Dermatology Practical & Conceptual

The Use of New Hematological Markers in the Diagnosis of Alopecia Areata

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ABSTRACT

Introduction: Alopecia areata (AA) is a non-cicatricial inflammatory and autoimmune hair loss disease. In recent studies, it has been reported that hematological parameters can be used as oxidative stress markers in the diagnosis of many inflammatory diseases due to their low cost and widespread use.

Objectives: In this study, it was aimed to reveal the significant cut-off points of hematological inflammatory markers in AA that can guide clinicians in clinical practice and determine how many times they increase the risk of disease.

Methods: The present study is retrospective case-control type. Seventy patients with AA and seventy healthy controls were included in the study. The hematological parameters in both groups were evaluated retrospectively.

Results: Hemoglobulin, monocyte, platelet, monocyte high-density lipoprotein cholesterol (HDL-C) ratio (MHR), monocyte lymphocyte ratio (MLR), platelet lymphocyte ratio (PLR) were high in patients with AA, while the number of lymphocytes was low. In ROC analysis, the optimal cut-off values for the diagnosis of AA were as follows: MLR 0.216, MHR 0.010, and PLR 111.715. In regression analysis, being above the following values of MLR 0.216, MHR 0.010, and PLR 111.715 increased the risk of developing AA by 6.3, 3.8, and 2.7 times, respectively.

Conclusions: It was seen that MHR and PLR, especially MLR, can significantly increase the risk of developing the disease in AA and can also be used as diagnostic markers.

Introduction

Alopecia areata (AA) is an inflammatory and autoimmune disease clinically ranging from small, round, well-defined hair loss patch to its complete disappearance on the body and scalp [1]. The incidence of AA, which is a non-scarring disease in which the hair follicle is preserved, is 2% [2]. The mean age at diagnosis of AA, which can be seen in all age groups without any difference between genders, is 30-39 years [3]. The etiopathogenesis of AA has not yet been fully elucidated. Although genetics and immunity are seen as the factors that cause the most disease, many factors such as melanocyte anomalies, keratinocyte degeneration, neurological factors, and emotional stress have also been blamed [4-6]. The disease develops as a result of T cell-mediated cytotoxic damage to the hair follicle. Since IL-17A, IL17F, IL21, IL22, IL6, and TNF alpha levels are elevated in AA patients, these cytokines are thought to play a role in the pathogenesis [7]. In recent studies, it has been discussed that the whole blood parameters can be used as an oxidative stress and diagnostic marker in many diseases associated with inflammatory processes. In clinical practice, these markers are important for objective and quantitative evaluation of the disease process and response to treatment, as well as the diagnosis [8]. Red-cell distribution width (RDW), monocyte high-density lipoprotein ratio (MHR), monocyte lymphocyte ratio (MLR), platelet lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR) and mean platelet volume (MPV) are investigated in many dermatological diseases such as psoriasis, rheumatological diseases of dermatology, cutaneous vasculitis, atopic eczema, pityriasis rosea, Behçet disease, recurrent aphthous stomatitis, and pemphigus vulgaris [9-12].

Although there are many studies on these dermatological diseases in the literature, studies investigating the relationship between AA and these inflammatory markers are limited. In addition, no studies have been found showing at which cutoff point these significant inflammatory markers start to be significant and how many times they increase the risk of developing the disease.

Objectives

In this study, it was aimed to compare the levels of RDW, MPV, MHR, MLR, NLR, PLR between patients with AA and healthy controls, and to reveal the significant cut-off points that can guide clinicians in clinical practice and determine how many times they increase the risk.

Methods

Study Design and Patient Selection

This study was conducted as a retrospective case-control study with patients with AA who applied to the dermatology outpatient clinic between June 2020 and June 2021 and healthy controls with no previous history of AA. Ethics committee approval of the study was received from Local Ethics Committee. Demographic characteristics and laboratory values were obtained from the database of the health center for both the case and control groups. Demographic data include age, gender, duration of illness (months). Laboratory data include the levels of white blood cell (WBC: K/μL), hemoglobin (Hb: g/dL), platelets (PLT: K/μL), RDW, MPV (K/μL), neutrophils (NE: K/μL), lymphocytes (LY: K/μL), monocytes (MN: K/μL), high-density lipoprotein cholesterol (HDL-C: mg/dL), NLR, PLR, MHR, and MLR.

Disease severity in patients with AA was evaluated according to the classification made by Kavak et al and classified as mild (3 or fewer patches with a diameter of 3 cm or less, or involvement limited to eyebrows and eyelashes), moderate (more than 3 alopecic patches or involvement of more than 3 cm without alopecia totalis or alopecia universalis), severe (alopecia totalis or alopecia universalis) [13].

Patients with AA who had an active infection, malnutrition, anemia, immunodeficiency, chronic inflammatory skin disease, rheumatological disease, heart disease, and drug use were excluded from the study. The laboratory values of the patients with AA at the application date were included. Laboratory values of the patients with AA regarding the follow-up and treatment couldn't be included because they were absent in the hospital record. Healthy controls were comprised of individuals without active infection, systemic or dermatological disease, and drug use. Both of two groups don't include members who got Covid-19 infection in recent six months.

Statistical Analysis

The data of the study were analyzed using SPSS 20 (Statistical Package for Social Sciences). Descriptive statistics were given as numbers, percentages, mean and standard deviation. The relationship between continuous variables was evaluated with the Pearson correlation test. The t-test was used for continuous variables between two independent groups. Significant cut-off points were determined using ROC (Receiver operating characteristic) analysis for markers with significant differences between the two groups in the t-test. The odds ratios of the cut points that were found to be causing high activity AA were analyzed using the logistic regression model. All findings were evaluated at a 95% confidence interval (CI) and 5% significance level (P).

Results

Seventy patients with AA and 70 healthy controls were included in this study. The mean age was 31.57 ± 9.92 years in the patient group and 31.51 ± 7.37 years in the control group.

There was no significant difference between the groups according to age (P = 0.969). The mean age of patients with AA was 29.78 ± 8.58 years in men and 33.47 ± 10.98 years in women, and the difference was not statistically significant. The gender distribution was the same in the patient and control groups, with 36 (51.4%) men and 34 (48.6%) women. While the mean duration of disease was 1.22 ± 2.21 months in men and 3.05 ± 5.43 months in women, it was 2.11 ± 4.17 months in the whole AA group, and there was no significant difference between the genders. Of the patients with AA, 41 (58.6%) had mild, 12 (17.1%) had moderate, and 17 (24.3%) had severe alopecia.

The laboratory findings of the patient and control groups are shown in Table 1. The mean of Hb (P = 0.004), MN (P < 0.001), PLT (P = 0.042), MHR (P < 0.001), MLR (P < 0.001) and PLR (P < 0.001) was higher in patients with AA compared to the control group, while the number of lymphocytes was lower (P = 0.005).

Table 2 shows the effect of laboratory parameters on disease duration in patients with AA. While the increase in HDL-C (r = 0.324, P = 0.013), MPV (r = 0.239, P = 0.046) and PLR (r = 0.297, P = 0.013) in patients with AA increased the duration of the disease (positive correlation); the increase in Hb (r = -0.301, P = 0.011), LY (r = -0.269, P = 0.024) and MHR (r = -0.289, P = 0.015) was a factor reducing disease duration (negative correlation). When classified according to disease severity, for those who have severe AA disease the increase in HDL-C (r = 0.620, p = 0.008) led to increasing the duration of the disease (positive correlation). Also the increase in Hb (r = -0.505, P = 0.039) led to decreasing the duration of the disease (negative correlation). While there was a positive correlation between disease severity and RDW (r = 0.242, P = 0.044) and PLR (r = 0.315, P = 0.008); a negative correlation between WBC (r = -0.236, P = 0.049), Hb (r = -0.285, P = 0.017), MN (r = -0.270, P = 0.024) and MHR (r = -0.356, P = 0.002) was present. There was a positive, weak and very significant correlation between disease duration and disease severity in patients with AA (r = 0.494, P < 0.001).

Table 3 and Figure 1 show the optimal value of laboratory parameters to diagnose AA using ROC analysis. In ROC analysis, it was found that MLR (P < 0.001), MHR (P < 0.001) and PLR (P = 0.001) values could be used as a diagnostic test in AA. The cut-off values of MLR 0.216 value (AUC = 0.873, good usefulness, 85.7% sensitivity and 70% specificity), MHR 0.010 value (AUC = 0.759, moderate useful, 82.9% sensitivity and 58.6% specificity), PLR 111.715 value (AUC = 0.727, moderate useful, 75.7% sensitivity and 58.6% specificity) were found to be useful as diagnostic tests.

Table 4 shows how many times the parameters found to be significant in diagnosing AA in the ROC analysis increase

Table 1. Comparison of laboratory values of patients and controls using t-test.

Group	N	Mean	SD	P value
WBC				
Patient	70	7.26	1.80	0.115
Control	70	7.67	1.16	
Hb (g/dL)				
Patient	70	14.91	1.65	0.004
Control	70	14.15	1.37	
RDW (%)				
Patient	70	11.95	1.67	0.026
Control	70	12.44	0.76	
MN(K/µL)				
Patient	70	0.57	0.17	<0.001
Control	70	0.38	0.66	
HDL-C (mg/dL)				
Patient	70	52.49	10.83	0.252
Control	70	50.31	11.62	
NE (K/µL)				
Patient	70	4.27	1.26	0.062
Control	70	4.63	0.95	
PLT (K/µL)				
Patient	70	248.81	57.91	0.042
Control	70	229.87	50.94	
LY (K/µL)				
Patient	70	2.21	0.80	0.005
Control	70	2.56	0.62	
MPV (K/µL)				
Patient	70	8.06	1.22	0.252
Control	70	8.26	0.76	
MHR				
Patient	70	0.011	0.004	<0.001
Control	70	0.007	0.001	
MLR				
Patient	70	0.281	0.111	<0.001
Control	70	0.158	0.050	
NLR				
Patient	70	2.140	0.986	0.127
Control	70	1.921	0.674	
PLR				
Patient	70	121.461	34.492	<0.001
Control	70	94.805	29.309	

Hb = Hemoglobin; HDL-C = high-density lipoprotein cholesterol; LY = lymphocytes; MN = monocytes; MHR = monocyte high-density lipoprotein cholesterol ratio; MLR = monocyte lymphocyte ratio; MPV = mean platelet volume; NE = neutrophils;NLR = neutrophil lymphocyte ratio; PLR = platelet lymphocyte ratio; PLT = platelets; RDW = red-cell distribution width; WBC = white blood cell.

Table 2. Correlation analysis between disease duration and Alopecia Areata group parameters.

Variables	Disease Duration (months)						Disease Severity	
	Mild&Moderate Patients (N = 53)		Severe Patients (N = 17)		All Patients (N = 70)			
	r	P	r	P	r	P	r	P
WBC	0.054	0.703	-0.223	0.390	-0.205	0.089	-0.236	0.049
Hb	-0.010	0.946	-0.505	0.039	-0.301	0.011	-0.285	0.017
RDW (%)	-0.128	0.361	0.201	0.440	0.113	0.351	0.242	0.044
MN (K/µL)	0.012	0.931	-0.179	0.492	-0.230	0.055	-0.270	0.024
HDL-C (mg/dL)	0.117	0.405	0.620	0.008	0.324	0.013	0.227	0.059
NE (K/µL)	0.024	0.865	0.375	0.138	0.193	0.110	0.083	0.496
PLT (K/µL)	0.304	0.027	-0.264	0.306	-0.065	0.593	0.044	0.715
LY (K/µL)	-0.013	0.926	-0.482	0.050	-0.269	0.024	-0.182	0.132
MPV (K/µL)	-0.150	0.284	0.312	0.222	0.239	0.046	0.195	0.106
MHR	-0.079	0.574	-0.355	0.161	-0.289	0.015	-0.356	0.002
MLR	-0.002	0.989	0.219	0.399	0.048	0.691	-0.064	0.601
NLR	0.024	0.865	0.375	0.138	0.193	0.110	0.083	0.496
PLR	0.167	0.231	0.366	0.149	0.297	0.013	0.315	0.008

Hb = Hemoglobin; HDL-C = high-density lipoprotein cholesterol; LY = lymphocytes; MN = monocytes; MHR = monocyte high-density lipoprotein cholesterol ratio; MLR = monocyte lymphocyte ratio; MPV = mean platelet volume; NE = neutrophils; NLR = neutrophil lymphocyte ratio; PLR = platelet lymphocyte ratio; PLT = platelets; RDW = red-cell distribution width; WBC = white blood cell.

Table 3. Findings of the ROC analysis.

Variables	AUC (p value)	95% CI	CO	Sen (%)	Spe (%)	PLR	NLR
MLR	0.873 (<0.001)	0.815- 0.931	0.216	85.7	70.0	2.85	0.20
MHR	0.759 (<0.001)	0.679- 0.840	0.010	82.9	58.6	2	0.29
PLR	0.727 (<0.001)	0.643- 0.810	111.715	75.7	58.6	1.82	0.41

AUC = Area under curve; CI = confidence interval; CO = cutoff value; MHR = monocyte high-density lipoprotein cholesterol ratio; MLR = monocyte lymphocyte ratio; NLR = negative likelihood ratio; PLR = platelet lymphocyte ratio; PLR = positive likelihood ratio; ROC = receiver operating characteristic; Sen = sensitivity; Spe = specifity.

the probability of catching AA at the determined cut-off values in the established logistic regression model. According to the logistic regression analysis result, an MLR value of 0.216 and above increases the risk of developing AA by 6.30 times (95% CI: 2.41-16.45 P < 0.001), an MHR value of 0.010 and above by 3.87 times (95% CI: 1.54-9.73 P = 0.004) and a PLR value of 111.715 and above by 2.76 times (95% CI:1.06-7.17 P = 0.037).

Conclusions

In this study, the relationship between complete blood count and biochemical parameters, which can be easily used by clinicians in routine, and AA disease is shown in detail. There is a limited number of studies on the subject in the literature, and it has not been investigated yet at what values hematological and inflammatory markers are diagnostic for the disease and how much they increase the risk of disease in these diagnostic values. This study is a pioneering study in terms of answering these questions that are not yet available in the literature.

AA is a non-cicatricial, autoimmune, inflammatory hair loss disease that has many factors in its etiology and has various clinical manifestations [1]. There is no significant difference between genders in terms of incidence. However, it was emphasized that the most common age of onset of the disease was between 50-59 years of age in women and 30-39 years in men and that the average age of diagnosis was older in women than in men (36.2 versus31.5 years) [14]. In this study, the mean age of patients with AA was 29.78 ± 8.58 years in men and 33.47 ± 10.98 years in women, which is consistent with the literature.

Whole blood parameters are a low-cost test and are widely used by clinicians. It provides important information about systemic inflammation. In this study, Hb, MN, PLT, MHR, MLR, and PLR values were higher in patients

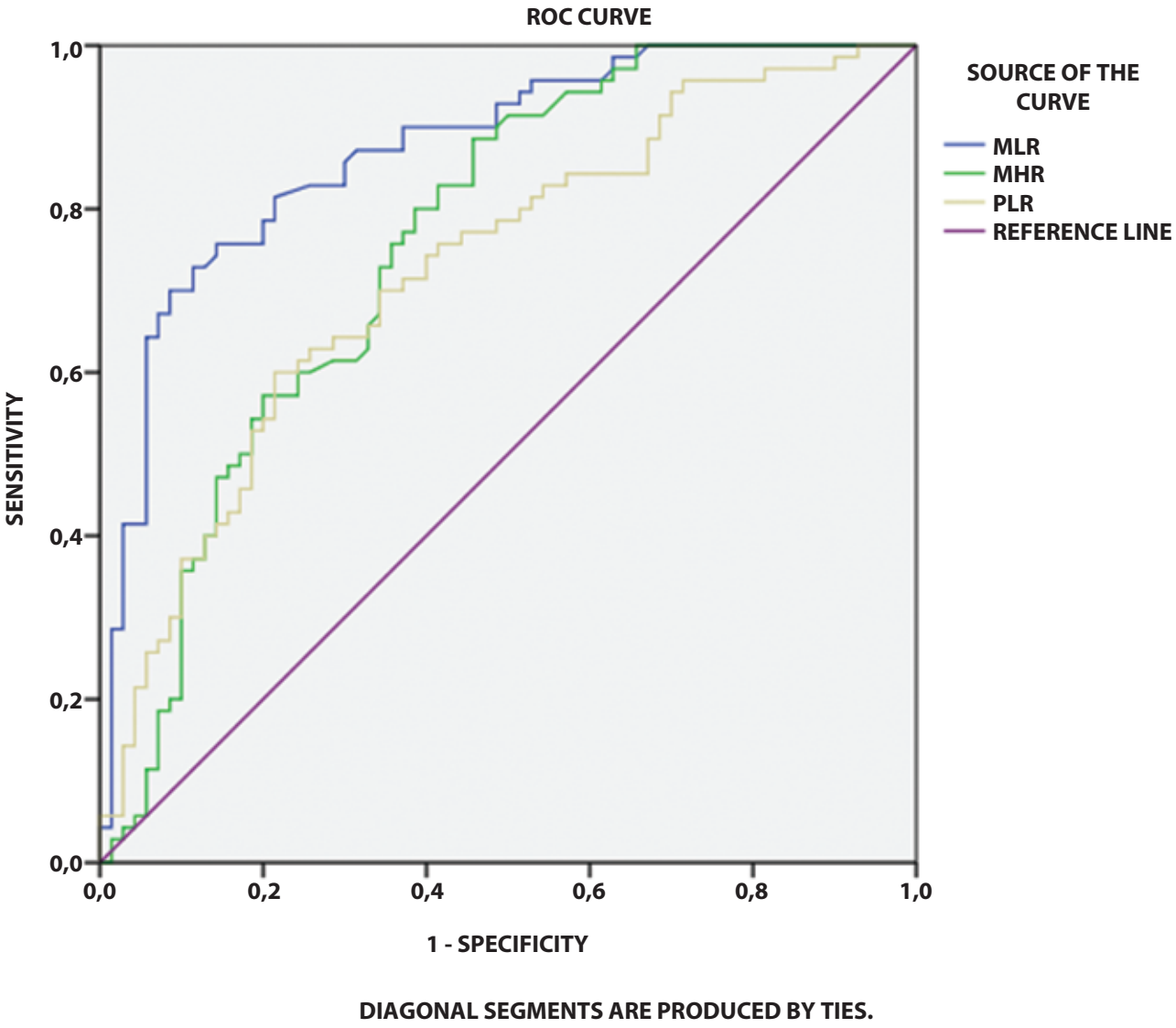

Figure 1. ROC Curve.

MHR: Monocyte high-density lipoprotein cholesterol ratio
MLR Monocyte lymphocyte ratio
PLR: Platelet lymphocyte ratio

Table 4. Logistic regression results.

Variables	OR	95% CI	P value
MLR			
0.216 and above	6.309	2.419- 16.456	<0.001
Below 0.216	1 (reference)		
MHR			
0.010 and above	3.879	1.546- 9.732	0.004
Below 0.010	1 (reference)		
PLR			
111.715 and above	2.761	1.062- 7.174	0.037
Below 111.715	1 (reference)		

CI = confidence interval; MHR = monocyte high-density lipoprotein cholesterol ratio; MLR = monocyte lymphocyte ratio; PLR = platelet lymphocyte ratio; OR = odds ratio.

with AA compared to the control group, while the number of lymphocytes was found to be lower. In addition, there was a positive correlation between AA durations and HDL-C, MPV, and PLR, and a negative correlation between Hb, LY, and MHR. But, when correlation analysis included only severe AA patients, there was a positive

correlation between AA durations and HDL-C, and a negative correlation between AA durations and Hb. In many studies in the literature, the relationship between dermatological diseases and these hematological markers has been investigated. In a study conducted by Ozlu et al WBC and MHR were found to be high and MPV was found to be low in patients with lichen planus [15]. It was shown that patients with psoriasis have higher levels of MHR and NLR compared to healthy controls [16]. Similarly, while there was a positive relationship between MHR, NLR, PLR, and MLR and disease duration in psoriasis, it has been reported that there was a negative relationship between NLR, PLR, and disease duration in vitiligo [17,18]. However, there are also studies stating that there is no significant relationship between AA and these hematological markers [19].

Monocytes are one of the cornerstones of the immune system that take on important tasks. They play a role in inflammatory processes in many diseases involving many systems such as rheumatologic, endocrine, dermatological, oncologic, and cardiovascular [20-23]. In this study, MLR, MHR, and PLR values were found to be good and moderately useful diagnostic tests for AA. The values that are above 0.216 for MLR, 0.010 for MHR, and 111.715 for PLR as cut-off increase the risk of alopecia areata by 6.3, 3.8, and 2.7 times, respectively. In a study by Yayla et al.; It has been reported that high NLR increases the risk of systemic sclerosis by 3.49 times [24]. In the study by Cosansu et al, it was stated that the MLR value of 0.192 was a moderately useful test in the diagnosis of patients with psoriasis, and similarly, MHR and MLR values were significant markers in the diagnosis of vitiligo [25,18].

There are some limitations to this study. Firstly, since it was in a retrospective style, the laboratory values of the patients at the time of application were included and no evaluation could be made regarding the follow-up data. Secondly, the fact that it is a single-center study, and third, the relatively small number of patients and controls may cause differences in findings. Fourth, it may assess as another limitation that The Severity of Alopecia Tool score wasn't used when classifying the severity.

In conclusion, in this study, MHR and PLR values, especially MLR, were shown to be low-cost and fast-accessible oxidative stress markers in the diagnosis of AA. It is believed that our results may provide important information for further studies on the use of hematological markers in AA.

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