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# Clinical significance of mean platelet volume, platelet distribution width, and neutrophil-lymphocyte ratio in children with familial Mediterranean fever

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## Abstract

***Clinical significance of mean platelet volume, platelet distribution width, and neutrophil-lymphocyte ratio in children with familial Mediterranean fever***

**Objective:** Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent fever and polyserositis. Studies conducted in recent years emphasize the importance of platelet parameters in chronic diseases. This study examined changes in attack and attack-free periods in children with FMF, focusing on Mean Platelet Volume (MPV), an indicator of disease severity.
**Method:** 150 FMF patients (90 girls, 60 boys) and 50 healthy individuals (29 men, 21 women) were included in the study. Data were analyzed according to colchicine treatment, attack, and attack-free periods. The severity of the disease was classified as mild, moderate, and severe.
**Results:** MPV levels of patients with FMF were higher than the healthy group. In particular, MPV levels decreased significantly during attacks, with a more pronounced decrease in severe cases.
**Conclusion:** As a result, MPV measurement is a cost-effective and rapid method that can support the evaluation of disease severity and attack periods in FMF patients.
**Keywords:** Familial Mediterranean Fever, mean platelet volume, Neutrophil/Lymphocyte Ratio, M694V mutation

## INTRODUCTION

Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of fever and polyserositis, particularly affecting ethnic groups around the Mediterranean, i.e., individuals of Sephardic Jewish, Armenian, Arab, and Turkish descent (1). The diagnosis of FMF is established based on the Tel-Hashomer criteria. With the detection of the gene causing the disease in 1997, mutational analysis became a viable auxiliary diagnostic method in suspicious cases (2,3). Although the etiopathogenesis of the disease has not been completely elucidated, it is thought that the innate immune system plays a significant role. A widely accepted hypothesis is that the pyrin/marenostrin protein encoded by the MEFV gene fails to suppress neutrophil-mediated inflammation, which results in a clinical picture of short-lived inflammatory episodes and periodic fever (3).

Typically, no clinical complaint occurs during attack-free periods in FMF. However, studies have indicated high cytokine levels in these periods, possibly linked to subclinical inflammation. Systemic inflammation leads to diminished anticoagulant and fibrinolytic activity after the secretion of coagulation precursors, predisposing the patient to thrombosis (4,5). Clinical and subclinical inflammation in FMF is known to cause endothelial dysfunction and thereby trigger the coagulation cascade. In addition, extracellular matrix proteins fibronectin and thrombospondin levels are shown to increase during FMF attacks (6,7).

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Accurate measurement of mean platelet volume (MPV) by electronic cell counters has made MPV a commonly assessed parameter in clinical studies and practice. In increased thrombopoiesis, high MPV has been reported due to high levels of circulating young platelets. Large platelets also called "stress" platelets, contain higher rates of dense granules and exhibit elevated biochemical, functional, and metabolic activity. MPV increases in accelerated peripheral platelet destruction and decreases in impaired platelet production. Higher MPV level is associated with elevated growth of megakaryocytes due to thrombopoietin response. Several clinical conditions linked to inflammatory responses demonstrate elevated MPV levels, although in certain cases, MPV may exhibit a decrease (7,8,9).

Platelet distribution width (PDW) is another marker of platelet activation linked with inflammation and atherothrombotic events. Various studies have reported that PDW is a more specific indicator of platelet activation than MPV . By established hematological protocols, PDW is derived in conjunction with other platelet volume indices (mean platelet volume, MPV; plateletcrit, PCT), serving as a parameter calculated mathematically from platelet volume measurement and the standard deviation of volume distribution among the platelet population (10,11). Recent studies have suggested that neutrophil-lymphocyte ratio (NLR) can also be used as a subclinical inflammation marker in FMF, but further evidence is necessary to establish the reliability of the parameter (12).

The parameters MPV (mean platelet volume), PDW(platelet distribution width), and NLR (neutrophil-to-lymphocyte ratio) may be potential utility as indicators of systemic inflammation (12-15).

This study aims to investigate the clinical importance of hematological parameters - especially mean platelet volume (MPV), platelet distribution width (PDW), and neutrophil-lymphocyte ratio (NLR) - in children with Familial Mediterranean Fever (FMF) disease. FMF is an autosomal inherited inflammatory disease characterized by recurrent fever attacks, peritonitis, pleuritis, and arthritis. However, there are limited studies on hematological markers of the disease.

This study aims to determine the clinical value of these markers in the pediatric population of FMF. The study's focus specifically on hematological parameters such as MPV, PDW, and NLR points to the existence of simple and widely accessible markers that may help in the early identification of inflammation-related complications of FMF. The results of this study may help us better understand the clinical use of hematological parameters in children diagnosed with FMF and develop more effective strategies for the management of the disease.

The present study investigated the correlation between disease severity and changes in MPV, PDW, and NLR levels during attacks and attack-free periods in children with FMF. We aimed to evaluate the clinical utility of these parameters as inflammation markers in FMF cases. This study aims to investigate the clinical importance of hematological parameters - especially mean platelet volume (MPV), platelet distribution width (PDW), and neutrophil-lymphocyte ratio (NLR) - in children with Familial Mediterranean Fever (FMF) disease. However, there are limited studies on hematological markers of the disease. This study aims to determine the clinical value of these markers in the pediatric population of FMF.

## METHOD

In this study, 150 patients who were followed up in Medeniyet University Göztepe Training and Research Hospital Pediatric Rheumatology Outpatient Clinic between 2009-2014 and diagnosed with FMF according to Tel-Hashomer criteria were retrospectively analyzed. Medeniyet University Göztepe Training and Research Hospital ethics committee approval was obtained on 23.09.2014 with the decision number 2014/0147. Patients with concomitant chronic diseases were excluded from the study. The patient group was examined in terms of demographic characteristics, symptoms, Pras severity score, development of amyloidosis, and genetic test results. Disease scoring(Pras severity score) was based on the age of onset, frequency, and severity of joint involvement, presence of erysipelas-like erythema, and colchicine dose required for symptom control; as a result, disease severity was classified as severe, moderate, or mild (15). Laboratory parameters, including hemoglobin, white blood cell (WBC) count, platelet count, MPV, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and proteinuria, were obtained during attacks and attack-free periods. Complete blood counts were analyzed with a daily-calibrated hemocytometer (Abbott Cell-Dyn 3700 System, Abbott Diagnostics, Santa Clara, CA, USA) using samples anticoagulated with K3EDTA. The control group consisted of 50 individuals who presented to the Ministry of Health Göztepe Training and Research Hospital Pediatrics Outpatient Clinic for routine control and had no complaints or chronic diseases. The healthy controls were compared with the patient group regarding hemogram parameters. The principles of the Declaration of Helsinki were complied with when the study was conducted.

### Statistical analysis

The conformity of continuous variables to the normal distribution was evaluated with the Shapiro-Wilk test. Levene's

test analyzed the homogeneity of variance. In comparisons, a t-test was used and shown with 't' for comparing the values during the attack and attack-free periods within the dependent groups in the same patient group. When the three groups including the control group were compared, a one-way ANOVA test was used for comparison and denoted by a. The results were presented as mean±SD. Two-way tables were evaluated with Pearson's chi-squared and Fisher's exact tests. All analyses were performed using the SPSS software package (SPSS version 16.0, SPSS Inc., Chicago, IL, USA). Results were presented in numbers (n) and percentages (%). A p-value of <0.05 was considered statistically significant.

**Table 1. Distribution of MEFV mutations in patients**

| Mutation | Mutation-positive patients (n: 150) | Percentage |
|---|---|---|
| M694V/ M694V | 48 | 29.8% |
| M694V/N | 23 | 14.3% |
| E148Q/N | 12 | 7.5% |
| M694V/M680I | 10 | 6.2% |
| M680I/N | 4 | 2.5% |
| M694V/E148Q | 4 | 2.5% |
| M694V/V726A | 3 | 1.9% |
| M680I/680I | 3 | 1.9% |
| M694I/V726A | 3 | 1.9% |
| M694V/R761H | 2 | 1.2% |
| V726A/N | 2 | 1.2% |
| M694V/P369S/ E148Q | 1 | 0.6% |
| M680I/V726A | 1 | 0.6% |
| M694V/M694I/ E148Q | 1 | 0.6% |
| E148Q/P369S | 1 | 0.6% |

Note: Two different mutations separated by "/" indicates a compound heterozygous mutation, single mutation/N indicates a single heterozygous mutation, and the same mutation written twice indicates a homozygous mutation.

## RESULTS

The patients' mean age at diagnosis was 8.1±4.0 years, and the mean attack frequency was 1.6 attacks per month. Twenty patients had mild FMF, 113 had moderate FMF, and 17 had severe FMF. All patients were evaluated regarding MEFV gene mutations (Table 1). The most frequent mutation was the M694V homozygous mutation in 29.8% of patients.

The patients' hemoglobin, WBC count, MPV, platelet count, PDW, NLR, CRP, and ESR values were studied during attacks and attack-free periods (Table 2). Hemoglobin and MPV levels were significantly lower during attacks, whereas no significant difference was observed between attacks and attack-free periods regarding platelet count. During attacks, the WBC count, CRP, ESR, PDW, and NLR levels were significantly higher.

**Table 2. Comparison of patient laboratory parameters between attacks and attack-free periods**

| | Attack | Attack-Free Period | Control | P-Value |
|---|---|---|---|---|
| Hemoglobin (g/dL) | 11.93±1.95 | 12.42±1.62 | 12.75±1.30 | <0.001 |
| WBC count (/mcL) | 10144±2042 | 9215±1855 | 8777±2679 | <0.001 |
| MPV (fl) | 6.95±0.20 | 7.47±0.36 | 7.62±1.32 | <0.001 |
| Platelet count (/mcL) | 372(K)±11(K) | 344(K)±62(K) | 307(bin)±66(bin) | 0.157 |
| AST (IU/L) | 28.63±12.44 | 29.45±9.85 | -- | <0.001 |
| ALT (IU/L) | 15.44±7.36 | 18.78±6.55 | -- | <0.001 |
| BUN (mg/dL) | 12.46±3.57 | 11.68±1.34 | -- | <0.001 |
| Creatinine (mg/dL) | 0.72±0.20 | 0.85±0.31 | -- | <0.001 |
| PDW | 17.6±4.0 | 15.5±2.20 | 17,20±0.87 | <0.001 |
| NLR | 2.57±0.37 | 1.16±0.18 | 1,44±0,79 | <0.001 |
| CRP (mg/L) | 37.55±24.48 | 0.25±0.08 | -- | <0.001 |
| ESR (mm/hour) | 28.17±7.50 | 14.52±5.40 | -- | <0.001 |

The patients MPV levels during attacks were significantly lower than those in the attack-free periods, and their MPV levels significantly decreased as disease severity increased. A significant negative correlation was observed between the patients' MPV levels during attacks and attack-free periods (p: 0.002) (Table 3).

**Table 3. Relationship between disease severity and attack and attack-free MPV levels**

| MPV Levels | Disease severity | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| Attack-free MPV (fL) | 8.93±1.15 | 8.72±0.84 | 8.49±0.98 |
| Attack MPV (fL) | 8.81±1.10 | 8.55±0.80 | 8.21±0.80 |

**Table 4. Relationship between disease severity and attack and attack-free PDW levels**

| Pdw Levels | Disease severity | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| Attack-Free Pdw | 15.74±0.95 | 16.02±1.02 | 16.15±1.23 |
| Attack Pdw | 18.23±2.13 | 18.45±2.50 | 18.62±2.24 |

**Table 5. Relationship between disease severity and attack and attack-free NLR levels**

| Neutrophil-Lymphocyte Ratio | DISEASE SEVERITY | | |
|---|---|---|---|
| | MILD | MODERATE | SEVERE |
| Attack-free NLR | 1.37±0.42 | 1.45±1.10 | 1.44±0.80 |
| Attack NLR | 2.04±1.17 | 2.89±3.18 | 4.75±4.00 |

An evaluation of the relationship between disease severity and PDW levels during attacks and attack-free periods revealed that PDW levels significantly increased as disease severity increased ($p<0.001$) (Table 4). A significant positive correlation was observed between the PDW levels during attacks and attack-free periods (p: 0.003) (Table 4).

An evaluation of the relationship between disease severity and NLR levels during attacks and attack-free periods revealed that NLR levels significantly increased as disease severity increased (p-<0.001) (Table 5). Although a positive correlation was observed between NLR levels during attacks and attack-free periods, no statistical significance was seen. (p: 0.073) (Table 5).

## DISCUSSION

Studies have shown that cytokine levels remain high and subclinical inflammation continues in the attack-free periods of FMF, suggesting a possible effect on patients' predisposition to thrombosis (4,16). MPV has been widely investigated as a marker of platelet activation in FMF patients (17). A study by Çoban et al. on adult patients reported higher MPV levels in attack-free FMF patients than in healthy controls (18). The findings of the present study are similar. It was thought the increased platelet production could explain high MPV levels in FMF patients having chronic low-grade inflammation, the elevated circulating platelet count, and the migration of young, reactive, and more giant platelets toward the site of inflammation. Contrary to the study conducted by Yorulmaz et al., in this study, when we compared FMF patients among themselves, it was seen that MPV levels during the attack were significantly lower than in the attack-free period (9). This can be attributed to the inflammatory destruction of more giant platelets migrating to the site of inflammation. It is expected that MPV levels will decrease when giant platelets disappear (19). As disease severity increases, MPV levels decrease. As the severity of the disease increases, the destruction of giant platelets increases and the MPV levels decrease further, which may also explain this result. In addition, among our FMF patients, PDW levels during attacks were significantly higher than those in the attack-free periods, and a significant positive correlation was observed between disease severity and PDW levels. In a study evaluating PDW and MPV, Uluca et al. indicated that MPV and PDW levels were unaffected in childhood FMF. The authors attributed this to the suppression of inflammation due to colchicine therapy (20). FMF patients in this study were also on colchicine therapy, but our results were different. In addition, NLR levels during attacks were significantly higher than those in attack-free periods, which was possibly linked to increased neutrophil counts due to inflammation.

### Limitations of the study

The study acknowledges certain limitations that warrant consideration when interpreting the findings. Firstly, the influence of colchicine therapy on laboratory parameters and disease severity in Familial Mediterranean Fever (FMF) patients, a crucial aspect of the management, is not comprehensively explored in this research. The impact of colchicine, a standard treatment for FMF, on the observed results remains a potential factor that requires further investigation. Secondly, the study primarily focuses on MEFV gene mutations, offering valuable insights into the genetic aspect of FMF. However, it's important to note that genetic diversity can vary significantly among different populations. The predominantly narrow focus on MEFV mutations may limit the generalizability of the findings to populations with diverse genetic backgrounds, and caution is needed when applying these results to broader demographic groups

## CONCLUSION

This is one of the few articles investigating the relationship between hematological parameters and inflammation in FMF attack, attack-free period, and control groups, and is important in terms of elucidating these periods. In this study, MPV levels were higher among FMF patients than healthy controls and dropped during attacks from levels in attack-free periods and decreased further as disease severity increased. These results suggest that MPV could be used as a negative marker for identifying attack phases in FMF patients. Additionally, increases in PDW and NLR levels were observed with escalating disease severity, highlighting their potential as indicators of inflammation severity.

Our study demonstrates that hematological parameters can serve as useful tools in the clinical management of FMF; however, further research is needed to fully understand the impact of colchicine treatment on these parameters. Future studies should expand upon our findings and include patients from diverse ethnic backgrounds to assess the applicability of our results to a broader population.

The integration of regular monitoring of hematological parameters, especially during attack periods and across different severity levels, could enhance clinical practices in FMF management. Continued research into the underlying mechanisms of these findings and their implications for disease management is essential. To conclude, MPV, PDW, and NLR measurements offer an easy, inexpensive, and rapid method to detect attacks and determine disease severity in FMF patients. Future studies will firmly establish the efficacy of MPV, PDW, and NLR as markers in FMF assessment.

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### Peer-Review

Both externally and internally peer reviewed.

### Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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The Authors report no financial support regarding content of this article.

### Ethical Declaration

Ethical permission was obtained from the İstanbul Medeniyet University, Medical Faculty Clinical Ethics Committee for this study with date 23.09.2014 and number 2014/0147 and Helsinki Declaration rules were followed to conduct this study.

### Authorship Contributions

Concept: GT, ME, Design: GT, ME, Supervising: ME, EOY, Financing and equipment: GT, DKI, Data collection and entry: GT, DKI, Analysis and interpretation: GT, ME, EOY, Literature search: GT, DKI, Writing: GT, Critical review: ME, EOY.

### Thesis

This study was prepared by rearrangement of the specialty thesis by Gül Trabzon entitled as “Clinical Significance of Mean Platelet Volume, Platelet Distribution Width, and Neutrophil-Lymphocyte Ratio in Children with Familial Mediterranean Fever”.

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