https://doi.org/10.31925/farmacia.2021.5.4 **ORIGINAL ARTICLE**

IDENTIFICATION AND QUANTIFICATION OF RISK FACTORS RELATED TO THE QUALITY OF LIFE OF MULTIPLE SCLEROSIS PATIENTS

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Abstract

Multiple sclerosis (MS) is a debilitating neurological disease which significantly impacts the patients' quality of life. The aim of this study was to identify and quantify the most important risk factors associated to the quality of life, as quantified through Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54). A retrospective observational study was designed. 54 patients were considered and three quality of life indicators were derived: physical health, mental health and perceived quality of life (QL Score). A correlation and causality analysis was performed, in order to describe the relationship between these three factors and relevant clinical characteristics, such as age, gender, Expanded Disability Status Scale (EDSS score) and treatment duration. The results indicated a strong positive correlation between all three quality of life indicators and a moderate negative correlation between age, EDSS and physical health and QL Score. In addition, the good cause-effect relationship between the clinical characteristics and the quality of life parameters may offer a basis of developing personalized machine learning prediction algorithms which might further optimize the physical health and mental health of MS patients.

Rezumat

Scleroza multiplă este o afecțiune neurologică severă care influențează în mod semnificativ calitatea vieții pacienților care suferă de această boală. Astfel, obiectivul acestui studiu a fost dat de identificarea și cuantificarea celor mai importanți factori de risc care pot influența calitatea vieții pacienților cu scleroză multiplă, cuantificată prin intermediul chestionarului MSQOL-54. A fost derulat un studiu retrospectiv observațional, în care au fost incluși 54 de pacienți; în urma analizei chestionarului, au fost luați în considerare 3 indicatori: sănătatea fizică, sănătatea psihică și scorul QL de percepție a calității vieții. În scopul identificării legăturii dintre acești indicatori și caracteristicile clinice ale pacienților (vârsta, sexul scorul EDSS, durata tratamentului), au fost puse la punct o analiză de corelație și una de cauzalitate. Rezultatele au indicat o corelație pozitivă semnificativă între toți cei 3 indicatori de calitate a vieții, precum și o corelație negativă moderată între vârstă, EDSS pe de o parte și sănătatea fizică și scorul QL pe de cealaltă parte. În plus, relația de cauzalitate dintre caracteristicile clinice și parametrii de cuantificare a calității vieții pot constitui un punct de plecare pentru dezvoltarea unor algoritmi personalizați de predicție care să îmbunătățească în mod suplimentar sănătatea fizică și psihică a pacienților cu SM.

Keywords: multiple sclerosis; quality of life; risk factors; causality analysis

Introduction

Multiple sclerosis (MS) is a severe and progressive neurological disease, which affects both young and old adults. The high variability related to disease prognosis, as well as the consistent levels of disability can significantly influence the quality of life in MS patients [6, 9, 12, 14]. Hence, relevant interventions must focus on limiting the disability, as well as on other factors which might influence the quality of life, from three important points of view: physical health, mental health and perceived quality of life [1]. However, the interventions must be developed after carefully considering the clinical and patient related characteristics which might optimize both on the short and long term the quality of life of MS patients, based on relevant assessment tools, one of the most frequently implemented being the Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54) [1-3, 26]. Therefore, the aim of the current study was to identify and quantify the most important patient related and clinical characteristics which might influence the MS patients' quality of life, as determined through MSQOL-54.

Materials and Methods

Study design

A retrospective observational study was conducted at Bucharest Emergency University Hospital (Department of Neurology). The patients which were included in the study were all diagnosed with MS and under

treatment with specific drug therapies. They were selected based on their availability of completing the MSQOL-54 questionnaire. Initially, 60 patients were selected, of which 6 were excluded, due to the lack of complete clinical and quality of life data (the quality of life questionnaire could not be validated for these patients) [26].

Hence, the study finally included 54 patients (77.77% (42 patients) females and 22.22% (12 patients) males) treated with 4 different drug therapies through the Multiple Sclerosis National Programme: interferon beta-1a (subcutaneous administration: 3 doses *per* week), interferon beta-1a (30 µg/0.5 mL – intramuscular administration: 1 dose *per* week), interferon beta-1b (250 µg/mL – subcutaneous administration: 1 dose every 2 days), glatiramer acetate (subcutaneous administration: 1 dose *per* day or 1 dose every 2 days depending on the concentration: 20 mg/mL or 40 mg/mL) [13].

The study received the approval of the Ethics Committee of the Emergency University Hospital Bucharest and was conducted in accordance with the ethical requirements of the Helsinki Declaration of 1975, as revised in 2000.

Data collection and Quality of Life Assessment

The data were collected from the patients' medical records. The following characteristics were taken into account: age at disease onset (Age_{onset}), age, gender, Expanded Disability Status Scale (EDSS: at disease onset – $EDSS_{onset}$, current EDSS - $EDSS_{present}$), current drug treatment and treatment duration [10, 25]. Age and gender were considered as relevant parameters because of their interrelationship with the selected clinical features (such as EDSS), as highlighted in relevant studies [3, 25]. In addition, the evolution of the EDSS score was computed based on the following formula:

$$EDSS\ (evolution) = \frac{EDSS_{present} - EDSS_{onset}}{Age - Age_{onset}}, \quad (1)$$

The patients were evaluated based on the MSQOL-54 questionnaire, which comprises a set of 54 items, which are then used to compute 12 health related subscales, 2 summary scores (physical health and mental health) and 2 single item measures (satisfaction with sexual function, change in health). After computing the specific subscales and scores related to the questionnaire, 3 parameters were selected for data analysis: physical health (can take values from 1 to 100), mental health (can take values from 1 to 100) and perceived quality of life (Quality of Life (QL) Score - can take values from 1 to 10). The choice was made based on the consideration that these three scores can thoroughly described the overall MS patients' health, as well as the perceived (self-reported) health [3, 16, 26].

Afterwards, the obtained data was processed by using several statistical techniques. Python programming language version 3.7.9 was used for data processing [18].

Data analysis

The data analysis comprised in three important parts: preliminary statistical analysis, correlation analysis and causality evaluation. The correlation and causality analyses were performed in order to establish certain dependencies between the clinical data extracted from the patients' medical records and the three selected QL indicators.

Preliminary statistical analysis

Aiming at offering a general characterization of the obtained data, several statistical measures were computed on the continuous variables: mean, standard deviation and relative standard deviation (RSD) [8]. The processed variables were: age, EDSS (evolution), treatment duration, physical health, mental health and QL score. The relative standard deviation was computed based on the following formula [8]:

$$RSD\ (\%) = \frac{Standard\ deviation}{Mean}\ x\ 100\ , \quad (2)$$

Correlation analysis

The correlation analysis was performed by computing the Pearson correlation coefficient available in the Scipy package, along with the p value which quantified the statistical significance of the results [8, 23]. Eight variables were included and the correlation was performed between each pair of variables: age, gender, $EDSS_{present}$, $EDSS_{evolution}$, treatment duration, physical health, mental health, QL score.

Causality analysis

In order to evaluate whether the patient related characteristics are related to the quality of life indicators in a cause-effect manner, a causality analysis was also performed, based on the CausalImpact Python package. The model evaluated the probability that the QL indicators' values (physical health score, mental health score, QL score) occurred in a causal manner, had they been predicted by using certain patient related (clinical) characteristics [17]. The analysis was implemented for each of the three QL indicators. The predictive variables were the same in each of the three cases, namely age, gender, $EDSS_{onset}$, $EDSS_{present}$, EDSS (evolution) and treatment duration. In order to apply the causality model, the dataset was randomly split into two parts: one part (41 patients) represented the training set (or the pre period) and the other part (13 patients) represented the test set (or the post period), corresponding to a 3:1 training set: test set ratio. For each of the three QL indicators, the causality evaluation was performed for three different random splits [17].

Results and Discussion

Preliminary statistical analysis

Table I presents the values which were obtained in terms of mean, standard deviation and relative standard

deviation for the continuous variables which were analysed, while Table II presents specific patient and quality of life characteristics within each of the 4 drug therapy groups. In addition, in order to allow a simplified visualization of the quality of life indicators, Figure 1 offers a graphical distribution of the QL Score values.

Table I

Preliminary Statistical Analysis Results

Variable	Mean ± Standard deviation	RSD%
Age	41.1482 ± 10.1533	24.67%
EDSS Evolution	0.0879 ± 0.1672	190.25%
Treatment duration (years)	5.3519 ± 4.2911	80.18%
Physical health	68.2718 ± 21.849	32.00%
Mental health	71.6848 ± 22.7201	31.69%
QL Score	7.3704 ± 1.9748	26.79%

Table II

Specific characteristics within the 4 drug therapy groups

	Interferon beta-1a (i.m. administration)	Interferon beta-1b (s.c. administration)	Glatiramer acetate (s.c. administration)	Interferon beta-1a (s.c. administration)
Age	41.6	41.0833	36.9091	42.8846
Physical health	74.894	69.7025	67.4618	66.6823
Mental health	79.374	73.76	69.55	70.1535
Male (%)	20.00%	16.67%	0.00%	34.62%
Female (%)	80.00%	83.33%	100.00%	65.38%
Number of patients	5	12	11	26
QL Score	8.2	7.4167	7.3636	7.1923
EDSS Evolution	0.25	0.1019	0.0913	0.0488
Treatment duration (years)	3.6	7.0833	3.4545	5.6923

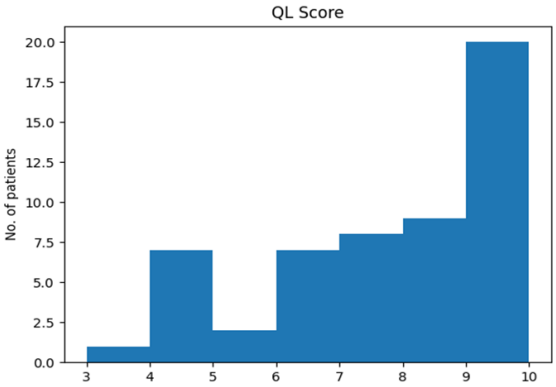

Figure 1.
QL Score values distribution

Causality analysis

Table III presents the results obtained in terms of causality analysis. The probability of a causal relationship was computed for 3 random splits of the data in training set and test set (3:1 ratio).

The obtained results showed an overall good physical health, mental health and quality of life for the MS patients for which the characteristics were analysed, which are consistent with the studies published in recent years, especially when considering the self-reported health status [15, 27].

Table III

Causality Analysis results. The given percentages represent the probabilities of a causal relationship between the predictive variables and the QL indicator

QL indicator	Physical health	Mental Health	QL Score
Split 1	73.83%	54.05%	81.52%
Split 2	99.20%	91.11%	88.41%
Split 3	73.43%	52.15%	82.22%
Mean	82.15%	65.77%	84.05%

First of all, the mean value in terms of physical health was 68.27, compared to a slightly higher value for mental health, 71.68 (Table I). Both scores were computed using a 0 - 100 scale, therefore yielding relatively high values, despite of the progressive nature of multiple sclerosis. No significant differences were found between the 4 drug therapy groups; however, the highest average values in terms of both physical health (74.89) and mental health (79.37) were obtained within the interferon beta-1a treated patients (intramuscular administration: 1 dose *per* week). However, these differences could not be considered statistically significant, since only 5 patients were treated with interferon beta-1a intramuscular, 1 dose *per* week, and hence the obtained values were more likely to be caused by other relevant patient-related characteristics.

In addition, the lower physical health values could be explained by a moderate negative correlation between this parameter and age (-0.3068 correlation coefficient, p = 0.0268, resulting in a statistically significant correlation), especially considering the fact that the average age was 41 years (Table I).

Secondly, the average QL Score was 7.37 (of a maximum value of 10), with an imbalanced distribution: 20 patients had a QL Score of 9 or 10 (7 patients – 10, 13 patients – 9), which resulted in 37% of the patients (20 out of 54) having a very good perceived quality of life (graded 9 or 10) (Table I, Figure 1). By contrast, only 10 patients (18.5%) had a perceived low quality of life - graded equal to or lower than 5 (2 patients – QL Score = 5, 7 patients – QL Score = 4, 1 patient – QL Score = 3). The QL Score was also negatively correlated with the patients' age (correlation coefficient = -0.2983, p = 0.0285).

In terms of correlation analysis results, besides the moderate negative correlation which was obtained between age and physical health (a correlation coefficient of -0.3068, p = 0.0241), as well as between age and QL Score (a correlation coefficient of -0.2983, p = 0.0285), other statistically significant relationships were found between two QL indicators and $EDSS_{present}$. A correlation coefficient of -0.3418 between $EDSS_{present}$ and physical health was computed (p = 0.0114), as well as a correlation coefficient of -0.2852 between $EDSS_{present}$ and QL Score (p = 0.0366). By contrast, the EDSS evolution was correlated with neither of the quality of life indicators, which can be explained by the fact that the quality of life of MS patients is significantly influenced by the current status (age, EDSS and other patient-related factors) and less by their evolution in time [20]. The three quality of life indicators which were analysed were all positively correlated two by two, with a correlation coefficient of 0.7655 between mental health and QL Score, 0.8149 between physical health and QL Score and 0.9063 between physical health and mental health; all three situations yielded a p value less than 0.0001 (10^{-4}), resulting in a very high degree of statistical significance.

Secondly, the data analysis yielded (unrelated to the quality of life indicators) a moderate positive correlation between age and $EDSS_{present}$ (a correlation coefficient of 0.3735, p = 0.0054), as well as a statistically significant negative correlation between female gender and treatment duration (a correlation coefficient of -0.5686, p value less than 0.0001). The moderate positive correlation between age and EDSS can be explained by the progressive nature of MS, while the negative correlation between female gender and the number of years of treatment could not be explained by current knowledge and was attributed to the observational, hence bias prone nature of the study [6, 13].

In addition, the lack of positive correlations between the quality of life parameters and other patient characteristics can be explained by the fact that there are other important factors which might influence on both the short and the long term the general well-being of MS patients, as outlined in recent studies. Therefore, as a first limitation of the current work, it should be mentioned that important parameters which were not included in the study are the depressive and cyclothymic temperament, anxiety disorders, relationship with caregivers and number of relapses [19-21]. Another important limitation of the current work was the small number of patients which were included in the study. The final dataset contained the clinical and demographical data for 54 MS patients, which, when also taking into account the small number of selected parameters, negatively influenced the statistical significance and clinical relevance of the obtained results.

Even though there were several important factors which could not be included in the current research, the causality impact results, as highlighted in Table III, showed satisfactory results in terms of cause-effect relationship between the predictive variables and physical health, mental health and QL Score. The computed probabilities which estimated the chance of a cause-effect relationship between the predictive variables and the quality of life indicators ranged from 73.43% to 99.20% for physical health (an average value of 82.15%), from 52.15% to 91.11% for mental health (an average value of 65.77%), while the causal impact algorithm applied to the QL Score values estimation yielded the highest average value, 84.05%, with a more compact range (81.52% - 88.41%). The higher variability in terms of causal probabilities which was observed for physical health and mental health, as opposed to the QL Score can be explained by the higher degree of complexity of the factors which lead to the computation of these two indicators [26], as well as by the high variance of the predictive variables, as reflected by the RSD% in Table I. By contrast, the QL Score was a self-reported measure which implied the perceived quality of life of MS patients and was not computed based on a standardized, objective approach [26].

Therefore, the obtained results could lead in future studies to the development of specific predictive algorithms which could be able to accurately estimate these indicators. Given the enhanced and more stable results obtained by applying the causal impact algorithm for the QL Score, one direction may concentrate on adding more patients to the processed data, while keeping the same variables as predictive parameters. The second objective, mandatory for the development of a predictive algorithm which might be able to estimate the physical health and mental health indicators, might be that of including more relevant patient-related characteristics, such as the number of relapses, as well as anxiety disorders, other relevant psychiatric conditions or relationship with caregivers [19-21].

The development of such machine learning algorithms is a growing need in many medical fields [24]. As for multiple sclerosis patients, the unpredictable nature of the disease, as well as the relapsing evolution of many individuals make such a purpose of an utmost importance, especially considering the fact that the majority of the machine learning algorithms focused on disease course prediction and diagnostic and prognostic modelling rather than on quality of life estimation [4, 5, 7, 11, 14, 22, 28].

Conclusions

A retrospective observational study which focused on the most important factors which might influence the MS patients' quality of life, as quantified through the MSQOL-54 questionnaire was described. The quality of life was assessed through three indicators, physical health, mental health and the self-reported QL Score, computed for 54 MS patients. A correlation analysis and a causality evaluation were undertaken. The correlation analysis results showed a strong positive correlation between all three quality of life indicators, as well as a moderate negative correlation between age, EDSS and physical health, QL Score. The causality analysis yielded satisfactory results given the small dataset and the limited number of predictive variables; the causal impact algorithm computed the probability of a causal relationship between the patient characteristics and the physical health, mental health and QL Score. The algorithm yielded an 82.15% causal probability for physical health and a 84.05% probability for the QL Score. The analysis proves the potential of implementing artificial intelligence into quantifying the quality of life of MS patients. Future studies must focus on developing clinically relevant predictive algorithms for estimating the physical health, mental health and perceived QL indicators; by doing this, important interventions can be made in order to improve on the long term the health status of MS patients.

Conflict of interest

The authors declare no conflict of interest.

References

1. Albuquerquea C, Geraldob A, Martinsa R, Ribeiroa O, Quality of life of people with multiple sclerosis: Clinical and psychosocial determinants. *Procedia - Social and Behavioral Sciences*, 2015, 171: 359-365.
2. Bandari D, Vollmer TL, Khatri BO, Tyry TM, Assessing Quality of Life in Patients with Multiple Sclerosis. *Int J MS Care*, 2010; 12(1): 34-41.
3. Baumstarck K, Boyer L, Boucekine M, Michel P, Pelletier J, Auquier P, Measuring the Quality of Life in Patients with Multiple Sclerosis in Clinical Practice: A Necessary Challenge. *Mult Scl Int.*, 2013; 524894: 1-8.
4. Chitnis T, Glanz BI, Gonzalez C, Healy BC, Saraceno TJ, Sattarnezhad N, Diaz-Cruz C, Polgar-Turcsanyi M, Tummala S, Bakshi R, Bajaj VS, Ben-Shimol D, Bikhchandani N, Blocker AW, Burkart J, Cendrillon R, Cusack MP, Demiralp E, Jooste SK, Kharbouch A, Lee AA, Lehár J, Liu M, Mahadevan S, Murphy M, Norton LC, Parlikar TA, Pathak A, Shoeb A, Soderberg E, Stephens P, Stoertz AH, Thng F, Tumkur K, Wang H, Rhodes J, Rudick RA, Ransohoff RM, Phillips GA, Bruzik E, Marks WJ, Weiner HL, Snyder TM, Quantifying neurologic disease using biosensor measurements in-clinic and in free-living settings in multiple sclerosis. *NPJ Digit Med.*, 2019; 2: 123: 1-8.
5. Fiorini S, Verri A, Tacchino A, Ponzio M, Brichetto G, Barla A, A machine learning pipeline for multiple sclerosis course detection from clinical scales and patient reported outcomes. *Annu Int Conf IEEE Eng Med Biol Soc.*, 2015; 2015: 4443-4446.
6. Gil-González I, Martín-Rodríguez A, Conrad R, Pérez-San-Gregorio MA, Quality of life in adults with multiple sclerosis: a systematic review. *BMJ Open*, 2020; 10(11): e041249: 1-21.
7. Goyal M, Khanna D, Rana PS, Khaibullin T, Martynova E, Rizvanov AA, Khaiboullina SF, Baranwal M, Computational Intelligence Technique for Prediction of Multiple Sclerosis Based on Serum Cytokines. *Front Neurol.*, 2019; 10: 781: 1-9.
8. James G, Witten D, Hastie T, Tibshirani R, An Introduction to Statistical Learning: with Applications in R. *Springer Texts in Statistics*, 2013; 103. Springer Science+Business Media New York.
9. Kefaliakos A, Pliakos I, Diomidous M, Managing the Quality of Life in Patients with Multiple Sclerosis: A Literature Review. *Stud Health Technol Inform.*, 2016; 226: 220-221.
10. Kurtzke JF, Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, 1983; 33(11): 1444-1452.
11. Lötsch J, Schiffmann S, Schmitz K, Brunkhorst R, Lerch F, Ferreiros N, Wicker S, Tegeder I, Geisslinger G, Ultsch A, Machine-learning based lipid mediator serum concentration patterns allow identification of multiple sclerosis patients with high accuracy. *Sci Rep.*, 2018; 8: 14884: 1-16
12. Maier S, Motataianu A, Barcutean L, Balint A, Hutanu A, Zoltan B, Stoian A, Romaniuc A, Andone S, Balasa R, Interferon-β 1A, an immunomodulator in relapsing remitting multiple sclerosis patients. The effect on pro-inflammatory cytokines. *Farmacia*, 2020; 68(1): 65-75.
13. Montalban X, Gold R, Thompson AJ, Otero-Romero S, Pia Amato M, Chandraratna D, Clanet M, Comi G, Derfuss T, Fazekas F, Hartung HP, Havrdova E, Hemmer B, Kappos L, Liblau R, Lubetzki C, Marcus E, Miller DH, Olsson T, Pilling S, Selmaj K, Siva A, Sorensen PS, Sormani MP, Thalheim C, Wiendl H, ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler.*, 2018; 24(2): 96-120.
14. Oprea S, Văleanu A, Negreș S, The development and validation of a disability and outcome prediction algorithm in multiple sclerosis patients. *Farmacia*, 2020; 68(6): 1147-1154.

15. Pittock SJ, Mayr WT, McClelland RL, Jorgensen NW, Weigand SD, Noseworthy JH, Rodriguez M, Quality of Life Is Favorable for Most Patients With Multiple Sclerosis: A Population-based Cohort Study. *Arch Neurol.*, 2004; 61(5): 679-686.
16. Preedy VR, Watson RR (Eds.), Handbook of disease burdens and quality of life measures, 2010; 6: 4265, *New York: Springer*.
17. Python Software Foundation, Causal-impact 1.3.0, 2020; https://pypi.org/project/causal-impact.
18. Python Software Foundation, Python Language Reference, version 3.7.9, 2020; www.python.org/ downloads/release/python-379.
19. Rezapour A, Almasian Kia A, Goodarzi S, Hasoumi M, Nouraei Motlagh S, Vahedi S, The impact of disease characteristics on multiple sclerosis patients' quality of life. *Epidemiol Health*, 2017; 39: e2017008: 1-7.
20. Salhofer-Polanyi S, Friedrich F, Löffler S, Rommer PS, Gleiss A, Engelmaier R, Leutmezer F, Vyssoki B, Health-related quality of life in multiple sclerosis: temperament outweighs EDSS. *BMC Psychiatry*, 2018; 18; 143: 1-6.
21. Santos M, Sousa C, Pereira M, Pereira MG, Quality of life in patients with multiple sclerosis: A study with patients and caregivers. *Disabil Health J.*, 2019; 12(4): 628-634.
22. Schwab P, Karlen W, A Deep Learning Approach to Diagnosing Multiple Sclerosis from Smartphone Data. *IEEE J Biomed Health Inform.*, 2021; 25(4): 1284-1291.
23. Scipy developers, Documentation of scipy 1.5.2, 2020; https://docs.scipy.org/doc.
24. Sidey-Gibbons J, Sidey-Gibbons C, Machine learning in medicine: a practical introduction. *BMC Med Res Methodol.*, 2019; 19: 64: 1-18.
25. Van Munster CE, Outcome measures in clinial trials for multiple sclerosis. *CNS Drugs*, 2017; 31(3): 217-236.
26. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW, A health-related quality of life measure for multiple sclerosis. *Qual Life Res.*, 1995; 4(3): 187-206.
27. Ysrraelit MC, Fiol MP, Gaitán MI, Correale J, Quality of life assessment in multiple sclerosis: different perception between patients and neurologists. *Front Neurol.*, 2018; 8: 729: 1-6.
28. Zhao Y, Healy BC, Rotstein D, Guttmann CR, Bakshi R, Weiner HL, Brodley CE, Chitnis T, Exploration of machine learning techniques in predicting multiple sclerosis disease course. *PLoS One*, 2017; 12(4): e0174866: 1-13.