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Can fatigue predict the worsening of multiple sclerosis one year later? An explorative study with participants referred to assess their ability to work

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ABSTRACT

Background: Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system and is triggered by several environmental factors in genetically predisposed people.
Objectives: To explore which evaluation battery items used for evaluation of work capacity at baseline can best predict MS progression at 1 year follow-up.
Methods: In this prospective single-centre study, participants with MS were recruited consecutively when visiting a neurologist for referral for the determination work capacity status at the Disability and Working Capacity Assessment Office. At baseline, a neurologist assessed patients using the following evaluation scales: Fatigue self-assessment, Fatigue Descriptive Scale (FDS), Memory self-assessment, Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), Short Form 36 (SF-36), and the Brief International Classification of Functioning and Disability (ICF) core set for MS. The Expanded Disability Status Scale (EDSS) was evaluated by neurologists at baseline and one year later. An increase in EDSS by 0.5 points after one year was defined as MS progression.
Results: During the one year period among 72 participants, 21 fulfilled the criteria for MS progression. In more than 75% of these participants, impairments were found in the following ICF subitems at baseline: "energy and drive functions", "muscle and power functions", and "moving around". Greater impairments were identified in progressing participants. Progressing participants scored higher on the FDS and scored lower on the BICAMS and SF-36. Regression analysis indicated that the FDS sum score predicted MS progression one year later.
Conclusions: Increased fatigue might indicate worsening in MS one year later.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating and neurodegenerative disorder of the central nervous system (Compston and Coles, 2002) that is triggered by several environmental factors (Alfredsson and Olsson, 2019; Olsson et al., 2017) in genetically predisposed patients (International Multiple Sclerosis Genetics C 2019). The risk for MS is associated with the following environmental exposures: smoking, childhood obesity, infectious mononucleosis, solvent exposure, vitamin D deficiency, and increasing latitude (Alfredsson and Olsson, 2019; Olsson et al., 2017). The incidence of MS in the Lithuanian population was on average 6.5 (95% CI 5.70–7.30) cases per 100,000 residents, and 4.9 (95% CI 4.46–5.34) and 8.1 (5.86–9.34) cases per 100,000 males and females, respectively, during the period 2001–2015 (Valadkeviciene et al., 2019). The incidence rate of MS in Lithuania is predicted to increase to 13 cases per 100,000 persons and females are expected to be diagnosed with MS two times more often than males in the coming years (Valadkeviciene et al., 2019).

Clinically, there are four MS phenotypes, namely clinically isolated syndromes, relapsing-remitting MS, progressive-relapsing MS, primary progressive MS, and secondary progressive MS (Lublin et al., 2014). The definition of MS progression is recommended by the European

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Medicines Agency (European Medicines Agency 2015), and is based on increased scores on the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) over time (Kalincik et al., 2015).

In a systematic review by Nelson et al., data synthesis of 27 studies indicated that urinary bladder symptoms at onset (hazard ratio, 1.1–3.1), incomplete recovery from the first attack (hazard ratio, 1.3–3.3), and a short interval between the first and second attack (hazard ratio, 1.6–1.9) were consistently and strongly associated with poor prognosis (Langer-Gould et al., 2006). Cognitive symptoms and changes in information processing speed predicted EDSS scores 5 and 7 years later (Deloire et al., 2010). Fatigue in early MS phases was associated with disability progression over 3 years (Debouverie et al., 2008).

Body fluid biomarkers might be also used as prognostic factors. In a registry-based study of 7322 MS patients, the presence of oligoclonal bands in the cerebrospinal fluid was associated with higher risk of reaching EDSS scores of 3 or 4 and converting to secondary progressive MS (Karrenbauer et al., 2021). In the cerebrospinal fluid, pathologically increased levels of the axonal damage biomarker neurofilament light chain were found to be associated with worse outcomes and with conversion to secondary progressive MS in a cohort of 99 relapsing/remitting MS patients (Salzer et al., 2010). Thus, there are few robust clinical, radiological, or biological markers for predicting the progress of MS from a multidimensional point of view.

Although the clinical course of MS might be different, one of the ways to analyse the disease is to assess functioning, activity, and disability according to the International Classification of Functioning, Disability and Health (ICF). The ICF was officially endorsed by all 191 WHO Member States at the 54th World Health Assembly on 22 May 2001 (resolution WHO 54.21) (WHO. World Health Organization). ICF is the WHO's framework for categorising health and disability at both the individual and population levels and is recommended to be used in clinical practice and research. The ICF core sets have been developed for several chronic health conditions, including MS (Coenen et al., 2011). Nevertheless, there is a lack of studies on biopsychosocial aspects of MS when combining functional, environmental and clinical parameters. This study for the first time presents a practical use of ICF categories in assessing functioning, activity and participation as well as environmental factors as part of biopsychosocial aspects of MS, including the progression.

Therefore, the aim of the present study was to use the multidimensional assessment of MS (including objective, clinical, and self-assessments) as well as ICF impairments in order to identify predictors for MS progression after one year. The hypothesis was that a multidimensional assessment of MS will identify predictors for MS progression.

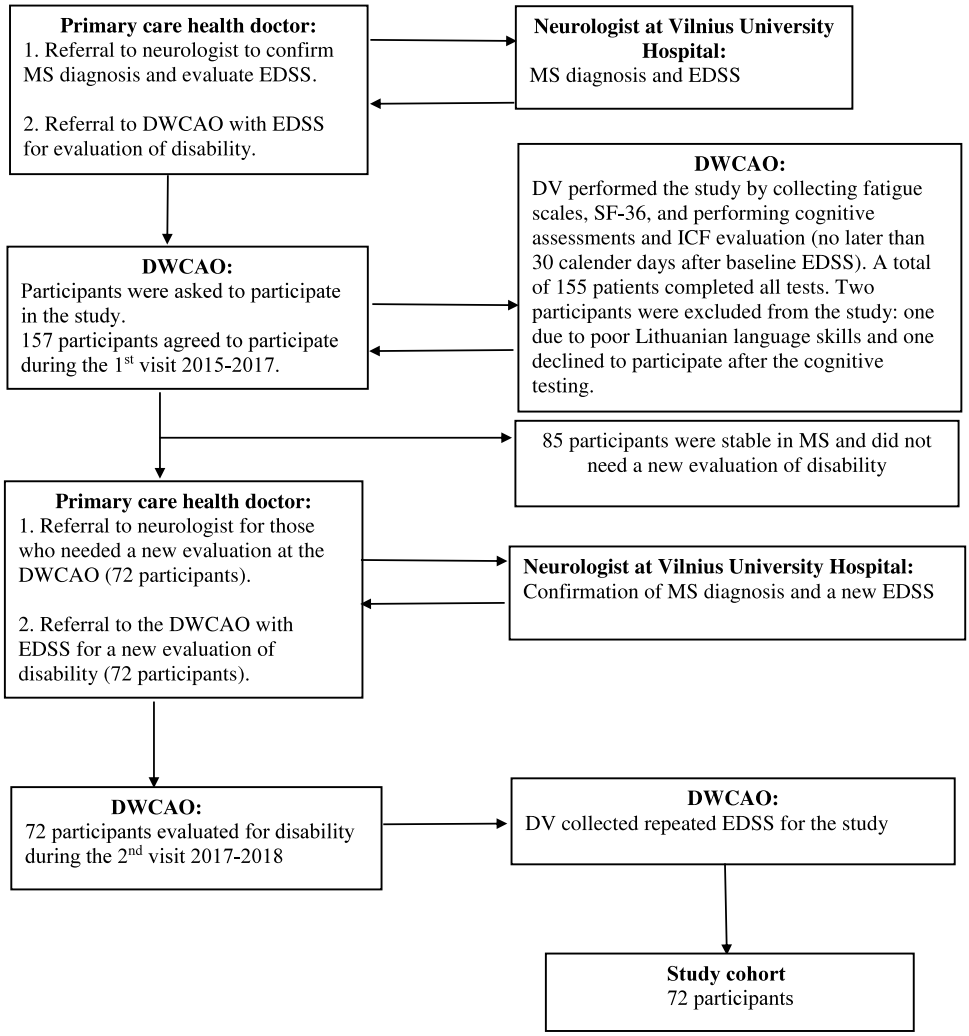

Fig. 1. Flow-chart diagram of the study cohort selection process.
Abbreviations: EDSS – Expanded Disability Status Scale; MS – Multiple sclerosis; DWCAO – Disability and Working Capacity Assessment Office under the Ministry of Social Security and Labour of the Republic of Lithuania.

2. Material and methods

2.1. Participants

This prospective MS cohort study was conducted at the Clinic of Neurology and Neurosurgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, and at the Disability and Working Capacity Assessment Office (DWCAO) under the Ministry of Social Security and Labour of the Republic of Lithuania. Patients were recruited consecutively as they visited the DWCAO for employment status evaluation during 2017–2018, and the study flow chart is presented in Fig. 1. The MS diagnosis for all patients was confirmed by a third-level neurology health care service using the McDonald criteria (2010 revision) (Polman et al., 2011). Patients were assessed using the EDSS by the treating neurologist during the yearly visit to the Department of Neurology, Santaros Klinikos, Vilnius, Lithuania, prior the referral for evaluation of work capacity status. The EDSS score was recorded in the documentation used for determining work capacity. EDSS data were collected twice – at baseline and at one year follow-up, provided that patients were 3-months relapse free. The EDSS is a clinician-administered assessment scale evaluating the functional systems of the central nervous system. The EDSS is used to describe disease progression in patients with MS and to assess the effectiveness of therapeutic interventions in clinical trials and is recommended by the EMA (European Medicines Agency 2015) but captures fatigue and cognitive impairment poorly (Kurtzke, 1983). All patients were studied during periods of MS remission.

The following inclusion/exclusion criteria were applied: 1) age over 18 years; 2) MS diagnosis confirmed using the McDonald criteria revised in 2010 (Polman et al., 2011); 3) MS at remission stage and stable neurological condition; 4) no other diseases related to the central or peripheral nervous systems, metabolic diseases, or other significant diseases that could affect the person's working capacity; 5) fluent in Lithuanian; 6) voluntary consent to take part in the study and the signing of an informed consent form including an agreement regarding personal data usage; 7) a duration of MS not longer than 5 years, and 8) the ability to visit the DWCAO twice during the study. Two participants were excluded after recruitment (Fig. 1).

Disease-modifying treatments were divided into high-efficacy (alemtuzumab and natalizumab) and moderate-efficacy (dimethyl fumarate, fingolimod, glatiramer acetate, INF-β preparations, and teriflunomide) according to the Association of British Neurologist's revised guidelines for prescribing disease-modifying treatments in MS (Scolding et al., 2015). The anti-CD-20 therapies ocrelizumab and rituximab are high-efficacy treatments according to network meta-analysis of annualized relapse rate (Samjoo et al., 2021).

2.2. Methods

The following battery of self-assessment scales and objective evaluations was used at baseline: The Fatigue self-assessment scale, the Fatigue Descriptive Scale (FDS) (Iriarte et al., 1999); Memory self-assessment; the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Giedraitiene et al., 2015); the Short Form 36 Medical Outcomes Study Questionnaire (SF-36) (Bunevicius, 2017; Rugiene et al., 2005; Staševičienė et al., 2020), and the Brief ICF Core Set for Multiple Sclerosis (Coenen et al., 2011). Characteristics of the assessment scales and the ICF evaluation are presented in Supplement 1 and 2, respectively.

The study was approved by the Lithuanian Bioethics Committee (No.158200–14–753–271) on December 9, 2014. The State Data Protection Inspectorate approved the Vilnius University's Plan for Legal Protection of Personal Data while conducting this study (04–20–2015, No.2R-2270(2.6–1)). Each participant signed an informed consent and an agreement regarding participation in the study and personal data usage.

2.3. Statistical analysis

Statistical analysis was performed using the statistical software package SPSS 17.0 (version for MS Windows). Descriptive statistics for the quantitative variables are presented using the mean and standard deviation and for discrete variables using the absolute value and the percentage of the analysed sample group. The normality of the variables was assessed using a Kolmogorov–Smirnov test. Student's *t*-test was used to compare the means of two independent groups of quantitative variables, and paired-samples t-tests were used to analyse the difference between the first and second measurements. To compare discrete variables, a Chi-square ($\chi 2$) independence criterion was used, and, due to the small sample size, Fisher's exact test was performed. The Mann–Whitney *U test* was used to compare the differences in the Brief ICF core set between groups. The effect size of the EDSS level between groups was measured by Cohen's d. A logistic regression analysis was used to identify variables related to MS progression after one year. A variable was included in the model if $p < .05$ between the groups, and it was excluded from the model if $p > .1$. An ROC analysis was conducted to obtain the critical values for predicting MS progression.

3. Results

3.1. Study cohort

Seventy-two participants referred to the DWCAO fulfilled the inclusion criteria. Details of the sociodemographic and clinical variables are presented in Table 1.

3.2. Definition of MS progression

An increase in the EDSS by at least 0.5 points over one year was defined as Progressing MS. Twenty-one participants (29.2%) fulfilled the definition for MS progression (effect size comparing two groups (Cohen's d) was 0.094 compared with the initial Cohen's d of 0.025)). The remaining 51 individuals were stable or improved according to the EDSS at one year follow-up and are referred to as the Stable MS group. No differences were found in sociodemographic or medical (MS type and medication) characteristics between the groups (Table 1).

3.3. Self-assessment scales and assessment of cognitive functions

Both the physical health and mental health of the MS participants were assessed as low according to the mean values of the SF-36 (Table 2). The comparison of SF-36 values between the two groups showed that Physical functioning ($p = .006$), Physical component summary ($p = .016$), and Mental component summary ($p = .039$) were scored lower in the Progressing MS compared to the Stable MS group (Table 2).

The analysis of cognitive functions with the BICAM showed that only the Brief Visuospatial Memory Test-Revised (BVMT-R) was statistically lower for Progressing MS (14.8, SD 4.6), as compared to Stable MS (19.0, SD 7.2, $p = .016$) (Table 2). The results on the California Verbal Learning Test, 2nd edition, and the Symbol Digit Modalities Test were similar between the groups (Table 2). Both groups self-assessed their memory in a similar way (Table 2).

Comparison of fatigue parameters revealed significant differences between the groups using both the self-assessment and the FDS scale (Table 2). The Progressing MS group had increased fatigue according to the self-assessment scale ($p = .007$) and the FDS, particularly for frequency ($p = 0.032$), severity ($p = .002$), initiative ($p = .009$), and in relation to the Uhthoff effect ($p = .005$) compared to the Stable MS group (Table 2).

Table 1
Clinical and sociodemographic characteristics of the enroled participants with MS at the start of the study and with Final EDSS level. Statistics between Progressing and Stable MS groups was performed by using Student's *t*-test and Chi Square exact tests.

Variables		Full sample *N* = 72	Progressing MS *N* = 21	Stable MS *N* = 51	p
Age, years		40.0 ± 11.9	43.5 ± 9.6	38.6 ± 12.45	.110
Time from symptoms, years		5.3 ± 5.2	5.3 ± 4.0	5.3 ± 5.6	.947
Time from diagnosis, years		3.4 ± 5.1	3.7 ± 4.0	3.3 ± 5.6	.733
Baseline EDSS score		3.3 ± 1.2	3.6 ± 1.1	3.3 ± 1.2	.321
Follow-up EDSS score		3.5 ± 1.2	4.1 ± 1.0	3.1 ± 1.2	<0.001
Sex	Male	24 (33.3%)	5 (23.8%)	19 (37.3%)	.206
Education	Basic	1 (1.4%)	0 (0.0%)	1 (2.0%)	.975
	Secondary	18 (25.0%)	5 (23.8%)	13 (25.5%)	
	Vocational	13 (18.1%)	4 (19.0%)	9 (17.6%)	
	College	14 (19.4%)	4 (19.0%)	10 (19.6%)	
	Higher	26 (36.1%)	8 (38.1%)	18 (35.3%)	
Profession	(has)	58 (81.0%)	17 (81.0%)	41 (80.4%)	.617
Employment	(yes)	54 (76.1%)	14 (66.7%)	40 (78.4%)	.184
Type of disease	SPMS	4 (5.6%)	2 (9.5%)	2 (3.9%)	.284
	PPMS	1 (1.4%)	0 (0.0%)	1 (2.0%)	
	PRMS	1 (1.4%)	1 (4.8%)	0 (0.0%)	
	RRMS	66 (91.7%)	18 (85.7%)	48 (94.1%)	
DMT	Moderate efficacy	53 (73.6%)	14 (66.7%)	39 (76.5%)	.433
	High efficacy	8 (11.1%)	2 (9.5%)	6 (11.8%)	
	Untreated	11 (15.3%)	5 (23.8%)	6 (11.8%)	

Abbreviations: DMT – Disease-modifying treatments, EDSS – Expanded Disability Status Scale, MS – Multiple sclerosis, N – number of individuals, PPMS – primary-progressive multiple sclerosis, PRMS – progressive-relapsing multiple sclerosis, RRMS – relapsing-remitting multiple sclerosis, SPMS – secondary-progressive multiple sclerosis.

3.4. The brief ICF core set for MS

Figs. 2–5 show the results of the Brief ICF core set for MS. Among eight body functions, only two of them – b130 (Energy and drive functions) and b730 (Muscle and power functions) – were impaired in more than 75% of all MS participants, mostly to a moderate degree (Fig. 2). Three of eight body functions – b130 (Energy and drive functions), b152 (Emotional functions), and b164 (Higher-level cognitive functions) – were significantly more impaired in the Progressing MS group compared to the Stable MS group (Fig. 2). Among these impairments, b130 (Energy and drive functions) and b152 (Emotional functions) were impaired in more than 75% of the Progressing MS group, while b164 (Higher-level cognitive functions) were impaired in 35% of the Progressing MS group (Fig. 2). Among body structures domains, s110 (Brain structures) were impaired in all participants and s120 (Spinal cord and related structures) were impaired in 59% of participants, but there was no difference between the two groups (Fig. 3). Among six activities and participation domains, only d455 (Moving around) was impaired in more than 75% of participants. Significantly higher impairments were found in the Progressing MS group for d450 (Walking), d455 (Moving around), d760 (Family relationships), and d850 (Remunerative employment) (Fig. 4). Impairments in at least 75% of the participants in the Progressing MS group were found for d450 (Walking) and d455 (Moving around).

Environmental factors, especially e310 (Immediate family) and e355 (Health professionals), were facilitators for functioning and activity in 50% and 40% of the MS patients, respectively (Fig. 5). No significant difference was found in environmental factors between the MS groups.

Table 2
Results of the assessment scales of Progressing MS and Stable MS. Differences between the groups was performed using Student's *t*-test.

Scales	Full sample *N* = 72	Progressing MS *N* = 21	Stable MS *N* = 51	p
SF-36 PF	47.4 ± 27.5	33.6 ± 21.2	53.0 ± 28.0	**.006**
SF-36 RF	26.7 ± 36.2	16.7 ± 33.9	30.9 ± 36.6	.122
SF-36 BP	51.9 ± 26.9	42.9 ± 25.2	55.6 ± 26.9	.064
SF-36 GH	31.2 ± 17.7	29.3 ± 13.9	32.0 ± 19.1	.511
SF-36 PCS	39.3 ± 21.7	30.6 ± 17.4	42.8 ± 22.4	**.016**
SF-36 VT	42.2 ± 19.4	36.0 ± 22.2	44.7 ± 17.8	.118
SF-36 SF	44.3 ± 21.9	35.5 ± 25.2	47.9 ± 19.4	.051
SF-36 RE	39.4 ± 42.7	25.4 ± 43.3	45.1 ± 41.5	.084
SF-36 MH	53.9 ± 20.5	49.0 ± 18.3	56.0 ± 21.2	.163
SF-36 MCS	44.9 ± 21.3	36.4 ± 22.0	48.4 ± 20.2	**.039**
Memory, self-assessed	6.6 ± 2.1	5.9 ± 2.5	6.9 ± 1.9	.103
SDMT	42.9 ± 13.9	38.3 ± 15.2	44.8 ± 13.0	.097
CVLT-II 1 attempt	6.2 ± 2.2	6.1 ± 2.1	6.3 ± 2.2	.688
CVLT-II 2 attempt	9.0 ± 2.5	9.0 ± 2.5	9.0 ± 2.5	.976
CVLT-II 3 attempt	10.2 ± 2.7	10.1 ± 2.3	10.3 ± 2.8	.699
CVLT-II 4 attempt	10.4 ± 2.7	9.8 ± 2.3	10.7 ± 2.8	.196
CVLT-II 5 attempt	11.0 ± 2.8	10.5 ± 2.4	11.2 ± 3.0	.313
CVLT-II sum	46.8 ± 11.2	45.4 ± 10.2	47.4 ± 11.6	.482
BVMT-R 1 set	4.0 ± 2.3	3.1 ± 1.8	4.4 ± 2.4	**.017**
BVMT-R 2 set	6.5 ± 2.4	5.6 ± 1.7	6.8 ± 2.6	**.044**
BVMT-R 3 set	7.3 ± 2.8	6.1 ± 2.1	7.8 ± 3.0	**.019**
BVMT-R sum	17.8 ± 6.8	14.8 ± 4.6	19.0 ± 7.2	**.016**
Fatigue, self-assessed	5.3 ± 2.2	6.3 ± 1.9	4.9 ± 2.2	**.007**
FDS-Initiative	1.6 ± 0.6	1.9 ± 0.4	1.5 ± 0.6	**.009**
FDS-Modality	0.9 ± 0.8	1.0 ± 0.8	.9 ± 0.9	.638
FDS-Frequency	1.6 ± 0.8	1.9 ± 0.7	1.5 ± 0.8	**.032**
FDS-Severity	1.6 ± 1.0	2.2 ± 0.8	1.4 ± 1.0	**.002**
FDS-Uhthoff's effect	0.8 ± 0.4	1.0 ± 0.0	.7 ± 0.5	**.005**
FDS sum	7.8 ± 4.4	10.3 ± 3.2	6.8 ± 4.5	**.001**

Abbreviation: BP – Bodily Pain, BVMT-R – Brief Visuospatial Memory Test-Revised, CVLT-II – California verbal learning test II ed., FDS – Fatigue Descriptive Scale, GH – General Health, MCS – Mental component summary, MH – Mental Health, PCS – Physical component summary, PF – Physical functioning, RE – Role emotional, RF – Role limitations due to physical health, SDMT – Symbol Digit Modalities Test, SF – Social functioning, N – number of individuals, SF-36 – Short Form 36 Medical Outcomes Study Questionnaire, VT – Vitality.

3.5. Variables predicting MS progression

To analyse the factors having the greatest predictive value for worsening of the condition (coded 1) compared to the stability or improvement of the condition (coded 0), a logistic predictive analysis was performed. To avoid multicollinearity, the following regressors were included in the analysis: The Physical functioning, Physical component summary, and Mental component summary of the SF-36, BVMT-R sum, FDS sum, b130 (Energy and drive functions), b152 (Emotional functions), b164 (Higher-level cognitive functions), d450 (Walking), d455 (Moving around), and d850 (Remunerative employment).

The results showed that the FDS sum and ICF domain b164 (Higher-level cognitive functions) predicted MS progression (model fit $\chi 2 = 24.4$, $p < .001$; Hosmer and Lemeshow $\chi 2 = 3.37$, $p = .909$). Using these factors, 81.2% of the data could be classified correctly and Nagelkerke's $R^2 = 0.426$ (Table 3).

Because the FDS sums varied from 0 to 17, an ROC analysis was conducted, showing an area under the curve equal to 0.728 (95% CI 0.614–0.843, $p = .002$) (Fig. 6). With a sensitivity of 0.762 and specificity of 0.627, the cut-off value was 8.5. The dispersion of b164 (Higher-level cognitive functions) was too small, and thus an ROC analysis was not performed.

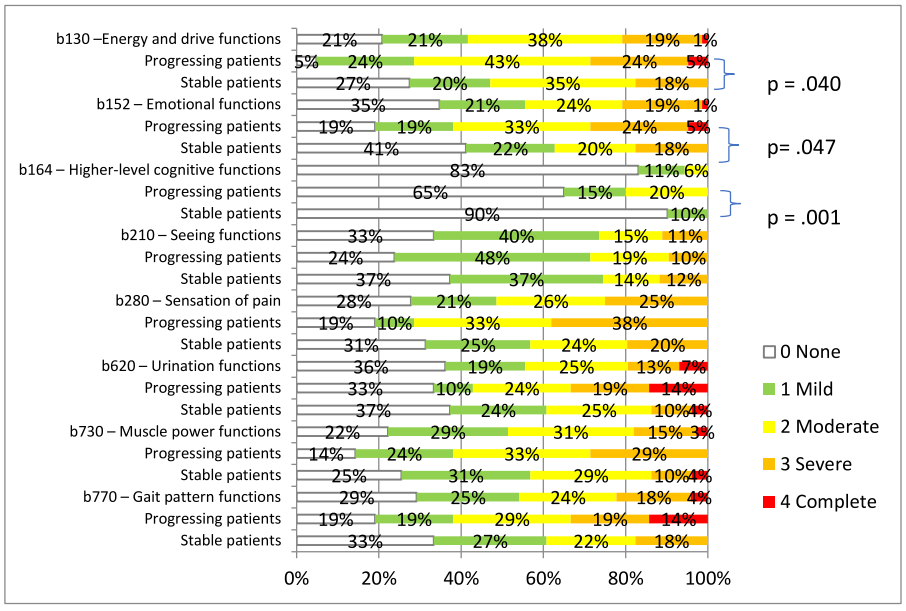

Fig. 2. Impairments in body functions according to Brief ICF core set for MS. Comparisons between Progressing MS and Stable MS were performed with the Mann–Whitney *U test, N* = 72.

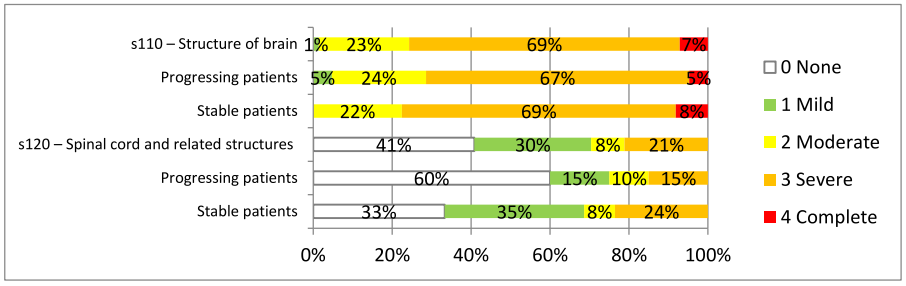

Fig. 3. Impairments in body structures according to Brief ICF core set for MS. Comparisons between Progressing MS and Stable MS were performed with the Mann–Whitney *U test, N* = 72.

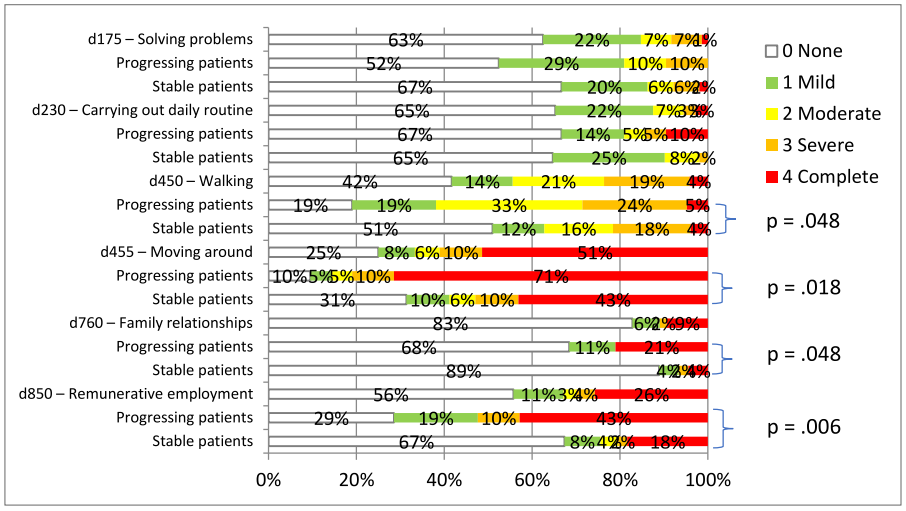

Fig. 4. Impairments in activities and participation according to Brief ICF core set for MS. Comparisons between Progressing MS and Stable MS were performed with the Mann–Whitney *U test, N* = 72, except for d760 (*N* = 19 in Progressing MS and *N* = 46 in Stable MS).

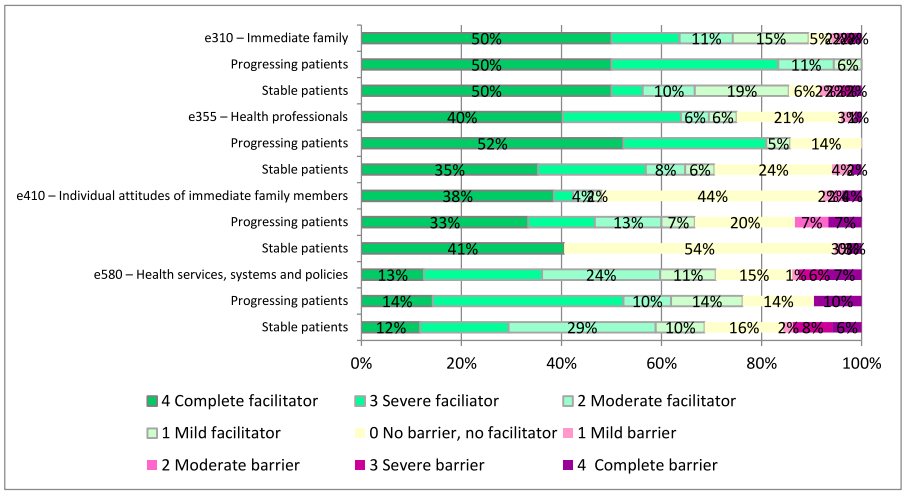

Fig. 5. Environmental factors and barriers/facilitators according to Brief ICF core set for MS. Comparisons between Progressing MS and Stable MS were performed with the Mann–Whitney *U test, N* = 72, except for e310 (*N* = 18 in Progressing MS and *N* = 48 in Stable MS) and e410 (*N* = 15 in Progressing MS and *N* = 37 in Stable MS).

Table 3
Variables predicting MS progression after one year.

Regressors	Regression coefficient (B) (standard error)	Wald statistics	p	Exp (B)
FDS sum	.206 (0.105)	3.881	**.049**	1.229
b164 – Higher-level cognitive functions	1.488 (0.660)	5.089	**.024**	4.428
Physical functioning	–.045 (0.028)	2.529	.112	.956
Physical component summary	.012 (0.010)	1.259	.262	1.012
Mental component summary	–.003 (0.007)	.165	.685	.997
BVMT-R sum	–.047 (0.061)	.596	.440	.954
b152– Emotional functions	.056 (0.385)	.021	.884	1.058
d450– Walking	–.399 (0.419)	.907	.341	.671
d455– Moving around	.214 (0.293)	.534	.465	1.238
d850 – Remunerative employment	.196 (0.214)	.846	.358	1.217
b130– Energy and drive functions	–.220 (0.478)	.212	.645	.802
Constant	–1.605 (2.420)	.440	.507	.201

Abbreviations: BVMT-R – Brief Visuospatial Memory Test-Revised; FDS – Fatigue Descriptive Scale.

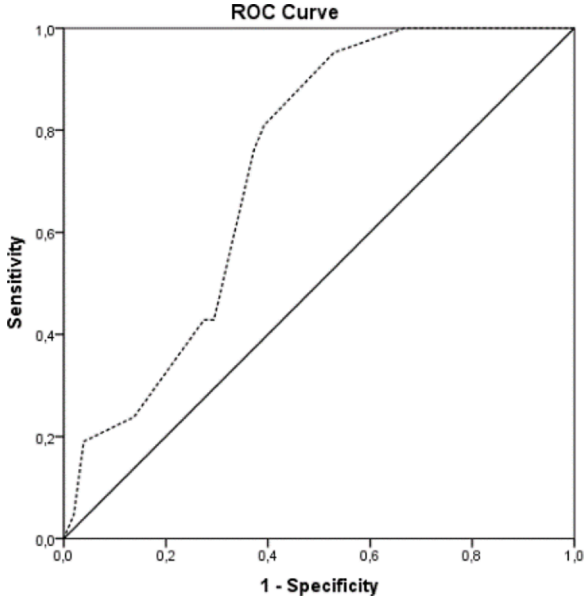

Fig. 6. The ROC curve analysis of FDS sum values in discriminating between progression or stability of MS after one year.

4. Discussion

In this prospective study of 72 MS participants, MS progression was determined using the EDSS at one year follow-up compared to baseline. Twenty-one participants were assessed to have an increase in EDSS by at least 0.5 points after one year. Interestingly, the sociodemographic characteristics, the type of disease, impairments in the central nervous system according to ICF s-domains, and disease-modifying treatments did not differ between the Progressing MS group and the Stable MS group. An increase in the FDS was identified as a predictor for disease progression after one year. The critical value of FDS as a risk for increased EDSS was a score of 8.5 out of a maximum score of 17. The ICF sub-item b164 (Higher-level cognitive functions) was another parameter predicting the increase in the EDSS after one year. However, the impairments in the higher cognitive functions were only light and moderate and were only seen in 35% in the Progressing MS group and thus cannot be used in clinical practice for predicting prognosis, at least in this cohort.

The cohort was also assessed using the SF-36 and BICAMS. In general, the mean values of SF-36 were below 50 in most of the categories, indicating decreased health-related quality of life in the participants. In the Lithuanian population, the SF-36 has been studied in patients with brain tumours (Bunevicius, 2017) and rheumatoid arthritis (Rugiene et al., 2005). However, the SF-36 values for the normal Lithuanian population are not available. The SF-36 values have been also characterised in a Lithuanian MS cohort (Staševičienė et al., 2020), with an overall SF-36 score of 53 in the age group 22–40 years and an overall score of 45 in the age group 41–71 years (Staševičienė et al., 2020). The mean overall value of the eight SF-36 domains in the present study was 40.3, indicating poor health-related quality of life in the study participants. Regarding the cognitive tests, the BICAMS has also been characterised in an MS cohort in Lithuania, showing that MS participants performed significantly lower in BICAMS compared to controls (Giedraitiene et al., 2015). The BICAMS values in the present MS cohort were lower compared to this previous MS cohort, except for the Symbol Digit Modalities Test, which was almost the same (Giedraitiene et al., 2015). Altogether, the results of SF-36 and BICAMS indicate that the present study cohort had lower health-related quality of life and lower cognitive

functions compared to previously reported studies on Lithuanian MS cohorts.

Fatigue is another disabling symptom known in MS (Bakshi, 2003). The FDS (Iriarte et al., 1999) is a fatigue scale assessing several parameters, including Uhthoff's effect, which is a temporary worsening of neurological symptoms in response to increased body temperature (Jain et al., 2020). In the present study, FDS was found to be a predictor for MS progression one year later. The results of this study suggest including fatigue assessments to evaluate the severity of MS. Previous studies, however, did not reveal any correlation between fatigue measurements and cerebral MRI abnormalities or with neurological disability as measured by the EDSS (van der Werf et al., 1998). No associations have been found between fatigue measurements using the Fatigue Severity Scale and disease-modifying drugs (Putzki et al., 2008). Interestingly, patient education, cognitive behavioural therapy and other psychological interventions have been reported to reduce MS-associated fatigue (Wendebourg et al., 2017; Phyo et al., 2018).

Although the ICF system is accepted in MS clinical practice, especially when evaluating symptomatology (Dorstyn et al., 2017), activity and participation (Karhula et al., 2013), rehabilitation (Madden and Bundy, 2019), and goals or outcome measures of physical therapy (Rasova et al., 2020), studies scoring ICF impairments by using ICF core sets (either Brief or Comprehensive) are absent in the literature on MS. To our knowledge, our study is the first to present the impairments according to the Brief ICF core set for MS. Assessments of body functions, activity and participation, and environmental factors were performed using a strict study protocol. The following ICF categories were impaired in more than 75% of all participants: Energy and drive functions (b130), Muscle and power functions (b730), and Moving around (d455). The most significant impairment was found in Moving around (d455) with a "total" impairment in more than 50% of the study participants. This indicates that a majority of participants were not able to climb stairs or walk without absolute support of surrounding persons or other help. Difficulties in walking function in the MS patients are well studied (Soler et al., 2020). However, Walking functions (d450) were impaired in fewer than 58% of the participants, and the impairments were mostly considered "moderate". Therefore, ICF assessments indicate that walking functions should be specified closer in terms of "moving around" than "walking" by oneself.

Limitations. This study included a limited number of participants in the Progressing MS group. A larger study cohort might reveal differences in such parameters as ICF domains for brain and spinal cord structures and drug treatments. We acknowledge the selection bias, and only participants that were referred for assessment of their work capacity at the DWCAO under the Ministry of Social Security and Labour of the Republic of Lithuania were recruited to the study. The lack of mood measures by broadly used self-scored scales, such as HADS (Hospital Anxiety and Depression Scale), is another study limitation in regards to results' transferability.

Strengths: Multiple scales, including ICF evaluations, were applied to cover the multidimensional aspects of MS. The EDSS was evaluated by an independent clinician who treated and managed the participant before the referral.

In summary, the results of the present study indicate the importance of a multidimensional approach in assessing MS and suggest that the FDS might be a predictor of increased EDSS after one year.

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CRediT authorship contribution statement

Daiva Valadkevičienė: Conceptualization, Software, Methodology, Formal analysis, Validation, Investigation, Resources, Data curation, Writing – original draft, Visualization, Project administration. **Irena Žukauskaitė:** Data curation, Methodology, Software, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Virginija Danylaitė Karrenbauer:** Validation, Writing – original draft, Writing – review & editing, Visualization. **Indre Bileviciute-Ljungar:** Validation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data statement

Any request for data by qualified scientific and medical researchers for legitimate research purposes should be submitted in contacting the first author (daiva.valadkeviciene@mf.vu.lt).

Supplementary materials

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