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Health-related quality of life and depressive symptoms in Friedreich ataxia

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Abstract

Purpose Friedreich ataxia (FRDA) is a chronic, progressive and highly disabling cerebellar degenerative disease. Despite this, little attention has been paid to the health-related quality of life (HRQOL) in this disease. The aim of the present study was to assess FRDA patients' perception of HRQOL and to determine the influence of depression, and demographic and clinical variables.

Method The sample consisted of 62 patients with genetically confirmed FRDA. The SF-36 Health Survey was used to assess HRQOL. Depressive symptoms were evaluated with the Beck Depression Inventory-II.

Results FRDA patients' mean scores were significantly lower than the values for the Spanish population in all SF36 dimensions. Average z scores ranged from -5.5 in physical functioning to -0.48 in mental health. Age and clinical variables were significant predictors of HRQOL in only several dimensions, whereas BDI scores were able to predict a significant percentage of variance in all SF36 dimensions, except physical functioning.

Conclusions Our study demonstrates the high impact of Friedreich ataxia on quality of life. This impact does not only occur in those aspects most related to motor disability but it is also present in non-motor dimensions. Depressive symptomatology is the most relevant variable for predicting quality of life.

Keywords Friedreich ataxia · Cerebellum · Quality of life · Depression · Neurological diseases

Introduction

Friedreich ataxia (FRDA) is the most common hereditary ataxia with an estimated prevalence of 2–4 cases per 100,000 [1, 2]. The causative genetic mutation in FRDA is a GAA triplet repeat expansion in the frataxin (FXN) gene which encodes a mitochondrial protein named frataxin [3]. The disease is characterized by progressive ataxia, dysarthria, pyramidal weakness, deep sensory loss, hypertrophic cardiomyopathy, skeletal abnormalities and diabetes mellitus [4–6]. Neuropsychological studies have indicated the presence of subtle cognitive impairments [7–11]. FRDA typically appears prior to 25 years of age, with the average age of symptom onset occurring in the early to mid-teens. The traditional view of FRDA as a disease that primarily affects the spinal cord and peripheral sensory nerves is not currently accepted. The progressive destruction of the dentate nucleus and the atrophy of the superior cerebellar peduncles are evident in neuropathological studies [12]. Neuroimaging studies have revealed abnormalities in cerebellar and cerebral white matter integrity, gray matter structure and connectivity with the cerebellum [13].

At present, there is no proven treatment that can slow the progression or eventual outcome of FRDA. The chronic, progressive nature of FRDA has a profound impact on the health and well-being of people with FRDA. In its typical form, the disease leads to severe disability by early adulthood, with substantial functional loss, wheelchair dependence and loss of quality of life [14]. Despite this, little attention has been paid to the health-related quality of life in this disease. Previous studies are scarce, but they have consistently reported that health-related quality of life (HRQOL) was perceived to be significantly worse for individuals with FRDA in practically all dimensions [15–17]. However, there are discrepancies about the factors that contribute to the deterioration in

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HRQOL. For example, Wilson et al. [17] say that patients with a more severe disease did not perceive a lower HRQOL than those with mild or moderate disease except in their physical functioning. In addition, the adult onset subgroup had significantly lower HRQOL in several dimensions. In the study of Epstein et al.'s [15] age, rather age at onset or length of GAA triplet expansion appears to influence physical functioning. These studies focused on demographic variables and, specially, severity-related variables: age at disease onset, disease duration, ataxia severity and number of GAA repeats in the frataxin (FXN) gene. However, severity of disease or related variables are not the only determinants of HRQOL in neurological chronic diseases and emotional factors may have a relevant influence on perceived quality of life. In Parkinson's disease, for example, depression is one of the factors most closely associated with HRQOL [18]. To the best of our knowledge, the relationship between HRQOL and depression in FRDA has not been studied.

The aim of the present study was to assess FRDA patients' perception of health-related quality of life and to determine the influence of depression and demographic and clinical variables on HRQOL.

Methods

Participants

Sixty-two persons homozygous for a GAA expansion in intron 1 of the FXN gene participated in the study (Table 1). Patients were recruited from three Spanish reference hospitals: Hospital Universitario Ntra. Sra. Candelaria (S/C de Tenerife) ($N=9$), Hospital Marqués de Valdecillas Hospital (Cantabria) ($N=15$), and Hospital La Paz (Madrid) ($N=38$). These hospitals have specialized services in the diagnosis and treatment of the FRDA and receive patients from various Spanish regions. Patients with a history of alcohol or drug dependence, major psychiatric illness (other than depression) or neurological disease (other than FRDA) were excluded. This study had the approval of the ethical review board of the Hospital Universitario Ntra Sra de la Candelaria (Tenerife. Spain; registration number: PI 36/15). All the patients gave their informed consent.

Instruments

The Scale for the Assessment and Rating of Ataxia (SARA) was used to quantify severity of disease. SARA scores range from 0 to 40, higher scores reflecting a greater disease severity [19].

Health-related quality of life was assessed with the Spanish version of the SF-36 Health Survey, a standardized and widely used generic HRQOL scale for assessing mental and physical aspects of HRQOL [20]. The SF-36 has 36 items measuring eight health dimensions, including physical functioning, role physical, bodily pain, general health perception, vitality, social functioning, role emotional and mental health. For each of the eight subscales, higher scores reflect better-perceived health. A physical component summary and a mental component summary can be calculated from the scales. However, the physical and mental components of the SF-36 were not used in this research work, since the characteristics of the sample (very low scores in the dimensions that evaluate physical functionality), distorted the scores of the components, which reduced their reliability.

Depressive symptoms were evaluated with the Spanish adaptation of the Beck Depression Inventory-II (BDI-II) [21]. BDI is a 21 item self-rating questionnaire, known for its practicality, reliability, and accuracy [22]. Scores on each item can range from zero (symptom absent) to three (pronounced presence of symptoms), yielding a potential range of scores from 0 to 63. A score of 0–13 is classified as minimal depressive symptoms, 14–19 as mild, 20–28 as moderate, and 29–63 as severe.

Procedure

The patients registered at each hospital were contacted and invited to participate in the study. Participants were informed about the aim of the investigation and

Table 1 Descriptive statistics of demographic and clinical data and ANOVA results

	Total sample ($N=62$)		Male ($N=28$)		Female ($N=34$)		F (1,60)	p
	M[a]	SD[b]	M	SD	M	SD		
Age	40.98	13.52	42.07	12.45	40.09	14.47	0.33	0.56
Age at disease onset	20.18	10.91	21.57	10.12	20.18	11.11	0.04	0.83
Disease duration (years)	20.81	10.61	20.50	10.05	19.91	11.72	0.26	0.61
Educational level	12.24	4.12	12.57	4.08	11.97	4.20	0.32	0.57
SARA	22.27	8.64	21.33	23.06	9.14	8.26	0.58	0.45

[a]Average scores in the clinical–demographic variables

[b]Standard deviations in the clinical–demographic variables

participated voluntarily and 94% of patients agreed to participate. All subjects gave their informed consent and were not provided with any incentives to participate. All procedures were in accordance with the Helsinki Declaration for human research and were approved by the ethics committee of the University of La Laguna. Demographic (age, gender, education), clinical (age at disease onset, duration of disease) and genetic data (length of expanded repeat in both shorter, GAA1, and longer, GAA2, alleles) were recorded. Each patient underwent a neurological examination. The questionnaires were completed and collected from patients after they agreed to participate. The questionnaires were self-administered. A psychologist from the study group (A. Hernández-Torres) was present to assist patients with completing the questionnaires when necessary.

Data analysis

First, descriptive statistics were calculated to know the demographic and disease characteristics of the sample. The possible sex differences in demographic and clinical parameters were studied using the one-way ANOVA method. Second, descriptive statistics of SF-36 dimensions of the sample were calculated and compared with norms of the Spanish population [23] with Student's *t* test for one sample and controlling Type I errors with the false discovery rate method [24]. An ANOVA Split-Plot was conducted to analyze sex differences. The effect sizes of comparisons were estimated with Cohen's d. Third, *z* scores of the participants in the different SF-36 dimensions were found, with the objective of calculating the percentage of the sample with an alteration. Fourth, correlation analyses between SF-36 dimension scores and demographic-disease variables were carried out. Fifth, descriptive statistics of BDI-II scores of the sample were calculated, sex differences were studied using the χ^2 test and the relationship with SF-36 dimension scores was studied by correlation analyses. Finally, the lineal regression model was used to determine the influence of depressive symptoms on the SF-36 dimension scores. Stepwise linear regression models were performed on the cases which had significant correlations with depression and clinical parameters. The most adjusted model was selected in each case, with the intention of not including redundant variance in the models and to later obtain a better calculation of the relative contribution of the depressive symptomatology on HRQOL. The percentage of explained variance for each variable was calculated using dominance analysis. The index used was the LMG measure, that is an average of R^2 for all possible order permutations for each predictive variable of the lineal regression [25]. Analyses were performed using the ULLR toolbox.v.1.0.R for R 3.4.4 version [26].

Results

Demographic and clinical characteristics are shown in Table 1. Of the 62 patients, 34 were women and 28 were men. Age at examination ranges from 19 to 79 years of age. The age range of disease onset was 3–44 years of age and the disease duration range was 1–47 years. Years of education ranged from 0 to 20 years. Most of the patients had not attended university. SARA scores range from 6 to 37, showing that the sample included people with a wide range of disease severity. One-way ANOVA showed that there were no significant differences in demographic and clinical parameters between males and females. An ANOVA Split-Plot was conducted to analyze sex differences in SF-36. The intragroup factor of the analysis was composed of the dimensions of the SF-36. The intergroup factor was sex. No effects of sex [$F(1, 60) = 0.04$, $p > .05$] or interaction between factors were identified [$F(1, 420) = 0.56$, $p > .05$].

FRDA patients' mean scores were significantly lower than the values for the Spanish population in all SF36 dimensions (Table 2). All the effect sizes of the differences could be considered medium or large, with a range of 0.40–3.82 [27].

The patients' raw scores were transformed to *z* scores using population norms adjusted for age and sex. The means of *z* scores are negative in all cases. The physical functioning dimension (PF) shows a large deviation compared to the normative population. General health (GH), social functioning (SF) and role physical (RP) are in a range between −2 and −1.5 standard deviations. Bodily pain (BP), vitality (VT), role emotional (RE) and mental health (MH) have a score lower than −1 standard deviation (Fig. 1).

Individual *z* scores equal to or below 2 SD were considered indicators of a reduced HQROL. Most of the patients (92%) had *z* scores ≤ 2 in PF. In RP and GH patients with a reduced HRQOL were 48% y 40%, respectively. A lower percentage of patients had *z* scores ≤ 2 in SF (35%) and RE (24%). The percentage of patients with an impaired HRQOL was similar in BP (19%) and VT (18%). Only 6% of patients had *z* scores ≤ 2 SD in MH.

Relationships between HRQOL and clinical and demographic variables were analyzed. PF scores were positively correlated with age at examination ($r = .73$, $p < .005$) and age at onset ($r = .65$, $p < .005$) and negatively correlated with triplet repeat length in GAA1 (shorter allele) ($r = -.59$, $p < .005$), and GAA2 (longer allele) ($r = -.39$, $p < .01$). Scores in the GH dimension were also associated with age and age of disease onset ($r = .43$, $p < .01$; $r = .28$, $p < .05$, respectively). Duration correlated negatively with Role Emotional Scores ($r = -.37$, $p < .01$).

The direction of the relationship between PF and GH scores with age at examination was opposite to that

Table 2 Descriptive statistics of SF-36 dimensions and *t* test results

	Participants		General population[a]		*t* (61)	*d* Cohen	*p*
	M[b]	SD[c]	*M*	SD			
Physical functioning	15.81	19.98	87.40	24.00	−28.21	3.82	< .005
Role physical	41.53	43.16	83.20	35.20	−7.60	1.03	< .005
Body pain	60.44	29.39	79.00	27.90	−4.97	0.67	< .005
General health	35.32	21.33	68.30	22.30	−12.17	1.65	< .005
Vitality	52.10	23.83	66.90	22.10	−4.89	0.66	< .005
Social functioning	65.93	29.53	90.10	20.00	−6.44	0.87	< .005
Role emotional	70.97	41.59	88.60	30.10	−3.34	0.45	< .005
Mental health	64.84	22.36	73.30	20.10	−2.98	0.40	< .005

[a]Spanis population normative data [28]

[b]Average scores in SF-36 dimensions

[c]Standard deviations in SF-36 dimensions

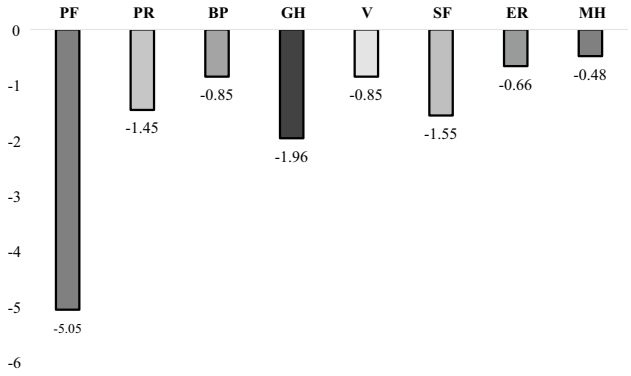

Fig. 1 Average *z* score for each SF-36 dimension

Table 3 Linear regressions of the SF-36 dimensions that only correlated significantly with the BDI-II total score

	β	SE	*t*	*p*
Criterion variable: role physical (DW[a] = 1.83; R^2 = 0.06)				
BDI-II total	−0.28	0.02	−2.22	< .05
Criterion variable: body pain (DW[a] = 2.04; R^2 = 0.06)				
BDI-II total	−0.28	0.01	−2.25	< .05
Criterion variable: vitality (DW[a] = 1.61; R^2 = 0.18)				
BDI-II total	−0.43	0.01	−3.73	< .005
Criterion variable: social functioning (DW[a] = 1.54; R^2 = 0.26)				
BDI-II total	−0.52	0.02	−4.76	< .005
Criterion variable: mental health (DW[a] = 1.90; R^2 = 0.51)				
BDI-II total	−0.72	0.01	−8.06	< .005

[a]DW = Durbin–Watson Test, $1.5 < DW < 2.5$ indicate accordance with the lineal regression model conditions

expected, considering the tendency of the general population, where there is a decrease in PF and GH scores as age increases [28]. Therefore, the direction of the relationship above was studied in greater depth. The variable "age at examination" was divided into three groups (corresponding to the percentile sections P33, P33–P66 and P66). The first of which had an average age of 28.62 ($n = 24$), the second an average age of 39.83 ($n = 18$) and the third an average age of 56.85 ($n = 20$). The first group had an average *z* score in PF of − 6.89 and − 2.54 in GH; the second of − 4.86 in PF and − 2.21 in GH; the third of − 3.00 in PF and − 1.02 in GH. The *z* scores were statistically different in both dimensions (PF: $F(2,59) = 30.63$, $p < .005$; GH: $F(2.59) = 10.19$, $p < .005$), showing that as the age advances, the deviation with respect to the normative group decreases. However, when using raw scores instead of *z* scores, no significant differences were found between the age groups in PF [$F(2.59) = 0.90$, $p > .05$] or in GH [$F(2.59) = 0.73$, $p > .05$].

The mean BDI score for FRDA patients was 15.32 (SD = 10.33). Minimal depressive symptoms were observed in 50% of participants, 23% of participants scored in the "mild" range, 23% had moderate depressive symptoms, and 5% scored in the "severe" range. The severity of depressive symptomatology and sex was independent variables [$\chi^2(2) = 1.33$, $p > .05$]. Scores in all SF36 dimensions, except PF, correlated negatively with BDI-II scores.

In the cases where the dimensions only correlated with depressive symptoms, a simple linear regression was used (Table 3). The regression models showed that depression explained 6% of RP variability [$F(1, 60) = 4.92$, $p < .05$)]; 6% of BP variability [$F(1, 60) = 5.07$, $p < .05$)]; 18% of VT variability [$F(1, 60) = 13.96$, $p < .005$)]; 26% of SF variability [$F(1. 60) = 22.64$, $p < .005$)]; and 51% of MH variability [$F(1, 60) = 65.04$, $p < .005$)].

Stepwise linear regression models were performed on the cases which had significant correlations with depression and clinical parameters and the most adjusted model was selected in each case. In addition, to determine the importance of each variable within the multiple regression models, the dominance analysis was used (Table 4). The best multiple

Table 4 Multiple linear regression analysis and dominance analysis to determine the influence of each predictor

	β	SE	t	p	Dominance analysis: *LMG* index
Criterion variable: physical functioning ([a]DW = 1.91; $R^2 = 0.59$)					
Age	0.56	0.02	5.33	< .005	0.38
GAA1 repeats	−0.31	0.00	−2.94	< .005	0.21
Criterion variable: general health (DW = 2.18; $R^2 = 0.36$)					
Age	0.48	0.01	4.66	< .005	0.22
BDI-II Total Score	−0.38	0.01	−3.67	< .005	0.14
Criterion variable: role emotional (DW = 1.72; $R^2 = 0.20$)					
BDI-II Total Score	−0.37	0.02	−3.24	< .005	0.12
Disease duration	−0.30	0.02	−2.66	< .01	0.08

[a]DW = Durbin–Watson Test, $1.5 < DW < 2.5$ indicate accordance with the lineal regression model conditions

regression model generated to predict GH included the age and the score of the BDI-II [$F(1, 60) = 13.48$, $p < .005$)]. The variance explained by the model was 36% and 22% of the variance corresponded to age, while 14% of the variance was attributed to depressive symptoms. In the case of RE, a multiple linear regression model that included BDI-II score and disease duration was selected as the most adjusted [$F(1, 60) = 8.64$, $p < .005$)]. This model explained 20% of the variance and 12% of the variance was attributable to depressive symptoms, while 8% of the variance corresponded to disease duration.

PF was the only dimension that did not correlate significantly with the BDI-II score. The best regression model generated for this dimension included the age and number of GAA repeats in allele 1 [$F(1, 60) = 35.55$, $p < .005$)]. This model explained 59% of the variance and 38% of the variance corresponded to age, while 21% of the variance was attributed to the number of GAA1 repeats.

Discussion

One of the more relevant aims of the clinical management of Friedreich ataxia is to ameliorate the impact of the disease on the quality of life of the affected patients. In this respect, it is of undoubted interest to know the subjective experience of the patients and the variables related to this experience.

The results found here demonstrate that HRQOL is significantly reduced in FRDA patients. Scores in all dimensions are significantly lower than scores in the general population. Given the clinical features of FRDA, it is not to be unexpected that dimensions directly related to motor disability showed low scores. But a poor HRQL is also observed in non-motor dimensions as social functioning, role emotional and mental health. These results coincide with those obtained in previous studies of Friedreich ataxia using the SF36 dimensions [15, 17].

After adjusting individual scores for age and sex, most patients had severely reduced scores in the physical functioning dimension and almost half had severely poor scores in the role physical and general health dimensions. A smaller but also relevant percentage of patients had a low score in the social functioning and role emotional dimensions. Therefore, FRDA patients not only perceived themselves as highly limited in performing physical activities, but they also perceived themselves as limited in social activities and daily life activities due to emotional problems. It is worth mentioning that 24% of patients perceived that emotional problems limited their daily life although only 6% of patients reported significant problems in mental health when they were directly asked about feelings of nervousness or depression. In other neurological disorders, it is also common to find a reduced HRQOL. However, if the results are compared with those generally reported by studies on Parkinson's disease or multiple sclerosis [29–32], the magnitude of the reduction in HRQOL and the amplitude of it appears to be greater in FRDA.

Correlational analyses indicate that a higher age at the time of examination and a later onset of the disease were associated with less limitations in physical activity and a better perception of health. The fact that the relationship with age is positive may be surprising but may be explained as a consequence of the use of adjusted scores. To confirm this fact, the sample was divided into three age groups. All groups obtained z scores which were indicative of severe physical limitations (z score range −3 to −6.89) but the highest scores were observed in the oldest group. Similarly, z scores on perception of health status were higher in the oldest group. In contrast, the differences in raw scores between the groups were not significant in any of the cases. Therefore, the observed positive association is due to the fact that the perception of youngest patients about their limitations in physical activity or their general health deviates more from their age reference group than that of the oldest patients.

Physical functioning was also negatively related with triplet repeat length, an expected result given that the triplet repeat length is directly proportional to frataxine deficiency [33, 34] and larger expansions are associated with a more severe disease [35]. In addition, the role emotional dimension had a negative association with duration of disease showing that as the period of time since the onset of disease increases the more emotional problems interfere with daily activities.

In recent years, there has been a growing interest in depression in patients with Friedreich ataxia [36–38] and mental health issues has been included as a topic in the recent Consensus Clinical Management Guidelines for Friedreich ataxia [39]. In the present study, the mean score of

FRDA patients in BDI-II is in the range considered as mild severity of depression [21] but 28% of patients scored in the moderate/severe range.

The scores in BDI-II were negatively related to all SF36 dimensions, except physical functioning, and for some of these dimension depression was the only associated variable: depressive symptomatology accounted for 6% of variance of the role physical and bodily pain dimensions, 18% of vitality, 26% of social functioning and 51% of mental health. In all cases, higher scores in BDI-II predicted a lower HRQOL. In addition, multiple regression analyses showed that age and depression were significant predictors of general health scores. Depression was also a significant predictor of role emotional along with the duration of the illness.

Physical functioning was the only dimension not related with depression. This result should be explained by the fact that impairment of physical functioning in our patients is extremely important ($z = -5.05$). Activities such as running, climbing stairs, walking or bathing oneself are completely impossible for the majority of our patients or tremendously difficult for them to perform. Therefore, patient's scores are grouped in the low end of this scale. Scarce variability limits the obtainment of significant correlations. In addition, the items that make up this scale are highly specific (i.e., *does your health limit you in walking more than a mile*?) and may be less sensitive to the effects of depression. Multiple regression analyses showed that scores in this dimension were significantly predicted by age and GAA1 size (shorter allele). The fact that GAA2 (longer allele) size was not a significant predictor of limitations in physical activities is consistent with previous studies that found that the association between GAA expansion size and clinical features is especially important in the case of the smallest allele, whereas GAA2 expansion size is a poor predictor of clinical variation [33, 40].

Regarding demographic and clinical variables, the results here show that quality of life is predicted by age, rather than age of onset, at least in terms of physical activity limitations and perceived general health. The relevance of age as a predictor of quality of life in FRDA is consistent with the results of Epstein et al. [15] who found that when age was included as a covariate, age predicted physical functioning scores while age of onset had no effect. On the other hand, duration and disease severity do not have a generalized effect on HRQOL, which is in line with previous observations [15, 17]. These results suggest that the reduction of quality of life in Friedreich ataxia occurs from the initial stages and when the severity of ataxia is still relatively low.

Depression is the variable that has been shown to have the most widespread association with quality of life. As is to be expected, the severity of the depressive symptomatology assessed by means of the BDI questionnaire has a markedly high relationship with the mental health dimension of the SF36. But this is not the only dimension related with depression. Although in some cases the predictive capacity is more limited (role physical and bodily pain), depression has a relevant predictive power in other dimensions. Thus, depression influences the self-reported problems in daily activities caused by physical health, the perceived pain and health status, the feelings of tiredness and the perceived limitations in social and daily activities due to emotional problems.

There are to the best of our knowledge no other reports on the impact of depression in health-related quality of life in Friedreich ataxia, although studies in other neurodegenerative disorders show that emotional variables play a relevant role on quality of life perception [41, 42]. To date, there are no tried and tested therapies that can alter the progression of this disease, although a number of promising compounds have been identified in [39, 43]. In this context, a notable challenge for clinicians is to improve the quality of life of patients. The results presented here suggest that intervention on depression may be a useful way to enhance the subjective experience of quality of life. This is in line with the proposal of the Consensus Clinical Management Guidelines for Friedreich ataxia [39], which recommends counseling that promotes adjustment to changes occurring during the disease. Similarly, the NICE guide for depression in adults with a chronic physical health [44], recommends participation in self-help groups based on Cognitive Behavior Therapy (CBT), or the application of CBT in an individual format, to prevent depressive symptoms in patients.

In conclusion, the present study demonstrates the high impact of Friedreich ataxia on quality of life. This impact does not only occur in those aspects most related to motor disability but is also present on non-motor dimensions. The poor quality of life experienced by patients with Friedreich ataxia is only partially related to demographic or disease variables, with depressive symptomatology being the most relevant variable for predicting quality of life. Therefore, the recognition and adequate treatment of depression are essential to improve the subjective experience of quality of life of Friedreich ataxia patients.

The present study has several limitations. Other variables that may be modulating the observed relationship such as social support or coping strategies have not been studied here. In addition, a greater sample size may be necessary to improve the representativeness.

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