

Assessment of the Mean Platelet Volume-to-Platelet Count Ratio in Alopecia Areata: A Retrospective Case Control Study

Alopesi Areata Hastalarında Ortalama Trombosit Hacminin Trombosit Sayısına Oranının Değerlendirilmesi: Geriye Dönük Vaka Kontrol Çalışması

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ABSTRACT Objective: Alopecia areata (AA) is an autoimmune disease characterized by non-scarring hair loss. Some biomarkers and clinical severity scores have been described for AA; however, a simple and inexpensive marker that correlates with disease activity may provide a more practical management strategy. The aim of the present study was to evaluate the serum mean platelet volume (MPV), platelet count (PC), and MPV/PC ratio in patients with AA and assess their association with disease activity and severity. **Material and Methods:** This retrospective study included 75 adult patients diagnosed with AA and 70 healthy controls. The white blood cell count, red blood cell count, hemoglobin, hematocrit, MPV, PC, and MPV/PC ratio were compared between the two groups. In addition, the same parameters were compared between the active and inactive; severe and mild/moderate; and acute and chronic AA subgroups. **Results:** The PC and MPV values were significantly lower and the MPV/PC ratio significantly higher in the AA group ($p<0.001$; $p=0.015$; $p<0.001$, respectively). There was no significant difference between patients and healthy controls in terms of other hematologic parameters ($p>0.05$). The PC was significantly lower in active and severe disease ($p>0.05$). Conversely, the MPV/PC ratio was significantly higher in the active and severe group as compared with that in the inactive and mild/moderate group ($p>0.05$). The cut-off value for the MPV/PC ratio was 0.036, with a sensitivity of 52.0% and a specificity of 85.7%. **Conclusion:** Based on our study findings, the MPV/PC ratio may be a useful tool for the practical assessment of disease activity in AA.

Keywords: Alopecia areata; mean platelet volume; platelet; ratio

ÖZET Amaç: Alopesi areata (AA), skarsız saç dökülmesi ile karakterize otoimmün bir hastalıktır. AA'da bazı biyobelirteç ve klinik şiddet skorları tanımlanmıştır, ancak hastalık aktivitesi ile ilişkili olan basit ve ucuz bir belirteç daha pratik bir tedavi yönetimi sağlayabilir. Bu çalışmanın amacı, AA hastalarında serum ortalama trombosit hacmi (OTH), trombosit sayısı (TS) ve OTH/TS oranını ve bunların hastalık aktivitesi ve şiddeti ile ilişkisini değerlendirmektir. **Gereç ve Yöntemler:** Bu retrospektif çalışma, AA tanısı almış 75 erişkin hasta ve 70 sağlıklı kontrolü içermektedir. Beyaz kan hücresi, hemoglobin, kırmızı kan hücresi, hematokrit, OTH, TS, OTH/TS parametreleri 2 grup arasında karşılaştırıldı. Ek olarak aynı parametreler; aktif ve inaktif, şiddetli ve hafif/orta, akut ve kronik AA alt grupları arasında karşılaştırıldı. **Bulgular:** AA grubunda TS ve OTH değerleri istatistiksel olarak anlamlı oranda düşüktü ve OTH/TS oranı anlamlı olarak yüksekti (sırasıyla $p<0.001$; $p=0.015$; $p<0.001$). Diğer hematolojik parametreler açısından hasta ve sağlıklı kontroller arasında istatistiksel olarak anlamlı bir fark yoktu ($p>0.05$). TS, aktif ve şiddetli hastalıkta istatistiksel olarak anlamlı oranda daha düşüktü ($p>0.05$). Tersine OTH/TS oranı, aktif ve ağır grupta inaktif ve hafif/orta şiddete göre istatistiksel olarak anlamlı oranda daha yüksekti ($p>0.05$). OTH/TS oranının kesme değeri 0,036; duyarlılık %52,0 ve özgüllük %85,7 idi. **Sonuç:** Çalışma bulgularına dayanarak, OTH/TS oranı, AA'daki hastalık aktivitesinin pratik değerlendirilmesi için yararlı bir araç olabilir.

Anahtar Kelimeler: Alopesi areata; ortalama trombosit hacmi; platelet; oran

Alopecia areata (AA) is an inflammatory condition that is among the common causes of non-scarring hair loss.^{1,2} Aside from genetic and certain

environmental factors, autoimmunity remains the main etiological factor.¹⁻⁴ Other systemic autoimmune diseases, including thyroid dysfunction, pernicious

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anemia, diabetes mellitus, and systemic lupus erythematosus (SLE), may be related to AA.^{3,4} Despite the fact that AA is a benign condition, its clinical course and treatment outcomes are unpredictable. Since disease progression varies, clinical examination alone may be insufficient to guide treatment and determine prognosis. Although some inflammatory markers, such as interleukins, and clinical severity scores have already been described for AA, a simple and inexpensive laboratory marker may be useful to determine the disease course.^{1,5,6} Moreover, this may be a more objective method than clinical findings to assess disease activity.

In addition to their main role in homeostasis and thrombosis, platelets are also important in the modulation of inflammatory reactions. In addition, the mean platelet volume (MPV) is known to be related to platelet function and activity, and an association has been reported with various inflammatory diseases, including autoimmunity.⁷⁻⁹ However, it has been suggested that these two parameters be considered as a ratio rather than individually.^{10,11} Previous studies have revealed a predictive role of the MPV-to-platelet count (MPV/PC) ratio regarding mortality in certain diseases such as ischemic cardiovascular diseases, sepsis, and non-alcoholic fatty liver disease.¹²⁻¹⁴

The primary aim of the present study was to assess the serum MPV, PC, and MPV/PC ratio in patients with AA and compare these parameters with those in healthy controls. The secondary aim was to compare the same parameters between patients with active and inactive disease.

MATERIAL AND METHODS

This retrospective study included 75 adult patients diagnosed with AA and 70 age- and gender-matched healthy controls. The study was approved by the University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Local Ethics Committee (09 December 2020, no: 2020-12/896), and informed consent was obtained from all participants. Medical data for all patients who had been admitted to our dermatology outpatient clinic between September 2019 and March 2020 were reviewed. Diagnosis of AA was made by

physical examination. Patients who had no treatment history for more than 6 months and those diagnosed with AA for the first time were included in the study. Patients who had any hematologic disease, cardiovascular disease, rheumatologic disease, diabetes mellitus, malignancy, active or chronic infectious disease, and autoimmune disorders, were using aspirin or any other drugs that could have influenced platelet function, were pregnant or breastfeeding or were under the age of 18 were excluded.

Firstly, patients with AA were determined to have active or inactive disease and separated into subgroups accordingly. A positive hair pull test, enlargement of an active patch, and the presence of exclamation mark hairs were defined as activity criteria.¹⁵ Secondly, patients were determined to have mild and moderate AA (less than 50% involvement) or severe AA (greater than 50% involvement) based on the extent of the disease.¹⁶ The third subgroup of patients was determined to have acute or chronic AA, the latter of which was defined as having disease lasting more than 1 year.¹⁵ The control group consisted of 70 healthy individuals who attended our dermatology outpatient clinic for a routine check-up, without any history of systemic disease or drug use. A complete blood cell count was performed using the CELL-DYN Ruby (Abbott Diagnostics, Illinois, USA) automated hematology analyzer. The reference ranges for the hemoglobin (Hb), white blood cell (WBC), red blood cell (RBC), hematocrit (Hct), platelet, and MPV are 11.7-17 g/dL, $4.2-10.2 \times 10^3/\mu\text{L}$, 4-6.1 M/ μL , 35-51, $142-450 \times 10^9/\text{L}$, 6.4-11 fL, respectively. The MPV/PC ratio was determined as the ratio of the MPV to the PC.

Data were statistically analyzed using the SPSS 25.0 software. The Kolmogorov-Smirnov or Shapiro-Wilks test was used to evaluate whether the distribution of continuous variables was normal. Homogeneity of variances was evaluated by Levene's test. Descriptive statistics are given as the frequency or percentage for categorical variables and as the mean±standard deviation for continuous data with a normal distribution or the median (range) for skewed distributions. Pearson's chi-square test or Fisher's exact test were used to compare categorical variables. The differences between groups in terms of continu-

ous variables were evaluated using the Mann-Whitney U test if the data were normally distributed and the Student's t-test if the data were not distributed normally. A p value less than 0.05 was considered statistically significant. A receiver operating characteristics (ROC) curve was generated to determine the cut-off values for the MPV, PC, and MPV/PC ratio. In addition the sensitivity and specificity of these three parameters were also calculated.

RESULTS

The study included 75 patients diagnosed with AA and 70 healthy controls. The median age in the patient and control groups was 32 (45) and 29.5 (46) years, respectively. The AA group comprised 40 male and 35 female patients, and the control group comprised 30 male and 40 female patients. There was no statistically significant difference in age ($p=0.055$) or gender ($p=0.207$) between the two groups. The median duration of symptoms was 7 (119) months. Patient demographics are presented in Table 1. As shown in Table 2 and Figure 1, the MPV and PC values were statistically significantly lower in the AA group than those in the healthy control group, but the MPV/PC ratio was higher ($p<0.001$; $p=0.015$; $p<0.001$, respectively). No significant difference was found between the patient and control groups in terms of the WBC, RBC, Hb, or Hct values ($p>0.05$; Table 2). Moreover, no significant difference was found between the acute and chronic AA groups ($p>0.05$;

		n (%)
Duration of symptoms	Acute	47 (62.7)
	Chronic	28 (37.3)
Family history	No	65 (86.7)
	Yes	10 (13.3)
Previous treatment	Yes	59 (78.7)
	No	16 (21.3)
Type of alopecia	Alopecia areata	68 (90.7)
	Alopecia totalis	3 (4.0)
	Alopecia universalis	4 (5.3)
Severity	Mild/moderate	49 (65.3)
	Severe	26 (34.7)
Activity	Active	33 (44.0)
	Inactive	42 (56.0)

Table 3). As shown in Table 3, the PC was significantly lower in patients with active and severe disease as compared with that in patients with inactive and mild/moderate disease. Conversely, the MPV/PC ratio was significantly higher in patients with severe disease as compared with that in patients with mild/moderate disease, and it was also higher in active disease as compared with inactive disease (Table 3). The area under the ROC curve for the MPV/PC ratio in AA patients was 0.742 (95% confidence interval=0.178-0.338) (Figure 2, Table 4). The cut-off value for the MPV/PC ratio was 0.036, with a sensitivity of 52.0% and a specificity of 85.7% (Table 4).

TABLE 2: Comparison of the hematologic parameters between the patient and control groups.

	Alopecia areata (n=75)	Control group (n=70)	p value
Hb*	14.52±1.64	14.17±1.52	0.188
WBC*	6.99±1.87	6.76±1.42	0.391
RBC ^β	4.95 (2.05)	4.68 (2.19)	0.312
Hct ^β	43 (38.8)	41.2 (17.2)	0.157
PC ^β	223 (272)	251.25 (318.80)	0.015
MPV ^β	6.5 (9.1)	8.09 (10.8)	<0.001
MPV/PC*	0.04±0.01	0.03±0.01	<0.001
MCV ^β	86.83 (40.9)	85.73 (22.3)	0.348

Continuous variables are expressed as either * the mean±standard deviation or ^β median (range). Continuous variables were compared using the Student's t-test or the Mann-Whitney U test. Statistically significant p values are shown in bold.

Hb: Hemoglobin; WBC: White blood cell; RBC: Red blood cell; Hct: Hemotocrit; PC: Platelet count; MPV: Mean platelet volume; MPV/PC: Mean platelet volume-to-platelet count ratio; MCV: Mean corpuscular volume.

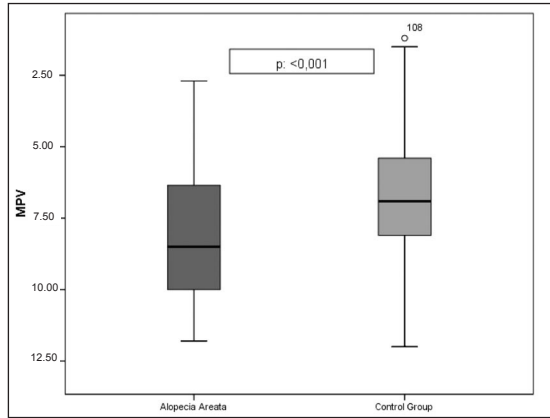


FIGURE 1A: Comparison of the mean platelet volume values between the patient and control groups.
MPV: Mean platelet volume.

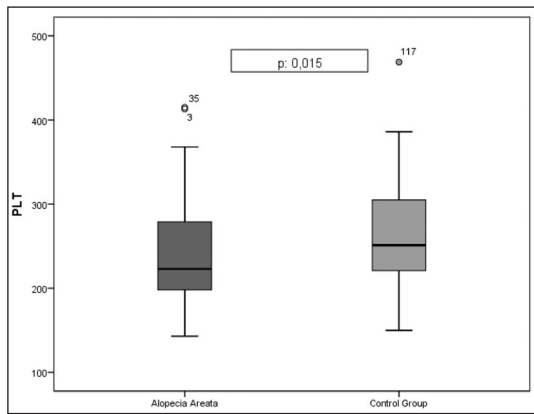


FIGURE 1B: Comparison of the platelet levels between the patient and control groups.
PLT: Platelet.

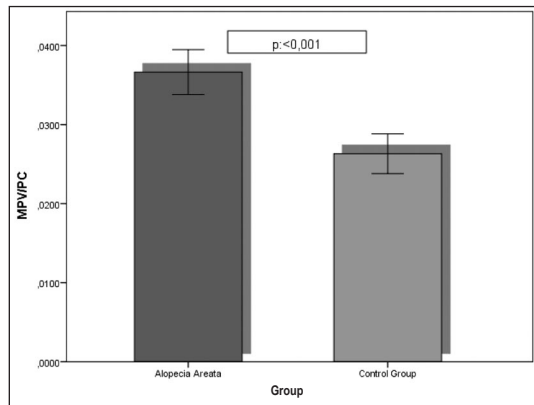


FIGURE 1C: Comparison of the mean platelet volume-to-platelet count ratio between the patient and control group.
MPV/PC: Mean platelet volume-to-platelet count ratio.

TABLE 3: Comparison of hematological parameters between subgroups.

	Acute AA (n=47)	Chronic AA (n=28)	p ¹	Mild/moderate (n=49)	Severe (n=26)	p ²	Active (n=33)	Inactive (n=42)	p ³
Hb [§]	14.5 (7.5)	14.75 (5.6)	0.689 [§]	14.54±1.74	14.48±1.48	0.891*	4.48±1.73	14.54±1.59	0.875*
WBC*	7.18±2.08	68±1.42	0.269*	7.05±1.91	6.89±1.82	0.718*	7.44 (10.9)	6.56 (6.5)	0.529 [§]
RBC*	4.94±0.51	4.86±0.53	0.514*	4.89±0.54	4.94±0.47	0.724*	4.94±0.53	4.89±0.50	0.641*
Hct [§]	43 (20.57)	42.69 (37.1)	0.797 [§]	43.31 (20.4)	41.74 (36.7)	0.676 [§]	43.02 (38.8)	42.59 (18.3)	0.869 [§]
PC [§]	220 (270)	229.2 (269)	0.543 [§]	254.81 (261)	216.46 (158)	0.028[§]	215.56±41.15	261.9±67.06	<0.001*
MPV*	6.67±2.12	6.82 ±2.07	0.772*	6.79 (9.1)	6.6 (7.3)	0.876 [§]	6.7 (6.2)	6.35 (9.1)	0.276 [§]
MPV/PC*	0.04±0.01	0.03±0.01	0.347*	0.03±0.01	0.04±0.01	0.001*	0.04±0.01	0.03±0.01	<0.001*
MCV [§]	87.7 (40.1)	86.45 (18.55)	0.390 [§]	86.6 (40.5)	85.62 (40.1)	0.751 [§]	88 (40.9)	86.8 (39.5)	0.709 [§]

Continuous variables are expressed as either * the mean±standard deviation (SD) or [§] median (range). Continuous variables were compared using the Student's t-test or the Mann-Whitney U test. Statistically significant p values are shown in bold. AA: Alopecia areata; Hb: Hemoglobin; WBC: White blood cell; RBC: Red blood cell; Hct: Hematocrit; PC: Platelet count; MPV: Mean platelet volume; MPV/PC: Mean platelet volume-to-platelet count ratio; MCV: Mean corpuscular volume.

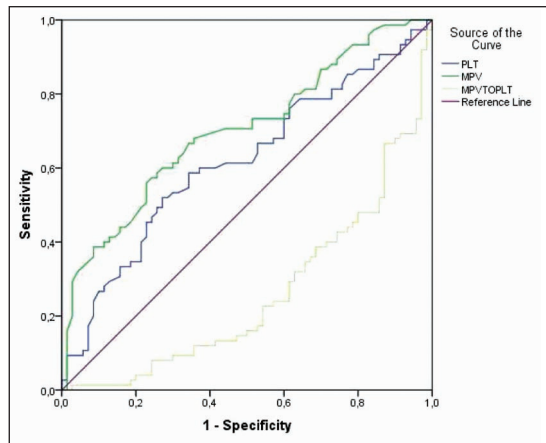


FIGURE 2: Receiver operating characteristic curve analysis for the mean platelet volume, platelet count, and mean platelet volume-to-platelet count ratio. MPV: Mean platelet volume; PLT: Platelet.

DISCUSSION

The presence of various surface receptors, glycoproteins, granules, and a smooth endoplasmic reticulum tubular system allow platelets to play a role as immune cells.^{17,18} Particularly in autoimmune diseases, where chronic inflammation is prominent, their role as immune cells is remarkable. Increasing evidence indicates a role for platelets in autoimmune diseases, with reports suggesting that these cells are a source of autoantigens.^{19,20} Long-term activation of platelets can lead to the recognition of surface molecules by autoantibodies.²¹ Platelets support autoimmune-mediated inflammation by synthesizing and releasing large amounts of bioactive compounds that facilitate autoimmune inflammatory processes, such as complement activation, circulating immune complexes, and impaired phagocytosis of apoptotic cells. In addition, platelets promote T helper leukocyte maturation toward type 1 and type 17.^{18,19}

Platelets are known to be the first cells to respond to endothelial damage during the early stages

of inflammation.^{8,22} However, in inflammatory and autoimmune diseases such as SLE and rheumatoid arthritis (RA), platelets are exposed to chronic stimuli, resulting in enhanced platelet activation.⁸ In addition, the MPV, which correlates with platelet activity, has been shown to be related to certain inflammatory and autoimmune diseases.⁹ Recent studies on AA have identified common pathways with other forms of autoimmune disease, including SLE and RA, indicating that changes in platelet function and MPV may also be observed in AA.²³ Although a possible relationship between a higher MPV value and various autoimmune and inflammatory disorders has been suggested, there also exist reports demonstrating contradictory findings.²⁴⁻³⁰ These discrepancies can be explained by platelet activation. Activated platelets become larger under inflammatory conditions, resulting in an elevated MPV; however, after the larger activated platelets have completed their role in inflammation, the remaining smaller platelets lead to a decrease in MPV as a result of ongoing inflammation.³¹ Lower MPV values in AA patients in the present study may also be related to platelet activation, similar to the situation in other autoimmune diseases such as SLE. On the other hand, although lower MPV values are associated with ongoing inflammation and disease activity in the literature, we did not find lower MPV values in patients with chronic and active AA. This finding may be related to the possibility that, even in acute cases, inflammation may have started long before clinical manifestation.

In a study by Peng et al., patients with polymyositis, another disease with an autoimmune etiology, had lower MPV values than healthy controls, which is consistent with our findings.³² The patients with active polymyositis had lower MPV values than patients with inactive disease; however, in our study,

TABLE 4: Cut-off value, sensitivity, and specificity levels for MPV, PC, and MPV/PC.

Test result variable(s)	Area under curve	Standard error	p value	95% Confidence interval	Cut-off	Sensitivity	Specificity
PC	0.617	0.047	0.015	0.526-0.709	223.35	52%	72.9%
MPV	0.701	0.043	<0.001	0.617-0.785	6.75	56%	77.1%
MPV/PC ratio	0.742	0.041	<0.001	0.178-0.338	0.036	52%	85.7%

PC: Platelet count; MPV: Mean platelet volume; MPV/PC: Mean platelet volume-to-platelet count ratio.

there was no significant difference between active and inactive disease in terms of MPV.

There are a limited number of studies evaluating the MPV and platelet levels in AA. Contrary to our findings, in a previous retrospective study by Şener et al., it was reported that serum Hb, Hct, and RBC values were higher in patients with AA as compared with those in healthy controls.³³ In addition, the PC, MPV, and MCV values did not significantly differ between the two groups.³³ These opposing findings may be explained by the difference in inclusion criteria, since only newly diagnosed and acute cases were included. In another study including 105 AA patients, the WBC and C-reactive protein (CRP) levels were significantly increased in patients with AA relative to the healthy controls.³⁴ On the other hand, the MPV values were lower in the AA group, which is similar to that seen in our study; however, the difference was not statistically significant.³⁴

In the present study, the PC was inversely correlated with disease severity. Conversely, a recent study reported no significant difference between the severe and mild/moderate AA groups in terms of PC; however, contrary to our study, patients with co-morbidities were not excluded.¹⁶

It has been reported that the inversely proportional relationship between MPV and PC is impaired in many diseases.³⁵ Recently, it was suggested that these two parameters be considered as a ratio rather than individually.^{9,10} We found lower MPV and PC values but a higher ratio of these two parameters in patients with AA, which appeared to be associated with a further reduction in PC as compared with MPV. Moreover, no significant difference in the MPV level between active and inactive disease was found, while the PC value was lower in active disease. These two findings may support the idea that the PC may be affected to a higher degree than MPV in disease. In the present study, the sensitivities of the MPV, PC, and MPV/PC ratio were similar for disease. On the other hand, the specificity of the MPV/PC ratio for disease was higher than that of both MPV and PC; therefore, these results support the suggestion of interpreting the MPV and PC values as a ratio rather

than using them alone. To the best of our knowledge, this is the first study to evaluate the MPV/PC ratio in AA patients and show a relationship between the MPV/PC ratio and disease activity.

One of the main limitations of the present study is that the smoking habits of the patients were not included, which may have influenced the laboratory parameters. Another limitation is that the diagnosis of AA could not be confirmed with biopsy due to the retrospective nature of the study. Moreover, the severity alopecia tool score and other inflammatory markers, such as the sedimentation rate and CRP, were not included.

CONCLUSION

As a result, based on the study findings, the MPV/PC ratio may be a practical tool for the evaluation of disease activity in patients with AA. Further prospective studies may be useful to elucidate the cause of the reduction in PC and size in AA.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Gül Aslıhan Çakır Akay; **Design:** Gül Aslıhan Çakır Akay, Burcu Tuğrul; **Control/Supervision:** Gül Aslıhan Çakır Akay, Burcu Tuğrul; **Data Collection and/or Processing:** Gül Aslıhan Çakır Akay; **Analysis and/or Interpretation:** Gül Aslıhan Çakır Akay, Burcu Tuğrul; **Literature Review:** Gül Aslıhan Çakır Akay; **Writing the Article:** Gül Aslıhan Çakır Akay, Burcu Tuğrul; **Critical Review:** Gül Aslıhan Çakır Akay, Burcu Tuğrul; **References and Fundings:** Gül Aslıhan Çakır Akay; **Materials:** Gül Aslıhan Çakır Akay.

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