PREVALENCE AND FACTORS ASSOCIATED WITH DISABILITY IN MULTIPLE SCLEROSIS PATIENTS

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ABSTRACT

Objectives: The study aimed to determine the prevalence and factors associated with disability progression in relapsing-remitting multiple sclerosis (RRMS) patients.

Methods: This is a retrospective observational study with analytical components based on the clinical medical records of 216 patients with RRMS who were followed up at King Hussien Medical Center's Neurology Department between January 2012 and December 2022. The patients were divided into two groups based on the Expanded Disability Status Scale (EDSS): Group A (EDSS ≤ 3) and Group B (EDSS > 3). Descriptive statistics were utilized to analyze the data. Multivariate Analysis of Variance (MANOVA) and chi-square tests (χ^2), or Fisher's exact tests, were employed to compare the groups as appropriate. Binary logistic regressions using stepwise method were employed to investigate disability-associated factors.

Results: Of the 216 RRMS patients, 15.3% had an EDSS score > 3. MANOVA and chi-square tests (χ^2) showed a statistically significant difference between the groups regarding age, age at diagnosis, sex, disease duration, body mass index (BMI), total cholesterol (TC), high-density lipoprotein (HDL), and location of brain lesions ($p < 0.05$). Binary logistic regression analysis showed that BMI, TC and age were independent influencing factors on disability in patients with RRMS ($p < 0.05$).

Conclusion: The value of accurately assessing patients and establishing their functional capacity at each visit is highlighted by the fact that several risk factors are modifiable. These results highlight the need for early intervention focusing on modifiable risk factors, including BMI and TC.

Keywords: Relapsing-remitting multiple sclerosis, disability, associated factors, prevalence

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, progressive, and neurodegenerative autoimmune disease affecting the brain and spinal cord, frequently leading to significant physical, psychological, and cognitive disabilities (1). The estimated global population living with MS is around 2.8 million, with a prevalence rate of 35.9 per 100,000 individuals (2). Women are more susceptible to MS than men, with a twofold increased risk (2).

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The estimated prevalence in Jordan ranges from 24 to 39 per 100,000 individuals (3, 4).
It is crucial to differentiate between the various subtypes of MS, including relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS), both for prognosis and treatment considerations. RRMS, the most common subtype (87%) of MS, is characterized by unpredictable acute episodes followed by periods of remission (5). In Jordan, the clinical courses of MS were distributed as follows: 65.3% for relapsing and remitting, 27.8% for clinically isolated syndrome, 3.9% for secondary progressive, and 3% for primary progressive cases (6).
The disease presents itself in diverse ways, including sensory and vision disturbances, motor impairments, fatigue, pain, and cognitive dysfunction (7). The observed clinical manifestations are directly correlated with the location and extent of lesions within the central nervous system (8).
Lifestyle, environmental, and genetic factors have all been recognized as potential contributors to the development of MS, although the precise cause of the disease remains uncertain. The well-established risk factors are Epstein-Barr virus infection during adolescence and early adulthood, active or passive smoking, insufficient sun exposure, low vitamin D levels, and adolescent obesity (8).
One of the pivotal aspects of evaluating MS is assessing disability (9). Consequently, many studies correlate prognostic factors with the Expanded Disability Status Scale (EDSS) score – a widely used scale for tracking the condition due to its applicability in routine neurological examinations (10). In the literature, risk factors contributing to worsening disability in MS have been identified through descriptions of prognostic variables related to this outcome (10). However, a statistical model that integrates socio-demographic, clinical, and radiological variables to elucidate the course of disability development in MS within the context of Jordan has yet to be established. Therefore, our study aimed to ascertain the prevalence and factors associated with disability progression in RRMS patients.

METHODS

Design

A retrospective analysis was conducted on the medical records of patients with MS who were under follow-up at the Neurology Department of King Hussein Medical Center between January 2012 and December 2022.

Study subjects

The study encompassed adult patients aged 18 years and older diagnosed with RRMS following McDonald's 2017 diagnostic criteria (11). Patients with clinically isolated syndromes, possible MS, a progressive course, other demyelinating diseases such as neuromyelitis optica (NMO) and acute disseminated encephalomyelitis (ADEM), malignant tumors, and other wasting diseases were excluded as part of the exclusion criteria.
The sample size was determined using G-Power software 3.1.8.7, based on the following formula: (Effect Size [ES] = 0.5, α Error = 0.05, Power [1 - Error] = 0.8) and using the F test (regression analysis) (12). The study necessitated a minimum of 160 subjects. Ultimately, we successfully recruited a convenient sample of 216 patients for this investigation.

Recorded data

The data encompassed socio-demographic characteristics, clinical parameters, and radiological parameters. These parameters included: age, age at diagnosis, duration of MS disease, gender, body mass index (BMI), utilization of disease-modifying treatment (DMT), family history of MS, presence of comorbidities (both physical diseases and psychiatric disorders), and smoking status. Laboratory tests comprised lipid profiles, specifically triglycerides (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and total cholesterol (TC). Radiological parameters encompassed the location of brain lesions on magnetic resonance imaging (MRI), the total count of these lesions, and the number of spinal MRI lesions.

Study measure

Multiple sclerosis-related disability is assessed using the EDSS (13). This scale is employed to gauge the severity of MS symptoms and consolidate the data into a singular score. The patient's level of disability is ranked on the EDSS, ranging from zero (indicating normal function) to ten (indicating MS-related mortality). According to Kurtzke's classification from 1983, the EDSS score falls within one of three categories: mild (0–3), moderate (3.5–6.5), or severe (greater than 6.5) (13). For this study, the EDSS scores will be grouped into two categories: EDSS ≤ 3 (Group A) and EDSS > 3 (group B). The reliability coefficient for the EDSS has been reported as 0.80 (14).

Ethical considerations

All patient information was handled with utmost confidentiality, and the data was analyzed anonymously using patient ID numbers. No direct contact was made with patients or their family members. This study received approval from the Ethics Review Board at Royal Medical Services (approval No, 29-6/2023).

Statistical analysis

Patients were stratified into two groups according to the severity of their disability (groups A and B). The data were analyzed using SPSS 25.0 statistical software. Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and proportions. Multivariate Analysis of Variance (MANOVA) and chi-square tests, or the Fisher exact test when applicable, were employed to compare the groups. The model was constructed using binary logistic regression analysis using the stepwise method. Variables that exhibited differences with a p value less than 0.02 between the two groups were incorporated into the binary logistic regression. The threshold for significance was set at a p-value of ≤ 0.05.

RESULTS

Patients' characteristics

A total of 216 patients with RRMS were enrolled in this study. These patients were categorized into two groups based on their EDSS scores: Group A (EDSS ≤ 3) and Group B (EDSS > 3). The prevalence of patients with an EDSS score > 3 was 15.3% (Group B). Out of the 216 patients, 183 (84.7%) exhibited an average EDSS score of ≤ 3 (Group A). Their mean age and age at diagnosis were 33.90 ± 9.84 and 27.83 ± 8.65 years, respectively. This group comprised 68 males and 115 females, with a mean EDSS of 2.11 ± 0.71.

Group B had a mean age and age at diagnosis of 40.06 ± 11.16 and 31.96 ± 10.59 years, respectively. Among them, six were males and 27 were females, with a mean EDSS of 4.45 ± 0.93.

One-way MANOVA was conducted to determine whether there is a difference between the groups on age and age at diagnosis. There was a significant difference in age (F (1, 1060.5) =10.50, p = 0.001, partial η2=0.047) and age at diagnosis (F (1, 478.9) =5.95, p = 0.015, partial η2=0.027) between the groups.
The mean BMI score was notably higher in Group B (mean = 25.45, standard deviation = 2.96) based on MANOVA test (F (1, 394.2) =74.94, p = 0.001, partial η2=0.259). Moreover, the mean disease duration score was significantly higher in Group B (mean = 8.03, standard deviation = 4.17) based on MANOVA test (F (1, 104.9) =7.70, p = 0.006, partial η2=0.035) (Table 1).

Significant differences were observed between the two groups regarding the male-to-female ratio ($p < 0.05$). The proportion of females in group B was higher than in group A. No significant distinctions were observed between the groups concerning family history of MS , comorbidities, smoking habits, or types of disease-modifying therapies ($p > 0.05$) (Table 2).
Concerning the lipid profile, patients within Group B displayed a notably higher mean TC value (mean = 201.78, standard deviation = 13.07) based on MANOVA test (F (1, 66786) =35.18, p = 0.001, partial η2=0.141). Conversely, patients in Group A demonstrated a significantly higher mean high-density lipoprotein (HDL) value (mean = 58.10, standard deviation = 9.56) than those in Group B based on MANOVA test (F (1, 1891) =10.38, p = 0.001, partial η2=0.046). However, no significant differences were observed between the groups concerning triglycerides (TG) and low-density lipoprotein (LDL) levels ($p > 0.05$) (Table 3).
Regarding radiological parameters, a notable distinction emerged between the groups concerning the location of brain lesions ($p < 0.05$). Most brain lesions in both groups were localized in the juxtacortical or cortical regions. However, disparities were evident in other brain regions. Conversely, no noteworthy difference was detected between the groups concerning the number of brain or spinal lesions ($p > 0.05$) (Table 4).

Factors influencing the degree of disability in RRMS patients

Binary logistic regression using the stepwise method was employed to explore the factors influencing the extent of disability in RRMS patients (progression of disability to a moderate or severe score on the EDSS). Factors that exhibited differences between the groups with a p value less than 0.20, as determined by MANOVA tests, Chi-square tests, and Fisher exact tests, were included as independent variables in the binary logistic regression analysis. These variables encompassed age, age at diagnosis, sex, disease duration, BMI, comorbidities, smoking habits, TC, TG, HDL, the number of brain lesions, the number of spinal lesions, and the location of brain lesions. The logistic regression model yielded that BMI, TC, and age were considered significant factors for disability progression ($p<0.05$). An escalation of these factors was linked to an elevated likelihood of the development of moderate to severe disability on the EDSS scale. This model expounded upon 48.4% of the variance in the disability scores among RRMS patients (Table 5).

Table 1. Differences in age, age at diagnosis, disease duration and BMI between the groups A and B of patients with relapsing-remitting multiple sclerosis (N=216)

Variables	EDSS		F	P	Partial η2
	Group A (n=183)	Group B (n=33)			
	EDSS=2.11 ± 0.71)	EDSS=4.45 ± 0.93)			
Age (years)	33.90 ± 9.84	40.06 ± 11.16	10.50	0.001	0.047

Age at diagnosis (years)	27.83 ± 8.65	31.96 ± 10.59	5.95	0.015	0.027
Disease duration (years)	6.09 ± 3.59	8.03 ± 4.17	7.70	0.006	0.035
BMI (Kg/m^2)	21.69 ± 2.15	25.45 ± 2.96	74.94	0.001	0.259

BMI: body mass index; EDSS: Expanded Disability Status Scale.

Table 2. Differences in categorical and nominal demographic and clinical variables between the groups of patients with relapsing-remitting multiple sclerosis (N=216)

Variables	**EDSS**		χ^2	**P**
	Group A (n=183)	**Group B (n=33)**		
Sex				
Male	**68** (37.2)	**6** (18.2)	4.47[a]	0.045
Female	**115** (62.8)	**27** (81.8)		
Family history				
No	**159** (86.9)	**31** (93.9)	[b]	0.384
Yes	**24** (13.1)	**2** (6.1)		
Comorbidities				
No	**108** (59)	**14** (42.4)	3.13[a]	0.088
Yes	**75** (41)	**19** (57.6)		
Smoking				
Never	**72** (39.3)	**10** (30.3)	5.668[a]	0.061
Past	**50** (27.3)	**5** (15.2)		
Current	**61** (33.3)	**18** (54.5)		
DMT types				
Interferon-β/glatiramer acetate	**59** (32.2)	**10** (30.3)	[b]	0.427
Natalizumab	**20** (10.9)	**6** (18.2)		
Fingolimod	**17**(9.3)	**2** (6.1)		
Dimethyl fumarate	**9** (4.9)	**2** (6.1)		
Ocrelizumab	**7** (3.8)	**3** (9.1)		
Cladribine	**6** (3.3)	**2** (6.1)		

χ^2: chi-square test; a: the χ^2 value of the chi-square test; b: Fisher exact test; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale.

Table 3. Differences in lipid profile between the groups of patients with relapsing-remitting multiple sclerosis (N=216)

Variables	EDSS		F	P	Partial η2
	Group A (n=183)	Group B (n=33)			
TC (mg/dl)	152.91± 11.15	201.78 ±13.07	35.18	0.001	0.141
TG (mg/dl)	135.02± 11.95	149.48±12.90	2.49	0.116	0.012
HDL (mg/dl)	58.10 ± 9.56	49.87 ±10.11	10.38	0.001	0.046
LDL (mg/dl)	121.27 ± 12.98	125.00 ±15.94	0.480	0.489	0.002

TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; EDSS: Expanded Disability Status Scale

Table 4. Differences in radiological parameters between the groups of patients with relapsing-remitting multiple sclerosis (N=216)

Variables	EDSS		χ^2	P
	Group A (n=183)	Group B (n=33)		
Site of brain lesions				
Periventricular	**47** (25.7)	**4** (12.1)	9.858	0.019
Juxtacortical or cortical	**72** (39.3)	**19** (57.6)		
Infratentorial	**39** (21.3)	**2** (6.1)		
Multiple	**25** (13.7)	**8** (24.2)		
Number of brain lesions				
No lesions	**6** (3.3)	**1** (3)	5.612	0.128
1-3	**49** (26.8)	**4** (12.1)		
4-9	**60** (32.8)	**9** (27.3)		
≥10	**68** (37.2)	**19** (57.6)		
Number of spinal lesions				
No lesions	**5** (2.7)	**4** (12.1)	6.874	0.076
1-3	**50** (27.3)	**7** (21.2)		
4-9	**69** (37.3)	**10** (30.3)		
≥10	**59** (32.2)	**12** (36.4)		

EDSS: Expanded Disability Status Scale; χ^2: chi-square test

Table 5. Binary logistic regression analysis of factors associated with the degree of disability in patients with relapsing-remitting multiple sclerosis

Variables		β	SE	Wald	P	OR	95% CI	
							Lower limit	Upper limit
Step 1	**BMI**	.528	.089	35.196	<.001	1.695	1.424	2.017
Step 2	**BMI**	.450	.089	25.572	<.001	1.568	1.317	1.866
	TC	.017	.005	11.254	.001	1.017	1.007	1.027
Step 3	**BMI**	.449	.092	24.074	<.001	1.567	1.310	1.875
	TC	.017	.005	10.410	.001	1.017	1.007	1.028
	Age	.057	.022	6.930	.008	1.059	1.015	1.105

BMI: body mass index; TC: total cholesterol; CI: confidence interval
Step 1 R^2 = .367
Step 2 R^2 = .440
Step 3 R^2 = .484

DISCUSSION

Given the substantial impact of the degree of physical and cognitive disability on the quality of life of individuals with MS (15,16), it is crucial to actively investigate all contributing factors. Therefore, the primary objective of this study was to explore these influential factors. The study encompassed 216 patients diagnosed with RRMS, with ages averaging 27.83 and 31.96 years for groups A and B, respectively. The literature indicates that the typical age range for the onset of pathology is between 20 and 40 years, with a global mean age of 32 years (2). Over the past five decades, the age of RRMS onset has shifted from 27.86 ± 9.22 to 34.28 ± 9.83 (17). This later onset of MS correlates with a higher prevalence of motor functional impairment (18).

Interestingly, this study's regression analysis did not identify age at disease diagnosis as a factor influencing disability, despite observing notable differences between the two groups. This outcome aligns with the findings of the Arteaga-Noriega et al. study (19). Patient age was determined to be an influencing factor in the progression of disability. The impact of age on disease progression was underscored in the study conducted by Scalfari et al. (2011) (20). As per these researchers, the accumulation of disability is shaped by the age of the initial RRMS diagnosis and the patient's current age. This is due to the likelihood that older patients experience a more progressive course of the illness and exhibit a shorter latency to progression (20).

The study's participant composition predominantly consisted of females (65.7%). Among them, 27 patients (19%) exhibited an EDSS score surpassing 3 points, exceeding the proportion of male patients (8.1%) with EDSS scores above 3 points. Segura-Cardona's findings unveiled disability progression rates of 20.48% for men and 38.0% for women (21). In other studies, women demonstrated a more favorable prognosis than men (22, 23). Until menopause, women tend to display elevated rates of inflammatory disease activity characterized by relapses when contrasted with men, suggesting a role for sex hormones in this distinction. Recent cohort studies highlight that the neurodegenerative aspects of MS more frequently impact men, particularly after age 45 (24).

Remarkably, this study's regression analysis did not identify sex as a factor influencing the disability of RRMS patients, despite observable variations between the groups.

Patients in Group B exhibited significantly longer disease durations than those in Group A.

Retrospective analysis of data from 2083 RRMS patients aimed to ascertain prognostic factors for Timed 25-Foot Walk (indicative of lower limb disability), Performance Scale Sum (reflecting perceived global disability), and Patient Health Questionnaire 9 (measuring depression). The analysis revealed that higher BMI, age, disease duration, median income, and depression scores predicted slower walking speed (25). Contrarily, a study reviewing the disability profiles of 2917 MS patients in New Zealand similarly identified disease duration as contributing to heightened disability (26). A plausible hypothesis suggests that the extended disease duration in MS patients is linked to vascular dysfunction. This connection may stem from chronic inflammation, autoimmunity, oxidative stress, and cardiovascular autonomic dysregulation. These mechanisms have been proposed as potential contributors to the observed vascular dysfunction in individuals with MS (27).

The relationship between higher BMI and MS disability remains unclear, but available evidence suggests a negative association. A longitudinal study involving 269 RRMS patients with mild to moderate disability spanning 24 months identified a negative correlation between baseline BMI and Patient Determined Disease Steps (PDDS) at month 12, although no such connection was observed between BMI at month 12 and PDDS at month 24 (31). Another longitudinal study covering 5 years with a cohort of 279 participants disclosed a positive link between baseline BMI and subsequent increments in the EDSS (32). In contrast, Bove et al. (2016) conducted a retrospective review of 1037 MS patients over 2 years and detected no statistically significant relationships between baseline BMI and ensuing EDSS scores (33).

Briggs et al. identified obesity and overweight as contributing factors to disability in RRMS patients (25). The elevation of inflammatory mediators interleukin (IL)-6 and leptin in obesity contributes to its pro-inflammatory nature (34). Furthermore, evidence points to a diminished response to interferon (IFN) treatment among MS patients with higher BMI (35).

Within this study, BMI was associated with EDSS scores. Notably, individuals with EDSS scores exceeding 3 points exhibited a significantly higher BMI than those with scores equal to or less than 3 points.

Alterations in lipid metabolism and heightened plasma lipids and lipoproteins have been linked to a more severe disease course in individuals with MS (36, 37). In this study, TC and HDL exhibited significant variations between the groups; however, in the binary logistic regression analysis, only TC was associated with disability.

were noted in the study by Boshra et al., where elevated levels of TC, TG, and LDL and decreased HDL levels were identified in MS patients compared to an age- and sex-matched control group. Notably, no significant correlation with disability was established (27). Weinstock-Guttman et al.2011 reported a modest impact of elevated LDL, TC, and TG levels on MS disability, alongside a protective effect conferred by HDL (38). In the context of relapsing-remitting MS (RRMS), Gafson et al. 2018 hypothesized – based on their findings – that plasma cytokines CCL-17 and IL-7 exhibited substantial associations with free cholesterol transported by VLDL-2, thereby emphasizing interconnections between disability, inflammatory responses, and systemic lipid metabolism (39).

LIMITATIONS

This study presents a few limitations. Given its retrospective design, it could not encompass all pertinent predictive factors, such as active lesions, relapse rates, and cerebrospinal fluid-related protein markers. Similarly, it could not track changes in the various markers as the disease progressed. Consequently, to provide more robust validation of the study's findings, larger sample sizes and prospective, longitudinal investigations are warranted. Nevertheless,

this study represents the inaugural attempt to delve into the patient profiles of MS patients in Jordan, aiming to uncover the prevalence and associated factors contributing to RRMS disability.

CONCLUSIONS

MS is an intricately complex condition. The prevalence of RRMS patients exhibiting an EDSS greater than 3 points was 15.3%. Notably, considerable disparities existed between the groups concerning age, age at diagnosis, sex, disease duration, BMI, TC, HDL, and the site of brain lesions. Concurrently, the regression analysis demonstrated a connection between heightened disability levels and increased age, elevated BMI, and increased TC.

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