



The Importance of MPV as a Marker of Subclinical Inflammation in FMF Patients and It's Correlation with Disease Severity

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Abstract

Objective: Inflammation markers increase during Familial Mediterranean Fever (FMF) attacks and often return to normal within a few days. It is known that a subclinical inflammation continues in FMF patients in the inter-episode period, which increases the risk of developing amyloidosis. In recent years, several works have been conducted showing the relationship between platelet indices and inflammation, such as platelet count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT). In this study, we aimed to investigate the relationship between platelet indices and disease severity in FMF patients without attacks.

Method: The records of all FMF patients followed by us were reviewed retrospectively. Patients with a hematological or oncological disease, patients with data deficiency for the study, and patients under 18 years of age were excluded. While the laboratory data were recorded, the condition of patients to be at least 3 months without attack was required. As the control group, the automation records of all healthcare professionals working in the internal medicine clinic of our hospital were examined. Our clinical staff, who did not have chronic diseases and regular drug use, were taken as a healthy control group. 173 patients and 20 control groups who met the conditions mentioned above were included in the study. Platelet indices were compared between patient and control groups.

Results: It was determined that the value of MPV, one of the platelet indices, in the patient group was statistically significantly higher than the value in the healthy control group ($p = 0.029$). MPV was also found to correlate with disease severity ($p < 0.001$ $r = 0.329$).

Discussion-Conclusion: In our study, it was determined that MPV was higher in FMF patients in the subclinical period compared to healthy controls and also correlated with disease severity. Studies investigating platelet indices and the risk of developing amyloidosis are needed in FMF patients.

Keywords: Familial Mediterranean Fever, Mean Platelet Volume, Subclinical inflammation

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MPV'nin FMF Hastalarında Subklinik İnflamasyon Belirteci Olarak Önemi ve Hastalık Şiddeti ile Korelasyonu

Öz

Giriş: Ailesel Akdeniz Ateşi (FMF) atakları anında inflamasyon belirteçleri artış göstermekte ve çoğu zaman birkaç gün içerisinde normale dönmektedir. Ataklar arası dönemde de FMF hastalarında subklinik bir inflamasyonun devam ettiği ve bunun da amiloidoz gelişme riskini artırdığı bilinmektedir. Son yıllarda, trombosit sayısı (PLT), trombosit dağılım genişliği (PDW), ortalama trombosit hacmi (MPV), plateletkrit (PCT) gibi trombosit indeksleri ile inflamasyon arasındaki ilişkiyi gösteren birçok çalışma yapılmıştır. Bu çalışmamızda ataksız dönemdeki FMF hastalarında trombosit indeksleri ile hastalık şiddeti arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Kliniğimizde takip edilen tüm FMF hastalarının dosyaları retrospektif tarandı. Hematolojik veya onkolojik bir hastalığa sahip olanlar, çalışma için veri eksikliği olan hastalar ve 18 yaşından küçük hastalar çalışmaya alınmadı. **Laboratuvar** verileri kayıt altına alınırken hastaların en az 3 aylık ataksız dönemde olmaları koşulu arandı. Kontrol grubu olarak hastanemiz iç hastalıkları kliniğinde çalışan tüm sağlık çalışanlarının otomasyon kayıtları incelendi. Kronik hastalık ve düzenli ilaç kullanımı olmayan klinik çalışanlarımız sağlıklı kontrol grubu olarak alındı. Yukarıda belirtilen koşulları sağlayan 173 hasta ve 20 kontrol grubu çalışmaya dahil edildi. Hasta ve kontrol grupları arasında trombosit indeksleri karşılaştırıldı.

Bulgular: Trombosit indekslerinden MPV'nin hasta grubundaki değeri sağlıklı kontrol grubundaki değerine göre istatistiksel olarak anlamlı derecede yüksek bulunduğu tespit edildi ($p = 0,029$). MPV'nin aynı zamanda hastalık şiddeti ile de korelasyon gösterdiği tespit edildi ($p < 0,001$ $r = 0,329$).

Tartışma-Sonuç: Çalışmamızda MPV'nin subklinik dönemde FMF hastalarında sağlıklı kontrollere göre yüksek olduğu ve aynı zamanda hastalık şiddeti ile de korelasyon gösterdiği saptanmıştır. FMF hastalarında trombosit indeksleri ve amiloidoz gelişim riskini artırıcı etkilere ilişkin araştırmalara ihtiyaç vardır.

Anahtar kelimeler: Ailevi Akdeniz Ateşi, Ortalama Trombosit Hacmi, Subklinik inflamasyon.

INTRODUCTION

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease with serosal inflammation characterized by recurrent episodes of fever¹. The disease was first described by Janeway and Rosenthal in 1908 as "unusual recurrent peritonitis" in a 16-year-old Jewish girl with recurrent fever, abdominal pain, and leukocytosis². In Turkey, the first adult FMF patient the name 'Strange Abdominal Pain Syndrome' was diagnosed by Abrevaya Marmaralı, in 1946³. The gene associated with the disease is the Mediterranean Fever (MEFV) gene on the short arm of the 16th chromosome⁴. The presence of two pathogenic mutations in the MEFV gene confirms the diagnosis, on the other hand mutation was detected in only one third of FMF cases diagnosed clinically^{5,6}.

During FMF attacks, many acute phase reactants such as C-reactive protein, serum amyloid A, fibrinogen, and sedimentation increase⁷. It is known that a subclinical inflammation

continues in FMF patients during the inter-attack period and this increases the risk of developing amyloidosis⁸⁻¹⁰. It has been shown that serum amyloid A levels are high in FMF patients even during in the attack-free period and can predict attacks¹¹. Although, in some clinics in our country serum amyloid A level is used as an indicator of subclinical inflammation and adjustment of colchicine dose, it has not found a comprehensive place in the routine evaluation of FMF patients. In the last few years, several works have shown the relationship between platelet indices, platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) and inflammation¹²⁻¹⁷. In this study, we aimed to investigate the relationship between platelet indices and disease severity in FMF patients between attacks.

METHOD

Patients and Control Group

For the study, all FMF patients data who were followed up and treated in our hospital's

Internal Medicine and Nephrology polyclinic between May 2018 and May 2019 were retrospectively reviewed. All patients whose data could be accessed through the hospital automation system and gave consent for the study were incorporate into the study. As exclusion criteria from the study, the presence of a history of hematological disease that may affect the platelet indices, having an oncological disease, lack of data and being younger than 18 years were determined. FMF-related disease information and laboratory values of the patients were recorded. While the laboratory data were being recorded, the criteria was determined as the patients were in a period of at least 3 months without attacks. A detailed history of all patients were recorded and systemic physical examination was performed for all patients. Information of the FMF clinic was obtained through face-to-face interviews and detailed inquiries made with the patients by the same physician. Laboratory values were recorded with using the hospital automation system.

As the control group, the automation records of all healthcare professionals working in our hospital's internal medicine clinic were examined. Clinical staff with no chronic diseases and regular medication use were taken as a healthy control group. 173 patients and 20 control groups who met the conditions mentioned above were included in the study. Platelet indices were compared between the patient and control groups.

Laboratory Measurements

For the study, blood count and biochemical measurements obtained in the routine controls of the patients were used. Complete blood count was studied with Mindray BC-6800 hematology analyzer, biochemical parameters were performed on Cobas 8000 c 702 series biochemistry autoanalyzer and genetic analysis was performed with Roche 454 pyrosequencing method.

Assessment of Disease Severity

The Pras scoring system was used for disease severity (Table I)¹⁸. The patients were divided into 3 categories by summing their scores according to the scoring system. Patients with a total score ≤ 5 were categorized as mild FMF, patients with 6-8 as moderate disease, and patients with ≥ 9 as severe FMF.

Table I: Pras Severity Scoring

Parameter	Specifications	Score
Age of onset	>31	0
	21-31	1
	11-20	2
	6-10	3
	<6	4
Attacks per month	<1	1
	1-2	2
	>2	3
Arthritis	Acute	2
	Chronic	3
Erysipelas Like Erythema		2
Amyloidosis		3
Colchicine Dosage (mg/day)	1	1
	1,5	2
	2	3
	>2	4

Statistical Analysis

The data were analyzed by IBM SPSS Statistics22. 0 (IBM Corp. NY, USA) package program. Categorical variables were presented with percentages and frequencies. Chi-square test was used for comparison of categorical data. The compliance of continuous variables to normal distribution was checked with Shapiro Wilk and Kolmogorov-Smirnov tests. Student's t test was used for parameters showing normal range in comparison of patient and control groups, and Mann-Whitney U test was used for parameters that did not show normal range. ROC analysis was also performed for the MPV

value, which was different from each other between the patient and control groups. While investigating the relationship between disease severity and platelet indices, normally distributed parameters were compared with the Oneway ANOVA test, and parameters not normally distributed were compared with the Kruskal-Wallis test. The pairwise comparison (Kruskal-Wallis) test was used as a post-hoc analysis for the MPV value with statistically significant difference between the groups. All p values presented in the study are bidirectional and values with ≤ 0.05 were considered statistically significant.

RESULTS

In this work 61.8% (n = 107) of our patients were female and 38.2% (n = 66) were male. The median age of the patient group was 37 (range: 18-72) years. Control group includes 55% (n = 11) female and 45% (n = 9) male. The median age of the control group was 31 (range: 26-44) years. The patient and control groups were found to be similar in terms of gender and age (p = 0.156 and p = 0.08, respectively). When the platelet indices of the patient and control groups were compared, only MPV value was found to be statistically significantly higher in the patient group compared to healthy controls (p = 0.029) (Table II).

Table II: Comparison of Platelet Indexes of Patient and Control Groups

Parameter	Patient	Control	P
PLT (10 ³ / μ L)	264,71 \pm 73,2	257,25 \pm 62,3	0,627
PDW(fL)	14,28 \pm 2,6	14,58 \pm 2,4	0,936
MPV(fL)	9,51 \pm 1,3	8,87 \pm 0,7	0,029
PCT(%)	0,261 \pm 0,07	0,252 \pm 0,05	0,564

PLT: Platelet PDW: Platelet Distribution Width MPV: Mean Platelet Volume PCT: Plateletcrit

In the ROC analysis, it was determined that MPV can be used for the separation of patient and control groups with 65.9% sensitivity and 65% specificity for 9.05 fl value (AUC: 0.649 p = 0.029% 95CI = 0.556- 0.742). Figure 1 shows the ROC analysis for MPV.

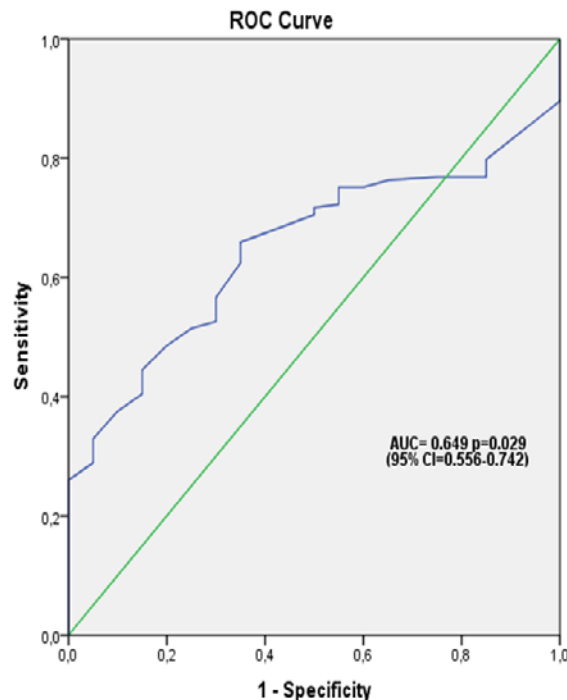
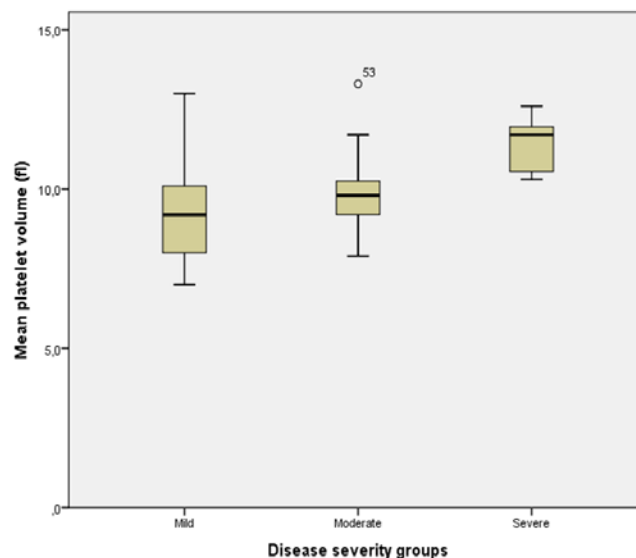


Figure 1. ROC analysis for MPV in differentiation of patient and control groups

The clinical and genetic features of FMF patients are summarized in Table III. The median Pras score of the patients was calculated as 5 (range: 2-12). According to the Pras severity score, 63.6% (n = 110) of the patients were in the mild FMF group, 31.8% (n = 55) in the moderate FMF, and 4.6% (n = 8) in the severe FMF group. MPV values according to disease severity are shown in Figure 2. Also Posthoc analysis results for MPV are shown in Table V.

Table III: Clinical and Genetic characteristics of FMF patients

Parameter	Number (n)	Percent(%)
Abdominal Pain		
Yes	137	79,2
No	36	20,8
Erysipelas Like Erythema		
Yes	31	17,9
No	142	82,1
Relapsing fever		
Yes	128	74
No	45	26
Arthritis		
Yes	55	68,2
No	118	31,8
Family		
Yes	128	74
No	45	26
Response to Colchicine		
Yes	163	94,2
No	10	5,8
Colchicine Dosage (mg/day)		
1	88	50,8
1,5	72	41,6
2	11	6,4
>2	2	1,2
Mutation		
Homozygous	29	16,8
Compound heterozygous	35	20,2
Heterozygous	49	28,3
Wild-type	25	14,5
Unchecked	35	20,2

**Figure 2.** Comparison of MPV values according to disease severity**Table IV:** Comparison of laboratory characteristics of patients according to the severity of FMF

Parameter	Mild FMF	Moderate FMF	Severe FMF	p
Urea(mg/dL)	27,76±9,3	31,72±23,1	25,28±23,7	0,495
Creatinine (mg/dL)	0,79±0,3	1,12±1,4	0,92±0,6	0,961
Sodium (mmol/L)	140,41±2,4	139,97±2,5	140,2±0,8	0,260
Potassium (mmol/L)	4,46±0,3	4,49±0,4	4,4±0,2	0,103
Glucose (mg/dL)	95,52±16,2	89,92±13,6	88,02±6,7	0,16
AST(U/L)	22,65±9,6	20,14±9,2	17,52±5,9	0,126
ALT(U/L)	24,27±16,7	18,99±10,1	16,76±11,1	0,209
Sedimentation(mm/s)	13,28±7,2	13,94±7,1	8,2±4,3	0,555
CRP(mg/dL)	0,571±0,5	0,468±0,4	0,392±0,3	0,612
Leukocyte (10 ³ /uL)	6927±1744	7522±1851	8996±3106	0,035
Neutrophil (10 ³ /uL)	4005±1352	4832±1793	5960±2278	0,002
Lymphocyte (10 ³ /uL)	2215±701	1757±662	2242±1084	0,740
Hemoglobin (g/dL)	14,15±1,8	13,93±2,04	14,5±2,2	0,715
PLT (10 ³ /uL)	258,4±73,3	272,4±75,9	274,6±65,8	0,582
PDW (fL)	13,93±2,5	14,14±3,1	13,7±2,8	0,874
MPV (fL)	9,23±1,3	9,82±1,1	11,72±0,7	<0,001
PCT (%)	0,258±0,07	0,262±0,07	0,284±0,05	0,366

Table V: Posthoc analysis results for MPV

Groups	Standard error	p
Mild FMF- Moderate FMF	8,264	0,012
Mild FMF-Severe FMF	18,323	<0,001
Moderate FMF-Severe FMF	18,934	0,009

In addition, the comparison of the laboratory

features of the patients according to the severity of FMF is shown in Table IV. When the correlation between MPV and the total scores obtained from Pras scoring was investigated, it was found that the Pras score showed a statistically significant but weak correlation with MPV ($p < 0.001$ $r = 0.329$). Figure 3 shows the correlation between Pras score and MPV.

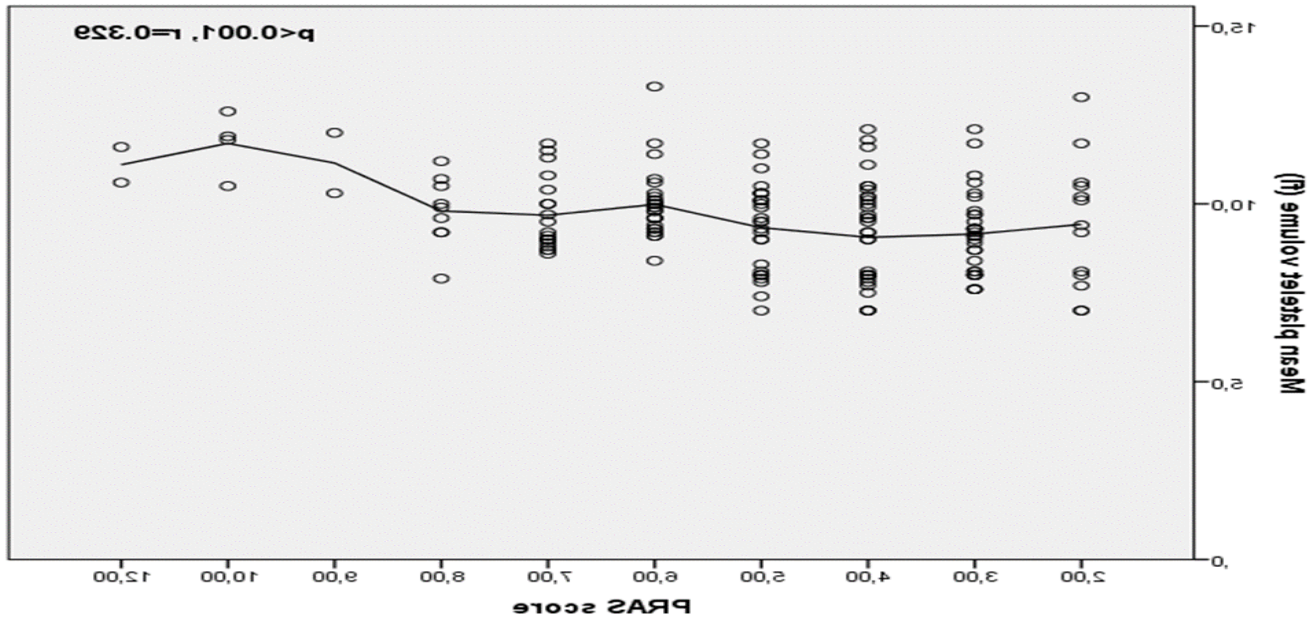


Figure 3. Correlation between Pras score and MPV

DISCUSSION

Unlike other inflammatory diseases, FMF patients clinically return to normal during the inter-attack periods. However, studies show that although the clinic is normal, a subclinical inflammation continues in the interval between attacks. Musabak et al. detected abnormal T cell activation in patients with FMF both during the attack period and during remission¹⁹. Bağcı et al. observed that IL-6, which is known to stimulate hepatic acute phase proteins, rises suddenly during attacks and remains high during remission²⁰. Erken et al. found that IL-12 levels in FMF patients were higher than healthy controls, regardless of the attacks²¹. A similar study was conducted by Şimşek et al. in patients with FMF, serum IL-12 and IL-18 levels were

found to be high during attack and during attack-free period; stated that increased IL-12 and IL-18 levels in the remission period showed Th1 activation and that a subclinical inflammation continued in the period without attacks²². However, none of the inflammatory markers evaluated in the studies performed are the parameters that are in routine use especially for developing countries such as our country and may be in the near future. Therefore, there is a need for an inflammation marker that can indicate subclinical inflammation in FMF patients and may be related to disease severity. MPV as the part of platelet indices; it has been used as a marker in many studies, especially in inflammation, due to the fact that the platelets that come into the environment in case of inflammation are young and large in volume.

The results of studies investigating MPV in FMF patients in the literature are quite heterogeneous. Çoban and Adanır found MPV to be high when comparing FMF patients in the attack-free period with the control group²³. Abanönü et al. examined the relationship between the use of colchicine and MPV in patients with FMF, and compared the patients with FMF in the attack-free period with the control group, and they found that MPV values did not create a statistical difference between the groups and suggested that this situation was due to the effect of colchicine on platelet functions²⁴. In the study of Özer et al. investigating subclinical inflammation indicators in children with FMF, MPV was found to be significantly higher in asymptomatic FMF patients compared to the control group⁸. In the study of Yıldırım Çetin et al. investigating subclinical inflammation indicators in adult FMF patients, MPV was found to be significantly lower in FMF patients in the attack-free period compared to the healthy control group²⁵. Our study revealed that in adult FMF patients, MPV in the inter-attack period is higher than the healthy control group in terms of age and gender. While this finding overlaps with some studies in the literature, it also contrasts with others. We think that this may be due to the criteria determined when selecting patients for studies in the literature. It was thought that the sensitivity and specificity level of 65% might be due to the fact that the control group included quite a few people compared to the patient group.

FMF and inflammation studies in the literature have been conducted to investigate new inflammation markers that can be used in the subclinical period. Özer et al. found that MPV was significantly higher in FMF patients in the inter-attack period compared to the control group, and found that MPV could be a candidate as an indicator of subclinical inflammation in FMF patients⁸. Çetin et al. investigated the

importance of MPV as a subclinical inflammation marker and thought that low MPV could indicate subclinical inflammation in FMF patients in the inter-attack period²⁶. Uslu et al. showed that the neutrophil-lymphocyte ratio, which can be reached with a complete blood count, such as MPV, was found to be higher in FMF patients in the attack-free period compared to the healthy control group, and this could be used as an indicator for subclinical inflammation²⁷. In our study, MPV was found to be higher in FMF patients in the subclinical period compared to healthy controls, and it was also found to be correlated with disease severity. We think that the lack of correlation might be due to the unequal distribution of patients according to the severity of the disease. In our study, when FMF patients were categorized according to Pras severity scoring, it was shown that MPV in the subclinical period increased as the severity of the disease increased. In the post-hoc analysis, it was determined that this difference continued in the comparisons of the three groups. Our findings support that high MPV in the subclinical period is associated with more severe FMF.

The use of platelet indices as a marker of inflammation began with a study about 16 years ago. In their study, Milovanovic et al. Found that MPV increased during active rheumatoid arthritis²⁸. After this study, many articles have been published investigating the roles and changes of platelet indices during inflammation, especially in recent years. In our study, although all platelet indices (PLT, MPV, PDW and PCT) were compared between the patient and control groups, it is striking that only MPV was found to be high in FMF patients in the subclinical period. According to our results, MPV has been found to be a reliable subclinical inflammation marker in adult patients with FMF. The risk of splenomegaly, heart diseases and especially amyloidosis increases with subclinical inflammation in FMF patients²⁷⁻²⁹. According to

the results of our study, thanks to the closer follow-up of FMF patients with high MPV in the attack-free period, complications that are closely related to mortality can be detected earlier.

In conclusion, although the retrospective design of our study has some limitations, such as the small number of the control group, and the fact that platelet indices were not evaluated according to the genetic mutation types; we did not find any other study investigating disease severity and thrombocyte indices in adult FMF patients in our literature review. The fact that the relation of MPV with FMF complications has not been investigated can be considered as another limitation of our study. There is a need for prospective studies investigating the importance of MPV as a subclinical inflammation marker in FMF patients and its relationship with the complications of FMF.

Ethics Committee Approval: The present study was approved by Afyonkarahisar Health Sciences University Faculty of Medicine Clinical Research Ethics Committee of Clinical Studies with dated 20.09.2019 and 302 decision number.

Conflict of Interest: No conflict of interest was declared by the authors.

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