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ORIGINAL ARTICLE

# The impairment of the functional system and fatigue at the onset of the disease predict reaching disability milestones in relapsing–remitting multiple sclerosis differently in female and male patients

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**Abstract**
Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system with variable types of disability progression (DP). Previous studies, defining different disability milestones (DMs), have reported symptoms at MS onset to be the predictors of DP and sex as a risk factor. Meanwhile, accounting for sex differences in MS, predictors in female and male patients might differ. To investigate whether the symptoms at MS onset predict reaching DMs in patients with relapsing–remitting (RR) MS and whether the predictors vary between different DMs and female and male patients. Data from 128 RR MS patients (84 females, 44 males) was retrospectively studied. EDSS scores 4 and 6 (associated with impaired ambulation) were taken as DMs. Association between symptoms at MS onset and time to reach DMs was assessed with Cox multiple regression model. Pyramidal symptoms and fatigue at MS onset predicted the progression to EDSS 4 in the whole study population (HR 1.84, 95% CI 1.07–3.2, $p=0.028$ and HR 2.01, 95% CI 1.12–3.4, $p=0.011$, correspondingly). The same symptoms predicted reaching DM in female, but not male patients. Bowel/bladder symptoms predicted reaching EDSS 6 in the whole study population (HR 4.31, 95% CI 1.47–12.6, $p=0.008$) and female patients only (HR 3.93, 95% CI 1.04–14.8, $p=0.043$). In female patients, fatigue was also the predictor of reaching EDSS 6 (HR 3.54, 95% CI 1.16–10.8, $p=0.026$). Impairment of functional symptoms at MS onset can predict reaching DMs in patients with RR-MS, but the predictors for EDSS 4 and EDSS 6 differ in female and male patients.

**Keywords** Multiple sclerosis · EDSS · Disability · Predictors

## Introduction

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS). Global MS prevalence is estimated to be 50–300 per 100,000 with 2–3 million people affected worldwide [1]. The peak incidence of the disease is in the third decade of life. It is the world-leading cause of disability in young people, among nontraumatic neurological diseases [2, 3]. MS has a variable presentation that depends on the CNS sites affected by demyelination and includes sensory, motor, visual and/or balance disturbances, pelvic organs dysfunctioning, as well as cognitive and emotional impairment.

The core MS phenotypes in terms of disease course are relapsing–remitting and progressive ones. In relapsing–remitting MS (RR-MS), which affects about 90% of MS patients, there are episodes of acute deterioration of neurological status (relapses) followed by either complete or incomplete restoration of neurological function (remissions) [4]. Incomplete recovery leads to the accumulation of disability in RR-MS. In contrast to RR-MS, in progressive phenotypes, there is a progressive decline in neurological function and inescapable accumulation of

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disability. RR-MS patients may at some point transit to a secondary progressive phenotype or reach a certain level of disability within the RR phenotype, but the rate and the extent of this transition are highly variable [1].

Although the exact factors leading to the transition from RR-MS to the progressive phenotype are unknown, there are several hypotheses to explain this phenomenon. One of them is a hypothesis postulated by Compston suggesting a two-stage pathophysiological process for the progression. The first stage is dependent on bouts of acute focal inflammation and corresponds to the relapsing–remitting phenotype. A second stage, an irreversible accumulation of disability, implies diffuse inflammation with subsequent axonal loss and neurodegeneration which is independent of bouts of focal inflammation and corresponds to the secondary-progressive phenotype [5].

Considering the possibility of such irreversible changes, predicting disability in MS, which is a key point for prevention, is one of the cornerstones of MS research. Various clinical, imaging and laboratory features have been extensively studied as possible predictors of disability in patients with MS [6–8]. Baseline clinical patient data is easily obtainable and available in every patient, thus predictors based on such data are the most suitable for the earliest possible prognosis. In particular, impairment of functional systems (FS) at the onset of MS can serve as a prognostic predictor in terms of disability in MS patients. Studies identified efferent systems involvement and multifocal onset as predictors of long-term disability, while the involvement of afferent systems (sensory and visual) at the onset appears to be associated with a better prognosis [9].

There are a few unaddressed questions in terms of identifying clinical predictors of disability in MS. Firstly, various studies use different endpoints and milestones to define disability. For example, a study conducted by Tedeholm et al. used EDSS 6, EDSS 7, and EDSS 10 as endpoints for predicting and found different predictive power of the same potential predictors based on the same cohort [10]. Such inconsistency makes it hard to collect the data and compare predictors in different cohorts across the studies performed all over the world. Secondly, most of the available studies consider sex itself as a predictor of disability [9]. Considering the sex differences in MS epidemiology and clinical course [1], predictors might also differ in male and female patients if analyzed separately, which might reflect sex-dependent features of MS pathogenesis.

Our study aimed to investigate whether the FS impairment at the disease onset can be predictive of reaching different disability milestones in patients with RR-MS and whether the exact predictors vary for different milestones. The secondary aim was to compare the predictors and their predictive value in males and females.

## Methods

### Data

We retrospectively reviewed medical data of 128 patients with RR-MS, who had been receiving care at the tertiary medical center in Odesa, Ukraine, from 2009 to 2018.

Data were extracted from the medical records according to a predefined protocol. The first presentation may have occurred in other centers. In the cases in which patients first presented to a neurologist not at the very onset of neurological symptoms, but after subsequent emergence of neurological symptoms consistent with the MS attacks, the initial FS impairment was reconstructed with the documented history. The records that did not contain such information were excluded from the analysis. Obtained information included patients' sex, age, age of MS onset, smoking, BMI, DMT, years to reaching EDSS 4 and 6 from MS onset, and symptoms at the disease onset. Symptoms at the disease onset were grouped by FS. We also separately included fatigue as an initial MS symptom because, although, not being considered in any of FS, it is a common complaint in MS patients which might result from disruption of cortical motor circuits [11].

### Outcome measures

Expanded Disability Status Scale (EDSS) scores 4 and 6 were chosen as disability milestones as those associated with a significant decrease in ambulation. EDSS is a widely accepted tool for assessment of disability in MS which considers impairment of eight neurological functional systems (FS) and motor function (ambulation) in the MS patients.

EDSS 4 is a point at which the distance patient can make without support is beginning to be considered (specifically, there is a significant disability but a patient is able to walk without aid or rest for 500 m), and EDSS 6 is a point at which at least unilateral assistance is needed to walk 100 m.

### Statistical analysis

Statistical analysis was performed using R (version 3.5.1) libraries and packages. For all applicable methods, the 2-tailed analysis was used and $p < 0.05$ was considered significant.

Continuous variables were assessed for normality (graphical visualization and D'Agostino K2 normality test) and processed with the methods of descriptive statistics, using the mean and standard deviation or median and interquartile range (IQR) as appropriate. Categorical variables were

described using frequencies indicated either in an absolute or relative fashion.

Cox proportional-hazards model with impairment of FS and fatigue at the disease onset as independent variables was used to identify whether consideration of a combination of these clinical parameters affects reaching the defined milestones.

## Results

### Study population

Study population included 84 female (65.6%) and 44 male (34.4%) patients (Table 1). The differences in characteristics of female and male patients were insignificant ($p > 0.05$) except for smoking ($p = 0.029$). The mean age of patients was $37.8 \pm 10.7$ years (females $38.7 \pm 11$ years, males $36 \pm 9.7$ years), the mean age of onset was $29.7 \pm 9.6$ years (females $30.6 \pm 10.2$ years, males $27.1 \pm 8.2$ years). 22 (17.2%) of the patients were smokers [10 females (11.9%), 12 males (27.2%)]. Only 58 patients (45.3%) received DMT at any point of the disease. 45 patients (34.9%) presented to a neurologist more than a year after the onset of symptoms (median delay 2 years, IQR 2–5 years). A median follow-up for the whole study population was 7 (IQR 3.0–11.25) years. FS affected in the patients at MS onset are shown in Table 2.

### Predictors of reaching EDSS 4

Impairment of the pyramidal system (HR 1.84, 95% CI 1.07–3.2, $p = 0.028$) and fatigue (HR 2.01, 95% CI 1.12–3.4, $p = 0.008$) at MS onset were statistically significant predictors of reaching EDSS 4 (Table 3). When analyzed by sex, in female patients, the same predictors were statistically significant (HR 1.97, 95% CI 1.04–3.8, $p = 0.039$ for impairment of pyramidal system, HR 2.26, 95% CI 1.12–4.6, $p = 0.023$ for fatigue) (Table 4), while in males, significant predictors were impairment of visual system (HR 6.24, 95% CI 1.78–21.9, $p = 0.004$) and brainstem system (HR 33.54, 95% CI 2.33–483.7, $p = 0.01$) (Table 5). Of note, when analyzing predictors for both sexes and for females and males separately, impairment of sensory system was the only factor associated with a lesser risk of reaching EDSS 4 although not statistically significant (HR 0.66, 95% CI 0.38–1.1, $p = 0.127$ for both male and female patients analysis, HR 0.65, 95% CI 0.33–1.3, $p = 0.205$ for female patients, HR 0.59, 95% CI 0.16–2.2, $p = 0.434$).

**Table 1** Baseline characteristics of the study population

| | Total ($N = 128$) | Female ($N = 84$) | Male ($N = 44$) |
|---|---|---|---|
| Age | $37.8 \pm 10.7$ | $38.7 \pm 11$ | $36 \pm 9.7$ |
| Onset age | $29.7 \pm 9.6$ | $30.6 \pm 10.2$ | $27.1 \pm 8.2$ |
| Smoking[a] | 22 (17.2%) | 10 (11.9%) | 12 (27.3%) |
| Received DMT[a] | 58 (45.3%) | 40 (47.6%) | 18 (40.9%) |
| BMI | $23 \pm 3.8$ | $22.9 \pm 3.8$ | $23.4 \pm 3.8$ |
| EDSS at onset[b] | 2.5 (1.5–3) | 3.0 (1.5–3.0) | 2.0 (1.0–3.0) |
| Follow-up (years)[b] | 7 (3.0–11.25) | 7 (3.0–10.25) | 8.5 (3.0–12.25) |
| Reached EDSS 4 | 67 (52.3%) | 50 (59.5%) | 17 (38.6%) |
| Reached EDSS 6 | 29 (22.7%) | 21 (25%) | 9 (20.5%) |

[a]Features for which $p < 0.05$

[b]Median (IQR)

**Table 2** FS affected in the patients at MS onset

| | Total ($N = 128$) | Female ($N = 84$) | Male ($N = 44$) |
|---|---|---|---|
| Pyramidal | 56 (43.8%) | 37 (44%) | 19 (43.2%) |
| Cerebellar | 52 (40.6%) | 37 (44%) | 15 (34.1%) |
| Bowel/bladder | 9 (7%) | 6 (7.1%) | 3 (6.8%) |
| Visual | 34 (26.6%) | 21 (25%) | 13 (29.5%) |
| Sensory | 61 (47.7%) | 40 (47.6%) | 21 (47.7%) |
| Brainstem[a] | 21 (16.4%) | 19 (22.6%) | 2 (4.5%) |
| Fatigue | 48 (37.5%) | 33 (39.3%) | 15 (34.1%) |

[a]Features for which $p < 0.05$

**Table 3** Association of impairment of different FS at MS onset with reaching EDSS 4 in both female and male patients

| Impaired FS | HR | CI (95%) | $p$ |
|---|---|---|---|
| Brainstem | | | |
| Not affected ($N = 107$) | – | – | 1 |
| Affected ($N = 21$) | 1.03 | 0.53–2.0 | 0.922 |
| Visual | | | |
| Not affected ($N = 94$) | – | – | 1 |
| Affected ($N = 34$) | 1.68 | 0.86–3.3 | 0.129 |
| Cerebellar | | | |
| Not affected ($N = 76$) | – | – | 1 |
| Affected ($N = 52$) | 1.23 | 0.73–2.1 | 0.441 |
| Pyramidal | | | |
| Not affected ($N = 72$) | – | – | 1 |
| Affected ($N = 56$) | 1.84 | 1.07–3.2 | 0.028* |
| Sensory | | | |
| Not affected ($N = 67$) | – | – | 1 |
| Affected ($N = 61$) | 0.66 | 0.38–1.1 | 0.127 |
| Bowel/bladder | | | |
| Not affected ($N = 119$) | – | – | 1 |
| Affected ($N = 9$) | 1.92 | 0.81–4.5 | 0.14 |
| Fatigue | | | |
| Not affected ($N = 80$) | – | – | 1 |
| Affected ($N = 48$) | 2.01 | 1.18–3.4 | 0.008* |

*Features for which $p < 0.05$

**Table 4** Association of impairment of different FS at MS onset with reaching EDSS 4 in female patients

| Impaired FS | HR | CI (95%) | *p* |
|---|---|---|---|
| Brainstem | | | |
| Not affected (*N* = 65) | – | – | 1 |
| Affected (*N* = 19) | 0.61 | 0.29–1.3 | 0.211 |
| Visual | | | |
| Not affected (*N* = 63) | – | – | 1 |
| Affected (*N* = 21) | 0.93 | 0.39–2.2 | 0.867 |
| Cerebellar | | | |
| Not affected (*N* = 47) | – | – | 1 |
| Affected (*N* = 37) | 0.84 | 0.44–1.6 | 0.599 |
| Pyramidal | | | |
| Not affected (*N* = 47) | – | – | 1 |
| Affected (*N* = 37) | 1.97 | 1.04–3.8 | 0.039* |
| Sensory | | | |
| Not affected (*N* = 44) | – | – | 1 |
| Affected (*N* = 40) | 0.65 | 0.33–1.13 | 0.205 |
| Bowel/bladder | | | |
| Not affected (*N* = 78) | – | – | 1 |
| Affected (*N* = 6) | 2.58 | 0.96–6.9 | 0.06 |
| Fatigue | | | |
| Not affected (*N* = 51) | – | – | 1 |
| Affected (*N* = 33) | 2.26 | 1.12–4.6 | 0.023* |

*Features for which $p < 0.05$

**Table 5** Association of impairment of different FS at MS onset with reaching EDSS 4 in male patients

| Impaired FS | HR | CI (95%) | *p* |
|---|---|---|---|
| Brainstem | | | |
| Not affected (*N* = 42) | – | – | 1 |
| Affected (*N* = 2) | 33.54 | 2.33–482.7 | 0.01* |
| Visual | | | |
| Not affected (*N* = 31) | – | – | 1 |
| Affected (*N* = 13) | 6.24 | 1.78–21.9 | 0.004* |
| Cerebellar | | | |
| Not affected (*N* = 29) | – | – | 1 |
| Affected (*N* = 15) | 1.61 | 0.42–6.1 | 0.483 |
| Pyramidal | | | |
| Not affected (*N* = 25) | – | – | 1 |
| Affected (*N* = 19) | 2.52 | 0.69–9.2 | 0.164 |
| Sensory | | | |
| Not affected (*N* = 23) | – | – | 1 |
| Affected (*N* = 21) | 0.59 | 0.16–2.2 | 0.434 |
| Bowel/bladder | | | |
| Not affected (*N* = 41) | – | – | 1 |
| Affected (*N* = 3) | 0.97 | 0.11–8.7 | 0.979 |
| Fatigue | | | |
| Not affected (*N* = 29) | – | – | 1 |
| Affected (*N* = 15) | 1.94 | 0.61–6.1 | 0.261 |

*Features for which $p < 0.05$

### Predictors of reaching EDSS 6

Impairment of pelvic organ control system was statistically significantly associated with reaching EDSS 6 when analyzing FS impairment in both female and male patients (HR 4.31, 95% CI 1.47–12.6, $p = 0.008$) (Table 6). In females, fatigue at the MS onset predicted reaching EDSS 6 (HR 3.54, 95% CI 1.16–10.8, $p = 0.026$) in addition to impairment of bowel/bladder control system (HR 3.93, 95% CI 1.04–14.8, $p = 0.043$) (Table 7). No statistically significant associations were found for male patients. Impairment of sensory system was the only factor with a trend for association with a lesser risk of reaching EDSS 6 (HR 0.62, 95% CI 0.27–1.4, $p = 0.257$).

## Discussion

In our study, we aimed to investigate whether FS impairment can predict disability in patients with RR-MS, and also whether the predictors have a different predictive value in male and female patients. We used two EDSS scores, 4 and 6, as disability milestones to check whether the predictors differ depending on the chosen milestone.

We found that impairment of efferent systems (pyramidal for EDSS 4 and bowel/bladder for EDSS 6) was associated with a higher risk of reaching EDSS 4 and EDSS 6 when analyzing both female and male patient groups. The same predictors remained significant for female patients when analyzed separately from male patients for both EDSS 4 and 6. In male patients, impairment of brainstem and visual systems was associated with a higher risk of reaching EDSS 4, but for this group of patients, we found no statistically significant predictors of reaching EDSS 6.

Onset with predominantly efferent symptoms has been shown to be a poor prognostic factor for reaching different disease progression and disability milestones as well. For example, in a 50-year natural history study, RR-MS patients with afferent symptoms at the onset moved on to secondary progressive phenotype 10 years later and reached EDSS 7 15 years later than patients with efferent symptoms, although it did not reach statistical significance [10]. This association seems to be independent of the chosen endpoint: e.g., Ramsaransing and colleagues report in their meta-analysis that pyramidal impairment at onset is associated with a lesser chance of benign course (defined as not reaching EDSS 3 after 10 years from disease onset) [12]. Pyramidal and bowel/bladder function occurring during relapses rather than at the onset was also shown to increase the risk of disability

**Table 6** Association of impairment of different FS at MS onset with reaching EDSS 6 in both female and male patients

| Impaired FS | HR | CI (95%) | *p* |
|---|---|---|---|
| Brainstem | | | |
| Not affected (*N* = 107) | – | – | 1 |
| Affected (*N* = 21) | 1.04 | 0.31–3.3 | 0.953 |
| Visual | | | |
| Not affected (*N* = 94) | – | – | 1 |
| Affected (*N* = 34) | 2.08 | 0.79–5.4 | 0.137 |
| Cerebellar | | | |
| Not affected (*N* = 76) | – | – | 1 |
| Affected (*N* = 52) | 1.51 | 0.66–3.4 | 0.331 |
| Pyramidal | | | |
| Not affected (*N* = 72) | – | – | 1 |
| Affected (*N* = 56) | 1.80 | 0.75–4.3 | 0.185 |
| Sensory | | | |
| Not affected (*N* = 67) | – | – | 1 |
| Affected (*N* = 61) | 0.62 | 0.27–1.4 | 0.257 |
| Bowel/bladder | | | |
| Not affected (*N* = 119) | – | – | 1 |
| Affected (*N* = 9) | 4.31 | 1.47–12.6 | 0.008* |
| Fatigue | | | |
| Not affected (*N* = 80) | – | – | 1 |
| Affected (*N* = 48) | 2.26 | 0.98–5.2 | 0.057 |

*Features for which $p < 0.05$

**Table 7** Association of impairment of different FS at MS onset with reaching EDSS 6 in both female and male patients

| Impaired FS | HR | CI (95%) | *p* |
|---|---|---|---|
| Brainstem | | | |
| Not affected (*N* = 65) | – | – | 1 |
| Affected (*N* = 19) | 1.04 | 0.29–3.7 | 0.955 |
| Visual | | | |
| Not affected (*N* = 63) | – | – | 1 |
| Affected (*N* = 21) | 1.45 | 0.34–6.2 | 0.617 |
| Cerebellar | | | |
| Not affected (*N* = 47) | – | – | 1 |
| Affected (*N* = 37) | 1.33 | 0.47–3.8 | 0.592 |
| Pyramidal | | | |
| Not affected (*N* = 47) | – | – | 1 |
| Affected (*N* = 37) | 1.65 | 0.57–4.8 | 0.357 |
| Sensory | | | |
| Not affected (*N* = 44) | – | – | 1 |
| Affected (*N* = 40) | 0.66 | 0.23–1.9 | 0.447 |
| Bowel/bladder | | | |
| Not affected (*N* = 78) | – | – | 1 |
| Affected (*N* = 6) | 3.93 | 1.04–14.8 | 0.043* |
| Fatigue | | | |
| Not affected (*N* = 51) | – | – | 1 |
| Affected (*N* = 33) | 3.54 | 1.16–10.8 | 0.026* |

*Features for which $p < 0.05$

accumulation. A study done by Stewart et al. conducted by analyzing data from more than 20,000 patients found that impairment of pyramidal, bowel/bladder and cerebellar systems during relapses yields a higher disability accumulation compared to involvement of other systems [13].

Such consistency of association of pyramidal lesions and bowel/bladder dysfunction across the studies might be explained by the specifics of EDSS scale which mainly considers ambulation which, in turn, depends on the proper function of pyramidal and cerebellar systems in particular. Although sensory impairment involving the lower extremities can cause sensory ataxia with subsequent worsening of ambulation, it was shown to be a much weaker contributor to gait impairment than pyramidal and cerebellar involvement [14]. Central bowel/bladder dysfunction is a symptom commonly seen in patients with spinal lesions and associated with lower limbs weakness. Thus, pyramidal involvement and bowel/bladder dysfunction at the MS onset which were associated with reaching EDSS 4 and 6 correspondingly and the similar association of these symptoms with different milestones in other studies might reflect the prognostic importance of spinal lesions in the progression of disability in patients with MS. Indeed, spinal cord lesions were shown to be associated both with short-term and long-term disability prognosis in patients with MS [13, 15]. This might raise the doubt regarding the feasibility of using clinical signs for prognostication because radiological assessment seems to provide more objective information regarding the extent of CNS involvement. However, clinicoradiologic paradox of the lack of correlation between the MRI lesions and severity of clinical symptoms should be taken into the account [15]. Ideally, clinical symptoms and the MRI correlates should be studied together for the models developing to predict the course of the disease.

Another consistency that can be traced across the studies is the association of the male sex with both a higher risk of MS progression and a higher risk of a primary progressive course of MS [16]. While female patients are at higher risk of MS development, male patients seem to have a more severe course of the disease and more active progression. Considering such sex differences in MS features, it is reasonable to suggest that the predictors of reaching certain disability milestones might also differ, but we could find none of the studies to reveal this topic during our scientific literature search. In our study, there indeed was the difference in functional systems-related risk factors of reaching EDSS 4 between male and female patients. We could not detect any predictors for male patients for reaching EDSS 6, most likely because the study was underpowered and did not involve enough male patients who reached EDSS 6.

The risk factors for the females to reach EDSS 4 followed the aforementioned trend for pyramidal symptoms to be associated with the worse prognosis. For male patients, the risk factors differed: impairment of the brainstem and visual system was significantly associated with the risk of reaching the milestone. Existing studies in mixed male–female populations, report optic neuritis at the onset of MS to be a sign of benign course of the disease [12, 17]. Our finding of a different prognostic value of this symptom in the male population contributes an understanding of the differences in the course of MS in male and female patients. At the same time, male sex and brainstem involvement were associated with a 4.63 and 13.1-fold increase in the risk of reaching EDSS 6 in the study done by Damasceno and colleagues in univariate, but not multivariate analysis [18]. A clinicoradiological study done by Rojas and colleagues found that male patients had a significantly lower brainstem volume compared to female patients in whom MS started before menopause but not after the menopause [19]. This may suggest the involvement of sex hormones into the distribution and impact of the CNS damage. Different anatomical distribution of the lesions within the same zone (e.g., brainstem) in males and females might explain the observed difference in the risk factors, and this hypothesis warrants further investigation.

Notably, fatigue at the onset of MS was associated with a higher risk of reaching both EDSS 4 and EDSS 6 and remained a significant predictor of acquiring disability in female patients. Fatigue is a frequent complaint in MS patients reported by up to 80% of MS patients during the first year of the disease [20]. There are several hypotheses to explain the mechanisms of fatigue in MS, including the lesion-attributed loss of connectivity between cortical and subcortical structures, the influence of inflammatory mediators released due to the inflammation, and neuroendocrine dysfunction resulting from the lesions in the hypothalamic-pituitary area [21]. Although fatigue is frequently undervalued due to its subjectiveness, it seems to have an important predictive value for various MS-related aspects. For example, the presence of fatigue in patients with clinically isolated syndrome increased the risk of the progression to clinically definite MS by 2.6 [22]. In the patients enrolled in the New York State Multiple Sclerosis Consortium, the presence of fatigue at the enrollment increased the risk of sustained EDSS worsening [23]. Fatigue was also found to be a statistically significant predictor of reaching EDSS 3 in the study conducted in Bosnia and Herzegovina, although the sample size was small [24]. Our findings from the multivariate analysis showing fatigue as a risk factor for reaching both EDSS 4 and 6 as the endpoint, support it as a valuable predictor of disability.

Of note, when the analysis was performed separately for both sexes, fatigue retained the predictive value only for women. The data which might explain this phenomenon is scarce, although the studies addressing the different aspects of fatigue in MS patients report its larger prevalence in female compared to male patients [23, 24]. Given the presumed attribution of fatigue to neuroinflammation-related processes, the gender difference in the predictive value of fatigue we found in our study might be linked to the differences in the mechanisms of MS development and course.

Our study has certain limitations. There is no centralized MS registry in Ukraine, so the data were obtained from medical records. The way patient-related information was reported and recorded might impact the quality of the retrieved data. This issue might be overcome with the prospective design of the study with standardized recording. Another major limitation is the subjectivity of self-reporting of the symptoms at the MS onset by the patients with a delayed first presentation to neurologist. In this case, the documented history of present illness was used to designate the systems affected at the disease onset. Although self-reported history seems to be the only way to reconstruct the patient's neurological status at the MS onset, it is less reliable than objective neurological assessment performed in an ideal scenario in which a patient with symptoms suspicious of MS presents to a neurologist shortly after the onset. We did not set the delayed presentation as a criterion of exclusion, so our dataset contains both information gathered from patients who presented shortly after the onset of neurological symptoms and the patients with delayed presentation and restored symptoms. With respect to the subgroup analysis (predictors in male and female patients separately), the size of the group of male patients was the major issue. Relatively small number of male patients might not allow some of the analyzed factors to reach statistical significance in the subgroup analysis. More patients should be included in the subgroups in further studies aiming to assess sex differences in predictors of the MS course. Finally, due to technical limitations, we did not use any radiological correlates to power the multivariate analysis.

## Conclusion

Impairment of functional symptoms at MS onset predicted reaching disability milestones in patients with RR-MS, but the predictors for EDSS 4 and EDSS 6 reaching were different. The clinical predictors also differed in male and female patients which contributes to the overall sex differences in MS mechanisms and course and warrant further investigation.

**Authors' contributions** Conceptualization: AI, YS, AS; Methodology: AI, YS; Formal analysis and investigation: AI, TM; Writing—original

draft preparation: AI; Writing—review and editing: YS, TM, AS; Supervision: YS, AS.

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**Data availability** The data used for this study are available from the corresponding author upon reasonable request.

## Compliance with ethical standards

**Ethics approval** Ethical approval was waived by the local Ethics Committee in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

**Consent for publication** Not applicable.

**Conflicts of interest** The authors declare that they have no conflict of interest.

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