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Neutrophil-to-Lymphocyte Ratio as an Inflammatory Marker in Familial Mediterranean Fever: A Systematic Review and Meta-analysis

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Abstract

Familial Mediterranean fever (FMF) is a genetic disease with inflammatory basis. Several studies have assessed the role of neutrophil-to-lymphocyte ratio (NLR) in detecting this inflammation; however, no systematic review or meta-analysis has assessed these studies together. The aim of this study is to systematically review and meta-analyze the NLR value between FMF patients and normal controls. Scopus, PubMed, Embase, and ISI Web of Science were searched using predesigned search strategy to find the studies that assessed NLR in FMF patients and compared the value with normal controls. There was no time limitation. Finally, two researchers extracted data including first author name, publication year, the country, study design, number of patients and controls, time of disease diagnosis, FMF diagnostic criteria, mean age of the patients, and the NLR value. The data were systematically reviewed and meta-analyzed. In total, 464 articles were found on search; however, only 12 studies qualified for enrollment in the systematic review and 10 studies, with appropriate effect size, in the meta-analysis. These studies were conducted between 2013 and 2019. Eleven studies were conducted in Turkey and one in Egypt. Out of 12 studies, 9 had enrollment criteria for FMF patients: 8 studies used Tel Hashomer criteria and 1 study used Yalçinkaya–Özen criteria. All studies, except for two, had genetic confirmation for FMF. The mean NLR values in attack-free (standard difference in means = 0.482; $p < 0.0001$) and attack groups (standard difference in means = 0.853; $p = 0.001$) were significantly higher than control group. The mean NLR value may be related to the underlying inflammation in FMF.

Keywords
- familial Mediterranean fever
- neutrophil-to-lymphocyte ratio
- inflammation

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Introduction

Familial Mediterranean fever (FMF) is a genetic autoinflammatory disorder with autosomal recessive inheritance that affects 1 out of every 500 childbirths, in Mediterranean endemic region.[1] FMF is mainly the disease in Turks, Armenians, Arabs, and Sephardic Jews that is caused by various mutations of the Mediterranean Fever (*MEFV*) gene, which is located on the short (p) arm of the 16th chromosome.[2] However, this disease is not only limited to the Mediterranean region, and reports from all around the world are available.[3,4] The disease also exists in Iranian Azeri Turks, as a varying range of 21 to 42.4% of *MEFV* gene mutations have been reported in this ethnicity.[5]

t is believed that mutation in the *MEFV* gene results in autoinflammatory processes that cause fever and inflammation of serous membranes. This serous inflammation demonstrates itself as abdominal and chest pains, which are another hallmarks of the disease.[2] Most of the cases present their first attack during the childhood; 65 and 95% of FMF patients experience their first attack before 10 and 20 years of age, respectively.[6,7] The duration of FMF attacks usually ranges from 1 to 3 days, and in this period, several laboratory markers of inflammation including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A (SAA), and fibrinogen arise.[8,9] All these inflammation markers usually return to normal levels in attack-free period; however, it is reported that subclinical inflammation still remains.[8,10]

Neutrophil-to-lymphocyte ratio (NLR) is a newly developed marker of inflammation that has been assessed in several autoimmune and autoinflammatory diseases, such as ankylosing spondylitis,[11] rheumatoid arthritis,[12] lupus erythematous,[13] Kawasaki's disease,[14] and Behçet's disease.[15] Recently, this marker has been used to assess baseline inflammation in FMF patients, during both attack and attack-free periods.[16,17] However, controversies regarding levels of NLR during clinical and subclinical periods of FMF remain. Some studies believe that the NLR level in FMF patients during attack-free periods is significantly higher than in normal controls[9,18,19]; however, other studies believe that the amount of NLR is significantly higher only during attack periods.[16,17,20] Therefore, we aimed to systematically review and meta-analyze the available evidence regarding the role of NLR in demonstrating clinical and subclinical inflammation in FMF patients.

Materials and Methods

Study Protocol

This study was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline.[21] The study protocol was previously registered in International Prospective Register of Systematic Reviews (PROSPERO).[22]

Search Strategy

A systematic electronic literature search was conducted in ISI Web of Science, Scopus, PubMed, and Embase databases using medical subject heading (MeSH). The following search terms were employed to include all relevant studies: ("Familial Mediterranean fever" OR "FMF" OR "familial paroxysmal polyserositis" OR "recurrent polyserositis" OR "benign paroxysmal polyserositis" OR "periodic disease" OR "periodic peritonitis") AND ((neutrophil* AND lymphocyte*) OR NLR). All databases were reviewed from inception to November 2, 2020, using the above-mentioned search strategy. There was no time limit for our search. Also, the references of the related studies were hand checked to find any remaining relevant publication.

Selection of the Studies

Two authors (A. O. and S. A.) screened related studies separately. In the first step, the studies were reviewed based on their titles and abstracts, and then their full texts were used to achieve the final screening for the studies. The results of the study selection by each reviewer were compared and disagreements and inconsistencies were resolved by an immunologist (B. F.), who was expert in this topic. All the studies that compared NLR level between patients with FMF and normal controls were included. Animal studies, case reports, review articles, and letter to editor were excluded from the review.

Data Extraction

Data extraction was performed by two authors (A. O. and A. G.) using a predesigned data extraction Excel form. The extracted information includes first author's name, year of publication, country where study was conducted, study design, inclusion criteria for FMF, number of subjects in each group, duration from the disease diagnosis, FMF diagnostic criteria, genetic confirmation, gender, mean age of subjects, age at FMF diagnosis, presence and dose of colchicine treatment, and NLR level for each of the study groups. In case of disagreement regarding the extracted data, a third reviewer (B. A.) resolved the disputes.

Quality Assessment of the Included Studies

The quality assessment of the studies was also done by two reviewers (A. O. and A. B.), and in case of any disagreements, these discrepancies were resolved by a social medicine specialist (M. D.) as an expert. The Joanna Briggs checklist[23] was used to assess the quality of the studies, all of which were case–control. This checklist consists of 10 questions that examine various areas of the methodology of the case–control studies and report the final quality. The answer to each of the questions is divided into four options, namely, yes (Y), no (N), unclear (U), and not applicable (NA). All studies with appropriate statistical analysis were included and those that lacked this item were excluded.

Heterogeneity, Risk of Bias, and Meta-analysis

Statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software version 2 (Biostat, Englewood, NJ, USA). The mean NLR values were pooled in the software as effect size and a random effect model was used to compare data between FMF attack or attack-free cases and normal controls. Results were presented as forest plots. Heterogeneity was tested by using the I^2 index and Cochran's Q statistic. $I^2 > 75\%$ and significant Cochran's Q test indicate heterogeneity

between studies. Moreover, funnel plot of the included studies was designed to assess publication bias.

Results

Study Selection Process

An electronic search through the PubMed, Scopus, Embase, and ISI Web of Science databases yielded 116, 106, 127, and 115 studies, respectively. Out of a total of 464 studies, 199 were removed as duplicates and 265 studies remained and underwent title and abstract reviewing. Totally, 244 articles were excluded after this procedure. As a result, the full texts of 21 studies were reviewed, of which 9 studies were excluded from the systematic review for various reasons, including lack of relevance to our study and irrelevant outcomes with those intended in our review. Finally, 12 studies were included for systematic review. To perform meta-analysis, 2 studies were excluded and finally only 10 studies were analyzed. One study was excluded because it was conducted only on pregnant women and the population was not similar to other studies. Another study did not have our intended effect size, and due to the abnormal distribution, it was not possible to convert the effect size. ►**Fig. 1** shows the PRISMA flowchart, which summarizes the study selection process.

Study Characteristics

►**Table 1** shows the characteristics of the included studies. As illustrated, all the studies were published between 2013 and 2019. Also, all studies, except for one in Egypt,[24] were conducted in Turkey. In 9 out of the 12 studies, the inclusion criteria were clear; 8 studies used the Tel Hashomer criteria[25] and one study[17] employed the Yalçinkaya–Özen criteria.[26] Furthermore, genetic validation was used in all publications, except for two studies.[27,28] All studies were case–controlled. ►**Table 1** shows details of the included studies.

Patient Characteristics

As demonstrated in ►**Table 2**, our study population consisted of 1,980 FMF patients (970 males and 1,010 females) and 880 controls (382 males and 498 females). Out of 1,980

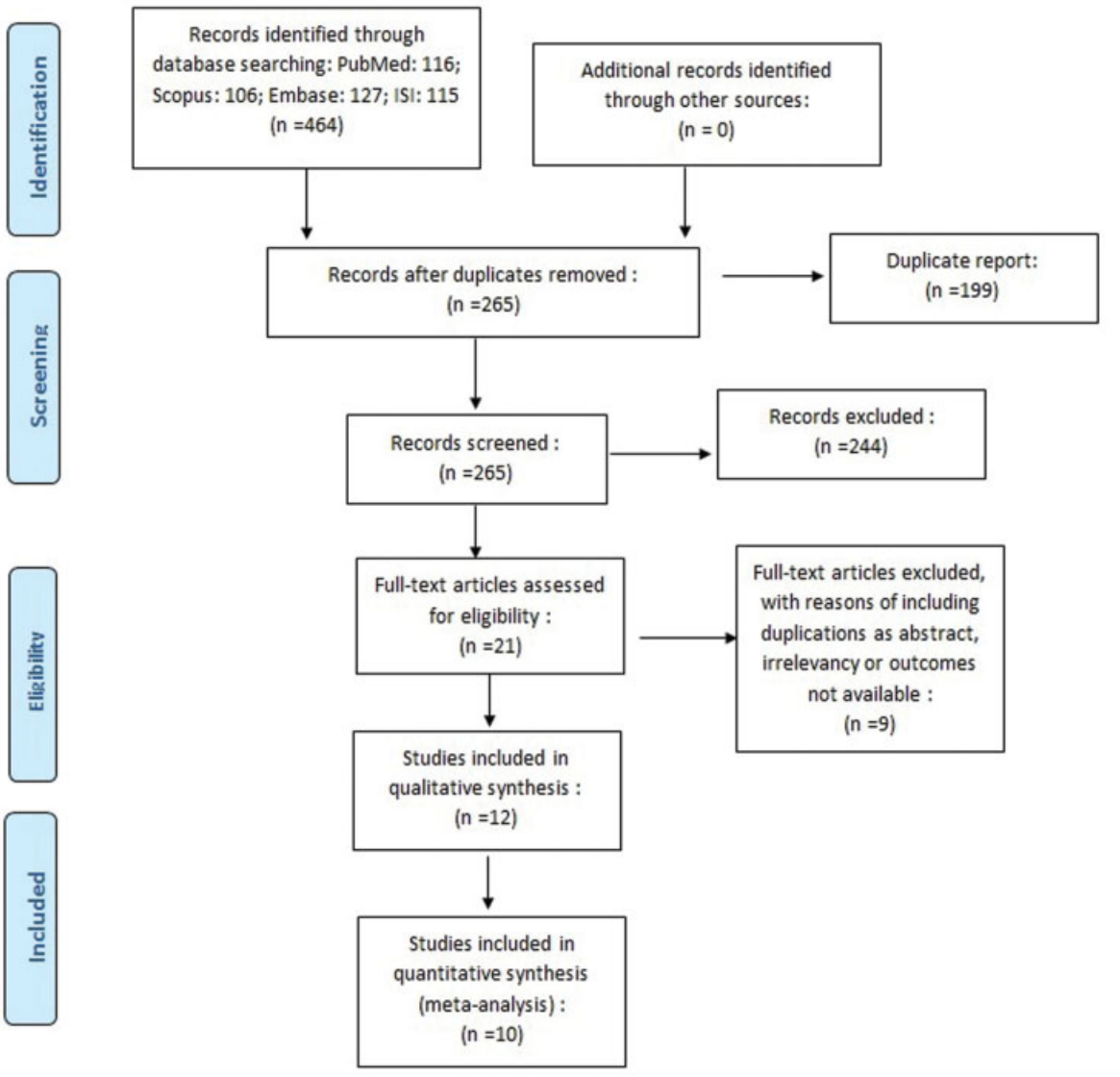

Fig. 1 PRISMA flowchart of paper selection.

Table 1 Characteristics of the enrolled studies including first author's name, publication year, country and area, type of study, inclusion criteria of the patients, FMF diagnosis criteria, and genetic confirmation

First author	Publication year	Country/area	Type of study	Inclusion and exclusion criteria	Genetic confirmation	FMF diagnosis criteria
Yorulmaz[16]	2019	Turkey/Konya	Case–control	Patients older than 1 mo and younger than 18 y with a diagnosis of FMF Patients with splenomegaly, diabetes, asthma, blood disorders, kidney and liver failure, uncontrolled hypertension, proteinuria, and those receiving nonsteroidal anti-inflammatory drugs and anticoagulants were excluded	Yes	Tel Hashomer[25]
Kholoussi[24]	2018	Egypt/Cairo	Case–control	Patients diagnosed with FMF were referred to the Egyptian National Genetic Diseases Research Clinic	Yes	Unknown
Basaran[17]	2017	Turkey/Ankara	Case–control	Patients did not have any other systemic or inflammatory diseases	Yes	Yalçinkaya–Özen[26]
Çakar[30]	2017	Turkey/Ankara	Case–control	Patients with other rheumatic diseases, atherosclerotic cardiovascular disease, hypertension, diabetes, and those under 18 y of age were excluded	Yes	Tel Hashomer[25]
Daglar[27]	2016	Turkey/ Gaziosmanpaşa	Case–control	Women with first pregnancies who had no abnormalities on their ultrasound and no systemic disease other than FMF	No	Tel Hashomer[25]
Kelesoglu[18]	2016	Turkey/Istanbul	Case–control	Patients should have complete laboratory and clinical information and should not be treated with anakinra	Yes	Unknown
Celikbilek[28]	2015	Turkey/Bezak	Case–control	Patients should not have diabetes, hypertension, liver disease, and acute or chronic infections and should have therapeutic compliance	No	Tel Hashomer[25]
Duksal[19]	2015	Turkey/Sivas	Case–control	Patients should not have any infectious or chronic disease and should not receive any treatment other than FMF treatment	Yes	Tel Hashomer[25]
Özer[29]	2015	Turkey/Tukat	Case–control	Patients should not have infection, pneumonia, diabetes, hypertension, acute or chronic renal failure, obstructive sleep apnea, coronary artery disease, connective tissue disease, inflammatory bowel disease, allergic rhinitis, asthma, or a history of any inflammatory disease	Yes	Tel Hashomer[25]
Uluca[20]	2014	Turkey/ Diyarbakir	Case–control	Patients included according to Tel Hashomer criteria	Yes	Tel Hashomer[25]
Uslu[9]	2013	Turkey Sivas	Case–control	Patients with diabetes, cardiovascular disease, metabolic syndrome, anemia, acute or chronic infection, other autoimmune diseases, chronic obstructive pulmonary disease, and a history of smoking were excluded. Also, patients should not take any medication other than colchicine	Yes	Tel Hashomer[25]
Ahsen[31]	2013	Turkey/ Afyonkarahisar	Case–control	Patients should not have infection, pneumonia, diabetes, hypertension, acute or chronic renal failure, chronic liver disease, obstructive pulmonary disease, obstructive sleep apnea, coronary artery disease, connective tissue disease, inflammatory bowel disease, allergic rhinitis, asthma, and smoking history	Yes	Unknown

Abbreviation: FMF, familial Mediterranean fever.

FMF patients, 1,605 patients were in the attack-free phase and 232 patients in the attack phase, and 143 patients were assessed both during attack-free and attack phases. The mean age was less than 18 years in seven studies[16–20,24,29] and more than 18 years in four studies.[9,27,30,31] One study[28] did not report the mean age. The dose of colchicine also varied in different studies and ranged from 0.5 to 2 mg per day. In all studies, except for one that was unclear,[19] patients were treated with colchicine at the time of the study.

Comparison of Neutrophil-to-Lymphocyte Ratio

As shown in ►**Table 3**, five studies[16–18,20,28] made comparisons among three groups (attack, attack-free, and control), while in the rest there were only two study groups (attack-free and control). In all publications with three study groups, NLR was significantly higher in the attack group compared with the attack-free and control groups. Among studies with two-group comparison, only two articles[24,27] showed no significant differences in NLR between the attack-free and control groups, while in all other studies the amount of NLR

Table 2 Characteristics of the studied population

First author	Number of participant			Gender						Age of participants (mean ± SD)			Age at diagnosis (mean ± SD)	Consumption of colchicine at the time of study	Dosage of colchicine (mg/d)
	AF	A	Control	AF		A		Control		AF	A	Control			
				Male	Female	Male	Female	Male	Female						
Yorulmaz[16]	143[a]	143[a]	143	83	60	83	60	83	60	164.62 ± 51.20 mo	164.62 ± 51.20 mo	164.92 ± 51.10 mo	98.10 ± 49.11 mo	Yes	0.5–2
Kholoussi[24]	42	–	20	23	19	–	–	11	9	2–7 y	–	2–14 y	Unknown	Yes	Unknown
Basaran[17]	90	70	74	35	55	29	41	38	36	12.81 ± 3.88 y	11.56 ± 4.30 y	10.74 ± 4.01 y	Unknown	Yes	A: 1.03; AF: 1.09
Çakar[30]	69	–	35	58	11	–	–	30	5	28.30 ± 4.90 y	–	27.00 ± 8.00 y	Unknown	Yes	1.1
Daglar[27]	33	–	32	0	33	–	–	0	32	25.00 ± 4.63 y	–	28.50 ± 7.20 y	Unknown	Yes	1–2
Kelesoglu[18]	509	61	73	239	270	33	28	34	39	11.20 ± 4.46 y	9.80 ± 4.63 y	10.40 ± 5.80 y	Unknown	Yes	Unknown
Celikbilek[28]	53	26	36	50[b]	29[b]	50[b]	29[b]	12	24	Unknown	Unknown	Unknown	Unknown	Yes	1.5
Duksal[19]	343	–	199	178	165	–	–	53	146	10.54 ± 3.61 y	–	10.21 ± 2.98 y	Unknown	Unknown	Unknown
Özer[29]	153	–	90	78	75	–	–	49	41	12.33 ± 4.41 y	–	10.96 ± 3.45 y	Unknown	Yes	0.5–1.5
Uluca[20]	157	75	77	73	84	33	42	38	39	9.10 ± 3.60 y	8.40 ± 3.50 y	8.30 ± 3.50 y	Unknown	Yes	0.5–2
Uslu[9]	94	–	60	30	64	–	–	20	40	29.90 ± 12.20 y	–	31.30 ± 9.40 y	23.10 ± 12.80 y	Yes	1.43
Ahsen[31]	62	–	41	28	34	–	–	14	27	32.64 ± 10.42 y	–	35.56 ± 7.46 y	Unknown	Yes	1.5

Abbreviations: A, attack; AF, attack-free.
[a]Cases in A and AF groups were same.
[b]The gender number was reported for all cases without discriminating between A and AF cases.

Table 3 Comparison of NLR values between attack, attack-free, and control groups in different studies

First author	Age of participants (mean ± SD)			*p*-Value
	AF	A	Control	
Yorulmaz[16]	2.88 ± 2.9	3.01 ± 1.17	1.59 ± 0.66	A and AF (0.001) A and control (0.001) AF and control (0.431)
Kholoussi[24]	1.23 ± 0.62	–	0.80 ± 0.16	0.10
Basaran[17]	1.71 ± 0.83	4.1 ± 3.11	1.91 ± 1.86	AF and A (<0.001) A and control (<0.001) AF and control (0.457)
Çakar[30]	2.5 ± 1.6	–	1.9 ± 0.6	0.037
Daglar[27]	1st trimester: 3.6 (1.70–7.06) 2nd trimester: 4.3 (2.0–9.55)	–	1st trimester: 3.25 (1.90–7.22) 2nd trimester: 3.54 (1.97–8.93)	1st trimester (0.23) 2nd trimester (0.19)
Kelesoglu[18]	1.47	4.1	1.36	AF and A (<0.001) A and control (<0.001) AF and control (0.740)
Celikbilek[28]	1.83 (2.23–1.21)	2.95 (3.46–1.91)	1.63 (2.23–1.41)	0.004
Duksal[19]	1.55 ± 1.92	–	0.49 ± 1.08	<0.0001
Özer[29]	1.7 ± 1.99	–	0.45 ± 1.26	<0.0001
Uluca[20]	0.8 ± 1.6	2.2 ± 2.6	1.3 ± 1.8	AF and A (<0.001) A and control (<0.001) AF and control (0.76)
Uslu[9]	0.61 ± 2.06	–	0.42 ± 1.59	<0.0001
Ahsen[31]	0.86 ± 2.21	–	0.59 ± 1.68	<0.0001

Abbreviations: A, attack; AF, attack-free.

in the attack-free group was significantly higher than the control.

Appraisal Results

As all studies were case–control, an appropriate checklist for this type of study was used for quality assessment. As obvious from the results in ►**Table 4**, only two studies[18,24] had notably lower quality compared with the other included articles. However, as all studies had our intended statistical analysis as inclusion criteria, none of them were excluded in this section.

Meta-analysis and Heterogeneity Analysis

►**Figs. 2** and **3** show the forest plot of the studies included in the meta-analysis in two subgroups, including FMF attack and FMF attack-free groups. Assessment of these 10 studies showed that the mean NLR in the attack-free group was 0.482 higher than the control group and this difference was reported to be significant ($p < 0.0001$; standard difference in means = 0.482). Also, the pooled analysis of four studies that compared the NLR during attack period with normal controls demonstrated that the mean NLR in the attack group was 0.853 higher than the control group and this difference was significant ($p = 0.001$; standard difference in means = 0.853).

The heterogeneity analysis reported an I^2 value of 73.30 ($Q = 30.568$ and $p < 0.0001$) for attack-free and normal comparison and an I^2 value of 90.18 ($Q = 33.718$ and $p < 0.0001$) for attack and control comparison. ►**Fig. 4** also shows the funnel plot of the included study, which shows no evident bias due to the symmetry of the triangle.

Discussion

Our results demonstrated that the NLR values were significantly higher in FMF patients compared with the normal controls; this was consistent for patients both during the attack and during attack-free periods. It implies that NLR may be an indicator of both clinical and subclinical inflammation as it was significantly higher during both disease phases.

The different mutations of the *MEFV* gene pyrin domain cause autoinflammation in FMF patients. The mutation in this domain triggers assembly of inflammasomes[32,33] and subsequent caspase-1 activation and interleukin 1 (IL-1) release. IL-1, along with interleukin 6 (IL-6) and tumor necrosis factor α, increases the level of acute-phase reactants such as ESR, CRP, and fibrinogen.[8,29] These acute-phase reactants usually return to their normal value during attack-free period.[9,29] However, the subclinical inflammation still exists in 30% of the patients during the attack-free phase. The inspection of this undercover inflammation is very important, as it is the cause of different complications of FMF such as amyloidosis, anemia, splenomegaly, and osteopenia.[16,17] Therefore, studies have tried to propose a suitable marker that can assess this inflammation.[9,20,29,34,35]

Table 4 Quality of studies based on the Joanna Briggs checklist

First author	1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	2. Were cases and controls matched appropriately?	3. Were the same criteria used for identification of cases and controls?	4. Was exposure measured in a standard, valid, and reliable way?	5. Was exposure measured in the same way for cases and controls?	6. Were confounding factors identified?	7. Were strategies to deal with confounding factors stated?	8. Were outcomes assessed in a standard, valid, and reliable way for cases and controls?	9. Was the exposure period of interest long enough to be meaningful?	10. Was appropriate statistical analysis used?
Yorulmaz[16]	N	Y	NA	Y	Y	Y	Y	Y	Y	Y
Kholoussi[24]	N	Y	NA	U	U	N	N	U	U	Y
Basaran[17]	Y	N	NA	Y	Y	Y	Y	Y	U	Y
Çakar[30]	Y	N	NA	Y	Y	Y	Y	Y	U	Y
Daglar[27]	Y	N	NA	Y	Y	Y	Y	Y	U	Y
Kelesoglu[18]	Y	N	NA	U	U	U	U	U	U	Y
Celikbilek[28]	Y	N	NA	Y	Y	Y	Y	U	U	Y
Duksal[19]	Y	N	NA	Y	Y	Y	Y	U	U	Y
Özer[29]	N	Y	NA	Y	Y	Y	Y	Y	U	Y
Uluca[20]	N	Y	NA	Y	Y	Y	Y	Y	U	Y
Uslu[9]	N	Y	NA	Y	Y	Y	Y	Y	Y	Y
Ahsen[31]	N	Y	NA	U	U	Y	Y	Y	U	Y

Abbreviations: N, no; NA, not applicable; U, unclear; Y, yes.

NLR is a cheap, easily accessible, and convenient-to-use tool for detecting inflammation. Most FMF patients have a complete blood cell count with differential analysis, and only with an easy division, the NLR marker can be measured and used for detecting the underlying inflammation. Moreover, this marker provides information about the two immune pathways of adaptive and acquired immune systems. In fact, neutrophils are markers of acute inflammation, lymphocytes show the prolonged part of the inflammatory pathway, and their ratio can demonstrate the state of acute or chronic inflammation. In other words, higher NLR values demonstrate that the acute inflammation persists, as studies have observed in FMF attack cases.[36,37] Our analysis showed that the NLR level was significantly higher in both FMF attack and FMF attack-free patients compared with that in normal controls. One of the included studies in our systematic review conducted by Özer et al[29] reported a strong positive correlation between CRP, as an acute-phase reactant, and NLR. A previous study by Gasparyan et al[38] reported that NLR is applicable in rheumatologic diseases with predominant neutrophil inflammations such as Behçet's disease and FMF.

All these findings can be a beacon to the future and offer a suitable cutoff for NLR in the assessment of subclinical inflammatory status in those with inflammation persisting during the attack-free phase. This is particularly beneficial as other inflammatory markers, such as ESR, CRP, and SAA, cannot detect subclinical inflammation in a small portion of FMF patients, and are also more expensive than NLR.[29] However, the hypothesis that NLR can be more sensitive than acute-phase reactants remains, and further investigations are needed to compare these markers.

We postulate that patients with high levels of NLR may need higher doses of colchicine, to control their inflammation. However, more studies are needed to assess and confirm these hypotheses. The clinical consequences of an elevated NLR as a marker of subclinical inflammation in FMF need further investigation. For instance, one of the reviewed studies reported that NLR is associated with development of amyloidosis[9]; however, further studies were found to be inconclusive. Another limitation of NLR is that it is a marker of inflammation and thus can be raised in any inflammatory cases, including an infectious disease[39]; however, acute-phase reactant proteins such as ESR and CRP have this limitation, too.[40] Moreover, like acute-phase reactants, NLR is dependent on the age of the patients,[41] which should also be considered.

One of the studies was conducted on a population of pregnant women and, due to the probability of imposing bias, was only entered in the systematic review and not in the meta-analysis. It reported no significant difference between those with attack-free FMF and normal controls. It should be considered that pregnancy itself has an immunomodulatory effect and this may affect the underlying inflammation.[42] Moreover, it is reported that FMF severity remains unchanged or even get better in two-thirds of pregnancies.[43]

Although our study provided a possible valuable marker for detecting inflammation in FMF patients, there is a further need to identify a set point for detecting inflammation.

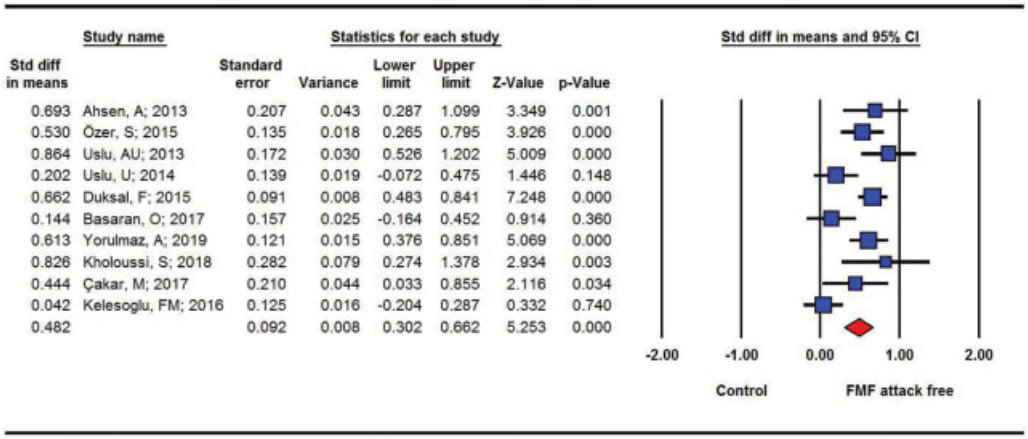

Fig. 2 Forest plot comparing FMF attack-free and control groups. FMF, familial Mediterranean fever.

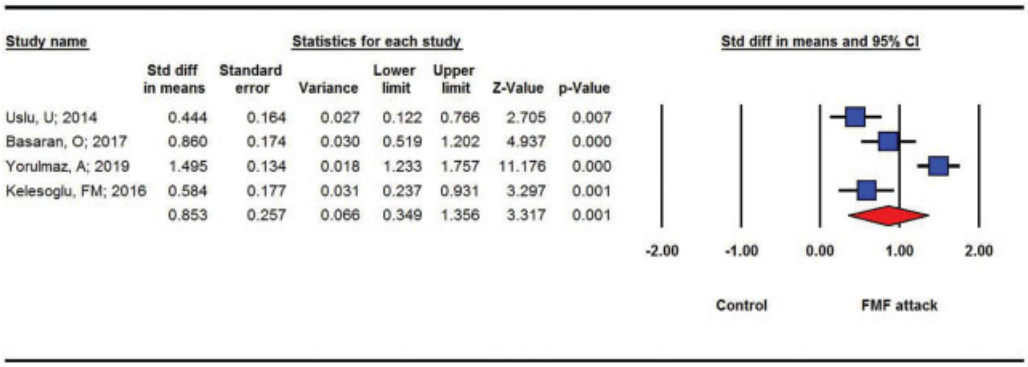

Fig. 3 Forest plot comparing FMF attack and control groups. FMF, familial Mediterranean fever.

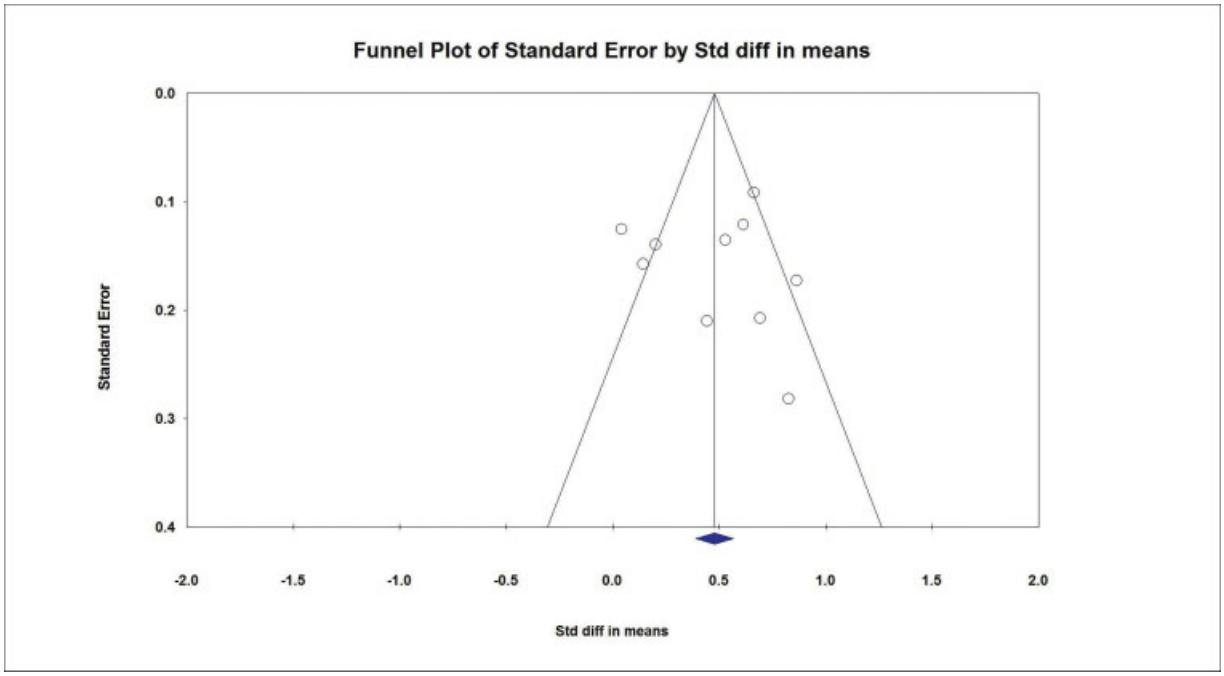

Fig. 4 Funnel plot of the included studies in meta-analysis.

Moreover, the available clinical criteria such as Tel Hashomer criteria[25]—which was used in all studies in our review except one—cannot discriminate between FMF and some other rare autoinflammatory diseases.[44] Due to this fact, a definite diagnosis of FMF is made only by genetic detection of its mutations.[45,46] Two of the reviewed publications in our study lacked genetic confirmation and this can be proposed as a limitation.[27,28] Different inflammatory status may also

affect the NLR level,[47] which is another limitation in our analysis—as some studies considered this factor in their inclusion and exclusion criteria, while others did not.

Furthermore, it is proposed that colchicine can halter both clinical and subclinical inflammation.[48] This may have confounding effects on the NLR values in FMF patients, and may be perceived as another shortcoming of our study. However, it is believed that colchicine mainly compromises neutrophil activity by interfering with activation of the microtubules and their chemotaxis and has no effect on the neutrophil count.[49,50] This should be considered in future studies, where there may be a need for further adjustment.

Conclusion

Our results showed that NLR values were significantly higher in both attack and attack-free groups compared with the normal controls. As acute-phase reactants are more expensive than NLR and cannot detect subclinical inflammation, NLR can be a valuable and cheap alternative. Further studies are necessary to propose a cutoff for NLR in FMF, taking into consideration the importance of inflammation in their prognosis. Further research in this field to uncover more information is encouraged.

Conflict of Interest
None declared.

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