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ORIGINAL RESEARCH ARTICLE

Discontinuing Colchicine in Pediatric Familial Mediterranean Fever: Real-Life Experience from a Long-Term Follow-Up Cohort

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Abstract

Background Colchicine is the cornerstone of treatment in familial Mediterranean fever and is generally recommended as lifelong therapy. However, a subset of pediatric patients may experience a milder disease course, raising questions about the feasibility and safety of colchicine discontinuation. Evidence guiding this decision remains limited, and no consensus exists on patient selection criteria or monitoring strategies.

Objective The objective of this study was to evaluate long-term outcomes after colchicine discontinuation in a large pediatric familial Mediterranean fever cohort and to identify clinical and genetic factors associated with sustained colchicine-free remission.

Methods We retrospectively analyzed medical records of 2316 pediatric patients diagnosed with familial Mediterranean fever and followed at the Pediatric Rheumatology Unit of Istanbul University, Istanbul Faculty of Medicine, Istanbul, Türkiye. Patients fulfilling at least one of the Tel-Hashomer or Eurofever/Pediatric Rheumatology International Trials Organization (PRINTO) classification criteria and carrying at least one pathogenic or likely pathogenic *MEFV* (Mediterranean fever) gene mutation were eligible. Colchicine was discontinued in 127 patients (5.48%), who were classified into two groups: Group 1 ($n = 31$), patients who required colchicine re-initiation because of recurrent attacks, and Group 2 ($n = 96$), patients who maintained sustained colchicine-free remission during follow-up. A contemporaneous comparator group of 118 patients who continued colchicine therapy without any attempt at discontinuation (Group 3) was included to provide clinical and genetic context. Demographic, clinical, genetic, and disease severity characteristics were compared across groups.

Results Sustained colchicine-free remission was maintained in 96 of 2316 patients (4.14%; Group 2). Among all patients who discontinued colchicine (Groups 1 and 2 combined), the median duration of colchicine treatment before discontinuation was 3.85 years (interquartile range 1.84–7.10), and the median follow-up after cessation was 4.91 years (interquartile range 1.92–7.23). Baseline clinical, demographic, and genetic characteristics were largely similar between Group 1 and Group 2, and no robust independent predictor of sustained remission was identified. Biallelic pathogenic exon 10 *MEFV* variants were significantly more prevalent in Group 3 (32.2%) compared with Group 1 (12.9%) and Group 2 (3.1%), reflecting a progressive genetic gradient across the three groups. Patients in Group 3 also exhibited higher frequencies of fever, chest pain, arthritis, arthralgia, erysipelas-like erythema, and exercise-induced leg pain compared with the discontinuation groups. Fulfillment of Eurofever/PRINTO classification criteria was significantly lower in Groups 1 (54.8%) and 2 (54.2%) than in Group 3 (87.3%), consistent with a milder phenotypic profile in patients considered for discontinuation. No patient in the discontinuation cohort developed amyloidosis during follow-up.

Conclusions Colchicine discontinuation is achievable in a small but consistent subset of patients with pediatric familial Mediterranean fever (4.14% of the total cohort), the majority of whom maintain sustained remission over a long-term follow-up. While patients requiring continuous therapy exhibit a more severe clinical and genetic profile, no robust baseline predictor reliably distinguishes those who will remain in remission from those who will relapse. These findings highlight the need for individualized withdrawal decisions guided by rigorous longitudinal monitoring, and underscore the importance of prospective studies incorporating emerging biomarkers of subclinical inflammation.

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Key Points

Colchicine can be safely stopped in a small group of children with familial Mediterranean fever who have milder disease, and most of these children remain well without the medication for years.

No single clinical or genetic feature reliably predicts which children will stay in remission after stopping colchicine, meaning each decision must be made individually with close monitoring.

Children who need lifelong colchicine tend to have more severe disease from the outset, suggesting that disease burden at diagnosis may help guide, but not determine, decisions about eventual treatment withdrawal.

1 Introduction

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent self-limited attacks of fever, polyserositis, and arthritis. In some patients, subclinical inflammation persists between attacks, and amyloidosis is a serious complication of the disease [1, 2]. The causative mutations are found in the *MEFV* (Mediterranean fever) gene, which encodes a proinflammatory protein called pyrin [3]. Pyrin plays a role in the formation of the pyrin inflammasome complex, which is required for the production of interleukin-1β and interleukin-18, and is also involved in pyroptosis [3, 4]. Colchicine is the gold standard for preventing flares and reducing subclinical inflammation, thereby preventing long-term complications in FMF [5, 6]. Although generally considered safe and effective, colchicine has a narrow therapeutic index and has been associated with overdose and death at toxic doses, as well as adverse events such as blood dyscrasias, gastrointestinal side effects, and neuromyopathy [7, 8]. Patients with hepatic or renal impairment are at increased risk of colchicine toxicity [9, 10]. In addition, colchicine should be avoided or a dose reduction considered when used concomitantly with medications that interact adversely [11]. Recently, in patients who are heterozygous carriers of the *MEFV* mutation and have milder forms of the disease, discontinuing colchicine under close monitoring has emerged as a concept. A limited number of studies have reported that in a selected group of patients with FMF, the disease may remain silent after colchicine discontinuation [12–17]. However, there is no consensus on which patients can discontinue colchicine treatment or on the algorithm for discontinuing it. This study aimed to describe the characteristics and follow-up outcomes of children diagnosed with FMF who had at least one *MEFV* gene mutation and received colchicine for at least 6 months, subsequently discontinuing treatment during the follow-up.

2 Methods

2.1 Study Design and Patient Population

The medical records of 2316 children diagnosed with FMF and followed regularly every 3–6 months at the Pediatric Rheumatology Unit of Istanbul University were retrospectively reviewed. Patients who fulfilled at least one of the Tel-Hashomer or Eurofever/Pediatric Rheumatology International Trials Organization (PRINTO) classification criteria and carried at least one pathogenic or likely pathogenic *MEFV* mutation in exons 2, 3, 5, or 10 were eligible for inclusion [1, 18].

Patients included in the study had a confirmed diagnosis of FMF according to established classification criteria (Tel-Hashomer and/or Eurofever/PRINTO) and were not treated with colchicine solely for diagnostic purposes or as a therapeutic trial before diagnosis. Patients in whom colchicine treatment was discontinued during the follow-up, either by physician decision or at the request of the patient or parents, were included in the colchicine-discontinuation cohort. Demographic characteristics, clinical features, *MEFV* genotype data, initial colchicine dose, and colchicine dose immediately prior to discontinuation were recorded.

The continuous-colchicine group consisted of consecutive pediatric patients with FMF attending routine outpatient follow-up visits during a predefined period. This time window was selected to ensure contemporaneous clinical practice and complete availability of clinical and genetic data, rather than based on disease characteristics or outcomes. Patients were included consecutively based on clinic attendance and ongoing colchicine treatment during a predefined study period, without selection based on genotype, disease severity, or clinical outcomes. Age comparability between the colchicine-discontinuation cohort and the continuous-colchicine group was ensured at the group level based on current age distributions; individual patient matching was not performed. In routine clinical practice at our center, follow-up visits are scheduled every 3–6 months depending on disease activity.

2.2 Eligibility Criteria for Colchicine Discontinuation

Colchicine discontinuation was considered by the treating pediatric rheumatologist for patients without homozygous

or compound-heterozygous pathogenic exon 10 *MEFV* mutations, without a family history of amyloidosis, without clinical attacks during the preceding 6 months of colchicine treatment, and without evidence of proteinuria. A minimum attack-free period of 6 months was chosen in line with routine clinical practice and prior pediatric colchicine discontinuation studies, balancing patient safety with feasibility in the long-term follow-up. Colchicine discontinuation was considered only in patients in sustained clinical remission with normal C-reactive protein (CRP; < 5 mg/L), erythrocyte sedimentation rate (ESR; < 20 mm/h) and serum amyloid A (SAA; < 10 mg/L) levels at the time of withdrawal. Acute-phase reactants (CRP, ESR, and SAA) at the time of colchicine discontinuation were extracted and analyzed.

After discontinuation, patients were monitored every 3–6 months for clinical attacks and elevated acute-phase reactants. Colchicine therapy was re-initiated in the presence of recurrent clinical attacks. Elevated acute-phase reactants were considered supportive but not used as the sole criterion for treatment reinitiation.

2.3 Group Definitions and the Follow-Up Protocol

Patients were classified into three groups based on their colchicine status during the follow-up: those who required reinitiation of colchicine (group 1), those who remained colchicine free after discontinuation (group 2), and those who continued colchicine therapy without attempting to discontinue it (group 3).

2.4 Selection of the Continuous-Colchicine Group

The continuous-colchicine group (group 3) was included to represent the broader pediatric FMF population in whom colchicine withdrawal is not clinically considered, allowing contextual interpretation of disease severity, genotype distribution, and clinical phenotype.

2.5 Data Collection

Demographic variables, clinical manifestations, *MEFV* mutations, and colchicine doses were compared across the three groups. Clinical features (e.g., fever, serositis, arthritis) were recorded as cumulative manifestations observed over the course of the disease, rather than being restricted to the time of colchicine discontinuation. For patients whose colchicine treatment was discontinued, reasons for re-initiation were documented. Disease severity was assessed using the International Severity Score for FMF (ISSF), calculated in groups 1 and 2 before colchicine discontinuation and reassessed in group 1 at the time of treatment re-initiation.

A subset of patients included in the present cohort was previously reported in Tanatar et al. [13]. The current study substantially extends that report by incorporating a larger cohort, a longer follow-up period, a contemporaneous comparator group, and a refined analytical focus comparing patients who remained colchicine free with those who required reinitiation of colchicine.

2.6 Statistical Analysis

Data were collected for analysis utilizing Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and SPSS 28.0 (IBM, Armonk, NY, USA). The distribution of numerical variables was investigated through both visual means (histograms and probability plots) and analytical methods, such as the Kolmogorov–Smirnov/Shapiro–Wilk tests. Descriptive statistics for numerical variables included the minimum, maximum, mean, standard deviation, interquartile range (IQR), and median, reported by distribution. Categorical variables were analyzed using frequency and percentage distributions. The Chi-square test or Fisher's exact test, with Bonferroni correction for multiple comparisons, was applied to compare categorical variables. Quantitative variables were compared using the Kruskal–Wallis test, the Mann–Whitney *U* test, or the independent-samples t-test, depending on their distribution. A *p*-value below 0.05 was considered statistically significant. Kaplan–Meier survival analysis was performed to evaluate time to colchicine re-initiation.

2.7 Ethics

The Ethics Committee of Istanbul University approved the study, Istanbul Medical Faculty (Date: 05.02.2024; No: 2405744). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients and/or parents prior to inclusion.

3 Results

3.1 Patient Characteristics and Disposition

The study cohort included 2316 pediatric patients diagnosed with FMF. Colchicine treatment was discontinued in 127 patients (5.48%), of whom 31 (24.4%) required re-initiation of colchicine (Group 1) and 96 (75.6%) remained colchicine free throughout the follow-up (Group 2). Discontinuation occurred either at the physician's discretion or at the request of the patient/parents. The comparator group (Group 3: continuous colchicine therapy) consisted of 118 consecutive patients attending routine outpatient follow-up visits during a predefined calendar period, selected based on clinic attendance and ongoing colchicine treatment, without selection based on genotype, disease severity, or clinical outcomes.

Age comparability between the discontinuation cohort and Group 3 was ensured at the group level; individual patient matching was not performed. Baseline demographic and clinical characteristics of the three groups are summarized in Table 1.

Among patients who discontinued colchicine (groups 1 and 2 combined), the median duration of colchicine treatment was 3.85 years (IQR 1.84–7.10), and the median age at colchicine discontinuation was 11.30 years (IQR 7.83–14.21). The median follow-up period after colchicine discontinuation was 4.91 years (IQR 1.92–7.23).

The median age at colchicine cessation was similar between group 1 and group 2 [11.2 years (IQR 8.0–13.8) vs 11.4 years (IQR 7.4–14.6); $p = 0.9$]. The duration of colchicine treatment before discontinuation was also comparable between these two groups [3.7 years (IQR 1.7–6.5) vs 3.8 years (IQR 1.8–7.2); $p = 0.6$].

Table 1 Baseline demographic, clinical, and disease classification features of patients according to colchicine status

	Group 1 (colchicine re-initiation; $n = 31$)	Group 2 (sustained colchicine-free remission; $n = 96$)	Group 3 (continuous colchicine therapy; $n = 118$)	p-Value
Demographic features				
Sex, *n* (%)				
Female	12 (38.7)	39 (40.6)	52 (44.1)	0.8
Male	19 (61.3)	57 (59.4)	66 (55.9)	
Age at onset, years, median (IQR 25–75)	5.2 (1.2–7.4)	4.7 (2.4–6.7)	4.2 (2.5–6.6)	0.9
Age at diagnosis, years, median (IQR 25–75)	6.6 (4.4–9.2)	6.3 (4–9.3)	6.1 (4–8.9)	
Follow-up period from the diagnosis (years), median (IQR 25–75)	8.7 (7.7–10.8)	9.2 (6.8–12.4)	5.4 (2.8–8.7)	< 0.001**
Age at colchicine cessation (years), median (IQR 25–75)	11.2 (8–13.8)	11.4 (7.4–14.6)	–	0.9
Duration of colchicine treatment (years), median (IQR 25–75)	3.7 (1.7–6.5)	3.8 (1.8–7.2)	5.4 (2.8–8.7)	0.02*
Follow-up period from the colchicine discontinuation (years), median (IQR 25–75)	4.6 (2.7–7.5)	4.9 (1.7–7.1)	–	0.6
Attack-free duration at the time of colchicine discontinuation (months), median (IQR 25–75)	25 (8.2–60)	24 (12–36)	–	0.6
Family history of FMF, *n* (%)	4 (12.9)	35 (36.5)	65 (55.1)	< 0.001**
Consanguinity, *n* (%)	5 (16.1)	28 (29.2)	20 (16.9)	0.07
Clinical findings				
Fever, *n* (%)	23 (74.2)	70 (72.9)	105 (89)	0.007*
Abdominal pain, *n* (%)	28 (90.3)	81 (80.4)	110 (93.2)	0.1
Chest pain, *n* (%)	6 (19.4)	7 (7.3)	25 (21.2)	0.01*
Arthritis, *n* (%)	7 (22.6)	11 (11.5)	28 (23.7)	0.06
Arthralgia, *n* (%)	15 (48.4)	43 (44.8)	77 (65.3)	0.08
Erysipelas like erythema, *n* (%)	1 (3.2)	0 (0)	10 (8.5)	0.004*
Exertional leg pain, *n* (%)	5 (16.1)	21 (21.9)	46 (39)	0.005*
Laboratory findings				
CRP (mg/dL), median (IQR 25–75)	1.2 (0.6–3)	1.8 (1–2)	–	> 0.05
Serum amyloid A (mg/L), median (IQR 25–75)	2.1 (0–4.2)	3.1 (1–4.6)	–	> 0.05
ESR (mm/h), median (IQR 25–75)	5.5 (0–11)	6.1 (0–12.1)	–	> 0.05
Classification criteria fulfillment				
Fulfilling the Eurofever/PRINTO classification criteria, *n* (%)	17 (54.8)	52 (54.2)	103 (87.3)	< 0.001**
Fulfilling the Tel- Hashomer criteria, *n* (%)	27 (87.1)	92 (95.8)	118 (100)	< 0.001**

Blank cells indicate that the variant was not observed in the respective group, – indicates that data were not applicable for that group

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *FMF* familial Mediterranean fever, *IQR* interquartile range, *PRINTO* Pediatric Rheumatology International Trials Organization

p-Values were calculated using the Chi-square or Fisher's exact test as appropriate. Statistically significant values are shown in italics, *$p < 0.05$; **$p < 0.001$, all other comparisons were not statistically significant

At the time of colchicine discontinuation, the median attack-free period was 25 months (IQR 8.2–60) in group 1 and 24 months (IQR 12–36) in group 2, with no significant difference between groups ($p = 0.6$). Similarly, the median follow-up duration after colchicine discontinuation did not differ between group 1 and 2 [4.6 years (IQR 2.7–7.5) vs 4.9 years (IQR 1.7–7.1); $p = 0.6$], respectively.

The median attack-free duration after colchicine discontinuation was 8 months (IQR 3.0–15.3), and the median time interval between colchicine cessation and re-initiation was 14.9 months (IQR 6.6–49.5) in group 1. Colchicine was restarted because of recurrent attacks accompanied by elevated acute-phase reactants in all cases. A Kaplan–Meier survival analysis demonstrated sustained colchicine-free survival in the majority of patients over time, and median colchicine-free survival was not reached during the follow-up (Fig. 1).

Colchicine was discontinued by physicians in 77 (60.6%) patients and by patients/parents in 50 (39.4%), with discontinuation in the latter group because of non-compliance. It is noteworthy that patients in whom discontinuation was requested by family may not have met all physician-defined criteria for discontinuation and may have had less structured monitoring after cessation. Of the 96 patients in group 2 who were not restarted on colchicine, 59 (61.5%) had their colchicine discontinued by their physician. Of the 31 patients in group 1 who were restarted on colchicine, 18 (58.1%) had their colchicine discontinued by their physician.

The frequency of a first-degree family history of FMF differed significantly among the three groups ($p < 0.001$). It was lowest in group 1 (12.9%), intermediate in group 2

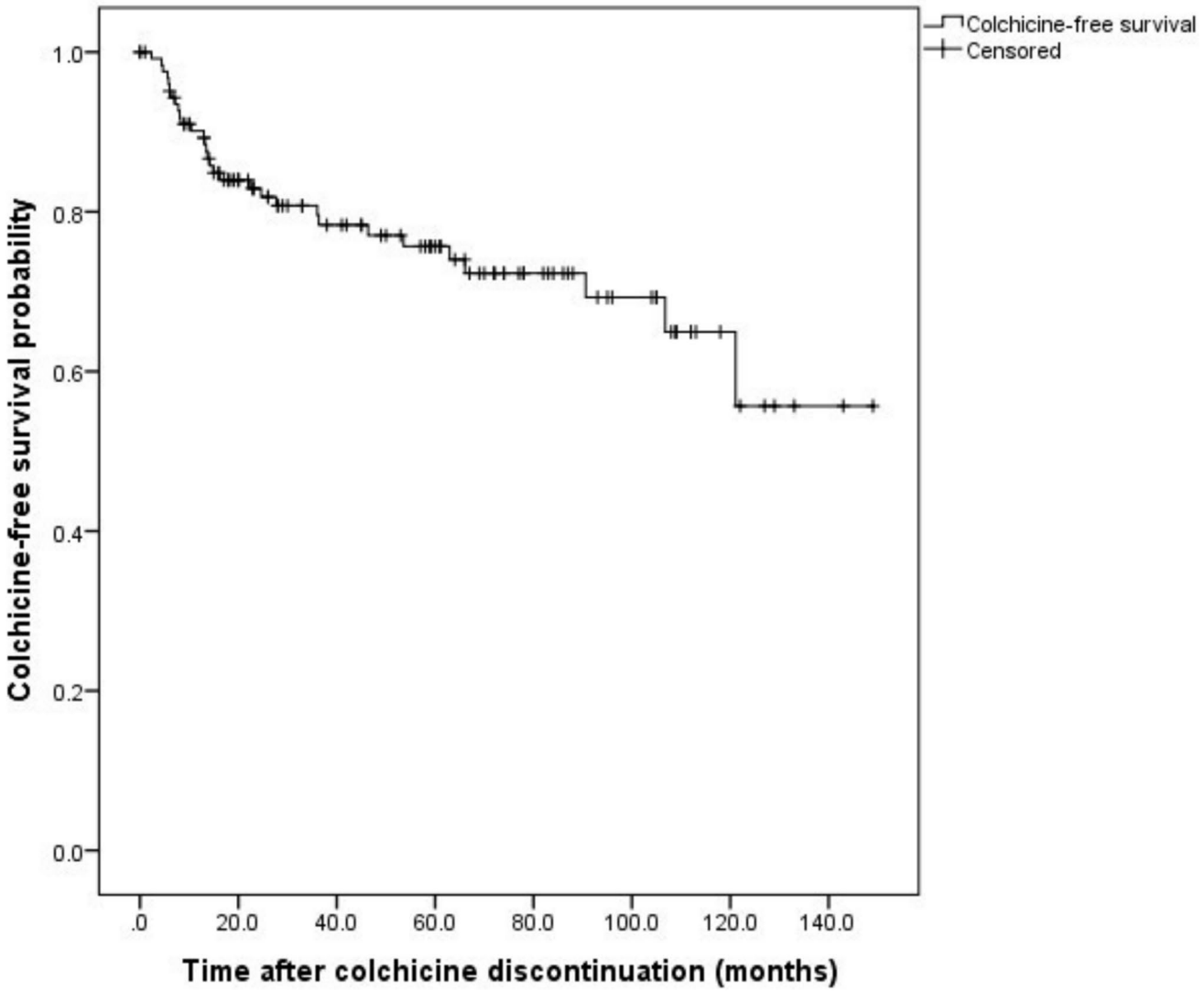


Fig. 1 Kaplan–Meier curve showing colchicine-free survival after colchicine discontinuation in pediatric patients with familial Mediterranean fever. Re-initiation of colchicine was defined as the event, whereas patients who remained colchicine free at the last follow-up were censored

(36.5%), and highest in group 3 (55.1%), with significant differences observed between all groups. The median ISSF score before colchicine discontinuation was 0 in both groups 1 and 2, with no significant difference ($p = 0.6$). In group 1, the median ISSF score at the time of colchicine re-initiation increased to 3 (IQR 1–6).

3.2 Clinical and Demographic Features

The frequency of fever differed significantly among the three groups ($p = 0.007$). Fever was more common in group 3 (89.0%) than in group 1 (74.2%) and group 2 (72.9%), while no significant difference was observed between groups 1 and 2. Chest pain ($p = 0.01$), arthritis ($p = 0.01$), arthralgia ($p = 0.008$), and erysipelas-like erythema ($p = 0.01$) demonstrated a similar distribution pattern across the groups: each was significantly more frequent in group 3 (21.2%, 23.7%, 65.3%, and 8.5%, respectively) compared with group 2 (7.3%, 8.3%, 44.8%, and 0%), while group 1 (19.4%, 22.6%, 48.4%, and 3.2%) showed intermediate frequencies without statistically significant differences from either group 2 or group 3. Exercise-induced leg pain differed significantly among the three groups ($p = 0.005$). It was more frequent in group 3 (39.0%) than in groups 1 (16.1%) and 2 (21.9%), whereas no significant difference was observed between groups 1 and 2. The frequency of abdominal pain did not differ significantly among the three groups ($p = 0.1$). At the time of colchicine discontinuation, all patients were in clinical remission without active symptoms.

At the time of colchicine discontinuation, all patients had normal CRP, ESR, and SAA levels (Table 1). During the follow-up, no persistent elevation of inflammatory markers necessitating re-initiation of treatment was observed, and no cases of amyloidosis were detected.

3.3 *MEFV* Genotype Patterns Across Study Groups

The frequency of heterozygous exon 10 variants differed significantly across the three groups ($p = 0.03$). While no significant difference was observed between groups 1 and 2 (64.5 vs 57.3), both groups had a significantly higher prevalence of these variants than group 3 (43.2). There was no statistically significant difference in the frequency of the *M694V* single variant across the groups, with rates of 29.0%, 33.3%, and 26.3% in groups 1, 2, and 3, respectively ($p = 0.5$). Biallelic pathogenic variants were significantly more common in group 3 (32.2%) compared with group 1 (12.9%) and group 2 (3.1%), and were also more frequent in group 1 than in group 2 (12.9% vs 3.1%) [$p < 0.001$]. The frequency of the *E148Q* single-allele variant differed significantly among the groups ($p < 0.001$). It was significantly more common in groups 1 and 2 than in group 3, whereas no statistically significant difference was observed between groups 1 and 2 ($p < 0.001$). Detailed genotype distributions are shown in Table 2.

3.4 Disease Classification Status Across Study Groups

Fulfillment of the Eurofever/PRINTO classification criteria differed significantly among the three groups ($p < 0.001$). The proportion of patients meeting the criteria was significantly higher in group 3 (87.3%) than in groups 1 (54.8%) and 2 (54.2%), whereas no statistically significant difference was observed between groups 1 and 2. Fulfillment of the Tel-Hashomer criteria varied significantly across the three groups ($p = 0.001$). All patients in group 3 met the criteria (100%), representing a significantly higher rate than in group 1 (87.1%) and group 2 (95.8%), whereas the difference between groups 1 and 2 was not statistically significant.

3.5 Colchicine Dosing Patterns

An age-adjusted low initial colchicine dose was observed in eight patients (25.8%) in group 1, 31 patients (32.3%) in group 2, and five patients (4.2%) in group 3. The use of a low initial dose was significantly more frequent in groups 1 and 2 compared with group 3 ($p < 0.001$). The proportion of patients receiving an age-adjusted appropriate dose versus a low dose of colchicine at the time of discontinuation was similar in groups 1 and 2, with no statistically significant difference between the groups ($p = 0.8$).

4 Discussion

Colchicine was discontinued in 5.48% of patients, and 4.14% of the overall cohort maintained sustained colchicine-free remission during a median follow-up of 4.91 years. Among those in whom treatment was stopped, nearly three-quarters remained off therapy without relapse. Although lifelong colchicine therapy remains the cornerstone of FMF management, accumulating literature suggests that disease severity and treatment requirements vary substantially, particularly in childhood FMF, and that a small but consistent subset of patients may experience a milder disease course permitting dose reduction or discontinuation under close supervision [16, 17, 19]. In our cohort, patients in whom colchicine was discontinued clustered within a clinically and genetically milder disease spectrum compared with those who continued therapy, who exhibited more frequent systemic and musculoskeletal manifestations and a higher prevalence of biallelic pathogenic variants. However, despite this overall phenotypic gradient, baseline clinical, demographic, and genetic characteristics did not clearly distinguish patients

Table 2 Distribution of Mediterranean fever gene (*MEFV*) variants in the three groups

MEFV variant	Group 1 (colchicine re-initiation; $n = 31$)	Group 2 (sustained colchicine-free remission; $n = 96$)	Group 3 (continuous colchicine therapy; $n = 118$)	*p*-Value
M694V/–	9 (29.0%)	32 (33.3%)	31 (26.3%)	0.5
E148Q/-	7 (22.6%)	31 (32.3%)	11 (9.3%)	< 0.001*
V726A/–	5 (16.1%)	13 (13.5%)	8 (6.8%)	
K695R/–	2 (6.5%)	2 (2.1%)	1 (0.8%)	
A744S/–	0 (0%)	4 (4.2%)	0 (0%)	
R761H/–	3 (9.7%)	1 (1.0%)	1 (0.8%)	
M680I/–	1 (3.2%)	3 (3.1%)	9 (7.6%)	
M694I/–	0 (0%)	0 (0%)	1 (0.8%)	
P369S/–	0 (0%)	0 (0%)	2 (1.7%)	
M694V/V726A	1 (3.2%)	2 (2.1%)	10 (8.5%)	
M694V/M680I	2 (6.5%)	1 (1.0%)	15 (12.7%)	
M694V/E148Q	0 (0%)	4 (4.2%)	6 (5.1%)	
M680I/V726A	0 (0%)	0 (0%)	5 (4.2%)	
V726A/E148Q	0 (0%)	1 (1.0%)	0 (0%)	
M680I/E148Q	0 (0%)	0 (0%)	3 (2.5%)	
M694I/V726A	0 (0%)	0 (0%)	1 (0.8%)	
M694V/R761H	0 (0%)	0 (0%)	3 (2.5%)	
V726A/R761H	0 (0%)	0 (0%)	2 (1.7%)	
M680I/R761H	0 (0%)	0 (0%)	1 (0.8%)	
M694V/M694I	0 (0%)	0 (0%)	2 (1.7%)	

*$p < 0.001$. All other pairwise comparisons were not statistically significant. Cells with 0 (0%) indicate that the variant was not observed in the respective group. Exon 10 variants include M694V, M680I, V726A, M694I, A744S, K695R, and R761H

who later required reinitiation of colchicine from those who maintained long-term remission. To our knowledge, this study represents one of the largest pediatric cohorts and the longest follow-up series evaluating outcomes after colchicine discontinuation in children with FMF.

An earlier study from our group [13] reported that colchicine could be discontinued in 3.58% of pediatric patients with FMF, with 2.6% remaining off treatment during a median follow-up of 37.4 months. The present study considerably extends these findings by evaluating a larger cohort with a substantially longer follow-up period and by providing a more detailed comparative analysis of patients who maintained colchicine-free remission and those who required re-initiation of treatment. Comparable rates of sustained remission after colchicine withdrawal have also been reported by others, despite differences in cohort characteristics, age distributions, and follow-up durations [12, 14–16]. Collectively, these data suggest that while colchicine-free remission remains uncommon, it is a reproducible phenomenon across diverse FMF populations.

Consistent with the overall phenotypic gradient described above, patients who continued colchicine (group 3) represented a more severe disease spectrum, with significantly higher frequencies of fever, chest pain, arthritis, arthralgia, exercise-induced leg pain, and erysipelas-like erythema. In contrast, patients who discontinued colchicine clustered into a milder clinical profile. The use of cumulative clinical features and ISSF scoring further supports that patients selected for colchicine discontinuation represent a milder disease spectrum rather than a diagnostically uncertain subgroup. Notably, however, those who maintained sustained remission (group 2) and those who later required re-initiation of colchicine (group 1) were clinically indistinguishable at baseline, with no meaningful differences in their initial manifestations. Although abdominal pain was the most common symptom across all groups, its similar distribution limits its discriminatory value for predicting withdrawal success. Overall, these findings underscore the current difficulty of identifying relapse-prone patients solely on the basis of initial clinical characteristics. The absence of sustained subclinical inflammation and amyloidosis during follow-up supports the safety of colchicine discontinuation in carefully selected pediatric patients with FMF.

Genotype–phenotype associations have long been recognized in FMF, particularly regarding exon 10 variants and the *M694V* mutation [20–23]. Our findings reveal a distinct genetic gradient among patients who successfully discontinue colchicine compared with those who require continuous therapy. The most significant genetic factor associated with treatment continuation was the presence

of biallelic pathogenic variants, predominantly observed in group 3. The frequency of these biallelic mutations decreased progressively from those requiring treatment re-initiation to those maintaining drug-free remission. This "dose–response" relationship suggests that a higher mutation burden, particularly involving two pathogenic alleles, serves as a substantial barrier to successful colchicine withdrawal and reflects a more severe disease phenotype. A key observation in our cohort was the distribution of single-allele (heterozygous) variants in exon 10. These variants were significantly more prevalent in both groups 1 and 2 than in group 3. This suggests that clinicians often identify patients with a single exon 10 mutation as ideal candidates for a trial of treatment cessation, likely because of their perceived milder clinical course. However, the finding that these heterozygous variants were similarly distributed between patients who remained in remission and those who relapsed indicates that, while a single exon 10 mutation may allow discontinuation, it does not reliably predict long-term success on its own. The distribution of the M694V single variant was remarkably similar across all three study groups. This implies that the presence of a single M694V variant alone may not necessarily preclude consideration of colchicine discontinuation in carefully selected patients, provided that deep clinical remission has been achieved. Furthermore, the *E148Q* single-allele variant was notably more common in patients who were considered for discontinuation than in those who continued therapy. As a low-penetrance variant, it is highly frequent in group 2, supporting the idea that such genotypes are associated with a milder disease spectrum [24–26]. Nevertheless, like the other single-allele variants, *E148Q* was not a definitive predictor of success, as its frequency did not differ significantly between groups 1 and 2.

An additional finding was a difference in first-degree family history of FMF across the study groups, with the lowest rate in patients who required colchicine re-initiation and the highest in those who continued treatment. Although this finding may appear counterintuitive, it should be interpreted cautiously. A family history may influence both disease recognition and follow-up patterns, and in real-life clinical practice, it may also affect treatment adherence, physician awareness, and thresholds for treatment continuation or discontinuation. Given the retrospective design, no firm conclusion can be drawn regarding the independent role of family history in predicting colchicine-free remission.

Classification criteria also provided insight into disease heterogeneity. Patients who discontinued colchicine were more likely to meet the Tel-Hashomer criteria than the Eurofever/PRINTO classification criteria. As the Tel-Hashomer criteria rely primarily on clinical features without mandatory genetic confirmation, they encompass a broader phenotypic spectrum, including milder and atypical cases [24, 27]. In contrast, the Eurofever/PRINTO criteria preferentially capture patients with a more typical and genetically supported FMF phenotype [28]. The lower fulfillment rate of Eurofever/PRINTO criteria in the discontinuation groups likely reflects the milder, less typical phenotype of this subgroup, as these criteria preferentially identify patients with a more classical, genetically supported FMF presentation. In this context, failure to meet these stricter criteria may serve as an indirect marker of a milder disease course. This discrepancy is therefore expected in real-life cohorts enriched for patients with milder disease in whom colchicine discontinuation is considered.

Colchicine dosing patterns provide additional insight into the observed differences in disease severity across the groups. In line with previous studies [14, 16], patients who discontinued colchicine were more likely to have received lower age-adjusted doses than those who continued therapy. This finding likely reflects a lower underlying inflammatory burden in these patients rather than a direct causal relationship between colchicine dose and subsequent relapse risk. The use of lower-than-recommended colchicine doses in some patients likely reflects individualized treatment decisions based on a milder disease phenotype or tolerability, rather than a standardized initial treatment strategy.

Severity scoring yielded similar conclusions. Both groups in whom colchicine was discontinued had low ISSF scores prior to cessation, whereas ISSF scores increased in patients who required re-initiation. Although no definitive severity threshold could be established, these findings suggest that a severity assessment may inform clinical decision making when considering discontinuation of colchicine [29].

The control group in this study was not intended to predict colchicine discontinuation; rather, it was intended to provide a clinical and genetic context. Patients who continued colchicine therapy represented a more severe end of the FMF spectrum, reinforcing the concept that sustained colchicine-free remission occurs predominantly in patients with milder disease [20, 23, 30, 31].

Beyond conventional inflammatory markers such as CRP, ESR, and SAA, emerging evidence suggests that molecular biomarkers may provide a more sensitive assessment of subclinical inflammation. Recent studies have highlighted the potential role of interferon-related signatures and other molecular markers in refining disease activity assessment and prognosis in autoinflammatory conditions [32].

Although such biomarkers were not available in our retrospective dataset, their integration into future prospective

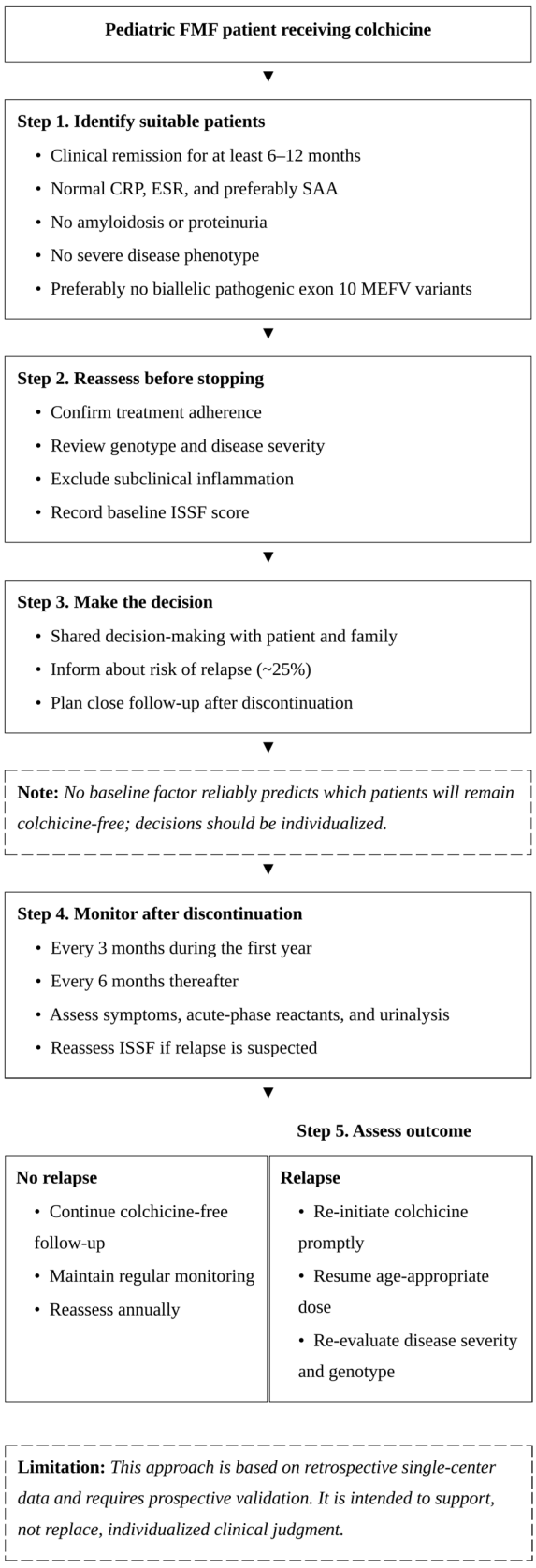


Fig. 2 Proposed clinical approach to colchicine discontinuation in pediatric familial Mediterranean fever (FMF). This flowchart summarizes a practical decision-making framework based on retrospective cohort data. It is intended to support clinical judgment and should not replace an individualized patient assessment. *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ISSF* International Severity Score for FMF, *MEFV* Mediterranean fever gene, *SAA* serum amyloid *A*

studies may improve the identification of patients who can safely discontinue colchicine. Based on these findings, a practical flowchart for considering colchicine discontinuation in carefully selected pediatric patients with FMF is proposed in Fig. 2.

Several limitations merit consideration. The retrospective single-center design may limit generalizability, and biomarkers of subclinical inflammation were not uniformly available. Patients with homozygous exon 10 variants were excluded from the colchicine-withdrawal comparison because discontinuation is not clinically acceptable in this group owing to the established risk of severe disease and amyloidosis. Including such patients would have introduced a clinically artificial comparison rather than reduced selection bias. This approach is consistent with EULAR recommendations and prior discontinuation studies, and the observed genetic differences therefore reflect real-life clinical practice rather than methodological bias. The major strengths of this study include its large well-characterized pediatric cohort and the extended follow-up period after colchicine discontinuation, which allow for a robust evaluation of long-term outcomes. In addition, the structured comparison of clinical, genetic, and treatment-related variables across distinct outcome groups provides a comprehensive framework for understanding the heterogeneity of treatment response in pediatric FMF.

5 Conclusions

In this large pediatric FMF cohort with a long-term follow-up, colchicine discontinuation was feasible in a small but consistent subset of patients, most of whom maintained sustained remission. While patients requiring continuous therapy exhibited a more severe clinical and genetic profile, no robust baseline predictors distinguished those who remained colchicine free from those who relapsed. These findings highlight the need for individualized withdrawal decisions and prospective studies incorporating

biomarkers to better guide safe discontinuation strategies in pediatric FMF.

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Declarations

Conflicts of Interest/Competing Interests Selen Duygu Arık, Gülşah Kavrul Kayaalp, Ayşenur Doğru Kılınç, Bengisu Menentoğlu, Büşra Başer Taşkın, Aslı Dudaklı, Ayşe Tanatar, Özlem Akgün, and Nuray Aktay Ayaz have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval The study was approved by the Ethical Committee of Istanbul University, Istanbul Medicinal Faculty (date: 05.02.2024; No: 2405744). The study was carried out and complied with the Declaration of Helsinki.

Consent to Participate Written informed consent was obtained from all patients and/or their parents or legal guardians prior to inclusion in this study.

Consent for Publication Not applicable.

Availability of Data and Material The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Authors' Contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by SDA, ÖA, and NAA. The first draft of the manuscript was written by SDA, and all authors commented on earlier versions. All authors read and approved the final manuscript.

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