Quality of life in patients with multiple sclerosis: The impact of depression, fatigue, and disability

6 authors, including:

Pınar Ortan Ce
University of Health Science Izmir Bozkaya Research and Education Hospital
38 PUBLICATIONS   264 CITATIONS

SEE PROFILE

Muhtesem Gedizlioglu
76 PUBLICATIONS   474 CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Multiple sclerosis View project

Research View project

Quality of life in patients with multiple sclerosis: the impact of depression, fatigue, and disability

Altınay Göksel Karatepe[a], Taciser Kaya[a], Rezzan Günaydın[a], Aylin Demirhan[a], Pınar Çe[b] and Muhteşem Gedizlioğlu[b]

Aim The aim of this study was to assess the quality of life (QoL) in patients with multiple sclerosis (MS), and to evaluate its association with disability and psychosocial factors especially depression and fatigue.

Methods Demographic characteristics, education level, disease severity, and disease duration were documented for each patient. QoL, fatigue level, cognitive status, and depression level of patients were assessed by Multiple Sclerosis Quality of Life-54, Fatigue Severity Scale, Mini Mental State Scale, and Beck Depression Inventory, respectively.

Results Seventy-nine patients with MS were included in the study. There was a moderate degree of impairment in the QoL scores of MS patients. The most affected parts of QoL were included: role limitation-related physical and emotional problems and physical and social functions. Both physical and mental health components of QoL showed a positive correlation with the educational level and employment status; a negative correlation with the level of disability, fatigue, and depression. Depression, disability level, and fatigue were the strongest variables associated with QoL, and the most important predictor of QoL was depression.

Conclusion Our results have shown that both physical and mental health components of QoL were negatively affected by MS. The most important predictor of QoL was depression followed by disability and fatigue. To improve the QoL for MS patients, in addition to physical disability, the influences of depression and fatigue on QoL should be taken into consideration.

Ziel Das Ziel der vorliegenden Studie war die Beurteilung der Lebensqualität (QoL) bei Patienten mit multipler Sklerose (MS) sowie die Evaluierung ihrer Assoziation mit der Behinderung und den psychosozialen Faktoren, insbesondere der Depression und Fatigue.

Methoden Demographische Eigenschaften, Bildungsstand, Schweregrad der Krankheit und Krankheitsdauer wurden bei jedem Patienten dokumentiert. Die Lebensqualität, der Grad der Fatigue, der kognitive Status und der Grad der Depression der Patienten wurden anhand der Multiple Sklerose Lebensqualitätsskala (MSQOL-54), der Skala zur Messung des Schweregrads der Müdigkeit (FSS), der Mini Mental State-Skala und des Beck-Depressions-Inventars beurteilt.

Ergebnisse Für die Studie wurden 79 Patienten mit MS rekrutiert. Bei den QoL-Scores der MS-Patienten konnte ein mäßiger Grad der Beeinträchtigung beobachtet werden. Die am stärksten betroffenen Aspekte der QoL waren körperliche und emotionale Probleme und körperliche und soziale Funktionen bedingt durch die Einschränkung der Rolle der Patienten. Sowohl die körperliche als auch die psychische Komponente der Lebensqualität korrelierte positiv mit dem Bildungsstand und dem Erwerbsstatus und negativ mit dem Grad der Behinderung, Fatigue und Depression. Depression, Behinderungsgrad und Fatigue waren die stärksten Variablen in Verbindung mit der Lebensqualität; der wichtigste Prädiktor der Lebensqualität war die Depression.

Schlussfolgerungen Unsere Ergebnisse haben gezeigt, dass die körperliche und psychische Komponente der Lebensqualität von MS beeinträchtigt wird. Der wichtigste Prädiktor der Lebensqualität war die Depression, gefolgt von Behinderung und Fatigue. Um die Lebensqualität von MS-Patienten verbessern zu können, sollte neben der körperlichen Behinderung der Einfluss der Depression und Fatigue berücksichtigt werden.

Objetivo El objetivo de este estudio fue evaluar la calidad de vida (CV) en pacientes con esclerosis múltiple (EM), así como la relación que existe entre esta y los factores psicosociales y de discapacidad, en particular la depresión y la fatiga.

Métodos Se documentaron las características demográficas, el nivel educativo, la gravedad de la enfermedad y la duración de la enfermedad de cada paciente. La CV, el nivel de fatiga, el estado cognitivo y el nivel de depresión de los pacientes fueron evaluados mediante Multiple Sclerosis Quality of Life-54, la escala de gravedad de la fatiga, la escala Mini Mental State y el Inventario de Depresión de Beck, respectivamente.

Resultados Setenta y nueve pacientes con EM participaron en el estudio. Se observó una discapacidad moderada a partir de las puntuaciones de la CV de dichos pacientes. Las áreas más afectadas de la CV fueron los problemas físicos y emocionales relacionados con la limitación de las funciones, además de las funciones físicas y sociales. Los componentes de la CV de salud física y salud mental presentaron una correlación positiva con el nivel educativo y la situación laboral, y una correlación negativa con el nivel de discapacidad, fatiga y depresión. La depresión, el nivel de discapacidad y la fatiga

fueron las variables más decisivas en relación con la CV, y el factor de predicción más importante fue la depresión.

Conclusiones Los resultados de este estudio han demostrado que los componentes de salud física y mental de la CV se vieron afectados de forma negativa por la EM. El factor de predicción más importante de la CV fue la depresión, seguido por la discapacidad y la fatiga. Con el fin de mejorar la CV de los pacientes con EM y discapacidad física, debería tenerse en cuenta la influencia de la depresión y la fatiga en la CV.

Objectif Cette étude avait pour objet d'évaluer la qualité de vie (QdV) chez les patients atteints de sclérose en plaques (SEP), et d'évaluer son association avec le handicap et les facteurs psychosociaux, en particulier la dépression et la fatigue.

Méthodes Les caractéristiques démographiques, le niveau d'éducation, la gravité de la maladie et sa durée ont été documentés pour chaque patient. La QdV, le niveau de fatigue, l'état cognitif et le niveau de dépression des patients ont été évalués respectivement par l'échelle 54 de qualité de vie-sclérose en plaques, l'échelle de gravité de la fatigue, la mini- échelle d'état mental et l'inventaire de dépression de Beck.

Résultats Soixante-dix-neuf patients atteints de SEP ont été inclus dans l'étude. On a constaté un degré modéré de déficience dans les scores de QdV des patients atteints de SEP. Les aspects les plus touchés de la qualité de vie étaient les problèmes de limitation des rôles et difficultés physiques et émotionnelles associées et les fonctions physiques et sociales. Les composantes de santé physique et mentale de la QdV ont montré une corrélation positive avec le niveau d'éducation et la situation d'emploi, et une corrélation négative avec le niveau de handicap, la fatigue et la dépression. La dépression, le niveau de handicap et la fatigue étaient les plus fortes variables associées à la qualité de vie, et la dépression était le plus important prédicteur de la qualité de vie.

Conclusion Nos résultats ont montré que les composantes de santé physique et mentale de la QdV étaient négativement affectées par la SEP. Le plus important prédicteur de la qualité de vie était la dépression, suivie du handicap et de la fatigue. Afin d'améliorer la qualité de vie des patients atteints de SEP, en plus du handicap physique, les influences de la dépression et de la fatigue sur la QdV doivent être prises en considération. *International Journal of Rehabilitation Research* 34:290–298 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

[a]Department of Physical Medicine and Rehabilitation and [b]Department of Neurology, Izmir Bozyaka Training and Research Hospital, Izmir, Turkey

Correspondence to Dr Altınay Göksel Karatepe, MD, AP, Izmir Bozyaka Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Izmir Bozyaka Egitim ve Arastirma Hastanesi, Fizik Tedavi ve Rehabilitasyon Klinigi, Bozyaka, 35380, Izmir, Turkey
Tel: +90 232 2505050/1591; fax: +90 232 2614444;
e-mail: altinaygoksel@yahoo.com

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disorder of the central nervous system characterized by progressive disability in young adults (Noseworthy *et al.*, 2000). In addition to physical disability, patients with MS commonly experience fatigue, gait imbalance, bowel and bladder dysfunction, visual disturbances, cognitive dysfunction, sexual dysfunction, pain, and depression; and these symptoms result in a reduction in patients' quality of life (QoL) (Lublin and Reingold, 1996; Noseworthy *et al.*, 2000; Calabresi, 2004).

QoL is a multidimensional concept related to individuals' perception of their general well-being and level of role fulfillment across a range of different physical, psychosocial, and symptom-related phenomena (Miltenburger and Kobelt, 2002). QoL has been widely examined as an outcome measure in MS. In previous studies, the QoL of MS patients has been measured in terms of physical symptoms, mobility, emotional life, and social interaction (Nicholl *et al.*, 2001; Miller *et al.*, 2003). Patients with MS assess their QoL lower than the general populations (Nortvedt *et al.*, 1999; Ford *et al.*, 2001) and also lower than patients with other chronic diseases such as epilepsy and diabetes (Hermann *et al.*, 1996). The current literature also highlights the importance of psychosocial factors as possible factors influencing the QoL of patients with MS (Somerset *et al.*, 2002, 2003). There is a growing interest in how the many specific problems associated with MS, such as fatigue and depression, impact on different dimensions of QoL independent of the contribution of physical disability (Ford *et al.*, 2001; Benito-Leon *et al.*, 2002; Janardhan and Bakshi, 2002; Bakshi, 2003). Furthermore, the importance of MS outcome assessment from the patients' perspective has been recognized (Rothwell *et al.*, 1997).

QoL can be measured by disease-specific or generic instruments. Several QoL scales such as the Medical Outcome Study Short Form-36 (SF-36), the Nothingham Health Profile, Multiple Sclerosis Quality of Life-54 (MSQOL-54), and the Functional Assessment of MS (FAMS) have been included in clinical studies in patients with MS during the past few years (Hunt *et al.*, 1981; Ware and Sherbourne, 1992; Vickrey *et al.*, 1995; Cella *et al.*, 1996). MSQOL is a disease-specific questionnaire to evaluate QoL, which includes the SF-36 items and provides the opportunity to compare with healthy controls or other disease groups.

Even though it was reported that QoL can be explained by demographic variables, disability, and also depression and other psychosocial factors, there are few studies about the specific and independent effects of fatigue and depression on QoL in MS patients (Forbes *et al.*, 2006; Pfaffenberger *et al.*, 2006; Turpin *et al.*, 2007). In contrast to disability, psychosocial factors, especially depression and fatigue, are usually preventable and remediable conditions. Therefore, managing of these conditions could potentially help to improve the QoL of MS patients. This study was designed to evaluate the QoL in patients with MS and to determine the relationship of QoL with disability, depression, and fatigue. We hypothesize that a negative relationship will be observed between the assessed factors and the QoL.

Patients and methods
Patients
All consecutive potentially eligible patients with definite MS according to McDonald's criteria (McDonald *et al.*, 2001), attending our MS outpatient clinic between January 2008 and May 2008 were invited to participate in the study. All patients were given detailed information regarding the study procedure and patients who accepted to participate in the study gave their verbal informed consent. Patients were excluded from the study if they (a) had a concomitant chronic disease, which was likely to impact on the patients' QoL such as rheumatologic disease, significant cardiovascular disease, malignancy or other neurologic diseases; (b) had exacerbation in the preceding month; (c) were on steroid medication; and (d) were unable to complete the questionnaires.

Measurements
Demographic characteristics, education level, and disease duration were documented for each patient. Course of MS and neurologic disability were assessed by a neurologist. Patients were classified as relapsing–remitting, primary progressive, and secondary progressive according to the disease course. Severity of neurologic disability was assessed using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) by an experienced neurologist (P.Ç.). Patients were also examined by a physiatrist on the same day. The fatigue level, cognitive status, and depression level of patients were assessed by Fatigue Severity Scale (FSS), Mini Mental State Scale, and Beck Depression Inventory (BDI), respectively (Folstein *et al.*, 1975; Krupp *et al.*, 1989; Spreen and Strauss, 1998). The QoL was determined using the Turkish version of the MSQOL-54 inventory (Idiman *et al.*, 2006).

EDSS score is determined by neurologic exam or calculated based on a patient survey. The EDSS quantifies disability in eight functional systems. The functional systems are pyramidal, cerebellar, brain stem, sensory, bowel and bladder functions, visual, mental, and other. The EDSS is divided in 20 half steps ranging from

0 (normal) and 10 (death due to MS) in 0.5 point increments. Patients were categorized according to the total EDSS score as having mild (0–2.5), moderate (3.0–6.0), and severe ($\geq$ 6.5) MS (Kurtzke, 1983).

The FSS is an instrument that measures the impact of fatigue on patients' daily life (Krupp *et al.*, 1989). This scale includes nine items; each item is rated on a scale from 1 to 7. The scale is scored by computing an average rating for the nine items, with higher scores indicating increasing fatigue severity. The suggested cut-off point is 4. Patients were classified as having severe fatigue ($\geq$ 4) and mild–moderate fatigue (< 4) according to this cut-off point. The Turkish version of the FSS was used in this study (Armutlu *et al.*, 2007).

For cognitive impairment, the Mini Mental State Scale was applied to the patients. This test includes 11 questions and problems in five areas: orientation, registration, attention and calculation, recall, and language. The maximum possible total score is 30 points and a score of 23 or lower indicates the presence of cognitive impairment (Folstein *et al.*, 1975).

The BDI was used to assess the severity of depression. The BDI is a self-administered inventory intended to measure presence and degree of depression. This scale includes 21 multiple-choice style questions, with each item ranging from 0 to 3. The total score on the BDI can range from 0, suggesting no depression, to a maximum score of 63, indicating a severe state of depression. Patients with scores of 0–9 on BDI were categorized as 'normal.' The classification of depression severity was defined as 10–15 = mild, 16–19 = mild/moderate, 20–29 = moderate/severe, and 30 + = severe (Spreen and Strauss, 1998). We used the cut-off score of 16 on the BDI to indicate clinically significant depression (Kendall *et al.*, 1987).

MSQOL-54 is a disease-specific instrument to measure the QoL of MS patients, which was based on the generic SF-36 QoL instrument (Vickrey *et al.*, 1995). This scale includes the SF-36 and 18 additional items that are specific to MS. It consists of 54 items and 12 subscales. MS-specific items are related health distress (four items), sexual function (four items), satisfaction with sexual function (one item), overall QoL (two items), cognitive function (four items), energy (one item), and social function (one item). Two composite scores can be obtained on the MSQOL-54, physical health composite, and mental health composite. The composite scores are calculated by transforming items score to a 0 to 100 scale, with 0 representing the worst health and 100 indicating the best health. The Turkish version of the MSQOL-54 was used in this study (Idiman *et al.*, 2006).

Statistical analyses
Descriptive statistics were used for assessing the demographic data and the parameters related to disease. The

Kolmogorov–Smirnov test was used to check for a normal distribution of data. Values were expressed as mean with SD for the normal distribution or as median and range for the nonparametric data. The mean difference in the composite scores were compared by sex, marital status, employment status, education level (< 5 years or ≥ 5 years), disease course, severity of disability (mild or moderate-severe), and level of depression and fatigue, using the independent sample *t*-test. We chose a cut-off value of five for the education level, because 5 years of education was the compulsory number of education years in Turkey for the period in which our patients were at school. The relationships between the QoL and the other parameters were examined with nonparametric analysis by using the partial correlation analysis corrected for disease course. The classification of the magnitude of correlation coefficients was based on Cohen's rule where < 0.3 is considered a low correlation, 0.3–0.6 moderate and > 0.6 high (Cohen, 1988).

We calculated *z* scores for each subscale score of MSQOL-54 using the mean and SD of the relevant age-specific reference norms, to compare the QoL scores of MS patients with the SF-36 scores of the general population (Demiral *et al.*, 2006). Any *z*-score greater than 1.65 falls into the region of rejection and is declared significantly different from the mean (*P* < 0.05). These *z* scores were then rescaled to a mean ± SD of 50 ± 10. The average QoL for the general population on any subscale is then represented by a score of 50. Scores lower than 50 for the MS population indicate that they have a worse state of health on average than the general population on this aspect of QoL (Pittock *et al.*, 2004).

Stepwise hierarchical regression analysis was used to determine predictors of QoL. In general, hierarchical regression analysis specifies two blocks of variables: a set of control variables entered in the first block and a set of predictor variables entered in the second block. Control variables are often demographics, which are thought to cause a change in the score on the dependent variable. Predictors are the variables, in whose effect our research question is really interested, but whose effect we want to separate out from the control variables (Petrocelli, 2003). We entered two blocks of control variables and two blocks of predictors into the regression model. The control variables consisted of disease-related variables (disease course and disease duration) and demographic variables (age, sex, marital status, employment status, and education level). The predictors were composed of the disability level (EDSS score) and other variables related with QoL (depression, fatigue, and cognitive function). Statistical analysis was carried out by using SPSS statistical program and level of significance was set as *P* value of less than 0.05.

Results

Seventy-nine patients with MS were included in the study. Demographic and disease-related characteristics of the patients are given in Table 1. The mean physical and mental health composite scores of patients were 53.2 ± 18.3 and 56.1 ± 19.4, and there was a moderate degree of impairment in the QoL. According to the MSQOL-54 subscales scores, the subscales indicating the most problems were role limitation-related physical and emotional problems and the subscale indicating the least problem was the sexual function. Table 2 shows mean and median scores on each MSQOL-54 subscale in our sample.

MS patients showed statistically significant lower mean scores for all dimensions of the QoL compared with age-adjusted scores in the general population except for the emotional well-being subscale. The largest of the differences between patients with MS and the healthy population were found for physical and emotional role limitations, and physical and social functions (Table 2).

In terms of partial correlation corrected for disease course, the physical health composite score showed a moderate positive correlation with the educational level and employment status; a moderate negative correlation with the level of disability and fatigue; and a high negative correlation with depression. Regarding the mental health composite score, this score showed a moderate positive correlation with educational level; a low positive correlation with employment status and cognitive status; and a low, moderate, and high negative correlation with the levels of disability, fatigue, and depression, respectively (Table 3). Both composite scores did not have a significant correlation with age, sex, disease duration, and marital status (*P* > 0.05). Patients who had a lower educational level, progressive disease course, severe disability, depression and fatigue, and those not working, reported lower QoL scores (Table 4).

Table 1 Demographic and clinical characteristics of patients

Age, years (mean ± SD)	40.6 ± 10.3
Sex (women/men)	55/24
Education level, years (median, range)	8 (0–15)
Marital status	
Single	15 (19%)
Married	57 (72.2%)
Separated/divorced/widowed	7 (8.9%)
Current employment status	
Employed	22 (27.8%)
Unemployed	57 (72.2%)
Duration of disease, years (median, range)	5 (1–32)
Current disease course	
Relapsing–remitting	58 (73.4%)
Secondary progressive	14 (17.7%)
Primary progressive	7 (8.9%)
Disability level (EDSS) (mean ± SD)	3.2 ± 2.2
Fatigue (FSS) (mean ± SD)	4.6 ± 1.8
Cognitive status (MMSE) (median, range)	29 (15–30)
Depression (BDI) (mean ± SD)	16.5 ± 9.9

BDI, beck depression inventory; EDSS, expanded disability status scale; FSS, fatigue severity scale; MMSE, mini mental state examination.

Table 2 The MSQOL-54 subscales score in patients with multiple sclerosis and comparison with the normative data of the general population

MSQOL-54 subscale	Mean score (±SD)	Median score	Standardized score mean (±SD)	z-score
Physical function	48.4 (26.1)	45	28.3 (14.7)	2.17*
Role limitation: physical	35.8 (39.9)	25	27.9 (17.8)	2.07*
Role limitation: emotional	43.9 (42.6)	33.3	23.3 (22.0)	2.68**
Pain	54.6 (25.5)	55	32.5 (14.2)	1.78*
Emotional well-being	60.7 (18.5)	60	38.5 (16.5)	1.21
Energy	44.6 (17.8)	44	32.5 (13.9)	1.74*
Health perception	45.9 (19.4)	45	32.6 (11.4)	1.74*
Social function	64.6 (23.1)	58.3	24.5 (18.7)	2.55**
Cognitive function	61.6 (24.6)	65	–	
Health distress	61.3 (22.3)	65	–	
Sexual function	69.6 (32.6)	83.3	–	
Change in health	46.5 (25.2)	50	–	
Sexual satisfaction	58.5 (28.3)	50	–	
Overall quality of life	56.2 (16.6)	56.7	–	

BDI, beck depression inventory; EDSS, expanded disability status scale; FSS, fatigue severity scale; MMSE, mini mental state examination; MSQOL-54, Multiple Sclerosis Quality of Life-54.
*$P<0.05$.
**$P<0.001$.

Table 3 Factors associated with the quality of life for the sample of 79 individuals with multiple sclerosis

	Education level	Employment status	MMSE score	EDSS score	BDI score	FSS score
MSQOL-54 physical health	0.395***	0.362**	0.200	− 0.495***	− 0.729***	− 0.461***
MSQOL-54 mental health	0.337**	0.246*	0.238*	− 0.265*	− 0.765***	− 0.411***

BDI, beck depression inventory; EDSS, expanded disability status scale; FSS, fatigue severity scale; MMSE, mini mental state examination; MSQOL-54, Multiple Sclerosis Quality of Life-54.
*$P<0.05$.
**$P<0.01$.
***$P<0.001$.

The results of the stepwise hierarchical regression analysis showed that 72.1% of the variance in physical health status was explained by a model of disease course, educational level, employment status, depression, disability level, and fatigue ($P = 0.000$). Depression, disability level, and fatigue were the strongest variables associated with physical health status in our patients (Table 5). As for the mental health status, 64% of the variance was explained by disease course, educational level, disability, depression, and fatigue ($P = 0.000$). Depression and fatigue were the most powerful predictors of mental health status (Table 5).

Discussion
In this study, MS patients have reported considerably lower scores than the healthy population on both physical and mental component of the QoL. According to our results, disease course, educational level, employment status, disability, depression, and fatigue explained more than 60% of the change in QoL. Our results indicated that QoL was associated especially with depression and fatigue, and disability. Most importantly, it was found that depression was the most powerful predictor of QoL.

In previous studies, it has been demonstrated that patients with MS have a poorer QoL than the healthy population and people with other chronic diseases (Hermann *et al.*, 1996; Rothwell *et al.*, 1997; Nortvedt *et al.*, 1999; Ford *et al.*, 2001). Miller and Dishon (2006) reported that MS patients had significantly lower SF-36 scores than controls on all dimensions. In this study, the largest of the differences between MS and controls were found for physical health and physical role limitations whereas the smallest were for pain and emotional well-being. In another study, it has been shown that physical well-being and occupational functioning domains of QoL were seriously affected (Fruehwald *et al.*, 2001). Isaksson *et al.* (2005) shown that MS had the most negative influence on QoL in the SF-36 questionnaires regarding vitality, general health, physical role, and physical function as well. Our findings are in line with the results obtained in these studies. We found lower QoL scores in MS patients relative to healthy population. The most evident difference between patients with MS and the healthy population were found for physical and emotional role limitations, and physical and social functions, whereas the smallest was for emotional well-being. These findings have been attributed to the unpredictable course of the disease and the fluctuating symptoms. In addition, ability of adaptation to MS, coping skills of patients, personal resource, and family support might play a role in predicting the QoL in MS patients.

Table 4 Mean dimension scores on MSQOL-54 by sex, marital status, employment status, education level, disease course, disability level, fatigue, and depression

	MSQOL-54 physical health	P^a	MSQOL-54 mental health	P^a
Sex				
Men ($n=24$)	51.2±22.1	0.522	55.7±21.9	0.915
Women ($n=55$)	54.0±16.5		56.2±18.4	
Marital status				
Married ($n=57$)	52.2±16.2	0.507	56.7±17.6	0.661
Single-separated ($n=22$)	55.8±23.0		54.3±23.8	
Employment status				
Employed ($n=22$)	65.9±17.9	0.000	65.7±19.9	0.005
Unemployed ($n=57$)	48.3±16.1		52.3±18.1	
Education level				
≥ 5 years ($n=39$)	60.4±17.3	0.000	62.8±19.1	0.001
<5 years ($n=40$)	45.8±16.4		49.1±17.4	
Disease duration				
≥ 5 years ($n=50$)	52.6±17.8	0.798	55.1±18.9	0.679
<5 years ($n=29$)	53.9±19.0		56.9±20.0	
Current disease course				
Relapsing−remitting ($n=58$)	57.2±17.7	0.001	59.2±19.6	0.016
Progressive ($n=21$)	42.1±15.4		47.4±16.1	
Disability level				
Mild ($n=38$)	62.3±16.6	0.000	62.5±19.1	0.004
Moderate-severe ($n=41$)	44.8±15.8		50.1±17.9	
Fatigue				
Mild ($n=29$)	64.1±18.6	0.000	65.3±16.9	0.001
Severe ($n=50$)	46.8±14.9		50.7±18.9	
Depression				
Normal−mild ($n=42$)	64.1±15.8	0.000	68.7±13.9	0.000
Clinically significant ($n=37$)	40.8±12.0		41.6±13.9	

[a]Independent sample *t*-test.

Table 5 Stepwise hierarchical regression analysis: predictors of quality of life

	Dependent variables									
	MSQOL-54 physical health					MSQOL-54 mental health				
Independent variables	Beta (95% CI)	P^*	R^2 change	P	R^2	Beta (95% CI)	P^*	R^2 change	P	R^2
Constant	79.023 (68.233, 89.813)	0.000				86.557 (73.752, 99.362)	0.000			
Disease course	1.073 (− 2.616, 4.763)	0.564	0.101	0.004		− 1.655 (− 6.033, 2.723)	0.454	0.060	0.029	
Education level	0.427 (− 0.295, 1.148)	0.243	0.140	0.000		0.307 (− 0.478, 1.091)	0.439	0.107	0.003	
Employment status	4.660 (− 1.544, 10.863)	0.139	0.039	0.048		−				
Disability level	− 2.729 (− 4.120, − 1.337)	0.000	0.161	0.000		− 0.472 (− 2.099, 1.154)	0.565	0.051	0.030	
Depression	− 0.963 (− 1.227, − 0.698)	0.000	0.257	0.000		− 1.301 (− 1.617, − 0.985)	0.000	0.401	0.000	
Fatigue	− 1.641 (− 2.993, − 0.288)	0.018	0.023	0.018	0.721	− 1.652 (− 3.263, − 0.041)	0.045	0.021	0.045	0.640

CI, confidence interval; MSQOL-54, Multiple Sclerosis Quality of Life-54.
*P-value for the estimated coefficient.

The relationship between the sociodemographic factors and QoL in patients with MS has been reported in several studies. Being female (Lobentanz *et al.*, 2004; Miller and Dishon, 2006; Pfaffenberger *et al.*, 2006; Turpin *et al.*, 2007) and older (Pekmezovic *et al.*, 2007; Turpin *et al.*, 2007; Alshubaili *et al.*, 2008), not working because of MS (Miller and Dishon, 2006; Pekmezovic *et al.*, 2007; Turpin *et al.*, 2007; Alshubaili *et al.*, 2008), having longer disease duration (Lobentanz *et al.*, 2004; Pfaffenberger *et al.*, 2006; Alshubaili *et al.*, 2008), and lower educational level (Pekmezovic *et al.*, 2007; Alshubaili *et al.*, 2008) were reported as associated factors with poorer QoL. However, other studies reported that age (Idiman *et al.*, 2006; Ayatollahi *et al.*, 2007; Ghaem *et al.*, 2007), sex (Solari *et al.*,

1999; Idiman *et al.*, 2006; Ayatollahi *et al.*, 2007; Ghaem *et al.*, 2007; Pekmezovic *et al.*, 2007), education (Solari *et al.*, 1999; Idiman *et al.*, 2006; Ayatollahi *et al.*, 2007; Ghaem *et al.*, 2007), marital status (Idiman *et al.*, 2006; Pekmezovic *et al.*, 2007), and disease duration (Shawaryn *et al.*, 2002) were unrelated to QoL. According to our results, although the relation of QoL with employment status and educational level was poor, the worse QoL was related with being unable to work and the lower educational level; but not with age, sex, disease duration, and marital status. This inconsistency between different studies may be related using cross-sectional studies to detect the factors effective on QoL, and different scales to assess deterioration of QoL in MS patients.

A number of factors have been identified as affecting QoL in patients with MS. These include physical disability (Amato *et al.*, 2001; Janardhan and Bakshi, 2002; Miller and Dishon, 2006), progressive disease (Benito-Leon *et al.*, 2002), fatigue (Amato *et al.*, 2001; Janardhan and Bakshi, 2002; Lobentanz *et al.*, 2004), pain (Nortvedt *et al.*, 1999), cognition (Benito-Leon *et al.*, 2002), anxiety, and depression (Fruehwald *et al.*, 2001; Benito-Leon *et al.*, 2002; Janardhan and Bakshi, 2002; Lobentanz *et al.*, 2004). In the past, outcome assessments in MS patients are focused on neurological examination or only on disability. QoL comprises not only perceptions of physical functioning and general health, but also perceived psychological functioning and social/role functioning (Fischer *et al.*, 1999). Furthermore, from the patients' perspectives, it seems the psychosocial components may be more of a concern than physical factors in terms of their QoL (Rothwell *et al.*, 1997; Shawaryn *et al.*, 2002; Somerset *et al.*, 2002, 2003). In our study, we evaluated the QoL with respect to both physical and mental health. We also found that disability was one of the determinants of QoL. However, different from the available studies, our results showed that QoL was mainly affected by depression, followed by disability, and fatigue. The effect of depression on QoL was more marked in the mental health dimension than in the physical health dimension. Contrary to this finding, the effect of disability on QoL was more pronounced in the physical health than in the mental health. Concisely, in addition to the disability, determination of 'invisible' symptoms of MS such as fatigue and depression is also essential for assessing QoL.

The strong correlation between the disability and QoL has been well described previously. Disability has been inversely correlated with overall QoL and physical health status in patients with MS (Rothwell *et al.*, 1997; Amato *et al.*, 2001; McDonald *et al.*, 2001; Lobentanz *et al.*, 2004), but the association between disability and mental health status is unclear (Solari *et al.*, 1999; Amato *et al.*, 2001; Ford *et al.*, 2001; Fruehwald *et al.*, 2001; Benito-Leon *et al.*, 2002; Shawaryn *et al.*, 2002; Somerset *et al.*, 2002; Miller *et al.*, 2003; Turpin *et al.*, 2007). Although most authors concluded that the EDSS is not a valuable factor when assessing the mental QoL of MS patients, others mentioned that disability has an important effect on mental health status (Brunet *et al.*, 1996; Nortvedt *et al.*, 1999; Miller and Dishon, 2006; Ozakbas *et al.*, 2007; Turpin *et al.*, 2007; Krokavcova *et al.*, 2008). According to our results, disability was negatively correlated with physical and mental health status in MS patients. The relationship between QoL and disability was stronger in physical health than in mental health (correlation coefficients −0.495 and −0.265, respectively).

In the course of MS, a lifetime prevalence of 36–54% of depressive disorders is reported (Schiffer *et al.*, 1983; Sadovnick *et al.*, 1996; Siegert and Abernethy, 2005). Similarly, in our study sample, we found the frequency of clinically significant depression as 46.8%. Despite the high prevalence of depression, it is obvious that the influence of depressive symptoms on QoL is overlooked to a great extent (Fruehwald *et al.*, 2001). In our study, depression was found to be the most important predictor for QoL. This result was valid for both health composite scores. Depression had a 25.7 and 40.1% of effect on physical and mental health status, respectively. Our results are in line with the results of Amato *et al.* (2001). The authors have found that depression and fatigue were more important determinants of QoL both for physical and mental health components. Depression was also presented to be the most important predictor for reduced QoL in many other studies (Provinciali *et al.*, 1999; Amato *et al.*, 2001; Fruehwald *et al.*, 2001; Ayatollahi *et al.*, 2007). These results can be explained by the fact that depressed mood may lead to less favorable perception and reporting of QoL. Depression may also influence QoL directly by affecting other MS symptoms such as fatigue, memory, and cognition. When the high frequency of depressive symptoms in MS patients and its proved influences on the QoL is taken into account, it seems reasonable to mention that the screening tools for the depressive symptoms should be included in QoL studies in MS.

QoL of patients with MS is also influenced by fatigue and cognitive dysfunction. The influence of MS-related fatigue on QoL has been analyzed in detail by several authors (Provinciali *et al.*, 1999; Solari *et al.*, 1999; Amato *et al.*, 2001; Janardhan and Bakshi, 2002; Lobentanz *et al.*, 2004). Even though these studies demonstrated that fatigue is independently associated with impairment of QoL in MS patients, there are few studies evaluating QoL by a multidimensional approach. In fact, there may be a complex interrelationship among the variables relevant to QoL in patients with MS. For instance, MS-related fatigue may overlap with the symptoms of depression (Amato *et al.*, 2001; Schwid *et al.*, 2002; Bakshi, 2003). Similarly, in our study, fatigue was moderately correlated with depression and strongly correlated with QoL. Patients who had a high fatigue level had higher depression score and lower QoL scores. To eliminate these relationships and to test the effects of the predictors independent of the influence of others, we used hierarchical multiple regression analysis. According to the results of this analysis, MS-related fatigue had a small, but significant effect on both physical and mental health components of QoL, whereas cognitive dysfunction does not. It has been reported that fatigue may reduce QoL by limiting daily activities and coping abilities, and the efforts to improve patients' fatigue levels may be a way to improve the QoL of patients with MS (Bakshi, 2003).

Our study has some limitations that warrant consideration. First, the cross-sectional design of this study precluded our ability to conclude a causal relationship between QoL and the relevant factors. Second, our

sample size was slightly small. Third, we assessed only a special patient group, which is a follow-up in our MS outpatient clinic. This may be limiting to generalize our findings to general MS patients' populations. Four, we did not consider other factors (such as pain, anxiety, social support, and self-efficacy) that might contribute to the unexplained variance in QoL. Further prospective studies, which have more patients, and include other variables that may affect the QoL, may be of value in MS to determine the association between the QoL and relevant factors.

Conclusion

In this study, we wanted to highlight the importance of the evaluation of QoL in MS patients. According to our results, all patients had a lower score than healthy controls on QoL. The most affected parts of QoL in our patients were those related to physical and emotional role limitations, and physical and social functions. In addition to the well-known relationship between the QoL and disability in MS patients, our results have shown that QoL was associated especially with depression and fatigue. Most importantly, it was found that depression was the most powerful predictor of QoL. We conclude that our results will be helpful in MS outcome studies, because the importance of evaluation for depression and fatigue in MS patients was stated clearly by our findings. Nevertheless, there is a need for more studies with a greater number of patients to determine the clinical importance of the relationships between depression, fatigue, and other invisible symptoms of MS with the QoL.

References

Alshubaili AF, Ohaeri JU, Awadalla AW, Mabrouk AA (2008). Quality of life in multiple sclerosis: a Kuwaiti MSQOL-54 experience. *Acta Neurol Scand* 117:384–392.

Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L (2001). Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Mult Scler* 7:340–344.

Armutlu K, Korkmaz NC, Keser I, Sumbuloglu V, Akbiyik DI, Guney Z, *et al.* (2007). The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. *Int J Rehabil Res* 30:81–85.

Ayatollahi P, Nafissi S, Eshraghian MR, Kaviani H, Tarazi A (2007). Impact of depression and disability on quality of life in Iranian patients with multiple sclerosis. *Mult Scler* 13:275–277.

Bakshi R (2003). Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult Scler* 9:219–227.

Benito-Leon J, Morales JM, Rivera-Navarro J (2002). Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients. *Eur J Neurol* 9:497–502.

Brunet DG, Hopman WM, Singer MA, Edgar CM, MacKenzie TA (1996). Measurement of health-related quality of life in multiple sclerosis patients. *Can J Neurol Sci* 23:99–103.

Calabresi PA (2004). Diagnosis and management of multiple sclerosis. *Am Fam Physician* 70:1935–1944.

Cella DF, Dineen K, Arnason B, Reder A, Webster KA, Karabatsos G, *et al.* (1996). Validation of the functional assessment of multiple sclerosis quality of life instrument. *Neurology* 47:129–139.

Cohen J (1988). *Statistical power analysis for the behavioural sciences*. 2nd ed. Hillsdale: Lawrence Erlbaum.

Demiral Y, Ergor G, Unal B, Semin S, Akvardar Y, Kivircik B, *et al.* (2006). Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. *BMC Public Health* 6:247.

Fischer JS, LaRocca NG, Miller DM, Ritvo PG, Andrews H, Paty D (1999). Recent developments in the assessment of quality of life in multiple sclerosis (MS). *Mult Scler* 5:251–259.

Folstein MF, Folstein SE, McHugh PR (1975). 'Minimental state.' A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198.

Forbes A, While A, Mathes L, Griffiths P (2006). Health problems and health-related quality of life in people with multiple sclerosis. *Clin Rehabil* 20:67–78.

Ford H, Gerry E, Johnson M, Tennant A (2001). Health status and quality of life of people with multiple sclerosis. *Disabil Rehabil* 23:516–521.

Fruehwald S, Loeffler-Stastka H, Eher R, Saletu B, Baumhackl U (2001). Depression and quality of life in multiple sclerosis. *Acta Neurol Scand* 104:257–261.

Ghaem H, Haghighi AB, Jafari P, Nikseresht AR (2007). Validity and reliability of the Persian version of the multiple sclerosis quality of life questionnaire. *Neurol India* 55:369–375.

Hermann B, Vickrey B, Hays RD, Cramer J, Devinsky O, Meador K, *et al.* (1996). A comparison of health-related quality of life in patients with epilepsy, diabetes and multiple sclerosis. *Epilepsy Res* 25:113–118.

Hunt SM, McKenna S, McEwan J, Williams J, Papp E (1981). The Nottingham Health Profile: subjective health status and medical consultations. *Soc Sci Med* 15:221–229.

Idiman E, Uzunel F, Ozakbas S, Yozbatiran N, Oguz M, Callioglu B, *et al.* (2006). Cross-cultural adaptation and validation of multiple sclerosis quality of life questionnaire (MSQOL-54) in a Turkish multiple sclerosis sample. *J Neurol Sci* 240:77–80.

Isaksson AK, Ahlström G, Gunnarsson LG (2005). Quality of life and impairment in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 76:64–69.

Janardhan V, Bakshi R (2002). Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol Sci* 205:51–58.

Kendall PC, Hollon SD, Beck AT, Hammen CL, Ingram RE (1987). Issues and recommendations regarding use of Beck Depression Inventory. *Cognit Ther Res* 11:288–299.

Krokavcova M, Nagyova I, van Dijk JP, Rosenberger J, Gavelova M, Middel B, *et al.* (2008). Mastery, functional disability and perceived health status in patients with multiple sclerosis. *Eur J Neurol* 15:1237–1244.

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 46:1121–1123.

Kurtzke JF (1983). Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 33:1444–1452.

Lobentanz IS, Asenbaum S, Vass K, Sauter C, Klösch G, Kollegger H, *et al.* (2004). Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand* 110:6–13.

Lublin FD, Reingold SC (1996). Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* 46:907–911.

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, *et al.* (2001). Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. *Ann Neurol* 50:121–127.

Miller A, Dishon S (2006). Health-related quality of life in multiple sclerosis: the impact of disability, gender and employment status. *Qual Life Res* 15:259–271.

Miller DM, Rudick RA, Baier M, Cutter G, Doughtery DS, Weinstock-Guttman B, *et al.* (2003). Factors that predict health-related quality of life in patients with relapsing remitting multiple sclerosis. *Mult Scler* 9:1–5.

Miltenburger C, Kobelt G (2002). Quality of life and cost of multiple sclerosis. *Clin Neurol Neurosurg* 104:272–275.

Nicholl C, Lincoln N, Francis V, Stephan TF (2001). Assessing quality of life in people with multiple sclerosis. *Disabil Rehabil* 23:597–603.

Nortvedt M, Riise T, Myhr K, Nyland HI (1999). Quality of life in multiple sclerosis: measuring the disease effects more broadly. *Neurology* 53:1098–1103.

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG (2000). Multiple sclerosis. *N Engl J Med* 343:938–952.

Ozakbas S, Akdede BB, Kösehasanogullari G, Aksan O, Idiman E (2007). Difference between generic and multiple sclerosis-specific quality of life instruments regarding the assessment of treatment efficacy. *J Neurol Sci* **256**:30–34.

Pekmezovic T, Kisic Tepavcevic D, Kostic J, Drulovic J (2007). Validation and cross-cultural adaptation of the disease-specific questionnaire MSQOL-54 in Serbian multiple sclerosis patients sample. *Qual Life Res* **16**: 1383–1387.

Petrocelli JV (2003). Hierarchical multiple regression in counseling research: common problems and possible remedies. *Meas Eval Couns Dev* **36**:9–22.

Pfaffenberger N, Pfeiffer KP, Deibl M, Höfer S, Günther V, Ulmer H (2006). Association of factors influencing health-related quality of life in MS. *Acta Neurol Scand* **114**:102–108.

Pittock SJ, Mayr WT, McClelland RL, Jorgensen NW, Weigand SD, Noseworthy JH, *et al.* (2004). Quality of life is favorable for most patients with multiple sclerosis: a population-based cohort study. *Arch Neurol* **61**:679–686.

Provinciali L, Ceravolo MG, Bartolini M, Logullo F, Danni M (1999). A multidimensional assessment of multiple sclerosis: relationships between disability domains. *Acta Neurol Scand* **100**:156–162.

Rothwell PM, McDowell Z, Wong CK, Dorman PJ (1997). Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *BMJ* **314**:1580–1583.

Sadovnick AD, Remick RA, Allen J, Swartz E, Yee IM, Eisen K, *et al.* (1996). Depression and multiple sclerosis. *Neurology* **46**:628–632.

Schiffer RB, Caine ED, Bamford KA, Levy S (1983). Depressive episodes in patients with multiple sclerosis. *Am J Psychiatry* **140**:1498–1500.

Schwid SR, Covington M, Segal BM, Goodman AD (2002). Fatigue in multiple sclerosis: current understanding and future directions. *J Rehabil Res Dev* **39**:211–224.

Siegert R, Abernethy DA (2005). Depression in multiple sclerosis: a review. *J Neurol Neurosurg Psychiatry* **76**:469–475.

Shawaryn MA, Schiaffino KM, LaRocca NG, Johnston MV (2002). Determinants of health-related quality of life in multiple sderosis: the role of illness intrusiveness. *Mult Scler* **8**:310–318.

Solari A, Filippini G, Mendozzi L, Ghezzi A, Cifani S, Barbieri E, *et al.* (1999). Validation of Italian multiple sclerosis quality of life 54 questionnaire. *J Neurol Neurosurg Psychiatry* **67**:158–162.

Somerset M, Sharp D, Campbell R (2002). Multiple sclerosis and quality of life: a qualitative investigation. *J Health Serv Res Policiy* **7**:151–159.

Somerset M, Peters TJ, Sharp DJ, Campbell R (2003). Factors that contribute to quality of life outcomes prioritised by people with multiple sclerosis. *Qual Life Res* **12**:21–29.

Spreen O, Strauss E (1998). *A compendium of neuropsychological tests: administration, norms, and commentary*. 2nd ed. New York: Oxford University Press.

Turpin KV, Carroll LJ, Cassidy JD, Hader WJ (2007). Deterioration in the health-related quality of life of persons with multiple sclerosis: the possible warning signs. *Mult Scler* **13**:1038–1045.

Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW (1995). A health-related quality of life measure for multiple sclerosis. *Qual Life Res* **4**:187–206.

Ware JE Jr, Sherbourne CD (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* **30**:473–483.

View publication stats