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Evaluation of neutrophil-lymphocyte ratio, lymphocyte-monocyte, and monocyte-high density lipoprotein ratios in patients with fibromyalgia and determination of their relationship with disease activity, pain, and depression levels

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Abstract. – OBJECTIVE: This study aimed to evaluate neutrophil-lymphocyte ratio, lymphocyte-monocyte, and monocyte high-density lipoprotein ratios in patients with fibromyalgia and determine their relationship with disease activity, pain, and depression levels.

PATIENTS AND METHODS: This study was conducted with 40 healthy controls and 87 newly fibromyalgia (FM) diagnosed patients. Demographic characteristics, duration of pain, body mass index (BMI), and laboratory test results were recorded. The hematological indices and ratios were determined with a hemogram test. Disease activity was evaluated with a fibromyalgia impact questionnaire (FIQ). Depression status was evaluated with the beck depression inventory (BDI).

RESULTS: A total of 127 participants, 40 in the control group and 87 in the patient group, were included in the study. BMI values of the patient group were statistically higher than the control group (p=0.025). The white blood cell count of the patient group was statistically higher than the control group (p=0.007). Monocyte values were statistically higher in the patient group (p<0.001). Monocyte to high-density lipoprotein-cholesterol ratio (MHR) values in the patient group were statistically higher than the control group (p<0.001). Lymphocyte-monocyte-ratio (LMR) values of the control group were statistically higher than the patient group (p<0.001).

CONCLUSIONS: This study shows that in fibromyalgia patients, monocyte level and MHR were higher than in healthy subjects. Also, high-density lipoprotein-cholesterol (HDL-C) level was found lower, and the total cholesterol level was found higher in patients with FM. Increased LMR and HDL-C values were found as responsible for decreasing the risk of developing FM and increased glucose and total cholesterol values were responsible for increasing the risk of FM developing.

Key Words:
Fibromyalgia, Neutrophil-lymphocyte ratio, Lymphocyte-monocyte ratio, Monocyte high-density lipoprotein ratio.

Introduction

Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread musculoskeletal pain, extreme fatigue, and sleep disturbances; the prevalence of FM is known as 1-5%[1]. Current evidence[2,3] suggests inflammation, specifically neuroinflammation, as a potential contributor to the etiology of FM, and that neuroinflammation is a potential contributor to the etiology of FM. Low-grade inflammation and altered cytokine profiles have been reported in FM. There are studies showing that these proinflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin-8 (IL-8), and interleukin-6 (IL-6) are increased[4-6]. These elevations in proinflammatory cytokines facilitate peripheral and central nociception and cause pain and hypersensitivity in FM[7,8]. Neutrophil to lymphocyte ratio (NLR), platelet distribution width (PDW), mean platelet volume (MPV), and monocyte to high-density lipoprotein-cholesterol ratio (MHR) have been associated as a systemic inflammatory marker and there are studies[9,10] showing the relationship of these markers with disease activity in FM.

There are some studies[11-16] evaluating the NLR, MHR, and lymphocyte-monocyte (LMR) ratios in inflammatory and cardiovascular diseases in the literature. But there is no study evaluating all of these markers in FM patients. In this study, we aimed to evaluate the neutrophil-lymphocyte

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ratio, lymphocyte-monocyte, and monocyte high-density lipoprotein ratios in patients with fibromyalgia and determine their relationship with disease activity, pain, and depression levels.

Patients and Methods

This study was conducted at Hitit University Faculty of Medicine, Department of Physical Medicine and Rehabilitation; 40 healthy controls (Group I) and 87 newly diagnosed FM (Group II) were included. Patients between the ages of 18 and 65 were diagnosed according to the American College of Rheumatology (ACR) 2016 FM diagnostic criterias[17]. Patients with thyroid disorders, diabetes mellitus, hypertension, hyperlipidemia, rheumatological diseases, malignancy, and pregnancy were excluded from the study. Age, sex, marital status, smoking, duration of pain, body mass index (BMI), and laboratory test results were recorded. The hematological indices and ratios (NLR, MHR, LMR) were determined with a hemogram test. Disease activity was evaluated with Fibromyalgia Impact Questionnaire (FIQ). This questionnaire consists of 10 items investigating physical function, job status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being. The first 10 questions are scored between 0-3 each. It is evaluated out of a total of 100 points. A low score indicates that the severity of the disease is low. Turkish validity and reliability study was conducted[18]. The pain intensity was measured using the visual analog scale (VAS). Patients were asked to rate their pain on a 10-cm line anchored by two descriptors: 0, no pain, and 10, unbearable pain[19]. Depression status was evaluated with the Beck Depression Inventory (BDI). The reliability and validity of the Turkish version of BDI were also shown. The BDI is a 21-item questionnaire that investigates the symptoms of depression. Total scores range from 0 to 63, higher scores indicate higher levels of depression[20]. A well-written informed consent was obtained from all participants according to the principles of the Helsinki Declaration.

Statistical Analysis

All statistical analyses were performed using the IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, NY, USA) and MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd, Ostend, Belgium). Descriptive statistics were given as a number of units (n), mean±standard deviation (mean±sd), median (M), minimum (min), maximum (max), and interquartile range (IQR). The normality of the data of numerical variables was evaluated using the Shapiro-Wilk test of normality. Homogeneity of variances was evaluated with Levene's test. Comparisons between groups were made with two independent samples *t*-test for normally distributed variables, and Mann-Whitney U test for non-normally distributed variables. Chi-square tests were used to compare groups with categorical variables. The performance of clinical variables in predicting fibromyalgia disease was evaluated with the Receiver operating characteristic (ROC) curve. Factors affecting fibromyalgia disease were investigated by binary logistic regression analysis. In the binary logistic regression analysis, the backward Wald method was used as the elimination method. Model compatibility was evaluated by the Hosmer-Lemeshow goodness of fit. The relationships between FIQ and BDI, NLR, lymphocyte-monocyte ratio (LMR), MPV and MHR were evaluated with Pearson correlation analysis, FIQ with Common Pain Scale, VAS and PLR relationships were evaluated with Spearman correlation analysis. Factors affecting FIQ were evaluated with multiple linear regression analysis. In the multiple linear regression analysis, the backward method was used as the elimination method. The suitability of the established model for multiple linear regression analysis; Shapiro Wilk normality test and Q-Q plot were used for normality of residuals, tolerance, and variance inflammation factor (VIF) statistics were used for collinearity. It was seen that the necessary assumptions for the established regression model were met. A value of $p<0.05$ was considered statistically significant.

Results

Age, sex, marital status, and smoking were similar between groups. BMI was statistically higher in the patient group than in the control group ($p=0.025$). The white blood cell (WBC) level was statistically higher in the patient group than in the control group ($p=0.007$). Hemoglobin, MPV, neutrophil, and lymphocyte values were similar in the groups. Monocyte level was statistically higher in the patient group ($p<0.001$). There were no statistical differences in the platelet, NLR, and PLR level between the groups. The MHR ratio was statistically higher in the patient group than

in the control group ($p<0.001$). LMR ratio was statistically higher in the control group than in the patient group ($p<0.001$). Glucose level was statistically higher in the patient group ($p=0.001$). Total cholesterol level was statistically higher in the patient group ($p=0.005$). High-density lipoprotein-cholesterol (HDL-C) level was statistically higher in the control group ($p=0.035$). Low-density lipoprotein-cholesterol (LDL-C), triglyceride, and creatinine levels were statistically similar between groups (Table I).

The performances of the variables that are statistically significant in the comparisons in Table I in predicting fibromyalgia disease were evaluated by ROC curve analysis and the results were given in Table II. According to Table II, the area under the curve-AUC values obtained for the WBC, monocyte, MHR, LMR, Glucose, and total cholesterol variables were found to be statistically significant. Monocyte had the highest AUC value. When the monocyte was >0.52, the sensitivity value was 77.0% and the specificity value was 85.0%.

The factors affecting fibromyalgia disease were evaluated in Table III by binary logistic regression analysis. In the comparisons in Table I, variables with a p-value of <0.20 were included in the regression model. The backward Wald elimination method was used to determine the final factors affecting the disease. As a result, LMR, glucose, total cholesterol, and HDL-C variables were found to be statistically significant. As LMR and HDL-C values increase, the risk of developing fibromyalgia decreases, and as glucose and total cholesterol values increase, the risk of developing the disease increases (Figure 1).

Table I. Comparison of clinical variables according to the groups.

	Groups Group I n=40	Group II n=87	Test statistics Test value	p
WBC count ^10³ (mm³)	7.09±1.27	7.81±1.39	t=2.766	**0.007**
Hemoglobin (g/dl)	13.34±0.88	12.98±1.48	t=1.439	0.153
Mean platelet volume (fL)	9.72±1.03	9.85±1.05	t=0.695	0.489
Neutrophil (%)	4.04±0.94	4.28±1.05	t=1.191	0.236
Lymphocyte (%)	2.23±0.56	2.42±0.71	t=1.445	0.151
Monocyte (%)	0.405±0.108	0.574±0.124	t=7.405	**<0.001**
NLR	1.87±0.51	1.94±0.96	t=0.410	0.683
PLR	120.6 (94.5)	115.9 (65.8)	z=0.099	0.921
MHR	0.009±0.003	0.013±0.003	t=7.375	**<0.001**
LMR	5.92±2.26	4.47±1.76	t=3.945	**<0.001**
Glucose	86.90±8.10	93.05±11.08	t=3.524	**0.001**
Triglyceride	114.4±19.9	120.7±23.7	t=1.469	0.144
Total Cholesterol	158.1±27.5	171.8±24.1	t=2.843	**0.005**
HDL-C	47.2±11.6	43.0±5.5	t=2.167	**0.035**
LDL-C	109.4±25.2	114.2±21.7	t=1.108	0.270
Creatinine	0.872±0.190	0.892±0.271	t=0.409	0.684

The results are expressed as mean±sd or median (interquartile range), t: Independent samples t-test, z: Mann-Whitney U test, WBC: White Blood Cell, NLR: Neutrophil Lymphocyte Ratio, MHR: Monocyte-high density lipoprotein- cholesterol ratio, LMR: Lymphocyte-monocyte ratio, PLR: Platelet-lymphocyte ratio, HDL-C: High-Density Lipoprotein Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol.

Table II. Evaluation of the performance of clinical variables in predicting fibromyalgia disease by ROC curve analysis.

Variable	AUC	p	95% CI for AUC	Cutoff point	Sensitivity	Specificity
WBC	0.657	0.002	0.567-0.739	>7.6	56.3	72.5
Monocyte	0.869	<0.001	0.797-0.922	>0.52	77.0	85.0
MHR	0.842	<0.001	0.767-0.901	>0.012	70.1	85.0
LMR	0.695	<0.001	0.607-0.774	≤4.375	54.0	80.0
Glucose	0.681	<0.001	0.593-0.761	>93	54.0	80.0
Total Cholesterol	0.645	0.005	0.556-0.728	>170	51.7	72.5
HDL-C	0.591	0.128	0.501-0.678	≤53	98.8	30.0

AUC: Area under the curve, CI: Confidence Interval, WBC: White Blood Cell, MHR: Monocyte-high density lipoprotein-cholesterol ratio, LMR: Lymphocyte-monocyte ratio, HDL-C: High-Density Lipoprotein Cholesterol.

Table III. Evaluation of factors affecting fibromyalgia disease by binary logistic regression analysis.

	β	Standard error	Wald Statistics	*p*	Odds ratio	Odds ratio for 95% CB Lower bound	Upper bound
Fixed	-4.322	2.931	2.174	0.140	0.013		
LMR	-0.412	0.124	10.981	0.001	0.662	0.519	0.845
Glucose	0.077	0.024	10.218	0.001	1.081	1.030	1.133
Total cholesterol	0.028	0.009	9.426	0.002	1.028	1.010	1.046
HDL-C	-0.097	0.034	8.161	0.004	0.908	0.849	0.970

β: Regression Coefficient, CB: Confidence Bounds. Independent variables included in the model: BMI, smoking, WBC, Hb, LE, Monocyte, MHR, LMR, glucose, triglyceride, total cholesterol L, HDL-C. Elimination method: Wald method with backward elimination Hosmer-Lemeshow Goodness of Fit Statistics: χ^2: 10.573; p=0.227.

In Table IV, the relationship between FIQ and widespread pain scale, VAS, BDI scores, NLR, PLR, LMR, MPV, and MHR ratios were investigated. According to the results in the table, there was a statistically moderate positive correlation between FIQ, VAS, and BDI scores. The other correlation coefficients in the table are not statistically significant.

Discussion

Our results demonstrated that the monocyte level and MHR were higher in patients with FM. NLR was similar to both FM patients and healthy controls. HDL-C level was found lower and total cholesterol level was found higher in patients with FM. LMR was found higher in healthy subjects. We found that increased LMR and HDL-C values were responsible for decreasing the risk of developing FM and increased glucose and total cholesterol values were responsible for increasing the risk of FM developing. There was no association between NLR, MHR, and disease activity in patients with FM. Oxidative stress may play a role in the development of FM and because of protein and lipid oxidation in the vascular wall,

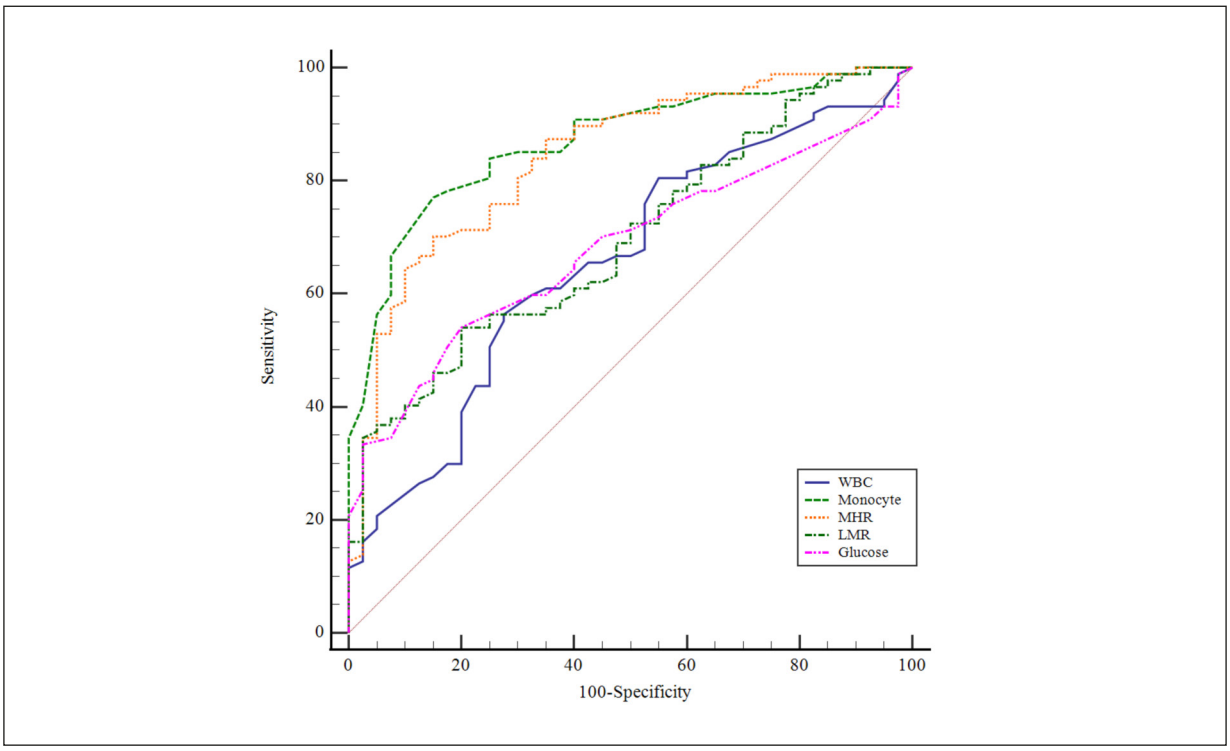

Figure 1. ROC curves for monocyte, MHR, LMR, WBC, and glucose in fibromyalgia patients.

increased oxidative stress is known as a factor in the development of atherosclerosis[21,22]. Paraoxonase-1 enzyme is an antioxidant enzyme and decreased paraoxanaze activity plays a role in coronary artery disease[23,24]. Some studies[22,25] showed reduced paraoxonase activity in patients with FM. Also, Bölük et al[26] found that carotid intima-media thicknesses were increased in patients with FM. Tseng et al[27] showed that diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease were more prevalent in patients with FM[24]. Additionally, monocytes and MHR were known as strong indicators of inflammation[11,12]. MHR was also associated with cardiovascular disease in patients with chronic kidney disease and ischemic stroke patients[13-15]. Thus, patients with FM can have an increased risk of atherosclerosis. Some of our results like increased glucose level, total cholesterol level, and some parameters (MHR) which are related to systemic inflammation, support the increased risk of atherosclerosis in patients with FM similar to the literature. In axial spondyloarthropathy, the neutrophil to lymphocyte ratio (NLR) and red blood cell distribution width (RDW) were found related to disease activity[16]. Increased NLR has a good association with ESR and CRP levels[27]. We did not find any differences in NLR between FM patients and healthy subjects in our study. Also, we did not evaluate RDW level in our study. Although the pathogenesis of fibromyalgia is not fully understood, ESR and CRP levels are usually normal. Therefore, the NLR ratio may not be increased in FM patients. LMR is a valuable marker for inflammation and *ITGA4* and *HLA-DRB1* genes affect LMR levels. Thus, some inflammatory diseases such as rheumatoid arthritis and axial spondyloarthropathy can increase the level of LMR[28]. LMR can be used in the diagnosis and prognosis of many cancers[29]. Differently, in our study, LMR was found higher in healthy subjects. LMR, NLR, and MHR were not found to correlate with disease activity in patients with FM in our study.

To the best of our knowledge, this is the first study evaluating neutrophil-lymphocyte ratio, lymphocyte-monocyte, and monocyte high-density lipoprotein ratios and determining their relationship with disease activity, pain, and depression levels in patients with fibromyalgia. We think that this study will provide valuable contributions to the literature for illuminating the pathogenesis of FM.

Table IV. Correlation of FIQ values with widespread pain scale, VAS, BDI, NLR, PLR, LMR, MPV, and MHR values.

	FIQ
Widespread Pain Scale	rho=0.107; p=0.324
VAS	rho=0.697; p<0.001
BDI	r=0.738; p<0.001
NLR	r=-0.107; p=0.323
PLR	rho=-0.179; p=0.098
LMR	r=0.162; p=0.135
MPV	r=-0.060; p=0.581
MHR	r=-0.054; p=0.617

rho: Spearman correlation coefficient, r: Pearson correlation coefficient, VAS: Visual Analog Scale, BDI: Beck Depression Inventory, WBC: White Blood Cell, NLR: Neutrophil Lymphocyte Ratio, MHR: Monocyte-high density lipoprotein- cholesterol ratio, LMR: Lymphocyte-monocyte ratio, PLR: Platelet-lymphocyte ratio, HDL-C: High-Density Lipoprotein Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, MPV: Mean Platelet Volume.

Conclusions

This study shows that in fibromyalgia patients, monocyte level and MHR were higher than in healthy subjects. There was no association between NLR, MHR, and disease activity in patients with FM. Also, HDL-C level was found lower, and total cholesterol level was found higher in patients with FM.

Increased LMR and HDL-C values were found responsible for decreasing the risk of developing FM and increased glucose and total cholesterol values were responsible for increasing the risk of FM developing.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Ethics Approval

This study was planned retrospectively. The study was carried out with the permission of Hitit University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 31.05.2022, Decision No.: 2022-03).

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Informed Consent

Not applicable.

Authors' Contributions
Doğan AG: Project development, research design, manuscript reviewing, writing, editing and revising.
All authors approved the final version of the study.

Data Availability
The author indicate that the data are available upon request.

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