Research Article / Araştırma Makalesi
doi: 10.18678/dtfd.1037824

Duzce Med J, 2022;24(1):18-25
Düzce Tıp Fak Derg, 2022;24(1):18-25

Evaluation of the Relationship between Simple Hemogram Indexes and Disease Severity Scores in Pediatric Familial Mediterranean Fever

Pediatrik Ailevi Akdeniz Ateşinde Basit Hemogram İndeksleri ile Hastalık Şiddet Skorları Arasındaki İlişkinin Değerlendirilmesi

Vildan GÜNGÖRER[1]
0000-0002-9838-2603
Şükrü ARSLAN[2]
0000-0001-5632-8273

[1]Department of Pediatric Rheumatology, University of Health Sciences Ankara City Hospital, Ankara, Turkey

[2]Department of Pediatric Nephrology and Rheumatology, Bakırçay University Faculty of Medicine, İzmir, Turkey

Corresponding Author
Sorumlu Yazar
Vildan GÜNGÖRER
vildan_61183@hotmail.com

Received / Geliş Tarihi : 17.12.2021
Accepted / Kabul Tarihi : 25.02.2022
Available Online / Çevrimiçi Yayın Tarihi : 07.04.2022

ABSTRACT

Aim: In recent years, it has been seen that simple complete blood count (CBC) parameters can be used to show subclinical inflammation in patients with familial Mediterranean fever (FMF). The aim of this study is to determine whether there is a difference in CBC parameters among FMF patient groups divided according to disease severity scores.

Material and Methods: FMF patients followed up in our clinic between 2016 and 2019, were reviewed for medical records. They were divided into three groups as those with mild, moderate, and severe diseases according to the disease severity scoring systems by Pras et al., Mor et al., and International Severity Score of FMF (ISSF). Red cell distribution width (RDW), platelet, neutrophil, lymphocyte, RDW-platelet ratio (RPR), platelet-lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR) of the patients were compared among the groups.

Results: According to the scoring system of Pras et al., lymphocyte value was found significantly higher in the group with severe disease compared to the groups with mild and moderate diseases (p=0.031). PLR was significantly lower in the group with severe disease compared to moderate diseases according to the scoring system of Mor et al (p=0.008). According to ISSF, there was no difference among the groups in terms of CBC parameters.

Conclusion: Different results were obtained according to all three scoring systems. Since the ISSF is the most common and suitable system for use in FMF patients, we can conclude that there is no relationship between disease severity and RDW, RPR, NLR and PLR.

Keywords: Complete blood count; disease severity index; familial Mediterranean fever.

ÖZ

Amaç: Son yıllarda, AAA hastalarında subklinik inflamasyonu göstermek için basit tam kan sayımı (TKS) parametrelerinin kullanılabileceği görülmüştür. Bu çalışmanın amacı, hastalık şiddeti skorlarına göre ayrılan AAA hasta grupları arasında TKS parametrelerinde farklılık olup olmadığını belirlemektir.

Gereç ve Yöntemler: Kliniğimizde 2016 ve 2019 yılları arasında takip edilen AAA hastalarının tıbbi kayıtları incelendi. Hastalar, Pras ve ark., Mor ve ark. ve AAA için uluslararası şiddet skorlama sistemi (International Severity Score for FMF, ISSF) hastalık şiddeti skorlama sistemlerine göre hafif, orta ve ağır hastalığı olanlar olmak üzere üç gruba ayrıldı. Hastaların eritrosit dağılım genişliği (red cell distribution width, RDW), trombosit, nötrofil, lenfosit, RDW-trombosit oranı (RDW-platelet ratio, RPR), trombosit-lenfosit oranı (platelet-lymphocyte ratio, PLR) ve nötrofil-lenfosit oranı (neutrophil-lymphocyte ratio, NLR) gruplar arasında karşılaştırıldı.

Bulgular: Pras ve ark.'nın skorlama sistemine göre, şiddetli hastalığı olan grupta lenfosit değerinin hafif ve orta derecede hastalığı olan gruplara göre anlamlı derecede yüksek olduğu bulundu (p=0,031). Mor ve ark.'nın skorlama sistemine göre PLR, şiddetli hastalığı olan grupta orta dereceli hastalıklara göre anlamlı olarak daha düşüktü (p=0,008). ISSF skorlamasına göre, TKS parametreleri açısından gruplar arasında fark yoktu.

Sonuç: Her üç skorlama sistemine göre de farklı sonuçlar elde edildi. ISSF, AAA hastalarında en yaygın ve kullanıma uygun sistem olduğundan, hastalık şiddeti ile RDW, RPR, NLR ve PLR arasında bir ilişki olmadığı sonucuna varabiliriz.

Anahtar kelimeler: Tam kan sayımı; hastalık şiddeti indeksi; ailesel Akdeniz ateşi.

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common and widely known autosomal recessively inherited monogenic autoinflammatory disease characterized by recurrent episodes of polyserositis and fever (1). FMF is mostly seen in Mediterranean cultures such as Arabs, Armenians, Jews, Greeks, Italians, and Turks (2,3). FMF patients have a mutation in the Mediterranean fever (MEFV) gene. This gene codes for a protein called pyrin. When there is a 63 gain of function mutation in the MEFV gene, pyrin protein becomes active and resulting in continuous inflammatory stimulation (4).

Infection, stress, menses, exposure to cold, some drugs, and fat-rich foods can trigger an FMF attack (5). The attacks are self-limiting and usually last between 6 hours and 3 days. (6,7). The patient's clinical condition returns to normal between attacks. However, inflammation markers do not always return to normal (7,8). Although the attacks resolve spontaneously, if attacks and inflammation are not prevented in FMF patients, amyloidosis develops and this can cause serious organ damage, especially in the kidneys. Therefore, it is vital to control inflammation in FMF patients. Studies have shown that 30% of FMF patients continue to have inflammation in the attack-free period (9). Subclinical inflammation can be demonstrated by the elevation of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, serum amyloid A, and various cytokines in the blood. In recent studies, it has been shown that subclinical inflammation can be measured in many diseases with very simple hemogram markers and various formulations (10-13). In particular, an increase in neutrophil and platelet counts, while a decrease in lymphocyte counts is observed. Platelets are rich in proinflammatory agents and their release plays a role in many inflammatory diseases. Circulating platelets can interact with erythrocytes, neutrophils, and lymphocytes in the vessel lumen at sites of vascular damage (14,15). Red cell distribution width (RDW) is a blood parameter that measures erythrocyte variability and size and reflects the degree of inflammation and oxidative stress. Studies have shown that there is a strong correlation between RDW and frequently used inflammation markers, CRP, and ESR (16). Simple blood parameters were investigated in terms of disease severity for many diseases (17-21).

Especially in the last 20 years, various scoring systems have been used to evaluate disease severity in many diseases including FMF. For this purpose, the first disease severity scoring system for FMF was developed in 1997 by Pras et al. (22) and it is still one of the best known scoring systems used for adult patients. In 2005, Mor et al. (23) developed a new scoring system to correct the deficiencies in the scoring system of Pras et al. (22), such as the lack of a cause and effect relationship between the severity markers and disease severity and the use of arbitrary differential values for each parameter. However, Kalkan et al. (24) showed that these two scoring systems were not congruent with each other. Thereupon, the international FMF expert group developed International Severity Score for FMF (ISSF) in 2012. The newly developed criteria are suitable for use in both clinical practice as well as drug trials in adult and pediatric FMF patents (25). These scores help clinicians to predict the severity and prognosis of the disease.

The aim of this study is to determine the relationship of these simple complete blood count parameters that can be measured in almost every laboratory, such as RDW, platelet (PLT), RDW-PLT ratio (RPR), PLT-lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR), with inflammation and disease severity scores of FMF patients.

MATERIAL AND METHODS

Patients

In this study, 165 FMF patients under 18 years of age in the Pediatric Rheumatology Outpatient Clinic between March 2016 and April 2019 were evaluated. Ethical approval for the study was obtained from local ethics committee on 27.07.2020 with the approval number 2020/311. Patients who did not follow up regularly and did not use their treatment regularly were not included in the study. Patients with comorbidities (eg., autoimmune disease, acute/chronic infection, malignancy, end-stage kidney disease, liver disease, hematological disease, hypertension, diabetes mellitus, cerebrovascular disease), patients with a BMI >30, smokers, and those who received a blood transfusion within the last 4 months for any reason were excluded from the study. For these reasons, a total of 106 patients were not included in the study.

The diagnosis of the patients was made according to the Ankara 2008 pediatric FMF diagnostic criteria, where at least 2 criteria were sufficient, including; fever >38 degrees (at least 3 attacks lasting between 6 hours and 72 hours), abdominal pain (at least 3 attacks lasting between 6 hours and 72 hours), chest pain (at least 3 attacks lasting between 6 hours and 72 hours), arthritis (at least 3 attacks lasting between 6 hours and 72 hours), family history of FMF (26). Since the genetic disease carrier rate is very high in Turkey, the use of these criteria, which only have clinical criteria, has been deemed appropriate for diagnosis.

Case Definition

The disease severity scores of the patients were evaluated according to the scoring systems of Pras et al. (22), Mor et al. (23), and ISSF (Table 1).

Pras et al. (22)'s scoring included age at onset of the disease (years), number of attacks per month, presence of arthritis (acute or prolonged), presence of erysipelas-like erythema, presence of amyloidosis, and colchicine dose (mg/day) used. According to the scoring system of Pras et al. (22), 3-5 points were classified as mild disease, 6-9 points as moderate disease, and >10 as severe disease.

Mor et al. (23)'s scoring system evaluated patients according to the age of onset, the number of areas involved in attacks and throughout the course of the disease, the dose of colchicine, the number of pleural involvement, and the number of attacks with erysipelas-like erythema. According to the scoring system of Mor et al. (23), presence of ≥3 points was considered as severe disease, 2 points as moderate disease, and ≤1 points as mild disease.

The ISSF included the presence of chronic sequelae, organ dysfunction and failure, frequency of attacks, acute phase reactants, the number of sites involved in a single attack, attack types during the course of the disease, attack duration, and exertional leg pain. According to ISSF, ≤2 points was evaluated as mild disease, 3-5 points as moderate disease, and ≥6 points as severe disease.

Table 1. Disease severity scoring systems in Familial Mediterranean fever

Pras et al.		**Mor et al.**	**ISSF**	
Criteria	**Score**	**Criteria**	**Criteria**	**Score**
Age of onset (year)		1. ≥1 site in a single attack (In	1. Chronic sequela (including amyloidosis, growth	
>31	0	at least 25% of the attacks)	retardation, anemia, splenomegaly)	1
21-31	1		2. Organ dysfunction (nephrotic range proteinuria, FMF related)	1
11-20	2		3. Organ failure (heart, renal, etc., FMF related)	1
6-10	3	2. ≥2 sites in the course of the	4. A. Frequency of attacks (average number of attacks	
<6	4	disease	between 1 and 2 per month)	1
			B. Frequency of attacks (average number of attacks	
Number of attacks per month			>2 per month)	2
<1	1	3. ≥2 mg/day colchicine to	5. Increased acute-phase reactants (any of C-reactive	
1-2	2	achieve remission	protein, serum amyloid A, erythrocyte sedimentation	
>2	3		rate, fibrinogen) during the attack-free period, ≥2 weeks	
			after the last attack (at least two times 1 months apart)	1
Arthritis		4. ≥2 pleuritic attacks during	6. Involvement of more than two sites during an	
Acute	2	the course of the disease	individual acute attack (pericarditis, pleuritis, peritonitis,	
Persistant	3		synovitis, ELE, testis involvement, myalgia, and so on)	1
Erysipelas-like eritem	2		7. More than two different types of attack during the course of	
Amyloidosis	3	5. ≥2 Erysipelas-like erythema	the disease (isolated fever, pericarditis, pleuritis, peritonitis,	
Colchicine dosage (mg/day)		attacks during the courseof the	synovitis, ELE, testis involvement, myalgia, and so on)	1
1	1	disease	8. Duration of attacks (more than 72 h in at least three	
1,5	2		attacks in a year)	1
2	3		9. Exertional leg pain (pain following prolonged	
>2**	4	6. Age of onset<10 years	standings and/or exercising, excluding other causes)	1
**2 mg/day unresponsive		**≥3 points was considered as**	*Criterion 4a/4b can give 0 or 1 or 2 points altogether	
3-5 points were classified as mild disease, 6-9 points as moderate disease, and >10 as severe disease		**severe disease, 2 points as moderate disease, and ≤1 points as mild disease**	according to the definition **Severe disease ≥6, intermediate disease 3-5, mild disease ≤2**	

Study Design

Information on patients was collected from computer data systems and patient files. Clinical findings, family history, drug responses, gene mutations, ESR, CRP, complete blood count parameters, NLR, RPR, and PLR of all cases were recorded. All FMF patients were evaluated during the attack-free period and under colchicine treatment. In all patients, blood parameters in the attack-free period of at least 3 months were used for evaluation.

The patients were divided into three groups according to the disease severity scores as mild, moderate, and severe, and the relationship between complete blood count parameters and disease severity scores was investigated.

Data Sources and Measurement

Complete blood count analysis was performed in a tube with K3 EDTA and with the Sysmex XE-2100 hemogram device, which was regularly controlled and maintained.

Among the mild, moderate, and severe disease groups, differences in CRP (mg/L), ESR (mm/hour), RDW (%), PLT (K/uL), neutrophil (K/uL), lymphocyte (K/uL), NLR, RPR, and PLR were investigated.

The NLR was calculated by dividing the neutrophil count by the lymphocyte count, RPR was calculated by dividing RDW by PLT count, and PLR was calculated by dividing the PLT count by the lymphocyte count.

Statistical Analysis

All data were analyzed in IBM SPSS Statistics v.21.0 package program. Mean, standard deviation, median, interquartile range, and minimum -maximum values were used for the descriptive statistics. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the normality distribution of variables. one-way ANOVA was used if the normality assumption was met, and the Kruskal-Wallis test was used if not. To examine the significant difference between groups after one-way ANOVA, the homogeneity of the variances was checked first, then the Tukey test was used in the post hoc analysis if the variances were homogeneous, and the Tamhane's T2 test was used if not. A p value of <0.05 was considered statistically significant.

RESULTS

Demographics and Clinic Characteristics of Patients

Eighty-five (51.5%) patients were male and 80 (48.5%) were female. The mean age of the patients at diagnosis was 7.4±2.2 years (median, 6; range, 10 months-17 years). The mean time between the onset of complaints and the diagnosis was calculated as 2.77±2.61 years (median, 2; range, 5 months-4 years). The mean attack duration of the patients was 2.6±1.1 (median, 0.5; range, 2-10) days. The attack frequency was 4.9±5.7 (median, 4; range, 1-52) weeks. Demographic features and laboratory parameters of the patients are summarized in Table 2.

Evaluation of Patients According to Disease Severity Scores

The distribution of patients into groups, such as mild, moderate, and severe diseases, according to disease severity scores is summarized in Table 3. While the number of patients with moderate disease was higher according to the scoring system of Pras et al. (22), the number of patients with mild disease was higher according to ISSF and the scoring system of Mor et al. (23).

Evaluation of Laboratory Parameters According to Disease Severity Scores

ESR and CRP

According to the scoring system of Pras et al. (22), CRP and ESR were different among the groups. When the source of this difference is investigated by post hoc test, CRP value was significantly lower in the group with

Table 2. Laboratory parameters of the patients

	Mean±SD	Median (IQR)	Min-Max
WBC (K/uL)	7193.5±2118.7	6800 (2500)	3800-15000
NEU (K/uL)	3816.3±1821.2	3210 (2050)	1500-11000
LYM (K/uL)	2597.7±68.1	2500 (880)	700-7000
PLT (x10^3 K/uL)	295.6±70.5	293 (83.5)	136-486
RDW (%)	14.4±1.4	14.2 (1.6)	11.9-19.5
CRP (mg/L)	4.9±8.3	1.9 (3.95)	0.12-84
ESR (mm/h)	12.2±10.0	9 (12.9)	2-49
PLR	123.1±43.2	115.7 (44.7)	49.2-347.5
RPR	0.05±0.01	0.05 (0.018)	0.01-0.10
NLR	1.66±1.17	1.42 (0.95)	0.39-8.58

SD: standard deviation, IQR: interquartile range, WBC: white blood cell, NEU: neutrophil, LYM: lymphocyte, PLT: platelet, RDW: red cell distribution width, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PLR: platelet-lymphocyte ratio, RPR: RDW-platelet ratio, NLR: neutrophil-lymphocyte ratio

Table 3. Distribution of patients according to Familial Mediterranean fever disease severity scores (n=165)

Severity Score	Pras et al.	Mor et al.	ISSF
Mild	43 (%26.1)	107 (%64.8)	99 (%60.0)
Moderate	85 (%51.5)	30 (%18.2)	54 (%32.7)
Severe	37 (%22.4)	28 (%17.0)	12 (%7.3)

ISSF: International Severity Score for Familial Mediterranean fever

moderate disease compared to the group with severe disease (p=0.001). In addition, ESR value was significantly different between the groups with mild and severe diseases and the groups with moderate and severe diseases. Accordingly, the ESR value in the group with mild disease was significantly lower compared to the ESR value in the group with moderate disease, and that value was significantly lower compared to the group with severe disease (both p vales were <0.001).

According to the scoring system of Mor et al. (23), there was a difference among the groups in terms of CRP, and ESR values. When the source of this difference is investigated by post hoc test, CRP was significantly lower in the group with mild disease compared to the group with moderate disease (p=0.020). ESR was significantly lower in the group with mild disease compared to the groups with moderate and severe diseases (p=0.012, p=0.006, respectively).

When the patients were evaluated according to ISSF, there was a difference among the groups in terms of ESR and CRP. When this difference is investigated by post hoc test, CRP was significantly higher in the group with severe disease compared to the groups with mild and moderate diseases (p=0.011, p=0.017, respectively). Similarly, ESR was significantly higher in the group with severe disease compared to the groups with mild and moderate diseases (both p vales were <0.001). ESR increased as the severity of the disease increased.

Lymphocyte, Neutrophil, PLT, RDW, NPR, RPR and LPR

According to the scoring system of Pras et al. (22), lymphocyte levels were different among the groups. When the source of difference among the groups was investigated by post hoc test, the lymphocyte value in the group with mild disease was significantly lower than the lymphocyte value in the group with moderate disease (p=0.050). There was no difference among the groups in terms of RPR, PLR, NLR, neutrophil, PLT, and RDW values (Table 4).

According to the scoring system of Mor et al. (23), there was a difference among the groups only in terms of PLR. In paired comparisons with post hoc test, PLR was found to be significantly higher in the group with mild disease compared to the group with severe disease (p=0.037). In addition, it was significantly higher in the group with moderate disease compared to the group with severe disease (p=0.006).

According to ISSF, there was no difference between the groups in terms of RPR, PLR, NLR, neutrophil, PLT, and RDW values.

DISCUSSION

Familial Mediterranean fever is an autoinflammatory disease common all over the world, and it is estimated that there are approximately 120.000 patients in the world (27). Therefore, the clinical forms of the disease, its genetics, disease severity, pathogenesis, and indicators of inflammation have been a matter of interest. Since it is an autoinflammatory disease, the most important problem for clinicians is to control inflammation and prevent amyloidosis resulting from uncontrolled inflammation.

Measuring disease severity scores helps predict the prognosis of the disease, provides an early and effective approach to treatment, and thereby contributes to the patient's quality of life. In addition, it provides objective evaluations for various scientific research. In recent years, many studies comparing complete blood count parameters with healthy controls have shown that inexpensive and practical markers, such as NLR and PLR, can be used to evaluate disease activity and severity in autoimmune and inflammatory diseases instead of expensive tests (28-30). Uslu et al. (31) compared the NLR ratio with healthy controls and found a significantly higher NLR in FMF patients. In addition, they found a significant difference in NLR of patients with and without amyloidosis. Uluca et al. (32) measured NLR during the attack and attack-free periods and found that it was significantly higher during the attack period. Özer et al. (30) compared the NLR of patients in the attack-free period with healthy controls and suggested that NLR could be a significant marker to show subclinical inflammation in FMF patients. Yorulmaz et al. (28) evaluated NLR during the attack period, attack-free period, and in healthy controls. They found a significant difference between the attack and attack-free periods; however, they could not detect a difference between the attack-free period and healthy controls, stating that NLR was a good marker for demonstrating systemic inflammation, but they could not find such significant evidence for subclinical inflammation. In the present study, NLR showed no difference among the groups divided with respect to disease severity scores, according to all three scoring systems. In terms of PLR, there was no difference among the groups divided according to the scoring system of Pras et al. (22) and ISSF, while there was a significant difference between the groups with moderate and severe diseases and mild and severe diseases in the

Table 4. Evaluation of laboratory values according to disease severity scores

	Mild Disease		Moderate Disease		Severe Disease		
	Mean±SD	**Median (IQR) [min-max]**	**Mean±SD**	**Median (IQR) [min-max]**	**Mean±SD**	**Median (IQR) [min-max]**	**p**
WBC (K/uL)							
Pras et al.	6940.9±2178.0	6600 (2900) [3800-14900]	7111.5±2135.8	6700 (2350) [3800-15000]	7516.2±1760.3	7500 (2200) [5000-13000]	0.444
Mor et al.	7108.3±2146.2	6700 (2300) [3800-15000]	7406.5±1758.2	7400 (3075) [5000-11200]	7064.3±2127.6	7000 (2775) [3800-14900]	0.755
ISSF	7107.9±2158.3	6800 (2400) [3800-15000]	7074.6±1998.2	6700 (2650) [3800-14300]	7933.3±1523.9	7950 (800) [5100-11100]	0.402
NEU (K/uL)							
Pras et al.	3663.6±1686.8	3200 (1900) [1800-11000]	3649.4±1912.8	3000 (1990) [1500-11000]	4271.6±1579.1	4140 (2050) [1800-8200]	0.182
Mor et al.	3703.9±1775.3	3200 (1880) [1500-11000]	4109.4±1807.8	3700 (3080) [1500-9010]	3772.5±1879.3	3250 (2133) [1800-11000]	0.542
ISSF	3705.6±1789.4	3200 (1830) [1500-11000]	3770.9±1877.6	3140 (1985) [1500-11000]	4590.0±1306.7	4550 (1540) [2400-7000]	0.272
LYM (K/uL)							
Pras et al.	2389.3±779.9	2300 (1000) [990-4470]	2769.4±1003.5	2600 (1045) [700-7000]	2441.6±576.8	2400 (650) [1100-4460]	**0.031**
Mor et al.	2609.3±943.0	2500 (900) [700-7000]	2415.2±672.7	2320 (923) [1100-3800]	2754.6±833.5	2550 (680) [1400-4700]	0.330
ISSF	2569.6±911.8	2510 (900) [700-7000]	2652.4±857.3	2500 (808) [1220-6300]	2583.3±800.2	2400 (840) [1560-4460]	0.855
RDW (%)							
Pras et al.	14.5±1.6	14.0 (1.8) [12.4-19.5]	14.3±1.3	14.1 (1.4) [12.1-18]	14.6±1.4	14.6 (1.8) [11.9-18.8]	0.531
Mor et al.	14.4±1.4	14.1 (1.6) [12.1-19.5]	14.6±1.5	14.4 (1.8) [11.9-18.8]	14.5±1.1	14.5 (1.6) [12.2-16.5]	0.774
ISSF	14.5±1.5	14.2 (1.6) [12.1-19.5]	14.3±1.3	14.15 (1.3) [11.9-18]	14.7±1.1	14.65 (1.4) [12.7-16.4]	0.558
CRP (mg/L)							
Pras et al.	4.6±12.6	1.60 (1.86) [0.39-84]	3.2±3.8	1.7 (2.46) [0.12-19.7]	9.3±8.4	5.93 (13) [0.18-28]	**0.001**
Mor et al.	3.0±3.9	1.59 (1.89) [0.12-28]	6.9±7.3	3.68 (10.23) [0.18-25]	10.1±16.1	5.06 (11.37) [0.16-84]	**0.001**
ISSF	3.9±9.1	1.62 (1.99) [0.12-84]	4.7±4.6	2.09 (6.12) [0.16-17.4]	14.1±9.5	16.5 (19.7) [1.11-25.4]	**0.001**
ESR (mm/h)							
Pras et al.	8.2±5.6	7 (7) [2-22]	10.2±8.3	8 (10) [2-43]	21.0±11.6	21 (17) [2-49]	**0.001**
Mor et al.	9.6±8.1	8 (10) [2-49]	15.3±9.4	13 (16) [2-35]	18.1±12.8	15 (23) [2-43]	**0.001**
ISSF	9.7±7.6	8 (10) [2-49]	12.8±10.0	11 (14) [2-43]	28.8±9.1	29.5 (10) [6-42]	**0.001**
PLR							
Pras et al.	131.6±45.9	120.0 (47.6) [65.9-347.5]	118.7±40.4	112.6 (45.8) [49.2-252.6]	123.3 ±46.1	114.6 (37.5) [69.3-281.1]	0.286
Mor et al.	122.9±42.7	115.8 (42.1) [55.4-347.5]	140.4±50.7	135.6 (63.4) [49.2-281.1]	105.6±28.1	108.2 (51.3) [58.3-162.2]	**0.008**
ISSF	125.7±46.8	118.3 (43.8) [55.4-347.5]	116.8±36.1	110.9 (46.9) [49.2-216.5]	129.7±41.9	117.5 (77.8) [71.5-198.1]	0.410
RPR							
Pras et al.	0.05±0.01	0.05 (0.016) [0.03-0.07]	0.05±0.01	0.05 (0.018) [0.01-0.09]	0.05±0.02	0.05 (0.016) [0.03-0.10]	0.273
Mor et al.	0.05±0.01	0.05 (0.017) [0.01-0.10]	0.05±0.01	0.05 (0.016) [0.03-0.07]	0.06±0.02	0.05 (0.016) [0.04-0.10]	0.199
ISSF	0.05±0.01	0.05 (0.017) [0.01-0.10]	0.05±0.01	0.05 (0.018) [0.03-0.10]	0.05±0.01	0.05 (0.014) [0.03-0.07]	0.770
NLR							
Pras et al.	1.62±0.76	1.37 (0.81) [0.62-4.23]	1.58±1.35	1.22 (0.94) [0.39-8.58]	1.94±1.14	1.55 (1.32) [0.69-6.00]	0.285
Mor et al.	1.63±1.15	1.38 (0.75) [0.39-8.58]	2.00±1.56	1.44 (1.60) [0.42-7.39]	1.45±0.67	1.47 (1.06) [0.47-2.88]	0.174
ISSF	1.67±1.20	1.39 (0.88) [0.39-8.58]	1.61±1.20	1.24 (0.89) [0.42-7.39]	1.95±0.80	2.02 (1.26) [0.69-3.37]	0.655

SD: standard deviation, IQR: interquartile range, WBC: white blood cell, NEU: neutrophil, LYM: lymphocyte, PLT: platelet, RDW: red cell distribution width, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PLR: platelet-lymphocyte ratio, RPR: RDW-platelet ratio, NLR: neutrophil-lymphocyte ratio

scoring system of Mor et al. (23), and PLR was significantly lower in the group with severe disease. This result was quite different from studies in the literature in which PLR in cancer and other inflammatory diseases increased as the disease severity increased (18,33,34). We can attribute this to the scarcity of studies on this subject, and perhaps to the heterogeneous division of disease severity in the scoring systems for FMF. We think that more studies are needed on PLR and disease severity scores of FMF. It should also be noted that the scoring systems of Pras et al. (22) and Mor et al. (23) are not as suitable for pediatric use as is ISSF.

Another measurement that has been popular in recent years is RDW and its ratio to PLT count. RDW is a parameter that reflects the variance of the sizes of circulating erythrocytes in standard automatic complete blood count. Although traditionally used in different types of anemia, it has been found to increase during inflammation (10,30). Many studies have revealed that RDW is also associated with liver, kidney, and cardiovascular diseases. In addition, RDW is known to be a recently used inflammation marker in inflammatory diseases, such as septic shock, inflammatory bowel disease, and acute appendicitis (19,35-37). In addition, RPR has been shown to be a new and rapid laboratory index for predicting mortality in many diseases. Chen et al. (38) concluded that RPR is an inexpensive and noninvasive marker for predicting fibrosis and cirrhosis in chronic hepatitis B compared to liver biopsy. Similarly, Cetinkaya et al. (21) used RPR to determine the severity of acute pancreatitis. It was also found that RDW and PLT count correlated with disease activity in patients with rheumatoid arthritis (39). In previous studies on adult and pediatric FMF patients, markers such as RDW and PLR were used as indicators of subclinical inflammation. In another study, it was concluded that in the case of systemic lupus erythematosus (SLE), which is one of the rheumatologic diseases, RPR was positively correlated with the SLE disease activity index and other inflammatory markers; therefore, RPR was a very good prognostic indicator for evaluating SLE patients (40). As far as we know, although there are studies showing that complete blood count parameters can be used as subclinical inflammation markers in pediatric FMF patients, no study has been conducted to date in which RPR is evaluated and the relationship between complete blood count parameters with disease severity scores is investigated. In the present study, we could not detect a difference between RDW, RPR, and disease severity scores. However, in the light of other studies, we think that further studies with larger cohorts are needed on this subject. This is because ESR and CRP, which are standard acute phase reactants, increased in correlation with disease severity according to all three scoring systems. Although scoring systems are heterogeneous in themselves, the increase in these frequently used and well-known acute phase reactants in correlation with disease severity still acknowledges the reliability of the scoring systems.

In this study, we tried to make a judgment on the subject by comparing three disease severity scores based on clinical and laboratory values observed in patients during the course of the disease and hemogram parameters that can show subclinical inflammation of patients in the attack-free period. However, since disease severity scores were developed to assess the state of the disease throughout the course of the disease and none of them were sufficient to measure disease activity, we did not have a separate group for patients who had severe disease according to some of the scores but were in remission with treatment. In addition, the number of patients was limited since only patients who followed their follow-up regularly were included in the study.

CONCLUSION

In conclusion, we evaluated the complete blood count parameters that can be easily accessed and calculated in FMF according to the three disease severity scoring systems used in FMF, which are actually different from each other in content. However, we obtained different results between disease severity scores and complete blood count parameters for all three scoring systems. Since ISSF is the most common and appropriate system used in pediatric FMF patients, it can be concluded that there is no relationship between disease severity and RDW, RPR, NLR, and PLR. However, we believe that there is a need for studies with larger series by examining the current clinical status (active disease, in remission, in partial remission) and disease severity scores, which include the entire disease course, in FMF patients. There is no study in the literature comparing RPR, PLR, and NLR after dividing patients into groups according to their disease severity scores. We think that this study is valuable in this respect.

Ethics Committee Approval: The study was approved by the Ethics Committee of Selçuk University Faculty of Medicine (27.07.2020, 2020/311).

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: The authors thank Enago – https://www.enago.com.tr/ceviri/ for their assistance in manuscript translation and editing.

The authors were working at Selçuk University Faculty of Medicine at the data collection phase of the study.

Author Contributions: Idea/Concept: VG, ŞA; Design: VG, ŞA; Data Collection/Processing: VG; Analysis/Interpretation: VG; Literature Review: VG, ŞA; Drafting/Writing: VG, ŞA; Critical Review: ŞA.

REFERENCES

1. Sönmez HE, Batu ED, Özen S. Familial Mediterranean fever: current perspectives. J Inflamm Res. 2016;9:13-20.
2. Daniels M, Shohat T, Brenner-Ullman A, Shohat M. Familial Mediterranean fever: high gene frequency among the non-Ashkenazic and Ashkenazic Jewish populations in Israel. Am J Med Genet. 1995;55(3):311-4.
3. Ozen S, Karaaslan Y, Ozdemir O, Saatci U, Bakkaloglu A, Koroglu E, et al. Prevalence of juvenile chronic

arthritis and familial Mediterranean fever in Turkey: a field study. J Rheumatol. 1998;25(12):2445-9.
4. Schnappauf O, Chae JJ, Kastner DL, Aksentijevich I. The pyrin inflammasome in health and disease. Front Immunol. 2019;10:1745.
5. Maggio MC, Corsello G. FMF is not always "fever": from clinical presentation to "treat to target". Ital J Pediatr. 2020;46(1):7.
6. Sarı İ, Birlik M, Kasifoğlu T. Familial Mediterranean fever: an updated review. Eur J Rheumatol. 2014;1(1):21-33.
7. Kucuk A, Gezer IA, Ucar R, Karahan AY. Familial Mediterranean fever. Acta Medica (Hradec Kralove). 2014;57(3):97-104.
8. Bilginer Y, Akpolat T, Ozen S. Renal amyloidosis in children. Pediatr Nephrol. 2011;26(8):1215-27.
9. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum. 1997;40(10):1879-85.
10. Yeşil A, Şenateş E, Bayoğlu IV, Erdem ED, Demirtunç R, Övünç AO. Red cell distribution width: a novel marker of activity in inflammatory bowel disease. Gut Liver. 2011;5(4):460-7.
11. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011;17(1):47-58.
12. Kisacik B, Tufan A, Kalyoncu U, Karadag O, Akdogan A, Ozturk MA, et al. Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. Joint Bone Spine. 2008;75(3):291-4.
13. Yazici S, Yazici M, Erer B, Erer B, Çalik Y, Bulur S, et al. The platelet functions in patients with ankylosing spondylitis: anti-TNF-α therapy decreases the mean platelet volume and platelet mass. Platelets. 2010;21(2):126-31.
14. Olumuyiwa-Akeredolu OO, Pretorius E. Platelet and red blood cell interactions and their role in rheumatoid arthritis. Rheumatol Int. 2015;35(12):1955-64.
15. Łukasik ZM, Makowski M, Makowska JS. From blood coagulation to innate and adaptive immunity: the role of platelets in the physiology and pathology of autoimmune disorders. Rheumatol Int. 2018;38(6):959-74.
16. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009;133(4):628-32.
17. Wang L, Cai Q. [Value of red blood cell distribution width-to-platelet count ratio in predicting the prognosis of children with sepsis]. Zhongguo Dang Dai Er Ke Za Zhi. 2019;21(11):1079-83.
18. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. Ann Lab Med. 2019;39(4):345-57.
19. Qiu L, Chen C, Li SJ, Wang C, Guo F, Peszel A, et al. Prognostic values of red blood cell distribution width, platelet count, and red cell distribution width-to-platelet ratio for severe burn injury. Sci Rep. 2017;7(1):13720.
20. Taefi A, Huang CC, Kolli K, Ebrahimi S, Patel M. Red cell distribution width to platelet ratio, a useful indicator of liver fibrosis in chronic hepatitis patients. Hepatol Int. 2015;9(3):454-60.
21. Cetinkaya E, Senol K, Saylam B, Tez M. Red cell distribution width to platelet ratio: new and promising prognostic marker in acute pancreatitis. World J Gastroenterol. 2014;20(39):14450-4.
22. Pras E, Livneh A, Balow JE Jr, Pras E, Kastner DL, Pras M, et al. Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet. 1998;75(2):216-9.
23. Mor A, Shinar Y, Zaks N, Langevitz P, Chetrit A, Shtrasburg S, et al. Evaluation of disease severity in familial Mediterranean fever. Semin Arthritis Rheum. 2005;35(1):57-64.
24. Kalkan G, Demirkaya E, Acikel CH, Polat A, Peru H, Karaoglu A, et al.; FMF Arthritis Vasculitis and Orphan Disease Research in Paediatric Rheumatology (FAVOR). Evaluation of the current disease severity scores in paediatric FMF: is it necessary to develop a new one? Rheumatology (Oxford). 2012;51(4):743-8.
25. Demirkaya E, Acikel C, Hashkes P, Gattorno M, Gul A, Ozdogan H, et al.; FMF Arthritis Vasculitis and Orphan disease Research in pediatric rheumatology (FAVOR). Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF). Ann Rheum Dis. 2016;75(6):1051-6.
26. Yalçinkaya F, Ozen S, Ozçakar ZB, Aktay N, Cakar N, Düzova A, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford). 2009;48(4):395-8.
27. Lidar M, Scherrmann JM, Shinar Y, Chetrit A, Niel E, Gershoni-Baruch R, et al. Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socioeconomic characterization. Semin Arthritis Rheum. 2004;33(4):273-82.
28. Yorulmaz A, Akbulut H, Taş SA, Tıraş M, Yahya İ, Peru H. Evaluation of hematological parameters in children with FMF. Clin Rheumatol. 2019;38(3):701-7.
29. Marzouk H, Mostafa N, Khalifa I, Badawi N, Mohamed Fathy Sabry NI. Red cell distribution width (RDW) as a marker of subclinical inflammation in children with familial Mediterranean fever. Curr Rheumatol Rev. 2020;16(4):298-303.
30. Özer S, Yılmaz R, Sönmezgöz E, Karaaslan E, Taşkın S, Bütün İ, et al. Simple markers for subclinical inflammation in patients with Familial Mediterranean Fever. Med Sci Monit. 2015;21:298-303.
31. Uslu AU, Deveci K, Korkmaz S, Aydin B, Senel S, Sancakdar E, et al. Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? Biomed Res Int. 2013;2013:185317.
32. Uluca Ü, Demir F, Ece A, Şen V, Güneş A, Aktar F, et al. Assessment of epicardial adipose tissue thickness and the mean platelet volume in children with familial Mediterranean fever. Ital J Pediatr. 2015;41:15.
33. Jiang S, Liu J, Chen X, Zheng X, Ruan J, Ye A, et al. Platelet-lymphocyte ratio as a potential prognostic

factor in gynecologic cancers: a meta-analysis. Arch Gynecol Obstet. 2019;300(4):829-39.
34. Hirahara T, Arigami T, Yanagita S, Matsushita D, Uchikado Y, Kita Y, et al. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. BMC Cancer. 2019;19(1):672.
35. Goyal H, Lippi G, Gjymishka A, John B, Chhabra R, May E. Prognostic significance of red blood cell distribution width in gastrointestinal disorders. World J Gastroenterol. 2017;23(27):4879-91.
36. Zvetkova E, Fuchs D. Medical significance of simultaneous application of red blood cell distribution width (RDW) and neopterin as diagnostic/prognostic biomarkers in clinical practice. Pteridines. 2017;28(3-4):133-40.
37. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci. 2015;52(2):86-105.
38. Chen B, Ye B, Zhang J, Ying L, Chen Y. RDW to platelet ratio: a novel noninvasive index for predicting hepatic fibrosis and cirrhosis in chronic hepatitis B. PloS One. 2013;8(7):e68780.
39. Tecer D, Sezgin M, Kanık A, İncel NA, Çimen ÖB, Biçer A, et al. Can mean platelet volume and red blood cell distribution width show disease activity in rheumatoid arthritis? Biomark Med. 2016;10(9):967-74.
40. Xie S, Chen X. Red blood cell distribution width-to-platelet ratio as a disease activity-associated factor in systemic lupus erythematosus. Medicine (Baltimore). 2018;97(39):e12342.