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Hematological indices and pain features in women with chronic pain: a study in fibromyalgia patients

Sofia Passaponti
sofia.passaponti2@unisi.it
University of Siena
Ilenia Casini
University of Siena
Livio Clemente
University of Bari Aldo Moro
Marina Tommaso
University of Bari Aldo Moro
Anna Maria Aloisi
University of Siena

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Abstract

Introduction: Chronic pain is a common and disabling condition in women. Fibromyalgia, one of the most prevalent chronic pain disorders, is characterized by widespread pain, fatigue, and reduced quality of life. Altered hematological and inflammatory parameters may contribute to symptom burden through impaired tissue oxygenation and low-grade inflammation.

Methods: In this retrospective observational study, 60 women with fibromyalgia were evaluated. Chronic pain severity and disease impact were assessed using the Visual Analogue Scale (VAS) and Fibromyalgia Impact Questionnaire (FIQ). Routine hematological parameters were collected, including red blood cell indices, hemoglobin, hematocrit, platelets, and leukocyte subsets. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammation response index (SIRI) were calculated. Correlations between pain measures and hematological variables were analyzed.

Results: Most participants reported severe chronic pain and marked disease impact. Several hematological values were close to the lower or upper limits of reference ranges, with some values outside normal ranges. Red blood cell count was negatively correlated with mean corpuscular hemoglobin ($r = -0.60$, $p < 0.0001$) and mean corpuscular volume ($r = -0.66$, $p < 0.0001$). PLR was negatively correlated with mean corpuscular hemoglobin ($r = -0.40$, $p < 0.05$), suggesting lower hemoglobin content in women with higher inflammatory burden and chronic pain status.

Conclusion: Women with fibromyalgia and chronic pain showed hematological patterns potentially consistent with altered oxygen transport and low-grade inflammation. Routine blood parameters may help improve the clinical assessment and management of chronic pain in women with fibromyalgia.

Introduction

Several studies have evaluated the possible association between tissue oxygenation and chronic pain, with particular attention to fibromyalgia (FM) patients, as recently reviewed [1, 2]. Interest in this topic arises from common FM symptoms, including fatigue, muscle pain, and brain fog, which may be linked to vascular and blood abnormalities. Reduced tissue oxygenation, potentially related to impaired blood flow or vasoconstriction driven by neural and endocrine factors, may compromise cellular function. A possible involvement of hypoxia in FM pain was suggested by Fassbender [3]. Later, other studies conducted to evaluate various aspects of the cardiovascular system found both functional and morphological abnormalities in FM patients; for example the presence of microcirculatory disturbances at the tender points in FM patients was correlated with the measured reduction in local blood flow with an imbalance between oxygen supply and demand [4]; increased concentration of red blood cells (RBC), decreased RBC velocity and consequent decrease in blood flow in the skin over the tender point [5], fewer capillaries per mm [6] and significantly more capillary dilation in FM patients than in control subjects [7] have been described.

Possible causes of reduced tissue oxygenation include vasoconstriction linked to hormonal factors (e.g. adrenaline, vasopressin, angiotensin), neuronal activity (reflex circuit with prolonged muscle contraction, sympathetic activity with release of noradrenaline) and platelet mediators such as serotonin [2]. All these substances can reduce blood flow to the tissues [5, 8]. Recently, blood values have been combined to obtain indices with clinical significance, i.e. neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic inflammation response index (SIRI) are recognized as accessible and affordable markers due to the blood count tests routinely performed on patients [9–12]. NLR is the ratio between neutrophils and lymphocytes. Neutrophils secrete cytokines and many other inflammatory factors, while lymphocytes are an important component of the host immune system. Therefore, NLR is a useful marker for evaluating the inflammatory response [13], and PLR, a ratio between platelet and lymphocyte counts, is also used as a biomarker for the systemic inflammatory response. SIRI is a new and more comprehensive marker based on the composition ratio of the number of neutrophils, monocytes and lymphocytes in the peripheral blood. It is considered an inflammatory marker that has been studied in rheumatoid arthritis [14]. However, the combined evaluation of routine hematological parameters,

oxygenation-related red blood cell indices, inflammatory ratios, and menopausal status in women with fibromyalgia remains poorly explored.

Therefore, this study aimed to investigate routine hematological parameters and inflammatory indices in women with fibromyalgia, and to explore their associations with pain severity and menopausal status.

Methods

Women who had been diagnosed with fibromyalgia for at least 6 months were asked to take part in a retrospective observational study conducted as part of routine clinical practice, in accordance with the informed consent form signed at first access to the pain centres. Data were collected from April 2023 to April 2025 in the Neurophysiopathology Unit, DiBrain Department, Policlinico General Hospital, Bari Aldo Moro University, Bari (ethics committee of the General Hospital of Aldo Moro University of Bari - approval number 7173 2022 1 22).

Among the cases visited, patients diagnosed with FM according to the 2016 ACR criteria [15] were selected. Inclusion criteria were an age of 18–65 years, female gender, no concomitant neurological and/or general medical diseases, including active rheumatological diseases, no concomitant or recent treatment with CNS-active drugs or excessive use of analgesics and FANS (more than 10 months), and availability of blood tests performed in the previous 3 months.

Women were divided into two groups: Pre-Menopausal women (Pre-MW), if still in the reproductive period and Menopausal women (MW), in menopausal condition for at least 1 year.

To quantify pain intensity and to evaluate FM features, the following scales were administered to the patients. 1) The visual analogue scale (VAS) is a unidimensional measure of pain. It consists of a 10-cm-long horizontal line (0-no pain, 10-maximum pain experienced). Patients were asked to indicate the average VAS experienced in the last week [16]. 2) The fibromyalgia impact questionnaire (FIQ) is a fibromyalgia-specific outcome instrument designed to assess health status, progress and outcomes in patients with FM. It contains ten subscales (e.g. function, pain level, fatigue, sleep disturbance, psychological distress, etc.) that are combined into a total score: a higher score indicates a worse condition. Each of the 10 items has a maximum possible score of 10. Thus, the maximum possible score is 100. The average FM patient score is about 50, while in severely afflicted patients, the score can reach 70 [17].

The following blood parameters were collected from reports supplied by the patients: red blood cells (RBC count, $x10^{12}$/L), hemoglobin (Hb, g/dL), hematocrit (HT, %), mean corpuscular volume (MCV, fL), mean corpuscular hemoglobin (MCH, pg), mean corpuscular hemoglobin concentration (MCHC, g/dL), platelet count ($x10^{9}$/L), white blood cells (WBC, $x10^{9}$/L), neutrophils ($x10^{9}$/L), lymphocytes ($x10^{9}$/L) and monocytes ($x10^{9}$/L).

The following ratios were calculated:

- The neutrophil-to-lymphocyte ratio (NLR) is the ratio between neutrophil and lymphocyte values and is used to measure the inflammatory state; in the healthy adult population, it is between 1 and 3 [18].
- The platelet-to-lymphocyte ratio (PLR) is the ratio of platelet count to lymphocyte count. The normal range of PLR in healthy individuals is between 90 and 210 [18, 19], while other studies have observed that values higher than 180 may be pathological [20]. For our analysis, we considered values between 90 and 180 as the normal range.
- The Systemic Inflammation Response Index (SIRI) is an inflammatory index calculated using three types of blood cells: neutrophils, monocytes, and lymphocytes. The most common formula to calculate it is: *SIRI = (Neutrophils × Monocytes) / Lymphocytes*. There is no universally standardized reference value for SIRI, as it can vary depending on the population and clinical context. However, in healthy individuals, SIRI values typically range around 0.5–1.2 [10, 21].

Statistical Analysis

Blood values were divided and reported in tables with arbitrary ranges to allow a better distribution of values within the 'normal' range. Data distribution was assessed using the Shapiro–Wilk test. One-way ANOVA was used to analyze the different data with the factor Menopause (2 levels: Pre-menopausal women, Pre-MW; Menopausal Women, MW). To assess the relationship between variables, Pearson's correlation coefficient was used as a measure of rank correlation. A $p < 0.05$ was considered significant. All analyses were performed with Statistica® (StatSoft Inc, Tulsa, USA) software. Data are reported as the mean and standard error of the mean (mean ± SEM).

Results

Fibromyalgic women (n = 60) were met in person in the Bari unit, and they all signed the informed consent form and filled out the questionnaires. All women suffered from FM for longer than 6 months. Based on their reproductive condition, women were divided into: Pre-MW (n = 16, mean age 41.0 ± 1.21 years) if still in the reproductive period, or MW if in menopause (n = 44, mean age 60.9 ± 0.9 years).

As reported in Fig. 1, most of the women showed VAS values equal to or higher than 7 (VAS 0–10) and FIQ values higher than 50 (FIQ 0-100), indicating high pain intensity and low quality of life. No correlations were found between pain scores and blood parameters.

A detailed list of blood parameters and the different ranges is reported in Table 1. Data were collected and evaluated considering the normal reference values present in the analysis. The table shows several values outside the normal range or in ranges at higher or lower normal limits.

For HT, the normal range considered was from 38% to 46%; both Pre-MW and MW had the highest number of subjects in the normal range, but close to the lower/upper limits; 7 subjects had values under the lower limit. In 4 women, the values were higher than the normal range.

For RBC, normal values were considered from $4x10^{12}$/L to $5.5x10^{12}$/L. As reported in Table 1, three women had RBC values lower than $4x10^{12}$/L, and three had values higher than $5.5x10^{12}$/L. RBC was negatively correlated with MCH ($r=-0.60$, $p < 0.0001$) and MCV ($r=-0.66$, $p < 0.0001$), indicating lower Hb content and lower RBC volume in women with high RBC numbers.

For Hb, the normal range for women was 12.00–15.00 g/dL; 2 MW women showed values lower than 12.00 g/dL, and 6 had values higher than 15.00 g/dL (2 Pre-MW and 4 MW).

Table 1

Hematocrit (HT, %), Red Blood Cells (RBC count, x10^{12}/L), Hemoglobin (Hb, g/dL), Mean Corpuscular Volume (MCV, fL), Mean Corpuscular Hemoglobin (MCH, pg), Mean Corpuscular Hemoglobin Concentration (MCHC, g/dL), Platelet count (x109/L), Withe Blood Cells (WBC, x109/L), Neutrophils (x109/L), Lymphocytes (x109/L) and Monocytes (x109/L) determined in Pre-MW (premenopausal women) and MW (menopausal women). Number of subjects in each range. Values in the normal ranges are in bold.

Blood parameters means ± SEM	***Range***	***Pre-MW (N=)***	***MW (N=)***	***Blood parameters means ± SEM***	***Range***	***Pre-MW (N=)***	***MW (N=)***	***Blood parameters means ± SEM***	***Range***	***Pre-MW (N=)***	***MW (N=)***
HT Pre-MW: 40.6 ± 0.9 MW: 43.3 ± 2.3	1) < 36.00	1	1	**WBC** Pre-MW: 6.1 ± 0.3 MW: 6.4 ± 0.3	1) 4.00-4.99	3	8	**MCV** Pre-MW: 87.7 ± 2.0 MW: 88.9 ± 1.2	1) 60.00–70.00	0	2
	2) 36.00-37.90	2	3		2) 5.00-5.99	4	17		2) 70.01-80.00	2	1
	3) 38.00-39.90	6	14		3) 6.00-6.99	2	5		3) 80.01-85.00	3	5
	4) 40.00-41.90	1	12		4) 7.00-7.99	5	2		4) 85.01-90.00	4	13
	5) 42.00-43.90	2	8		5) > = 8.00	0	9		5) 90.01-95.00	2	13
	6) 44.00-45.90	3	3	**Neutrophils** Pre-MW: 3.3 ± 0.3 MW: 3.3 ± 0.2	1) < 2.00	1	3		6) 95.01–100.00	4	6
	7) 46.00-47.90	1	1		**2) 2.00-4.99**	12	31	**MCH** Pre-MW: 29.2 ± 0.6 MW: 29.3 ± 0.4	1) 20.01-26.00	2	2
	8) > = 48.00	0	2		**3) 5.00–7.00**	0	3		2) 26.01-28.00	2	3
RBC Pre-MW: 4.6 ± 0.1 MW: 4.7 ± 0.1	1) 3.50-4.00	2	1		4) > 7.00	0	1		3) 28.01-30.00	4	15
	2) 4.01–4.50	3	14	**Lymphocytes** Pre-MW: 2.3 ± 0.1 MW: 2.3 ± 0.1	1) < 1.50	0	5		4) 30.01-32.00	6	12
	3) 4.51-5.00	9	22		**2) 1.50–2.50**	9	22		5) > 32.00	1	0
	4) 5.01–5.50	2	4		**3) 2.5–3.50**	4	7	**MCHC** Pre-MW: 33.5 ± 0.3 MW: 33.1 ± 0.2	1) 30.00-31.99	0	5
	5) 5.51-6.00	0	3		4) > 3.5	0	4		2) 32.00-33.99	11	21
HB Pre-MW: 13.6 ± 0.3	1) < 12.10	0	2	**Monocytes** Pre-MW: 0.6 ± 0.0	**1) 0.20–0.80**	13	33		3) 34.00-35.99	4	5
	2) 12.10-	5	15		2) 0.81-	0	3				

Blood parameters means ± SEM	***Range***	***Pre-MW (N=)***	***MW (N=)***	***Blood parameters means ± SEM***	***Range***	***Pre-MW (N=)***	***MW (N=)***	***Blood parameters means ± SEM***	***Range***	***Pre-MW (N=)***	***MW (N=)***
MW: 13.5 ± 0.2	**12.99**			MW: 0.6 ± 0.0	1.00						
	3) 13.00-13.99	6	14		3) > 1.00	0	2				
	4) 14.00–15.00	3	9	**Platelet** Pre-MW: 257.9 ± 9.5 MW: 260.5 ± 8.5	**1) 150–200**	1	4				
	5) 15.10–16.00	2	4		**2) 201–250**	6	14				
					3) 251–300	6	10				
					4) 301–350	1	8				
					5) 351–400	0	1				

As shown in Table 2 and Fig. 2, although most of the subjects had NLR within the normal range (1–3 score), 2 Pre-MW and 8 MW showed values lower than 1, while 1 MW had this ratio higher than 3.

For PLR, 8 women showed values lower than 90 (2 Pre-MW and 6 MW) and 4 MW had values higher than 180. PLR was negatively correlated with MCH ($r=-0.40$, $p < 0.05$) indicating lower Hb content in RBC in women with high PLR.

SIRI values were lower than 0.5 in 10 subjects (2 Pre-MW and 8 MW) and higher than 1.2 in another 10 subjects (2 Pre-MW and 8 MW). SIRI tended to be correlated with platelets ($r = 0.27$, $p = 0.06$, Fig. 2) indicating a possible involvement of platelets in the inflammatory condition.

Table 2
Neutrophile-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR) and Systemic Inflammation Response Index (SIRI) determined in Pre-MW (premenopausal women) and MW (menopausal women). Number of subjects in each range in both groups.

Ratio ***mean ± SEM***	***Range***	***Pre-MW***	***MW***
NLR	LOW (< 1)	2	8
Pre-MW: 1.5 ± 0.2	NORMAL (1–3)	11	29
MW: 1.5 ± 0.1	HIGH (> 3)	0	1
PLR	LOW (< 90)	2	6
Pre-MW: 120.4 ± 7.4	NORMAL (90–180)	11	23
MW: 120.3 ± 6.1	HIGH (> 180)	0	4
SIRI	LOW (< 0.5)	2	8
Pre-MW: 0.9 ± 0.1	NORMAL (0.5–1.2)	9	22
MW: 0.9 ± 0.1	HIGH (> 1.2)	2	8

Discussion

This study evaluated routine haematological parameters and derived inflammatory indices in women with fibromyalgia. Although most values fell within laboratory reference ranges, several patients had results close to the upper or lower limits of normal, whilst some values were outside the expected range. Furthermore, specific associations emerged between certain selected variables, particularly between PLR and MCH, suggesting a possible relationship between inflammatory balance and erythrocyte function. Overall, these results support the hypothesis that mild haematological alterations may contribute to the manifestation of symptoms in a subgroup of patients with fibromyalgia.

Red blood cell (RBC) counts were ‘normally’ elevated in several women, close to or above 5×10^{12}/L, whilst haematocrit (HT) was close to or below 38% in several women. We therefore hypothesise that in these patients, haematological characteristics may compromise oxygen delivery to cells, causing tissue hypoxia. Indeed, a higher red blood cell count can impair blood flow, reduce blood supply and increase erythropoietin release, creating a vicious cycle capable of abnormally increasing the red blood cell count; on the other hand, lower-than-normal levels of red blood cells, haemoglobin (Hb) and haematocrit may be considered capable of inducing hypoxia.

Many morphological and/or clinical factors may be involved in determining tissue hypoxia, and among the primary causes to consider are the various physiological events leading to vasoconstriction. Oxygen supply to certain areas of the body can be strongly influenced by a range of vasoconstrictors released or produced under various conditions [2], such as adrenaline and noradrenaline, released by the sympathetic nervous system during stress. Similarly, both angiotensin and vasopressin are potent vasoconstrictors capable of significantly reducing blood flow when blood volume is low.

On the other hand, nitric oxide (NO) has significant vasodilatory effects. It is interesting to note that an altered NO metabolism has been observed in patients with FM [22]. The synthesis of this gaseous transmitter is induced by many compounds, including estrogens [23]; indeed, it is well known that pre-menopausal women have a lower incidence of heart attacks due to the presence of estrogens [24]. The estrogen-induced NO-mediated vasodilation may be altered due to the decrease in estrogen observed following the menopause, surgical intervention (ovariectomy), stressful events capable of reducing hypothalamic-pituitary-adrenal/gonadal activity, or drug-induced endocrinopathies[25, 26]. As these events occur

at all ages, it is not uncommon for young women to have low estrogen levels. Women with FM often experience heavy menstrual bleeding, which may be considered an indicator of low estrogen levels [27]. Therefore, a lack of estrogen may reduce blood flow to the muscles, decreasing NO production both directly and indirectly through heavy and prolonged menstruation.

Another hypothesis suggests that FM is associated with increased levels of NO in the circulating blood due to the stimulatory effect of estrogen on NO. Indeed, it has been suggested [28] that structural abnormalities in the muscle tissue of FM patients may be induced by the production of various intracellular second messengers, such as NO; this condition may induce abnormal cell death in muscle tissue, which could contribute to the structural and metabolic defects that have been identified in the muscle of FM patients.

In patients with FM, a low blood count may be due to alterations in intestinal function, which have already been demonstrated in women with FM [29], and which can significantly reduce the absorption of essential nutrients such as vitamin B12 and folic acid. Another important gut-related factor that can induce tissue hypoxia is the release of 5-HT by intestinal enterochromaffin cells into the blood, leading to widespread vasoconstriction [30]. Once in the blood, this neurotransmitter can be taken up by platelets, which may release it under altered vascular conditions, for example, during low-grade inflammation, when blood vessels alter their characteristics by increasing wall adhesion [31].

It should be noted that the elevated levels of red blood cells, haemoglobin and blood pressure observed in some women with FM may also be considered the result of dehydration. Water intake should be assessed in patients with FM, particularly in older individuals, in whom a reduced sense of thirst is also observed. Therefore, elevated blood values may suggest this simple need, which requires 'behavioural' treatment, namely an increase in water consumption and/or a change in diet to avoid diarrhoea.

An increased red blood cell count may coexist with suboptimal tissue oxygen delivery when accompanied by higher blood viscosity and impaired microcirculatory flow. Under these conditions, tissue perfusion may be reduced despite apparently adequate cell numbers [32]. In the present study, the negative correlation between RBC count and MCH/MCV suggests that a higher erythrocyte number may be associated with smaller cells and lower hemoglobin content, potentially reducing oxygen transport efficiency.

Chronic low-grade inflammation, frequently reported in fibromyalgia, may further contribute to vascular dysfunction and altered rheology. Interactions among blood cells, platelets, leukocytes, and the endothelium have been described in inflammatory states and may slow microvascular flow. In line with this hypothesis, previous studies have reported increased inflammatory markers, including erythrocyte sedimentation rate (ESR), in subsets of patients with fibromyalgia [33, 34].

Persistent alterations in tissue perfusion could also be relevant for peripheral nerve function, as small nerve fibers are particularly sensitive to metabolic stress. This may be of interest considering reports of small fiber abnormalities in some patients with fibromyalgia [35].

In the present study, MCHC was in the normal range for most of the patients, although in some subjects it was at the lower limit, similar to other studies (i.e. [34]). This suggests that the RBC of FM patients may contain a lower concentration of Hb than that of healthy subjects, with consequent impairment of tissue oxygen delivery and fatigue.

Neutrophils constitute the major component of the leukocyte population. They secrete cytokines, chemokines and enzymes, including neutrophil elastase, matrix metalloproteinase 9 (MMP9) and vascular endothelial growth factor (VEGF) [36]. Lymphocytes, in turn, are an important component of the host's immune system [37]. The neutrophil-to-lymphocyte ratio (NLR) is a useful marker in the assessment of the inflammatory response [13]. In the present study, most of the women were in the normal range. Similarly, only a few showed an elevated PLR. An elevated PLR has been linked with an array of adverse health conditions, including severe coronary atherosclerosis, heart failure and malignancy, signifying a

higher inflammatory state and increased risks of adverse events in these conditions [19]. FIQ, a specific FM pain parameter, showed a strong tendency to be positively correlated with PLR, suggesting that platelets, with their ability to carry 5-HT and induce vasoconstriction and thrombosis, can be involved in FM pain. Likewise, SIRI, a more comprehensive indicator based on the composition ratio of blood cell subgroups, tended to be correlated with platelets, supporting the functional interaction between inflammation and platelet activation.

Overall, all these factors can contribute to hypoxemia, a condition that can be present with both lower or higher numbers of RBC, and hypooxygenation can be the basis for some of the main symptoms in FM, i.e. muscle pain and tenderness.

In conclusion, blood parameter values can be useful in FM management due to the possible direct effects on pain and quality of life conditions.

Declarations

Ethics approval and consent to participate

This retrospective observational study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the General Hospital of Aldo Moro University of Bari (approval number: 7173/2022/1/22). Written informed consent for the anonymous use of clinical data for research purposes was obtained from all participants at their first access to the centre.

Consent for publication

Not applicable, as no identifiable personal data are included in this manuscript.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contribution

SP, AMA, IC, LC, MDT: data analysis, literature review, results interpretation, manuscript drafting and revision; AMA, MDT: concept and design, data analysis, literature review, results interpretation, manuscript drafting and revision. All authors have read and agreed to the published version of the manuscript.

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to institutional and ethical regulations.

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Figures

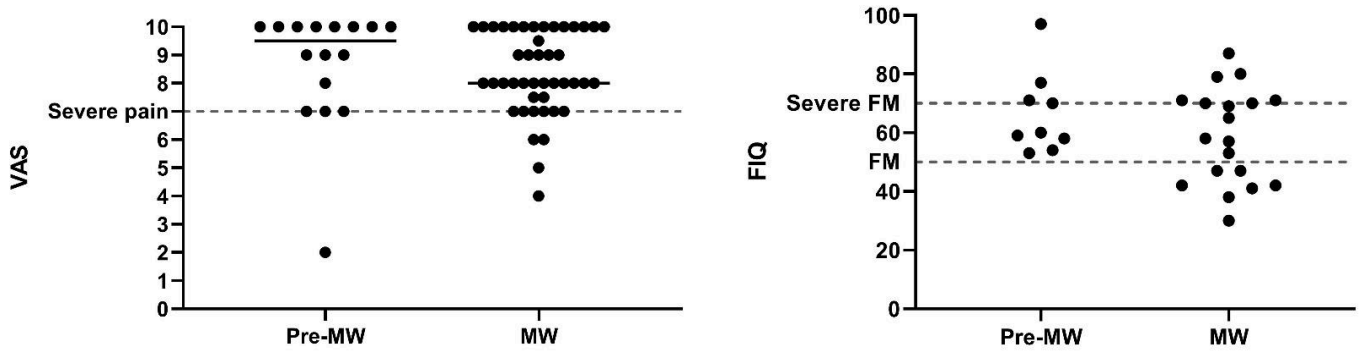


Figure 1

Visual analogue scale, VAS and fibromyalgic impact questionnaire, FIQ, were determined in premenopausal women, Pre-MW and menopausal women, MW groups.

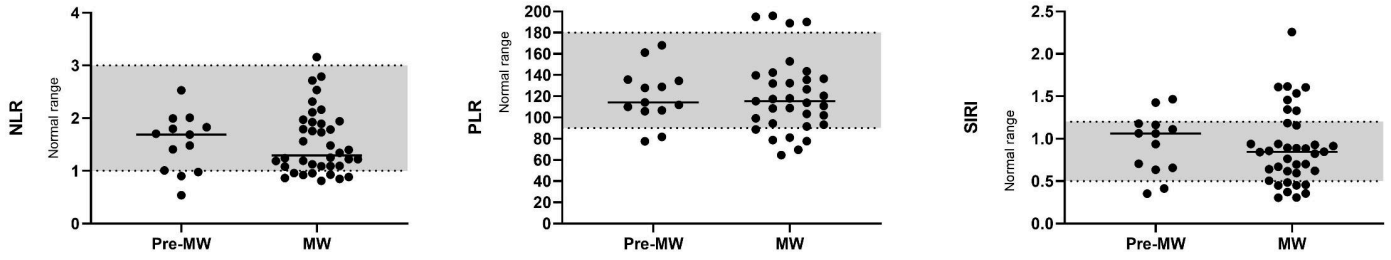


Figure 2

Neutrophile-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR) and Systemic Inflammation Response Index (SIRI) were determined in premenopausal women (Pre-MW) and menopausal women (MW) groups.