

QUALITY OF LIFE AND MENTAL HEALTH IN MULTIPLE SCLEROSIS PATIENTS IN BOSNIA AND HERZEGOVINA MEASURED BY GENERIC AND DISEASE-SPECIFIC QUESTIONNAIRE

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SUMMARY

Background: Multiple sclerosis (MS) as chronic neurodegenerative disease significantly impact patients' quality of life (QoL). QoL instruments can be generic (EQ-5D, SF-36) and disease-specific like MSQoL-54. Use of disease-specific instruments is preferred since it captures broader symptoms related to MS than generic instruments. Mental health is impacted by MS and different psychiatric conditions significantly impact QoL. We have conducted prospective non-interventional study among MS patients. Aim was to measure and compare MS patients QoL by generic and disease-specific instrument at baseline and after one year and to identify potential correlation between these two types of measurements and to assess mental health scores among MS patients in Bosnia and Herzegovina (B&H) and other countries.

Subjects and methods: Study included 62 patients diagnosed with MS and treated at Neurology clinic in Sarajevo from April 2016 to May 2017. Study was approved by Ethical Committee. QoL has been measured by EQ-5D and MSQoL-54. Measurement has been performed at baseline and after 12 months.

Results: Average utility score measured by EQ-5D at the baseline and end of the study were 0.688 and 0.639 respectively with no significant difference ($p=0.850$). EQ-5D utility and MSQoL-54 score showed high correlation at baseline; $\rho=0.873$ $p=0.0001$ for physical health and $\rho=0.711$ $p=0.0001$ for mental health. At the end of the study no significant correlations have been found ($p>0.05$). High negative correlation found between EDSS and scores measured by EQ-5D and MSQoL-54; at baseline ($\rho=-0.744$ $p=0.0001$) and at the end of the study ($\rho=-0.832$ $p=0.0001$). Similar MS impact and loss of QoL found in B&H and other countries.

Conclusions: Both instruments can be used in measuring QoL but disease-specific are preferred since they capture broader symptoms impacting MS patient QoL. Using QoL instruments could drive clinician decision and patient-centric care as well as reimbursement and policy decision by recording treatment outcomes.

Key words: quality of life - multiple sclerosis - mental health - MSQoL-54 - EQ-5D

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INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated demyelinating, neurodegenerative, disease of the central nervous system characterized by neurologic symptoms (or relapses) and increasing disability. Common symptoms of MS include fatigue, walking difficulties leading to reduced mobility, bowel/bladder disturbances, optic neuritis and other visual changes, modification in cognitive function, pain, sensory loss, and depression (O'Connor 2002). It is estimated that more than 2.5 million people have multiple sclerosis worldwide (Rosati 2001). The prevalence of multiple sclerosis varies regionally, and is the largest in the countries of Northern Europe, Australia and the United States of America (Sadovnick et al. 1993). The prevalence rates of MS have been reported to vary by continent and geographical latitude. The condition is of high prevalence (>30 per 100,000) in northern parts of Europe and North America; medium

prevalence (5-30 per 100,000) in southern Europe and southern United States; and Central and South America (10-20 per 100,000); and low prevalence (<5 per 100,000) in Asia and South America (Koch-Henriksen & Sørensen 2010). MS typically begins between the ages of 20 and 40 years and it is the leading cause of non-traumatic disability in young adults. Initial symptoms rarely occur before age 10 years or after age 60 years, affecting mostly young and productive population. Women are affected approximately twice as often as men (Pugliati et al. 2006).

It is estimated, based on data from clinics health insurance funds than MS affects more than 3,000 patients in Bosnia and Herzegovina (Portal Buka 2015). Kingwell et al published a study in 2013 stating that the incidence of MS in Bosnia and Herzegovina is 1.6/100,000 (Kingwell et al. 2013).

The clinical manifestations of MS are highly variable, but an attack of neurologic dysfunction (e.g., optic

neuritis, incomplete transverse myelitis, brain stem or cerebellar syndrome), referred to as a clinically isolated syndrome (CIS), heralds the onset of the disease in approximately 90% of patients (Tullman 2013). Symptoms, which depend on lesion location and extent of tissue destruction, range from mild to severe. Common symptoms of an MS exacerbation (relapse or attack) include numbness, tingling, weakness, impaired balance, blurred vision, double vision, vertigo, and bladder or bowel dysfunction (Berger 2011).

MS-related disability is commonly measured with the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke 1983). While the physical disability aspect of multiple sclerosis (MS), the most common demyelinating disease of the central nervous system in young adults, is of great importance, it is now well recognized that it does not reflect all of the facets that patients consider important in their life. Fatigue, depression, and physical disability are only one aspect of a person's experience with MS; it is well documented that cognitive, emotional, and psychological functions contribute to their quality of life (QoL) (Zwibel & Smrtka 2011). Some mood disorders occur more often in people with MS than in the general population (Marrie et al. 2013). One-third to one-half of people with MS will have a major depressive episode in their lifetimes. This compares with less than one-fifth in the general population (Patten et al. 2003). Anxiety disorders affect more than one-third of people with MS, and adjustment disorders nearly one-fourth (Marrie et al. 2015). Bipolar disorder occurs in 13% of people with MS and in less than 5% of people without MS (Carta et al. 2014). Suicide may be twice as common in people with MS (Brenner et al. 2016).

The QoL measurements are being considered increasingly important with regard to evaluating disease progression, treatment and the management of care provided to MS patients (Mitchell et al. 2005).

QoL is a subjective measure of a patient's life satisfaction that is affected by mood, coping mechanisms, life experiences, and emotional support as well as disease state. According to the National Multiple Sclerosis Society (NMSS), MS diminishes QOL by interfering with ability to work, pursue leisure activities, and carry on usual life roles (National Multiple Sclerosis Society 2006). QoL is commonly assessed using self-reported questionnaires (Solari 2005).

Varieties of QoL instruments are available for use in patients with MS, including generic and MS-specific measures (Moore et al. 2015). Instruments specific to MS may offer a more comprehensive assessment of the disease's impact on health compared with generic instruments, but they do not enable cross-disease comparisons as it is a case with generic instruments (Patrick & Deyo 1989).

The EQ-5D is a widely used, standardised, health-related quality of life measure developed by the EuroQol Group to provide a simple generic assessment

for use in clinical and economic studies. It consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system has five dimensions: Mobility, Self-care, Usual activities, Pain/discomfort and Anxiety/depression. Each dimension has 3 levels: no problems, some problems or severe problems, and this provide a health profile of the respondents. By taking the five digit responses, the health profiles can be translated into weighted health indices. The EQ-VAS allows respondents to indicate their self-assessed health state on a visual analogue scale with 0 being their worst imagined health state, and 100 the highest (EuroQol Group 1990).

One of the most widely used MS-specific questionnaires is the Multiple Sclerosis Quality of Life-54 (MSQOL-54) instrument (Vickrey et al. 1995). This questionnaire includes the generic Short-Form 36-item QoL instrument, supplemented with 18 MS-specific items that were based on expert opinion and literature review. The 54 items of this questionnaire is distributed into 12 multi-item scales and 2 single items. Two summary scores physical health composite (PHC) and mental health composite (MHC) can be derived from a weighted combination of scale scores. The MS International QoL (MusiQoL) questionnaire is a self-administered, multi-dimensional, MS-specific questionnaire that is available in many languages (Simeoni et al. 2008). Reliability and validity in MS patient samples in several countries have been reported (Heiskanen et al. 2007). Recently a study conducted in Bosnia and Herzegovina has confirmed Bosnian translation to be reliable and valid (Catic et al. 2017).

We have conducted prospective non-interventional study among MS patients treated with different therapeutic modalities (disease modifying therapies, corticosteroid therapy or no treatment). The aim of our study was to measure and compare MS patients QoL by generic and disease specific questionnaire at baseline and after one year and to identify potential correlation between these two types of measurements in clinical practice as well as compare QoL of MS patients in Bosnia and Herzegovina and other countries.

SUBJECTS AND METHODS

This study has been performed at Neurology clinic of University Clinical Center from April 2016 to May 2017. Sixty two patients diagnosed with MS participated in this study signed informed consent and study has been approved by Institutional Ethical Committee. Inclusion criteria were that they are older than 18 years, have diagnosed relapsing remitting MS according to McDonald's criteria and written informed consent. Exclusion criteria were an exacerbation in the last month, pre-existing other chronic illness and/or psychiatric disorders.

Quality of life has been measured by generic instrument EQ-5D translated into Bosnian and approved to be used by EuroQoL Group and disease specific instrument MSQoL-54 already translated and culturally adopted into Bosnian language. Translated questionnaire has been provided and licenced out by Optum Inc for this research.

Out of 95 patients seen in this period 65 met inclusion criteria, and 62 submit properly filled questionnaires, which has been taken into analysis. Questionnaires were filled in by the patients with presence of physician who could assist in of eventual problems in understanding questions and technical way of filling the questionnaire. Patient disability has been assessed by the neurologist using the Expanded Disability Status Scale (EDSS) score. Socio-economic data and current treatment regimen has been also recorded.

Measurement has been conducted at the beginning of the study - baseline (Month 1 – M1) and at the end of the study after 12 months (Month 12 - M12).

Statistical analysis has been performed in SPSS v 16. We have used descriptive statistics and applied Wilcoxon Signed Ranks Test and Man-Whitney test to identify possible correlation between measured QoL utilities.

We have also compared mental health component and its impact on QoL between our study population and available literature data from different countries and patient populations.

RESULTS

Demographic and clinical characteristics of patients enrolled in the study are presented in Table 1, including type of treatment receiving at the moment of filing the questionnaire. All patients were diagnosed as relapsing remitting multiple sclerosis and 33 are treated with immunomodulatory therapy (53.2%), corticosteroid (pulse) therapy is applied at 20 (32.3%) patients while 9 (14.5%) patients are not treated at the moment of study conduction.

Table 1. Demographic and clinical characteristics of patients with multiple sclerosis

Characteristic	Number	%
Gender		
Male	24	38.7
Female	38	61.3
Therapy		
IM	33	53.2
SPT	20	32.3
WoT	9	14.5
Age (years) ^a	39.8±10.9	(31.0-46.5)
Male	40.9±12.4	(31.0-50.5)
Female	39.1±9.9	(33.5-46.0)
EDSS ^a	2.9±1.9	(1.0-4.5)

IM - immunomodulatory therapy; SPT - steroid pulse therapy; WoT - without therapy; ^aMean ± SD (range); EDSS - Expanded Disability Status Scale

Measuring QoL at the baseline using EQ-5D questionnaire average utility score was 0.688 ranging from 0.48 to 0.90. At the end of the study period average utility score was 0.639 ranging from 0.48 to 0.78, as presented in Table 2. No significant change have been found between these two measurements ($p=0.850$).

In Table 3 correlations between EQ-5D utility scores and composite mental and composite physical scores measured by disease specific instrument MSQoL-54 at baseline and end of the study have been presented. At the baseline we have found high correlation between these two instrument measurements; $\rho=0.873$ $p=0.0001$ for physical health and $\rho=0.711$ $p=0.0001$ for mental health. At the end of the study we did not find statistically significant correlations for both domains ($p>0.05$).

Comparison of EDSS score and utility scores measured by EQ-5D and MSQoL-54 composite scores at baseline and end of the study are presented in Table 4.

There is significant high negative correlation at the baseline ($\rho=-0.744$ $p=0.0001$) and similar finding at the end of the study ($\rho=-0.832$ $p=0.0001$) meaning that the higher utility score corresponds to the lower EDSS score.

Table 2. EQ-5D utility scores at baseline and end of the study period

	N	Mean	S.D.	Min	Max.	25 th	Percentiles 50 th (Median)	75 th	WSR Test* p
EQ-5D-3L baseline	62	0.3	0.280	0.034	1.000	0.480	0.639	0.903	0.850
EQ-5D-3L end of study	62	0.2	0.269	0.074	10.000	0.480	0.688	0.780	

*WSR Test - Wilcoxon Signed Ranks Test

Table 3. Correlations between EQ-5D and composite physical and composite mental scores measured by MSQOL-54 at baseline and end of the study

	Spearman's rho	Physical Health Composite Score	Mental Health Composite Score
EQ-5D-3L baseline	Correlation Coefficient p	0.873 0.0001	0.711 0.0001
EQ-5D-3L end of study	Correlation Coefficient p	0.038 0.772	0.136 0.297

Table 4. Correlations between EDSS score and EQ-5D and MSQoL-54 scores at baseline and end of the study

	Spearman's rho	EQ-5D-3 values 1	EDSS	Mental Health Composite Score	Physical Health Composite Score
EQ-5D-3L baseline	Correl. Coefficient p	1.0000	-0.7440 0.0001	0.7110 0.0001	0.8730 0.0001
EDSS baseline	Correl. Coefficient p	-0.7440 0.0001	1.0000	-0.5950 0.0001	-0.7870 0.0001
EQ-5D-3L end of the study	Correl. Coefficient p	1.0000	-0.8320 0.0001	0.0380 0.7720	0.1360 0.2970
EDSS end of the study	Correl. Coefficient p	-0.8320 0.0001	1.0000	-0.0950 0.4650	-0.2190 0.0870

Table 5. Comparison of mental, physical and overall QoL domains among MS patient in different populations

Reference	Instrument	Population	QoL dimension		
			Mental health composite (MHC)	Physical health composite (PHC)	Overall QoL
Čatić T et al. 2017	MSQoL-54	B&H	49.82 (36.05-61.38)	51.84 (34.93-70.20)	63.06 (45.00-79.18)
Šabanagić-Hajrić S et al. 2015	MSQoL-54	Federation of B&H	66.74 (47.39-80.29)	49.36 (32.38-70.93)	55.00 (40.00-68.35)
Tadić D et al.2013	MSQoL-54	Republic of Srpska B&H	56.5±19.4	52.3±19.0	30.7±9.3
Hadgkiss EJ et al. 2013	MSQoL-54	International	66.7 (65.8–67.6)	59.1 (58.1–60.0)	66.9 (66.1–67.7)
Kisić Tepavčević D et al.	MSQoL-54	Serbia	56.3±19.5	51.3±17.9	54.6±42.9
Szilasiova J et al.	SF-36	Slovakia	43.8 (+11.1)	39.9 (+10.5)	NR
Smoljanac I.	SF-36	Croatia	63.25 (+25.10)	53.49 (+29.93)	NR
Yozbatiran N et al. 2006	MSQoL-54	Turkey	61.28±20.28	65.01±21.68	NR

NR=Not Reported; B&H=Bosnia and Herzegovina

Table 5 provide measurement of quality of life among patient with MS reported in previous studies in different populations using MSQoL-54 or SF-36 instrument (which is integral part of MSQoL-54).

DISCUSSION

Multiple sclerosis (MS) as a chronic progressive neurology disease mainly cause physical disability measured by EDSS score in routine clinical practice, it is now well recognized that it does not reflect all of the facets that patients consider important in their life. Symptoms like fatigue, depression, and physical disability are only one aspect of a person's experience with MS but also cognitive, emotional, and psychological functions contribute to their quality of life (QoL) (Baumstarck et al. 2013). The QoL measurements are being considered increasingly important with regard to evaluating disease progression, treatment and the management of care provided to MS patients (Mitchell et al. 2005). A large number of disease-specific QoL instruments have been validated for use in MS patients like Multiple Sclerosis Quality of Life questionnaire (MSQOL54), the Functional Assessment of Multiple Sclerosis questionnaire (FAMS), the Multiple Sclerosis Quality of Life Index (MSQLI) and many others, but also generic QoL instruments like SF-36 or EQ-5D are often used (Simeoni et al. 2008). Use of QoL instruments

are recommended by health authorities like the US Food and Drug Administration (FDA) and the European Medicines Agency (Opara et al. 2010, FDA 2010). Many clinical trials include QoL instruments in protocols (EMA 2012), but less utilization have been reported in routine clinical practice (Doward et al. 2004). Comparison of MS specific instruments have been evaluated (Al-Tahan et al. 2011) and it has been identified that there is need to introduce it more in clinical practice on order to increase patient-centric care (Hancinova & Simor 2016). There are different attitudes toward using generic or disease specific instruments in routine practice. It has been confirmed that generic instruments cannot cover all domains that are important to people with MS (Miller et al. 2010).

In our study we found high correlation between generic and disease specific questionnaire scores at the beginning of the study, but after one year there was no significant difference. This could be the result of treatment outcomes, meaning that using of different instruments at the beginning of treatment could give different information to clinicians and introduction of the therapy. It is also important to notice that, since there is no significant difference between instruments at the end of study period and one year of treatment, it suggest that both instruments could be used as treatment outcome assessment. This is particularly important in case of conditional reimbursement and measuring treatment

outcomes (Kuspinar & Mayo 2013). High correlation between QoL measures by EQ-5D have been identified at the beginning and the end of the study suggesting that there is strong reliability of this generic instrument. EQ-5D is widely used instrument, but it has been also reported that it does not capture some of MS related symptoms like fatigue (Özakbas et al. 2007). Average utility in our patient sample was 0.639. It is similar QoL loss of 28% compared to general population as identified in European countries (Hemmett et al. 2004). In our study we have used utility value set for UK population which is well explained and mostly used across pharmacoeconomic studies. Correlation between EDSS and EQ-5D has also been identified and it was significant negative correlation (Mossman et al. 2016). Similar correlation between EDSS score and MSQoL-54 was also reported in other studies. Similar correlation found in Serbia (Drulovic et al. 2007) and Slovakia (Szilasiova et al. 2011). Study conducted in Croatia used different tool to assess QoL in patients with MS but it has also showed loss of QoL among this population (Smoljanac 2016). Comparing physical and mental dimensions of QoL among different countries it is confirmed that mental health is significantly impacted and decreased in patients with MS.

Psychiatric comorbidity relates to its higher than expected frequency in MS. Depression and anxiety are associated with lower health-related quality of life, independent of physical disability (Janssens et al. 2003). Mental health is affected by MS and vice-versa impacting and causing lower overall QoL in patients with MS (Sommerlad et al. 2008).

Mental health should be also taken into consideration and adequately treated by mental health professionals in order to improve overall therapeutic outcomes (Minden et al. 2013).

Mental component and other comorbidities should be taken into consideration during treatment and management of MS patients in clinical practice in order to improve their QoL and overall outcomes.

CONCLUSIONS

Quality of life of patients with MS is significantly reduced comparing to general population and reduction level of QoL in Bosnia and Herzegovina is similar to those in European and neighbouring countries. It is recommended to use disease specific measurement like MSQoL-54 in clinical practice since it capture broader and important MS related symptoms like fatigue rather than generic instruments. We have also showed than in order to follow up treatment outcomes application of QoL instruments is useful for improving patient centric care and could be used in reimbursement decision and selection of treatment. Mental health significantly contribute to overall QoL of MS patients

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Contribution of individual authors:

Tarik Čatić: study design, first draft, statistical analysis, data collection, approval of the final version.

Josip Čulig: study design, approval of the final version.

Enra Suljić: study design, data collection, approval of the final version.

Admir Mašić: data collection, first draft.

Refet Gojak: statistical analysis, first draft.

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