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Early Versus Late Onset Familial Mediterranean Fever: Similarities, Discrepancies, and the Value of Neutrophil to Lymphocyte Ratio in Detecting Autoinflammation

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ABSTRACT

Objective: The objective of this study was to compare the clinical and laboratory characteristics of early-onset familial Mediterranean fever patients (EOFPs), adult-onset familial Mediterranean fever (FMF) patients (AOFPs), and late-onset FMF patients (LOFPs).

Materials and Methods: This study included a total of 202 FMF patients aged 18 years and above. Mediterranean fever (MEFV) gene mutations, demographic data, clinical characteristics, medications patients are on, neutrophil to absolute lymphocyte ratio (NLR), and C-reactive protein (CRP) levels obtained during an attack period, and three weeks after the attack were recorded. Based on the age of symptom onset, patients were divided into three groups: <20 years (EOFPs), 20–39 years (AOFPs), and ≥40 years (LOFPs).

Results: The most common symptom was abdominal pain, followed by fever. Fever was statistically significantly more common in EOFPs compared to LOFPs (p=0.001). Most patients with the M694V homozygous mutation had a disease onset below 20 years of age, whereas no compound heterozygous mutation was found in LOFPs. The body mass index (BMI) in EOFPs was lower than in AOFPs and LOFPs (p=0.002). In the attack-free group, patients with the M694V homozygous mutation had significantly higher NLRs (median, 2.36 vs. 2.01, p=0.042).

Conclusion: LOFPs had a milder form of the disease with less frequent abdominal pain and fever. We would like to advise clinicians that the NLR can be used to detect acute and subacute inflammation, especially in patients with the M694V homozygous mutation among EOFPs.

Keywords: Acute inflammation, familial Mediterranean fever, M694V, neutrophil to lymphocyte ratio, serum amyloid A.

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INTRODUCTION

Familial Mediterranean fever (FMF), which follows an autosomal recessive inheritance pattern, is a disorder primarily characterized by autoinflammation. It presents with recurrent inflammatory febrile attacks and serosal inflammation, such as peritonitis, unilateral pleuritis, pericarditis, as well as arthritis, myalgia, and skin manifestations like erysipelas-like erythema (ELE) and pruritic

skin rashes.[1–3] The mean age of onset for FMF is between 3–9 years,[4] with the first attack occurring before the second decade in approximately 90% of patients and within the first decade in about 50% of patients.[3,5] However, onset after the age of 40 is very rare.[6–8] Consequently, information about late-onset FMF patients (LOFPs) is scarce. To the best of our knowledge, there is no established definition in the literature for early-onset FMF patients (EOFPs) and LOFPs.

Nonetheless, previous studies have deemed it acceptable to define adult-onset FMF patients (AOFPs) and LOFPs as having an onset over the ages of 20 and 40 years, respectively. These subgroups have been shown to possess different demographic, clinical, and possibly genetic characteristics.[6] On the other hand, issues such as disease presentation, attack characteristics, response to colchicine treatment, and differential diagnosis in these groups are yet to be further elucidated.

Acute phase proteins, such as erythrocyte sedimentation rate (ESR), serum amyloid A (SAA), fibrinogen, and C-reactive protein (CRP), which are elevated during an attack, usually return to normal levels during symptom-free periods.[9] In addition to acute inflammation detected during attacks, some patients may develop persistent subclinical inflammation, leading to amyloidosis.[10] Ultimately, long-term inflammation can also result in chronic renal failure due to amyloidosis.[11] The absolute neutrophil to lymphocyte ratio (NLR), associated with chronic inflammation in diseases such as cardiovascular disease, malignancies, ulcerative colitis, hepatic cirrhosis, and systemic lupus erythematosus, may indicate systemic subclinical inflammation.[11–14] NLR reflects decreased cell turnover, an alteration of the immune system associated with age. It is unknown whether NLR could serve as a biomarker of frailty and predict life expectancy in elderly multiple myeloma patients.[15] Moreover, a high NLR has been found to have prognostic significance in FMF.[16] Considering all this information, in our current study, we aimed to compare the clinical characteristics of early-onset FMF patients (EOFPs), AOFPs, and LOFPs and to evaluate NLR measured in patients with or without attack periods as a prognostic factor in terms of indicating subclinical inflammation.

MATERIALS AND METHODS

The study was designed as a retrospective study conducted at three rheumatology outpatient clinics. Files of a total of 507 patients diagnosed with FMF and followed up between 2015 and 2021 were analyzed. Exclusion criteria included malignancy, diabetes, primary amyloidosis, thyroid disease, and lack of clinical data or laboratory results. After applying the exclusion criteria, a total of 202 patients over the age of 18 years with complete medical histories, laboratory, and FMF attack data were included in the study. All patients met the Tel-Hashomer criteria.[7] Data on Mediterranean fever (MEFV) gene mutations, demographic data, family history, age at symptom onset, duration of diagnosis, diagnostic delay, frequency of FMF attacks (per year), clinical characteristics, and current medications used in treatment (such as colchicine, canakinumab, anakinra) were recorded on case report forms. An FMF attack was defined as the presence of clinical symptoms of the disease and a serum CRP level of >5 mg/L. Complete blood count (CBC) parameters (white blood cell [WBC] count, neutrophil count [NC], lymphocyte count [LC], NLR] and CRP data obtained during an attack period, as well as CBC parameters [WBC, NC (/mm^3), LC (/mm^3), NLR], CRP, ESR, and SAA levels obtained three weeks after the attack, were recorded as laboratory findings. Based on the age of symptom onset, patient groups were divided into three categories: <20 years (EOFPs), 20–39 years (AOFPs), and ≥40 years (LOFPs) (17). Mutation analysis of the MEFV gene was performed using direct sequencing of the polymerase chain reaction. Exons 1, 2, 3, 5, and 10 have been studied. For the healthy group, blood samples were collected from 30 healthcare workers with no history of disease, working in our hospital, for CBC, CRP, and ESR measurements. Standard tubes containing Ethylenediaminetetraacetic acid (EDTA) were used for the CBC. The local ethics committee approved this study (dated 06.12.2022 and numbered 350).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive results were expressed as median, minimum, and maximum values. Spearman's test was used to ascertain relationships among laboratory parameters. The Kolmogorov-Smirnov test was applied to assess the normality assumption; a p- value of <0.05 indicated a non-normal distribution. Differences among categorical variables were analyzed using the chi-square test. Comparison between groups for non-normally distributed continuous variables was assessed using the Kruskal-Wallis test. Post-hoc analysis of the non-normally distributed data was performed with Tamhane's T2 test. The Mann-Whitney U test was used for NLR according to the M694V homozygous mutation status. We evaluated the area under the curve using the receiver operating characteristic curve to quantify the discrimination value of NLR for FMF patients, with or without an attack. The cut-off value was determined at the point where sensitivity and specificity were closest to each other. In all analyses, a p-value less than 0.05 was considered statistically significant.

Table 1. Clinical and demographic characteristics of patients with FMF

	Early onset FMF patients (n=120)	Adult onset FMF patients (n=58)	Late onset FMF patients (n=24)	p
Age (years), median (range)	28 (18–89)[a]	40 (20–62)[b]	52 (41–69)[c]	**0.001**
Sex (M/F)	(65/35)[a]	(51/49)[a]	(50–50)[a]	0.065
BMI (kg/m^2), median (range)	24 (16–34)[a]	25 (18–34)[b]	27.07 (19–29)[a,b]	**0.002**
Smoking (%)	35[a]	37[a]	41[a]	0.064
Disease duration (years), median (range)	17 (1–59)[a]	10 (2–40)[b,c]	6.5 (1–20)[b,c]	**0.001**
Diagnosis duration (years), median (range)	10 (1–49)[a]	5 (0–30)[b,c]	4.5 (1–15)[b,c]	**0.004**
Delay in diagnosis (years), median (range)	6 (0–44)[a]	4 (0–30)[a,b]	2 (0–5)[b]	**0.008**
Positive family history (%)	54.2[a]	50[a]	79.1[a]	0.064
Concomitant rheumatologic diseases, n (%)	4 (3.3)[a]	10 (17.2)[b]	2 (8.3)[a,b]	**0.019**
Fever, n (%)	97 (80.8)[a]	37 (64)[a,b]	12 (50)[b]	**0.005**
Abdominal pain, n (%)	110 (91.7)[a]	49 (85)[a,b]	17 (70.8)[b]	**0.042**
Chest pain, n (%)	26 (21.7)[a]	8 (13.7)[a]	5 (20.8)[a]	0.317
Arthritis, n (%)	35 (29.2)[a]	13 (22.4)[a]	4 (16.6)[a]	0.360
Arthralgia, n (%)	39 (32.5)[a]	24 (41.3)[a]	7 (29.1)[a]	0.504
Myalgia, n (%)	29 (24.2)[a]	20 (34.4)[a]	8 (37.5)[a]	0.218
Erysipelas-like erythema (ELE), n (%)	9 (7.5)[a]	4 (6.8)[a]	0 (0)[a]	0.595
Amyloidosis, n (%)	2 (1.7)[a]	2 (3.4)[a]	2 (8.3)[a]	0.398
Renal insufficiency, n (%)	2 (1.7)[a]	1 (1.7)[a]	1 (4.1)[a]	0.309
Frequency of attacks (per year)	1 (0–12)[a]	0 (0–7)[a]	1 (0–7)[a]	**0.047**
Good response to colchicine, n (%)	104 (86.7)[a]	56 (96.5)[a]	22 (91.6)[a]	0.055
Administration to anakinra, n (%)	5 (4.2)[a]	1 (1.7)[a]	1 (4.1)[a]	0.425
Administration to canakinumab, n (%)	7 (5.8)[a]	1 (1.7)[a]	0 (0)[a]	0.248

FMF: Familial Mediterranean fever. Continuous data are presented as the median, with minimum and maximum values. The 'p' value represents the significance of the comparisons among the three groups. Post hoc group comparisons are defined as follows: the same subscript letter indicates a subset of FMF subgroups that do not differ significantly from each other at the 0.05 level. A different subscript letter, however, indicates a subset of FMF categories that are significantly different from each other at the 0.05 level.

RESULTS

A total of 202 patients with FMF and 30 healthy subjects were included in the study. According to the age at symptom onset, the patient groups consisted of 120 (59.4%) patients in the EOFPs group, 58 (28.7%) patients in the AOFPs group, and 24 (11.9%) patients in the LOFPs group. The male/female ratio did not differ between the groups.

The body mass index (BMI) in EOFPs was lower than in AOFPs and LOFPs patients. However, disease duration (p=0.001) and time to diagnosis (p=0.004) in EOFPs were longer compared to the other groups, reaching statistically significant differences. Diagnostic delay was also longer in all groups except for the LOFPs, with a statistically significant difference.

A family history of the condition was present in more than 50% of all groups (EOFPs: 54.2%, AOFPs: 50%, LOFPs: 79.1%). However, there was no statistically significant difference between the groups (p=0.064).

When all the groups were compared regarding clinical findings, the most common symptom in all three groups was abdominal pain, followed by fever. EOFPs showed a statistically significantly greater prevalence of fever compared to LOFPs (p=0.001). There was no significant difference in other clinical findings (such as chest pain, arthralgia, arthritis, myalgia, ELE) among the three groups. Detailed demographic and clinical characteristics of FMF patients are presented in Table 1.

M694V was the most dominant MEFV gene mutation in all groups. Most patients with a homozygous M694V mutation had

Table 2. Detailed analysis of Mediterranean fever gene mutations in patients with FMF

	Early Onset FMF patients (n=120)	Adult onset FMF patients (n=58)	Late onset FMF patients (n=24)	p
M694V Homozygotes, n (%)	23 (19.1)[a]	2 (3.4)[b]	2 (8.3)[c]	**0.001**
M680I Homozygotes, n (%)	6 (5)[a]	2 (3.4)[a]	0 (0)[a]	0.463
R202Q Homozygous, n (%)	4 (3.3)[a]	1 (1.7)[a]	0 (0)[a]	0.472
V726A Homozygous, n (%)	2 (1.7)[a]	0 (0)[a]	0 (0)[a]	0.434
M694V Heterozygous, n (%)	30 (25)[a]	35 (60.3)[a]	10 (41.6)[a]	0.861
M680I Heterozygous, n (%)	3 (2.5)[a]	7 (12)[a]	1 (4.1)[a]	0.162
E148Q Heterozygous, n (%)	2 (1.7)[a]	4 (6.8)[a]	1 (4.1)[a]	0.231
V726A Heterozygous, n (%)	1 (0.8)[a]	2 (3.4)[a]	0 (0)[a]	0.203
Compound heterozygotes, n (%)	29 (24.1)[a]	15 (26.3)[a]	0 (0)[a]	0.065
No identifiable mutation, n (%)	2 (1.7)[a]	0 (0)[a]	1 (4.1)[a]	0.506
Positivity of each mutation				
E148Q, n (%)	4 (3.3)[a]	4 (6.8)[a]	1 (4.1)[a]	0.273
R202Q, n (%)	8 (6.6)[a]	2 (3.4)[a]	1 (4.1)[a]	0.484
V726A, n (%)	9 (7.5)[a]	12 (20.6)[a]	2 (8.2)[a]	0.308

FMF: Familial Mediterranean fever. The 'p' value represents the significance of the comparisons among the three groups. Post hoc group comparisons are defined as follows: the same subscript letter indicates a subset of FMF subgroups that do not differ significantly from each other at the 0.05 level. A different subscript letter, however, indicates a subset of FMF categories that are significantly different from each other at the 0.05 level.

Table 3. Detailed analysis of Mediterranean fever gene mutations in patients with FMF

	Attack group (n=104)	Attack-free group (n=126)	Healthy subjects (n=30)	p
CRP (mg/L), median (range)	81.40 (30–200)[a]	2.9 (0–30)[b,c]	2.1 (0–10)[b,c]	**0.001**
Neutrophil count, /mm^3, median (range)	7550 (3250–15780)[a]	4530 (2130–8250)[b,c]	3540 (1620–6960)[b,c]	**0.001**
Lymphocyte count, /mm^3, median (range)	2745 (1240–4580)[a]	2345 (1085–4720)[a]	2845 (1110–4800)[a]	0.634
NLR, median (range)	3.43 (0.68–96)[a]	2.01 (0.69–67)[b]	1.57 (0.87–2.93)[c]	**0.001**
MPV, median (range)	9.5 (6.3–13.5)[a]	9.3 (7.7–13.9)[a]	9.3 (7.9–11.4)[a]	0.141
ESR (mm/hour), median (range)	28 (4–82)[a]	7 (1–80)[b,c]	5 (1–40)[b,c]	**0.001**

FMF: Familial Mediterranean fever; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MPV: Mean platelet volume; NLR: Neutrophil to lymphocyte ratio. The 'p' value represents the significance of the comparisons among the three groups. Post hoc group comparisons are defined as follows: the same subscript letter indicates a subset of FMF subgroups that do not differ significantly from each other at the 0.05 level. A different subscript letter, however, indicates a subset of FMF categories that are significantly different from each other at the 0.05 level.

a disease onset below 20 years of age, whereas no compound heterozygous mutations were found in patients with a disease onset above 40 years of age. Detailed MEFV gene mutation analyses of FMF patients are presented in Table 2.

SAA levels were measured to evaluate subclinical inflammation in FMF patients during attack-free periods. There was no significant difference between the groups in terms of SAA levels (p=0.741).

There were no differences in terms of age and gender among the attack group, attack-free group, and healthy subjects (p=0.765 and p=0.612, respectively). The medians of NLR were 3.43 in the attack group and 2.01 in the attack-free group. Statistically, the NLR was significantly higher in the attack group (p<0.001). Also, NLR was significantly higher in the attack-free group than in healthy subjects (p=0.028). The median CRP level was 81.40 mg/L in the attack group and 2.9 mg/L in the attack-free group (Table 3). No statistically significant correlation was

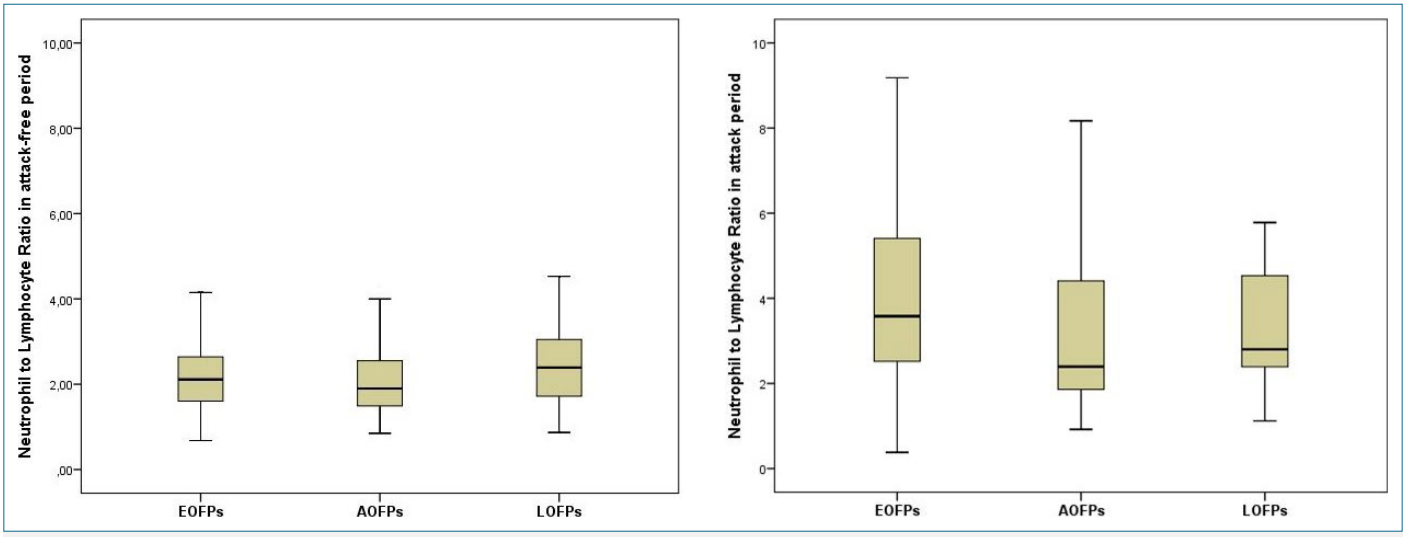

Figure 1. Neutrophil to lymphocyte ratio for all age groups during attack and non-attack periods.

found between CRP levels and NLR in either group (r=-0.089, p=0.540; r= 0.028, p=0.713, respectively).

The number of patients in whom NLR was measured during an attack is 37; in the attack-free period, it is 32 among M694V homozygous patients. NLR was found to be similar based on M694V homozygous mutation status in the attack group (p=0.827). In the attack-free group, patients with the M694V homozygous mutation had significantly higher NLR (median, 2.36 vs. 2.01, p=0.042).

When evaluating the NLR of patients during the attack-free period, no statistically significant difference was found between the groups (median values were 2.00, 1.72, 2.10, respectively, for EOFPs, AOFPs, LOFPs; p=0.512, p=0.346, p=0.516, respectively). The NLR value during the attack period was significantly higher in EOFPs with a median value of 3.58 compared to the other groups (median values were 3.58, 2.33, 2.95, respectively, for EOFPs, AOFPs, LOFPs; p=0.047) (Fig. 1). Based on the receiver operating characteristic curve with an area under the curve of 0.749, a cut-off NLR value of 2.38 had 68% sensitivity and 66% specificity (95% confidence interval, 0.60–0.89) in differentiating FMF patients with or without attacks (p=0.001) (Fig. 2).

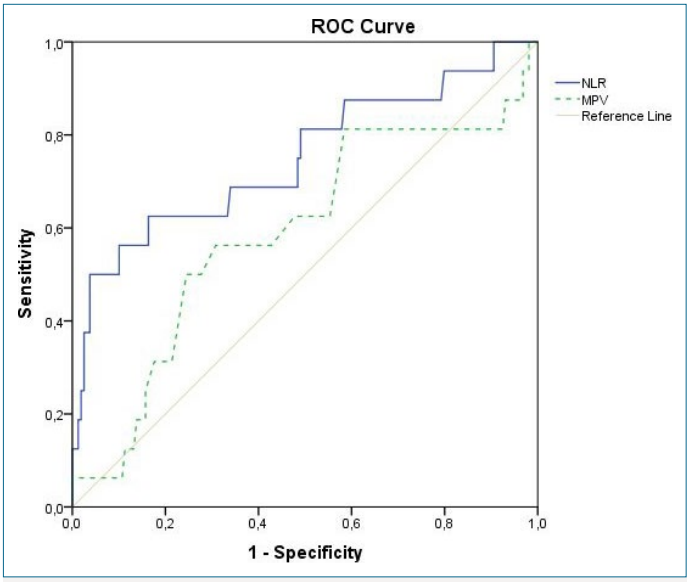

Figure 2. Receiver operating characteristic curve analysis of neutrophil to lymphocyte ratio in predicting FMF attacks.

DISCUSSION

The most important finding of our study was that LOFPs had less diagnostic delay. Fever and abdominal pain attacks were more frequent in the EOFPs group, while there was no difference in age at onset for other FMF symptoms. Another significant finding was the observation of early disease onset in the case of the M694V homozygous mutation. Another striking result was that NLR not only detects FMF attack status but is also found to be higher in FMF patients without attacks compared to healthy controls. This suggests that FMF patients have ongoing subclinical inflammation and that a simple, cheap, and practical method such as NLR can be used.

While there was a slight male dominance in EOFPs, the male-to-female ratio was found to be equal in LOFPs. This finding regarding EOFPs is similar to the study published by Tirosh et al. in 2021.[18] However, in contrast to our study, some other

studies in the literature report LOFPs with a slight female dominance.[6,19] In the present study, BMI was found to be lower in EOFPs. Decreased growth is a common complication in chronic inflammatory diseases of childhood,[20] and FMF patients with clinically attack-free periods may have ongoing inflammatory activity.[21] This low-grade systemic inflammation in FMF patients may underlie the clustering of metabolic risk factors, but their role in children has yet to be determined. Adipokines and cytokines seem to be important in this respect.[22] In light of these suggestions, we believe that low-grade chronic inflammatory status alone is not sufficient to explain the low BMI scores in EOFPs in this study. This may be attributed to the fact that the disease mostly develops before the age of 20 years and is more severe in patients with M694V positivity.[14] Even in endemic areas, there may be a diagnostic delay for FMF.7 It was also found that the mean diagnostic delay (six years for EOFPs vs. two years for LOFPs) was longer in EOFPs, and these findings were similar to those in a previous study by Yasar Bilge et al.[19] (ten years for EOFPs vs. three years for LOFPs). This observation may be due to the fact that children are less adept than adults at expressing FMF-associated symptoms. Additionally, since such symptoms are more common in children, they may be overlooked, whereas in adults, similar symptoms should be investigated more carefully as they may indicate more serious diseases.

Family history was found to be more prevalent in LOFPs in a study conducted by Aydin et al.,[23] which compared FMF patients with onset at younger than 20 years and those 40 years and older (62.5% for EOFPs vs. 70% for LOFPs). However, some other studies suggest that this finding is more prevalent in EOFPs.[17,19] This difference may be a result of the fact that, in these studies, the group between 20–40 years of age was not included as a separate group according to the age of symptom onset. In our study, we did not find any differences between the groups in terms of family history. We believe that studies involving a larger number of patients are needed to further investigate the role of family history. Despite being too few in number for meaningful comparisons across all groups, ankylosing spondylitis (AS) was the most common concomitant rheumatic disease, and it was the only prominent feature in the AOFPs group among all parameters evaluated in our study. This observation may be attributable to the fact that AS also has autoinflammatory features. When the groups were compared in terms of clinical findings, fever was noted as a dominant characteristic in EOFPs compared to the LOFPs. When compared with the literature, this finding is similar to the findings of many previous studies.[19,22] Additionally, abdominal pain, though similar to AOFPs, was also found to be more common in EOFPs compared to LOFPs. This is in line with the results of many studies in the literature as well.[17,18] The higher prevalence of the two major symptoms of FMF in EOFPs compared to LOFPs may be related to greater exposure to inflammation and a more severe course of FMF in EOFPs, due to the longer duration of the disease and diagnostic delay in EOFPs patients. Some studies have reported that symptoms such as chest pain, ELE, and arthritis were observed more frequently in this group of patients compared to LOFPs;[6,18,24] however, we observed no significant difference regarding these symptoms. This may be related to the fact that the number of patients and the study design in the other studies were different from ours. There are conflicting reports on the correlation between the M694V mutation and age at disease onset in FMF.[25,26] However, in our study, the M694V mutation was the most frequently detected mutation in all groups, with the M694V homozygous mutation being particularly prominent among all gene mutations analyzed in EOFPs compared to other groups. Our data align with the results obtained by Yasar Bilge et al.[19] (20.9% for EOFPs vs. 11.6% for LOFPs)20 in a study involving 2,246 patients aged <20 years and ≥20 years. Furthermore, high penetrance of M694V mutations is associated with early onset and severe phenotypes.[27] We propose that the milder course of disease in LOFPs is due to the fact that MEFV gene mutations in this patient group are not homozygous, but are instead single heterozygous mutations.

In our study, unlike previous studies comparing EOFPs and LOFPs, three groups were compared in terms of NLR during attack and attack-free periods, and its correlation with CRP was evaluated. To the best of our knowledge, no study in the literature has compared NLR levels in LOFPs. NLR, as a novel marker of inflammation, has been associated with subclinical inflammation in many inflammatory diseases, including FMF.[11–16] Being cheap, fast, and easy to measure even in basic healthcare settings, NLR may be practical for replacing acute phase proteins like CRP in monitoring chronic inflammatory conditions, including FMF. In our study, NLR values obtained during the attack period were found to be significantly higher in EOFPs compared to other groups. However, no statistically significant correlation was found between CRP and NLR in either the attack and attack-free group. In the literature, there are studies both supporting[28] and not supporting our findings regarding the correlation between CRP and NLR.[17] NLR has been found to be correlated with CRP levels in many chronic inflammatory diseases, such as ulcerative colitis.[29] This finding indicates that NLR increases independently of CRP during both the attack and attack-free periods. We consider that the discrepancy in results could be due to not recording the specific day of the attack when the

blood sample was taken. Our observations suggest that CRP elevation may occur on the first day of the attack, with NLR elevation occurring later. We believe that this will be clarified through blood sampling studies specific to FMF attack days. The relationship between NLR and amyloidosis could not be evaluated due to the insufficient number of patients who developed amyloidosis. Clearly, studies with a larger number of patients and a prospective design are needed to assess this relationship. When considering all these results, NLR values significantly increase in EOFPs compared to LOFPs during the attack period, similarly to acute phase proteins. Patients with the M694V homozygous gene exhibit higher NLR, suggesting heightened inflammation. This indicates that NLR may have prognostic value in identifying acute inflammation in EOFPs and subacute inflammation in patients with the M694V homozygous mutation during the post-attack period.

The limitation of our study is its retrospective design. Another potential limitation is that NLR may be affected by aging, which could influence the evaluation of LOFPs patients.

CONCLUSION

In summary, this study found that EOFPs had lower BMI values and more frequent abdominal pain and fever in terms of clinical symptoms and findings, and were diagnosed at a later stage. It is noteworthy that concomitant AS was more common in the AOFPs group compared to EOFPs. Furthermore, our results suggest that NLR values in EOFPs may have prognostic value in indicating both acute and subacute inflammation in patients with the M694V homozygous mutation during the post-attack period. We believe that prospective studies involving a larger number of patients will lend greater significance to all these results.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: The Sakarya University Clinical Research Ethics Committee granted approval for this study (date: 06.12.2022, number: 350).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions: Concept – NK, HH, MK; Design – NK, HH, MK; Supervision – NK, HH; Data Collection and/or Processing – NK, HH, MK; Analysis and/or Interpretation – NK, HH, MK; Literature Search – NK, HH, MK; Writing – NK, HH; Critical Reviews – NK, HH, MK.

Conflict of Interest: The authors have no conflict of interest to declare.

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