Significance of inflammation markers in complete blood count in patients with fibromyalgia

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Abstract

Objective: Fibromyalgia is a chronic pain disorder mostly seen in women, it mainly characterized by diffuse body pain accompanied by chronic fatigue and depression-like mood disorders. Its etiology still remains unknown but in some studies, fibromyalgia has been reported to be an inflammatory disease several cytokines shown to be responsible for the possible inflammatory basis of the disease. No laboratory marker is currently available to diagnose the disease. We aimed to investigate the diagnostic significance of inflammation markers in fibromyalgia, including platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte (MLR) ratio, and mean platelet volume (MPV).

Material and Methods: This retrospective and case-control study included 188 patients who were followed up and treated for fibromyalgia in physical therapy and rehabilitation outpatient clinic from 2017 through 2019 and 64 age-matched healthy controls. The PLR, NLR, MLR, MPV and vitamin D were calculated from the results of complete blood count test. The differences between the two groups were examined.

Results: The mean age, hemoglobin levels, and erythrocyte sedimentation rates were not different between the groups. In fibromyalgia group, the values of PLR (p = 0.031), NLR (p = 0.044), MLR (p = 0.023), and MPV (p = 0.013) were higher than those in control group, whereas vitamin D levels were significantly lower (p = 0.021). In multivariate regression analysis, PLR, NLR and MLR were not found to be independent predictors (p> 0.05).

Conclusion: The findings of this study reveal that NLR, MLR, PLR, and MPV are not independent markers for the diagnosis of fibromyalgia, suggesting that fibromyalgia does not appear to be an inflammatory disease.

Keywords: fibromyalgia, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, monocyte to lymphocyte ratio, inflammation marker.

Introduction

Fibromyalgia is a chronic pain condition characterized by a constellation of symptoms, including pain, tenderness, fatigue, anxiety, sleep dysfunction, cognitive impairment, and mood disturbances. Although the etiology of fibromyalgia remains unclear, changes in sleep stages, hormonal and biochemical alterations, mood disorders, and central nervous system dysfunction have been suggested to have a role in the etiologic process (1,2) .

In some studies, fibromyalgia has been reported to be an inflammatory disease, with several cytokines shown to be responsible for the possible inflammatory basis of the disease, such as IL-8 and tumor necrosis factor (TNF) (3-5). Mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) are the markers that can be simply detected by complete blood count (CBC) and are reported to increase in the presence of inflammation.

There are studies indicating that PLR and MPV are higher in rheumatoid arthritis patients compared to healthy subjects and their levels are directly proportional to disease activity. Similar findings are also available for other inflammatory diseases (6-9). We aimed to investigate the PLR, NLR, MLR, and MPV levels in fibromyalgia patients in order to determine whether inflammation plays a role in fibromyalgia

Material and Method

Study population: From 2017 through 2019, a total of 188 patients who were admitted to physical therapy and rehabilitation outpatient clinic and diagnosed with fibromyalgia based on the American School of Rheumatology (ACR) 2010 criteria and 64 age-matched healthy subjects were included in the study. Patients with follow-up fibromyalgia and newly diagnosed fibromyalgia were included.

People without any known disease was included to control group. Exclusion criteria were defined as follows; pregnancy, any cancer history, the presence of leukocytosis and active infection.

Data collection: The patient demographic and laboratory characteristics including age, gender, CBC parameters, erythrocyte sedimentation rate (ESR), and serum 25OH vitamin-D levels were recorded after a retrospective scan of the written archive files or hospital digital automation recording system. The values of the patients at the time of admission to the physical therapy and rehabilitation outpatient clinic were recorded. The PLR, NLR, and MLR were calculated by dividing the platelet count, the neutrophil count, and the monocyte count by the lymphocyte count, respectively. The values (PLR, NLR, MLR, MPV, Vitamin D) were compared between the two groups in order to examine whether to have a significant relationship. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis: All statistical analyses were performed using SPSS Statistics version 22.0. Shapiro-Wilk test was used to determine whether or not the data were normally distributed. Student-t test was used for normally distributed data and Mann-Whitney-U test was used for non-normally distributed data. Pearson and Spearman tests were used for correlation analysis. Logistic regression analysis was used to determine the independent predictors. $p < 0.05$ was considered as statistically significant.
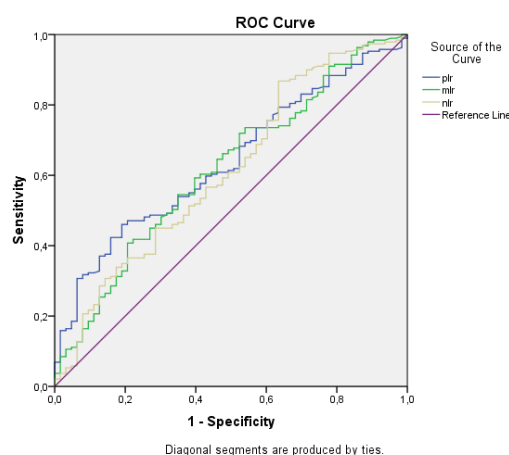
Results

A total of 252 subjects, including 188 patients with fibromyalgia and 64 age-matched healthy controls, were analyzed. The mean age was 48.4 ± 9.3 years for patients and 45.8 ± 10.9 years for the control group, with no significant difference between the groups ($p = 0.066$). In the fibromyalgia group, MPV values were higher ($p = 0.013$) and vitamin D levels were significantly lower than those in the control group ($p = 0.021$). PLR, MLR, and NLR were significantly higher in fibromyalgia group compared to healthy subjects. Hemoglobin and ESR levels were similar between the two groups ($p = 0.352$ and $p = 0.124$, respectively).

The comparisons between the groups are shown in Table 1. When ROC analysis was performed for PLR, MLR, and NLR, the area under the curve was 0.642, 0.614, and 0.623, respectively. According to ROC analysis, the threshold values were 120.3 for PLR, 0.16 for MLR, and 1.76 for NLR (Graphic 1). Multivariate logistic regression analysis including 'age' and levels of 'hemoglobin' (Hb<12 gr/dl - Hb≥12 gr/dl),, 'vitamin D' (<30 IU - ≥30IU),, and 'ESR' (<20 mm Hg - ≥ 20 mm Hg) which might affect CBC results revealed that, PLR, MLR, and NLR were not independent markers for the diagnosis of fibromyalgia ($p = 0.074$, $p = 0.091$, and $p = 0.234$, respectively).

Table 1. Comparison of Hb, MPV, ESR, platelet counts, vitamin-D levels, PLR, NLR, and MLR between fibromyalgia patients versus healthy controls (N=252).

Variables	Fibromyalgia group (n=188)	Control group (n=64)	P
Hb, (gr/dL) mean ± SS	12.76 ± 1.27	12.93 ± 1.28	0.352*
MPV, mean ± SS	10.51 ± 1.30	10.09 ± 1.14	**0.013***
Platelet (x10³/µL), mean ± SS	287.79 ± 67.53	276.16 ± 58.88	0.224*
ESR, (mm Hg) mean ± SS	20.21 ± 10.24	17.41 ± 7.59	0.124*
Vitamin D (IU), mean ± SS	13.95 ± 9.08	20.14 ± 10.34	**0.021***
PLR, median (range)	133.01 (86 - 354.23)	117.61 (55.92 - 218.95)	**0.031¶**
MLR, median, (range)	0.19 (0.02 - 0.95)	0.16 (0.01 - 0.49)	**0.023¶**
NLR, median, (range)	1.86 (0.13 - 19.83)	1.27 (0.59 - 6.11)	**0.044¶**

PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; ESR, erythrocyte sedimentation rate; Hb, Hemoglobin; MPV, mean platelet volume. ¶Data reported as median (min-max),*Data reported as mean ± standart deviation

Graphic 1. ROC curve for PLR, NLR, and MLR (the values of area under the curve; PLR: 0.642, NLR: 0.614, MLR: 0.623)

Discussion

According to the results of this study, although the values of NLR, PLR, MLR, and MPV were significantly higher in fibromyalgia patients than those in healthy controls, regression analysis revealed that these parameters were not independent biomarkers for predicting the diagnosis of fibromyalgia.

These above-mentioned markers can be easily detected by simple CBC test and are used to determine the inflammation (10, 11). In addition, they are very helpful in determining both activity and prognosis of most rheumatic and proliferative diseases; however, such relation was not found in our study. In fact, the role of inflammation in fibromyalgia is highly controversial and the findings of our study therefore support the absence of inflammatory pattern in fibromyalgia (12). In another study including smaller number of patients and controls than those in our study, no significant differences were shown between the groups in terms of PLR, NLR, and MPV levels (13). In a study analyzing the MPV levels, it was shown that MPV did not have an independent predictive significance for the diagnosis of fibromyalgia (14). In another study with a similar hypothesis, PLR was found to be significantly higher in fibromyalgia patients compared to healthy subjects, but no significant difference was found between the two groups in terms of NLR, showing different results from our findings; however, the authors included smaller sample size than that in our study and did not perform a regression analysis (15). In another study examining the NLR and MPV levels in fibromyalgia, these values were found to be significantly higher in patients with fibromyalgia than those in healthy subjects; however, whether they were independent markers for the diagnosis of fibromyalgia were not examined by a regression analysis (16). By contrast, in another study, which found NLR, but not PLR and MLR, to be significantly higher in fibromyalgia patients than healthy subjects, reported that MLR, NLR, and MLR were the independent determinants for the diagnosis of fibromyalgia in regression analysis performed for fibromyalgia impact questionnaire, suggesting these markers as predictive in determining the severity of the disease. However, these factors (i.e., age, hemoglobin, vitamin D, ESR) that could affect inflammation markers were not differentiated by regression analysis (17). Moreover, it is also possible that the increase in inflammation makers by pain severity may be associated with another inflammatory event that may increase the pain at that time.

Because of the retrospective nature of our study, the fibromyalgia impact questionnaire and its relation with inflammation markers could not be evaluated, but the above-mentioned factors such as age, hemoglobin, vitamin D, and ESR that could affect inflammation markers were analyzed in cox regression analysis.

In patients with rheumatoid arthritis, which is an inflammatory disease, these values were found to be significantly higher than those in the control group, while the results in patients with osteoarthritis are conflicting (18-21). According to the findings of some studies we can say that Chronic low-grade systemic inflammation may also underlie the pathophysiology in chronic generalized pain conditions, such as fibromyalgia (22, 23). Aside from its retrospective nature, not recording the data regarding comorbidities and drug use were the other limitations in our study. Especially vitamin D treatment may affect the blood parameters but unfortunately vitamin D supplementation was not recorded. By adding these missing data, it will be useful to conduct further prospective studies with larger study groups.

Conclusion

In conclusion, the presence or absence of inflammation in the etiopathogenesis of fibromyalgia still remains controversial and unclear. In our study, although the indirect inflammation parameters in CBC were found to be higher in fibromyalgia patients, none of them could be shown to have an independent association with fibromyalgia

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