Original Article

Can the Monocyte-To-HDL Ratio be Used as an Inflammation Marker in Patients with Fibromyalgia Syndrome?

E Erden, AC Turk, E Erden[1]

Department of Physical Medicine and Rehabilitation, Hitit University, Faculty of Medicine, Çorum, [1]Department of Physical Medicine and Rehabilitation, Hitit University Erol Olçok Education and Research Hospital Çorum, Turkey

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Abstract

Background and Aim: The monocyte-to-high-density lipoprotein (HDL) ratio (MHR) may be used as a marker of inflammation and oxidative stress. This study aimed to evaluate the use of MHR and platelet markers in patients with fibromyalgia syndrome (FMS) and demonstrate MHR's relationship with inflammation, the Fibromyalgia Impact Questionnaire (FIQ), and quality of life. **Materials and Methods:** Ninety FMS patients and 90 healthy controls, whose clinical and laboratory evaluations were performed simultaneously, were included in the study. The monocyte, platelet, HDL, MHR, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), mean platelet volume (MPV), and platelet distribution width (PDW) values of all patients were evaluated. The quality of life of the participants was assessed using the FIQ and their general health using the health assessment questionnaire (HAQ). **Results:** Age, body mass index (BMI), and marital status distribution were similar in both groups. The FMS patients had a mean disease duration of 11.29 ± 2.62 months. The median monocyte, platelet, MPV, visual analog scale (VAS), FIQ, and HAQ values and the mean MHR of the FMS patients were significantly higher than the control group, while the mean HDL level was significantly lower ($P < 0.05$). There was a weak negative correlation between the MPV and HAQ score and the PDW and HAQ score (rs = −0.225, $P = 0.042$ and rs = −0.249, $P = 0.024$, respectively), whereas no correlation was detected between the MHR and the FIQ and HAQ scores in FMS patients. According to the receiver operating characteristic curve analysis, MHR had prediction of FMS ($P = 0.002$; *sensitivity* = 0.63, *specificity* = 0.50, *cut-off point* ≥8.4). **Conclusions:** Our results suggest that the monocyte, platelet, HDL, MHR, and MPV parameters can be used in the evaluation of inflammation in FMS patients.

Keywords: *Fibromyalgia Impact Questionnaire, fibromyalgia syndrome, mean platelet volume, monocyte-to-HDL ratio*

Introduction

Fibromyalgia syndrome (FMS) is a chronic musculoskeletal disease characterized by widespread pain in company with symptoms such as joint stiffness, fatigue, sleep disturbance, cognitive problems, anxiety, and depression.[1] The disease is seen three times more frequently in women, with a prevalence varying between 0.2% and 6.6%.[2] In addition to its psychosocial and economic repercussions, FMS is one of the rheumatic diseases that has a great impact on the quality of life and health status of the individual.[3]

The etiology and pathophysiology of FMS have not been fully elucidated yet. The dysfunction of the central and autonomic nervous system, immunological mechanisms,

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Address for correspondence: Dr. E Erden, Department of Physical Medicine and Rehabilitation, Hitit University, Faculty of Medicine 19200, Çorum, Turkey. E-mail: enderden19@hotmail.com

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genetic, hormonal, and environmental factors are thought to play a role in etiopathogenesis.[2] Chronic inflammation was also suggested to play a role in the pathophysiology of the disease. The plasma and/or serum levels of proinflammatory cytokines interleukin (IL) 6 and IL 8 have been shown to increase in FMS patients.[4]

Researchers have recently suggested the use of the monocyte-to-high-density lipoprotein (HDL) ratio (MHR) as a marker of inflammation and oxidative stress.[5-9] Monocytes, which make up 3–8% of the leukocytes in the blood, cause the secretion of proinflammatory and pro-oxidant cytokines during inflammation.[10] High-density lipoprotein, on the other hand, acts as an antioxidant and anti-inflammatory mediator and also protects the endothelium from the harmful effects of low-density lipoprotein (LDL).[11] An abnormal lipid profile has been related to disease activity in patients with active rheumatoid arthritis.[12]

The mean platelet volume (MPV) decreases in active clinical conditions of rheumatic diseases and can be used as a negative acute phase reactant.[13,14] In FMS patients, MPV increases in the presence of cardiovascular disease.[15] Platelets, one of the hematologic parameters, not only have been proven to play a role in hemostasis but are also an important component of the inflammatory response.[16] Platelet distribution width (PDW), on the other hand, is an indicator of the volume variability in platelet size and a more specific marker of platelet activation than MPV since its level does not increase during thrombocytosis.[17] Studies have shown that PDW and MPV can be used as systemic inflammatory markers; MPV is significantly high and PDW is a predictive marker in FMS patients.[18]

The current study aimed to evaluate the use of affordable and easily accessible complete blood count and lipid profile parameters such as monocytes, platelets, HDL, MHR, MPV, and PDW in patients with FMS and demonstrate MHR's relationship with inflammation, the Fibromyalgia Impact Questionnaire (FIQ), and quality of life.

Materials And Methods

Female patients aged 18 years and older and presented to the Department of Physical Medicine and Rehabilitation of our hospital between February 2021 and February 2022 were included in this prospective study. Ninety people diagnosed with FMS, based on the 2016 American College of Rheumatology (ACR) criteria for FMS, constituted the patient group while 90 age- and sex-matched healthy individuals comprised the control group. The Ethics committee approval was obtained from the Clinical Research Committee of University (date: Jan 20, 2021, decision no: 371). Written informed consent was obtained from all patients before the study, which was performed in accordance with the Declaration of Helsinki.

Patients with systemic illnesses such as hyperlipidemia, hypertension, coronary artery disease, diabetes mellitus, thyroid disease, or malignancy, patients with local or systemic infections, active smokers, and those with a history of smoking-alcohol, corticosteroids, lipid-lowering agents, non-steroidal anti-inflammatory drugs, antioxidants, and vitamin supplements were excluded from the study.

Demographic data (age, marital status, body mass index [BMI]) and laboratory results (monocytes, platelets, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], HDL, MPV, PDW) of all participants, and disease durations of the FMS patients were recorded. The MHR was determined by dividing the number of monocytes by the HDL value.

According to the 2016 ACR criteria for FMS, patients should have a widespread pain index (WPI) of at least 7 and a somatic symptom scale (SSS) score of at least 5, or a WPI of 4-6 and a SSS score of at least 9 to receive FMS diagnosis. Generalized pain is defined as pain in at least four of the five following regions of the body (upper left, upper right, lower left, lower right, and axial). In addition, the patient should have persistent symptoms for at least three months. The diagnosis of FMS is made when all the above conditions are met. The diagnosis of FMS can be made independent of other diagnoses. The sensitivity of the above criteria has been reported as 86% and specificity as 90% in the diagnosis of FMS. As for the measurement of the WPI, which ranges between 0 and 19, five body regions and a total of 19 areas have been identified. On the other hand, the SSS score aims to evaluate the fatigue, restless sleep, and cognitive symptoms within the last week and headache, pain or cramps in the lower abdomen, and depression symptoms within the last six months. The SSS score ranges between 0 and 12. The fibromyalgia severity scale (FSS) is calculated by adding the WPI and SSS values and thus ranges between 0 and 31.[19]

We evaluated the quality of life and functionality level of FMS patients using the FIQ. The questionnaire, which evaluates the features associated with FMS, consists of 10 parts (physical functioning, job difficulty, well-being, missed days of work, fatigue, pain, rested, anxiety, stiffness, and depression). The first part, the level of physical functioning, is evaluated with 11 questions, with each question consisting of four grades: 0 (always), 1 (mostly), 2 (occasionally), and 3 (never). The second

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and third parts inquire about "the number of days the participant felt well or was unable to work during the last week" and the answers are given over a seven-grade scale. Sections four through ten are scored using a 10-grade scale and evaluate the symptoms. The total score of the scale ranges between 0 and 100. A score of 50 points indicates a moderate case of FMS, while scores of 70 and above indicate severe cases.[20] The Turkish validity and reliability study of the questionnaire was conducted by Sarmer *et al*.[21]

We evaluated the pain level of the participants using a visual analog scale (VAS). A 10 cm line, with numbers ranging from 0 to 10, was drawn and the patients were requested to mark their pain levels on this line. A score of 0 indicated "no pain" and 10 "the most severe pain."[22]

The general health assessment of the patients was performed using the health assessment questionnaire (HAQ). The HAQ evaluates the daily activities including dressing, walking, arising, eating, reaching, hygiene, gripping, and usual activities under eight headings and a total of 20 questions. All questions are recorded between 0 and 3, and the overall score ranges between 0 and 60. The mean test score is calculated by dividing the total score by the number of questions answered and ranges between 0 and 3.[23] An increase in the test score indicates low health. The Turkish validity and reliability study of the HAQ was conducted by Küçükdeveci *et al*.[24]

Statistical analysis

Statistical analyses were accomplished using the IBM SPSS v. 21 (IBM Corp., Chicago, IL, USA) and the NCSS v. 21.0.3 (NCSS, LLC, Kaysville, UT, USA) software. The descriptive statistics were expressed as mean ± standard deviation for the normally distributed continuous variables, median (*interquartile range*) for the non-normally distributed variables, and frequencies and percentages for the categorical variables. The conformity of the continuous variables with normal distribution was investigated using the Shapiro–Wilk test. The comparisons of the FMS patients and the control group were made by applying the independent sample *t*-test for the normally distributed variables and the Mann–Whitney U test for the non-normally distributed variables. The comparison of the percentages of categorical variables was tested with the Chi-square test. Pearson's correlation analysis was used to explore the relationship between the normally distributed continuous variables and Spearman's correlation analysis for the relationship between the non-normally distributed ones. The performance of the MHR in the prediction of FMS was tested with the ROC curve analysis. A P value < 0.05 was considered statistically remarkable in all analyses.

Results

The FMS patients had a mean age of 40 years and the control group had a mean age of 38 years. Age, marital status, and BMI distribution were correlative in both groups. The patients had a mean disease duration of 11.29 ± 2.62 months. The median monocyte, platelet, MPV, FIQ, WPI, SSS, FSS, VAS, HAQ score and mean MHR of the FMS patients were considerably higher than the control group, while the mean HDL value was significantly lower (P < 0.05). The comparison of demographic data, laboratory findings, and clinical evaluations of the FMS patients and healthy controls is given in Table 1.

The correlation analysis between the MHR, MPV, and PDW values of FMS patients and their FIQ, HAQ, CRP, and ESR was confirmed. There was a weak negative correlation between the MPV and HAQ score and the PDW and HAQ score (rs = −0.225, P = 0.042 and rs = −0.249, P = 0.024, respectively). The results of the correlation analysis of FMS patients are shown in Table 2.

The results of the ROC curve analysis for the prediction of MHR in FMS patients are shown in Figure 1. As a result of the analysis, the area under the curve (AUC) was found 0.633 (95% CI [0.551–0.716]; P = 0.002).

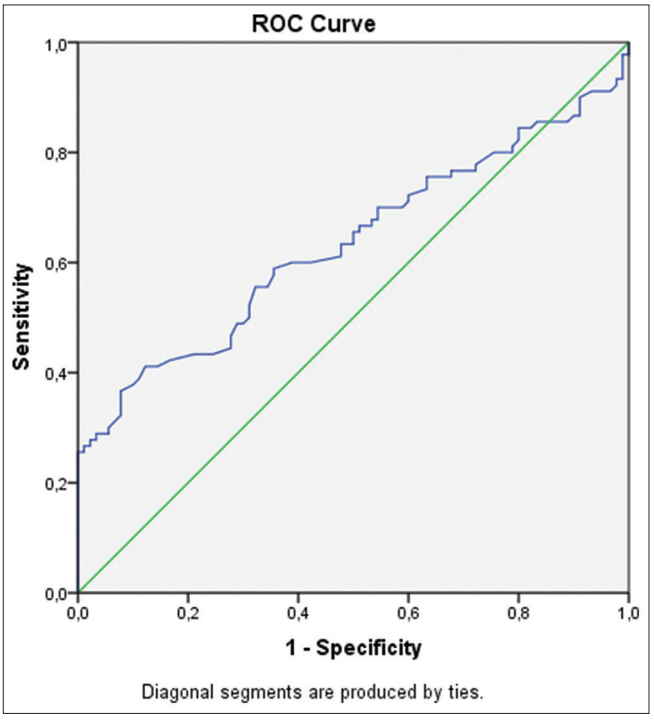

Figure 1: Receiver operating characteristic curve analysis for determining the prediction of the monocyte-to-HDL ratio in fibromyalgia syndrome

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Table 1: Comparison of the demographic, laboratory, and clinical data of the study and control groups

Parameters	FMS patients	Controls	*P*
Age (years), median (range)	40 (20–52)	38 (24–56)	0.269
BMI (kg/m^2)	26.2 (19.1–33.8)	24.8 (22–36)	0.140
Marital status, *n* (%)			
Single	11 (12.2)	16 (17.8)	0.060
Married	79 (87.8)	74 (82.2)	
Duration of the disease (months)	11.3±2.6	-	-
Monocyte (×10^9/L)	0.53 (0.17–0.91)	0.50 (0.28–0.78)	**0.048**
Platelet (×10^9/L)	285 (164–484)	250 (161–450)	**0.025**
HDL (mg/dL)	56.2±11.2	59.7±10.7	**0.032**
MHR	9.6±3.0	8.3±1.7	**<0.001**
CRP (mg/dL)*	3.24 (3.13–4.42)	3.21 (3.13–3.3)	0.651
ESR (mm/hour)*	13 (9.75–20.25)	13 (10–16)	0.488
MPV (fL)	10. 6 (7.8–13.5)	10.3 (2–12.7)	**0.012**
PDW (%)	12.5 (9.2–20.1)	12.3 (4–16.9)	0.239
FIQ score	69.9 (23.9–70.2)	26.2 (6.8–71.4)	**<0.001**
WPI	13 (6–19)	2 (0–9)	**<0.001**
SSS score	8 (5–12)	4 (0–7)	**<0.001**
FSS score	21.5 (12–30)	7 (1–11)	**<0.001**
VAS score	6 (2–9)	3 (1–6)	**<0.001**
HAQ score	0.3 (0–1.8)	0 (0–0.6)	**<0.001**

BMI: Body mass index, HDL: High-density lipoprotein, MHR: Monocyte-to-high-density lipoprotein ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MPV: Mean platelet volume, PDW: Platelet distribution width, FIQ: Fibromyalgia Impact Questionnaire, WPI: Widespread pain index, SSS: Somatic symptom scale, FSS: Fibromyalgia severity scale, VAS: Visual analog scale, HAQ: Health assessment questionnaire. The data are expressed as mean±standard deviation, median, and interquartile range, or *n*, (%). Significant *P* values are written in bold. **n*=82 (FMS group) *n*=54 (Control group)

Table 2: Correlation analyses of the laboratory and clinical parameters of FMS patients

	FIQ	HAQ	CRP	ESR
MHR				
r_s	−0.031	−0.003	−0.022	0.207
P	0.785	0.981	0.847	0.062
MPV				
r_s	−0.225	−0.167	−0.129	0.023
P	**0.042**	0.133	0.248	0.835
PDW				
r_s	−0.249	−0.161	−0.130	0.003
P	**0.024**	0.149	0.244	0.980

MHR: Monocyte-to-high-density lipoprotein ratio, MPV: Mean platelet volume, PDW: platelet distribution width, FIQ: Fibromyalgia Impact Questionnaire, HAQ: health assessment questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate. Significant *P* values are written in bold

According to the ROC curve analysis, MHR was found as a statistically significant variable in differentiating patients with FMS (P = 0.002; *sensitivity* = 0.63, *specificity* = 0.50, *cut-off point* ≥ 8.4).

Discussion

In our study, the monocyte, platelet, MHR, and MPV values were significantly higher in FMS patients alongside of the control group, while the mean HDL value was significantly lower. There was a weak negative correlation between MPV and HAQ score and PDW and HAQ score in FMS patients. In addition, MHR also had a prediction of FMS.

The pathophysiology of fibromyalgia is quite complex and depends on many factors such as neuronal, hormonal, genetic, and psychological. Besides, there are still points in the pathophysiology that are not understood. Inflammation is a defense of the organism against any stimulus and it may be a potential factor that can fill the unclear points in the pathogenesis of fibromyalgia. Inflammation may have a place in the central modulation of pain in fibromyalgia through neuroinflammation. At the same time, peripheral neuroimmune interactions may also alter peripheral nociception.[25] Cytokines, free radicals, and lipid mediators act on the inflammatory cascade. Some of the proinflammatory mediators have been found in high concentrations in fibromyalgia patients.[26] There is evidence of mast cell involvement in fibromyalgia. Thalamic mast cells can affect neuroinflammation by releasing molecules such as IL-6, IL-1β, tumor necrosis factor-α, histamine, calcitonin gene-related peptide, and substance P in fibromyalgia.[27] However, there is not enough information about the role of inflammation in fibromyalgia.[25] Previous studies findings support the idea that immune disorders

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resulting in inflammation may contribute to the etiology of FMS-related symptoms.[28,29] Considering the interaction of proinflammatory cytokines in increasing pain, the idea that peripheral inflammation drives FMS-related symptoms seem plausible.[29-31] In their study, Merriwether *et al*.[32] showed that spontaneous and lipopolysaccharide-stimulated secretion of monocytes, IL-5, and other cytokines in the circulation is at higher contraction than painless women in women with FMS.

The number of studies on MHR in FMS patients is limited. In a study evaluating the relationship of stress with inflammation and pain between 20 FMS patients and 20 age- and sex-matched controls, Taylor *et al*.[33] reported that the percentages of monocytes were similar in both groups, however, there was an inverse relationship between pain and monocyte count. In another study in which 150 FMS patients were evaluated, Al-Nimer and Mohammad found the percentage of monocytes significantly higher than the control group, while they found MHR similar in the two groups.[34] In our study, both monocyte count and MHR were significantly higher in FMS patients. In addition, according to the ROC curve analysis results, we concluded that MHR had a significant prediction of FMS (P = 0.002; sensitivity = 0.63, specificity = 0.50, cut-off point ≥8.4). This shows that MHR is a useful marker for disease activity and inflammatory response in FMS patients.

Patients with FMS are expected to possess a greater risk for metabolic disorders. These patients are prone to the development of dyslipidemia due to both obesity and physical inactivity.[35] Studies have shown increased triglyceride and cholesterol levels in FMS patients.[36,37] In a study evaluating 183 patients with FMS, Cordero *et al*.[38] reported that approximately half of the patients were overweight and had lipid profile disorders. In their study, 62.3% of the patients were overweight or obese. Gurer *et al*.[36] reported that total cholesterol and LDL levels were higher in patients with FMS compared to controls, whereas HDL levels were similar between the groups. In another study, FMS patients with myofascial pain syndrome and the control group were compared and no difference was detected between the two groups with regards to lipid profile (triglycerides, total cholesterol VLDL, LDL, HDL).[37] In addition, the number of tender points and pain severity in the patient group were not related to cholesterol levels. Again, in the same study, FMS patients were found to be heavier compared to the control group. Studies have shown that obesity and the tendency to be overweight increase in FMS patients, and these patients have a lower quality of life, decreased physical activity, and higher pain sensitivity than normal-weight individuals.[39-41] It has been reported in reviews that obesity is characterized by a low-grade chronic inflammatory condition.[42,43] In our study, our patients were overweight and their HDL values were significantly lower than the control group.

It has been reported that positive acute phase reactants increase, negative acute phase proteins decrease and ESR is higher in fibromyalgia patients compared to healthy controls as an indicator of inflammation in fibromyalgia.[44] However, there are also studies reporting that ESR is unchanged in fibromyalgia patients.[15,18,45] Similarly, data on CRP are contradictory. While the CR*P* value was found to be high in fibromyalgia patients in some studies, it was found to be similar in others.[18,45-48] In our study, ESR and CRP levels were similar between groups. In addition, no significant relationship was found between these inflammation parameters and MHR.

The literature has inconsistent results regarding platelet count and platelet markers in FMS patients. In their study evaluating 283 FMS patients and 72 healthy control patients, Haliloğlu *et al*.[15] found the mean MPV values to be significantly higher in FMS patients (8.09 vs. 7.73 fL), while they found the platelet counts to be similar between both groups. In their study of 197 FMS patients and 53 healthy controls, Aktürk and Büyükavcı found the mean MPV value to be significantly higher (10.46 vs. 8.56 fL) and the mean PDW value to be significantly lower (12.97% vs. 19.7%) in the patient group, whereas the mean platelet count was similar in both groups.[18] Contrary to Aktürk and Büyükavcı's findings, Molina *et al*.[49] found that the mean MPV value was significantly lower (8.14 vs. 10.24 fL) and the mean platelet count was significantly higher (272 vs. 214 × 10^9/L) in FMS patients, whereas the PDW value was similar in both groups. Al-Nimer *et al*.[50] evaluated 130 female FMS patients and 35 female controls and reported that the mean MPV (10.6 vs 8.73 fL) and the mean PDW (16.25% vs. 15%) were significantly higher in the patient group, while the mean platelet count was similar in both groups. There are also studies reporting that the platelet count, MPV, and PDW values are similar between FMS patients and controls.[51,52] In our study, the platelet count and MPV were found to be significantly higher in FMS patients compared to healthy controls, while the PDW was similar in both groups.

In the evaluation of the relationship between clinical examinations and laboratory parameters in FMS patients, Al-Nimer and Mohammad found a significant positive correlation between the MHR and FIQ score in FMS patients.[34] In another study, 183 FMS patients were evaluated, and no significant correlation was found

between the FIQ score and HDL.[38] In the current study, we could not find a significant relationship between the FIQ score and MHR. However, significant negative correlations were observed between MPV and HAQ score and PDW and HAQ score in FMS patients.

The fact that patients were not classified as symptomatic and asymptomatic is a limitation of our study. Further assessment of the parameters that we evaluated in our study in the asymptomatic period in FMS patients might be useful in explaining disease activity. In addition, larger patient groups must be examined to generalize the results.

Conclusions

In conclusion, inflammation may be thought to play a role in fibromyalgia syndrome, the etiopathogenesis of which is still not clear. The monocyte, platelet, HDL, MHR, and MPV parameters, which can be easily and affordably derived from complete blood count and lipid profile, can be used in the evaluation of inflammation in FMS patients.

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Conflicts of interest

There are no conflicts of interest.

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