Dermatology Practical & Conceptual

Evaluation of Serum Inflammatory Markers and Their Relationship to Treatment Response in Alopecia Areata Patients

Icim Komurcugil[1], Nermin Karaosmanoglu[1]

1 Health Sciences University, Ankara Training and Research Hospital, Ankara, Turkey

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Corresponding Author: Icim Komurcugil, Hacettepe, Hamamönü, Talatpaşa Boulevard, No:128, Altındağ/Ankara.
Telephone: +90 552 454 23 31 E-mail: icim.komurcugil@yahoo.com

ABSTRACT

Introduction: Alopecia areata is a type of non-scarring alopecia which is thought to be associated with T-cell mediated immune response.

Objective: This study aimed to compare the levels of serum inflammatory markers before and after treatment in patients with alopecia areata. The study explored the utility of the systemic immune-inflammation index (SII) in assessing the severity and treatment response in alopecia areata patients.

Methods: The study included 60 alopecia areata patients and 40 control patients diagnosed with tinea unguium, aged between 18 and 65 years. Sociodemographic characteristics such as age, sex, and medical history were recorded for both groups. For alopecia areata patients, serum inflammatory markers were recorded before and at the third month of treatment. Serum inflammatory markers for the control group were also recorded. Furthermore, the Severity of Alopecia Tool (SALT) score was calculated for alopecia areata patients before and at the third month of treatment.

Results: The alopecia areata group had a significantly higher neutrophil-lymphocyte ratio, mean platelet volume, and SII values compared to the control group, while high-density lipoprotein (HDL) values were significantly lower. Serum inflammatory markers, assessed at the third month of treatment in the alopecia areata group, were lower, and HDL values were significantly higher compared to pre-treatment levels. A statistically significant correlation was observed between disease severity and the SII.

Conclusion: The SII is a cost-effective marker that can be utilized in assessing the severity of alopecia areata and treatment response.

Introduction

Alopecia areata (AA) is a chronic autoimmune disease that results in non-scarring hair loss. The scalp is the most commonly affected area, but eyebrows, eyelashes, and body hair can also be involved [1]. AA is classified based on disease severity and clinical presentation. Patchy AA is characterized by well-defined, oval, or circular alopecic patches, occasionally extending to total scalp hair loss (alopecia totalis) or complete body hair loss (alopecia universalis). Other atypical variants include ophiasis, characterized by occipital and retroauricular alopecia, inverse ophiasis which is marked by hair loss in vertex as well as diffuse, reticular, and perinevoid forms [2]. The estimated prevalence is 0.1%, with a lifelong risk of 2%. AA can be associated with autoimmune disorders such as vitiligo, diabetes mellitus, pernicious anemia, and hypothyroidism [1]. The exact etiology of AA is not fully understood; it is thought to be associated with genetic predisposition and T-cell-mediated autoimmunity [2]. CD4+ and CD8+ T-cells, along with natural killer cells and dendritic cells, form an infiltrate around the anagen hair bulb, producing interferon-gamma, tumor necrosis factor-α, and interleukin (IL) 12/23. Consequently, the hair growth cycle is disrupted, resulting in premature hair loss and alopecia.

The systemic immune-inflammation index (SII: platelet count × neutrophil-lymphocyte ratio) is a novel marker, developed in 2014 by Hu and colleagues to evaluate hepatocellular cancer severity. SII has been used to assess the severity of various inflammatory conditions, including acne vulgaris, rosacea, psoriasis, psoriatic arthritis, and Behçet disease [3-5]. Moreover, mean platelet volume (MPV), monocyte-HDL ratio (MHR), monocyte-lymphocyte ratio (MLR), and neutrophil-lymphocyte ratio (NLR) are hematologic markers that have been shown to increase in inflammatory diseases like psoriasis and acne vulgaris, serving as indicators of disease severity [5,6]. The objective of this study was to compare the levels of inflammatory markers before and at the third month of treatment of AA patients. This study also aimed to investigate the utility of SII in assessing disease severity and treatment response in AA patients.

Methods

The institutional ethics committee of Ankara Training and Research Hospital approved the study (23-1187). The study included 60 AA patients, aged 18–65, who presented to the Dermatology Outpatient Clinic of the Ankara Training and Research Hospital between November 2022 and April 2023. Additionally, 40 control patients, matched for age and sex, were included. Exclusion criteria included patients with systemic diseases, active infections, malignancies, hematological disorders, pregnancy, and breastfeeding. In the AA group, serum inflammatory markers were recorded before and at the third month of intralesional triamcinolone acetonide treatment. The Severity of Alopecia Tool (SALT) score was calculated for AA patients before and at the third month of treatment. All data were analyzed by using SPSS (Statistical Package for Social Sciences) for Windows 22.0. Students t-test and Mann-Whitney u-test were used to compare the data of the two groups. Spearman rho correlation analysis was used to examine relationships. Significance was evaluated at the $P < 0.05$ level. All participants were informed about the study, and written informed consent was obtained. The study was performed following the latest version of the Helsinki Declaration and Guidelines for Good Clinical Practice.

Results

This study included 100 patients, consisting of 60 AA patients (58.3% male, 41.7% female) and 40 patients for the control group (45% male, 55% female). The average ages of the AA group and control group were 28.93 and 40.85, respectively. The mean age of the AA group was significantly lower than that of the control group (P : 0.001; $P < 0.05$). There was no statistically significant difference in terms of sex distribution between the two groups ($P > 0.05$). Among the 60 AA patients, six individuals (10%) had coexisting diseases and were taking medications (Table 1).

The pre-treatment parameters of the AA patient group were compared with the control group. Neutrophil-lymphocyte ratio (NLR) in the patient group was 2.09, while it was 1.73 in the control group. The MPV for the patient group was 10.31, while in the control group, it was 9.65. The SII for the patient group was 562, whereas it was 455 in the control group. The NLR, MPV, and SII in the patient group were statistically significantly higher than those in the control group ($P < 0.05$). The HDL for the patient and control groups were 50.4 and 55.88, respectively. The HDL in the patient group was statistically significantly lower than that in the control group (P: 0.015; $P < 0.05$). There were no statistically significant differences between the two groups in terms of other hematologic parameters ($P > 0.05$) (Table 1).

Parameters before and at the third month of treatment in the AA group were compared. Before treatment, the average erythrocyte sedimentation rate (ESR) was 7.27, which decreased to 4.63 in the third month of treatment. The average C-reactive protein (CRP) before treatment was 4.31, which decreased to 1.6 in the third month of treatment. The decline observed in ESR and CRP values in the third month of treatment was found to be statistically significant (P: 0.001; $P < 0.05$). The average monocyte counts before and at the third month of treatment were 0.58 and 0.52, respectively. The MHR was 0.013 before treatment and decreased to 0.010 in the third month of treatment. The decrease observed

Table 1. Coexisting Diseases, Pre-Treatment Blood Values in Alopecia Areata (AA) Group and Control Group, Blood Values Before and at the Third Month of Treatment in AA Group

Coexisting Diseases and Medications Used in AA Patient Group		
Coexisting Disease	**Medication Used**	**N**
Hypercholesterolemia	Atorvastatin	1
Pyelonephritis	Nitrofurantoin	1
Hypothyroidism	Levothyroxine, fluoxetine	1
Diabetes, Hypertension	Metformin, metoprolol	1
Hashimoto thyroiditis	Levothyroxine	1
Iron deficiency anemia	Iron (III) hydroxide	1

Assessment of Pre-treatment Blood Values in AA Patient Group and Control Group					
	Pre-treatment Patient		**Control**		
	Min-Max	**Mean±SD (median)**	**Min-Max**	**Mean±SD (median)**	**P**
ESR (mm/h)	2-40	7.27±8.04 (4)	0.2-18	4.36±2.88 (4.5)	0.343
CRP (mg/L)	0.1-87	4.31±12.41 (1.3)	0.1-5	1.6±1.32 (1.3)	0.624
Monocyte (10^9/L)	0.29-1.48	0.58±0.22 (0.5)	0.32-0.9	0.58±0.14 (0.6)	0.398
Neutrophil (10^9/L)	1.41-9.31	4.26±1.48 (4)	2.66-6.69	3.86±0.84 (3.8)	0.147
Lymphocyte (10^9/L)	1.09-4.5	2.18±0.76 (2.1)	1.14-4.37	2.45±0.82 (2.3)	0.087
MLR	0.11-0.65	0.28±0.1 (0.3)	0.12-0.53	0.26±0.09 (0.2)	0.316
NLR	0.85-4.85	2.09±0.84 (1.9)	0.83-3.14	1.73±0.61 (1.6)	0.035*
HDL (mg/dl)	26-80	50.4±11.74 (50.5)	35-83	55.88±9.41 (55.5)	+0.015*
MHR	0-0.04	0.01±0.01 (0)	0-0.02	0.01±0 (0)	0.253
MPV (fl)	8.8-12.9	10.31±0.84 (10.2)	8.1-11.2	9.65±0.66 (9.7)	+0.001*
Platelet (10^9/L)	162-465	269.62±59.18 (262.5)	158-358	265.7±44.75 (265.5)	+0.723
SII	187-1644	562.43±264.27 (480.5)	204.86-943.4	454.77±164.62 (427.7)	0.035*

Assessment of blood values before and at the Third month of treatment in AA Patient Group					
	Before Treatment		**Month 3 of Treatment**		
AA Patient Group	**Min-Max**	**Mean±SD (median)**	**Min-Max**	**Mean±SD (median)**	
ESR (mm/h)	2-40	7.27±8.04 (4)	1-34	4.63±5.07 (3)	0.001*
CRP (mg/L)	0.1-87	4.31±12.41 (1.3)	0.1-11	1.53±2.28 (0.5)	0.001*
Monocyte (10^9/L)	0.29-1.48	0.58±0.22 (0.5)	0.2-1.07	0.52±0.16 (0.5)	0.029*
Neutrophil (10^9/L)	1.41-9.31	4.26±1.48 (4)	1.4-8.38	4.09±1.65 (3.6)	0.173
Lymphocyte (10^9/L)	1.09-4.5	2.18±0.76 (2.1)	0.91-5.7	2.21±0.81 (2)	0.673
MLR	0.11-0.65	0.28±0.1 (0.3)	0.06-0.96	0.26±0.14 (0.2)	0.110
NLR	0.85-4.85	2.09±0.84 (1.9)	0.67-5.53	2.11±1.25 (1.8)	0.749
HDL (mg/dl)	26-80	50.4±11.74 (50.5)	30-95	57.17±13.32 (59.5)	+0.001*
MHR	0-0.04	0.013±0.01 (0)	0-0.03	0.010±0.01 (0)	0.002*
MPV (fl)	8.8-12.9	10.31±0.84 (10.2)	7.9-12.1	9.89±0.89 (10.1)	+0.001*
Platelet (10^9/L)	162-465	269.62±59.18 (262.5)	160-504	258.17±60.18 (250)	+0.005*
SII	187-1644	562.43±264.27 (480.5)	147-1809	553.48±377.09 (490.5)	0.387
SALT	1-20	6.73±5.02 (5)	0-12	3.55±3.73 (2)	0.001*

N = number of patients, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, MLR: Monocyte-lymphocyte ratio, NLR: Neutrophil-lymphocyte ratio, HDL: High density lipoprotein, MHR: Monocyte-HDL ratio, MPV: Mean platelet volume, SII: Systemic Immune-Inflammation Index; SD = standard deviation, SALT: Severity of Alopecia Tool

in the monocyte count and MHR after treatment was statistically significant (*P*: 0.029, *P*: 0.001; $P < 0.05$).

Before treatment, the average platelet count was 269.62, and the MPV was 10.31. At the third month of treatment, the average platelet count was 258.17, and the MPV was 9.89. The decrease observed in the average platelet count and MPV values was found to be statistically significant (*P*: 0.005, *P*: 0.001; $P < 0.05$). No statistically significant

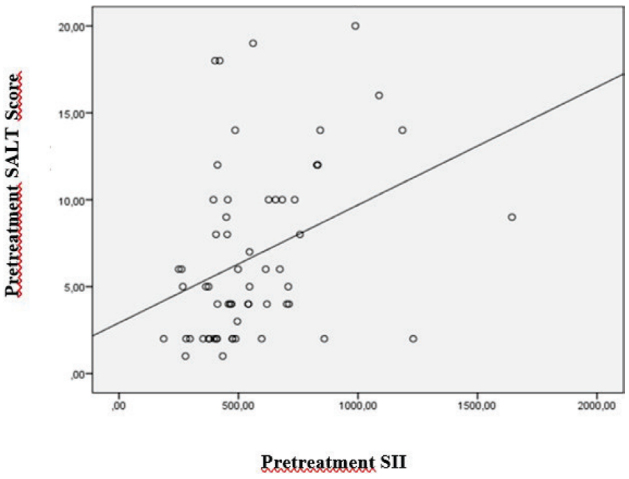

Figure 1. Correlation graph depicting the relationship between Severity of Alopecia Tool (SALT) score and systemic immune-inflammation index (SII) in the alopecia areata (AA) patient group.

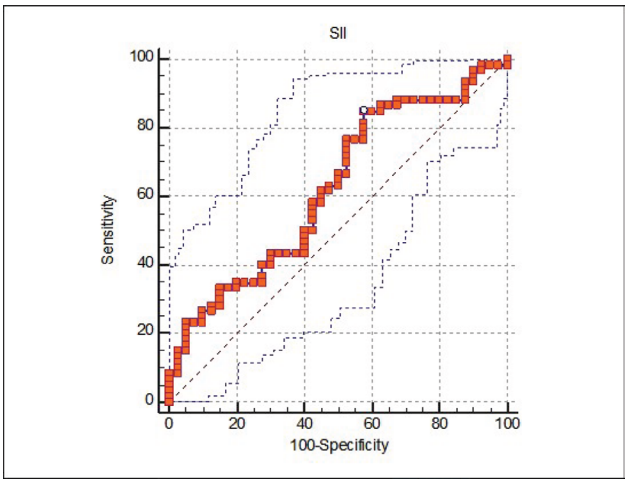

Figure 2. ROC curve for systemic immune-inflammation index (SII).

changes were observed in neutrophil and lymphocyte count, MLR, NLR, and SII at the third month of treatment compared to pre-treatment values (Table 1).

In the AA group, a statistically significant relationship was observed between the SALT score, indicative of disease severity, and SII (*P*: 0.002; $P < 0.05$) (Figure 1). After three months of treatment, SALT scores of AA patients were compared to their pre-treatment values. Seventeen patients (28.3%) achieved a SALT score of "0," while 37 patients (61.7%) experienced a reduction in their SALT scores, and six patients (10%) maintained unchanged SALT scores. Six patients, who maintained unaltered SALT scores, exhibited an increase in SII values at the third month of treatment. Patients who achieved a SALT score of "0" or experienced a reduction in SALT scores showed lower SII values in comparison to their pre-treatment values. There was a statistically significant difference between pre-and post-treatment values ($P < 0.05$).

The ROC curve was plotted to assess the performance of SII (AUC: 0.625). It was found that SII can discriminate AA patients from healthy individuals at a rate of 62.5% (moderate level). The threshold value for SII was determined as 368.67, with a sensitivity of 85% and specificity of 57.5%. Using this threshold value, SII can identify AA patients at a rate of 85% and healthy individuals at a rate of 57.5%. SII can correctly classify individuals with AA with a probability of 95%, ranging from at least 52.2% to a maximum of 71.9% (AUC: 0.625; 95% CI: 0.522–0.719; *P*: 0.030; $P < 0.05$) (Figure 2).

Discussion

AA is an autoimmune disease characterized by hair loss on the scalp, beard, eyebrows/eyelashes, and/or body hair. Various clinical variants of AA exist, including ophiasis, inverse ophiasis, diffuse, reticular, and perinevoid types [7]. In daily practice, the most common clinical presentation is localized, round, or oval alopecic patches on the scalp. The course of the disease is unpredictable, with spontaneous remissions and relapses occurring in approximately 80% of patients.

AA affects both males and females, with no significant sex-based difference in prevalence. In a study by Lundin et al., female:male ratio was found to be 2.3:1 [8]. The higher incidence of AA in women is attributed to their increased sensitivity to hair loss. In a retrospective study by Uzuncakmak et al., including a total of 1,641 patients, the female:male ratio was found to be 1.15:1 [9]. Another retrospective cohort study by Lyakhovitsky and colleagues involving 29 AA patients reported that 86.2% of the patients were female, resulting in a female:male ratio of 6.2:1 [10]. On the contrary, Kavak and colleagues suggested a higher incidence of AA in males, with a female:male ratio of 1:1.6 [11]. In this study, the female:male ratio for AA patients was found to be 1:1.4.

It has been demonstrated that several other diseases can coexist with AA. The results of a meta-analysis showed a frequent association of AA with thyroid disease, iron deficiency anemia, vitamin D deficiency, systemic lupus erythematosus, atopic dermatitis, allergic rhinitis, metabolic syndrome, and psychiatric disorders [12]. In a retrospective study by Laitinen et al. including a total of 176 AA patients, it was found that 27.3% of patients had atopic dermatitis, 17% had thyroid disease, and 13.1% had cardiovascular disease [13]. A systematic review by Fricke et al. reported the rates of atopic dermatitis, thyroid diseases, and diabetes in AA patients as 15.6%, 8.9%, and 11.1%, respectively [14]. In this study, 10% of AA patients had coexisting diseases, including hypercholesterolemia, pyelonephritis, hypothyroidism, diabetes, hypertension, Hashimoto thyroiditis, and iron deficiency anemia.

There are limited studies investigating hematological markers in AA patients. In a case-control study by Saraç et al., it was demonstrated that elevated MHR, MLR, and platelet-lymphocyte ratio (PLR) values had diagnostic importance and also increased the risk of developing AA [15]. On the other hand, in a retrospective study by İslamoğlu et al., no significant relationship was found between hematological markers and AA in comparison to the control group, except for CRP [16]. Another study, by Dere et al., suggested that PLR, NLR, and MPV values in AA patients were not significantly different from those in the control group, and these markers were not useful in reflecting the inflammatory status of the patients [17].

This study revealed that AA patients exhibited higher levels of NLR, MPV, and SII and lower levels of HDL when compared to the control group. Consequently, NLR, MPV, and SII were identified as useful markers in indicating increased inflammation in AA patients. The marked decrease in HDL, known for its anti-inflammatory and antioxidant properties, along with its rise after the treatment, indicates the involvement of inflammation and oxidative stress in the pathogenesis of AA.

The SII (platelet count × NLR) is a marker that has been used to evaluate the disease activity of several inflammatory diseases. Tanaçan et al., demonstrated that patients with active Behçet disease had significantly higher SII values compared to those in remission. Additionally, the study suggested that SII could be a useful marker in assessing the severity of Behçet disease [4]. In a case-control study by Karaosmanoğlu et al., patients with rosacea were found to have higher SII values compared to healthy controls. However, there was no significant relationship between SII and the severity of rosacea [18]. In a study by Coşansu et al. involving patients with acne vulgaris, SII values calculated after three months of systemic isotretinoin treatment were significantly lower compared to pre-treatment SII values [19]. In another study including patients with acne vulgaris, Turan et al. found that patients with nodulocystic acne exhibited elevated SII values compared to those with mild to moderate acne. Additionally, the SII showed a weak correlation with the number of nodulocystic lesions and acne severity [20].

Yorulmaz et al. observed that SII values were higher in psoriasis patients compared to the control group. Moreover, the study found that SII values were significantly higher in patients with moderate to severe psoriasis compared to those with mild psoriasis [21]. In a case-control study by Melikoğlu et al., it was demonstrated that psoriasis patients had higher SII values compared to healthy controls. However, no statistically significant correlation was found between SII and psoriasis severity [22]. In a study by Dinçer et al., SII values were found to be higher in patients with moderate to severe psoriatic arthritis compared to those with mild psoriatic arthritis [23]. In a retrospective cohort study involving patients with recurrent aphthous stomatitis, a positive correlation was observed between SII and the disease severity (24). In this study, a positive correlation between the SII and the SALT score suggests that SII could be used to assess the severity of AA.

Limitations

This study has some limitations. A longer follow-up including a period of 6-12 months could be carried out. The single-center nature of the study and the relatively small number of patients and controls can be considered as other limitations. Additionally, the hematological markers examined in the study may show an increase in existing inflammatory conditions including active infections, rheumatoid arthritis, ankylosing spondylitis, autoimmune diseases, inflammatory bowel diseases, and internal organ malignancies. Therefore, active infections or inflammatory diseases may serve as restrictive factors for the use of these parameters. In addition, it is crucial to consider that the positive correlation between SII and SALT scores might not be entirely accurate. The presence of preexisting inflammatory conditions, as mentioned earlier, could elevate SII, potentially introducing bias into its association with the SALT score. Given the potential for confounding factors, further research is warranted to clarify the association between SII and SALT scores.

Conclusion

This study demonstrates that SII is a useful marker for distinguishing between patients with AA and healthy controls. Furthermore, it has been demonstrated that SII can be used to evaluate the severity of AA and response to treatment. The significant differences in MPV, NLR, SII, and HDL values in AA patients compared to the control group indicate that these parameters are useful in reflecting inflammation in AA. In this regard, multicenter studies involving a larger patient population are needed.

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