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Comparison of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and red blood cell distribution width during the attack phase of familial Mediterranean fever with the silent phase of the disease in patients referred to the emergency department

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Abstract: **Objective:** As patients with acute-phase familial Mediterranean fever (FMF) require prompt diagnosis for optimal management, we are conducting a study to compare inflammatory markers during the attack and silent phases in individuals referred to the emergency department.

Methods: This case-control study involved 184 FMF patients under 16 years old, with data collected at Bo Ali Hospital's emergency department in Ardabil city throughout 2022. Patients in the attack phase were assessed by emergency medicine specialists, while those in the silent phase were recruited from the rheumatology clinic. Hematological parameters were obtained from venous blood samples, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and red blood cell distribution width (RDW) were calculated. Statistical analyses included 1-Sample Kolmogorov-Smirnov, ANOVA, Tukey's-b post hoc, Independent Samples T-test, Kruskal-Wallis, and Pearson Chi-squared tests.

Results: In the attack group, the NLR correlated with increased leukocytes (r=0.652, P<0.001) and RDW (r=0.310, P=0.003). The non-attack group showed a correlation between the NLR and higher leukocytes (r=0.384, P<0.001) and ESR (r=0.214, P=0.04). Additionally, the attack group exhibited a correlation between the PLR and higher leukocytes (r=0.711, P=0.009), and ESR (r=0.285, P=0.014) while no correlation was found in the non-attack group.

Conclusion: Our study revealed that RDW levels were significantly higher in FMF patients, indicating clinical inflammation. During FMF attacks, NLR and PLR ratios were notably elevated, making them key markers for systemic inflammation in these patients.

Keywords: Attack Phase; Familial Mediterranean Fever; Lymphocyte; Neutrophil; Platelet

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1. Introduction

Familial Mediterranean fever (FMF) stands as an intriguing and intricate autoinflammatory disorder with a genetic basis, primarily affecting populations around the Mediterranean sea (1). Characterized by recurrent episodes of fever, accompanied by abdominal pain, chest pain, joint inflammation and other symptoms. FMF poses significant challenges in both diagnosis and management (2). The prevalence of this disease worldwide stands at 116 per 100,000 people, while in Iran, it is notably lower than 18 per 100,000 people. However, owing to the rarity of this condition, the prevalence across various provinces in Iran, including Ardabil province, remains largely unexplored (3). Understanding the dynamics of inflammatory markers during different phases of the disease becomes crucial for enhancing diagnostic precision and tailoring effective therapeutic strategies (4).

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The investigation of these hematological parameters is not arbitrary; rather, it is rooted in the intricate interplay between the immune system, inflammatory response, and hematopoietic elements in the context of FMF(5).Neutrophils and lymphocytes, integral components of the immune system, reflect the ongoing inflammation and immune activation. The neutrophil to lymphocyte ratio (NLR), calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, has emerged as a valuable indicator of systemic inflammation, with elevated levels often associated with various inflammatory conditions (6).

Similarly, platelets and their interaction with lymphocytes unveil crucial insights into the inflammatory landscape. Platelets play multifaceted roles, not only in hemostasis but also in immune responses (7).The platelet to lymphocyte ratio (PLR), derived from the ratio of platelet count to lymphocyte count, provides a composite measure of both proinflammatory and anti-inflammatory components, offering a dynamic perspective on the immune-inflammatory balance (8).

Beyond cellular components, the RDW, a measure of the variability in red blood cell size, adds an additional layer to our understanding. While traditionally known as a marker for anemia, RDW has recently gained attention for its potential role as a marker of systemic inflammation (9).

Changes in RDW may reflect alterations in erythropoiesis and the overall inflammatory milieu, making it a valuable parameter in assessing disease states characterized by chronic inflammation, such as FMF (10,11).

FMF, with its characteristic recurrent attacks of inflammation, presents a unique scenario for exploring the dynamics of these hematological parameters. The differentiation between the attack and silent phases is pivotal, as it allows for the examination of variations in these markers during active inflammatory episodes and quiescent periods (12).The emergency department setting serves as a critical backdrop for this investigation, as it is often the frontline for managing acute FMF episodes, where early and accurate identification of disease activity is of paramount importance (13).

This study aims to contribute to the existing body of knowledge by elucidating how NLR, PLR, and RDW evolve during the distinct phases of FMF in emergency department patients. By undertaking this comparative analysis, we aspire to unravel patterns that may serve as potential diagnostic and prognostic markers, ultimately aiding clinicians in making informed decisions regarding the management of FMF patients in acute settings.

The dynamic nature of these hematological parameters during different phases of FMF offers a window into the complex interplay between inflammation and the immune system. Insights gleaned from this study may pave the way for more tailored and timely interventions, moving beyond the conventional diagnostic paradigms (14).

In a study conducted by Dinçer et al. in 2022, it was noted that the sample size was small, and the researchers acknowledged this as a limitation of the study, recommending future investigations with larger sample sizes. Moreover, the study primarily focused on adults, overlooking the unique considerations of children, who represent a sensitive and vulnerable population requiring timely diagnosis and treatment. Therefore, recognizing the need to address this gap, we have decided to undertake the present study, specifically targeting children to enhance our understanding of inflammatory markers during different phases of FMF in this critical demographic (15). Given that patients referred to the emergency room with FMF during the acute phase require a swift diagnosis, early identification serves as the foundation for effective management. Recognizing the pivotal role of immune system markers in promptly identifying these patients, we have undertaken a study aimed at comparing the NLR, PLR and RDW during the attack phase of FMF with the silent phase of the disease in individuals referred to the emergency department.

2. Methods

2.1. Study design

This current research is a case-control study involving 184 FMF patients under the age of 16 who were referred to the emergency department of Bo Ali Hospital in Ardabil city from the beginning to the end of 2022.

2.2. Sampling

Sample size was determined using the following formula, based on the results of a similar study (5) among patients with FMF:

$n=(Z_{1-\beta}+Z_{1-\alpha}/2)^2.(S_1{}^2+S_2{}^2/(\mu_1-\mu_2)^2$

In accordance with this formula, a type I error rate of 0.05 and a type II error rate of 0.2 were considered, resulting in $Z1-\beta=0.85$, $Z1-\alpha/2= 1.96$.

The standard deviation of the NLR ratio in the patient group (S1) was 3.07, and in the control group (S2) was 3.50. Additionally, the mean NLR ratio was 6.3 in the patient group ($\mu1$) and 14.1 in the control group ($\mu2$). Applying the formula, the sample size was calculated as 184 individuals (92 in each group). These children were included in the study using convenience sampling.

2.3. Eligibly criteria

The key inclusion criteria for entry into the study comprised patients under the age of 16, a definitive diagnosis of FMF (FMF diagnosis relied on the Hashomer diagnostic criteria and was confirmed by a rheumatologist), individuals presenting during the attack phase to the emergency department (case group), and those in the silent phase seeking emergency care (control group), with both patient and legal guardian consenting to participation. The exclusion criteria involved individuals receiving blood or blood products within the last 24 hours, patients with a history of trauma or surgery within the last 3 days, individuals undergoing treat-

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Table 1 Demographic characteristics

Variables	Groups (n=184)		P- value
	Case (n=92)	Control (n=92)	
Age (year), mean±sd	9.56±4.03	9.89±4.33	0.989
Disease duration (month), mean±sd	15.15±4.59	14.88±5.27	0.991
Male	54 (58.69%)	54 (58.69%)	0.999

Table 2 Comparison of laboratory parameters among the three study groups

Variables	Mean±sd			Pairwise comparisons			
Leukocytes (/mm^3)	C	Afp	Ap	P value	Afp-C	Ap-C	Ap-Afp
Neutrophils (%)	7296.41±1596.50	7144.34±1715.29	12581.73±5182.31	0.001>	0.898	0.001>	0.001>
Lymphocytes (%)	45.5±9.61	49.35±12.16	66.04±16.4	0.001>	0.054	0.001>	0.001>
Platelets (/mm^3)	43.9±9.54	43.83±11.28	28.85±15.91	0.001>	1	0.001>	0.001>
ESR (mm/h)	281923.91±70303.30	286695.65±69427.12	328836.95±109354.07	0.001>	0.954	0.02	0.06
Leukocytes (/mm^3)	6.81±3.41	10.10±7.36	33.65±21.66	0.001>	0.001>	0.001>	0.001>

Ap:Attack period; Afp: Attack-free period; C: Control group; ESR: Erythrocyte sedimentation rate; SD: Standard deviation

Table 3 Comparison of the NLR, PLR, and RDW in three groups

Variables	Confidence interval			Pairwise comparisons			
	C	Afp	Ap	P value	Afp-C	Ap-C	Ap-Afp
NLR	1.11 (1.02-1.23)	1.35 (1.18-1.49)	3.59 (3.28-3.89)	0.001>	0.29	0.001>	0.001>
PLR	94.01 (75.43-102.23)	101.69 (69.05-135.27)	125.51 (86.97-195.31)	0.04	0.449	0.001	0.012
RDW	13.24 (12.03-14.49)	13.71 (12.24-15.03)	15.23 (13.77-17.50)	0.001>	0.013	0.001>	0.001>

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; RDW: Red blood cell distribution width; Ap: Attack period; Afp: Attack-free period; C: Control group; SD: Standard deviation

Table 4 Correlation between NLR and PLR Ratios and other laboratory parameters in the case group

NLR: Neutrophil to leukocyte ratio; PLR: Platelet to leukocyte ratio

Variables		ESR (mm/h)		RDW (%)		Platelet (/mm^3)		Leukocytes (/mm^3)	
	p	r	p	r	p	r	p	r	
NLR	Attack period	0.165	-0.146	0.003	0.310**	0.273	0.115	0.001>	0.652**
	Attack-free period	0.04	0.214*	0.668	0.045	0.476	-0.075	0.001>	0.384**
PLR	Attack period	0.014	0.285**	0.231	-0.102	0.359	0.222	0.009	0.711**
	Attack-free period	0.077	0.102	0.569	0.083	0.701	0.071	0.563	0.07

*: Poor correlation; **: Moderate to strong correlation; NLR: Neutrophil to leukocyte ratio; PLR: Platelet to leukocyte ratio

ment for hematological or solid malignancy, receiving other drugs besides colchicine, opioid users, and those with psychiatric disorders. Also Patients with anemia, splenomegaly, diabetes mellitus, asthma, hematological disorders, liver or kidney failure, chronic heart or lung diseases, uncontrolled hypertension, those suffering from acute or chronic infections, individuals with other autoimmune disorders such as SLE, and those undergoing treatment with anticoagulants or medications influencing the quantity and function of neutrophils and lymphocytes, such as non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressive drugs, were excluded from the study (16,17). Any factors that lead to an elevation in inflammatory markers observed during examination and treatment prompted us to exclude the affected patients from the study. In this study, the Hashomer criteria were employed for the diagnosis of FMF, with relevant experts utilizing this guideline to expedite the diagnosis of their patients. The Hashomer criteria served as a valuable tool in the clinical assessment, helping to identify individuals who met the established criteria for FMF diagnosis based on recurrent febrile episodes, abdominal pain, chest pain, arthritis or arthralgia, and positive family history.

2.4. Study protocol

2.4.1. FMF attack phase symptoms:

during the attack phase of FMF, individuals commonly experience a sudden onset of high fever often accompanied by severe abdominal pain characterized as colicky and generalized. Chest pain resembling pleuritic or pericardial pain, joint inflammation primarily affecting larger joints, such as knees, ankles, and skin manifestations like rashes or redness are prevalent symptoms.

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Additionally, muscle pain, arthritis, and in testicular pain may occur. These attacks typically last between 12 to 72 hours and spontaneously resolve. It's important to note that FMF individuals return to a state of relative health between attacks, known as the "silent" or asymptomatic phase. The frequency and severity of FMF attacks can vary, underscoring the importance of consulting with healthcare professionals for accurate diagnosis and timely management. Early intervention can help alleviate symptoms and prevent complications associated with this autoinflammatory disorder. The FMF attack phase encompasses several distinct periods, each playing a crucial role in the overall course of the condition. Initially, individuals endure the attack period, marked by recurrent episodes of intense symptoms such as fever, abdominal pain, chest discomfort, joint inflammation and sporadic rashes. These manifestations vary widely in severity and duration among patients, reflecting the unpredictable nature of FMF. Following this tumultuous phase, individuals transition into the attack-free period, characterized by a temporary cessation of symptoms, though not indicative of a permanent resolution. During this respite, individuals return to a semblance of normality, albeit with a latent risk of future attacks looming. Meanwhile, some may enter a silent period, where overt symptoms subside. Yet the underlying genetic predisposition and inflammatory processes persist, necessitating ongoing vigilance and management to preempt potential flare-ups and mitigate long-term complications.

2.4.2. Initial actions:

Patients exhibiting the mentioned symptoms and referred to the emergency department underwent an initial examination by an emergency medicine specialist. After registering the symptoms, they received a rheumatology consultation to facilitate additional examinations and emergency treatments by a rheumatology specialist. Simultaneously, a skilled nurse collected a venous blood sample to assess whole blood cells which were sent to the hematology laboratory. The specified procedures were implemented for patients presenting symptoms of the FMF attack phase in the emergency room. Blood samples were gathered from children attending the rheumatology clinic in the silent phase and sent to the laboratory. To ensure accurate and high-quality results applicable to broader populations, we endeavored to assimilation variables such as age, sex, duration of disease, and gene mutation between the two study groups. It is important to mention that venous blood samples were collected from patients experiencing FMF attacks who were referred to the emergency room in two stages. The first collection took place during the attack phase and the second occurred after the conclusion of the attack phase when the patients were admitted to the ward based on the decision of the rheumatology specialist.

2.5. Data collection

Comprehensive information, including age, sex, duration of disease, and gene mutation, neutrophil, lymphocyte, and platelet counts, along with red blood cell distribution width (RDW) collected and record in data collection forms. The NLR was computed by dividing the absolute neutrophil count by the absolute lymphocyte count while the PLR was derived by dividing the platelet count by the lymphocyte count. Additionally, RDW representing the coefficient of variation of red blood cell volume, was directly measured from complete blood counts. We categorized our patients into three groups: homozygous, heterozygous, and compound heterozygous, based on their genetic profiles and mutations in the Mediterranean fever (MEFV) gene. Homozygous individuals carry two identical mutations, leading to a more severe phenotype, while heterozygous individuals possess only one mutation, resulting in generally milder symptoms. Compound heterozygous individuals harbor two different mutations, each inherited from one parent, with clinical manifestations varying depending on the specific mutations present.

2.6. Statistical analysis

Continuous quantitative variables were presented as mean±standard deviation and categorical variables were depicted as frequencies and percentages. The 1-Sample Kolmogorov-Smirnov test was employed to assess the distribution of data (normal or non-normal). To examine the differences among the means of quantitative variables with a normal distribution across three groups, parametric analysis of variance (ANOVA) was applied and pairwise group comparisons were conducted using Tukey's-b post hoc test for multiple comparisons. Additionally, the independent samples t-test was utilized for comparing two groups. For the comparison of non-normally distributed quantitative variables among three groups, the non-parametric Kruskal -Wallis test was implemented. The Pearson Chi-squared test was employed for comparing qualitative variables. A statistically significant threshold was set at a P-value less than 0.05. Pearson correlation analysis was utilized to explore the relationships between quantitative variables. Statistical analyses were performed using SPSS version 26 software. We ensured that both the case and control groups were meticulously matched in terms of entry and exit criteria, age, sex, type of treatment, and duration of the disease to minimize the influence of confounding variables. This rigorous matching process aimed to eliminate any potential bias stemming from these factors, thereby enhancing the validity and reliability of our study results. We also conducted pairwise comparisons to examine various variables between our groups.

2.7. Ethical considerations

To safeguard patient information, a unique code has been assigned to each participant instead of using their names. Patient enrollment in this study was voluntary and optional. Before entering the study and following a comprehensive explanation of its objectives, informed written consent was obtained from each participant (including the child themselves and their legal guardians) in adherence to legal standards.

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Moreover, the research proposal has been approved by the Ethics Committee of Ardabil University of Medical Sciences with the identifier IR.ARUMS.MEDICINE.REC.1400.029.

3. Results

Most participants in the study were boys (108-69.58%), with an average age of 9.72±4.15 years. The duration of the disease in participants was 14.96±5.27 months. Based on MEFV gene mutations, FMF patients were categorized into three groups: homozygous (15.2%), heterozygous (24.5%), and compound heterozygous (43.4%). The most frequent mutations were E148Q/WT (12%), M694V/V726A (9.8%), M694V/M694V (8.2%), M680I/M694V (4.3%), M694V/WT (4.3%), V726A/WT (3.8%), and M680I/V726A (3.8%). 16.8% of patients lacked gene mutations (wild type). Considering the homogeneity of the groups, no statistically significant difference was observed between the two groups (Table 1).

To assess the distribution of data (normal or non-normal), the 1-Sample Kolmogorov-Smirnov statistical test was utilized. In this study, the values of leukocytes, neutrophil percentage, lymphocyte percentage, platelet count, and ESR in all three groups had a normal distribution.

Therefore, for comparison between two groups, ANOVA and Tukey's-b post hoc test for pairwise comparisons were employed. However, the RDW values in the non-attack group and PLR in the attack group, as well as NLR in both groups, exhibited non-normal distributions. Hence, for their comparison between groups, the non-parametric Kruskal-Wallis test was used. The examination of results indicated that the levels of leukocytes, neutrophils, platelets, and ESR during the attack period were significantly higher compared to the attack-free period and the control group. Additionally, lymphocyte levels during the attack period were insignificantly lower compared to the attack-free period and the control group (Table 2).

In our study, there was a statistically significant difference in the mean values of RDW between the attack and non-attack groups (P-value<0.001) and between the attack group and the control group (P-value<0.001) (P-value<0.05). Additionally, there was a difference in RDW values between the non-attack group and the control group (P-value=0.013), indicating clinical inflammation in patients with FMF without attacks. Overall, the NLR and PLR showed significant differences among the three study groups (P-value<0.001 and P-value=0.04, respectively). In pairwise comparisons, the NLR in the attack group significantly differed from both the non-attack group (P value<0.001) and the control group (P-value<0.001), while there was no significant difference between the non-attack group and the control group (P-value=0.29). Additionally, the PLR showed a significant difference between the attack group and both the non-attack group (P-value=0.012) and the control group (P-value=0.001), but there was no significant difference between the non-attack group and the control group (P-value=0.449) (Table 3).

Using the Pearson correlation coefficient test, in the disease attack group, there was a direct correlation between the increase in the NLR and the increase in leukocyte levels (r=0.652, P<0.001), as well as RDW (r=0.310, P=0.003). In the non-attack group, there was a direct correlation between the increase in the NLR and the increase in leukocyte levels (r=0.384, P<0.001), as well as ESR (r =0.214, P=0.04).

Additionally, in the disease attack group there is a direct correlation between the increase in the PLR and the increase in leukocyte levels (r=0.711, P=0.009), as well as ESR (r=0.285, P=0.014). It is worth mentioning in the non-attack group, no correlation was found (Table 4).

4. Discussion

The observed differences in RDW, NLR, and PLR among the study groups in our research explain potential mechanisms underlying these hematological changes in FMF.

Elevated RDW levels in both attack and non-attack phases indicate ongoing subclinical inflammation in FMF patients. RDW is recognized as a marker of erythrocyte dynamics, and its elevation often correlates with inflammatory states (18). In FMF, increased RDW in the non-attack group compared to the control group suggests the presence of clinical inflammation even during asymptomatic periods, possibly due to persistent low-grade inflammation characteristic of FMF (19).

The significant differences in NLR and PLR among the study groups underscore their roles as inflammatory indicators in FMF. During attack phases, the raised NLR signifies an increased neutrophilic response, reflecting the acute inflammatory state characteristic of FMF attacks. The elevated PLR in the attack group further implicates platelets in the inflammatory cascade during these episodes (20,21).

The significant differences in NLR and PLR between the attack group and both the non-attack and control groups highlight the specificity of these ratios to the inflammatory state during FMF attacks. The lack of significant differences between the non-attack group and the control group in NLR and PLR suggests that these ratios might not be accurate enough to discern subtle inflammatory changes in asymptomatic periods (22,23).

Monitoring RDW, NLR, and PLR could offer a non-invasive means of assessing inflammation and disease activity. However, the lack of significant differences in NLR and PLR between the non-attack group and the control group emphasizes the challenge of identifying inflammation during asymptomatic periods, suggesting the need for additional markers or more accurate assays (24,25).

The strong positive correlation between NLR and leukocyte levels during disease attacks (r=0.652) suggests a synchronized increase in neutrophils and leukocytes, emphasizing the acute inflammatory nature of FMF attacks. Neutrophilia is a hallmark of the inflammatory response, and the correlation supports the role of neutrophils in FMF pathogenesis during active phases. Similarly, the positive correlation between NLR and leukocyte levels in the non-attack group (r=0.384) indicates a persistent inflammatory state even in

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the absence of overt symptoms. This aligns with the concept of subclinical inflammation in FMF during asymptomatic periods (11,26).

The positive correlation between RDW and leukocyte levels during disease attacks (r=0.310) suggests a potential association between erythrocyte dynamics and acute inflammation. RDW is known to increase in response to inflammatory stimuli, reflecting changes in red blood cell size and volume. The absence of a significant correlation between RDW and leukocyte levels in the non-attack group might indicate that RDW is more influenced by acute inflammatory responses during active disease phases (11,27).

The strong positive correlation between PLR and leukocyte levels during attacks (r=0.711) highlights the involvement of platelets in the inflammatory cascade during acute episodes. Additionally, the correlation between PLR and ESR (r=0.285) further supports the association between platelet activation and systemic inflammation. The lack of correlation in the non-attack group indicates that the platelet response might be more specific to active inflammatory processes rather than baseline chronic inflammation (11,26,28).

The correlations observed align with the known pathophysiology of FMF, characterized by episodic inflammatory attacks. Neutrophil involvement, reflected in NLR, is consistent with the acute nature of FMF attacks. RDW and PLR associations highlight the potential of these indices as inflammatory markers, especially during active disease phases. Lack of correlation in the non-attack group supports the concept of varying inflammatory states in FMF patients during symptomatic and asymptomatic periods (29,30).

5. Limitations

Our study is subject to several limitations. The first limitation is the single-center nature of the study. The second limitation is that all patients were under treatment with colchicine, which affects the level of inflammation and study biomarkers by reducing them. Additionally, due to the case-control nature of the study, we lacked data obtained over time, disregarding the possibility that the status of inflammatory markers might change over time. The treatment and diagnosis processes conducted by various doctors posed a notable limitation in our study, potentially introducing variability and inconsistency in the collected data. Additionally, the possibility of sample loss further compounded this limitation, potentially impacting the overall integrity of our findings. Furthermore, we acknowledge that the absence of genetic allele status representation in our study constitutes another limitation. Genetic alleles can contribute to divergent clinical manifestations and treatment responses among individuals and their exclusion may have overlooked important insights into the observed outcomes. Recognizing these limitations underscores the need for cautious interpretation of our results and emphasizes avenues for future research to address these gaps comprehensively.

Considering the mentioned limitations, it is recommended that future studies address and overcome these constraints

6. Conclusion

Our study results revealed that the mean values of RDW in FMF patients during the attack-free phase and silent period were significantly higher than those in the healthy control group. RDW can serve as an indicator to demonstrate clinical inflammation in FMF patients. The NLR and PLR ratios in FMF patients during attacks were significantly higher than those in FMF patients in the non-attack period and the control group.

However, there was no significant difference between the non-attack group and the control group. Consequently, NLR and PLR ratios can be crucial markers for indicating systemic inflammation in FMF patients during attacks, being cost-effective, readily accessible, and easily calculable, aiding in disease detection when combined with other markers. However, they may not identify clinical inflammation in asymptomatic FMF patients.

7. Declarations

7.1. Acknowledgement

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7.2. Authors' contribution

All the authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

7.3. Conflict of interest

We declare no conflict of interest.

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