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Serum ADAM8, ADAM10, and ADAM17 levels in attack-free familial Mediterranean fever patients: A cross-sectional case-control study

Ertugrul Yigit[a], *, Osman Cure[b], Huseyin Cinar Zihni[c], Mehtap Atak[d], Merve Huner Yigit[d]

[a]Karadeniz Technical University, Faculty of Medicine, Department of Medical Biochemistry, Trabzon, Türkiye
[b]Recep Tayyip Erdogan University, Faculty of Medicine, Department of Rheumatology, Rize, Türkiye
[c]Karadeniz Technical University, Graduate School of Health Sciences, Department of Medical Biochemistry, Trabzon, Türkiye
[d]Recep Tayyip Erdogan University, Faculty of Medicine, Department of Medical Biochemistry, Rize, Türkiye
*Corresponding author: ertugrulyigit@ktu.edu.tr (Ertugrul Yigit)

MAIN POINTS

- Serum ADAM8 and ADAM10 levels were significantly higher in clinically attack-free FMF patients than those in healthy controls, and both remained independently associated with FMF after adjustment for age, sex, body mass index, and smoking status.
- ADAM17 levels did not differ between FMF patients and controls, suggesting a distinct regulatory profile among ADAM family members.
- ADAM10 showed weak-to-moderate associations with classical inflammatory markers, whereas ADAM8 and ADAM17 showed limited correlations.
- ROC analyses indicated that ADAM8 and ADAM10 had moderate discriminatory performance; however, these findings are exploratory and not intended for clinical diagnostic use.

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ABSTRACT

Aim: Familial Mediterranean Fever (FMF) is a monogenic autoinflammatory disease characterized by recurrent inflammatory attacks and persistent subclinical inflammation. The role of the ADAM (a disintegrin and metalloproteinase) family of metalloproteinases in FMF pathogenesis remains unclear. This study aimed to compare serum levels of ADAM8, ADAM10, and ADAM17 between FMF patients during attack-free periods and healthy controls and evaluate their associations with inflammatory markers.

Materials and Methods: This single-center, cross-sectional, case--control study included 36 FMF patients and 36 age and sex-matched healthy controls. All patients received regular colchicine therapy, and blood samples were collected during attack-free periods. Serum levels of ADAM8, ADAM10, and ADAM17 were measured by ELISA. Acute-phase reactants [C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen] were analyzed using routine laboratory methods. Between-group comparisons, correlation analyses, multivariable binary logistic regression analyses, and receiver operating characteristic (ROC) analyses were performed.

Results: Serum ADAM8 and ADAM10 levels were significantly higher in FMF patients than in controls ($p<0.001$), whereas ADAM17 levels did not differ between groups. ADAM10 showed weak-to-moderate positive correlations with CRP and fibrinogen, while ADAM8 and ADAM17 exhibited limited associations with inflammatory markers. ROC analysis demonstrated moderate discriminatory performance for ADAM8 and ADAM10; however, these findings should be interpreted as exploratory due to the cross-sectional design and potential confounding factors.

Conclusion: Serum ADAM8 and ADAM10 levels were higher in clinically attack-free FMF patients than in healthy controls. In multivariable analyses adjusted for age, sex, body mass index, and smoking status, ADAM8 and ADAM10 remained independently associated with FMF, whereas ADAM17 did not. These findings should be interpreted cautiously and may reflect the chronic/subclinical inflammatory burden of FMF rather than disease-specific pathogenic mechanisms. Furthermore, larger longitudinal studies are needed.

Keywords: Familial Mediterranean fever, ADAM8, ADAM10, ADAM17, Autoinflammatory diseases, Inflammation

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INTRODUCTION

Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease, caused by pathogenic variants in the *MEFV* gene and characterized by recurrent attacks of fever and serositis [1,2]. In the pathogenesis of the disease, dysregulation of inflammasome control due to mutant pyrin protein leads to caspase-1 activation and excessive release of proinflammatory cytokines, particularly interleukin-1 beta (IL-1β) [2-4]. This process results in intense neutrophil-mediated inflammatory attacks occurring in the absence of an infectious trigger [5].

Inflammatory responses driven by the IL-1β and IL-6 axes

have been shown to play a central role in FMF, both in terms of clinical manifestations and therapeutic response [6,7]. The efficacy of colchicine and IL-1 inhibitors further supports the pivotal role of these cytokine pathways in disease pathogenesis [8]. However, inflammation is shaped not only by cytokine production but also by proteolytic mechanisms that regulate cytokine shedding and bioavailability [9].

In this context, the ADAM (a disintegrin and metalloproteinase) family, which is responsible for the proteolytic cleavage of cell surface cytokines and receptors, plays an important regulatory role in the modulation of inflammatory responses [9,10]. In particular, ADAM8, ADAM10, and ADAM17 have been associated with several inflammatory processes relevant to FMF pathogenesis, including neutrophil activation, IL-6 trans-signaling, and tumor necrosis factor-alpha (TNF-α) release [11,12]. The ability of ADAM17 to activate IL-6 trans-signaling through cleavage of the IL-6 receptor, as well as the association of ADAM8 with neutrophil migration, supports the biological plausibility of a role for these proteases in FMF pathogenesis [11-13]. Given the attack-based, neutrophil-dominant, and IL-1β/IL-6-driven inflammatory nature of FMF, ADAM proteases capable of regulating these pathways may be associated with disease pathogenesis.

Nevertheless, clinical data regarding ADAM8, ADAM10, and ADAM17 levels in FMF patients are limited in the literature, and no study has evaluated these molecules collectively. Accordingly, it has been hypothesized that ADAM levels may be increased in FMF patients, and that this increase may be associated with disease activity. The present study aimed to compare serum ADAM8, ADAM10, and ADAM17 levels between clinically attack-free FMF patients and healthy controls, and to investigate their relationships with conventional inflammatory markers.

MATERIALS AND METHODS

Study design and participants

This study was conducted using a single-center, cross-sectional case–control design comparing patients with FMF (n=36) and healthy controls (n=36). In all FMF cases, sampling was performed during the clinically attack-free period; individuals who were asymptomatic at presentation and had not experienced an acute attack within at least the preceding two weeks were included [14]. Among FMF patients, the time elapsed since the last documented attack ranged from 20 days to 11 months at the time of blood sampling. We acknowledge that this criterion reflects clinical remission but does not necessarily indicate complete biological remission because low-grade inflammatory activity may persist between attacks. The primary rationale for excluding patients during overt attack periods was that acute inflammatory responses may be associated with transient elevations in inflammation-related biomarkers, which could hinder the assessment of persistent low-grade inflammatory activity. Accordingly, inclusion of clinically attack-free patients was methodologically preferable for evaluating whether circulating levels of ADAM8, ADAM10, and ADAM17 are associated with the chronic or subclinical inflammatory component of FMF. All FMF patients were receiving regular colchicine therapy, with doses ranging from 1 to 2 mg/day. The healthy control group was selected from volunteers who were matched to the patient group for age and sex. Based on a sensitivity analysis performed using G*Power (v3.1), the available sample size (total n=72; FMF=36, control=36) was calculated to be sufficient to detect at least moderate-to-large differences between the means of two independent groups (Cohen's d≈0.70) with 80% power at a two-sided α level of 0.05.

The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Recep Tayyip Erdoğan University (Approval No: 2025/476, Date: 24.11.2025). Written informed consent was obtained from all participants prior to enrollment in the study.

Inclusion and exclusion criteria

The inclusion criteria for the study were a confirmed diagnosis of FMF according to the Tel Hashomer criteria (defined by the presence of either one major criterion or two minor criteria), including major clinical manifestations (recurrent febrile attacks, peritonitis, pleuritis, and arthritis) and minor features (incomplete attacks, exertional leg pain, and response to colchicine therapy), and the exclusion of other autoinflammatory diseases. In addition, participants were required to be aged between 18 and 65 years and to be in an attack-free period at the time of sampling. The exclusion criteria included the presence of active or chronic infection, malignancy, advanced hepatic or renal failure, and diabetes mellitus; pregnancy; and the use of systemic corticosteroids, immunosuppressive agents, or biological therapies—other than colchicine—that could affect biomarker levels [15,16].

Clinical data collection

Demographic data (age, sex), smoking and alcohol use, body mass index (BMI), symptoms (fever, abdominal–chest pain, arthritis), and colchicine dose (as recorded in the clinical files) were extracted from medical records using a standardized data collection form.

Blood sampling and pre-analytical procedures

Biochemical analyses were performed on an AU5800 automated analyzer (Beckman Coulter, Brea, CA, USA) in accordance with the manufacturer's procedures and the laboratory's routine internal quality control protocols. Acute-phase reactants C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen were measured using immunoturbidimetric methods. Following measurement, serum samples were stored at −80 °C until the day of analysis.

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Measurement of serum ADAM8, ADAM10, and ADAM17

Serum levels of ADAM8 (E-EL-H0264), ADAM10 (E-EL-H0263), and ADAM17 (E-EL-H2305) were measured using commercially available ELISA kits according to the manufacturer's instructions (Elabscience, Houston, TX, USA). A standard curve based on polynomial regression was generated from the absorbance values of the standards, and sample concentrations were calculated from it.

Statistical analysis

All statistical analyses were performed using OriginPro 2025 (OriginLab Corp., Northampton, MA, USA). Data were tabulated and archived in Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous data are presented as median (Q1–Q3) for non-normally distributed variables and as mean ± standard deviation for normally distributed variables, whereas categorical variables are summarized as frequency (percentage). Between-group comparisons (FMF vs healthy controls) were performed using the Mann–Whitney U test for non-normally distributed variables and the independent two-sample t-test for normally distributed variables. Categorical variables (sex, smoking, alcohol use, and genetic mutations) were compared using the Chi-square test. Associations between circulating ADAM8, ADAM10, and ADAM17 levels and clinical and laboratory parameters were evaluated using Spearman's rank correlation coefficient (ρ); correlation heatmaps were generated in OriginPro. To address potential confounding, multivariable binary logistic regression analyses were additionally performed, with FMF status as the dependent variable and each ADAM protein was entered into a separate model adjusted for age, sex, BMI, and smoking status. The diagnostic performance of ADAM proteins in discriminating FMF patients from healthy controls was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) with 95% confidence intervals and p-values was reported, and optimal cut-off values were used to estimate sensitivity and specificity. All tests were two-tailed, and $p < .05$ was considered statistically significant. Given that three ADAM proteins were evaluated simultaneously, the potential for type I error from multiple comparisons is acknowledged. No formal correction was applied, and, accordingly, all findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory.

RESULTS

Demographic and anthropometric characteristics of the study population and MEFV genotype distribution in FMF patients

Comparison of demographic characteristics between the FMF patient group (n=36) and the healthy control group (n=36) showed no statistically significant differences in age distribution ($p = .97$) or sex distribution ($p = .13$). Similarly, the groups were comparable with respect to smoking status ($p = .20$) and alcohol consumption ($p = 1.00$). Evaluation of anthropometric measurements revealed no significant differences between the groups in either height or body weight ($p > .05$). However, BMI analysis showed that the median BMI in the control group (27.58 kg/m^2) was significantly higher than that in the FMF group (24.86 kg/m^2) ($p = .03$). Detailed demographic and anthropometric data for the groups are presented in Table 1. Assessment of mutation distribution within the FMF group demonstrated that 66.7% of patients (n=24) carried a single heterozygous mutation, 30.6% (n=11) had a homozygous mutation, and 2.8% (n=1) had a compound heterozygous mutation. The detailed distribution of the genetic analysis results is also shown in Table 1.

Comparison of acute-phase reactants between study groups

Comparison of acute-phase reactant levels between the study groups revealed CRP, SAA, and fibrinogen levels ($p < .05$ for all). In the FMF patient group, median levels of CRP (9.89 mg/dL), SAA (17.3 mg/L), and fibrinogen (313 mg/dL) were significantly higher than those in the healthy control group (1.69 mg/dL, 9.48 mg/L, and 270 mg/dL, respectively) ($p < .001$, $p = .004$, and $p = .006$). A detailed comparison of acute-phase reactants is presented in Table 2.

Comparison of circulating ADAM8, ADAM10, and ADAM17 levels between FMF and control groups

In the FMF patient group, circulating ADAM8 and ADAM10 levels were significantly higher than in the healthy control group, whereas no significant difference in ADAM17 levels was observed between the groups. For ADAM8, the median (Q1–Q3) level was 2567.18 (2064.26–3214.93) pg/mL in the FMF group and 1938.10 (1598.63–2470.46) pg/mL in the control group; this difference was statistically significant (Mann–Whitney U test, $p < .001$).

Because the Shapiro–Wilk test for ADAM10 did not indicate a significant deviation from normality, an independent two-sample t-test was used. Mean ± standard deviation values were 6291.37 ± 3828.30 pg/mL in the FMF group and 3312.68 ± 1950.23 pg/mL in the control group, and the between-group difference was statistically significant ($p < 0.001$). To further summarize the distribution of this parameter, median (Q1–Q3) values were calculated 3114.54 (1732.85–4527.07) pg/mL in the control group and 6115.46 (3495.34–8663.67) pg/mL in the FMF group.

In contrast, for ADAM17, the median (Q1–Q3) level was 278.05 (232.81–364.31) pg/mL in the FMF group and 270.07 (239.53–322.24) pg/mL in the control group, and this difference was not statistically significant (Mann–Whitney U test, $p = .74$) (Figure 1).

Multivariable binary logistic regression analyses

To further evaluate whether the associations of serum ADAM8, ADAM10, and ADAM17 with FMF were inde-

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Table 1. Demographic and anthropometric characteristics of the study population and *MEFV* mutation distribution in the FMF group.

Parameters	Control (n=36) Median (Q1-Q3)	FMF (n=36) Median (Q1-Q3)	p *Chi-Square †Mann-Whitney U
Age (years)	31.5 (25.5-37.75)	32 (25.5-43.75)	†p > .05
Sex [female (n) / male (n)]	28/8	22/14	*p > .05
Smoking [yes (n) / no (n)]	23/13	28/8	*p > .05
Alcohol consumption [yes (n) / no (n)]	2/34	3/33	*p > .05
Weight (kg)	77.5 (71.25-84)	71.5 (55.75-84.5)	†p > .05
Height (cm)	163.5 (160.25-169.75)	167.5 (160.25-170.75)	†p > .05
BMI (kg/m²)	27.5 (25.7-30.4)	24.6 (20.5-30.09)	†p = .03
Genetic Mutations (MEFV)			
Single heterozygous mutation		24 (66.7 %)	
Homozygous mutation		11 (30.6 %)	
Compound heterozygous mutation		1 (2.8 %)	

BMI: body mass index. *MEFV:* Mediterranean fever (pyrin) gene.

Table 2. Comparison of acute-phase reactants between familial Mediterranean fever patients and healthy controls.

Parameters	Control (n=36) Median (Q1-Q3)	FMF (n=36) Median (Q1-Q3)	p †Mann-Whitney U
CRP (mg/dL)	1.68 (0.86-4.15)	9.88 (2.1-13.9)	†p < .001
Fibrinogen (mg/dL)	270 (230.25-320.75)	313 (263.5-362.25)	†p = .006
SAA (mg/L)	9.4 (5.9-12.6)	17.3 (8.52-27.5)	†p = .004

CRP: C-reactive protein; SAA: serum amyloid A.

Table 3. Multivariable binary logistic regression analyses assessing the association of serum ADAM8, ADAM10, and ADAM17 levels with FMF status.

	ADAM8 aOR (95% CI)	p value	ADAM10 aOR (95% CI)	p value	ADAM17 aOR (95% CI)	p value
ADAM biomarker	1.16 (1.05--1.28)	0.003	1.05 (1.02--1.08)	<0.001	1.05 (0.89--1.24)	.561
Age	1.08 (1.00--1.16)	0.065	1.05 (0.96--1.14)	0.323	1.05 (0.98--1.13)	.150
Male sex	3.39 (0.81--14.12)	0.093	8.27 (1.58--43.43)	0.013	3.81 (0.98--14.78)	.053
Body mass index	0.88 (0.76--1.01)	0.064	0.80 (0.66--0.95)	0.013	0.88 (0.76--1.00)	.053
Smoking	0.44 (0.11--1.79)	0.249	0.16 (0.03--0.83)	0.029	0.26 (0.07--1.00)	.049

FMF status was entered as the dependent variable (control = 0, FMF = 1). Model 1 included ADAM8, age, sex, body mass index, and smoking status; Model 2 included ADAM10, age, sex, body mass index, and smoking status; and Model 3 included ADAM17, age, sex, body mass index, and smoking status. Sex was coded as female = 0 and male = 1, and smoking status as absent = 0 and present = 1. For interpretability, odds ratios for ADAM8, ADAM10, and ADAM17 are presented per 100 pg/mL increase. aOR, adjusted odds ratio; CI, confidence interval.

pendent of potential confounding factors, multivariable binary logistic regression analyses were performed, with FMF status as the dependent variable and age, sex, BMI, and smoking status included as covariates. As presented in Table 3, higher serum ADAM8 and ADAM10 levels remained independently associated with FMF, whereas ADAM17 did not. When expressed per 100 pg/mL increase, the adjusted odds ratios were 1.16 (95% CI 1.05–1.28; p = .003) for ADAM8, 1.05 (95% CI 1.02–1.08; p< .001) for ADAM10, and 1.05 (95% CI 0.89–1.24; p = .561) for ADAM17. The complete model results for each covariate are shown in Supplementary Table S1.

Spearman correlation analyses: Whole-cohort and FMF-restricted results

When Spearman's rank correlation analysis (two-tailed) was performed across all participants (n=72), significant positive correlations were identified between age and BMI (ρ = 0.415, p< .001), CRP (ρ = 0.387, p< .001), and fibrinogen levels (ρ = 0.265, p= .024). In contrast, no significant correlations were observed between age and levels of SAA, ADAM8, ADAM10, or ADAM17 (p> .05 for all). Regarding interrelationships among inflammatory parameters, CRP levels showed positive correlations with SAA (ρ = 0.374) and fibrinogen (ρ = 0.311), and a weak-to-moderate positive correlation with ADAM10 (ρ = 0.240) (p< .05; Figure 2). Fibrinogen levels were positively correlated with SAA (ρ = 0.264) and showed significant positive correlations with ADAM10 (ρ = 0.344) and ADAM17 (ρ = 0.265) among the ADAM proteins (p< .05; Figure 2). Regarding ADAM proteins, ADAM10 levels were positively correlated with ADAM8 levels (ρ = 0.286; p < .05), whereas ADAM17 correlated significantly only with fibrinogen. ADAM8 levels did not show significant associations with other clinical or laboratory parameters, with the exception of ADAM10 (Figure 2).

When the correlation analysis was restricted to the FMF

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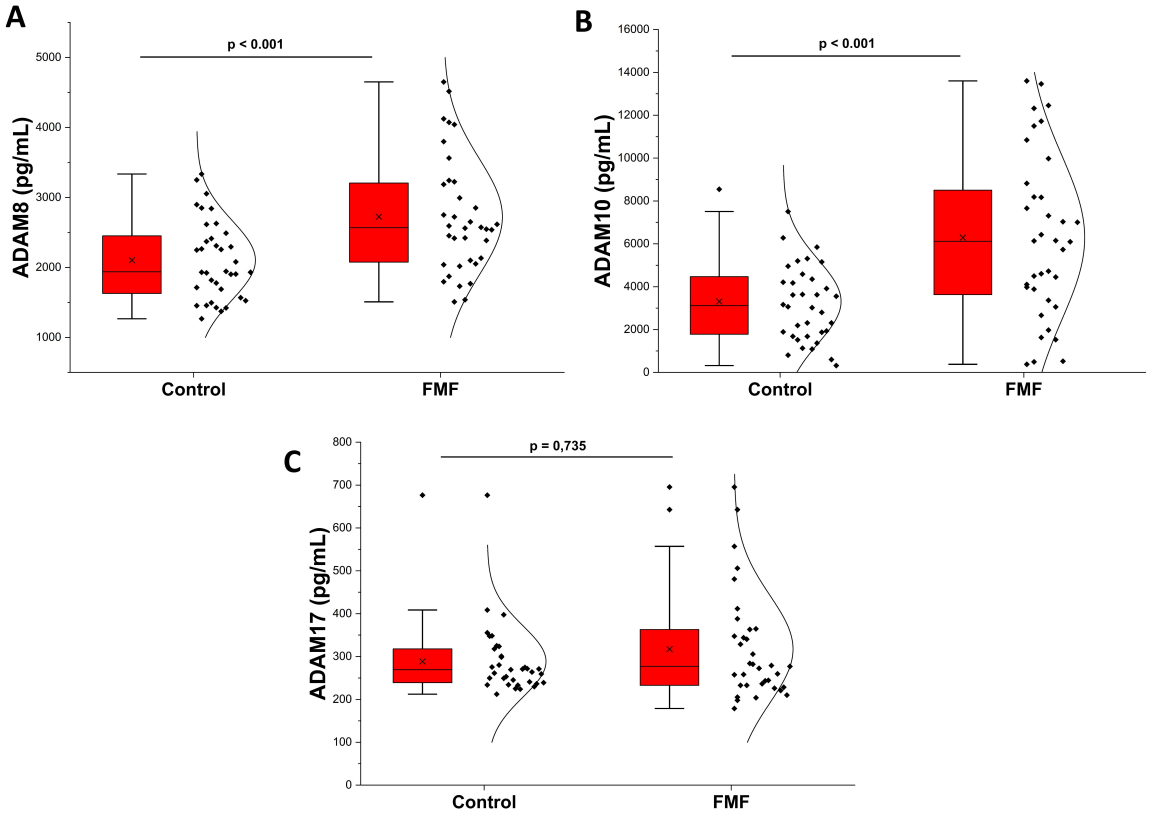

Figure 1. Circulating ADAM8, ADAM10, and ADAM17 levels in FMF patients versus healthy controls. (A) ADAM8, (B) ADAM10, and (C) ADAM17 concentrations (pg/mL) are shown for the FMF group (n=36) and the healthy control group (n=36). Data are presented as violin plots overlaid with box-and-whisker plots and individual data points. The box denotes the interquartile range (Q1--Q3), the horizontal line inside the box indicates the median, and the "×" symbol represents the mean; whiskers indicate the data spread (min--max). Between-group comparisons were performed using two-sided tests according to distributional assumptions: the Mann--Whitney U test for ADAM8 and ADAM17, and the independent two-sample t-test for ADAM10, for which Shapiro--Wilk testing did not indicate a significant deviation from normality. P values are displayed above each panel (A and B: p<0.001; C: p=0.74). Statistical significance was set at p<0.05. FMF: Familial Mediterranean Fever; ADAM: a disintegrin and metalloprotease.

group alone (n=36), the pattern of associations differed notably from that observed across the entire cohort. Age remained positively correlated with BMI (ρ = 0.606, p< .001), whereas its previously significant associations with CRP and fibrinogen were no longer statistically significant (p> .05 for both). Within the FMF group, no significant intercorrelations were identified among CRP, SAA, and fibrinogen (p> .05 for all). None of the ADAM proteins demonstrated significant associations with CRP or SAA. The only statistically significant ADAM-related association within the FMF group was between ADAM17 and fibrinogen (ρ = 0.383, p = .021). Notably, the previously observed correlations of ADAM10 with CRP, fibrinogen, and ADAM8 across the full cohort were not replicated in this subgroup analysis. Additionally, BMI showed a significant positive correlation with ADAM10 within the FMF group (ρ = 0.394, p = .018), which was not observed in the full-cohort analysis. The FMF-group correlation heatmap is presented in Supplementary Figure S1. These subgroup findings should be interpreted with caution, given the reduced statistical power (n=36) and the exploratory nature of the analysis.

Diagnostic performance of ADAMs in distinguishing FMF and controls

The diagnostic performance of circulating ADAM proteins in discriminating between FMF patients and healthy controls was evaluated using ROC curve analysis. For ADAM8, the AUC was 0.728 (standard error = 0.059; 95% confidence interval: 0.613–0.844), indicating statistically significant discriminatory performance (p< .001). Similarly, for ADAM10, the AUC was 0.738 (standard error = 0.060; 95% confidence interval: 0.620–0.857), and this performance was statistically significant (p< .001). In contrast, the discriminatory ability of ADAM17 was not statistically significant (AUC 0.524; 95% confidence interval: 0.386–0.661; p = .73).

Based on the optimal cut-off values derived from this dataset, thresholds of 2415.28 pg/mL for ADAM8 and 5524.09 pg/mL for ADAM10 yielded sensitivities of 66.7% and 55.6% and specificities of 75.0% and 88.9%, respectively (Figure 3). These cut-offs were determined within the present sample and should be considered exploratory; they are not intended for direct clinical implementation without independent replication and validation in larger, BMI-matched cohorts (Figure 3).

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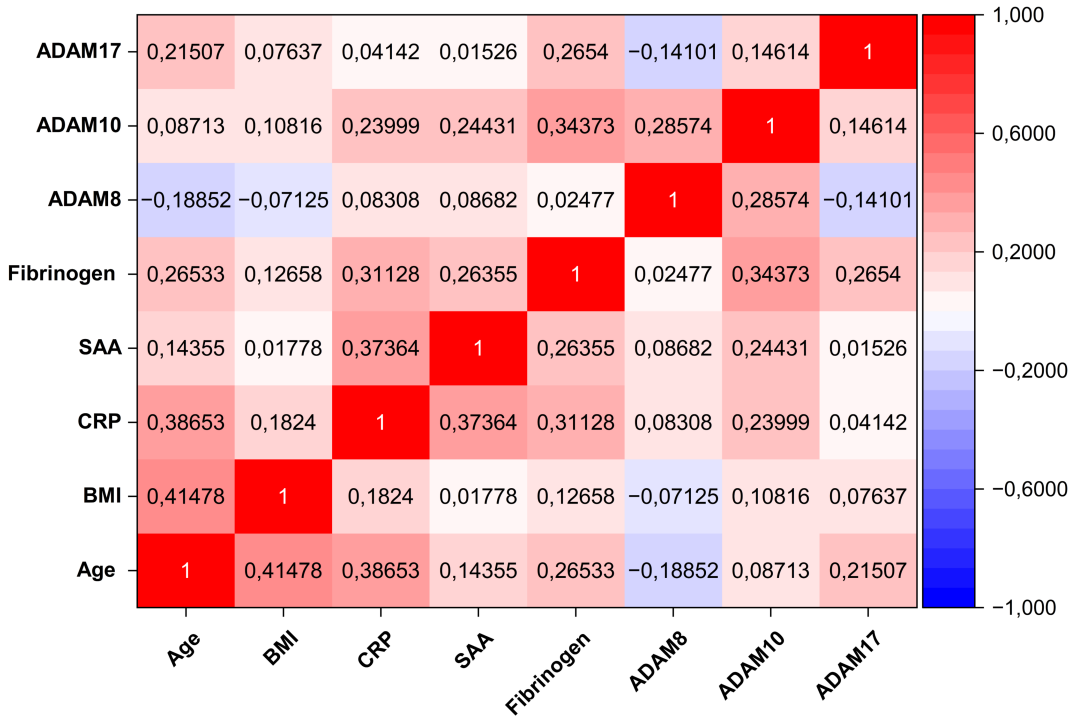

Figure 2. Spearman correlation matrix of demographic variables, acute-phase reactants, and circulating ADAM levels (n=72). The heatmap summarizes Spearman's rank correlation coefficients (ρ) for age, body mass index, C-reactive protein, serum amyloid A, fibrinogen, and circulating ADAM8, ADAM10, and ADAM17 levels. Abbreviations: BMI, body mass index; CRP, C-reactive protein; SAA, serum amyloid A; ADAM, a disintegrin and metalloprotease.

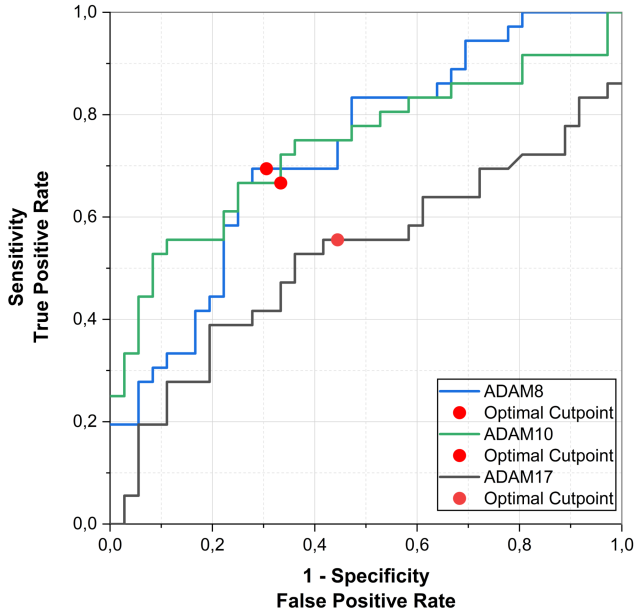

Figure 3. Receiver operating characteristic (ROC) curves of circulating ADAM8, ADAM10, and ADAM17 for discrimination of FMF patients from healthy controls. ROC curves were generated using ADAM8, ADAM10, and ADAM17 concentrations, with FMF defined as the positive state (n=36) and healthy controls as the negative state (n=36). AUC values are presented with standard errors, 95% confidence intervals, and p values. Optimal cut-off values and their corresponding sensitivity and specificity are reported in the text.

DISCUSSION

In this study, circulating levels of ADAM8, ADAM10, and ADAM17 were compared between clinically attack-free FMF patients and healthy controls, and the relationships between these molecules and conventional inflammatory markers were evaluated. Our findings demonstrated that levels of ADAM8 and ADAM10 were significantly increased in clinically attack-free FMF patients, while ADAM17 levels remained unchanged. Importantly, in multivariable binary logistic regression analyses adjusted for age, sex, BMI, and smoking status, ADAM8 and ADAM10 remained independently associated with FMF, whereas ADAM17 did not. Although these results suggest that certain metalloproteinases of the ADAM family may be associated with the inflammatory milieu present in FMF, the cross-sectional design and serum-based measurement approach preclude causal inference or the interpretation of these associations as disease-specific pathophysiological mechanisms. Instead, the observed elevations—together with the significantly higher acute-phase reactants in the FMF group—are more consistent with circulating reflections of intercritical or subclinical inflammatory burden rather than with a direct mechanistic signature. In this context, the present data provide complementary and descriptive information regarding the inflammatory biological background of FMF rather than propose a novel pathogenic mechanism.

Metalloproteinases of the ADAM family contribute to

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the shaping of inflammatory responses by regulating the ectodomain shedding of numerous cell surface proteins, including cytokines, cytokine receptors, and adhesion molecules [17-19]. The core of FMF pathogenesis involves increased IL-1 release as a result of excessive activation of the pyrin inflammasome, accompanied by neutrophil-dominant systemic inflammation [16,20-22]. Within this framework, the observed increases in ADAM8 and ADAM10 levels in clinically attack-free FMF patients appear more consistent with being circulating reflections of intercritical (chronic/subclinical) inflammatory activity rather than indicators of FMF-specific pathological pathways. Notably, acute-phase reactants were significantly higher in the FMF group, supporting the view that a biochemical inflammatory signal may persist even in the absence of overt clinical attacks.

ADAM8 is a metalloproteinase that is highly expressed in neutrophils and monocytes and plays a role in regulating cell migration and inflammatory tissue responses [23,24]. Increased ADAM8 expression has previously been reported to be associated with activated inflammatory cell responses in autoinflammatory and rheumatologic diseases [12,24]. Given that FMF attacks are characterized by prominent neutrophil-driven inflammation, the persistence of elevated ADAM8 levels even during attack-free periods in our study may be considered biologically plausible. However, the absence of significant correlations between ADAM8 and classical inflammatory markers such as CRP, SAA, and fibrinogen indicates that ADAM8 may not behave as a simple surrogate for the acute-phase response. Rather than excluding biomarker potential, this pattern may suggest that ADAM8 captures a distinct biological dimension of inflammation—particularly neutrophil-related activation or priming—that is not fully represented by conventional systemic markers. Therefore, increased ADAM8 levels may reflect specific aspects of inflammatory cell activation that can persist even when classical acute-phase reactants show limited dynamic range.

ADAM10 is known to play a role in immune system regulation, particularly through Notch signaling–mediated cell–cell interactions and modulation of inflammatory responses [25,26]. The significantly elevated ADAM10 levels observed in FMF patients, together with weak-to-moderate positive correlations with CRP and fibrinogen, suggest that ADAM10 may vary in parallel with inflammatory burden. However, the modest correlation coefficients indicate that ADAM10 is unlikely to be a simple surrogate for the acute-phase response; rather, it may capture additional biological processes that partially overlap with systemic inflammation (e.g., endothelial activation or shedding-related pathways). Accordingly, ADAM10 should be interpreted as a complementary marker reflecting the broader inflammatory environment, not as a standalone indicator of severity. Nevertheless, the relatively modest correlation coefficients and the cross-sectional nature of the study preclude interpreting ADAM10 as a causal or driving mechanism in FMF pathogenesis. Accordingly, the increase in ADAM10 should be regarded as a biochemical reflection of inflammation rather than as direct evidence of a fundamental disease mechanism.

ADAM17 is a key sheddase responsible for the proteolytic release of various transmembrane cytokines and receptors, most notably TNF-α, and plays an important role in inflammatory processes [10,27]. Although the IL-1β axis is central to FMF pathogenesis, TNF-α levels have also been reported to increase, particularly during periods of active inflammation [5,6]. Despite this, no significant difference in ADAM17 levels was observed between FMF patients and healthy controls. From a pathophysiological standpoint, this finding may be biologically plausible: FMF is predominantly driven by the IL-1β/pyrin inflammasome axis, and TNF-related pathways appear to play a comparatively subordinate role in disease pathogenesis [2,4,16]. Unlike TNF-dominant autoinflammatory or autoimmune conditions in which ADAM17-mediated shedding is expected to be more pronounced, the IL-1 central inflammatory milieu of FMF may not sufficiently engage ADAM17 at a systemic level, particularly during intercritical periods [5,6]. Furthermore, colchicine therapy, which attenuates neutrophil-mediated inflammation, may additionally dampen ADAM17 activity in treated patients, potentially narrowing any between-group differences [16]. This finding should be interpreted with caution because the control group had a significantly higher BMI than the FMF group (Table 1), and BMI-related low-grade inflammation may influence circulating inflammatory mediators. To address this issue, we performed multivariable binary logistic regression analyses adjusted for age, sex, BMI, and smoking status. In these analyses, ADAM17 was not independently associated with FMF. Nevertheless, residual confounding cannot be fully excluded. In this context, the absence of a systemic difference does not necessarily rule out a role for ADAM17 in FMF; rather, ADAM17-related effects may be context-dependent, potentially varying according to local tissue environments or specific clinical or genetic subgroups.

Finally, the positive but limited associations observed between ADAM proteins and conventional inflammatory markers indicate that these molecules may, to some extent, parallel the acute-phase response but should not be considered independent indicators that directly reflect the severity of inflammation. These findings support a cautious approach and underscore the need to avoid overinterpretation of the results. Overall, our study provides descriptive, methodologically balanced data on the relationship between ADAM family metalloproteinases and the inflammatory environment in FMF and establishes a conceptual framework for future studies, particularly longitudinal and tissue-level investigations.

Limitations and recommendations

This study has several important limitations. First, the relatively small sample size and the single-center, cross-sectional design limit the generalizability of the findings. Owing to

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the cross-sectional nature of the study, temporal changes in ADAM levels, dynamics before and after attacks, and causal relationships could not be assessed. In addition, only serum ADAM levels were measured; tissue expression, cellular sources, and analyses of functional activity were not performed, thereby limiting comprehensive understanding of the biological roles of ADAM proteins.

Second, although demographic characteristics were largely comparable, the control group had a significantly higher BMI than the FMF group (Table 1). This difference may have acted as a confounding factor, particularly for molecules potentially influenced by metabolic or adiposity-related inflammatory signals. To address this issue, we performed multivariable binary logistic regression analyses adjusted for age, sex, BMI, and smoking status. In these adjusted models, the associations of ADAM8 and ADAM10 with FMF remained statistically significant, whereas ADAM17 did not. Nevertheless, residual confounding cannot be fully excluded.

Third, all FMF patients were receiving colchicine therapy, making it difficult to distinguish treatment-related modulatory effects from disease-related alterations in inflammatory responses and ADAM levels. Furthermore, although daily colchicine doses ranged from 1 to 2 mg/day across the cohort, the limited variability within this clinically guided dose range precluded a meaningful exploratory analysis of dose–biomarker relationships; this constitutes an additional methodological limitation of the present study. In addition, standardized disease activity indices, such as AIDAI or ISSF, were not available in this cohort, thereby limiting more detailed clinical characterization of disease activity during the attack-free period. Similarly, detailed stratified analyses by variables such as *MEFV* genotype, disease duration, and subclinical inflammation duration could not be performed. Therefore, future studies should adopt larger, multicenter, prospective designs, include BMI-matched and externally validated analyses, incorporate genotype-stratified approaches, and evaluate both attack and intercritical periods, ideally together with tissue-level assessments. Additionally, ROC-derived cut-off values were estimated within the present dataset and were not externally validated; thus, they should be interpreted as exploratory and not directly transferable to clinical decision-making.

CONCLUSION

In conclusion, serum ADAM8 and ADAM10 levels were higher in clinically attack-free FMF patients than those in healthy controls, whereas ADAM17 levels did not differ significantly between the groups. In multivariable analyses adjusted for age, sex, BMI, and smoking status, ADAM8 and ADAM10 remained independently associated with FMF, whereas ADAM17 did not. Nevertheless, these findings should be interpreted cautiously in view of the cross-sectional design, limited sample size, universal colchicine exposure, lack of standardized disease activity indices, genotype heterogeneity, and the possibility of residual confounding. Accordingly, the present results should be considered descriptive and hypothesis-generating rather than directly diagnostic or mechanistic. In this context, the observed alterations in ADAM protein levels may be more appropriately interpreted as circulating reflections of the systemic inflammatory burden present in FMF. Further, larger, longitudinal, externally validated, and mechanistic studies are needed to clarify the biological and clinical relevance of ADAM family proteins in FMF.

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