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# The relationship between fibromyalgia syndrome and inflammation parameters in hemodialysis patients

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## ABSTRACT

**Objectives:** Diagnosing fibromyalgia, a condition characterized by widespread body pain of unknown origin accompanied by various additional symptoms, poses a challenge in hemodialysis patients, who frequently experience musculoskeletal disorders. To investigate the relationship between fibromyalgia syndrome and inflammation parameters in hemodialysis patients.

**Methods:** The study enrolled 311 hemodialysis patients undergoing treatment for over three months. Demographic characteristics, complete blood count, and biochemical values were documented as part of the study. To assess fibromyalgia, the researchers recorded the patients scores on the Generalized Pain Scale and Symptom Severity Scale based on data provided by the American College of Rheumatology. The patients were then divided into two groups: those with fibromyalgia and those without fibromyalgia, and their laboratory values and rates were compared. Inflammatory parameters such as erythrocyte sedimentation rate, c reactive protein, monocyte-to-lymphocyte ratio, lymphocyte-to-c reactive protein ratio, and c reactive protein to albumin ratio were recorded.

**Results:** The study included 311 patients on hemodialysis for more than three months. Among the study participants, 48.9% of the patients and 62.9% of those with fibromyalgia were women. The mean age was 54±26 years and was significantly higher in patients with fibromyalgia (P<0.001). Monocyte (P<0.03), C-reactive protein (P<0.01), erythrocyte sedimentation rate (P<0.02), Monocyte to lymphocyte ratio (P=0.028), c reactive protein to albumin ratio (P<0.005) were significantly higher, lymphocyte to c reactive protein ratio (P<0.004) and albumin (P=0.018) were significantly lower in the fibromyalgia group.

**Conclusions:** Fibromyalgia should be considered in the presence of high inflammation parameters in hemodialysis patients with diffuse musculoskeletal pain.

**Keywords:** Fibromyalgia, hemodialysis, inflammation parameters, hematological indices

Chronic kidney disease represents a significant public health concern and has a detrimental impact on the quality of life [1]. Hemodialysis is the most commonly employed renal replacement therapy for individuals with chronic kidney disease, a condition frequently associated with musculoskeletal disorders [2]. Fibromyalgia syndrome (FS) is a prevalent pain disorder characterized by tenderness and stiffness in specific anatomical regions. Mood and sleep disturbances, fatigue, and functional impairments often ac-

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company it. FS is an extra-articular rheumatic disease influenced by non-modifiable risk factors such as age, gender, cultural and ethnic background, genetics, inflammation, and low socioeconomic status. The pain experienced in fibromyalgia tends to worsen with movement, leading to reduced physical activity and limited sun exposure. These factors contribute to an increased risk of osteoporosis and pose challenges in diagnosing and treating both bone mineral disorders and fibromyalgia in hemodialysis patients [3-7].

The 2010 American College of Rheumatology (ACR) criteria for fibromyalgia syndrome, which can affect all ages and genders and for which no clear pathophysiologic cause is known, have facilitated diagnostic evaluation [8]. Since there are no predictable biomarkers for the diagnosis, evaluation requires more active use of questionnaire methods questioning the severity, location, and prevalence of pain. Complete blood counts and laboratory tests are requested from every patient admitted to the hospital. Many diseases are associated with inflammatory processes, and standard parameters such as erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) have been used in the past. The role of non-routinely used indices in defining inflammation is increasing. Many studies have shown that tests such as neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), mean platelet volume (MPV), red blood cell distribution volume (RDW), CRP, monocyte lymphocyte ratio (MLR), CRP albumin ratio (CRPABO), lymphocyte CRP ratio (LCRPO) are associated with inflammatory processes [9-21].

Hemodialysis patients are known to be in an inflammatory process. It has been stated that half of the patients with the glomerular filtration rate (GFR) level of 15-60 mL/min had a CRP level of>2.1 mg/dL [22]. Uremic environment, decreased clearance and increased proinflammatory cytokines, oxidative stress, acidosis, acute and chronic diseases related to the dialysis process. Factors related to infections, changing adipose tissue metabolism and extracorporeal circulation (purity of dialysis water, microbiological quality, membrane compatibility) also play an additional role in inflammation [23]. The aim of this study was to investigate the guiding value of inflammatory parameters in the diagnosis of fibromyalgia in hemodialysis patients in the inflammatory process.

This study aimed to investigate the guiding value of inflammatory parameters in diagnosing fibromyalgia in hemodialysis patients with inflammatory processes.

## METHODS

The study included 311 patients on hemodialysis for more than three months. Patients with known rheumatologic disease, osteoporosis, malignancy, hemiplegia, hypothyroidism or hyperthyroidism, malnutrition, inflammatory bowel disease, and those on hemodialysis for less than three months were excluded. Demographic data such as age and gender and history of hypertension, diabetes mellitus, coronary artery disease, cerebrovascular diseases, hypothyroidism, anxiety, depression, and dementia were recorded. Monthly income level and home heating type were recorded for socioeconomic status. Complete blood count and neutrophil-lymphocyte ratio (NLO), monocyte lymphocyte ratio (MLO), platelet mean platelet volume ratio (PMPVO), CRP albumin ratio (CRPALBO), platelet lymphocyte ratio (PLO), lymphocyte CRP ratio (LCRP) and albumin, Laboratory results including calcium, phosphorus, ferritin, parathormone (PTH), uric acid, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), thyroid stimulating hormone (TSH), bicarbonate, alkaline phosphatase (ALP) were recorded.

The diagnosis of fibromyalgia is based on the examination of tenderness at specific anatomical sites and is made using the widespread pain scale (WPI) and symptom severity scale (SS) in the American College of Rheumatology (ACD) 2010 update. The degree of physical disability is determined with the Fibromyalgia Impact Scale (FES). In our study, FS diagnosis and FES were determined by applying these questionnaires to the patients. The widespread pain scale (WPI) is a scoring scale ranging from 0 to 19 for persistent pain in at least four of the five zones (upper and lower left, upper and lower right abdomen, upper and lower right abdomen, and axial region) in the last seven days. The SS consists of two groups. First group A (all items including fatigue, waking up without rest, cognitive findings, and somatic symptoms in the last week are scored between 0-3) and second group B (headache in the last six months, pain-cramps in the lower abdomen, presence of depression are assessed)

A+B total is a maximum of 12 points. The maximum WPI+SS total is 31 points. Accordingly, scores below a total of 12 points are not suggestive of fibromyalgia. The data obtained from each patient were summed for these scores, and those with fibromyalgia were identified.

The fibromyalgia impact scale (FES) was recorded according to the American College of Rheumatology (ACD) criteria. The FES consists of 4 components, and in the first component, 11 activities of daily living, such as shopping, laundry, cooking, and making the bed, are evaluated on a Likert scale from 0-3. The total score obtained is divided by the number of questions, and the average score is obtained. This score is multiplied by 3.33 for normalization. In the second component, the number of days the participant feels well is scored inversely proportional to the severity of the disease and multiplied by 1.43 for normalization. In the third component, the number of days unable to go to work and do household chores is multiplied by 1.43 for normalization. In the fourth component, the scores of questions 4-10 are taken. A total of 50 points and above means that physical disability has increased.

The study group was divided into two groups as those with fibromyalgia (FS+) and those without (FS-). Inflammation and hematologic parameters, ratios, and biochemistry parameters were compared between the groups.

The study was approved by Health Sciences University Ankara Training and Research Hospital Ethical Committee (Decision no: E-22-1011, Date: 27. 07.2022). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Statistical Analysis

Analyses were conducted using UN Statistical Package for the Social Sciences 22.0 version (IBM SPSS Corp.; Armonk, NY, USA). Categorical variables were expressed as frequency (n) and percentage (%). Continuous variables were tested for conformity to a normal distribution by Kolmogorov-Smirnov and expressed as arithmetic mean, standard deviation, median, minimum, and maximum values. The student-t test was used to compare continuous variables with normal distribution, while those without normal distribution were analyzed by the Mann-Whitney U test. Pearson-$\chi 2$ and Fisher's exact tests were used for categorical variables. Spearmen's correlation was used for correlation analysis, and $P<0.05$ was accepted as the significance level. Receiving operating characteristic (ROC), curve was used to find the sensitivity and specificity threshold values of hematologic ratios.

## RESULTS

Among the patients who participated in the study, 48.9% were women, and 62.9% of patients with fibromyalgia were women. The mean age was 54 years (IQR 26). Age was significantly higher in FS+ hemodialysis patients ($P<0.001$), and female gender was significantly higher ($P<0.002$). FS+ hemodialysis patients had significantly higher rates of hypertension ($p<.027$), anxiety ($P=0.016$), depression ($P<0.001$), and dementia ($P=0.010$). In the FS+ group, the rate of catheter access to hemodialysis was high ($P<0.002$), and home heating was stove ($P=0.024$). A comparison of demographic and laboratory data of the groups is presented in Table 1, and co-morbid conditions and socioeconomic status are presented in Table 2.

There was no difference in the duration of dialysis and KT/V ratio between FS+ and FS- groups on hemodialysis. There was no difference between white cell count, lymphocyte, and neutrophil cell counts in both groups. Monocyte cell count was significantly higher in the FS+ group ($P<0.03$). Hemoglobin, platelet, and mean platelet volume did not differ between the groups.

There was no significant difference between the groups in glucose, calcium, phosphorus, magnesium, total protein, uric acid, alkaline phosphatase, total cholesterol, thyroid stimulating hormone, total iron saturation, vitamin B12, creatinine kinase, and bicarbonate levels. PTH was significantly lower in FS+ patients compared to non-FS+ patients ($P=0.013$). The folic acid level was significantly lower in the FS+ group. CRP, a marker of inflammation, was significantly higher in the FS+ group ($P<0.01$), and erythrocyte sedimentation rate was significantly higher ($P<0.02$). Ferritin, a negative acute phase reactant, was significantly higher in the FS+ group ($P<0.05$). Albumin level was significantly lower in the FS+ group ($P=0.018$).

In the ratios of inflammation parameters, CRPALBO was significantly higher ($P<0.005$), MLO was

**Table 1. Group demographic and laboratory data**

| | Total (n=311) | FS (+) (n=89) | FS (-) (n=222) | t, z, x² | P value |
|---|---|---|---|---|---|
| Age (years) | 54 (26) | 62 (21) | 51 (27) | -4.458 | **<0.001** |
| Gender | | | | | |
| Female | 48.9% | 62.9% | 43.2% | | **<0.002** |
| Male | 51.1% | 37.1% | 56.8% | | |
| Dialysis time (h) | 4 (4.5) | 4 (4.5) | 4 (4.5) | -0.392 | 0.695 |
| KT/V | 1.6 (0.48) | 1.63 (0.49) | 1.60 (0.52) | 0.973 | 0.330 |
| WBC ($\times 10^9$/L) | 6.98 (3.09) | 7 (2.91) | 6.93 (3.14) | -0.089 | 0.929 |
| Neutrophil ($\times 10^9$/L) | 4.66 (2.42) | 4.62 (2.36) | 4.66 (2.46) | -0.347 | 0.729 |
| Lymphocyte ($\times 10^9$/L) | 1.6 (0.86) | 1.55 (0.86) | 1.61 (0.87) | -1.015 | 0.310 |
| Monocytes ($\times 10^9$/L) | 0.60 (0.28) | 0.64 (0.33) | 0.57 (0.27) | -2.169 | **<0.030** |
| Hb (g/dL) | 10.97±1.6 | 10.79±1.54 | 11.05±1.63 | 1.291 | 0.198 |
| PLT ($\times 10^9$/L) | 202 (94) | 208 (96) | 199.5 (89) | -0.869 | 0.385 |
| MPV (fL) | 10.32±1.11 | 10.43±1.09 | 10.27±1.11 | -1.142 | 0.254 |
| CRP (mg/dL) | 7.4 (13.7) | 8.6 (18.8) | 6.3 (12.5) | -2.588 | **<0.010** |
| ESR (mm/h) | 27 (33) | 33 (37.5) | 24.5 (29.2) | -2.331 | **<0.020** |
| Glucose | 105 (63) | 106 (78) | 104.5 (54) | -0.440 | 0.660 |
| Calcium | 8.63 (0.92) | 8.55 (0.93) | 8.68 (0.91) | -1.057 | 0.290 |
| Phosphorus | 4.72±1.5 | 4.54±1.55 | 4.78±1.47 | 1.284 | 0.200 |
| Magnesium | 2.04 (0.74) | 2.01 (0.60) | 2.08 (0.79) | -0.995 | 0.320 |
| Total protein | 6.7±0.80 | 6.8±0.90 | 6.65±0.88 | -1.712 | 0.088 |
| Albumin | 3.9 (0.5) | 3.8 (0.5) | 3.9 (0.5) | -2.361 | **0.018** |
| Uric acid | 6.1 (1.80) | 5.9 (1.55) | 6.2 (1.92) | -1.791 | 0.073 |
| ALP (IU/L) | 121.09 (83) | 113.98 (75) | 123.2 (84) | -0.621 | 0.535 |
| PTH (IU/L) | 389 (488.7) | 346.7 (366.3) | 405 (505.9) | -2.497 | **0.013** |
| Cholesterol (mg/dL) | 155 (50) | 162 (56) | 151 (50) | -1.609 | 0.109 |
| Ferritin (ng/mL) | 575 (479.1) | 663.3 (503.4) | 560.2 (477.4) | -1.936 | 0.053 |
| TSH (mlU/L) | 1.7 (1.8) | 1.82 (2) | 1.65 (1.6) | -1.396 | 0.163 |
| B12 vitamin (pg/mL) | 479 (495) | 494 (520) | 465 (483) | -0.457 | 0.648 |
| Folate (ng/mL) | 10.5 (17.7) | 8.65 (14.2) | 12.38 (17.8) | -2.132 | 0.033 |
| CK (U/L) | 60 (61) | 54 (72) | 61 (57) | -0.232 | 0.817 |
| Bicarbonate (mEq/L) | 21.2 (4.5) | 21.1 (5.2) | 21.3 (4.1) | -0.364 | 0.716 |
| NLO | 2.88 (1.88) | 2.73 (1.9) | 2.98 (1.88) | -0.079 | 0.937 |
| MLO | 0.354 (0.20) | 0.38 (0.18) | 0.33 (0.20) | -2.204 | **0.028** |
| PMPVO | 20 (10.08) | 20 (12.09) | 20 (9.01) | -0.407 | 0.684 |
| CRPALBO | 1.89 (3.49) | 2.45 (5.5) | 1.57 (3.04) | -2.814 | **<0.005** |
| PLO | 126.7 (71.2) | 131 (75.7) | 125.9 (69.9) | -1.196 | 0.232 |
| LCRPO | 0.217 (0.41) | 0.167 (0.29) | 0.243(0.42) | -2.876 | **<0.004** |

Data are shown as mean±standard deviation[a] or mean (IQR)[b]. WBC=White blood cell, Hb=Hemoglobin, PLT=Platelets, MPV=Mean platelet volume, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, ALP=Alkaline phosphatase, PTH=Parathormone, TSH=Thyroid stimulating hormone, CK=Creatinine kinase, NLO=Neutrophil lymphocyte ratio, MLO=Monocyte lymphocyte ratio, PMPVO=Platelet MPV ratio, CRPALBO= CRP albümine ratio, PLO= Platelet lymphocyte ratio, LCRPO=Lymphocyte CRP ratio.

**Table 2. Co-morbid diseases and socioeconomic status of groups**

| | | FS (-) | FS (+) | P value |
|---|---|---|---|---|
| **Diabetes mellitus** | No | 71.6% | 61.8% | 0.091 |
| | Yes | 28.4% | 38.2% | |
| **Hypertension** | No | 37.8% | 24.7% | **0.027** |
| | Yes | 62.2% | 75.3% | |
| **Coronary artery disease** | No | 80.2% | 75.3% | 0.340 |
| | Yes | 19.8% | 24.7% | |
| **Cerebrovascular accident** | No | 96.8% | 92.1% | 0.070 |
| | Yes | 3.2% | 7.9% | |
| **Hypothroidi** | No | 95% | 98.9% | 0.113 |
| | Yes | 5% | 1.1% | |
| **Anxiety** | No | 92.3% | 83.1% | **0.016** |
| | Yes | 7.7% | 16.9% | |
| **Depression** | No | 92.8% | 79.8% | **<0.001** |
| | Yes | 7.8% | 20.2% | |
| **Dementation** | No | 99.5% | 95.5% | **0.010** |
| | Yes | 0.5% | 4.5% | |
| **Vascular Acces** | AVF | 71.2% | 52.8% | **<0.002** |
| | Catheter | 28.8% | 47.2 | |
| **Warming** | Stove | 63.1% | 76.4% | **0.024** |
| | Radiator | 36.9% | 23.6% | |
| **Monthly income** | <5.000 | 75.7% | 78.7% | .853 |
| | 5.000-10.000 | 21.6% | 19.1% | |
| | >10.000 | 2.7% | 2.2% | |

AVF=arteriovenous fistula

significantly higher (P=0.028), and LCRPO was significantly lower (P<0.004) in the FS+ group. There was no significant difference between NLO, PMPVO, and PLO between the two groups.

There was a negative correlation between the fibromyalgia effect score and LCRPO (r=-.237, P<0.001), a positive correlation between CRPALBO (r=.237, P<0.001), a positive correlation with ESR (r=.166, P<0.003), a positive correlation with MLO (r=.116, P=0.041) and a strong positive correlation with CRP (r=.223, P<0.001) between the FS+ group and the FS- group.

When ROC analysis was performed for MLO, CRPALBO, and LCRP, which showed significant differences in the FS+ group, the area under the curve was found to be significant at P=0.028, P<0.005 and P<0.004, respectively (Fig. 1).

## DISCUSSION

This study showed that inflammation was more prominent in the group with fibromyalgia in hemodialysis patients. In addition to the significant difference in MLO, CRPALBO, and LCRPO ratios between FS+ and FS- groups, these ratios were correlated with fibromyalgia effect score, and ROC analysis supported these data. This study suggests that inflammatory

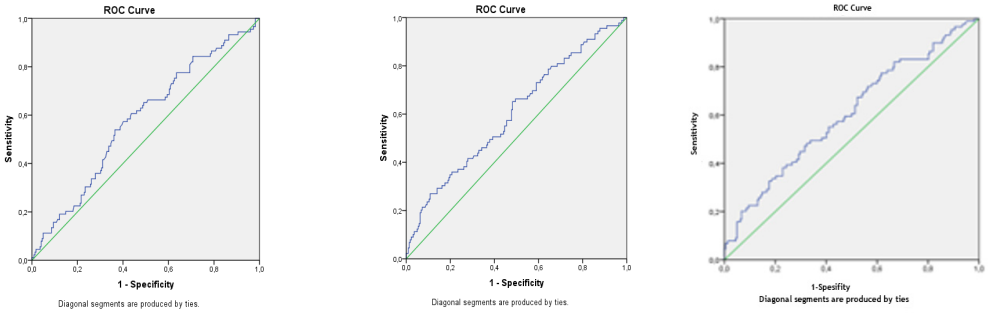


**Fig. 1. ROC analysis of MLO, CRPALBO and LCRPO between FS (+) and FS (-) groups.**

| Ratio | AUC (95%) | Cutt-off | P value | Sensitivity (%) | Spesifity (%) |
|---|---|---|---|---|---|
| MLO | .580(.510-.650) | .36 | **0.028** | .419 | .581 |
| CRPALBO | .602(.532-.672) | 1.97 | **<0.005** | .450 | .550 |
| LCRP | .604(.534-.674) | .20 | **<0.004** | .562 | .563 |

MLO=Monocyte lymphocyte ratio, CRPALBO= CRP albümine ratio, LCRPO=Lymphocyte CRP ratio

markers may serve as predictors for the diagnosis of fibromyalgia in hemodialysis patients.

The absence of differences in dialysis duration and KT/V between FS+ and FS- hemodialysis patients indicate the comparability of the two groups and suggests the absence of bias. Furthermore, the significant findings of MLO, CRPALBO, and LCRPO in FS+ hemodialysis patients suggest the involvement of inflammation in the condition. In a previous study by Varim *et al*. [11], it was reported that the lymphocyte-to-monocyte ratio was significantly lower in the fibromyalgia group compared to healthy volunteers, which aligns with the significantly higher Monocyte lymphocyte ratio and monocyte count observed in this study involving hemodialysis patients.

NLO, PLO, and PMPVO, which have started to be used in the diagnosis of systemic inflammation from non-traditional hematologic ratios, were not found significant in this study. This study's findings, which show a lack of clinically significant correlation between pain severity and MPV in patients with fibromyalgia, are consistent with the study conducted by Jayakrishnan *et al*. [15]. This increase in acute exacerbations may be attributed to chronic inflammation in chronic hemodialysis patients. This study was not compatible with the study of Aktürk and Büyükavcı [16], who found NLO and MPV to be significantly higher and PDW to be significantly lower in the comparison of healthy controls and fibromyalgia patient group. Haliloğlu *et al*. [19] found no difference between ESR, CRP, white blood cell count, and platelet count in the control group and fibromyalgia group; only MPV was found to be significantly higher and interpreted as increased platelet activation and increased risk of cardiovascular disease. Korniluk *et al*. [20] reported that the hematology standardization committee approved MPV as an acceptable parameter for many diseases. The two groups in the present study consisted of hemodialysis patients, and there was no significant difference in MPV.

In a study conducted by Yazıcı *et al*. [24] in rheumatoid arthritis patients compared with a control group, MPV was found to be correlated with disease activity, ESR, and CRP. In this study, ESR and CRP inflammation markers were significantly higher in the fibromyalgia group. It was not associated with MPV. In a large-scale community screening study by Feinberg *et al*. [189, a significant positive association of fibromyalgia with serum CRP was found in hemodialysis patients with fibromyalgia in this study.

Yücetürk *et al*. [7] found a high fibromyalgia effect score (FES) in hemodialysis patients with fibromyalgia compared to the control group. In this study, FES was found to be high in hemodialysis patients with fibromyalgia and correlated with MLO, CRPALBO, and LCRPO. No difference was found between albumin, calcium, phosphorus, ALP, TSH, and PTH in the study by Yücetürk *et al*. In this study, only PTH and albumin were significantly lower in hemodialysis patients with fibromyalgia. It was evalu-

ated as a low-cycling bone mineral disorder due to immobilization. The increase in fibromyalgia pain with movement is considered a factor in this situation's development. In a comparison of healthy volunteers and the fibromyalgia group by Al-Nimer *et al*. [17], it was reported that the evaluation of hemotologic ratios with FES could be used in diagnosis and prognosis follow-up. This study showed a significant positive correlation between the FES score and MLO, CRP, ESR, and CRPALBO.

The study by Taylor *et al*. [14], which investigated monocyte subpopulations in healthy controls and fibromyalgia patient groups, reported a positive correlation between stress, pain, and monocyte subpopulations. This finding aligns with the significantly higher monocyte count observed in hemodialysis patients with fibromyalgia in the current study. Both studies suggest a potential relationship between stress, pain, and alterations in monocyte populations in fibromyalgia, supporting the notion of a similar pattern of association.

In a study by Çağlıyan Türk *et al*. [21] with hemodialysis, peritoneal dialysis, and transplant patients, the relationship between the frequency of depressive symptoms and anxiety in patients with fibromyalgia was also found in this study. Laboratory parameters were not significantly different in hemodialysis, peritoneal dialysis, and transplantation patients. In this study, inflammation parameters MLO, CRPALBO, CRP, ESR, and LCRPO were significant in hemodialysis patients with fibromyalgia. It is known that half of the patients with GFR 15-60% ml/min had CRP >2.1mg/dL [22]. The effect of inflammation in fibromyalgia syndrome is also known. Changes in parameters and rates monitored in hemodialysis patients who are exposed to the same inflammation load, which may also be affected by environmental and genetic factors, may be guiding in patients clinically suggestive of fibromyalgia. The frequency of fibromyalgia, which is found at 2-8% in the general population, in patients receiving renal replacement therapy is not fully known [5].

As in many studies, fibromyalgia was found to be more common in the female gender in this study. Since the gender distribution is not normal, the absence of a significant relationship other than age in the FS+ and FS- group comparisons made only in females can be explained by further studies.

### Limitations

The limitations of our study include not to study pro-inflammatory cytokines, adhesion molecules, adipokines and related factors, and anti-inflammatory cytokines and the relatively small number of cases.

## CONCLUSION

The results of this study show that inflammation parameters and hematologic ratios can be used in the diagnosis of fibromyalgia, the pathophysiology of which has not been fully elucidated. Monocytes, MLO, CRP, CRPALBO, ESR, and LCRPO and their relationship with fibromyalgia effect score suggest that they can be used in prognosis follow-up. Since the items under the curve in ROC analysis are significant, further studies are needed to determine the exact cut-off values.

*Authors' Contribution*

Study Conception: SKŞ, RB; Study Design: SKŞ; Supervision: RB; Funding: SKŞ; Materials: SKŞ; Data Collection and/or Processing: SKŞ; Statistical Analysis and/or Data Interpretation: SKŞ, RB; Literature Review: SKŞ; Manuscript Preparation: SKŞ and Critical Review: SKŞ, RB.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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