Health-related quality of life in Egyptian patients with familial Mediterranean fever

Original Article

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ABSTRACT

Background: Familial Mediterranean fever (FMF) is an auto-inflammatory disease, characterized by frequent attacks of fever and polyserositis. The chronic disease course and its burden with the life-long medications have an effect on the outcomes of health-related quality of life (HRQoL) in patients with FMF.
Objectives: To evaluate the outcomes of HRQoL and related risk factors in a large cohort of Egyptian patients with FMF.
Patients and Methods: A total of 118 patients and 100 controls were enrolled from the Clinical Genetics Department, National Research Center, Cairo, Egypt. The Arabic version of Pediatric Quality of Life (PedsQLTM) Inventory 4.0 Generic Core Scale was used to assess the HRQoL outcomes.
Results: The outcome scores of HRQoL were lower in patients with FMF in comparison with the controls in all domains (*P<0.0001*). Mild cases had better HRQoL outcomes than severe cases (*P<0.0001*). HRQoL outcomes were significantly higher in patients with fewer attacks than those who had many attacks per month (*P<0.0001*). There was a significant association between the emotional functioning and sex (*P=0.042*), with more affection of females.
Conclusion: This is the first study conducted on a large number of Egyptian patients with FMF demonstrating the negative effect of FMF disease on HRQoL. The number of attacks and disease severity significantly affect HRQoL. Psychosocial support is recommended to improve HRQoL of patients with FMF.

Key Words: Emotional functioning, familial Mediterranean fever, health-related quality of life, physical functioning, school functioning, social functioning.

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INTRODUCTION

Familial Mediterranean fever (FMF) is a persistent weakening and provocative disease influencing principally the inhabitants of the Mediterranean area mostly including Arabs, Turks, Armenians, and non-Ashkenazi Jews (**Mohamed *et al*., 2020**). It is a well-established disease with destructive consequences for all the characteristics of personal life satisfaction (**Unal-Ulutatar and Duruoz, 2021**).

The course of disease and presence of subclinical inflammation in-between the attacks markedly decrease the patients' quality of life (QoL). The risk of amyloidosis in untreated patients worsens the clinical condition with higher rates of mortality contribute to the lowered health-related quality of life (HRQoL) (**Giese *et al*., 2013**).

FMF management main goal is to control and reduce the number of attacks and inflammation in-between the attacks and consequently ameliorating the patients' general QoL. Proper FMF management also prevents the long-term complications like amyloidosis and its effect on the kidneys (**Malik *et al*., 2021**).

The wellbeing-related QoL is meant to define the clinical manifestations, physical status, and disease impacts on mental and social functioning. Like most long-lasting chronic diseases, the QoL of patients with FMF has become a significant well-being subject, especially during the last decades (**Sönmez *et al*., 2020**).

Persistent illness can influence patients' satisfaction QoL because of shifting ways of life all through the direction of the infection. A good QoL is significant in youngsters with persistent sickness as far as dealing with the illness, deciding sickness anticipation, and forestalling constant inconveniences from the illness. FMF has considerable sway on day-by-day exercises, tutoring, and family working in kids. Specifically, patients with FMF who have a serious illness course or potentially amyloidosis have a diminished QoL (**Koşan *et al*., 2019**).

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Besides, the issue of QoL has alternate points of view including agony, tiredness, mindset issues like tension, gloom, and rest quality that reason trouble in assessing their effects on patients with FMF (**Bodur *et al*., 2020**). Patient-documented result measures have been used for the evaluation of the QoL in patients with persistent crippling diseases. These estimations help doctors and wellbeing policy makers to decide psychosocial issues in patients with constant illnesses to play out a normalized evaluation of these problems (**Öztürk *et al*., 2015**).

The tools in the literature to estimate FMF HRQoL and other rheumatological diseases are few. Examples include PedsQoL, Short Form 36 (SF-36), Hospital Anxiety Despondency Scale (HADS), the BREF World Health Association Quality of Life Scale (WHOQOL-BREF), the Health Assessment Survey (HAQ), and the Functional Evaluation of Chronic Illness Therapy (FACIT) – Fatigue Scale (**Makay *et al*., 2009; Alayli *et al*., 2014; Sönmez *et al*., 2020**). However, there is no agreement on the utilization and use of these scales or records because of troubles like the need for quantitative measures and application in an occupied clinical setting (**Unal-Ulutatar and Duruoz, 2021**).

The aim of the study was to evaluate the outcomes of HRQoL in a large cohort of Egyptian patients with FMF.

PATIENTS AND METHODS:

This study was conducted at the National Research Center (NRC) in Cairo, Egypt, during the period from June 2019 till March 2021. It included 118 children diagnosed with FMF and recruited from the outpatient clinic of the Clinical Genetics Department at the Medical Center of Excellence, NRC. A total of 100 healthy children matched in age and sex served as controls. The enrolled control group included patients' siblings and relatives with similar socioeconomic conditions, that is, living in a similar environment, educational level, income, and civil status. Detailed history was collected with respect to demographic data and age at the onset of disease. A detailed three-generation pedigree analysis was taken with emphasis on the parental consanguinity and similarly affected family members. Patients were clinically evaluated. The clinical diagnosis of FMF was established according to the Tel-Hashomer criteria revised by **Livneh *et al*. (1997)**. Assessment of the disease severity was done using the scoring systems by **Pras *et al*. (1998),** and **Ozen *et al*. (2009)**. Clinical and laboratory data were collected from the patients' medical records. Patients or their caregivers gave consent. The performed study was consistent with the requirements of the NRC Ethical Scientific Committee. It was implemented in adherence to the NRC's human research bylaws. It obeys the provisions of the 1964 Helsinki Declaration or its later 2000 amendments.

The evaluation of HRQoL was done by the Pediatric Quality of Life (PedsQLTM) Inventory 4.0 Generic Core Scale (Arabic version). Four age groups were included (2–4 years, 5–7 years, 8–12 years, and 13–18 years). It was composed of four different categories: the physical functioning, the emotional functioning, the social functioning, and school functioning. There are pediatric forms (including ages 5–7 years, 8–12 years, and 13–18 year), filled in by children, and parental forms (including ages 2–4, 5–7, 8–12, 13–18 years), filled in by their parents depending on a standard recall period before the enrollment by 1 month. Every question had a probability of one answer out of five, with a range from 0 for 'never' to 4 for 'almost always.' Calculating the total score was done by dividing the sum of all the recorded scores over the number of answered questions. The resulting scores were then converted to standardized scores on a 0–100 scale. The higher scores represented better functioning levels (**Varni *et al*., 2001**).

Statistical analysis

SPSS 23 (Statistical Package for the Social Sciences) for Windows was used to perform data analysis. Quantitative variables were presented in the form of means and SD. The qualitative variables were presented in the form of numbers and percentage. Comparison of means of the quantitative variables between FMF and the controls was done after the exploration of data for normality by Shapiro–Wilk test of normality. Mann–Whitney U test was used for comparison of not normally distributed data. The independence between the groups and the qualitative variables were detected by χ^2 test. Instead, Fisher's exact test was used when one expected cell or more were less than or equal to 5. Spearman rho correlation was used for binary correlations. The results were expressed in the form of correlation coefficient (R) and P values. The significance level for all tests was set at P value less than or equal to 0.05.

RESULTS:

A total of 118 patients with FMF were enrolled in this study (62 males and 56 females), with a male to female ratio of 1.1 to 1. Their age range was from 5 to 14 years with a mean±SD of 9.18±2.10 years. Consanguinity was present in 49 (41.5%) patients. A total of 100 healthy controls were included in the study (47 males and 53 females). Their age range was from 5 to 12.16 years, with a mean±SD of 7.89±2.03 years. Regarding the education level, the majority of cases and controls were in the primary school (85/118, 72% and 70/100, 70%, respectively), whereas 26/118 (22%) of cases and 18/100 (18%) of controls were in the preparatory school. However, 7/118 (6%) cases and 12/100 (12%) controls were in the preschool, with no significant difference. Similarly, affected family members were found in 50/118

(42.4%) patients (Table 1). Patients with FMF were classified according to the clinical severity into mild (13/118 cases, 11%), intermediate (60/118 cases, 50.8%), and severe (45/118 cases, 38.1%) (Table 2).

The outcomes of HRQoL in patients with FMF were put into comparison with the controls. Patients with FMF had significantly lower scores in comparison with the control group in all domains, including the physical health (*P<0.0001*), the emotional domain (*P<0.0001*), the social domain (*P<0.0001*), and the school functioning domain (*P<0.0001*). Moreover, the psychosocial health and total scale score were more significantly affected in patients with FMF compared with the control group *(P<0.0001* and *0.0001*, respectively) (Table 3).

The degree of clinical severity in patients with FMF significantly affected HRQoL outcomes on all scales. Mild cases had better HRQoL outcomes than severe cases (*P<0.0001*). HRQoL outcomes were significantly higher in patients with fewer attacks than those who had many attacks per month (*P<0.0001*).

There was a significant association between the emotional functioning and sex (*P=0.042*), with more affection of females, but there was no association between the other HRQoL domains and sex. Similarly, there was no significant correlation between the HRQoL outcomes and age, consanguinity, family history, and level of education (Table 4).

In the control group, the total score outcomes of HRQoL were significantly associated with the age and patients' education (*P=0.012* and *0.014*, respectively). The social score outcomes were also significantly associated with age and patients' education (*P<0.0001* and *0.0001*, respectively) (Table 5).

Table 1: Demographic data in familial Mediterranean fever and control groups

	FMF (N=118) [n (%)]	Control (N=100) [n (%)]	*P value*
Sex			
Male	62 (56.9)	47 (43.1)	0.497
Female	56 (51.4)	53 (48.6)	
Consanguinity			
Negative	69 (51.9)	64 (48.1)	0.486
Positive	49 (57.6)	36 (42.4)	
Family history			
Negative	68 (57.6)	–	–
Positive	50 (42.4)	–	–
Level of education			
Preschool	7 (36.8)	12 (63.2)	
Primary school	85 (54.8)	70 (45.2)	0.252
Preparatory school	26 (59.1)	18 (40.9)	
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χ^2 test to detect the independence between groups and the categories of each of the qualitative variables.
FMF, familial Mediterranean fever.

Table 2: Frequency of attacks and clinical severity in patients with familial Mediterranean fever

Variables	Categories	FMF (N=118) [n (%)]
Frequency of attacks (month)	<1	17 (14.4)
	1–2	38 (32.2)
	>2	63 (53.4)
Severity	Mild	13 (11)
	Intermediate	60 (50.8)
	Severe	45 (38.1)

FMF, familial Mediterranean fever.

Table 3: Health-related quality of life scores comparison between familial Mediterranean fever and control groups

	FMF (N=118) (mean±SD)	Control (N=100) (mean±SD)	*P value*
Physical health	30.83±13.34	91.12±13.88	*<0.0001**
Psychosocial health	36.06±12.32	84.27±13.63	*<0.0001**
Emotional	34.20±14.49	77.80±13.54	*<0.0001**
Social	45.89±14.45	87.75±14.16	*<0.0001**
School	28.04±17.17	84.97±18.81	*<0.0001**
Total	33.97±12.61	85.29±14.03	*<0.0001**

FMF, familial Mediterranean fever.
*Statistically significant *P value* less than or equal to 0.05.

Table 4: Correlation between each of the quality of life outcome scores with different variables in patients with familial Mediterranean fever

	Physical health		Psychosocial health		Emotional functioning		Social functioning		School functioning		Total score	
Patient's characteristics	Corr.	*P value*	Corr.	*P value*	Corr.	*P value*	Corr.	*P value*	Corr.	*P value*	Corr.	*P value*
Sex	–0.116	0.210	–0.114	0.217	–0.187	0.042*	0.121	0.191	–0.102	0.270	–0.136	0.143
Age	–0.012	0.900	–0.004	0.968	–0.070	0.453	0.141	0.127	–0.092	0.324	0.0001	0.999
Consanguinity	0.043	0.645	–0.006	0.948	0.037	0.693	–0.034	0.717	–0.034	0715	–0.005	0.954
Family history	0.030	0.747	–0.077	0.405	0.002	0.980	–0.063	0.500	–0.131	0.157	–0.068	0.466
Education level	0.024	0.793	0.001	0.987	–0.096	0.303	0.116	0.211	–0.066	0.476	0.024	0.796
Frequency of attacks (month)	–0.435	<0.0001*	–0.474	<0.0001*	–0.338	<0.0001*	–0.312	0.001*	–0.450	<0.0001*	–0.491	<0.0001*
Severity	–0.690	<0.0001*	–0.737	<0.0001*	–0.609	<0.0001*	–0.435	<0.0001*	–0.652	<0.0001*	–0.735	<0.0001*

*Statistically significant P value less than or equal to 0.05.

Table 5: Correlation between each of the quality of life outcome scores with different variables in control

	Physical health		Psychosocial health		Emotional functioning		Social functioning		School functioning		Total score	
Patient's characteristics	Corr.	*P value*	Corr.	*P value*	Corr.	*P value*	Corr.	*P value*	Corr.	*P value*	Corr.	*P value*
Sex	–0.007	0.945	–0.038	0.709	–0.076	0.450	–0.065	0.520	–0.026	0.796	–0.102	0.312
Age	0.095	0.347	0.180	0.073	0.139	0.168	0.365	<0.0001*	0.086	0.397	0.251	0.012*
Consanguinity	–0.116	0.251	–0.044	0.666	–0.075	0.460	0.091	0.368	–0.007	0.943	0.018	0.856
Education level	0.171	0.089	0.167	0.097	0.166	0.098	0.352	<0.0001*	0.113	0.264	0.245	0.014*

*Statistically significant *P value* less than or equal to 0.05.

DISCUSSION

FMF is a chronic auto-inflammatory disease that has a negative influence on the patients' QoL. HRQoL is much affected by the patients and their parents' perception of the disease on the physical and emotional states (**Schumacher *et al*., 1991**). The outcome measures of HRQoL have an important role in the management plans (**Buskila *et al*., 1997; Keystone *et al*., 2008**). In the current study, we investigated the effect of FMF on the HRQoL in a large cohort of Egyptian patients using PedsQoL.

The PedsQoL was studied in patients with FMF (**Alayli *et al*., 2014; Sönmez *et al*., 2020**). Our study reported lower HRQoL scores in all domains in addition to the psychosocial health and total score. Of note, we found that the school functioning domain reported the lowest scores compared with other scores. This observation could be owing to the recurrent absence from school during disease attacks or for hospital visits. Lower HRQoL outcome scores were previously reported in patients with FMF compared with their matched peers. **Makay *et al*. (2009)** reported lower scores in all QoL domains in pediatric patients with FMF. Similar findings were also described by **Alayli *et al*. (2014)**. In addition, previous studies reported impaired QoL for both children and adults with FMF (**Buskila *et al*., 1997; Sahin *et al*., 2013**). On the contrary, **Kazem *et al*. (2021),** and **Yildirim *et al*. (2021)**, reported lower QoL scores in some domains only, including the physical health, emotional functioning, and school functioning. A significant attrition in the physical function in patients with FMF was also reported in previous studies (**Giese *et al*., 2013; Sahin *et al*., 2013). Deger *et al*. (2011)**, elaborated the important effect of FMF on the physical functioning domain of QoL. However, **Guler *et al*. (2018)**, depicted the negative effect of FMF on QoL scores of pain, energy, physical, social, and emotional functions with no affection of the mental health. Another study by **Sahin *et al*. (2013)**, reported that FMF had a noxious effect on all domains of HRQoL sparing the vitality.

In the present study, there was a significant association between the emotional functioning and sex, but there was no association between the other HRQoL domains and sex. The lower score in the emotional functioning could be explained by the negative thoughts affecting patients' lives when compared with their peers. In our study, females had lower scores in the emotional functioning compared with males. This was in accordance with **Bodur *et al*. (2020),** and **Unal-Ulutatar** and **Duruoz (2021)**, who showed more affection of the FMF-QoL scores in females. Opposite to our results, **Sönmez *et al*. (2020)**, found no association between PedsQL scores and sex.

In the current study, no significant effect of age was observed on HRQoL outcome scores. **Unal-Ulutatar** and **Duruoz (2021)**, also reported a weak correlation with age.

In the present study, no significant difference was noticed regarding the educational level between patients with FMF and the controls. This conforms to the study by **Unal-Ulutatar** and **Duruoz (2021)**, which reported no association with the level of education. In contrast, **Bodur *et al*. (2020),** and **Yildirim *et al*. (2021)**, found an association between FMF QoL scores and the level of education in patients.

The degree of clinical severity in patients with FMF significantly affected HRQoL outcomes on all scales. Mild cases had better HRQoL outcomes than severe cases (*P<0.0001*). This elaborates the importance of controlling the disease activity aiming to achieve a better QoL. In agreement with previous studies, better HRQoL outcomes were reported in the milder form of the FMF disease (**Buskila *et al*., 1997; Sahin *et al*., 2013**; **Guler *et al*., 2018**). On the contrary, previous studies found no association between HRQoL outcomes and disease severity (**Buskila *et al*., 1997; Giese *et al*., 2013; Sahin *et al*., 2013; Alayli *et al*., 2014; Bodur *et al*., 2020; Sönmez *et al*., 2020**). Of note, HRQoL outcomes were significantly higher in patients with fewer attacks than those who had many attacks per month (*P<0.0001*). This was in line with previous studies (**Buskila *et al*., 1997; Duruöz *et al*., 2018; Bodur *et al*., 2020). Yildirim *et al*. (2021**), reported worse QoL in the physical well-being scores in patients with FMF experiencing more number of attacks. However, **Sahin *et al*. (2013)**, reported an insignificant association between HRQoL and the number of attacks. They owed it to their smaller number of patients.

Of note, HRQoL outcome scores in the controls were significantly related to age and patient education in terms of total score and social score outcomes. Hence, the sequelae of long-term complications on HRQoL in patients with FMF outweigh other socioeconomic factors influencing the HRQoL in the unaffected peers.

There are few data in the literature evaluating the HRQoL in children with FMF, and it was never evaluated in Egyptian children with FMF. In addition, most studies comprise a small number of patients; however, our study has a higher number of children and adolescents evaluated for the HRQoL.

CONCLUSION

This is the first study conducted on a large number of Egyptian patients with FMF. Our study demonstrated that FMF had a negative effect on HRQoL in all domains in patients when compared with healthy peers. Besides, a relationship between HRQoL, the number of attacks, and severity of the disease has been delineated. Our study highlights the importance of psychosocial support in the management plans aiming at improving HRQoL of patients with FMF.

CONFLICT OF INTEREST

There are no conflicts of interest.

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