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Original Article

Evaluation of the controlling nutritional status score and prognostic nutritional index in patients with familial Mediterranean fever

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Abstract

Objective: Familial Mediterranean fever (FMF) is the most common disease that leads to secondary amyloidosis in Turkish population. The prognostic nutritional index (PNI) and the controlling nutritional status (CONUT) score were recently investigated in many clinical conditions as predictors of disease activity and prognosis of underlying disease. We aimed to evaluate these indexes in FMF patients.

Methods: We included a total of 135 patients with FMF without amyloidosis at baseline. Demographic characteristics, particular attack features, treatment modalities, disease complications of patients, and a follow-up time for each patient were obtained. Disease complications were defined as amyloidosis or end stage renal disease. Baseline laboratory parameters in the attack-free period were used to assess the subclinical inflammation. Spearman's rho correlation analysis was used for numerical variables. Univariate and multivariate logistic regression analyses were used to determine factors that had an impact on the development of amyloidosis. Receiver operating characteristic (ROC) curve analysis was used to discover the appropriate cutoff points of CONUT score and PNI for predicting the development of amyloidosis.

Results: ROC analysis revealed that the optimal cutoff points for neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), CONUT score, and PNI were >1.9, >145, >2, and ≤54, respectively. The area under the curve values of CONUT score and PNI for predicting the development of amyloidosis were 0.830 (95% CI: 0.76-0.89, $P < .001$) and 0.940 (95% CI: 0.88-0.97, $P < .001$), respectively. Correlation analyses revealed significant positive correlations between CONUT score, NLR, and PLR. The high CONUT score was associated with the development of amyloidosis in FMF patients in addition to age and M694V homozygous mutation.

Conclusion: Low PNI and high CONUT score at diagnosis may have a poor prognostic value for the development of amyloidosis in patients with FMF in addition to older age and M694V homozygous mutation. These indexes may be a useful and inexpensive screening biomarkers in clinical practice for predicting amyloidosis in patients with FMF.

Keywords: Amyloidosis, inflammation, controlling nutritional status score, prognostic nutritional index, familial Mediterrenean fever

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Introduction

Familial Mediterranean fever (FMF) is a common autoinflammatory disease that is symbolized by periodic attacks of serositis and fever.[1] FMF is frequently seen in individuals of Turkish, Armenian, Jewish, and Arab descent.[2] Although interregional differences have been reported in our country, a higher incidence rate (0.82%) was obtained in Tokat and the surrounding region in the north of Turkey.[3] Amyloidosis is the most serious complication of FMF, and it is well known that patients with amyloidosis have a poor prognosis and significant risk of mortality due to end stage renal disease (ESRD).[4] FMF is also the most frequent reason for secondary amyloidosis in Turkey.[5] Although the clear pathophysiological mechanisms underlying amyloidosis are not definitely known, subclinical persistent inflammation in attack-free periods has been reported to be the main culprit factor for the development of amyloidosis.[6] Recently, the prognostic nutritional index (PNI) and the controlling nutritional status (CONUT) score were investigated in many clinical conditions as predictors of immune-related nutritional status, disease activity, and prognosis of underlying disease. Three variables described later are used to calculate PNI and CONUT. First, albumin is a well-known negative acute

phase reactant that inversely changes with inflammation burden.[7] Inflammation reduces albumin synthesis by inducing anorexia and protein catabolism and also facilitates transfer of albumin out of the vascular compartment.[8] Second, reverse cholesterol transport to the liver is blocked by an inflammatory response, and this condition promotes cholesterol accumulation in macrophages and other immune cells. When subclinical inflammation is prolonged, atherosclerosis occurs.[9] Finally, recent studies also demonstrated high rates of neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) in FMF patients during asymptomatic periods, and NLR has been defined more confident ratio than PLR for subclinical inflammation.[10] The PNI is calculated by using serum albumin and peripheral blood lymphocyte count, whereas serum albumin, total cholesterol levels, and peripheral blood lymphocyte count were used for the CONUT score.

It is well known that nutritional situation is a significant determinant of the immune reply. Recent studies revealed inflammation triggering effect of nutrition with the salty and fatty foods on chronic inflammatory diseases. Ekinci et al[11] detected efficacy of low-salt and low-fat diet in the management of FMF patients. These studies prompted us to examine nutritional status in FMF patients. To date, the prognostic roles of PNI and CONUT score have not been investigated in patients with FMF. Hence, we aimed to investigate these indexes in FMF patients, the relationship between these indexes and baseline subclinical inflammation, and their association with long-term prognosis of disease.

Methods

Design of study and population

This is a retrospective study approved by the Ethics Committee of Pamukkale University School of Medicine (protocol no.: 41138 and approval date: July 8, 2020) in accordance with the provisions of the Helsinki statements. We included a total of 135 patients with FMF in this study.

Main Points

- Amyloidosis is the most serious complication of FMF, and patients with amyloidosis have a poor prognosis and significant risk of mortality due to ESRD.
- Subclinical persistent inflammation in attack free periods plays the main culprit factor for the development of amyloidosis.
- Low PNI and high CONUT score at diagnosis may have a poor prognostic value for development of amyloidosis in patients with FMF.

Inclusion criteria: Having a regular follow-ups up to the present as defined as the existence of at least three clinical evaluations per year, patients age with 18 years and above, having diagnosis with FMF for the first time at the tertiary health center, between 1990 and December 2020 in accordance with the Tel Hashomer criteria.[1]

Exclusion criteria: Having comorbidities including diabetes mellitus, hypertension, vasculitis, and pulmonary-renal syndromes in the follow-up, patients with FMF, and amyloidosis at baseline.

Data collection and clinical definitions

Demographic features of patients including age, gender, disease duration, clinical manifestations, detailed attack characteristics (serositis or arthritis/arthralgia), treatment modalities, disease complications, and Mediterranean fever (MEFV) mutations of patients (if available) were obtained. MEFV exon 2 and exon 10 variant analyses were present in some suspected FMF patients who did not fullfil the Tel Hashomer criteria or in patients with nephrotic syndrome to determine prognosis. Disease duration was noted as the total follow-up time from the diagnosis to the present. Laboratory results obtained at diagnosis containing erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), serum albumin, NLR, and PLR. All of these laboratory parameters were obtained in the attack-free period to assess subclinical inflammation. The researched indexes and ratios were also calculated in the attack-free period after the first attack resolved at the diagnosis.

Diagnosis of FMF was based on clinical decision in accordance with the current classification criteria in each patient after detailed physical examination and laboratory evaluation.[1] Disease complications were defined as amyloidosis or ESRD. For amyloidosis, biopsy-proven evidence was accepted. All patients with FMF and nephrotic syndrome (proteinuria >3.5 g/24 h) had a kidney biopsy, whereas others who had lower proteinuria levels underwent colon or duodenum biopsy. ESRD was defined as a marked loss of kidney function, ultimately requiring dialysis.

PNI and CONUT scores were computed by using baseline laboratory parameters. PNI was calculated using the formula: (0.005 × lymphocyte count + 10 × serum albumin [g/dL]).[12] Serum albumin, total cholesterol levels, and peripheral blood lymphocyte count were used for CONUT score. Each variable was scored in four groups in the following order: albumin (≥3.5 = 0, 3.0-3.4 = 2, 2.5-2.9 = 4, <2.5 = 6), serum total cholesterol (≥180 = 0, 140-179 = 1, 100-139 = 2, <100 = 3), and total lymphocyte count (≥1600 = 0, 1200-1599 = 1, 800-1199 = 2, <800 = 3). The sum of these variables gave us the total CONUT score. Total score (as an indicator of undernutrition) was accepted as in the sequence: 0-1: normal, 2-4: mild, 5-8: moderate, and 9-12: severe.[13]

Statistical analysis

Illustrative statistics are given as mean ± standard deviation and median with 25%-75% quartiles for continuous variables depending on their distribution. Numbers and percentages are used for categorical variables. Normality of numerical variables was checked using Kolmogorov–Smirnov and Shapiro–Wilk tests. Independent samples t-test was applied when numerical variables had a normal distribution, whereas Mann–Whitney U test was applied for variables without normal distribution. For comparison of differences between categorical factors, Pearson's chi-square and Fisher's exact tests were used in 2 × 2 tables, and Fisher–Freeman–Halton test was used in R×C tables. Spearman rho correlation coefficients (r) were used to analyze associations between numerical variables. Univariate and subsequent multivariate logistic regression analyses were performed to analyze factors that had an impact on the development of amyloidosis. Independent variables with multicollinearity problems were not included in the multivariate model. Receiver operating characteristic (ROC) curve analysis was applied to define optimal cutoff points of NLR, PLR, CONUT, and PNI scores predicting the development of amyloidosis. Area under curve (AUC) was calculated using the DeLong method (MedCalc Statistical Software Trial version-MedCalc Software bvba, Ostend, Belgium, http://www.medcalc.org, 2015) with Youden's index and 95% confidence interval. For statistical analysis and figures, Microsoft Office Excel and "Jamovi project (2020)," Jamovi (Version 1.2.24) [Computer Software] (retrieved from https://www.jamovi.org) and JASP (Version 0.13.1) (retrieved from https://jasp-stats.org) were used. The statistically significant *P* value was accepted as ≤0.05 in all assays.

Results

Description of studied data

There were 135 patients with FMF. The average age was 34.9 ± 12.2 years. The median

Table 1. Detailed description of demographic and clinical characteristics and laboratory findings of the whole study group (n = 135).

Age (year)*	34.9 ± 12.2
Duration of the disease (year)†	7 (1-29)
Presentation‡	
Serositis and fever	100 (74.1)
Arthritis and fever	35 (25.9)
Development of ESRD‡	
No	133 (98.5)
Yes	2 (1.5)
Amyloidosis‡	
No	124 (91.9)
Yes	11 (8.1)
Biopsy localization‡	
Colon	5 (45.5)
Kidney	5 (45.5)
Duodenum	1 (9.0)
ESR (mm/h)†	19 (2-102)
CRP (mg/dL)†	0.5 (0-10)
Albumin(g/dL)†	4.6 (2.6-5.1)
NLR†	2 (0.7-12.2)
PLR†	129 (62-371)
CONUT score†	1 (0-8)
PNI score†	56 (26-68)
Colchicine only‡	122 (90.4)
Other treatments (anakinra, canacinumab, and tocilizumab)‡	13 (9.6)

*Mean ± standard deviation.
†Median (interquartile range).
‡N (%).
ESRD, end-stage renal disease; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CONUT, controlling nutritional status; PNI, prognostic nutritional index.

duration of FMF in the study group was 7 years. In 100 patients (74.1%), serositis and fever were the presenting symptoms. We detected amyloidosis in 11 patients (8.1%) and ESRD in two patients (1.5%). The colon and the kidneys were the most frequent anatomic biopsy locations of amyloidosis, seen in five patients for each (45.5%). The median values of PNI and CONUT scores were 56 and 1, respectively. Demographic and clinical features and laboratory findings are summarized in Table 1.

ROC analysis revealed that the appropriate cutoff ratios for NLR, PLR, CONUT scores, and PNI were >1.9, >145, >2, and ≤54, respectively. Their matching sensitivity, specificity, and AUC values are given in Table 2 and Figure 1. The AUC of CONUT score and PNI for predicting the development of amyloidosis were 0.830 (95% CI: 0.76-0.89, $P < .001$) and 0.940 (95% CI: 0.88-0.97, $P < .001$). For NLR and PLR, the AUC values were calculated as 0.712 (95% CI: 0.63-0.79, $P = .002$) and 0.703 (95% CI: 0.62-0.78, $P = .032$).

In 111 patients (82.21%), there was not any mutation analysis in the medical record system. M694V mutation was present in 46 FMF patients (41.4%), 28 (25.2%) of which were heterozygous, and 18 (16.2%) were homozygous.

Comparison of clinical features and laboratory indexes between FMF patients with and without amyloidosis

There were significant differences in terms of age, values of ESR, serum albumin, CRP, NLR, PLR, and the scores of CONUT and PNI between patients with and without amyloidosis ($P < .05$ for all) (Table 3). The mean age of patients with amyloidosis was remarkably higher than patients without amyloidosis ($P = .002$). In patients with amyloidosis, ESR, CRP, NLR, and PLR were higher ($P < .001$, $P = .033$, $P = .020$, and $P = .026$, respectively), whereas serum albumin was notably lower ($P < .001$). There were statistically higher median scores of CONUT in patients with amyloidosis compared with patients without amyloidosis (3 vs. 1) ($P < .001$). However, the median PNI score was 43 (interquartile range [IQR]: 26-54) for patients with amyloidosis compared with the value of 56 (IQR: 43-68) for patients without amyloidosis ($P < .001$).

Results of correlation analyses

Correlation analyses revealed significant positive correlations between CONUT score and serum values of CRP, NLR, and PLR (Table 4). But there was a significant negative relation between CONUT score and PNI ($r = –0.346$, $P < .001$). Multivariable logistic regression analysis revealed that age (odds ratio [OR] = 1.11, 95% CI: 1.03-1.20, $P = .010$), M694V homozygous mutation (OR = 9.37, 95% CI: 1.45-60.44, $P = .019$), and CONUT score (OR = 2.48, 95% CI: 1.43-4.30, $P = .001$) were independent risk factors after adjustment for the

Table 2. The ROC analysis of NLR, PLR, CONUT, and PNI scores for the development of amyloidosis.

	AUC	Sensitivity	Specificity	Cutoff	95% CI	Youden index	*P*
NLR	0.712	90.91	52.42	>1.9	0.63-0.79	0.43	.002
PLR	0.703	72.73	67.74	>145	0.62-0.78	0.40	.032
CONUT score	0.830	63.64	93.55	>2	0.76-0.89	0.57	<.001
PNI	0.940	100.00	72.58	≤54	0.88-0.97	0.73	<.001

ROC, receiver operating curve; AUC, area under curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; CONUT, controlling nutritional status.

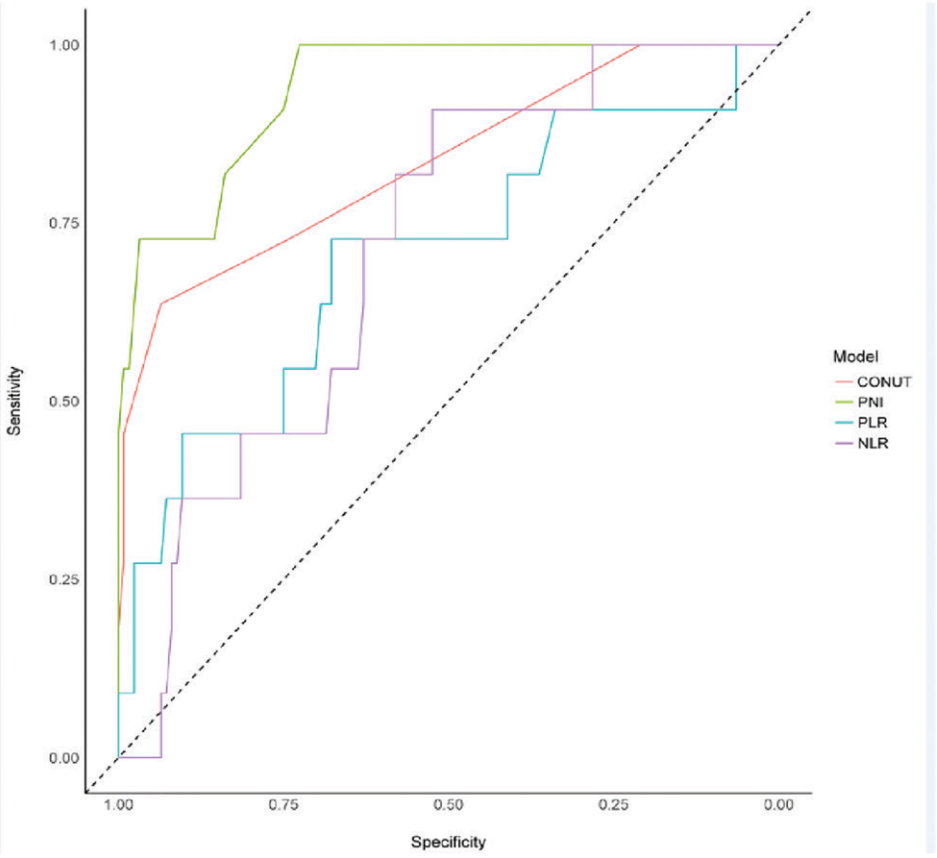

Figure 1. Receiver operating characteristic analysis of NLR, PLR, CONUT, and PNI scores in predicting the development of amyloidosis in patients with FMF. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CONUT, controlling nutritional status; PNI, prognostic nutritional index

Table 3. Comparison of all variables between the patients with amyloidosis (n = 11) and without amyloidosis (n = 124).

	Amyloidosis (+) (n = 11)	Amyloidosis (–) (n = 124)	*P*
Age (year)*	46.6 ± 11.7	33.9 ± 11.7	.002
Duration of the disease (year)†	7 (4-15)	7 (1-29)	.663
Presentation‡			
Serositis and fever	8 (72.7)	92 (74.2)	.999
Arthritis and fever	3 (27.3)	32 (25.8)	
Development of ESRD‡			
Yes	2 (18.2)	0 (0)	–
No	9 (81.8)	124 (100)	
ESR (mm/h)†	42 (12-102)	18 (2-95)	<.001
CRP (mg/dL)†	1 (0.1-5.3)	0.5 (0-10)	.033
Albumin (g/dL)†	3.9 (3.8-4.3)	4.8 (4.1-5.1)	<.001
NLR†	2.6 (1.5-4.7)	1.9 (0.7-12.2)	.020
PLR†	162 (81-371)	125.5 (62-330)	.026
CONUT score†	3 (1-8)	1 (0-6)	<.001
PNI score†	43 (26-54)	56 (43-68)	<.001
MEFV mutation, yes‡	10 (90.9)	101 (81.5)	.688

*Mean ± standard deviation.
†Median (interquartile range).
‡N (%).
ESRD, end-stage renal disease; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CONUT, controlling nutritional status; PNI, prognostic nutritional index; MEFV mutation, Mediterranean fever mutation.

Table 4. Correlation of the CONUT score with demographic and clinical characteristics and laboratory findings of the study group.

	CONUT score	
	r	*P*
Age (year)	0.054	.534
Duration of the disease (year)	0.017	.845
ESR (mm/h)	0.143	.099
CRP (mg/dL)	0.190	.027
NLR	0.393	<.001
PLR	0.338	<.001
PNI	−0.346	<.001

r, Spearman correlation coefficient.
CONUT, controlling nutritional status; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

development of amyloidosis in FMF patients (Table 5). Older FMF patients with a M694V homozygous mutation and higher CONUT scores were significantly associated with amyloidosis.

Discussion

The prognostic values of PNI and CONUT score were first evaluated in FMF patients. The conclusion is that high CONUT score and low PNI were detected in FMF patients who have been complicated with amyloidosis, and the CONUT score was positively correlated with other inflammation markers including CRP, NLR, and PLR. NLR has been already detected to be increased in FMF patients compared with healthy subjects in attack-free periods, and its prognostic role in the development of amyloidosis has also been shown.[14] The relationship between CONUT score and NLR and other inflammation markers in FMF patients has been first analyzed in our study. CONUT score was reported to be related to poor prognosis in patients with different chronic inflammatory diseases.[15] Ahn et al[16] stated that CONUT score ≥3.5 was an indicator of all-cause mortality in newly diagnosed vasculitis patients. Zhou et al[17] also stated that a high CONUT score (CONUT score >3) was detected in 74% of patients with peritoneal dialysis commencement with having a higher risk of mortality. The median duration of FMF was 7 years in this study. Although mortality risk was not calculated, there was no dead patient at the end of the study. An appropriate cutoff value for CONUT of >2 was determined as a poor prognostic factor in patients with FMF.

Ahn et al[18] found that the mean PNI at diagnosis was 43.4 in 160 antineutrophil cytoplasmic antibody-associated vasculitis patients. Birmingham vasculitis activity (BVAS) was inversely correlated with PNI. The association between PNI and BVAS was greater than albumin and lymphocytes. PNI was also noted to be related to prognosis and disease activity in patients with systemic lupus erythematosus.[19] In a large cohort of rheumatoid arthritis, low PNI was significantly more common in the subgroup with infections, and the authors noticed that poor nutritional status was an important risk factor for serious infections.[20] Mean PNI values were significantly lower in the amyloidosis group, in support of previous literature.

Colchicine is still the mainstay of treatment. No more effective alternative treatment modality than colchicine was present among resistant cases. Successful daily treatment of FMF patients with colchicine may prevent the development of renal amyloidosis and provide stabilization of or improvement in renal function for those with amyloidosis.[21] The main part of patients in our study group was treated only with colchicine. It was noticed that colchicine treatment was not stopped when either anakinra, canacinumab, or tocilizumab treatments were started, except for two patients with ESRD. In a large cohort in which the MEFV mutations was investigated in Turkish FMF patients, M694V homozygosity was present in 24% of all patients, and next to half of the patients were detected to have at least one M694V mutation.[22] In our study, homozygous and heterozygous M694V mutations were less commonly seen compared with the earlier study. This could be attributed to the relatively small sample size and the geographic area of the study. Also, the vast majority of patients had no MEFV mutation analysis in the medical record system. On the other hand, Mukhin et al[23] noticed that the presence of recurrent arthritis was associated with AA amyloidosis, and this condition was attributed to the active serum amyloid A production in the joint synovial membrane. There were no important distinctions in terms of clinical presentation and attack characteristics (serositis or arthritis/arthalgia dominance) in amyloidosis and non-amyloidosis groups. While there was no variation between the groups in terms of disease duration, the mean age was higher in the amyloidosis group. This situation can be explained by a possible diagnostic delay or late application of patients in the amyloidosis group.

Recent studies also showed that the kidney is usually the only involved organ in FMF amyloidosis, and biopsy of the involved organ gives the most sensitive results for recognizing secondary amyloidosis.[24] In our study, colon biopsy was positive for amyloidosis in five patients, as well as kidney biopsy. Involved biopsy cites

Table 5. Multivariable logistic regression analysis of the associations between amyloidosis and patient characteristics.

	Crude OR (95% CI)	Crude *P*	Adjusted OR (95% CI)	Adjusted *P*
Age (year)	1.08 (1.03-1.14)	.003	1.11 (1.03-1.20)	.010
Duration of the disease (year)	1.00 (0.89-1.12)	.958	–	–
M694V heterozygot: present vs. absent	0.36 (0.04-2.93)	.339	–	–
M694V homozygot: present vs. absent	7.12 (1.90-26.60)	.004	9.37 (1.45-60.44)	.019
CRP	1.30 (0.91-1.85)	.146	–	–
NLR	1.25 (0.92-1.70)	.158	–	–
CONUT score	2.75 (1.64-4.64)	<.001	2.48 (1.43-4.30)	.001
PNI	0.71 (0.59-0.84)	<.001	–	–

OR: odds ratio; CI, confidence interval; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CONUT, controlling nutritional status; PNI, prognostic nutritional index.

had a selection bias in this study. The biopsy cites were decided according to the proteinuria levels of the patients. Colon biopsy was primarily preferred for non-nephrotic proteinuria to avoid of bleeding from kidneys. With this result, we noted that colon biopsy is a convenient and less-invasive method to determine non-nephrotic proteinuria levels. Cakar et al[25] followed 48 Turkish FMF patients with amyloidosis for a period of 4.5 ± 2.23 years. None of the patients were on regular colchicine therapy, and two of them developed ESRD. In our study, 2 of 11 patients with amyloidosis developed ESRD.

A few limitations of this study are present. A retrospective design and a relatively small size of the study are the first items to be mentioned. The baseline researched indexes were also calculated in the attack-free period after the first attack resolved at the diagnosis. The effect of this timing is debatable. Another bias in this study is related to biopsy cites. Although biopsy proven evidence was accepted for diagnosis of amyloidosis, biopsy cites were decided according to the proteinuria levels of the patients.

In conclusion, amyloidosis is the most serious complication of FMF. Subclinical persistent inflammation in attack-free periods plays the main culprit factor for the development of amyloidosis. Low PNI and high CONUT score at diagnosis may have a poor prognostic value for the development of amyloidosis in patients with FMF in addition to older age and M694V homozygous mutation. These indexes may be a useful and inexpensive screening biomarkers in clinical practice for predicting amyloidosis in patients with FMF. These indexes may help us to prioritize patients who need more intensive adjuvant therapy and closer monitoring for amyloidosis. This relationship should be investigated in prospective, randomized controlled studies.

Ethics Committee Approval: It was received for this study from the Ethics Committee of Pamukkale University School of Medicine (Approval Date: July 8, 2020; Approval Number: 41138).

Informed Consent: It was not obtained due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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