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Individual factors enhance poor health-related quality of life outcome in multiple sclerosis patients. Significance of predictive determinants

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ABSTRACT

Background: Individual factors in multiple sclerosis (MS) patients may modify the reliability of health-related quality of life (HRQOL) assessment. Knowledge of these effects may enable physicians to identify patients at risk for poor perceived health.
Objective: To investigate what individual factors may interact with MS symptoms and their severity to modify the reliability of HRQOL assessment; to explore the predictive values of the significant variables identified.
Methods: HRQOL was assessed in 57 patients by the 36-Item Short Form Health Survey (SF-36). The Physical Component Summary and Mental Component Summary were dichotomized and applied as dependent variables for logistic regression analysis. The Functional Independence Measure (FIM), Expanded Disability Status Scale (EDSS), Fatigue Severity Scale (FSS), Cognitive Behavioral Assessment (CBA) and specific individual factors were tested as independent variables. Two-way contingency tables were used to calculate the predictive values.
Results: Unemployment, smoking, and night waking were the most significant individual factors. Introversion, physical pain and difficulty falling asleep were also significant. EDSS-total ≥ 2, EDSS-pyramidal ≥ 2, FIM ≤ 123, FSS ≥ 5, depressive manifestations and bowel/bladder dysfunction were significant MS-related determinants. Sensitivity and specificity differed widely for each variable.
Conclusions: Individual factors have relevance in HRQOL assessment. Their identification may help physicians construct the patient's risk profile. Sensitivity and specificity add weight to the significance of variables.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) which impacts on patients'behavioral traits and life-style. It is progressive and characterized by various motor, sensory and psycho-cognitive impairments, reducing patients' physical and mental performance, as well as social participation.

Since MS affects everyday life, quality of life (QOL) has frequently been investigated in these patients and has been found to be lower than in the general population [1–3]. The QOL concept is used to identify how a subject feels about his health status in terms of participation and perceived wellbeing [4]. Health-related quality of life (HRQOL) measures the degree to which a disease affects an individual's self-reported life perception [5].

Some reports show that common MS symptoms, such as fatigue [6,7], depression [8–10], impaired mental function [11] and bladder [12], cognitive and emotional dysfunction [13] significantly decrease a patient's perceived health. When impairment of functional systems (pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, cerebral and other) was scored with the widely used Expanded Disability Status Scale (EDSS) [14], the correlation with disability level and HRQOL score was unsatisfactory [3,15,16].

Thus, the burden of the disease may not be adequately quantified by considering only impairment or disability closely related to the symptoms usually assessed in regular clinical measurements. This is mainly because there is a stronger correlation between HRQOL and individual factors, e.g. unemployment [6,17], poor sleep [18], sexual problems [19], pain [20], emotional adjustment and restricted participation [21]. The aims and results of the above reports suggest that certain individual factors, not directly or commonly ascribed to disease-related impairment, may interact with and depress HRQOL with respect to HRQOL based on routinely assessed symptoms and their severity.

In our opinion, individual factors may modify the reliability of HRQOL assessment. Knowledge of these effects may enable physicians

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to identify patients at risk for poor perceived health. This is because common disease-related symptoms may not be the only source of poor reported QOL. In addition, variables may have more meaning when interpreted in terms of predictive values.

The aims of the present study were: 1) to investigate what individual factors may modify the reliability of HRQOL assessment by interacting with common significant MS symptoms and their severity; 2) to explore the predictive values of the significant variables identified, in terms of sensitivity, specificity and positive/negative predictive values.

2. Methods

2.1. Design and procedures

The total study population consisted of 57 MS patients who were recruited from the neurological day hospital/day service of the University Hospital of Siena. This prospective cohort study consisted in the administration of a series of clinical and self-administered questionnaires during regular scheduled clinical visits, without patient pre-alert before the assessments. Clinical and self-assessments were administered by two expert MS neurologists, two trained physiotherapists and one clinical psychologist. Written informed consent was obtained from all participants. The study was approved by the University of Siena Human Subjects Ethics Committee, in accordance with the Declaration of Helsinki.

2.2. Subjects

Diagnosis of MS was based on the McDonald criteria [22]. Enrolment criteria for the study were: 1) a diagnosis of MS; 2) no disease exacerbation in the previous 3 months; 3) age at least 18 years; 4) no disabling medical history due to other pathologies; 5) absence of other concomitant neurological diseases; 6) absence of psychiatric disorders before diagnosis of MS; 7) ability to perform self-reported assessment independently; 8) control scale score within cut-off values for reliability of the Cognitive Behavioral Assessment (CBA) [23]; 9) moderate disability status without ambulatory disability (EDSS score $\leq$5.5, i.e. "ability to walk without aid for about 100 m; disability severe enough to preclude full daily activities") [14]; 10) written informed consent to the study.

2.3. Dependent variables

Self-perceived health was assessed using the 36-Item Short Form Health Survey (SF-36) [24], Italian version [25]. The SF-36 is the most widely used generic multi-dimensional health survey assessment for MS patients [26]. It assesses eight domains: physical functioning (PF), role limitations due to physical health problems (role-physical) (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional health problems (role-emotional) (RE) and mental health (MH). The first four subscales make up the Physical Component Summary (PCS) and the last four, the Mental Component Summary (MCS). The SF-36 also allows patients' perceived health to be compared with a reference population [2]. The scores of each subscale are standardized from 0 to 100, with higher values representing better HRQOL. The summary scores, PCS and MCS, are standardized to a mean of 50, with a score above 50 representing better than average function and below 50 poorer than average function [27]. PCS and MCS may be compared with the normal average of 50 $\pm$ 10 (SD) in the Italian population [25,28]. For the present study, PCS and MCS were dichotomized as follows: 1, poorer than average self-perceived health <40 (SD −1); 0, average or better than average self-perceived health compared to the general population, i.e. $\geq$40.

2.4. Independent variables

Independent variables were chosen in line with the aims of the study: 1) functionality evaluated with the Functional Independence Measure (FIM) [29] — the clinimetrics of FIM for the impact of disability in MS patients is well established [30]; 2) neurological impairment of functional systems, evaluated with Kurtske's eight EDSS functional systems [14], i.e. pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, cerebral and other; EDSS total score; 3) self-reported severity of perceived fatigue evaluated with the Fatigue Severity Scale (FSS) [31]; 4) cognitive–behavioral status, assessed by Cognitive Behavioral Assessment (CBA) [23], a validated self-administered series of questionnaires on personality characteristics and emotional adjustment. The questionnaires comprising CBA are listed below.

- The reduced Eysenck Personality Questionnaire [32] which investigates four factors: neuroticism (EPQ/R-N), psychoticism (EOQ/R-P) and extroversion/introversion (EPQ/R-E) combined with a lie scale (EPQ/R-L). Higher scores on the extroversion/introversion factor represent extroversion (>65th percentile), which indicates sociability, liveliness and *surgency*, whereas lower scores ($\leq$40th percentile) represent introversion. Higher scores on the neuroticism factor suggest anxiety and worry ($\geq$95th percentile). Higher scores on the psychoticism factor ($\geq$95th percentile) suggest solitude and difficulty adapting to the external environment. The lie scale represents unsophisticated dissimulation and social naiveté or conformity, and the battery is not reliable for scores $\geq$95th percentile.
- Fear inventory (a short version of Wolpe and Lang's Fear Survey Schedule) [33] based on two overall indexes (number of fears [IP-F] and fear intensity [IP-PH]), as well as five subscales that investigate specific groups of fear, i.e. fear of death (IP-1), fear of social rejection (IP-2), fear of repulsive animals (IP-3), fear of separation (IP-4) and fear of blood/medical procedures (IP-5). Factors were present for scores $\geq$95th percentile.
- The Maudsley Obsessive–Compulsive Questionnaire [34], consisting of the overall score (MOCQ/R) and three indexes. This instrument studies thought patterns and compulsive behavior, such as repetitive and redundant checking (MOCQ/1); overconcern about hygiene, cleanliness, disease spread and contamination (MOCQ/2); recurrent doubts and intrusive nagging thoughts (MOCQ/3). Factors were present for scores $\geq$95th percentile.
- The State-Trait Anxiety Inventory [35], which investigates the state and trait of anxiety (STAI-X2), as well as anxiety about the questionnaire, before (STAI-X1) and after (STAI-X1/R) its compilation. If the control scale scores (before and after) are $\geq$99th percentile, the assessment is not reliable. In STAI-X2, scores $\geq$95th percentile mean "factor present".
- Reduced form of a Psychological Questionnaire [36] (QPF/R) which investigates psycho-physiological reactions and disturbances of potential clinical significance for scores $\geq$95th percentile.
- A 24-item Questionnaire on Depression [36] (QD) that measures dysphoria and depressive manifestations of subclinical significance. Factor present for scores $\geq$95th percentile.

The CBA also includes a questionnaire investigating patient autobiography and individual factors to better define personality characteristics and psycho-cognitive status. The following items are selected on the basis of their presence or absence: 1) employment; 2) relationship with parents and/or brothers and sisters (negative/positive); 3) stable relationship with a partner; 4) satisfying sexual activity; 5) sexual problems; 6) satisfying working activity; 7) economic difficulties; 8) smoking; 9) drinking alcoholic beverages; 10) poor sleep; 11) difficulty falling asleep; 12) night waking; 13) early morning waking; 14) night waking caused by nightmares and unpleasant sensations; 15) use of sleeping pills; 16) physical pain; and 17) sporting activity.

2.5. Data analysis

For statistical analysis, FIM, EDSS total score, Kurtske's EDSS functional systems and FSS were dichotomized (1/0) versus the dependent variables (PCS and MCS), applying Receiver-Operating Characteristic

(ROC) curve analysis to determine the optimal cut-off points on the basis of sensitivity/1-specificity. To dichotomize the CBA questionnaire scores, the cut-offs were based on factor presence or absence according to the questionnaire-specific discrimination percentiles described above. Otherwise, autobiographical and individual factors were dichotomized on the basis of their presence or absence, negative or positive meaning.

To determine bivariable association between independent determinants and poor PCS and MCS scores in ambulatory MS patients, binary logistic regression was performed to calculate significances, odds ratios (OR) and 95% confidence intervals (95% CI). To predict the determinants significantly associated with poor HRQOL (PCS and MCS respectively) in composite measurements (EDSS and CBA), separate stepwise backward multivariable logistic regressions were run, including determinants obtained from binary logistic regression output: 1) presence of the variable in the equation; 2) significance level $p \leq 0.2$. To prevent spurious relationships, Spearman's rho (r_s) colinearity diagnostics between selected variables should not reveal high association (≥ 0.70). If r_s was high, only one of the determinants was selected for further use in multivariable analysis, on clinical grounds. For the aims of this study, four stepwise backward multivariable logistic regressions were developed: 1) Kurtske's EDSS functional systems and PCS 2); CBA questionnaires and PCS; 3) Kurtske's EDSS functional systems and MCS; 4) CBA questionnaires and MCS.

The analyses were two-tail tested using critical p-values for entry and removal of p-values ≤ 0.05 and ≥ 0.10, respectively. Finally, two-way contingency tables were used to calculate the models' sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), including their 95% CIs.

All contingency table tests were two-tailed with a significance level of $p < 0.05$ using SPSS, version 19.

3. Results

The sample's main characteristics and the mean values of the SF-36 domains are shown in Table 1.

Table 2 shows dichotomization cut-offs and binary logistic regressions outputs, in terms of OR, CI and significance level of each determinant. For composite measures (EDSS and CBA) and dependent variable PCS, the candidate determinants ($p \leq 0.2$) for inclusion in the subsequent stepwise backward multivariable logistic regressions were: EDSS pyramidal, EDSS cerebellar, EDSS brainstem, EDSS bowel/bladder, as well as CBA EPQ/R-E introversion and CBA QD. When the dependent variable was MCS, the candidate determinants were: EDSS cerebellar, EDSS sensory, EDSS bowel/bladder, as well as CBA EPQ/R-E extroversion and CBA QD. No high correlation ($r_s \geq 0.70$) was found between the selected variables of each composite measurement, so that all could be included in the multivariable logistic regressions analysis.

Table 3 shows the significant factors ($p < 0.05$) on final analysis that predicted poor HRQOL in terms of cut-offs, OR, CI, accuracy, sensitivity, specificity, PPV and NPV in ambulatory MS patients. Accuracies ranged from 0.68 to 0.82. Binary logistic regression analysis indicated that unemployment (accuracy 0.75, sensitivity 0.60, specificity 0.80, PPV 0.53, NPV 0.85), smoking (accuracy 0.72, sensitivity 0.57, specificity 0.77, PPV 0.44, NPV 0.85), difficulty falling asleep (accuracy 0.68, specificity 0.68, NPV 1.00), night waking caused by nightmares and unpleasant sensations (accuracy 0.72, sensitivity 0.56, specificity 0.78, PPV 0.50, NPV 0.82), physical pain (accuracy 0.69, specificity 0.69, PPV 0.00, NPV 1.00), EDSS total score ≥ 2 (accuracy 0.77, sensitivity 0.63, specificity 0.84, PPV 0.68, NPV 0.82), FIM ≤ 123 (accuracy 0.82, sensitivity 0.79, specificity 0.84, PPV 0.61, NPV 0.92) and FSS ≥ 5 (accuracy 0.79, sensitivity 0.68, specificity 0.85, PPV 0.68, NPV 0.85) were predictive of poor HRQOL when the dependent variable was PCS. Physical pain (accuracy 0.71, specificity 0.71, PPV 0.00, NPV 1.00) and FSS score ≥ 5 (accuracy 0.77, sensitivity 0.61, specificity 0.85, PPV 0.65, NPV 0.82) were predictive of poor HRQOL when the dependent variable was MCS. For composite measurements (EDSS and CBA), the subsequent stepwise backward multivariable logistic regressions revealed that EDSS-pyramidal ≥ 2 (accuracy 0.81, sensitivity 0.82, specificity 0.80, PPV 0.50, NPV 0.95) and introverted personality (accuracy 0.74, sensitivity 0.61, specificity 0.77, PPV 0.44, NPV 0.87) were predictive of poorer PCS, whereas an EDSS-bowel/bladder >0 (accuracy 0.74, sensitivity 0.60, specificity 0.77, PPV 0.35, NPV 0.90) and dysphoria/depressive manifestations (accuracy 0.74, sensitivity 0.75, specificity 0.74, PPV 0.17, NPV 0.97) were predictive of poorer MCS than in the general population.

Table 1
Patient characteristics at assessment time.

N	57	
Gender, male/female	18/39	
Type of multiple sclerosis, RR/PP/SP	46/2/9	
Age (years)[a]	41.71 (12.60)	
Duration of disease (years)[a]	9.05 (7.94)	
Education: primary and/or secondary school/high school and/or university	13/44	
MS pharmacological treatment (yes/no)	30/27	
Antidepressant, yes/no	3/54	
Psychotherapy, yes/no	6/51	
EDSS, total score[b]	1.5 (2.25)	
SF-36 PCS (<40/≥40)	18	39
SF-36 MCS (<40/≥40)	17	40
SF-36 PCS[a]	30.06 (5.83)	49.03 (5.40)
SF-36 MCS[a]	32.05 (5.21)	51.35 (6.02)
SF-36 physical functioning (PF)[a]	45.28 (21.73)	86.67 (16.83)
SF-36 role-physical (RP)[a]	15.28 (22.91)	80.12 (27.01)
SF-36 bodily pain (BP)[a]	51.50 (28.70)	80.82 (21.72)
SF-36 general health (GH)[a]	29.00 (11.44)	56.31 (20.35)
SF-36 vitality (VT)[a]	35.88 (18.56)	61.12 (17.12)
SF-36 social functioning (SF)[a]	46.88 (19.00)	79.80 (18.14)
SF-36 (role-emotional) (RE)[a]	25.29 (32.15)	88.22 (25.76)
SF-36 mental health (MH)[a]	46.35 (14.28)	76.90 (12.43)

Legend: RR, relapsing remitting; PP, primary progressive; SP, secondary progressive; MS, multiple sclerosis; SF-36, 36-Item Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary; EDSS, Expanded Disability Status Scale.
[a] mean and standard deviation.
[b] median and interquartile ranges.

4. Discussion

This study aimed to show that low HRQOL in ambulatory MS patients may be due to: 1) symptoms and their severity, which may be identified by widely used disease measurement cut-offs; and 2) individual factors not directly ascribed to disease impairment.

Unemployment, smoking, and night waking caused by nightmares and unpleasant sensations were the most robust individual factors. Introversion, physical pain and difficulty falling asleep were also significant. These determinants may be interpreted as phenomenological factors, related to a psycho-cognitive state and interacting with poor HRQOL caused by significant common disease variables, such as EDSS total score ≥ 2 (minimal disability in one functional system), EDSS-pyramidal ≥ 2 (minimal disability related to the pyramidal system), FIM ≤ 123, FSS ≥ 5 (severe fatigue), depressive manifestations, and bowel/bladder dysfunction.

These determinants became clinically meaningful, especially if interpreted in terms of sensitivity and specificity values. Sensitivity measures the proportion of positives (poor HRQOL) identified by the presence of the determinant and specificity measures the proportion of negatives (HRQOL as in the general population), identified by the absence of the determinant. A determinant is a perfect predictor when it is 1.00 sensitive and 1.00 specific.

Data analysis revealed that an EDSS total score ≥ 2 (minimal disability in one of the functional systems) was associated with poorer

Table 2
Dichotomization cut-offs and binary logistic regression outputs, in terms of OR, CI and significance level of each single analyzed determinant, with PCS or MCS as dependent variable.

Determinants	PCS				MCS			
	Cut-offs	OR	95% CI	p-Value	Cut-offs	OR	95% CI	p-Value
Individual factors								
Employed	0 = Yes/1 = No	6.187	1.704–22.474	<0.001	0 = Yes/1 = No	0.879	0.233–3.314	0.849
Relationship with parents and/or brothers and sisters	0 = positive/1 = negative	1.750	0.348–8.795	0.497	0 = positive/1 = negative	0.938	0.163–5.359	0.938
Stable relationship with a partner	0 = Yes/1 = No	1.455	0.264–8.027	0.667	0 = Yes/1 = No	0.361	0.079–1.658	0.190
Satisfying sexual activity	0 = Yes/1 = No	0.918	0.218–4.091	0.918	0 = Yes/1 = No	3.000	0.729–12.349	0.128
Sexual problems	1 = Yes/0 = No	0.000	0.000	0.999	1 = Yes/0 = No	2.133	0.500–9.102	0.306
Satisfying working activity	0 = Yes/1 = No	1.821	0.360–9.215	0.468	0 = Yes/1 = No	0.971	0.168–5.612	0.971
Economic difficulty	1 = Yes/0 = No	2.042	0.561–7.432	0.279	1 = Yes/0 = No	2.917	0.716–11.874	0.135
Smoker	1 = Yes/0 = No	4.400	1.232–15.718	0.023	1 = Yes/0 = No	0.565	0.136–2.354	0.433
Drinker of alcoholic beverages	1 = Yes/0 = No	1.167	0.381–3.569	0.787	1 = Yes/0 = No	0.982	0.315–3.062	0.976
Poor sleep	1 = Yes/0 = No	1.121	0.296–4.243	0.867	1 = Yes/0 = No	3.333	0.657–16.921	0.146
Difficulty in falling asleep	1 = Yes/0 = No	2.283	0.088–0.908	0.034	1 = Yes/0 = No	1.964	0.583–6.619	0.276
Night waking	1 = Yes/0 = No	0.443	0.141–1.388	0.162	1 = Yes/0 = No	2.026	0.627–6.545	0.238
Early morning waking	1 = Yes/0 = No	1.000	0.306–3.270	1.000	1 = Yes/0 = No	3.111	0.769–12.594	0.112
Night waking caused by nightmares and unpleasant sensations	1 = Yes/0 = No	4.571	1.331–15.701	0.016	1 = Yes/0 = No	2.411	0.713–8.151	0.157
Use of sleeping pills	1 = Yes/0 = No	0.484	0.092–2.555	0.393	1 = Yes/0 = No	1.010	0.228–4.482	0.989
Physical pain	1 = Yes/0 = No	3.526	1.063–11.699	0.039	1 = Yes/0 = No	4.400	1.261–15.347	0.020
Sporting activity	0 = Yes/1 = No	0.263	0.065–1.064	0.061	0 = Yes/1 = No	1.718	0.521–5.668	0.374
Clinical variables								
FIM [a]	1 ≤ 123; 0 > 123	18.857	4.159–85.505	<0.001	1 ≤ 123; 0 > 123	3.300	0.932–11.682	0.064
EDSS total score [a]	1 ≥ 2; 0 < 2	9.143	2.551–32.765	0.001	1 ≥ 1.5; 0 < 1.5	1.050	0.331–3.331	0.934
EDSS pyramidal[a]	1 ≥ 2; 0 < 2	7.184	2.055–25.117	0.002	1 > 0; 0 = 0	1.071	0.187–6.152	0.938
EDSS cerebellar[a]	1 > 0; 0 = 0	4.571	1.331–15.701	0.016	1 > 0; 0 = 0	2.411	0.713–8.151	0.157
EDSS brainstem [a]	1 > 0; 0 = 0	9.250	1.644–52.056	0.012	1 > 0; 0 = 0	1.500	0.315–7.137	0.610
EDSS sensory [a]	1 > 0; 0 = 0	1.282	0.359–4.576	0.702	1 > 0; 0 = 0	0.130	0.015–1.088	0.060
EDSS bowel & bladder[a]	1 > 0; 0 = 0	6.800	1.822–25.383	0.004	1 > 0; 0 = 0	3.300	0.932–11.682	0.064
EDSS visual[a]	1 > 0; 0 = 0			V.N.I.	1 > 0; 0 = 0			V.N.I
EDSS cerebral [a]	1 > 0; 0 = 0			V.N.I.	1 > 0; 0 = 0			V.N.I
EDSS others [a]	1 > 0; 0 = 0			V.N.I.	1 > 0; 0 = 0			V.N.I
FSS[a]	1 ≥ 5; 0 < 5	11.000	2.967–40.782	<0.001	1 ≥ 5; 0 < 5	8.643	2.388–31.283	0.001
CBA EPQ/R-N [b]	1 ≥ 95; 0 < 95			V.N.I.	1 ≥ 95; 0 < 95			V.N.I.
CBA EOQ/R-P [b]	1 ≥ 95; 0 < 95	2.235	0.132–37.855	0.577	1 ≥ 95; 0 < 95	0.000	0.000	0.999
CBA EPQ/R-E extroversion[b]	1 > 65; 0 ≤ 65	0.950	0.311–2.903	0.928	1 > 65; 0 ≤ 65	0.403	0.124–1.307	0.130
CBA EPQ/R-E introversion[b]	1 ≤ 40; 0 > 40	4.375	1.052–18.190	0.042	1 ≤ 40; 0 > 40	1.744	0.423–7.193	0.442
CBA IP-F [b]	1 ≥ 95; 0 < 95			V.N.I.	1 ≥ 95; 0 < 95			V.N.I.
CBA IP-PH [b]	1 ≥ 95; 0 < 95			V.N.I.	1 ≥ 95; 0 < 95			V.N.I.
CBA IP-1 [b]	1 ≥ 95; 0 < 95	0.000	0.000	1.000	1 ≥ 95; 0 < 95	0.000	0.000	1.000
CBA IP-2 [b]	1 ≥ 95; 0 < 95			V.N.I.	1 ≥ 95; 0 < 95			V.N.I.
CBA IP-3 [b]	1 ≥ 95; 0 < 95	0.000	0.000	1.000	1 ≥ 95; 0 < 95	0.000	0.000	0.999
CBA IP-4 [b]	1 ≥ 95; 0 < 95	0.000	0.000	1.000	1 ≥ 95; 0 < 95	0.000	0.000	1.000
CBA IP-5 [b]	1 ≥ 95; 0 < 95			V.N.I.	1 ≥ 95; 0 < 95			V.N.I.
CBA MOCQ/R [b]	1 ≥ 95; 0 < 95	0.571	0.106–3.073	0.514	1 ≥ 95; 0 < 95	0.571	0.106–3.073	0.514
CBA MOCQ/1 [b]	1 ≥ 95; 0 < 95	2.235	0.132–37.885	0.577	1 ≥ 95; 0 < 95	2.235	0.132–37.885	0.577
CBA MOCQ/2 [b]	1 ≥ 95; 0 < 95	2.235	0.132–37.885	0.577	1 ≥ 95; 0 < 95	2.235	0.132–37.885	0.577
CBA MOCQ/3 [b]	1 ≥ 95; 0 < 95	3.706	0.000	1.000	1 ≥ 95; 0 < 95	4.039E9	0.000	1.000
CBA STAI-X2 [b]	1 ≥ 95; 0 < 95	2.235	0.132–37.885	0.577	1 ≥ 95; 0 < 95	4.308E9	0.000	0.999
CBA QPF/R [b]	1 ≥ 95; 0 < 95			V.N.I.	1 ≥ 95; 0 < 95			V.N.I.
CBA QD [b]	1 ≥ 95; 0 < 95	7.600	0.732–78.967	0.089	1 ≥ 95; 0 < 95	8.357	0.802–87.114	0.076

Abbreviations: OR = odds ratio; 95%CI = 95% confidence interval; V.N.I. variable not included in the equation; PCS = physical component summary; MCS = mental component summary; FIM = Functional Independence Measure; EDSS = Expanded Disability Status Scale; FSS = Fatigue Severity Scale; CBA Cognitive Behavioral Assessment; EPQ/R-N = neuroticism; EOQ/R-P = psychoticism, EPQ/R-E = extroversion/introversion; IP-F = number of fears; IP-PH = fear intensity; IP-1 = fear of death; IP-2 = fear of social refusal; IP-3 = fear of repulsive animals; IP-4 = fear of separation; IP-5 = fear of blood/medical procedures; MOCQ/R = Obsessive–Compulsive Questionnaire, total score; MOCQ/1 = repetitive and redundant controls; MOCQ/2 = hygiene, cleanliness, unlikely disease spread and contamination; MOCQ/3 = recurrent doubts and unpleasant, intrusive, nagging thoughts; STAI-X2 = anxiety state and trait; QPF/R = psycho-physiological reactions and disturbances; QD = dysphoria and depressive manifestations of subclinical significance.

[a] Cut-offs points are based on analysis of receiver-operating characteristic curves.

[b] Cut-offs points are based on clinical relevance by percentile score.

perceived physical health. The EDSS showed good specificity but less good sensitivity. These results may confirm the divergence in the literature regarding the correlation between SF-36 and EDSS, as well as the unclear relationship between disability level and HRQOL [3,16]. On the other hand, sensitivity increased sharply and specificity remained roughly the same as for EDSS total score alone, when predictive values were calculated for the dichotomized factor "EDSS-pyramidal functional system ≥2", suggesting that dysfunction of the pyramidal system is the critical neurological factor contributing to perception of poor physical health.

The FIM showed good sensitivity and specificity when associated with the level of reported physical health. The cut-off of 123, only three points lower than the maximum score, suggests that MS patients are highly sensitive to the slightest loss of independence.

When fatigue was self-evaluated with the FSS, the cut-off point that best predicted poor HRQOL was a mean score of five. The score

Table 3
Predictive values of final significant determinants ($p < 0.05$) in each logistic regression analysis for poor HRQOL in PCS and MCS of ambulatory MS patients.

HRQOL components	Determinants	True negatives, N	False negatives, N	False positives, N	True positives, N	OR (95% CI)	Accuracy	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
PCS	Individual factors										
	Employed (yes/no)[c]	33	6	8	9	6.187 (1.704–22.474)	0.75	0.60 (0.36–0.80)	0.80 (0.72–0.88)	0.53 (0.32–0.70)	0.85 (0.75–0.92)
	Smoker (yes/no)	33	6	10	8	4.400 (1.232–15.718)	0.72	0.57 (0.32–0.79)	0.77 (0.69–0.84)	0.44 (0.25–0.61)	0.85 (0.76–0.92)
	Difficulty falling asleep (yes/no)	39	0	18	0	0.283 (0.088–0.908)	0.68	–	0.68 (0.68–0.68)	–	1.00 (1.00–1.00)
	Night waking caused by nightmares and unpleasant sensations (yes/no)	32	7	9	9	4.571 (1.331–15.701)	0.72	0.56 (0.33–0.76)	0.78 (0.69–0.86)	0.50 (0.30–0.68)	0.82 (0.73–0.90)
	Physical pain (yes/no)[c]	38	0	17	0	3.526 (1.063–11.699)	0.69	–	0.69 (0.69–0.69)	0.00 (0.00–0.00)	1.00 (1.00–1.00)
	Clinical variables										
	FIM $\leq$123[a]	36	3	7	11	18.857 (4.159–85.505)	0.82	0.79 (0.53–0.93)	0.84 (0.75–0.89)	0.61 (0.41–0.73)	0.92 (0.83–0.98)
	EDSS total score $\geq$2[a]	32	7	6	12	9.143 (2.551–32,765)	0.77	0.63 (0.43–0.78)	0.84 (0.74–0.91)	0.68 (0.45–0.82)	0.82 (0.72–0.89)
	EDSS-pyramidal $\geq$2[a]	37	2	9	9	4.639 (1.162–18.523)	0.81	0.82 (0.51–0.97)	0.80 (0.73–0.84)	0.50 (0.31–0.59)	0.95 (0.86–0.99)
	FSS $\geq$5 [a]	33	6	6	12	11.000 (2.937–40–782)	0.79	0.68 (0.46–0.82)	0.85 (0.75–0.92)	0.68 (0.46–0.82)	0.85 (0.75–0.92)
	CBA EPQ/R-E introversion[b]	34	5	10	8	4.475 (1.034–19.375)	0.74	0.61 (0.35–0.83)	0.77 (0.69–0.84)	0.44 (0.25–0.60)	0.87 (0.78–0.94)
MCS	Individual factors										
	Physical pain (yes/no)[c]	39	0	16	0	4.400 (1.261–15.347)	0.71	–	0.71 (0.71–0.71)	0.00 (0.00–0–00)	1.00 (1.00–1.00)
	Clinical variables										
	FSS $\geq$5[a]	33	7	6	11	8.643 (2.388–31.283)	0.77	0.61 (0.40–0.77)	0.85 (0.75–0.92)	0.65 (0.43–0.82)	0.82 (0.73–0.90)
	EDSS-bowel & bladder >0[a]	36	4	11	6	4.322 (1.058–17.650)	0.74	0.60 (0.29–0.85)	0.77 (0.70–0.82)	0.35 (0.17–0.50)	0.90 (0.82–0.96)
	CBA QD[b]	39	1	14	3	13.482 (1.125–161.533)	0.74	0.75 (0.23–0.99)	0.74 (0.69–0.75)	0.17 (0.05–0.23)	0.97 (0.92–1.00)

Abbreviations: HRQOL, health related quality of life; OR, odds ratio; CI, confidence interval; PPV, positive predictive value; NPV negative predictive value; PCS = physical component summary; MCS = mental component summary; FIM = Functional Independence Measure; EDSS = Expanded Disability Status Scale; FSS = Fatigue Severity Scale; CBA Cognitive Behavioral Assessment; EPQ/R-E = extroversion/introversion; QD = dysphoria and depressive manifestations of subclinical significance.

[a] Cut-off points are based on analysis of receiver-operating characteristic curves.

[b] Cut-off points are based on clinical relevance by percentile score.

[c] Missing values.

was the same when calculated for SF-36 PCS and SF-36 MCS. Previous findings indicated that an FSS mean score ≥5 may be interpreted as "severe fatigue" [37,38], suggesting that fatigue must be severe to significantly lower perceived HRQOL, both in the mental and physical dimensions. However, specificity was somewhat higher than sensitivity.

On the basis of the large spectrum of emotional and other adjustments, as well as mental disorders evaluated with the CBA, our results confirm that "dysphoric and depressive manifestations" were the main significant determinants associated with low self-reported mental health [10], showing acceptable sensitivity and specificity values.

As in this study, bowel/bladder dysfunctions proved to be associated with low HRQOL [19]. However, although deficits are the consequence of motor control disorders, this factor was significant for poor perceived mental health, emphasizing the relevance of incontinence for subjective psychological status and showing high specificity.

The significant factors already mentioned and their severity may be regarded as determinants closely associated with the spectrum of MS symptoms and as possible causes of poor HRQOL. Our results show that perceived health status assessed in ambulatory MS patients may not only be depressed by disease-related impairment, but also by other individual factors that may enhance or reflect the psychological profile and disturbances of patients who report poor QOL.

A quite similar number of false positives and false negatives, indicating good discriminating properties of variables, as well as accuracy values produced by the regression analysis, suggest that the three individual factors that most strongly lower QOL were unemployment, smoking, and night waking. More specifically, with respect to PCS and MCS as outcome, an introverted personality increased the risk of perceiving physical health as poor, as did unemployment, smoking, difficulty falling asleep and night waking, while physical pain was significant for poor perceived mental and physical health. In this study, pain, sleep problems and employment were significant individual determinants, as previous reports have shown [6,18,20,39]. We underline that this finding is in line with observational studies on the general population regarding the relationship between introversion, smoking and QOL. Smokers show a lower QOL than non-smokers, and there is evidence that they consume more antidepressant drugs and tranquilizers, drink more alcohol and get less physical exercise [40]. At the same time, introverts lack close social relationships and report less well-being than extraverts [41]. However, the meaning of the specificity values suggests that patients who do not report these individual factors seldom perceive a major decline in health. On the other hand, when the HRQOL is lower, one of the above variables may be the cause or the cause of amplification.

Since each significant individual factor may lower or reveal the patient's risk profile for poor HRQOL, it may be worthwhile investigating their presence or absence in routine assessments. Related outcome may be important for individual care. Indeed, when one of these factors is reported by a patient, or QOL assessment is poor, better multidisciplinary intervention is needed, for example promoting health education for smokers, increasing social support for the unemployed, promoting social participation for introverts and taking better care of symptoms such as sleep disorders and physical pain, in order to prevent or manage poor perceived health status. Psycho-cognitive assessment and/or support may also be necessary.

The PPV and NPV are measures which assess the performance of a predictive model and their outputs depend on the prevalence of the outcome of interest. Our results confirm that despite deficits and symptoms, MS patients continue to report mainly good QOL [16].

The present study has some limitations. Firstly, the sample was quite small and the accuracy and predictive values require cross-validation with an independent sample of MS patients selected with the same inclusion criteria. Secondly, contextual factors of patients (indoors and outdoors), which could influence HRQOL, were not investigated.

5. Conclusions

In ambulatory MS patients, unemployment, smoking, and night waking caused by nightmares and unpleasant sensations can be interpreted as the major individual factors affecting the robustness of disease variables in lowering HRQOL. Pain, introversion and difficulty falling asleep are other significant determinants which may help physicians identify risk profile and optimize individual care. An EDSS total score of ≥2 (minimal disability in one functional system), EDSS-pyramidal score ≥2 (minimal related pyramidal system disability), FIM ≤123, FSS ≥5 (severe fatigue), depressive manifestations and bowel/bladder dysfunctions are common significant disease variables. However, the weight of each significant determinant depends on sensitivity and specificity values.

Conflict of interest

The authors declared no potential conflicts of interests.

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