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ORIGINAL RESEARCH

Sociodemographic and Clinical Determinants of Colchicine Adherence in Adults with Familial Mediterranean Fever: A Cross-Sectional Study

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ABSTRACT

Introduction: Colchicine is the cornerstone of familial Mediterranean fever (FMF) treatment, effectively preventing attacks and amyloid A (AA) amyloidosis. Its effectiveness depends on long-term adherence; however, data on adult adherence remain sparse. We aimed to evaluate colchicine adherence in adults with FMF and identify factors associated with low adherence.

Methods: This cross-sectional study consecutively enrolled adults with FMF fulfilling Livneh/Tel-Hashomer criteria and receiving colchicine for ≥3 months. Adherence was assessed using the Turkish 8-item Morisky Medication Adherence Scale (MMAS-8™) alongside sociodemographic and clinical characteristics.

Results: Of 104 patients (median age 37.6 years; 32.7% male), adherence was low, moderate, and high in 28.8%, 45.2%, and 26.0%, respectively. MMAS-8™ scores correlated with physician- and patient-rated adherence ($r=0.53$ and 0.50, respectively; $p<0.001$ for both). Low-adherence patients were younger (median ages of 31.2, 42.6, and 43.1 years; $p<0.001$), and age increased across adherence categories ($p=0.001$). In multivariable analysis, low income (≤1 × national minimum wage; odds ratio (OR) 4.78; 95% confidence interval (CI) 1.01–22.56; $p=0.04$) was associated with higher odds of low adherence, whereas older age (OR 0.92 per year; 95% CI 0.87–0.96; $p<0.001$) was associated with lower odds of low adherence (vs. moderate-high adherence). No statistically significant associations were detected between adherence and the evaluated disease activity measures, family history, or immune-mediated inflammatory diseases, and no robust association was identified between available Mediterranean fever gene (*MEFV*) genotype data and colchicine adherence.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-026-00883-w.

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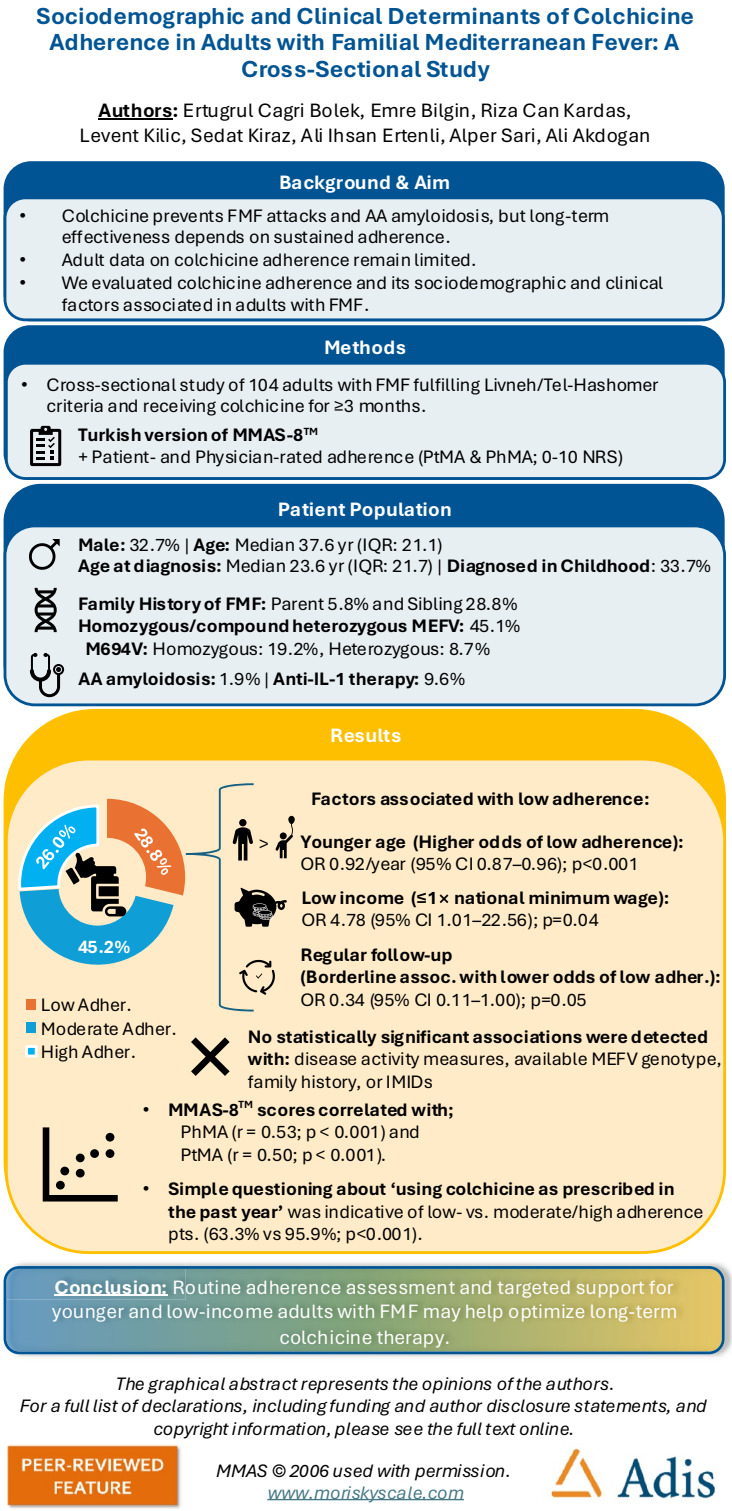
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***Conclusion*:** Nearly one-third of adult patients with FMF exhibit low adherence to colchicine. Younger age and low household income were associated with low adherence. Routine adherence assessment and targeted support for potentially vulnerable subgroups may help optimize long-term outcomes. Graphical Abstract available for this article.

Graphical Abstract:



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PEER-REVIEWED FEATURE

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Keywords: Familial Mediterranean fever; Colchicine; Medication adherence; Autoinflammatory disease; Amyloidosis; Socioeconomic factors; Young adults; Follow-up

Key Summary Points

Why carry out this study?

Colchicine is the cornerstone of familial Mediterranean fever (FMF) treatment and requires sustained long-term adherence to prevent attacks and amyloid A (AA) amyloidosis; however, data on colchicine adherence in adults with FMF remain limited.

Sociodemographic factors that may contribute to low colchicine adherence in adults with FMF, particularly age and socioeconomic status, are not well characterized.

This study evaluated colchicine adherence in adults with FMF and investigated the clinical and sociodemographic factors associated with low adherence.

What was learned from the study?

Among 104 adults with FMF, 28.8% had low, 45.2% moderate, and 26.0% high colchicine adherence. Younger age and low household income were independently associated with higher odds of low adherence. At the same time, attendance at follow-up at the physician-recommended frequency showed a borderline association with lower odds of low adherence.

No statistically significant associations were detected between adherence and the evaluated disease activity measures, family history, or immune-mediated inflammatory diseases. No robust association was identified between available *MEFV* genotype data and colchicine adherence.

These findings support routine assessment of colchicine adherence and suggest that younger and lower-income patients may benefit from more individualized adherence support and follow-up strategies.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.33758095.

INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory disorder characterized by recurrent self-limited attacks of fever and serositis due to pathogenic variants in the *MEFV* gene and dysregulated inflammasome activation [1]. Colchicine remains the cornerstone of therapy because it reduces attack frequency and, critically, prevents amyloid A (AA) amyloidosis, the primary determinant of long-term morbidity and mortality in FMF [2–4]. Despite its favorable safety profile and low cost, real-world effectiveness depends on sustained adherence [3, 5, 6].

Medication adherence in FMF brings some unique challenges. The disease course is episodic; asymptomatic intervals may diminish perceived need for continuous treatment, while brief clinic encounters often occur during attack-free periods, limiting clinicians' ability to infer adherence from cross-sectional disease activity alone [2, 7, 8]. Inadequate assessment of adherence risks misclassifying apparent "colchicine resistance," potentially prompting unnecessary escalation to biologic therapy [7, 9, 10]. Although data on adherence in adults with FMF are sparse, adherence has occasionally been examined in pediatric cohorts and is heterogeneous across measurement tools and reported rates [5, 8, 10–25]. Moreover, the social determinants of adherence among adults with FMF, such as income level, educational attainment, employment status, and visit regularity, need to be clearly defined [8, 10].

To address these gaps, we conducted a cross-sectional study of adults with FMF using the Turkish-validated 8-item Morisky Medication Adherence Scale (MMAS-8™) to assess adherence to colchicine and to identify clinical and sociodemographic factors associated with low adherence [26–34].

METHODS

Study Design and Patient Population

Patients aged 18 years or older with a confirmed diagnosis of FMF, as defined by the Livneh and/or Tel-Hashomer criteria, who consecutively attended the adult rheumatology outpatient clinic at Hacettepe University (Ankara, Türkiye) over 6 months were invited to participate in the study [35, 36]. Exclusion criteria were as follows: (1) insufficient or incomplete medical records, (2) age under 18 years, (3) not currently receiving colchicine therapy for FMF or having received it for less than 3 months, (4) patients who were experiencing an attack at the time of assessment, and (5) unwillingness to participate or inability (e.g., psychiatric/cognitive disorders affecting survey reliability) to complete the drug adherence questionnaire. For patients with multiple visits during the recruitment period, we used data only from the first appropriate visit for analysis.

Data Collection

Sociodemographic and clinical characteristics, comorbidities, concurrent medications, *MEFV* variant types, and laboratory parameters related to FMF outcomes were obtained from electronic medical records. *MEFV* genotyping had been performed as part of routine clinical care and was not repeated or systematically completed for study purposes. Because genotyping was performed as part of routine clinical care at different time points and, in some patients, at other centers, analytical methods and variant coverage may have varied, and genotype data were unavailable for a subset of the cohort. Therefore, all genotype-related analyses were considered exploratory. *MEFV* variant nomenclature and available clinical genetic reports were cross-checked against the INFEVERS database [37].

Additional information was collected through patient interviews, including family and social history (number of siblings, family members affected by FMF), educational level, occupation, physical activity, and socioeconomic status, which were assessed relative to Türkiye's national minimum wage [38]. Patients were also questioned regarding attack frequency and its impact on daily life, prescribed and self-reported colchicine doses, adherence to scheduled follow-up visits, treatment duration, and self-reported adverse events. Patients and physicians (the treating rheumatologists at the end of the routine clinical encounter) provided a patient global assessment (PtGA) and physician global assessment (PhGA) of disease activity, respectively, as well as patient-rated medication adherence (PtMA) and physician-rated medication adherence (PhMA), using a 0–10 numeric rating scale (NRS). "Persistently elevated acute phase reactants" were defined as C-reactive protein (CRP) and/or serum amyloid A values remaining above the upper limit of normal during clinically attack-free visits on repeated measurements over ≥ 1 year, in the absence of any other identifiable cause of inflammation. "The regular attack pattern over the last year" was defined as recurrent attacks with a relatively stable, predictable periodicity (similar frequency and interval between episodes), as reported by the patient.

Medication Adherence Assessment

Medication adherence to colchicine therapy was evaluated using the validated Turkish version of MMAS-8™ (Supplementary Table 1) [29–34]. MMAS-8™ consists of eight items. Each of the first seven items has two possible responses (yes/no), while the eighth item is answered with a 5-point Likert scale. The possible total medication adherence score ranges between 0 and 8, and the higher the score, the better the adherence level. A total score < 6 is considered low adherence, while a total score of ≥ 6 but < 8 indicates moderate adherence, and a score of 8 indicates high adherence [29–34].

MMAS-8™ is a widely used self-report questionnaire that assesses patient adherence to prescribed therapies across various chronic diseases [26–34]. The scale has also been validated in Turkish across various chronic conditions, including hypertension, type 2 diabetes, Behçet's syndrome, and asthma/chronic obstructive pulmonary disease, demonstrating high internal

consistency (Cronbach's α ranging from 0.71 to 0.89) and linguistic validity [29–31, 34].

During the visit, MMAS-8™ was self-administered in a standardized manner, supervised by a physician (E.C.B., E.B., or R.C.K.) who was not involved in the patient's clinical evaluation and, where feasible, was blinded to the patient's clinical data and FMF-related outcomes. For participants unable to read, a physician (R.C.K.) read the questionnaire items aloud and recorded the participant's responses under the same standardized conditions. Patients were grouped accordingly for subsequent analysis.

Ethical Considerations

The study protocol was approved by the Non-interventional Clinical Research Ethics Committee of Hacettepe University (Approval No. GO18/542) and was conducted in accordance with the principles of the Declaration of Helsinki [39]. Written informed consent was obtained from all participants included in the study. MMAS-8™, content, name, and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from Morisky Medication Adherence Research (MMAR), LLC. The authors obtained a license to use the validated Turkish version of MMAS-8™. MMAS © 2006 used with permission. www.moriskyscale.com.

Statistical Analysis

No formal a priori sample-size calculation was performed; the study included all eligible consecutive patients recruited during the prespecified 6-month study period. All analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10.4.0 (GraphPad Software, Boston, Massachusetts, USA). Normality was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were expressed as median (interquartile range) or mean ± standard deviation, depending on distribution, while categorical variables were summarized as frequencies and percentages.

Group comparisons for categorical variables were conducted using the chi-square test or Fisher's exact test, as appropriate. For ordinal categorical variables, trends across ordered groups were evaluated using the linear-by-linear association chi-square test (trend test). Continuous variables were compared using the Mann–Whitney U test or Student's t test, depending on normality. For comparisons among three or more groups, one-way analysis of variance (ANOVA) (for parametric data) or the Kruskal–Wallis test (for non-parametric data; KW) was applied, followed by Bonferroni or Dunn's post hoc tests, respectively, to identify intergroup differences. For ordered group comparisons to assess monotonic trends, the Jonckheere–Terpstra test (JT) was used. Correlation analyses between continuous variables were evaluated using Spearman's rank correlation coefficient for non-normally distributed data and Pearson's correlation coefficient for normally distributed variables.

Candidate variables for multivariable logistic regression were selected on the basis of clinical relevance, the results of univariable analyses ($p \leq 0.20$), and their suitability as independent predictors. Variables with substantial conceptual overlap with the adherence outcome, redundancy, collinearity, or sparse category counts were not included in the multivariable model. The remaining candidate variables were entered into a binary logistic regression model and reduced using the backward likelihood-ratio method. Age was analyzed as a continuous variable, whereas all other covariates were coded as binary. Multicollinearity was assessed before model entry using variance inflation factors and tolerance values. Given the limited number of low-adherence events, the multivariable analyses were considered exploratory and the estimates were interpreted cautiously.

Missing data were not imputed; analyses used available cases for each variable, with variable-specific denominators indicated where applicable. All statistical tests were two-tailed, and a p value < 0.05 was considered statistically significant.

Table 1 Demographic and clinical characteristics of patients according to MMAS-8™

	All patients (*n* = 104)	Low adherence (*n* = 30)	Moderate adherence (*n* = 47)	High adherence (*n* = 27)	*p*
Demographics & family history					
Sex, male, *n* (%)	34 (32.7)	7 (23.3)	20 (42.6)	7 (25.9)	0.15
Age, years, median (IQR)	37.6 (21.1)	31.2 (15.2)	42.6 (17.2)	43.1 (18.0)	< 0.001*
Age at diagnosis, years, median (IQR)	23.6 (21.7)	18.3 (16.5)	28.1 (23.0)	25.9 (25.0)	0.001*
Symptom-onset to diagnosis, years, median (IQR)	7.6 (14.0)	4.0 (9.4)	9.5 (19.3)	3.5 (18.3)	0.09
Pediatric-diagnosed disease, *n* (%)	35 (33.7)	14 (46.7)	12 (25.5)	9 (33.3)	0.16
Parental history of FMF, *n* (%)[a]	6 (5.8)	3 (10.0)	2 (4.3)	1 (3.8)	0.51
Sibling history of FMF, *n* (%)	30 (28.8)	7 (23.3)	14 (29.8)	9 (33.3)	0.69
Family history of AA amyloidosis, *n* (%)[a]	10 (9.7)	4 (13.3)	3 (6.4)	3 (11.5)	0.57
MEFV gene analysis					
Homozygous					
M694V/M694V, *n* (%)	20 (19.2)	8 (26.7)	6 (12.8)	6 (22.2)	0.29
Other homozygous variants, *n* (%)	6 (5.8)	5 (16.7)	1 (2.1)	0 (0)	0.009*
Compound heterozygous					
M694V/other variant, *n* (%)	17 (16.3)	3 (10.0)	10 (21.3)	4 (14.8)	0.41
Other compound heterozygous variants, *n* (%)	4 (3.8)	1 (3.3)	2 (4.3)	1 (3.7)	0.98
Heterozygous					
M694V heterozygous, *n* (%)	9 (8.7)	2 (6.7)	5 (10.6)	2 (7.4)	0.80
Other heterozygous variants, *n* (%)	5 (4.8)	0 (0)	3 (6.4)	2 (7.4)	0.34
No pathogenic variant detected, *n* (%)	6 (5.8)	2 (6.7)	2 (4.3)	2 (7.4)	0.83
MEFV genotype data unavailable, *n* (%)	37 (35.6)	9 (30.0)	18 (38.3)	10 (37.0)	0.75
Disease activity					
CRP at last visit, mg/dL, median (IQR)	0.4 (0.6)	0.4 (0.7)	0.4 (0.5)	0.3 (0.6)	0.58
ESR at last visit, mm/h, median (IQR)	10.0 (13.0)	10.0 (20.5)	10.0 (13.0)	11.0 (8.6)	0.90
Persistently elevated APR, *n* (%)	16 (15.4)	5 (16.7)	7 (14.9)	4 (14.8)	0.98
PhGA (NRS; 0–10), median (min–max)	4.0 (1–9)	4.0 (1–8)	4.0 (1–9)	4.0 (1–8)	0.73
PtGA (NRS; 0–10), median (min–max)	5.0 (1–10)	5.0 (1–10)	5.0 (1–10)	5.0 (1–9)	0.45
Number of FMF attacks					
In last 3 months, median (min–max)	0 (0–10)	0 (0–4)	0 (0–3)	1 (0–10)	0.79

Table 1 continued

	All patients ($n = 104$)	Low adherence ($n = 30$)	Moderate adherence ($n = 47$)	High adherence ($n = 27$)	p
In last 6 months, median (min–max)	1 (0–10)	1 (0–5)	1 (0–6)	1 (0–10)	0.85
In last 12 months, median (min–max)	2 (0–10)	1 (0–10)	2 (0–10)	1 (0–10)	0.98
FMF attack course					
Regular attack pattern in last 1 year, *n* (%)	16 (15.4)	4 (13.3)	7 (14.9)	5 (18.5)	0.86
Having a potential trigger for attacks, *n* (%)	67 (64.4)	21 (70.0)	32 (68.1)	14 (51.9)	0.28
FMF attack characteristics					
Fever, *n* (%)	92 (88.5)	24 (80.0)	44 (93.6)	24 (88.9)	0.19
Peritonitis, *n* (%)	95 (91.3)	28 (93.3)	43 (91.5)	24 (88.9)	0.84
Pleuritis, *n* (%)	32 (30.8)	7 (23.3)	19 (40.4)	6 (22.2)	0.15
Pericarditis, *n* (%)	19 (18.3)	7 (23.3)	7 (14.9)	5 (18.5)	0.65
Orchitis, *n* (%)	1 (1.0)	0 (0)	1 (2.1)	0 (0)	0.54
Arthritis, *n* (%)	56 (53.8)	22 (73.3)	21 (44.7)	13 (48.1)	0.04*
Erysipelas-like erythema, *n* (%)	22 (21.2)	10 (33.3)	8 (17.0)	4 (14.8)	0.15
Most bothersome domain, reported by Pts[a]					
Fever only, *n* (%)	7 (6.8)	4 (13.3)	0 (0)	3 (11.1)	0.04*
Serositis only, *n* (%)	19 (18.4)	9 (30.0)	7 (15.2)	3 (11.1)	
Arthritis only, *n* (%)	1 (1.0)	1 (3.3)	0 (0)	0 (0)	
Fever + serositis, *n* (%)	65 (63.1)	11 (36.7)	35 (76.1)	19 (70.4)	
Fever + arthritis, *n* (%)	4 (3.9)	2 (6.7)	2 (4.3)	0 (0)	
Serositis + arthritis, *n* (%)	7 (6.8)	3 (10.0)	2 (4.3)	2 (7.4)	
FMF-associated IMIDs & complications					
IBD, *n* (%)	2 (1.9)	0 (0)	0 (0)	2 (7.4)	0.05*
SpA, *n* (%)	19 (18.3)	5 (16.7)	7 (14.9)	7 (25.9)	0.48
Vasculitis, *n* (%)	1 (1.0)	1 (3.3)	0 (0)	0 (0)	0.29
Prolonged febrile myalgia, *n* (%)	7 (6.7)	4 (13.3)	1 (2.1)	2 (7.4)	0.16
Proteinuria, *n* (%)	4 (3.8)	1 (3.3)	1 (2.1)	2 (7.4)	0.52
AA amyloidosis, *n* (%)	2 (1.9)	0 (0)	1 (2.1)	1 (3.7)	0.59
ESKD including HD, PD or RT, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	1
History of abdominal surgery, *n* (%)	44 (42.3)	9 (30.0)	21 (44.7)	14 (51.9)	0.23

Table 1 continued

	All patients ($n = 104$)	Low adherence ($n = 30$)	Moderate adherence ($n = 47$)	High adherence ($n = 27$)	p
Other					
Use of biological therapy for FMF, *n* (%)	17 (16.3)	7 (23.3)	5 (10.6)	5 (18.5)	0.32
Anti-IL-1, *n* (%)	10 (9.6)	4 (13.3)	3 (6.4)	3 (11.1)	0.57
Anti-IL-6, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	1
Anti-TNF, *n* (%)	7 (6.7)	3 (10.0)	2 (4.3)	2 (7.4)	0.61
Having non-inflammatory comorbidities, *n* (%)	33 (31.7)	6 (20.0)	18 (38.3)	9 (33.3)	0.24
Non-FMF medication use, *n* (%)	42 (40.4)	7 (23.3)	20 (42.6)	15 (55.6)	0.04*

For variables presented as a single multicategory distribution (e.g., most bothersome domain), the p value shown for the first category represents the overall comparison across the complete category distribution. For individual *MEFV* genotype categories, p values represent row-specific comparisons across adherence groups. Individual IMIDs were reported separately and were not mutually exclusive; therefore, percentages across IMID categories should not be summed. Note: MMAS © 2006 used with permission. www.moriskyscale.com

Abbreviations: *AA* amyloid A, *APR* acute phase reactants, *CRP* C-reactive protein, *ESKD* end-stage kidney disease, *ESR* erythrocyte sedimentation rate, *FMF* familial Mediterranean fever, *HD* hemodialysis, *IBD* inflammatory bowel disease, *IL* interleukin, *IMID* immune-mediated inflammatory disease, *IQR* interquartile range, *MEFV* Mediterranean fever gene, *MMAS-8*™ 8-item Morisky Medication Adherence Scale™, *NRS* Numeric Rating Scale, *PD* peritoneal dialysis, *PhGA* physician global assessment, *PtGA* patient global assessment, *Pts* patients, *RT* renal transplantation, *SpA* spondyloarthritis, *TNF* tumor necrosis factor

[a]Data on the most bothersome domain were unavailable for one patient in the moderate-adherence group (overall $n = 103$; moderate-adherence group $n = 46$), while data on family history of AA amyloidosis and parental history of FMF were unavailable for one patient in the high-adherence group (overall $n = 103$; high-adherence group $n = 26$). Percentages were calculated on the basis of available data

*Statistically significant ($p < 0.05$)

RESULTS

Of 106 consecutively screened patients, two were excluded: one did not receive colchicine therapy, and the other could not complete the MMAS-8™ questionnaire. A total of 104 patients with FMF were included in the analysis (Table 1). The median age of the study population was 37.6 years (21.1), and 32.7% of the participants were male. One-third were diagnosed in childhood (33.7%), and nearly half carried homozygous (25.0%) or compound heterozygous (20.2%) *MEFV* variants. Most patients experienced recurrent febrile attacks (88.5%) and peritonitis (91.3%), whereas arthritis and erysipelas-like erythema were observed in 56 (53.8%) and 22 (21.2%) patients, respectively. Regarding sociodemographic features, 68 patients (65.4%) were married, and among the 103 patients with available education data, 80 (77.7%) had at least a high school education. Based on national income standards, 11 patients (10.6%), 50 (48.1%), and 43 (41.3%) were classified as low-, middle-, and high-income, respectively. Fifty-four patients (51.9%) were employed, and 75 (72.1%) attended follow-up visits at the frequency recommended by their physicians.

According to MMAS-8™, 30 patients (28.8%) showed low, 47 (45.2%) moderate, and 27 (26.0%) high adherence. Patients with low

adherence were significantly younger than those with moderate or high adherence (median ages of 31.2, 42.6, and 43.1 years, respectively; KW test; $p<0.001$), with a significant monotonic increase in age across the adherence categories (JT test; $p=0.001$). They also had a lower age at diagnosis (18.3 vs. 28.1 and 25.9 years; $p=0.001$). Homozygous *MEFV* variants other than M694V were more frequent in the low-adherence group than in the moderate- and high-adherence groups (16.7% vs. 2.1% and 0%, respectively; $p=0.009$). Arthritis during attacks was reported more frequently in the low-adherence group (73.3% vs. 44.7% and 48.1%; $p=0.04$), with a similar but non-significant pattern for erysipelas-like erythema (33.3% vs. 17.0% and 14.8%; $p=0.15$). No differences were found in sex distribution, family history of FMF, or presence of AA amyloidosis across three adherence groups. Disease activity parameters, including CRP, erythrocyte sedimentation rate, persistently elevated acute-phase reactants, PhGA, and PtGA, did not differ significantly across adherence categories (Table 1).

Comorbid immune-mediated inflammatory diseases (IMIDs) were observed in a subset of patients: 19 (18.3%) with spondyloarthritis and 2 (1.9%) with inflammatory bowel disease; however, no statistically significant differences were observed ($p=0.48$ and $p=0.05$, respectively). A total of 17 patients (16.3%) received biological therapy, predominantly anti-interleukin-1 (anti-IL-1) agents (9.6%). The overall use of any biologic and of specific subclasses (anti-IL-1; anti-interleukin-6, anti-IL-6; anti-tumor necrosis factor, anti-TNF) was similar across adherence categories ($p=0.32$, 0.57, 1.00, and 0.61, respectively). Non-inflammatory comorbidities were present in 33 patients (31.7%), and 42 patients (40.4%) reported regular use of non-FMF medications. The proportion of patients using non-FMF medications increased across the low-, moderate-, and high-adherence groups (23.3%, 42.6%, and 55.6%, respectively; $p=0.04$; $p_{trend}=0.01$). Basic demographics and clinical features are summarized in Table 1.

While education level and marital status did not differ significantly between groups, low-income status (≤1 × the national minimum wage) was more frequent in the low-adherence group (23.3% vs. 6.4% vs. 3.7%; $p=0.02$; $p_{trend}=0.02$). Employment rate and occupational activity levels were similar across groups. Most patients (72.1%) complied with the recommended visit frequency. Although the proportion was numerically lower in the low-adherence group (60.0% vs. 78.7% and 74.1%), this difference did not reach statistical significance ($p=0.20$). Regarding treatment-related variables, adherence behavior was closely aligned with reported medication use. Over the past year, 90 patients (86.5%) reported taking colchicine as prescribed; however, this proportion dropped to 63.3% in the low-adherence group, compared with 93.6% and 100% in the moderate- and high-adherence groups, respectively ($p<0.001$; $p_{trend}<0.001$). Thirty-seven patients (35.6%) reported having used colchicine obtained without a prescription or borrowed from another person, with no significant difference across adherence categories (43.3%, 34.0%, and 29.6%; $p=0.54$). The median number of colchicine boxes available at home was 2 (2), with no statistically significant difference among the three groups ($p=0.10$). Adverse events requiring temporary colchicine discontinuation (3.3%, 4.3% and 11.1%; $p=0.38$) or dose reduction (13.3%, 6.4% and 22.2%; $p=0.14$) during the preceding year were numerically more frequent in the high-adherence group, without reaching statistical significance. PtMA and PhMA scores increased across MMAS-8™ adherence categories: median scores of 7, 9, and 9 for PtMA, and 7, 8.5, and 9 for PhMA, for the low, moderate, and high adherence groups, respectively ($p<0.001$ for both comparisons). Sociodemographic factors of patients are summarized in Table 2.

Moderate positive correlations (Fig. 1 and Supplementary Table 2) were demonstrated between MMAS-8™ scores and both PhMA ($r=0.53$; $p<0.001$) and PtMA ($r=0.50$; $p<0.001$). MMAS-8™ scores were also positively correlated with patient age ($r=0.35$, $p<0.001$) and age at diagnosis ($r=0.26$, $p=0.01$). No statistically significant correlations were observed between adherence scores and disease activity measures (PhGA and PtGA; Supplementary Table 2).

Univariable two-group comparisons to evaluate factors related to low adherence (vs. moderate/high adherence) according to MMAS-8™

Table 2 Sociodemographic, work-related, and treatment adherence characteristics of patients according to MMAS-8™

	All patients (*n* = 104)	Low adherence (*n* = 30)	Moderate adherence (*n* = 47)	High adherence (*n* = 27)	*p*
Married, *n* (%)	68 (65.4)	15 (50.0)	35 (74.5)	18 (66.7)	0.09
Non-smoker, *n* (%)	67 (64.4)	22 (73.3)	28 (59.6)	17 (63.0)	0.46
No alcohol use, *n* (%)	79 (76.0)	24 (80.0)	32 (68.1)	23 (85.2)	0.21
Level of education[a]					
Illiterate, *n* (%)	2 (1.9)	0 (0)	2 (4.3)	0 (0)	0.32
Primary school graduate, *n* (%)	15 (14.6)	2 (6.7)	9 (19.6)	4 (14.8)	
Secondary school graduate, *n* (%)	6 (5.8)	1 (3.3)	4 (8.7)	1 (3.7)	
High school graduate, *n* (%)	37 (35.9)	14 (46.7)	11 (23.9)	12 (44.4)	
University graduate, *n* (%)	43 (41.7)	13 (43.3)	20 (43.5)	10 (37.0)	
Total monthly household income[b]					
≤ 1 × national minimum wage (low income), *n* (%)	11 (10.6)	7 (23.3)	3 (6.4)	1 (3.7)	0.02*
1–3 × national minimum wage (middle income), *n* (%)	50 (48.1)	8 (26.7)	25 (53.2)	17 (63.0)	
> 3 × national minimum wage (high income), *n* (%)	43 (41.3)	15 (50.0)	19 (40.4)	9 (33.3)	
Work-related impact					
Employed, *n* (%)	54 (51.9)	13 (43.3)	29 (61.7)	12 (44.4)	0.19
Daily occupational activity level (NRS; 0–10), median (min–max)[c]	6.0 (1–10)	4 (1–9)	7.0 (2–10)	5 (3–8)	0.08
Impact of FMF attacks on daily activity (NRS; 0–10), median (min–max)	8 (0–10)	8 (0–10)	8 (0–10)	8 (2–10)	0.76
Treatment compliance & monitoring					
Number of annual visits, median (IQR)	2 (1)	2 (1)	2 (1)	2 (2.3)	0.32
Attending follow-up visits at the frequency recommended by the physician, *n* (%)	75 (72.1)	18 (60.0)	37 (78.7)	20 (74.1)	0.20
Adverse event in the past year requiring temporary colchicine discontinuation, *n* (%)	6 (5.8)	1 (3.3)	2 (4.3)	3 (11.1)	0.38
Adverse event in the past year requiring colchicine dose reduction, *n* (%)	13 (12.5)	4 (13.3)	3 (6.4)	6 (22.2)	0.14
Using colchicine as prescribed in the past year, *n* (%)	90 (86.5)	19 (63.3)	44 (93.6)	27 (100.0)	< 0.001*

Table 2 continued

	All patients ($n = 104$)	Low adherence ($n = 30$)	Moderate adherence ($n = 47$)	High adherence ($n = 27$)	p
Use of colchicine without prescription or borrowed from others, *n* (%)	37 (35.6)	13 (43.3)	16 (34.0)	8 (29.6)	0.54
Number of colchicine boxes available at home, median (IQR)	2 (2)	1 (1.5)	2 (3)	2 (2.3)	0.10
Medication adherence evaluation					
Patient-rated medication adherence (NRS; 0–10), median (min–max)	9.0 (0–10)	7 (0–9)	9 (3–10)	9 (7–10)	< 0.001*
Physician-rated medication adherence (NRS; 0–10), median (min–max)	8.0 (0–10)	7 (0–9)	8.5 (3–10)	9 (7–10)	< 0.001*

For variables with multiple categories, the reported p value represents the overall comparison across the complete category distribution. Note: MMAS © 2006 used with permission. www.moriskyscale.com

Abbreviations: *FMF* familial Mediterranean fever, *IQR* interquartile range, *MMAS-8™* 8-item Morisky Medication Adherence Scale™, *NRS* Numeric Rating Scale

[a]Education data were unavailable for one patient in the moderate-adherence group (overall $n = 103$; moderate-adherence group $n = 46$); percentages were calculated on the basis of available data

[b]Income categories were defined on the basis of the official national minimum wage in Türkiye for the study year and self-reported by participants [38]

[c]The assessment was based on patient self-report among employed individuals ($n = 54$)

*Statistically significant ($p < 0.05$)

are shown in Supplementary Table 3. Univariable logistic regression (Table 3) showed that older age (odds ratio (OR) 0.92 per year; 95% confidence interval (CI) 0.88–0.96; $p < 0.001$), being married (OR 0.40; 95% CI 0.16–0.95; $p = 0.04$) and use of non-FMF medications (OR 0.34; 95% CI 0.13–0.89; $p = 0.03$) were associated with lower odds of low adherence, whereas low income (≤ 1 × national minimum wage; OR 5.33; 95% CI 1.43–19.9; $p = 0.01$) was associated with higher odds. In the final multivariable model (Table 3), older age and low income remained independently associated with low adherence. Low income (≤ 1 × national minimum wage) was associated with higher odds of low adherence (OR 4.78; 95% CI 1.01–22.56; $p = 0.04$), whereas older age was associated with lower odds of low adherence (OR 0.92 per year; 95% CI 0.87–0.96; $p < 0.001$). Attendance at follow-up at the physician-recommended frequency showed a borderline association with lower odds of low adherence (OR 0.34; 95% CI 0.11–1.00; $p = 0.05$).

DISCUSSION

In this cross-sectional analysis of 104 adults with FMF treated at a tertiary clinic, we observed that approximately 28.8% of patients had low adherence to colchicine according to MMAS-8™, with the remainder having moderate (45.2%) or high (26.0%) adherence. Notably, younger age and low socioeconomic status (defined as income ≤ 1 national minimum wage) were independently associated with low adherence, while attendance at follow-up at the frequency recommended by the physician showed a borderline association with lower odds of low adherence. These findings provide key insights into some of the characteristics and associated factors of patients with

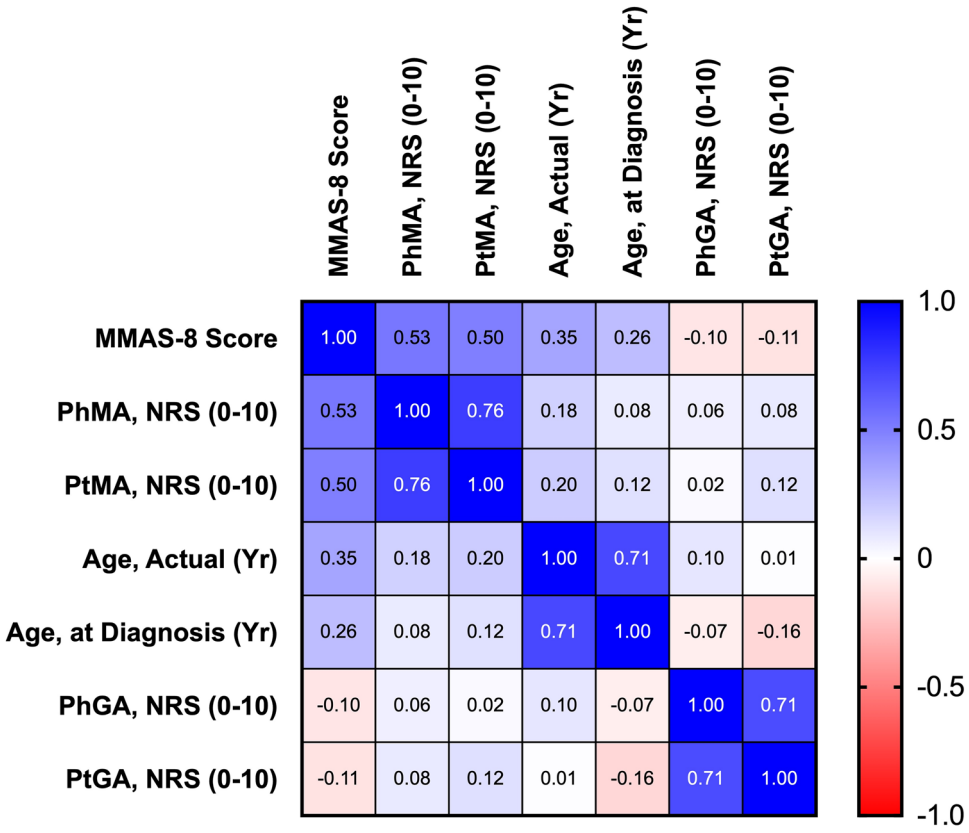


Fig. 1 Spearman correlation matrix demonstrating the relationships among MMAS-8™ scores, physician-rated medication adherence (PhMA), patient-rated medication adherence (PtMA), age, age at diagnosis, physician global assessment (PhGA), and patient global assessment (PtGA). Blue represents positive and red represents negative correlations, with coefficients ranging from − 1.0 to 1.0. The strongest positive correlations were observed between PhMA and PtMA ($r = 0.76$), age and age at diagnosis ($r = 0.71$), and PhGA and PtGA ($r = 0.71$). MMAS-8™ score showed moderate positive correlations with PhMA ($r = 0.53$) and PtMA ($r = 0.50$). Abbreviations: *MMAS-8™* 8-item Morisky Medication Adherence Scale™, *NRS* Numeric Rating Scale, *PhGA* physician global assessment, *PhMA* physician-rated medication adherence, *PtGA* patient global assessment, *PtMA* patient-rated medication adherence, *r* Spearman's rank correlation coefficient. Note: MMAS© 2006 used with permission. www.moriskyscale.com

low medication adherence, which can inform interventions to optimize long-term colchicine therapy and improve outcomes in FMF.

The frequency of low adherence in FMF in our cohort falls within the wide range of adherence rates (9.3–94%; likely reflecting heterogeneity in populations, instruments, and cutoffs) reported for other autoimmune rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), and psoriatic arthritis (PsA) [40].

Most of the available data in the literature derive from pediatric cohorts, and adherence to colchicine in FMF has been reported inconsistently across these studies, owing to differences in assessment tools and populations [13–15, 18–22, 24, 25]. Only a few studies have evaluated treatment response and adherence in adult patients with FMF [5, 8, 10–12, 15–17]. Earlier adult FMF studies reported considerably lower adherence, including non-adherence rates approaching 80% when instruments such as the Compliance Questionnaire on Rheumatology (CQR) were used [5, 10]. More recently, however, a Turkish study of 304 adults with FMF using the disease-specific Medication Adherence Scale in

Table 3 Univariable and multivariable logistic regression analyses of factors associated with low medication adherence according to MMAS-8™ in patients with FMF

	Univariable analysis		Multivariable analysis			
			Initial model		Final model	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Male sex	0.53 (0.20–1.40)	0.20	0.47 (0.15–1.52)	0.21		
Age, years	0.92 (0.88–0.96)	< 0.001*	0.93 (0.88–0.98)	0.01*	0.92 (0.87–0.96)	< 0.001*
Married	0.40 (0.16–0.95)	0.04*	0.69 (0.20–2.37)	0.55		
≤ 1 × national minimum wage (low income)[a]	5.33 (1.43–19.9)	0.01*	4.45 (0.96–20.64)	0.06	4.78 (1.01–22.56)	0.04*
History of abdominal surgery	0.48 (0.19–1.18)	0.11	0.78 (0.27–2.25)	0.64		
Having non-inflammatory comorbidities	0.44 (0.16–1.20)	0.11	1.08 (0.32–3.68)	0.90		
Non-FMF medication use	0.34 (0.13–0.89)	0.03*	0.51 (0.16–1.66)	0.26		
Attending follow-up visits at the frequency recommended by the physician	0.45 (0.18–1.11)	0.08	0.33 (0.10–1.06)	0.06	0.34 (0.11–1.00)	0.05*

Age was analyzed as a continuous variable; all other predictors were binary. Candidate predictors were selected on the basis of clinical relevance, univariable findings, and suitability as independent predictors. Variables with substantial conceptual overlap with the outcome, redundancy, collinearity, or sparse category counts were not included simultaneously. MMAS © 2006 used with permission. www.moriskyscale.com

Abbreviations: *CI* confidence interval, *FMF* familial Mediterranean fever, *MMAS-8™* 8-item Morisky Medication Adherence Scale™, *OR* odds ratio

[a]Income categories were defined on the basis of the official national minimum wage in Türkiye for the study year and self-reported by participants [38]

*Statistically significant ($p < 0.05$)

FMF Patients (MASIF) reported good adherence in 75.3% of patients, illustrating the substantial heterogeneity of adherence estimates across populations and measurement instruments [41]. By contrast, adherence rates as high as 90.5% have been reported in young children under parental supervision [22]. Although adolescents may exhibit greater autonomy and variable behaviors regarding medication use, adherence patterns in children are often influenced by intense parental supervision until complete independence is achieved [13, 20, 22].

The marked variation in reported adherence rates across FMF studies also underscores the potential influence of the measurement instrument used. Differences in questionnaire content, scoring algorithms, cutoff values, study populations, and administration methods may substantially affect the proportion of patients classified as non-adherent. Self-reported adherence measures are susceptible to recall and social desirability biases and may overestimate actual medication-taking behavior [42]. A ceiling effect cannot be excluded; however, because our study did not directly compare MMAS-8™ with the CQR or other adherence instruments, we cannot determine whether differences across studies primarily reflect instrument sensitivity, scoring thresholds, population characteristics, or other study-level factors.

MMAS-8™ was selected because a validated Turkish version was available and licensed for

use in the present study, and its widespread application across chronic diseases facilitates comparison with the broader medication-adherence literature. Nevertheless, MMAS-8™ is a generic self-reported adherence instrument and may not fully capture FMF-specific aspects of medication-taking behavior. MASIF was originally developed and validated in a Turkish pediatric FMF cohort and was subsequently evaluated in a multicenter adult FMF cohort [21, 43]. More recently, MASIF has also been used to assess adherence in a large adult Turkish FMF cohort [41]. Concurrent assessment with MASIF was not performed in our study; therefore, disease-specific dimensions of adherence and cross-validation between generic and FMF-specific adherence measures could not be evaluated.

The episodic nature of FMF may further complicate adherence assessment because asymptomatic intervals can reduce the perceived necessity for continuous colchicine therapy. Moreover, cross-sectional disease activity may be an imperfect proxy for medication adherence because most patients are evaluated during attack-free periods.

Interestingly, attack frequency did not differ significantly across adherence categories. This finding should not be interpreted as evidence that colchicine adherence is unrelated to disease control. The cross-sectional design does not establish the temporal relationship between adherence and subsequent attack burden, and attack frequency was assessed retrospectively and may therefore be affected by recall bias. In addition, adherence was evaluated using a self-reported instrument, which may be influenced by social desirability bias and may overestimate actual medication-taking behavior. Reverse causation is also possible, whereby patients experiencing a greater disease burden may subsequently become more adherent to treatment. Moreover, attack frequency may be influenced by underlying disease phenotype, colchicine dose, concomitant biological therapy, and treatment modifications prompted by previous disease activity. Longitudinal studies incorporating objective adherence measures are therefore needed to clarify the relationship between colchicine adherence and subsequent FMF activity. Although not statistically significant, adverse events requiring temporary discontinuation or dose reduction were numerically more frequent in the high-adherence group; given the small numbers, this pattern should be interpreted cautiously.

Failure to adequately assess or accurately interpret medication adherence may not only lead to suboptimal disease control and long-term complications for the patient but also result in unnecessary escalation to biologic therapies due to a misclassification of apparent treatment resistance [7–10]. Interestingly, real-world data by Levinsky et al. reported no significant difference in colchicine adherence between colchicine-resistant patients with FMF treated with IL-1 inhibitors and matched colchicine-sensitive controls: the mean medication possession ratio (MPR) was 78.9 ± 41.4 vs. 82.5 ± 80.6, respectively ($p = 0.5$), and > 50% of patients in both groups had suboptimal adherence (MPR < 80%) [11].

Older age may reflect greater treatment experience, more established medication-taking routines, and greater awareness of long-term disease-related risks [44, 45]. Conversely, younger adults may face distinct barriers related to increasing treatment autonomy and the transition from pediatric to adult care.

The association between younger age and low adherence may have practical implications for clinical care. Developmentally appropriate education, structured transitional care, shared decision-making, and individualized adherence support may help address barriers during the transition to adult care [46, 47]. Digital or reminder-based strategies may also provide additional opportunities to support medication-taking behavior, although their effectiveness specifically in FMF remains to be established [48–50].

Diagnostic delay is a recognized issue in FMF [51]; however, in our cohort, the delay from symptom onset to diagnosis was not significantly associated with adherence, and no consistent pattern was observed across adherence categories. To our knowledge, the potential influence of family disease experience on colchicine adherence has not been directly evaluated in FMF; interestingly, in our cohort, neither a family history of FMF nor a family history of AA amyloidosis was significantly associated with adherence.

Moreover, no robust associations were detected between adherence and family history, coexisting IMIDs, or the reported impact of attacks on occupational function. An isolated nominal association was observed for homozygous *MEFV* variants other than M694V; however, this category included only six patients, and genotype data were unavailable for 37 patients. Given the sparse cell counts and multiple exploratory genotype comparisons, this finding does not provide robust evidence of a relationship between *MEFV* genotype and colchicine adherence. While other comorbidities showed only a non-significant trend toward low-to-moderate-high adherence, previous studies have suggested that the comorbidity burden itself may be a factor associated with suboptimal adherence. In contrast, in our cohort, the relevant signal appeared to be captured more specifically by non-FMF medication use, which was associated with lower odds of low adherence in univariable analysis but did not remain independently associated in the final multivariable model; this finding should therefore be regarded as exploratory [10].

FMF involves multiple social dimensions that may influence adherence [8, 10, 13, 24, 25]. Being married was associated with lower odds of low adherence in univariable analysis but not after multivariable adjustment. This finding may nevertheless reflect broader social-support mechanisms that have been associated with medication-taking behavior in other chronic disease populations [52–54]. In our analyses, low income was associated with low adherence, whereas educational level was not. This pattern mirrors observations from other chronic diseases, in which financial and healthcare-access barriers have been identified among factors that may influence medication adherence [54]. These results emphasize that socioeconomic barriers, independent of education or awareness, remain a critical challenge to achieving sustained treatment adherence in FMF. Assessing medication affordability and access, facilitating continuity of follow-up, and addressing practical barriers to obtaining or regularly taking colchicine may therefore be particularly relevant for lower-income patients [55].

Validated adherence instruments provide a standardized framework for assessment, although their routine use may not always be feasible in busy outpatient settings [42, 55]. In our cohort, MMAS-8™ scores correlated moderately with both patient- and physician-rated adherence, suggesting that brief direct inquiry may provide a useful initial indication of adherence in clinical practice. However, it should not be considered equivalent to a validated or objective adherence assessment. Tekgöz et al. reported marked discordance between patient-reported regular colchicine use and CQR-based adherence assessment, further illustrating the limitations of relying solely on unstructured self-report [10]. In our cohort, self-reported prescribed use also exceeded moderate-to-high adherence classified by MMAS-8™ (86.5% vs. 71.2%), reinforcing the value of structured assessment when adherence is clinically uncertain.

Our study has several strengths. It integrates clinical and sociodemographic data in the assessment of colchicine adherence among adults with FMF. Colchicine adherence was assessed using a validated, widely recognized instrument (MMAS-8™), enabling standardized comparison with adherence data from other chronic disease populations. In addition, patient- and physician-rated adherence assessments provided complementary information and showed moderate correlations with MMAS-8™ scores.

However, several limitations should be acknowledged. First, the cross-sectional, single-center design precludes causal or temporal inference regarding the relationship between adherence and clinical outcomes. Recruitment was conducted in an outpatient clinic, so patients who had disengaged from follow-up entirely could not be sampled. If non-attendance is associated with poorer medication-taking behavior, this selection mechanism may have led to underestimation of the prevalence of low adherence in the broader adult FMF population. The borderline association between attendance at the recommended visit frequency and adherence should be read in this light, and is additionally susceptible to reverse causation, since patients committed to treatment are also more likely to attend.

Second, adherence was assessed using a self-reported instrument without corroboration by objective measures such as pharmacy refill records, pill counts, or electronic medication monitoring; therefore, recall and social desirability biases cannot be excluded. However, pharmacy refill-based measures may also incompletely capture medication use in this setting, as more than one-third of participants reported obtaining colchicine without their own prescription or borrowing it from another person. Although questionnaire administration was standardized and performed by physicians who were not involved in the patients' clinical assessment, physician supervision may nevertheless have influenced participants' responses and potentially led to overestimation of adherence, particularly among participants requiring physician-assisted administration.

Third, MMAS-8™ is a generic adherence measure and was not administered concurrently with an FMF-specific instrument such as MASIF; therefore, disease-specific dimensions of adherence and cross-validation between instruments could not be evaluated.

Fourth, no formal a priori sample-size or power calculation was performed. The relatively modest sample size and small numbers in several clinical subgroups, including patients with AA amyloidosis and those receiving biological therapy, may have limited statistical power and increased the possibility of type II error; consequently, nonsignificant findings should be interpreted cautiously. In addition, *MEFV* genotype data was unavailable in 37 patients (35.6%), further reducing the effective sample size for genotype-related analyses. Finally, potentially relevant determinants such as medication beliefs, illness perceptions, and health-system barriers were not comprehensively assessed.

Future multicenter longitudinal studies incorporating both validated self-report and objective adherence measures are needed to clarify the relationship between colchicine adherence and subsequent clinical outcomes. Such studies should also evaluate targeted interventions addressing modifiable adherence barriers, particularly among younger and socioeconomically disadvantaged patients.

CONCLUSION

Nearly one in three adults with FMF receiving colchicine had low adherence. Younger age and low income were independently associated with low adherence, while attendance at follow-up at the physician-recommended frequency showed a borderline association with lower odds of low adherence. Routine adherence assessment and targeted support for potentially vulnerable subgroups may help optimize long-term colchicine therapy and inform clinical decision-making before treatment escalation.

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Declarations

Conflict of Interest. Ertugrul Cagri Bolek, Riza Can Kardas, Levent Kilic, Sedat Kiraz, Ali Ihsan Ertenli, Alper Sari, and Ali Akdogan have nothing to disclose. Emre Bilgin is an Editorial Board member of *Rheumatology and Therapy*. Emre Bilgin was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Use of MMAS-8™ was authorized through a license agreement with Morisky Medication Adherence Research (MMAR), LLC; however, Donald E. Morisky, Philip Morisky, MBA, and MMAR, LLC had no role in the study design, data collection, analysis, interpretation of data, manuscript preparation, or the decision to submit this work for publication.

Ethical Approval. The study protocol was approved by the Non-interventional Clinical Research Ethics Committee of Hacettepe University (Approval No. GO18/542) and was conducted in accordance with the principles of the Declaration of Helsinki [39]. Written informed consent was obtained from all participants included in the study. MMAS-8™, content, name, and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from Morisky Medication Adherence Research (MMAR), LLC. The authors obtained a license to use the validated Turkish version of MMAS-8™. MMAS © 2006 used with permission. www.moriskyscale.com.

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