Egyptian Rheumatology and Rehabilitation

RESEARCH

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Familial Mediterranean Fever reduces the quality of life

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Abstract

Background Familial Mediterranean Fever (FMF) is a lifelong autoinflammatory disease that typically begins in childhood and requires continuous treatment and follow-up. The disease is characterized by recurrent inflammatory attacks, and the unpredictable nature of these episodes often leads to anxiety, depression, and a decreased quality of life. The aim of this study was to evaluate the quality of life in patients with FMF and to identify the clinical and psychological factors that influence it, with a particular focus on the roles of disease severity, anxiety, and depression.

Methods This cross-sectional study included 150 patients diagnosed with Familial Mediterranean Fever according to the Tel-Hashomer or Sheba Medical Center criteria. Participants completed the Short Form-36 and Hospital Anxiety and Depression Scale questionnaires. Clinical data and MEFV gene mutations were retrieved from the hospital registry. Disease severity was assessed using the International Severity Score for FMF. Associations between quality of life and clinical features, disease severity, anxiety, and depression were analyzed. Statistical analyses were performed using SPSS, with $p \leq 0.05$ considered significant.

Results Among the participants, anxiety was more prevalent than depression (84% vs. 70%). However, no significant correlation was found between anxiety (HADS-A) or depression (HADS-D) scores and age, gender, presence of comorbidities, or FMF severity scores. This suggests that psychological symptoms in FMF patients may occur independently of clinical or demographic characteristics, indicating that the disease itself may contribute directly to the development of anxiety and depression.

Conclusions FMF negatively affects quality of life both physically and psychologically. The high rates of anxiety and depression, independent of clinical factors, highlight the importance of incorporating psychosocial evaluation into routine FMF care.

Keywords Familial Mediterranean fever, Anxiety, Depression, Quality of life

Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disease characterized by recurrent episodes of fever and serositis. In addition to the classic clinical features, the dominant symptoms can vary depending on ethnicity and environmental factors. Patients with mutations in exon 10 of the *MEFV* gene—particularly those homozygous for the M694V mutation—often experience a more severe disease course [1].

Colchicine remains the lifelong standard treatment for FMF, provided there is no intolerance or significant side effect. In cases of colchicine resistance, interleukin-1

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inhibitors are used. Despite advances in treatment, the exact pathogenesis of FMF attacks remains unclear. Most patients report a consistent pattern of attacks, often triggered by factors such as physical or emotional stress, cold exposure, or menstruation [2].

Depression and anxiety are common comorbidities in chronic diseases like diabetes and asthma [3, 4], and are known to negatively impact quality of life (QoL) [5]. These psychiatric conditions are also frequently seen in rheumatic diseases such as systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis [6]. Given its lifelong nature and the unpredictability of attacks, FMF is associated with increased rates of depression and anxiety, which further contribute to diminished QoL [7].

While previous studies have documented elevated levels of anxiety and depression in FMF patients [8], limited research has explored their relationship with specific clinical parameters. Therefore, the aim of this study is to assess the quality of life in FMF patients and identify contributing factors, particularly the impact of clinical features, disease severity, and the risk of anxiety and depression.

Methodology

Study group

Patients included in this study were diagnosed with Familial Mediterranean Fever (FMF) based on either the Tel-Hashomer or Sheba Medical Center diagnostic criteria [9, 10].

A minimum of 145 FMF patients was calculated to be sufficient to achieve 95% power for the study. To account for potential data loss, 150 patients were ultimately enrolled. All participants provided written informed consent and completed the Short Form-36 (SF-36) and Hospital Anxiety and Depression Scale (HADS) questionnaires. Clinical findings and *MEFV* gene mutation data were retrieved from the hospital's registry system.

The relationship between patients' quality of life and clinical features, FMF severity scores, anxiety, and depression was assessed. This single-center study was conducted in accordance with the principles of the Declaration of Helsinki (1975) and was approved by the local ethics committee (Approval date: 29.07.2021; Decision number: 2021/04).

Inventories

Quality of life was assessed using the SF-36, while anxiety and depression were evaluated using the HADS-A and HADS-D subscales. Both scales have been validated for use in the Turkish population [11, 12].

The SF-36 is a widely used questionnaire designed to measure health-related quality of life [11]. The HADS is not intended to diagnose psychiatric conditions but rather to screen for anxiety and depression in patients with physical illnesses [12].

Hospital Anxiety Depression Scale (HADS)

Originally developed by Zigmond and Snaith [13], the HADS is a self-report questionnaire used to assess the risk and severity of anxiety and depression. Its Turkish version was validated by Aydemir et al. [12]. The scale consists of 14 items: seven odd-numbered items assess anxiety, and seven even-numbered items assess depression. Each item is rated on a four-point Likert scale.point Likert-type scale.

Short Form- 36 (SF-36)

Developed by Ware and Sherbourne [14], the SF-36 is a generic, easy-to-administer questionnaire for evaluating health-related quality of life. It comprises 36 items and is divided into two main components: physical and mental health. The physical component includes: general health, physical functioning, role limitations due to physical health, and bodily pain. The mental component includes: mental health, role limitations due to emotional problems, vitality/energy, and social functioning. Each subscale is scored from 0 to 100, with higher scores indicating better health status. The Turkish version of the SF-36 was validated by Koçyiğit et al. [11].

International Severity Score for FMF (ISSF)

The ISSF was used to assess FMF disease severity. The score incorporates several clinical factors: presence of chronic sequelae, organ dysfunction or failure, attack frequency, acute phase reactants, the number of sites affected in a single attack, attack types during the disease course, attack duration, and exertional leg pain. A score of ≤ 2 indicates mild disease, 3–5 indicates moderate disease, and ≥ 6 indicates severe disease [15].

Statistical analysis

Data were analyzed using SPSS software. A p-value of ≤ 0.05 was considered statistically significant. Qualitative variables were expressed as frequency and percentage. Quantitative variables were presented as mean ± standard deviation.

Normality of distribution was assessed using the Kolmogorov–Smirnov test. The Mann–Whitney U test was used for comparisons between two groups, while the Kruskal–Wallis test was used for comparisons involving three or more groups. The Pearson Chi-Square and Fisher's Exact Chi-Square tests were used to analyze categorical data in contingency tables.

Results

Of the 150 patients included in the study, 91 (60.7%) were female and 59 (39.3%) were male. The mean age was 37.4 ± 11.9 years (range 16–71). The mean age at symptom onset was 15.39 ± 11.08 years, and the mean age at diagnosis was 24.02 ± 12.76 years.

The most common clinical manifestations were fever ($n=127$, 84.6%) and peritonitis ($n=124$, 82.6%), followed by arthritis ($n=72$, 48%), pleuritis ($n=64$, 42.6%), myalgia ($n=67$, 44.6%), erysipelas-like erythema ($n=55$, 36.6%), amyloidosis ($n=13$, 8.6%), vasculitis ($n=9$, 6%), and chronic renal failure ($n=8$, 5.3%).

All patients were treated with colchicine at a mean daily dose of 2.04 ± 0.88 mg.

Based on the International Severity Score for FMF (ISSF), 43 patients (28.7%) had severe disease, 67 (44.7%) had moderate disease, and 39 (26%) had mild disease.

Comorbid conditions were present in 73 patients (48.7%), with details summarized in Table 1. The most common comorbidities were hypertension (12.7%), hypothyroidism (6.7%), ankylosing spondylitis (4.9%), diabetes mellitus (4.9%), and fibromyalgia (4.3%). Less frequent comorbidities included chronic renal failure, multiple sclerosis, juvenile idiopathic arthritis, anxiety disorders, and various autoimmune and vascular conditions, each affecting less than 2% of the patients.

Table 1 The list and the frequency of comorbid diseases in FMF patients

Comorbid disease	Number of patients (n)	%
Hypertension	21	12.7
Ankylosing Spondylitis	8	4.86
Fibromyalgia	7	4.25
Hypothyroidism	11	6.68
Diabetes Mellitus	8	4.86
Henoch-Schönlein Purpura	2	1.21
Chronic renal failure	4	2.42
Juvenile idiopathic arthritis	2	1.21
Multiple Sclerosis	2	1.21
Anxiety disorders	2	1.21
Behcet's disease	1	0.60
Hyperlipidemia	2	1.21
Celiac disease	1	0.66
Pulmonary thromboembolism	1	1.21
Cerebrovascular disease	1	0.60
Osteoporosis	1	0.60
Sacroiliitis	1	0.60
Breast cancer	1	0.60
Hashimoto thyroiditis	2	1.21
Epilepsy	1	0.60

Regarding psychological status, 126 patients (84%) exhibited anxiety per HADS-A scores, while 24 (16%) scored within the normal range. Depression was observed in 105 patients (70%) based on HADS-D scores; 45 patients (30%) scored normal.

No significant associations were found between HADS-A or HADS-D scores and age, gender, comorbidity presence, or FMF severity ($p>0.05$). However, patients with arthritis had significantly higher anxiety scores ($p=0.038$).

Male patients scored significantly higher than females in SF-36 Physical Component Summary, Physical Function, General Health, and Mental Component Summary Emotional Role subscales ($p=0.001$, 0.036, and 0.010, respectively). There was a significant negative correlation between FMF severity and all SF-36 components, with quality of life decreasing as disease severity increased ($p\leq0.05$ for all) (Table 2). The SF-36 scores revealed that as FMF severity increased, patients' quality of life significantly declined, especially in physical health areas. Those with severe FMF had lower physical functioning (67.43 ± 29.81) compared to moderate (75.96 ± 21.01) and mild cases (84.18 ± 16.18, $p=0.043$). Role limitations due to physical problems were also much worse in severe cases (41.44 ± 39.11) than in moderate (66.10 ± 37.93) and mild disease (72.85 ± 38.52, $p=0.001$). Severe patients experienced more bodily pain (53.72 ± 30.37) than others ($p=0.007$), and general health perception decreased with severity (42.83 ± 15.61 in severe vs. 56.76 ± 17.53 in mild, $p=0.004$). Mental health aspects like vitality and social functioning also dropped significantly as severity increased, but emotional role limitations and perceived mental health did not differ much among groups. This shows that FMF severity mainly affects physical quality of life, while some mental health aspects remain relatively stable.

Patients with comorbidities scored lower in Physical Function, Physical Role, General Health, and Social Function compared to those without comorbidities (Table 3). FMF patients with comorbid diseases have lower quality of life, especially in physical areas. Those with comorbidities scored lower in physical functioning (69.63 ± 26.55) compared to those without (81.66 ± 18.65, $p=0.009$). They also had more limitations in daily activities due to physical problems (53.17 ± 39.27 vs. 68.21 ± 39.90, $p=0.021$). General health perception was worse in patients with comorbidities (44.68 ± 17.05 vs. 53.67 ± 15.46, $p=0.001$). Social functioning was also lower in these patients (62.32 ± 29.08 vs. 72.36 ± 28.52, $p=0.032$). However, there were no significant differences in other mental health areas. In summary, comorbid diseases mainly affect physical quality of life and social functioning in FMF patients.

Table 2 The comparison of FMF severity scores and SF-36 components

SF 36 components	FMF severity scores			p
	Severe	Moderate	Mild	
Physical Component Score				
Physical Functioning	67.43 ± 29.81	75.96 ± 21.01	84.18 ± 16.18	**0.043**
Role limitations due to physical problems	41.44 ± 39.11	66.10 ± 37.93	72.85 ± 38.52	**0.001**
Bodily pain	53.72 ± 30.37	67.26 ± 30.88	72.94 ± 24.88	**0.007**
General health perceptions	42.83 ± 15.61	48.64 ± 15.19	56.76 ± 17.53	**0.004**
Mental Component Score				
Vitality/Fatigue	48.48 ± 21.47	48.19 ± 22.06	58.37 ± 21.28	**0.044**
Social Functioning	60.46 ± 27.53	65.03 ± 30.79	78.52 ± 25.15	**0.007**
Role limitations due to emotional problems	56.86 ± 41.46	61.49 ± 42.71	60.78 ± 41.41	0.876
Perceived mental health	58.13 ± 20.42	61.62 ± 19.81	65.94 ± 17.06	0.287

SF-36 Short Form-36, *FMF* Familial Mediterranean Fever

Significance level: $p \leq 0.05$ was considered statistically significant

Table 3 Comparison of SF -36 components and presence of comorbid diseases

SF 36 components	Comorbid disease		p
	Yes	No	
Physical Component Score			
Physical Functioning	69.63 ± 26.55	81.66 ± 18.65	**0.009**
Role limitations due to physical problems	53.17 ± 39.27	68.21 ± 39.90	**0.021**
Bodily pain	62.18 ± 29.90	67.76 ± 30.14	0.176
General health perceptions	44.68 ± 17.05	53.67 ± 15.46	**0.001**
Mental Component Score			
Vitality/Fatigue	50.43 ± 23.35	52.12 ± 21.35	0.759
Social Functioning	62.32 ± 29.08	72.36 ± 28.52	**0.032**
Role limitations due to emotional problems	56.28 ± 41.06	64.14 ± 42.28	0.267
Perceived mental health	61.35 ± 20.62	62.48 ± 18.60	0.883

SF-36 Short Form-36

Significance level: $p \leq 0.05$ was considered statistically significant

Among clinical symptoms, arthritis, pleuritis, and vasculitis were significantly associated with reduced quality of life (Table 4). Among the clinical symptoms studied, only pleuritis had a significant negative effect on physical functioning, with patients showing lower scores (79.84 ± 23.63, $p = 0.019$). Other symptoms like fever, peritonitis, and erysipelas-like erythema did not significantly affect any physical or mental quality of life measures. Mental health scores were similar regardless of these clinical findings. In summary, pleuritis is linked to worse physical functioning in FMF patients, while other symptoms do not appear to impact quality of life significantly.

Patients with arthritis showed significantly lower scores in physical functioning (68.8 ± 25.7 vs. higher), role limitations due to physical problems (51.2 ± 39.9), bodily pain (56.8 ± 31.4), general health perceptions (44.4 ± 15.8), vitality/fatigue (46.6 ± 22.9), social functioning (59.9 ± 31.0), and perceived mental health (58.0 ± 21.1), all with p-values ≤ 0.05. Similarly, patients with myalgia had reduced scores in physical functioning (70.6 ± 25.3, $p = 0.028$), bodily pain (59.2 ± 30.3, $p = 0.017$), general health perceptions (44.0 ± 14.4, $p = 0.002$), and vitality/fatigue (45.1 ± 21.5, $p = 0.002$). Vasculitis only significantly lowered general health perceptions (39.4 ± 12.7, $p = 0.046$), while amyloidosis did not significantly affect any SF-36 component scores.

Age negatively correlated with the SF-36 Physical Component Score and Physical Function, indicating a decline in quality of life with increasing age.

Patients without *MEFV* mutations had higher SF-36 quality of life scores compared to those with mutations.

Patients with anxiety showed higher pain, general health, vitality/fatigue, social function, emotional role, and mental health scores ($p \leq 0.05$ for all) (Table 5). In contrast, patients with depression had significantly lower

Table 4 Comparison of SF -36 components and clinical findings

a

SF 36 components	Clinical findings							
	Fever	p	Peritonitis	p	Pleuritis	p	Erysipelas like erythema	p
Physical Component Score								
Physical Functioning	75.96±23.65	0.762	76.46±23.37	0.439	79.84±23.63	**0.019**	74.81±24.58	0.742
Role limitations due to physical problems	60.68±40.27	0.704	61.00±40.17	0.973	63.33±40.77	0.480	67.30±34.84	0.225
Bodily pain	65.18±30.49	0.737	63.99±30.93	0.462	64.72±31.65	0.980	68.37±26.76	0.469
General health perceptions	48.65±16.40	0.559	48.41±16.29	0.326	46.79±17.29	0.239	49.40±16.08	0.584
Mental Component Score								
Vitality/Fatigue	50.92±22.47	0.708	50.25±21.79	0.179	50.90±20.56	0.690	51.48±24.31	0.783
Social Functioning	67.94±29.22	0.699	65.49±29.80	0.073	68.25±28.38	0.962	68.64±30.26	0.616
Role limitations due to emotional problems	58.09±42.12	0.160	59.29±41.79	0.523	68.45±39.39	0.059	59.18±42.63	0.804
Perceived mental health	62.78±19.50	0.156	61.43±19.74	0.642	61.00±19.15	0.618	61.60±20.87	0.841

b

SF 36 components	Clinical findings							
	Arthritis	p	Myalgia	p	Vasculitis	p	Amyloidosis	p
Physical Component Score								
Physical Functioning	68.80±25.70	**0.001**	70.64±25.27	**0.028**	80.55±22.56	0.635	70.00±30.68	0.644
Role limitations due to physical problems	51.17±39.94	**0.005**	54.66±41.12	0.106	65.62±37.64	0.851	60.00±35.74	0.816
Bodily pain	56.83±31.43	**0.001**	59.16±30.28	**0.017**	57.22±34.89	0.513	67.11±24.34	0.959
General health perceptions	44.36±15.77	**0.002**	44.01±14.42	**0.002**	39.37±12.65	**0.046**	42.27±23.06	0.215
Mental Component Score								
Vitality/Fatigue	46.61±22.92	**0.014**	45.07±21.53	**0.002**	50.62±28.46	0.726	49.23±26.04	0.966
Social Functioning	59.85±30.97	**0.004**	64.77±30.76	0.382	62.50±34.79	0.706	69.23±30.02	0.787
Role limitations due to emotional problems	54.02±43.63	0.146	56.36±42.00	0.313	83.33±35.63	0.101	53.33±42.16	0.648
Perceived mental health	57.97±21.13	**0.027**	59.38±18.68	0.101	52.00±23.32	0.205	60.30±23.80	0.936

SF-36 Short Form-36

Significance level: $p \leq 0.05$ was considered statistically significant

Table 5 Relationship between SF -36 components and anxiety and depression

SF 36 components	Anxiety			Depression		
	Under thershold n (%)	Above thershold n (%)	p	Under thershold n (%)	Above thershold n (%)	p
Physical Component Score						
Physical Functioning	74.19 ± 24.60	76.82 ± 22.94	0.582	74.49 ± 24.17	82.39 ± 19.29	0.152
Role limitations due to physical problems	55.17 ± 39.94	65.66 ± 40.01	0.100	63.28 ± 39.57	50.00 ± 42.25	0.172
Bodily pain	59.01 ± 28.48	69.28 ± 30.57	**0.014**	66.46 ± 29.67	58.10 ± 31.60	0.180
General health perceptions	44.00 ± 14.15	53.22 ± 17.58	**0.000**	49.16 ± 16.54	50.21 ± 18.36	0.971
Mental Component Score						
Vitality/Fatigue	42.19 ± 21.56	57.41 ± 20.72	**0.000**	53.26 ± 22.17	41.66 ± 20.67	**0.020**
Social Functioning	60.24 ± 30.14	72.67 ± 27.42	**0.015**	69.67 ± 28.74	57.00 ± 29.33	**0.047**
Role limitations due to emotional problems	47.05 ± 42.25	69.29 ± 39.16	**0.002**	61.63 ± 41.60	53.96 ± 42.78	0.437
Perceived mental health	54.10 ± 20.14	67.30 ± 17.31	**0.000**	64.99 ± 18.94	46.50 ± 15.00	**0.000**

SF-36 Short Form-36

Significance level: $p \leq 0.05$ was considered statistically significant

scores in vitality/fatigue, social function, and mental health subscales ($p \leq 0.05$ for all) (Table 5). Patients with anxiety had higher scores in bodily pain (69.3 vs. 59.0, $p = 0.014$), general health (53.2 vs. 44.0, $p < 0.001$), vitality (57.4 vs. 42.2, $p < 0.001$), social functioning (72.7 vs. 60.2, $p = 0.015$), emotional role (69.3 vs. 47.1, $p = 0.002$), and mental health (67.3 vs. 54.1, $p < 0.001$). Patients with depression showed lower vitality (41.7 vs. 53.3, $p = 0.020$), social functioning (57.0 vs. 69.7, $p = 0.047$), and mental health (46.5 vs. 65.0, $p < 0.001$). No significant difference in physical functioning or role limitations was found for either group.

Discussion

Familial Mediterranean Fever (FMF) is a lifelong disease that begins in childhood and requires continuous treatment and follow-up. FMF progresses with unpredictable attacks, which often lead to anxiety, depression, and a reduced quality of life (QoL).

In our study cohort, anxiety was more prevalent than depression (84% vs. 70%). However, no significant associations were found between HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D) scores and age, gender, presence of comorbidities, or FMF severity score. This suggests that the disease itself, independent of clinical features, is a risk factor for depression and especially anxiety. Previous studies in pediatric FMF patients reported a negative correlation between disease severity and anxiety/depression [5, 7]. It is possible that, as patients age and treatment reduces the frequency and severity of attacks, anxiety and depression become less pronounced. Similarly, Giese et al. observed a correlation with anxiety but not depression among German FMF patients [6].

Several studies have demonstrated the negative impact of FMF on QoL [6, 8]. While FMF severity did not correlate with anxiety or depression in our study, it showed a significant inverse relationship with QoL. Using the SF-36 questionnaire, we found that QoL was impaired across all patients regardless of disease severity, although those with more severe disease experienced greater impairment. Among clinical manifestations, pleuritis, arthritis, myalgia, and vasculitis were associated with poorer QoL, whereas fever and peritonitis did not significantly affect any SF-36 subscales. This may be because fever and peritonitis are typically early symptoms that respond well to treatment, and our cohort primarily consisted of patients under follow-up with controlled disease.

Patients presenting with pleuritis, arthritis, myalgia, and vasculitis reported significantly lower QoL. Arthritis, in particular, impacted both physical and mental health components.

According to HADS results, 84% of patients experienced anxiety and 70% depression. Except for arthritis, anxiety and depression were not associated with sex, age, comorbidities, ISSF scores, or other clinical features. Arthritis likely contributes to anxiety by worsening physical function.

Symptoms of anxiety and depression are easily overlooked and often mistaken as inherent to the disease itself, leading to underdiagnosis and undertreatment, which further deteriorates QoL.

The main limitation of our study is the reliance on self-reported data without objective clinical assessments. We also did not investigate socioeconomic or other social factors that might influence anxiety, depression, or QoL. The lack of a control group is another limitation; however, our primary aim was to evaluate relationships within the FMF population rather than compare to healthy individuals, which has been addressed in previous research. Additionally, since most patients were in remission during the study, selection bias may have influenced the findings.

Conclusion

FMF adversely affects both physical and mental well-being. Even without formal psychiatric diagnoses, the high rates of anxiety, depression, and reduced quality of life highlight the need for psychosocial evaluation. A multidisciplinary approach may improve patient outcomes.

Abbreviations

FMF	Familial Mediterranean Fever
HADS	Hospital Anxiety Depression Scale
HADS-A	Hospital Anxiety Depression Scale-Anxiety
HADS-D	Hospital Anxiety Depression Scale-Depression
ISSF	International Severity Score for FMF
QoL	Quality of Life
SF-36	Short Form- 36

Authors' contributions

NSYB, YS: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. BCEU, RY, MD: Methodology, Investigation, Data curation, Conceptualization. UB, TK: Methodology, Investigation, Formal analysis, Conceptualization. All authors read and approved the final manuscript.

Funding

This research is not funded.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study involving human participants was reviewed and approved by the local ethics committee with approval code (decision date 29.07.2021, decision number: 2021/04). All tests were explained to all participants before having their written informed consent to participate in our study.

Competing interests
The authors declare no competing interests.

Received: 25 April 2025 Revised: 19 July 2025 Accepted: 23 July 2025
Published online: 13 August 2025

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