ORIGINAL ARTICLE

Assessment of neutrophil to lymphocyte ratio and mean platelet volume in pediatric familial Mediterranean fever patients

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Background: Blood neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV) both have been used as a simple marker of inflammation in many disorders. Here, we aimed to investigate the relationship between NLR, MPV, and familial Mediterranean fever (FMF). **Materials and Methods:** In this retrospective study, the files of FMF patients in pediatric rheumatology outpatient clinic were reviewed. There were 160 participants (68.4%) in the FMF patient group and 74 participants (31.6%) in the control group. Ninety of patients were in attack-free period, and 70 were in attack period. **Results:** The highest values of NLR were found in the patients at attack period. Patients in attack-free period and the participants in control group had similar levels of NLR (1.71 ± 0.83 and 1.91 ± 1.86 respectively) (P = 0.457), and they had lower ratios than the patients did at attack period (4.10 ± 3.11) (P < 0.001 for both). There was no significant difference between MPV values of attack patients (8.35 ± 4.91) and attack-free patients (8.43 ± 1.15) (P = 0.074). MPV values of attack patients and attack-free patients were significantly higher than control group (7.99 ± 0.81) (P < 0.001 for both). **Conclusion:** NLR ratio may indicate FMF attack period. Since there was no significant difference between attack-free patients and control groups, NLR ratio cannot be used as a subclinical inflammation marker. However, NLR could be a useful predictor of inflammation in FMF patients. On the other hand, since our attack and attack-free patients have similar MPV values and both had greater MPV values than control group, we suggest that MPV may be used to show subclinical inflammation.

Key words: Familial Mediterranean fever, mean platelet volume, neutrophil to lymphocyte ratio, pediatric

How to cite this article: Basaran O, Uncu N, Celikel BA, Aydın F, Cakar N. Assessment of neutrophil to lymphocyte ratio and mean platelet volume in pediatric familial Mediterranean fever patients. J Res Med Sci 2017;22:35.

INTRODUCTION

Familial Mediterranean fever (FMF) is a genetic, autosomal recessive disease affecting primarily non-Ashkenazi Jews, Turks, Arabs, and Armenians.[1] This disease is characterized by acute, short episodes of serosal membrane inflammation, and fever. The FMF gene, called as Mediterranean fever (MEFV) gene that encodes pyrin/marenostrin, is mapped to the short arm of chromosome 16. Mutant form of pyrin causes inflammation. Pyrin interacts with caspase-1 to modulate interleukin-1β (IL-1β) production. Therefore, the inflammatory phenotypes of FMF patients are induced by IL-1β activation.[2-4] Although IL-1β plays a fundamental role in pathogenesis of FMF, tumor necrosis factor-alpha (TNF-α), soluble IL-2 receptor, IL-6, and IL-8 have also been shown to stimulate this process.[5] Attack periods of the disease last in 1–3 days. Patients have an increased erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen levels during these attacks and usually, this increase returns to normal values in attack-free periods.[5,6] However, it is now known that subclinical inflammation may continue in attack-free periods of FMF patients.[5,7,8] This type of inflammation may lead to developing of amyloidosis, which is the most devastating complication of FMF.[9] Subclinical inflammation may also induce development and progression of atherosclerosis. Therefore, it seems important to represent subclinical inflammation in FMF patients.[10]

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/1735-1995.202140

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Received: 17-03-2016; **Revised:** 19-11-2016; **Accepted:** 28-12-2016

Neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV) were used to show the inflammation in both cardiac and noncardiac disorders before.[11-13] NLR and MPV may be the indicators of subclinical inflammation. However, contradictory results for MPV have been reported.[14-17]

In this study, we aimed to investigate whether NLR and MPV could be used to indicate the subclinical inflammation in pediatric FMF patients.

MATERIALS AND METHODS

Study design, participants, and variables assessment

Patients with the diagnosis of FMF in our Pediatric Rheumatology Department were reviewed retrospectively. The study included 160 pediatric patients diagnosed with FMF and a 74 healthy group. Ninety of the patients were in attack-free period, and seventy were in attack period. The diagnosis of FMF was made according to the Yalçinkaya *et al*. criteria.[18] Attack-free period was described as at least 2 weeks from the end of an FMF attack according to the symptoms and acute phase reactants levels. Control group was selected from the patients who had no acute or chronic disease that could cause inflammation and who were attended to pediatric clinics of our hospital for other reasons. Patients and controls having any other systemic disease or infection and using medication other than colchicine were excluded from the study. The clinical symptoms, laboratory values, and MEFV gene mutations were recorded. Laboratory data such as ESR, CRP, hemoglobin level, white blood cell count, platelet count, and MPV were noted using the electronic patient database of the last visit. Standard tubes containing ethylenediaminetetraacetic acid were used to analyze the complete blood counts. The analyses were performed with the same analyzer (Beckman Coulter, LH 780) in our center. NLR was calculated as a simple ratio between the absolute neutrophil count and absolute lymphocyte count.

As this study represents a retrospective chart review, the Local Ethical Committee permission was not sought. However, all patients signed an informed consent that allows our institution to use their clinical data.

Statistical analyses

Chi-square statistics was used for the comparisons of categorical variables between independent groups. The normal distributions of the numerical variables were evaluated by the Shapiro–Wilk test. Kruskal–Wallis nonparametric analysis of variances test was used for the comparisons of numerical variables between more than two independent groups, and Mann–Whitney U-test was used for the comparisons between two groups. Results for qualitative variables were presented as percentages, and quantitative variables were presented as mean and standard deviation. When a statistically significant difference was found by Kruskal–Wallis test, then, *post hoc* pairwise comparisons were performed using Mann–Whitney U-test. Bonferroni correction was also utilized for the modification of statistical significance level. The associations between the numerical variables of the study were evaluated using Spearman nonparametric correlation analysis. The Type-I error level was accepted as 5% in the study, and all statistical analyses were performed as two-tailed. For the statistical analysis of the data, the Statistical Package for the Social Sciences 17.0 (SPSS Inc., Chicago, IL, USA) was used

RESULTS

There were 160 participants (68.4%) in the patient group and 74 participants (31.6%) in the control group. Ninety of patients (38.5%) were in attack-free period, and 70 (29.9%) were in attack period. The male/female distribution in the groups was 29 (41.4%)/41 (58.6%) in FMF attack group, 35 (38.9%)/55 (61.1%) in attack-free group, and 38 (51.4%)/36 (48.6%) in control group. The statistical analyses revealed that the sex distribution between groups was similar ($P = 0.25$). The mean age of the entire participants was 11.78 ± 4.13 years. Ages according to the groups were 11.56 ± 4.3 years in attack period, 12.81 ± 3.88 years in attack-free period, and 10.74 ± 4.01 years in the control group. The age differences between groups were statistically significant ($P = 0.005$).

The levels of complete blood count parameters are presented in Table 1. The general group comparisons revealed that hemoglobin ($P < 0.001$), leukocyte ($P < 0.001$), thrombocyte ($P = 0.016$), CRP ($P < 0.001$), MPV ($P < 0.001$), neutrophil ($P < 0.001$), and lymphocyte ($P < 0.001$) levels were significantly differed between study groups. We found that MPV values of attack patients and attack-free patients had no significant difference ($P = 0.07$). MPV values of attack patients were significantly higher than the control group ($P < 0.001$), and MPV values of attack-free patients were also significantly higher than the control group ($P < 0.001$) [Table 1]. We also found a negative correlation between MPV and thrombocyte count in all groups and it was significant in attack and attack-free periods ($P = 0.002$ and $P < 0.001$, respectively).

The values of NLR in study groups are presented in Table 2. According to this, general group comparisons revealed a statistically significant difference between groups ($P < 0.001$), and *post hoc* pairwise comparisons showed that the highest values of NLR were found in the patients at attack period. The patients in attack-free period and the participants in control group had similar levels of NLR ($P = 0.45$), and they had lower ratios than the patients did at attack period ($P < 0.001$ for both). Correlations between the neutrophil/lymphocyte

ratio and the other parameters in the study groups are summarized in Table 3. There were positive weak correlation between CRP and NLR levels in attack ($r = 0.049$, $P = 0.68$) and attack-free patients ($r = 0.086$, $P = 0.07$), but they were not statistically significant.

The distribution of MEFV gene mutations are summarized in Table 4. Patients carrying M694V (either homozygous or heterozygous) were compared with patients carrying other mutations. NLR and MPV values did not have significant difference between different mutation groups ($P = 0.30$ and $P = 0.37$). Only patients with M694V homozygous and M694V/M680I compound heterozygous mutations have higher CRP levels ($P < 0.001$).

The colchicine usage was evaluated in attack and attack-free periods. Accordingly, the patients in attack period used colchicine with a mean dose of 1.03 ± 0.34 mg/day, and the patients in attack-free period used colchicine with a mean dose of 1.09 ± 0.29 mg/day. The difference of colchicine usage between groups was not statistically significant ($P = 0.25$).

DISCUSSION

The main aim of our study is to determine the subclinical inflammation in pediatric FMF patients using MPV and NLR. FMF is an autoinflammatory disease caused by abnormalities confined to the innate immune system and the result of reduced or complete loss of pyrin function.[19] Pyrin mutations and FMF link have been well established before. Both pro- and anti-inflammatory roles have been suggested for this protein. Pyrin is an important element of inflammasome and mutations in pyrin result in increased inflammation.[9,19,20] When a signal is received, inflammasome assembles. This activates caspase-1 and the processing and release of active IL-1β. IL-1 with other cytokines IL-6 and TNF-α results in high levels of acute phase reactants.[5] ESR, CRP, fibrinogen, and SAA are all used as markers for acute phase response in FMF.[14] These acute phase proteins increase during attack period and usually return to normal in attack-free period.[6,14] Subclinical inflammation continues in up to 30% of the FMF patients during attack-free period. At this point, persistent elevation of acute phase proteins is important as it reflects the subclinical inflammation, which has the key role in the development of amyloidosis and other complications such as anemia, splenomegaly, and osteopenia. As a result, several studies have aimed to discover new markers to determine the subclinical inflammation.[6,11,14-17,21-23]

NLR can be calculated simply by dividing neutrophil count to lymphocyte count. It has been reported as an indicator of

Table 1: Complete blood count parameters in study groups

	Mean±SD			*P*	Pairwise comparisons		
	Af	Afp	C		Ap-Afp	Ap-C	Afp-C
Hemoglobin (g/dl)	12.42±1.29	13.21±1.17	13.52±1.29	<0.001	<0.001	<0.001	0.176
Leukocyte (/mm^3)	10,802.86±4378.7	7128.89±1816.05	8281.08±2339.93	<0.001	<0.001	<0.001	0.002
Thrombocyte (/mm^3)	313,328.57±102,671.8	279,377.78±55,661.41	319,175.68±78,923.47	0.016	0.100	0.449	0.003
ESR (mm/h)	40.86±20	12.66±7.86	10.62±5.79	<0.001	<0.001	<0.001	0.150
CRP (mg/dl)	15.71±74.91	0.69±1.92	0.4±0.51	<0.001	<0.001	<0.001	0.918
MPV	8.35±4.91	8.43±1.15	7.99±0.81	<0.001	0.074	<0.001	<0.001
Neutrophil (%)	65.98±15.96	54.13±11.42	52.77±12.76	<0.001	<0.001	<0.001	0.236
Lymphocyte (%)	24.61±13.85	36.19±10.31	36.45±12.19	<0.001	<0.001	<0.001	0.687

Ap = Attack period; Afp = Attack-free period; C = Control group; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; MPV = Mean platelet volume; SD = Standard deviation

Table 2: Neutrophil/lymphocyte ratios in study groups

	Mean±SD				*P*	Pairwise comparisons		
	Ap	Afp	C	Entire groups		Ap-Afp	Ap-C	Afp-C
Neutrophil/lymphocyte ratio	4.10±3.11	1.71±0.83	1.91±1.86	2.49±2.31	<0.001	<0.001	<0.001	0.457

Ap = Attack period; Afp = Attack-free period, C = Control group

Table 3: Correlations between neutrophil/lymphocyte ratio and the other parameters in study groups

	ρ (*P*)							
	Age (years)	Colchicine (mg/day)	Hemoglobin (g/dl)	Leukocyte (/mm^3)	Thrombocyte (/mm^3)	ESR (mm/h)	CRP (mg/dl)	MPV (mpv)
Neutrophil/ lymphocyte ratio								
Ap	0.288 (0.016)	0.163 (0.178)	0.245 (0.041)	0.553 (<0.001)	−0.058 (0.635)	−0.152 (0.211)	0.049 (0.686)	0.136 (0.262)
Afp	0.370 (<0.001)	0.293 (0.005)	0.105 (0.323)	0.363 (<0.001)	−0.097 (0.361)	−0.025 (0.816)	0.186 (0.078)	0.114 (0.286)
C	0.250 (0.031)	-	0.301 (0.009)	0.450 (<0.001)	0.033 (0.782)	0.075 (0.525)	0.293 (0.011)	0.207 (0.077)

ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; MPV = Mean platelet volume; Ap = Attack period; Afp = Attack-free period; C = Control group

Table 4: Mediterranean fever gene mutation analysis

	n (%)
M694V+/+	53 (33.1)
M694V+/−	17 (10.6)
M694V/M680I	16 (10)
M694V/E148Q	8 (5)
M680I/V726A	7 (4.4)
M694V/V726A	7 (4.4)
E148Q+/−	6 (3.8)
V726A+/+	5 (3.1)
M694V/R202Q	4 (2.5)
V726A+/−	4 (2.5)
M680I/E148Q	2 (1.3)
M680I+/+	2 (1.3)
M694V/R761H	2 (1.3)
A745S+/−	1 (0.6)
E148Q+/+	1 (0.6)
K695R+/−	1 (0.6)
M680I+/−	1 (0.6)
M694V/E148Q/V726A	1 (0.6)
M694V/P369S	1 (0.6)
P369S+/−	1 (0.6)
V726A/K695R	1 (0.6)
V726A/P369S	1 (0.6)
−/−	18 (11.3)
Total	160 (100)

systemic inflammation in various conditions.[6,24] NLR was shown as a useful indicator of clinical outcome and disease severity in diseases having malign and inflammatory components.[21,25-27] There have also been some studies discussing the usefulness of NLR in FMF patients. Uslu *et al*. compared NLR in FMF patients and healthy controls. They concluded that NLR is higher in FMF patients. They also found that NLR was significantly higher in patients with amyloidosis than in amyloidosis-free patients.[6] Ahsen *et al*. concluded that in FMF patients NLR can be used as an acute phase response such as CRP.[11] Both of these studies did not include FMF patients during attack period. Celikbilek *et al*. reported NLR of adult FMF patients during attack and attack-free period. They found that NLR of FMF patients during attack period was significantly higher than those of attack-free patients and control group. There was no significant difference between attack-free patients and controls.[21] There have been two FMF studies with pediatric age group comparing the NLR levels.[14,16] Uluca *et al*. found that NLR levels were higher in patients in attack-free period and they concluded that NLR may be an indicator for attack period but not attack-free period.[16] Özer *et al*. also reported NLR values of pediatric symptom-free FMF patients and healthy controls. They found that NLR had the strongest correlation with CRP. They concluded that NLR could be a reliable marker for subclinical inflammation. However, in this study, they did not compare the NLR values of patients in attack period and attack-free period.[14]

Our results provide evidence which supports the thought that NLR may be a parameter to show the inflammation in attack period. However, it may not be useful to define the subclinical inflammation according to our study groups since there was no significant difference between attack-free patients and control group. As it is cost-effective, available and can be calculated easily, NLR could be used to predict systemic inflammation in pediatric FMF patients during attack period.

MPV has been investigated many times before to show disease activity, inflammatory load, and systemic inflammation in diseases.[14] Large platelets are hemostatically more active.[17,28] Thrombocyte activation is associated with increased atherosclerotic risk. MPV is an easily available and cost-effective test that can show thrombocyte activation and function.[16,29,30] There is limiting data discussing the relationship between MPV and atherosclerosis in FMF patients. Nevertheless, the results are not compatible to each other. Most of them have found higher MPV levels in FMF patients, while others have reported lower MPV values.[14-17,22,23,31] Uluca *et al*. published two studies discussing the relationship between MPV and atherosclerosis in FMF patients.[10,16] In the first study, they found that MPV values were similar in FMF patients and healthy controls. They concluded that MPV did not predict atherosclerosis risk in pediatric FMF patients.[16] In the later study, they compared the MPV values and epicardial adipose tissue thickness in children with FMF. They found significantly greater epicardial adipose tissue thickness and higher MPV values in children with FMF. They concluded that MPV values might indicate an increased risk of atherosclerosis in FMF.[10] In our study, both attack and attack-free patients had significantly higher MPV values compared to control group similar to most of the literature results. However, there were no significant differences between MPV values of attack and attack-free periods. Therefore, we concluded that MPV is not useful to show the attack periods in FMF, but it may be valuable to show the risk of atherosclerosis and subclinical inflammation in pediatric FMF patients.

Many studies have reported that M694V mutation is related with high disease activity and amyloidosis in FMF.[10,11] Although we could not find any significant difference of NLR and MPV values between FMF patients carrying M694V mutation, patients with M694V homozygous and heterozygous mutations had higher CRP values.

A possible limitation of our study is that all of our study groups were under colchicine treatment, which may reduce inflammation. In addition, our study was performed in one center, so our results do not reflect all pediatric FMF population. The mean age of the patients differ significantly between study groups; however, this should

be accepted as a drawback rather than a positive finding as we did not perform an age-matched analysis. In addition, parameters were evaluated by cross-section, and no other follow-uP values were measured.

CONCLUSIONS

NLR and MPV could be a useful predictor of inflammation in FMF patients. However, our results did not support that MPV might show attack and attack-free period. There were conflicting results in the literature about the role of MPV and NLR in inflammation and subclinical inflammation. Hence, further investigations are needed to assess the validity of those values.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

AUTHORS' CONTRIBUTION

- OB contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- NU contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- BAC contributed in the conception of the work, revising the draft , approval of the final version of the manuscript, and agreed for all aspects of the work.
- FA contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- NC contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work

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