status [18].

While scalp lesions in patients with moderate to severe AA exhibit high levels of immune activation, there is limited knowledge about the broader systemic immune changes that may be occurring in these patients [19]. There are few studies in the literature investigating systemic inflammation in AA [19,20]. In our study, both the NLR and the SII in the patient group were significantly higher than those in the control group. Furthermore, there was a significant positive correlation between the SALT score and both the NLR and the SII. A significant positive correlation was also observed between disease duration and both NLR and SII. When we considered the 31 patients with the most severe form of the disease, alopecia universalis, as a separate subgroup, it was observed that their NLR and SII values were statistically significantly higher compared to the other patients in the study group.

In a recent study by Glickman et al., broad proteomic panels from OLINK were used to comprehensively assess immune and cardiovascular biomarkers in serum samples from patients with moderate-to-severe AA [19]. The study compared these findings to those from healthy control individuals and patients with moderate-to-severe atopic dermatitis and psoriasis. The results showed that AA is associated with more pronounced abnormalities than even other inflammatory conditions such as atopic dermatitis and psoriasis [19]. Several proteins that were significantly elevated in alopecia areata (AA) are known prognostic indicators or potential therapeutic targets related to atherosclerosis and cardiovascular risk. These proteins include E-selectin (SELE), matrix metalloproteinases MMP9 and MMP10, lectin-like oxidized LDL receptor 1 (LOX-1 or OLR1), myeloperoxidase (MPO), fatty acid-binding protein 4 (FABP4), P-selectin (SELP), oncostatin-M (OSM), proteinase-3 (PRTN3), peptidoglycan recognition protein 1 (PGLYRP1), and caspase-3 (CASP3) [19]. This observation confirms that AA, like psoriasis, is associated with systemic inflammation [19]. Among the 35 AA patients included in the study, 11 were part of the alopecia totalis/alopecia universalis subgroup. This subgroup exhibited the highest systemic inflammation compared to other AA patients, as well as those with atopic dermatitis/psoriasis, and healthy control individuals [19]. These results align with the findings from our current study, which demonstrate that hematological markers associated with systemic inflammation are elevated in AA and correlate with disease severity.

In a study by İslamoğlu et al., hematological and inflammatory parameters were investigated in AA, but the findings did not align with those from our study [20]. The study included 105 AA patients and 108 healthy controls, and retrospectively examined the red cell distribution width (RDW), mean platelet volume (MPV), plateletcrit (PCT), NLR, Platelet-to-Lymphocyte Ratio (PLR), ESR, and CRP. No statistically significant differences were found

between AA patients and the healthy control group in terms of RDW, MPV, PCT, NLR, and PLR levels, while only CRP values were significantly higher in the AA group [20].

The most significant limitations of our study are the relatively small sample size and its single-center nature. Additionally, due to its retrospective design, potential biases and data gaps cannot be entirely ruled out.

## Conclusion

Our study observed elevated inflammatory parameters indicating the presence of systemic inflammation in AA. The NLR and the SII were higher in the patient group compared to the control group.

Additionally, as the SALT score, an indicator of disease severity, increased, there was a corresponding rise in the levels of NLR and SII. The group with alopecia universalis exhibited the highest levels of these inflammatory parameters. As the disease duration increased, the levels of NLR and SII also rose.

We suggest further studies to investigate how these parameters change with AA treatment in the future. Our findings support the use of these parameters as biomarkers for disease activity and treatment response, similar to their use in psoriasis, potentially aiding in the design of personalized treatment regimens in AA.

## Conflict of interest

The authors declare no conflict of interest regarding this article.

## Ethical approval

The study protocol was approved by Ankara Bilkent City Hospital Ethics Committee, decision number: TABED-224-127, date: 17.04.2024.

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