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# Accompanying autoimmune diseases may have a role in colchicine resistance in adult familial mediterranean fever patients

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## Abstract

Colchicine is the primary treatment for familial Mediterranean fever (FMF); however, colchicine resistance poses a major challenge, affecting about 5–10% of patients. This study aimed to compare colchicine-response and colchicine-resistant patients and identify predictors of resistance. A retrospective analysis was performed in a tertiary rheumatology clinic. FMF patients (≥18 years) diagnosed per Tel-Hashomer criteria, on colchicine ≥6 months, compliant per the modified Morisky scale, with exon 10 mutations and complete data were included. Colchicine resistance was defined as ≥1 episode/month for >3 months despite maximum tolerated colchicine doses. Comparative analyses were performed. The study included 123 colchicine-response (65.9% female, median age 39) and 64 colchicine-resistant patients (62.5% female, median age 31.5). Colchicine-resistant patients were younger at diagnosis and symptom onset ($p<0.05$). In age-adjusted multivariate logistic regression, autoimmune comorbidity was the strongest predictor of colchicine resistance (OR: 19.17, 95% CI: 4.46-89.48, $p<0.001$), followed by age ≤7 years at symptom onset, current smoking, ≥ 3 day-long attack under colchicine, number of attacks/year before colchicine, International FMF Severity Score ≥ 4, and diarrhea during attack (OR=1.19–8.56, $p<0.05$). In the ROC analysis of laboratory parameters, C-reactive protein, fibrinogen, lymphocytes, erythrocyte sedimentation rate, neutrophils, and mean platelet volume predicted colchicine resistance with area under the curve values ranging from 0.769 to 0.995. Autoimmune comorbidities, early symptom onset, smoking, frequent and prolonged attacks, high disease severity, and diarrhea are important predictors of colchicine resistance in FMF. Laboratory parameters also aid in prediction, allowing earlier identification and personalized treatment approaches.

**Keywords:** FMF, colchicine resistance, predictive, adult

## Introduction

Familial Mediterranean fever (FMF) represents the most widespread monogenic autoinflammatory condition on a global scale. The main features of the disease are recurrent episodes of fever and polyserositis that are self-limited within approximately 1-3 days [1]. It is more common among Armenians, Turks, Arabs, Greeks, Jews, and Italians [2]. The global prevalence of FMF is reported to be 1:1000, with considerable geographical differences, with Türkiye presumably exhibiting the highest prevalence [3]. This disorder is marked by an autosomal recessive inheritance pattern and results from alterations in the Mediterranean FeVer (MEFV) gene, which encodes the protein pyrin. The MEFV gene is located on the short arm of chromosome 16 and consists of 10 functional segments (exons). Pathogenic mutations are predominantly located in the 10th functional region of the gene, with M680I, M694V, and V726A being the most prevalent alterations. [4].

The efficacy of colchicine treatment in individuals diagnosed with FMF was first observed in the year 1972 [5]. Long-term clinical experience and randomized controlled trials have demonstrated the efficacy and safety of colchicine in the treatment of FMF [1]. Colchicine therapy in FMF enhances quality of life by diminishing the intensity, duration, and frequency of episodes, while also alleviating subclinical and chronic inflammation

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to avert long-term harm, including AA amyloidosis. [6]. The optimal dose required to prevent AA amyloidosis and attacks in the majority of patients is 1-1.5 mg/day. However, if the response is inadequate, the dose may be increased to a maximum of 3 mg/day [7]. Nonetheless, despite the maximal permissible dosage of colchicine, 5-10% of patients exhibit inadequate response to treatment and are classified as colchicine-resistant [1]. Treatment non-response may occur due to factors that affect colchicine bioavailability and disease severity, including genetic variations, potential drug-drug interactions, and colchicine metabolism. There is no clear consensus definition of colchicine resistance [8]. The existence of monthly bouts or consistently elevated inflammatory markers despite maximum tolerated colchicine administration is the most frequently proposed criteria [1]. The guidelines established by the European League Against Rheumatism delineate this condition as occurring one or more episodes each month in adherent patients who are administered the maximum permissible dosage of colchicine for a duration of no less than six months [7]. Erden et al. showed in their study that definitions that included both laboratory and clinical criteria found a higher proportion of patients with colchicine resistance [9].

Research indicates that patients exhibiting musculoskeletal and dermatological symptoms, prolonged attack length, M694V homozygosity or biallelic exon 10 variations, and elevated severity of disease were less likely to react to colchicine treatment. Conversely, patients exhibiting fever or serositis-type episodes with single heterozygous mutations demonstrated a higher likelihood of responding to colchicine [10-13].

The assessment of colchicine resistance in FMF patients is crucial to avert long-term consequences. The literature contains a limited number of research examining the factors related with colchicine resistance in adult patients. This study aimed to compare the clinical, laboratory, and genetic mutation characteristics of colchicine-resistant and response FMF patients, identify factors associated with colchicine resistance, and evaluate the predictive power of laboratory parameters related to colchicine resistance.

## Material and Methods

### Participants and study design

The research was performed as a retrospective, single-center, cross-sectional investigation. During the period spanning from 2020 to 2023, the medical records of patients diagnosed with FMF and monitored at a tertiary rheumatology institution were meticulously examined. The research involved participants aged 18 years and older, who were diagnosed with FMF based on the Tel-Hashomer criteria and had received colchicine treatment for a minimum of six months, who were colchicine tolerant (according to the Modified Morisky Scale (MMS)), who had scheduled follow-up visits twice a year at least 6 months apart, and who had a known exon 10 mutation. Patients with irregular follow-up, patients who were non-compliant with colchicine treatment, patients who developed side effects that limited continuous colchicine use, patients who used colchicine for less than 6 months, and patients with missing data were excluded. Finally, because the MEFV gene mutations in the colchicine-resistant patient group consisted of exon 10, patients with mutations other than exon 10 were excluded from the study. The research was sanctioned by the Gülhane Scientific Research Ethics Committee, affiliated with the University of Health Sciences (Approval date: January 25, 2023, No: 2022/172). The research adhered to the tenets established by the Helsinki Declaration.

Clinical characteristics, laboratory parameters, demographic data, colchicine doses, MEFV mutation analysis results, and International Severity Score for FMF (ISSF), and MMS score results were taken from patients' medical records. Clinical and demographic parameters were as follows: Age, gender, body mass index, age at onset/diagnosis, disease duration, symptom onset at age 7 years or younger, attack characteristics (fever, erysipelas-like erythema (ELE), pleuritis, myalgia/protracted febrile myalgia (PFM), peritonitis, pericarditis, bowel disorder during attack (diarrhea and constipation), and arthritis), family history of FMF and amyloidosis, comorbidity before colchicine resistance, especially autoimmune comorbidity (such as ankylosing spondylitis (AS), Hashimoto's disease (HD), multiple sclerosis (MS), vitiligo, Crohn's disease (CD), hidradenitis suppurativa (HS), and Behçet's disease (BD) etc.), current smoking status, presence of amyloidosis, history of appendectomy, history of penicillin prophylaxis, colchicine dose (maximum tolerable colchicine dose in non-responders), duration of attacks on colchicine treatment and before colchicine.

Before anti-IL-1 treatment, colchicine-resistant patients' laboratory data were documented during attack-free periods. Laboratory values were obtained at the last follow-up visit in the colchicine-response group during the attack-free time between patient recruitment dates. The following laboratory values were recorded: C-reactive protein (CRP) (0-5 mg/L), neutrophils (1.82-7.42 x $10^3$ cells/μL), mean platelet volume (MPV) (8.4-12.7 fL); erythrocyte sedimentation rate (ESR) (0-20 mm/h), platelets (171-388 x $10^3$ cells/μL), red cell distribution width-coefficient of variation (RDW-CV) (11.7-15.3%), white blood cells (WBC) (4-10 x $10^3$ cells/μL), lymphocytes (1.26-3.35 x $10^3$ cells/μL), urea (15-40 mg/dL), serum creatinine (0.5-0.9 mg/dL), alanine aminotransferase (0-33 U/L), fibrinogen (193-412 mg/dL), aspartate aminotransferase (0-32 U/L), and hemoglobin (13.5-17.5 g/dL).

The ISSF was used to assess disease severity. The ISSF was developed for clinical practice and research purposes to measure disease severity in pediatric and adult FMF patients. It includes nine laboratory and clinical variables: organ failure, organ dysfunction, frequency of attacks, chronic sequelae,

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involvement of more than two sites in a single episode, elevated acute phase reactants, more than two types of attacks during the disease, exertional leg pain, and attack duration. Scores range from mild (≤2) to severe (≥6), with a maximum of 10 [14]. In colchicine-resistant patients, the ISSF score was recorded prior to initiation of anti-IL-1 treatment. In the colchicine-response group, it was recorded at the last follow-up visit between patient recruitment dates.

The Turkish validity and reliability of MMS is a short, easily applicable and reliable test that can separately assess the level of knowledge and motivation for medication use habits. The MMS consists of 6 items. Answers are scored as "yes" or "no"; in the 2nd and 5th questions, yes was scored as 1 point and no was scored as 0; in the other questions, yes was scored as 0 and no was scored as 1. A total score of 0 or 1 in questions 1, 2, and 6 indicates a low level of motivation, while scores above 1 point indicate a high level of motivation. A total score of 0 or 1 in questions 3, 4, and 5 indicates a low level of knowledge, and scores above 1 point indicate a high level of knowledge. This study comprised patients with elevated motivation and knowledge levels based on the score results [15].

Colchicine resistance was characterized by one or more episodes per month despite administration of the highest tolerable dose of colchicine over the preceding three months [8]. This study categorized patients into two groups: colchicine-resistant and colchicine-response, and comparative analyses were conducted based on established criteria.

### Statistical analysis

Statistical analyses were conducted employing the Statistical Package for the Social Sciences (Armonk, NY, USA: IBM Corp), version 26 compatible with the Windows operating system. The adherence of the variables to a normal distribution was evaluated through comprehensive statistical techniques (Shapiro-Wilk/ Kolmogorov-Smirnov). Comparative assessments were executed between the colchicine-resistant and colchicine-response groups. The analytical comparisons utilized the Mann-Whitney U test for continuous variables that were not normally distributed, while the independent t-test was applied to continuous variables that demonstrated a normal distribution. To facilitate the comparison of categorical variables across the groups, either the Pearson chi-squared test or Fisher's exact test (in situations where the assumptions underlying the chi-squared test were not satisfied) was employed. The outcomes are articulated as numerical values and percentages for categorical variables, and as mean ± standard deviation or median (interquartile range) for quantitative variables. Receiver operating characteristic (ROC) analysis was implemented to assess the effectiveness of laboratory parameters in identifying colchicine resistance. Both univariate and multivariate logistic regression analyses, adjusted for age, were conducted to investigate the factors associated with colchicine resistance in patients with FMF. A multivariate regression model was systematically developed utilizing the factors that were significantly correlated with colchicine resistance as determined in the univariate analysis. The forward likelihood ratio (LR) method was employed for the selection of the model. The fit of the model was evaluated using the Hosmer-Lemeshow test. Type 1 error rates below 5% were deemed statistically significant.

### Results

A total of 338 FMF patients were assessed for study inclusion (shown in Figure 1). The study included 123 colchicine-response FMF patients (65.9% female, median age 39 years) and 64 colchicine-resistant FMF patients (62.5% female, median age 31.5 years), as per the exclusion criteria.

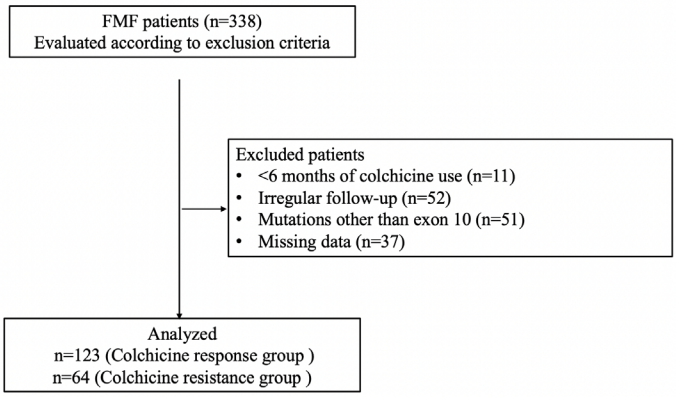


**Figure 1.** Flow diagram of adult patients with FMF evaluated for inclusion in the study. FMF: Familial Mediterranean fever

Colchicine-resistant patients were younger at diagnosis and symptom onset (median age was 15 versus 25 years and 7 versus 18 years, respectively). The presence of attacks lasting 3 days or more under colchicine treatment and the presence of attacks occurring once a month or more in the last 1 year before colchicine treatment was higher in colchicine-resistant patients ($p<0.05$). ELE, fever, arthralgia, diarrhea, arthritis, pleuritis, myalgia, PFM, and pericarditis were significantly more common in colchicine-resistant patients than in colchicine-response patients ($p<0.05$). In addition, history of appendectomy, current smoking, and history of penicillin prophylaxis were more common in colchicine-resistant patients than in colchicine-response patients ($p < 0.05$) (Table 1).

Autoimmune comorbidities were more common in colchicine-resistant patients than in colchicine-response patients ($p<0.001$). Comorbidities observed in the colchicine-resistant group included AS, HD, MS, CD, HS, BD, Ig A vasculitis (IgAV), and vitiligo. In the colchicine-response group, IgAV, AS, MS, HD, HS, BD, vitiligo, rheumatoid arthritis, and sarcoidosis were observed. AS was the most common disease observed in both groups. Ankylosing spondylitis and Hashimoto's disease were more common in colchicine-resistant patients than in colchicine-response patients ($p<0.05$) (Table 2).

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**Table 1.** The clinical characteristics of colchicine-resistant and response groups

| Parameters | Colchicine resistance group (n=64) | Colchicine response group (n=123) | p |
|---|---|---|---|
| Age, years* | 31.5 (16) | 39 (24) | **0.002** |
| Age at symptom onset, years* | 7 (15.75) | 18 (18) | **<0.001** |
| Age at diagnosis, years* | 15 (16.75) | 25 (22) | **<0.001** |
| Disease duration, years | 16 (13) | 11 (13) | **0.008** |
| BMI** | 24±4.1 | 25.1±.9 | 0.080 |
| ≤7 years at symptom onset, n (%) | 38 (59.4) | 15 (12.2) | **<0.001** |
| Comorbidity, n (%) | 26 (40.6) | 34 (27.6) | 0.071 |
| Autoimmune comorbidity*** n (%) | 24 (37.5) | 13 (10.6) | **<0.001** |
| Gender, female, n (%) | 40 (62.5) | 81 (65.9) | 0.649 |
| Current smoking, n (%) | 42 (65.6) | 38 (30.9) | **<0.001** |
| Family history of FMF, n (%) | 55 (85.9) | 93 (75.6) | 0.099 |
| Family history of amyloidosis, n (%) | 5 (7.8) | 8 (6.5) | 0.739 |
| History of appendectomy, n (%) | 23 (35.9) | 18 (14.6) | **0.001** |
| History of penicillin prophylaxis**** | 28 (43.8) | 19 (15.4) | **<0.001** |
| **Clinical findings, n (%)** | | | |
| Peritonitis | 60 (93.8) | 113 (91.9) | 0.643 |
| Pleuritis | 47 (73.4) | 41 (33.3) | **<0.001** |
| Pericarditis | 16 (25) | 10 (8.1) | **0.002** |
| Fever | 62 (96.9) | 107 (87) | **0.030** |
| Arthralgia | 52 (81.3) | 52 (42.3) | **<0.001** |
| Arthritis | 39 (60.9) | 20 (16.3) | **<0.001** |
| Persistant arthritis | 4 (6.3) | 4 (3.3) | 0.449 |
| Prolonged febrile myalgia | 7 (10.9) | 2 (1.6) | **0.005** |
| Erysipelas-like erythema | 44 (68.8) | 28 (22.8) | **<0.001** |
| Myalgia | 51 (79.7) | 39 (31.7) | **<0.001** |
| Diarrhea | 44 (68.8) | 17 (13.8) | **<0.001** |
| Constipation | 1 (1.6) | 6 (4.9) | 0.425 |
| **Amyloidosis, n (%)** | 4 (6.3) | 0 (0) | **0.013** |
| **Colchicine dose , mg/day*** | 2 (0) | 1 (0.5) | **<0.001** |
| **Under colchicine treatment** | | | |
| Attack duration, days* | 3 (1) | 2 (1) | **<0.001** |
| ≥ 3 days attack n (%) | 31 (68.9) | 14 (11.4) | **<0.001** |
| Number of attacks /year* | 9 (3.7) | 2 (1) | **<0.001** |
| **Before colchicine treatment** | | | |
| Attack duration, days* | 4 (0) | 4 (1) | **<0.001** |
| Number of attacks /year* | 14 (7.7) | 9 (6) | **<0.001** |
| Attacks ≥1/month n (%) | 38 (59.4) | 33 (26.8) | **<0.001** |
| **Disease severity (ISSF score)*** | 4.5 (1) | 0 (1) | **<0.001** |

*Median (interquartile range); **Mean ± standard deviation; FMF: Familial Mediterranean fever; ISSF: International Severity Score for FMF, *** Diagnosed before colchicine resistance, **** in childhood; BMI: body mass index.

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**Table 2.** Distribution of autoimmune comorbidities according to colchicine-resistant and response groups

| Autoimmune comorbidities *n (%) | Colchicine resistance group (n=64) | Colchicine response group (n=123) | p |
|---|---|---|---|
| Ankylosing spondylitis | 13 (20.3) | 5 (4.1) | **<0.001** |
| Hashimoto's disease | 4 (6.3) | 1 (0.8) | **0.048** |
| Multiple sclerosis | 2 (3.1) | 1 (0.8) | 0.270 |
| Vitiligo | 2 (3.1) | 2 (1.6) | 0.607 |
| Crohn's disease | 1 (1.6) | 0 (0) | 0.342 |
| Hidradenitis suppurativa | 2 (3.1) | 0 (0) | 0.116 |
| Behçet's disease | 1 (1.6) | 1 (0.8) | 1 |
| IgA vasculitis | 1 (1.6) | 1 (0.8) | 1 |
| Rheumatoid arthritis | 0 (0) | 1 (0.8) | 1 |
| Sarcoidosis | 0 (0) | 1 (0.8) | 1 |

* Diagnosed before colchicine resistance

The levels of neutrophil, ESR, CRP, WBC, platelet, and fibrinogen were markedly elevated in the colchicine-resistant group in comparison to the colchicine-response group ($p<0.05$). On the other hand, haemoglobin, lymphocyte, and MPV levels were significantly lower in the colchicine-resistant group compared to the colchicine-response group ($p<0.05$). Homozygosity for exon 10 MEFV mutations (45.3% vs 11.4%) was more frequent in colchicine-resistant patients than in responders ($p<0.05$). The most common homozygous exon 10 MEFV mutation was M694V/M694V (43.8%). In colchicine-response patients, 77.2% of exon 10 MEFV mutations were heterozygous and the most common mutation was V726A/- (26%) (Table 3).

**Table 3.** Laboratory results of FMF patients under colchicine treatment ***and MEFV gene mutations

| Parameters | Colchicine resistance group (n=64) | Colchicine response group (n=123) | p |
|---|---|---|---|
| ESR, mm/h* | 32 (15.5) | 7 (9) | **<0.001** |
| CRP, mg/L* | 16.8 (11.7) | 1.4 (1.8) | **<0.001** |
| Haemoglobin, g/dL * | 13.3 (2.3) | 14.1 (1.9) | **<0.001** |
| WBC, 109/L* | 7.4 (3.7) | 6.5 (1.6) | **0.006** |
| Lymphocyte, 109/L* | 1.2 (0.3) | 2.2 (0.6) | **<0.001** |
| Neutrophil, 109/L* | 5.7 (2.8) | 3.8 (1.3) | **<0.001** |
| Platelet, 109/L* | 283.5 (110.7) | 243.5 (62.5) | **<0.001** |
| Fibrinogen, mg/dL* | 374.5 (82.5) | 243 (42.2) | **<0.001** |
| Urea, mg/dL* | 22.5 (4) | 24.5 (8.4) | 0.058 |
| Serum creatinin, mg/dL* | 0.75 (0.19) | 0.77 (0.2) | 0.459 |
| ALT, U/L* | 16 (25.7) | 19 (12.2) | 0.472 |
| AST, U/L* | 19 (17.2) | 20 (9) | 0.978 |
| MPV (fL)** | 9.2±1.16 | 10.4±1.27 | **<0.001** |
| RDW-CV (%)* | 13.9 (2.4) | 13.5 (1) | **0.028** |
| Heterozygous mutations | 27 (42.2) | 95 (77.2) | **<0.001** |
| Homozygous mutations | 29 (45.3) | 14 (11.4) | **<0.001** |
| Compound Heterozygous mutations | 8 (12.5) | 14 (11.4) | 0.822 |
| M694V/- | 12 (18.8) | 33 (27) | 0.209 |
| M680I/- | 6 (9.4) | 16 (13) | 0.464 |
| V726A/- | 4 (6.3) | 32 (26) | **0.001** |
| M694I/- | 2 (3.1) | 11 (8.9) | 0.138 |
| M694V/M680I | 6 (9.4) | 5 (4.1) | 0.143 |
| M694V/M694V | 28 (43.8) | 10 (8.2) | **<0.001** |

*median (IQR); **mean ± SD; MEFV: Mediterranean FeVer, FMF: Familial Mediterranean fever, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, WBC: White blood cell, ESR: erythrocyte sedimentation rate; MPV: mean platelet volume; RDW-CV: red cell distribution width- coefficient of variation; CRP: C-reactive protein; *** attack-free period

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In an age-adjusted multivariate logistic regression analysis to investigate the most influential clinical and genetic factors that we thought might be associated with colchicine resistance in FMF patients, ≤7 years at symptom onset (odds ratio (OR): 5.79, 95% CI: 1.14-23.18, p=0.003), current smoking (OR: 4.71, 95% CI: 1.52-14.58, p=0.007), autoimmune comorbidity (OR: 19.17, 95% CI: 4.46-89.48, p<0.001), diarrhea during attack (OR: 8.56, 95% CI: 2.38-30.81, p=0.001), ≥ 3 days attack under colchicine treatment (OR: 7.45, 95% CI: 1.93-28.64, p=0.003), ISSF score ≥ 4 (OR: 5.35, 95% CI: 1.40-20.36, p=0.014), and number of attacks within 1 year before colchicine treatment (OR: 1.19, 95% CI: 1.04-1.37, p=0.010) significantly predicted colchicine resistance (Table 4).

In the ROC analysis of laboratory parameters that appeared to be associated with colchicine resistance, CRP, fibrinogen, lymphocyte, ESR, neutrophil, MPV, platelet, haemoglobin, WBC, and RDW-CV area under the curve (AUC) values predicted colchicine resistance (0.995, 0.955, 0.951, 0.913, 0.788, 0.769, 0.672, 0.662, 0.621, and 0.601, respectively) (Figure 2, Table 5).

**Table 4.** Univariate and multivariate logistic regression analyses to investigate the clinical characteristics associated with colchicine resistance in FMF patients

| Parameters | OR | Univariate analysis 95% CI | p value | OR | Multivariate analysis 95% CI | p value |
|---|---|---|---|---|---|---|
| Age at diagnosis | 1.00 | 0.96-1.04 | **<0.001** | | | |
| ≤7 years at symptom onset | 9.02 | 4.11-19.83 | **<0.001** | 5.79 | 1.14-23.18 | **0.013** |
| Disease duration | 1.07 | 1.03-1.11 | **<0.001** | | | |
| Current smoking | 3.85 | 2.00-7.44 | **<0.001** | 4.71 | 1.52-14.58 | **0.007** |
| History of appendectomy | 3.45 | 1.63-7.28 | **0.001** | | | |
| Autoimmune comorbidity | 6.20 | 2.75-13.99 | **<0.001** | 19.97 | 4.46-89.48 | **<0.001** |
| History of penicillin prophylaxiss | 4.26 | 2.07-8.77 | **<0.001** | | | |
| Pleuritis | 5.43 | 2.72-10.82 | **<0.001** | | | |
| Pericarditis | 4.05 | 1.66-9.92 | **0.001** | | | |
| Arthritis | 7.51 | 3.69-15.27 | **<0.001** | | | |
| Prolonged febrile myalgia | 6.67 | 1.30-34.17 | **0.023** | | | |
| Erysipelas-like erythema | 7.55 | 3.75-15.24 | **<0.001** | | | |
| Diarrhea | 13.41 | 6.27-28.64 | **<0.001** | 8.56 | 2.38-30.81 | **0.001** |
| ≥ 3 days attack* | 6.99 | 3.25-14.99 | **<0.001** | 7.45 | 1.93-28.64 | **0.003** |
| Attacks ≥1/month** | 3.82 | 1.98-7.38 | **<0.001** | | | |
| Number of attacks /year** | 1.28 | 1.28-141 | **<0.001** | 1.19 | 1.04-1.37 | **0.010** |
| M694V/ M694V | 7.73 | 3.36-17.77 | **<0.001** | | | |
| ISSF score ≥ 4 | 22.55 | 10.01-50.77 | **<0.001** | 5.35 | 1.40-20.36 | **0.014** |

FMF: Familial Mediterranean fever; * Under colchicine treatment; ** Before colchicine treatment, OR: odds ratio, CI: confidence interval, ISSF: International Severity Score for FMF

**Table 5.** ROC analysis results for laboratory parameters associated with colchicine resistance

| Parameters | AUC | Std Error | 95% CI | p value |
|---|---|---|---|---|
| CRP | 0.995 | 0.005 | 0.98-1.00 | <0.001 |
| Fibrinogen | 0.955 | 0.016 | 0.92-0.98 | <0.001 |
| Lymphocyte | 0.951 | 0.016 | 0.92-0.98 | <0.001 |
| ESR | 0.913 | 0.024 | 0.86-0.96 | <0.001 |
| Neutrophil | 0.788 | 0.038 | 0.71-0.86 | <0.001 |
| MPV | 0.769 | 0.037 | 0.69-0.84 | <0.001 |
| Platelet | 0.672 | 0.045 | 0.58-0.76 | <0.001 |
| Haemoglobin | 0.662 | 0.043 | 0.57-0.74 | <0.001 |
| WBC | 0.621 | 0.047 | 0.52-0.71 | 0.007 |
| RDW | 0.601 | 0.046 | 0.51-0.69 | 0.024 |

WBC: White blood cell; ESR: erythrocyte sedimentation rate; MPV: mean platelet volume; RDW: red cell distribution width; CRP: C-reactive protein, AUC: area under the curve, ROC: Receiver operating characteristic; CI: confidence interval

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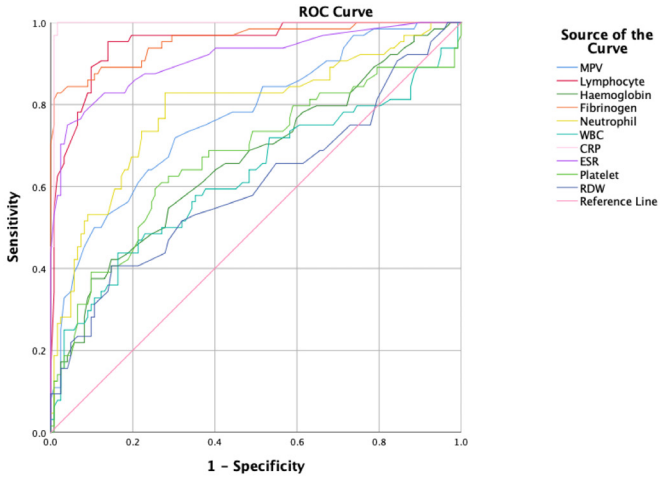


**Figure 2.** ROC analysis of laboratory parameters associated with colchicine resistance. WBC: White blood cell, ESR: erythrocyte sedimentation rate; MPV: mean platelet volume; RDW: red cell distribution width; CRP: C-reactive protein; ROC: Receiver operating characteristic

## Discussion

Colchicine resistance, which affects approximately 5-10% of FMF patients, remains a clinical challenge because of its impact on disease control and patient outcomes [1]. By identifying factors associated with colchicine resistance, clinicians can better predict which patients may require alternative or additional treatment approaches. This study offers significant insights into the clinical and laboratory parameters linked to colchicine resistance in adult patients with FMF. In this study, colchicine resistance was associated with especially autoimmune comorbidity, ≤7 years at symptom onset, current smoking, ≥ 3 day-long attacks under colchicine, number of attacks/year before colchicine, ISSF score ≥ 4, and diarrhea during attacks. In addition, laboratory parameters including CRP, fibrinogen, lymphocytes, ESR, neutrophils, and MPV, showed moderate to strong predictive value for colchicine resistance.

Previous studies have shown that many characteristics of FMF patients predict colchicine resistance. Frequent and severe attacks in FMF patients lead to poor quality of life, severe disease and, most importantly, secondary amyloidosis [16,17]. Özçakar et al. [11] associated leg pain, prolonged attacks, ELE and M694V homozygosity with colchicine resistance. In another study, colchicine resistance correlated with increased disease severity, diminished socioeconomic position, and reduced educational attainment [18]. Batu et al. [19] recently showed that attack frequency, age at symptom onset, chest pain, the presence of two exon 10 mutations, and arthritis were determinants of colchicine resistance in pediatric FMF patients. A separate study indicated that an earlier age of symptom onset correlated with M694V homozygosity and increased disease severity [17]. In this study, consistent with previous studies, more severe disease, younger age at onset, longer duration, and more frequent attacks were associated with colchicine resistance. The association between early onset and resistance may reflect a more aggressive inflammatory phenotype that requires early intervention to prevent complications.

Şahin et al. [20] observed in their study of pediatric FMF patients that more than four attacks per year, diagnosis before six years of age, and elevated ESR levels during the attack-free period may correlate with colchicine resistance. In addition, diarrhea and musculoskeletal involvement were observed more frequently in the colchicine-resistant group. A further study within the pediatric cohort revealed a significant correlation between a high frequency of attacks and colchicine resistance. In addition, diarrhea frequency was found to be higher in the resistance group. The authors proposed that possible causes of gastrointestinal intolerance should be investigated prior to assessing colchicine resistance in the context of diarrhea status [21]. In this study, diarrhea, which is a known side effect of colchicine, emerged as an important determinant of resistance, although it has not been previously reported in adult patients. This finding may reflect suboptimal drug absorption or gastrointestinal intolerance limiting the therapeutic efficacy of colchicine. Alternative formulations, such as colchicine use in combination with probiotics, could be explored to address this limitation. Furthermore, the strong predictive value of diarrhea for resistance suggests that its role in disease pathophysiology warrants further investigation.

No data exist regarding the impact of smoking on colchicine pharmacokinetics. However, based on the results of studies in FMF, it is clear that smoking has a poor effect on disease prognosis. Bodur et al. [22] found that smoking and severe disease were associated with poor quality of life. Babaoğlu et al. [23] reported colchicine resistance, smoking history, and other factors as predictors of damage according to the autoinflammatory disease damage index score. Gursoy et al. [13] found a high rate of smoking in colchicine-resistant FMF patients. This may be interpreted as follows: The pro-inflammatory effects of smoking may exacerbate disease activity by counteracting the anti-inflammatory properties of colchicine. These findings highlight the importance of smoking cessation programs as part of FMF management. Future research could investigate whether smoking interacts with specific genetic or metabolic pathways involved in colchicine resistance.

Individuals with the MEFV mutation are susceptible to inflammation. Consequently, inflammatory disorders are more prevalent among FMF carriers. It has been documented in the literature that FMF patients are more susceptible to other autoimmune diseases such as BD, vasculitis, HS, inflammatory bowel disease, HS, MS, vitiligo, sarcoidosis, rheumatoid arthritis, and HD due to defects in the inhibition of inflammation [24-27]. The research reports a heightened frequency of AS among FMF patients [28]. The M694V allele has been observed with greater frequency in patients with AS [29]. AS was the most common

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autoimmune comorbidity observed in this study. In contrast to other studies, this study for the first time presented autoimmune comorbidities (such as AS, CD, MS, HD, BD, vitiligo, and HS, etc.) as a clinical factor associated with colchicine resistance. In this study, all autoimmune diseases occurred after the diagnosis of FMF and before colchicine resistance. In line with the results of this study, It is reasonable to conclude that same pathophysiological pathways are present in FMF and other autoimmune illnesses, and that cytokine production in FMF may predispose individuals to further autoimmune disorders. These features suggest that immune dysregulation is increased in resistant patients.

In FMF patients, complete blood count parameters and acute phase reactants during the attack-free period can be used to predict the risk of disease complications, including amyloidosis and subclinical inflammation [30,31]. Research indicates that indices derived from hematologic characteristics can predict disease severity in patients with FMF [32,33]. According to the literature, data on the relationship between colchicine resistance and hematologic parameters are limited. In the study by Ocak et al. [31] in FMF patients with amyloidosis, WBC, neutrophils, RDW, platelets, ESR, and CRP levels were dramatically elevated, but lymphocytes and hemoglobin levels were significantly diminished compared to those without amyloidosis. This study revealed that MPV was considerably lower in the colchicine-resistant group. There are inconsistencies in the relationship between MPV and FMF in previous studies. However, in studies conducted in FMF patients with AA amyloidosis, MPV was found to be lower compared to FMF patients without AA amyloidosis or controls [34-36]. The mechanism of low MPV is still unclear. The results of this study may be confirmed in future studies using colchicine resistance and hematologic parameters and indices derived from them.

### Limitations

This study possesses limitations. The retrospective design may result in selection bias, and the single-center methodology restricts generalizability. Furthermore, although colchicine drug adherence was assessed using the modified Morisky scale, a relatively subjective scale, more objective measures such as colchicine blood levels may provide more information on adherence and pharmacokinetics. Laboratory parameters were assessed at a single time point. This may not reflect dynamic changes during disease progression.

### Conclusion

Colchicine resistance in FMF is influenced by especially autoimmune comorbidities, the younger onset of symptoms, smoking, frequent and prolonged attacks, disease severity, and the presence of diarrhea during attack. Laboratory parameters add predictive value regarding colchicine resistance. Identifying patients at risk for colchicine resistance early in the disease process allows for rapid intervention, including alternative therapies such as biologics or adjunctive therapies targeting specific inflammatory pathways. In addition, the integration of clinical features and laboratory biomarkers into predictive models may improve personalized treatment approaches. Finally, lifestyle changes, especially smoking cessation, should be emphasized as part of a comprehensive treatment plan. Future research should focus on optimizing alternative therapeutic approaches for colchicine-resistant FMF. Further multicenter, prospective investigations are required to validate these findings and explore the mechanisms underlying colchicine resistance.

**Conflict of Interests**

*The authors declare that there is no conflict of interest in the study.*

**Financial Disclosure**

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**Ethical Approval**

*The Ethics Committee of Health Sciences University, Gulhane Training and Research Hospital approved this study in accordance with the Declaration of Helsinki (date: 25.01.2023, decision number: 2022/172).*

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