scientific reports

Check for updates

OPEN

Factors affecting fatigue progression in multiple sclerosis patients

Dima Machtoub[1,8], Callie Fares[2,8], Hassan Sinan[3], Moustafa Al Hariri[4], Rim Nehme[1], Joelle Chami[1], Ronny Joukhdar[1], Raya Tcheroyan[5], Salim Adib[6] & Samia J. Khoury[7]✉

Fatigue is one of the most prevalent and disabling symptoms among patients with MS, but there is limited research investigating the longitudinal determinants of fatigue progression. This study aims to identify the sociodemographic, behavioral and clinical characteristics, and therapeutic regimens that are correlated with worsening fatigue over time in patients diagnosed with MS. This is a retrospective chart review of 483 patients. The primary outcome was a change in the Modified Fatigue Impact Scale-5 (MFIS-5) score from first to last visit during the study interval, from November 2018 to November 2020. The study found that progressive MS subtypes, worsening depression, worsening pain, use of antidepressants, and use of fatigue medications were significantly associated with negative fatigue outcomes. Meanwhile age, sex, smoking frequency, use of pain medications, disease-modifying therapies, BMI, number of relapses, visits, steroid courses, and co-morbidities did not show an association. The clinical characteristics associated with worsening fatigue include progressive MS subtypes, worsening depression, worsening pain, use of antidepressants, and use of fatigue medications. Further studies are needed in order to elucidate a causal relationship and determine whether the management of fatigue in patients with MS should include interventions that address the aforementioned variables to optimize patient care and improve quality of life.

Keywords Fatigue, Depression, Pain, Progressive MS, Relapse-remitting MS

Fatigue is one of the most prevalent symptoms of Multiple Sclerosis (MS) and is regarded as a severe symptom because of its disabling effect on the patients' physical, mental, and emotional health, often leading to a reduction in quality of life[1]. The exact mechanism of fatigue in MS is thought to be multifactorial; it is considered to be a direct consequence of MS pathology (primary) and treatment, and as an indirect effect of the mental and psychosomatic distress associated with the diagnosis (secondary)[2,3]. Despite the pharmacological and behavioral approaches for the treatment of fatigue, it continues to be the most pervasive and disabling symptom in patients with MS at baseline and last follow up visit[4].

Numerous cross-sectional studies have been conducted assessing the determinants of fatigue, associations with other major symptoms, and its prevalence in the different types of MS. It was shown that longer disease duration, increased disability, and progressive subtypes of MS reported higher levels of fatigue and depression[5]. Additionally, lower levels of education among patients are correlated with higher levels of fatigue[1]. Certain co-morbidities also associated with increased fatigability in patients, with the most notable ones being depression, sleep disorders, mobility limitations, migraines, and irritable bowel syndrome[6,7].

In light of the clinical impact of fatigue, there is scant literature exploring long-term determinants that affect its evolution among MS patients. A longitudinal analysis of fatigue can contribute to a better understanding of the different prognostic factors that lead to favorable fatigue outcomes.

Here we investigated fatigue in MS patients that were treated at the American University of Beirut Medical Center (AUBMC), the largest tertiary hospital in Lebanon. A study on the epidemiology of MS in the Levant region found that 85% of a Lebanese cohort had relapsing–remitting MS at onset and about 8% had primary

[1]Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon. [2]Department of Dermatology, American University of Beirut Medical Center, Beirut, Lebanon. [3]John Hopkins School of Medicine, Baltimore, MD, USA. [4]College of Medicine, QU Health Sector, Qatar University, Doha, Qatar. [5]Department of Internal Medicine, Cooper University Hospital, Camden, NJ, USA. [6]Department of Public Health, American University of Beirut, Beirut, Lebanon. [7]Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Riad El-Solh, PO Box 11-0236, 1107 2020 Beirut, Lebanon. [8]Dima Machtoub and Callie Fares: Contributed equally to this work. ✉email: sk88@aub.edu.lb

progressive MS[8]. In Lebanon, MS has a crude prevalence of 62.91 cases per 100,000 persons nation-wide, with a higher prevalence in females (81.84 per 100,000) compared to males (42.72 per 100,000)[9].

We analyzed the change in fatigue score during follow up visits in relation to sociodemographic, behavioral and clinical characteristics, and therapeutic regimens of the patients. The aim of this study is to explore the factors associated with long-term fatigue prognosis of MS patients in Lebanon.

Methods

Patients and settings

This non-concurrent longitudinal study analyzed medical records of MS patients aged 18 or older at AUBMC Nehme and Therese Tohme MS center who fulfill the 2017 revised McDonald criteria. The study interval was between November 2018 and November 2020. Patients with other neurological diseases and those with only one recorded visit were excluded. The study was approved by the Institutional Review Board with protocol number BIO-2020–0522, and participants provided written informed consent (Fig. 1).

Definition of variables

Outcome variable

Fatigue The Modified Fatigue Impact Scale-5 (MFIS-5), a self-administered questionnaire that includes five statements exploring the existence of fatigue, its manifestations, and its impact on the patient, was used to assess fatigue[10]. Patients rated their agreement to these statements on a 5-point Likert scale during every clinic visit. The MFIS-5 questionnaire was used as it is a validated, widely used metric for measuring fatigue, which allows for better comparability between studies. MFIS-5 scores were compared between the first and last available visit within the study interval. All patients with 2 visits within the specified time period were included, even with a fatigue score of 0 indicating "no fatigue".

The scores were categorized as low or high based on the median score of all available scores. This was a practical approach for categorizing fatigue levels in the absence of validated score cutoffs[11,12]. The median was calculated using all existing scores, excluding 0, and was found to be 6. Scores below the median were considered low fatigue and scores equal to or above the median were considered high fatigue.

Patients with "positive fatigue outcomes" were those whose low fatigue level was maintained or those whose fatigue levels decreased from high to low. Conversely, those with "negative fatigue outcomes" were patients who maintained a high level of fatigue or whose fatigue level increased from low to high.

Independent variables

The independent variables included three categories: sociodemographic and behavioral, clinical, and therapeutic variables.

Sociodemographic and behavioral variables Demographic characteristics included age at first visit (years) and sex (male or female) for all patients, as per their social history listed on the electronic medical record. Smoking status and frequency of use was assessed by asking the patients the type, frequency, and quantity of tobacco use. Smoking status categories were subsequently divided into: never smoker, ex-smoker (> 6 months since quitting), occasional smoker (< 1 cigarette per day or < 1 hubble-bubble per week), regular-light smoker (less than half a pack of cigarettes per day or > 1 hubble-bubble per week), and regular-heavy smoker (more than half a pack of cigarettes per day or daily hubble-bubble).

Clinical variables *Depression* All patients underwent routine clinical evaluations for depression reported through medical history or screened using the Hopkins system-checklist[13]. Depression was then classified using "present" for patients with depression and "absent" for patients without. Two main outcomes were used to evaluate how depression progressed between the first and last visits, namely "positive" and "negative depression outcomes."

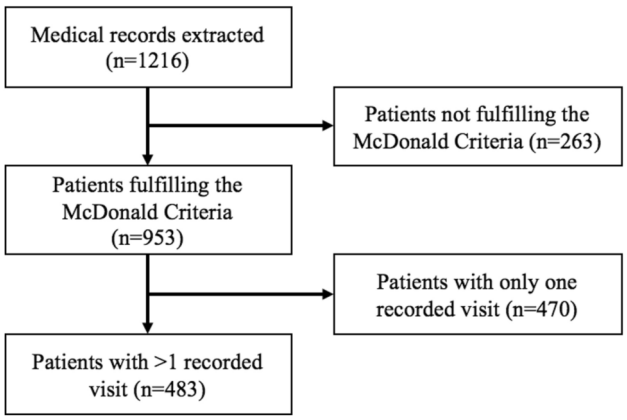

Fig. 1. Flow chart of inclusion and exclusion criteria of participants in the current analysis.

Positive depression outcomes entail depression to be absent at both visits or present at the first visit, but absent at the last. Negative depression outcomes entail depression to be present at both visits or absent at first visit, but present at last.

Use of antidepressants All patients were assessed for antidepressant use during the study interval, the information of which was collected from the electronic medical record after a review of their medications. They were subsequently divided into "yes" and "no" groups. The antidepressants analyzed included citalopram, doxepin, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine.

Pain All patients were routinely evaluated for symptoms of pain using the Lykert scale of 0–10; which was then classified using "present" for patients with pain and "absent" for patients without. Two main outcomes were used to evaluate how pain progressed between the first and last visits, namely "positive" and "negative pain outcomes."

Positive pain outcomes entail pain to be absent at both visits or present at the first visit, but absent at the last. While negative pain outcomes entail pain to be present at both visits or absent at first visit, but present at last.

Use of pain medication All patients were assessed for pain-relief medication use during the study interval, the information of which was collected from the electronic medical record after a review of their medications. The patients were subsequently divided into "yes" and "no" groups. The pain medications analyzed included amitriptyline, carbamazepine, duloxetine, gabapentin, lamotrigine, and pregabalin.

Use of fatigue medication All patients were assessed for fatigue-relief medication use during the study interval, the information of which was collected from the electronic medical record after a review of their medications. The patients and were subsequently divided into "yes" and "no" groups. The fatigue medications analyzed included amantadine and modafinil.

Chronic comorbidities Each patient's medical history was taken during their first visit in the study interval. This included chronic comorbidities diagnosed at least 3 months prior.

Clinical MS subtype The clinical MS subtypes for the patients were grouped into two categories: progressive subtypes and relapse-remitting MS (RRMS).

Number of relapses The number of relapses during the study interval. Those with progressive forms of the disease were placed in a separate category.

Other parameter definitions Other study parameters included BMI, interval between first and last visit (in days), the number of visits, and the number of steroid courses during the study interval.

Therapeutic regimens *Disease modifying therapy (DMT)* Both the number and type of DMT(s) used by patients during the study interval were assessed.

The DMT included in our study were divided into three groups based on efficacy. High efficacy DMTs included natalizumab, rituximab, ocrelizumab, alemtuzumab, and cladribine. Moderate efficacy DMTs included fingolimod and dimethyl fumarate. Low efficacy DMTs included interferon beta-1a, interferon beta-1b, and teriflunomide.

Patients were receiving one DMT at a time, but may have used more than one DMT (from the same or different efficacy group) during the study interval due to failed response.

Statistical analysis test

Categorical variables, such as sex, smoking frequency, clinical subtype, depression outcome, pain outcome, and medications used, were presented as frequencies and percentages. While continuous variables, such as age, number of visits, number of chronic comorbidities, number of days between first and last visit, and BMI, were presented as means with standard deviation (SD). The t-test or Chi-square test was used to evaluate associations between independent variables, listed previously, and the outcome, fatigue, for categorical or continuous variables, respectively. A significant association was set at a p value ≤ 0.05.

The variables with a significant bivariate association, clinical subtype, depression and pain outcome, antidepressant use, and fatigue medication use, were included in the multivariate logistic regression, which produced adjusted odds ratio (aOR) for each association. An aOR was considered significant if the 95% confidence interval did not contain 1. A best fit model was created using significant variables to predict fatigue outcomes among patients who come for their first visit.

Results

Description of participants

A total of 1216 medical records were extracted and 483 patients were included, approximately half of the population reported fatigue at first visit. The population was found to have a mean age of 38.1 ± 12.3 years, with 66.9% being females. The mean number of visits was 2.8 ± 0.8 for the positive fatigue outcomes and 2.8 ± 0.9 for the negative fatigue outcomes (Table 1).

Based on the MFIS-5 scores, 46.9% of the patients included in the study had scores of 0 at any encounter. Of the patients who reported fatigue at first visit, 65.7% had a low fatigue score. Over the study period, 63.6% of patients had positive fatigue outcomes and 36.4% had negative fatigue outcomes. In the studied sample, 84.3% of participants had RRMS and 15.7% patients had progressive MS.

Positive depression outcomes were found in 85.2% of patients; in addition, anti-depressants were used by 29% of patients. As for pain, 87% of participants had positive pain outcomes and 11.4% of patients were using pain medications. In the RRMS group, 62.5% had zero relapses, 16.8% patients had one relapse, and 5.0% had two or more relapses during the study interval (Table 2).

Variables	Total	Positive fatigue outcomes[a]	Negative fatigue outcomes[a]	*p* value[b]
n (%)	483	307 (63.6)	176 (36.4)	--
Age in years (mean ± SD)	38.1 ± 12.3	36.9 ± 12	40.3 ± 12.5	**0.004**
Age categories				
< 30	146	103	43	0.102
31–40	151	97	54	
41–50	98	55	43	
> 50	88	52	36	
Sex category				
Female	323 (66.9)	196 (60.7)	127 (39.3)	0.071
Male	160 (33.1)	111 (69.4)	49 (30.6)	
Number of visits (mean ± SD)	2.8 ± 0.8	2.8 ± 0.8	2.8 ± 0.9	0.590
Smoking frequency[c] (n, %)				
Regular-heavy smoker Regular-light Occasional Ex-smoker Never smoker	117 (24.2) 61 (12.6) 34 (7.0) 71 (14.7) 200 (14.4)	75 (64.1) 42 (68.9) 22 (64.7) 45 (63.4) 123 (61.5)	42 (35.9) 19 (31.1) 12 (35.3) 26 (36.6) 77 (38.5)	0.888

Table 1. Sociodemographic and behavioral characteristics associated with fatigue evolution among MS patients treated at AUBMC (2018–2020). [a]"Positive fatigue outcomes" are indicated by maintenance of a low level of fatigue or decrease in fatigue intensity between the first and last visit in the follow-up period, as indicated by scores on the MFIS-5. All other evolution patterns in fatigue are considered as "negative fatigue outcomes." [b]The *p* value represents the statistical significance of the relationship between the fatigue outcome and the independent variables. $p \leq 0.05$ was considered significant. [c]Never smoker, ex-smoker (> 6 months since quitting), occasional smoker (< 1 cigarette per day or < 1 hubble-bubble per week), regular-light smoker (less than half a pack of cigarettes per day or > 1 hubble-bubble per week), and regular-heavy smoker (more than half a pack of cigarettes per day or daily hubble-bubble).

Bivariate analysis

A significant association was found between fatigue outcomes and age, with the mean age of patients with negative fatigue outcomes being higher than those of patients with positive fatigue outcomes (40.3 vs. 36.9 years, respectively) (Table 1).

Patients with progressive disease had higher rates of negative fatigue outcomes (60.5%), as compared to RRMS (31.9%). RRMS patients showed positive fatigue outcomes regardless of the number of relapses.

There was a significant difference in fatigue outcomes in participants taking high efficacy DMTs, with 57.2% having positive fatigue outcomes. Patients taking antidepressants, pain medications, and fatigue medications had significantly more negative fatigue outcomes (Table 2).

Patients with negative depression outcomes had higher rates of negative fatigue outcomes; but outcomes were markedly different in those not taking antidepressants, with 69.4% having positive fatigue outcomes.

Patients with positive pain outcomes had significantly higher rates of positive fatigue outcomes (68% vs. 32%). In patients with negative pain outcomes, 70.5% had negative fatigue outcomes. In patients not using pain medications, 66.8% had positive fatigue outcomes.

Multivariate logistic regression

In the multivariate regression, MS subtype, depression outcomes, pain outcomes, antidepressant use, and fatigue medication use were significantly associated with negative fatigue outcomes and were used for the best fit model. Age, sex, use of steroids, use of pain medications, BMI at first encounter, use of high efficacy DMTs, number of relapses, and smoking frequency did not show an association with the outcomes of fatigue.

When examining the predictors in relation to negative fatigue outcomes, an association was found between MS-subtype and negative fatigue outcomes, with remitting MS being correlated with lower negative fatigue outcomes compared to progressive MS (OR=0.42, $p = 0.002$). Additionally, a relationship was identified between depression outcomes and fatigue outcomes, with positive depression outcomes being associated lower negative fatigue outcomes (OR=0.34, $p = 0.001$). A similar association was found with pain outcomes, where positive outcomes were linked with lower negative fatigue outcomes compared to negative pain outcomes (OR=0.23, $p < 0.001$).

Furthermore, the results suggest a relationship between antidepressant use and fatigue outcomes, with antidepressant use being associated with negative fatigue outcomes (OR=1.61, $p = 0.042$). Similarly, the use of fatigue medications was linked to negative outcomes (OR=4.23, $p = 0.003$).

The predictive best fit model based on results from the multivariate regression is presented in Table 3. The higher probability of negative fatigue outcomes is associated with progressive MS subtype, negative depression and pain outcomes, use of antidepressants, and use of fatigue medications.

Variables	Total	Positive Fatigue Outcomes[a]	Negative Fatigue Outcomes[a]	*p* value[b]
n (%)	483	307 (63.6)	176 (36.4)	–
Clinical subtype (n, %)				
Progressive MS	76 (15.7)	30 (39.5)	46 (60.5)	**< 0.001**
Relapse-remitting	407 (84.3)	277 (68.1)	130 (31.9)	
Chronic co-morbidities (mean ± SD)	2 ± 1.2	1.9 ± 1.2	2 ± 1.3	0.410
Depression outcomes[c] (n, %)				
Positive outcomes	397 (85.2)	269 (67.8)	128 (32.2)	**< 0.001**
Negative outcomes	69 (14.8)	23 (33.3)	46 (66.7)	
Pain outcomes[d] (n, %)				
Positive outcomes	409 (87)	278 (68)	131 (32)	**< 0.001**
Negative outcomes	61 (13)	18 (29.5)	43 (70.5)	
Interval in days between first and last visit (mean ± SD)	400.3 ± 168.5	405.3 ± 171.9	391.5 ± 162.4	0.386
BMI Score First Encounter (mean ± SD) (kg/m^2)	25.4 ± 4.9	25.1 ± 5.0	26.1 ± 4.8	**0.035**
Use of steroids (n, %)				
Yes	99 (20.5)	57 (57.6)	42 (42.4)	0.165
Never	384 (79.5)	250 (65.1)	134 (34.9)	
Antidepressant use (n, %)				
Yes	140 (29)	69 (49.3)	71 (50.7)	**< 0.001**
No	343 (71)	238 (69.4)	105 (30.6)	
Number of relapses (n, %)				
Zero	302 (62.5)	207 (68.5)	95 (31.5)	**< 0.001**
One	81 (16.8)	53 (65.4)	26 (34.6)	
Two & more	24 (5.0)	17 (70.8)	7 (29.2)	
Progressive	76 (15.7)	30 (39.5)	46 (60.5)	
Number of steroid courses (n, %)				
Zero	384 (79.5)	250 (65.1)	134 (39.4)	0.111
One	78 (16.1)	41 (52.6)	37 (47.4)	
Two & more	21 (4.3)	16 (76.2)	5 (23.8)	
Pain medication use (n, %)				
Yes	55 (11.4)	21 (38.2)	34 (61.8)	**< 0.001**
No	428 (88.6)	286 (66.8)	142 (33.2)	
Use of fatigue medications (n, %)				
Yes	25 (5.2)	7 (28)	18 (72)	**< 0.001**
No	458 (94.8)	300 (65.5)	158 (34.5)	
Disease modifying therapy (DMT) (n, %)				
High efficacy drugs	208 (43.1)	119 (57.2)	89 (42.8)	**0.012**
Moderate efficacy drugs	197 (40.8)	132 (67)	65 (33)	0.192
Low efficacy drugs	125 (25.9)	86 (68.8)	39 (31.2)	0.157
Number of DMT used (n, %)				
Zero	40 (8.3)	26 (65)	14 (35)	**0.042**
One	333 (16.1)	211 (63.4)	122 (36.6)	
Two & more	110 (22.8)	70 (63.6)	40 (36.4)	

Table 2. Clinical and therapeutic characteristics associated with fatigue evolution among MS patients treated at AUBMC (2018 –2020). [a]"Positive fatigue outcomes" are indicated by maintenance of a low level of fatigue or decrease in fatigue intensity between the first and last visit in the follow-up period, as indicated by scores on the MFIS-5. All other evolution patterns in fatigue are considered as "negative fatigue outcomes." [b]The *p* value represents the statistical significance of the relationship between the fatigue outcome and the independent variables. $p \leq 0.05$ was considered significant. [c]"Positive depression outcomes" means the absence of depression or resolution of depression in the follow-up period. All other evolution patterns in depression are considered as "negative depression outcomes." [d]"Positive pain outcomes" are indicated by the absence of pain or resolution of pain in the follow-up period. All other evolution patterns in pain are considered as "negative pain outcomes."

	aOR[a]	*p* value[a]	CI
MS subtype (remitting vs progressive)	0.41	0.002	[0.24, 0.71]
Depression outcome (pos vs. neg)	0.34	0.001	[0.19, 0.63]
Pain outcome (pos vs. neg)	0.23	< 0.001	[0.12, 0.42]
Antidepressant use (yes vs. no)	1.61	0.042	[1.02, 2.54]
Fatigue medication use (yes vs. no)	4.23	0.003	[1.63, 11.00]

Table 3. Predictors of negative MFIS outcomes among MS patients treated at AUBMC (2018 –2020). Variables included in the model were: MS subtype (reference was progressive MS), pain outcome (reference was negative), depression outcome (reference was negative), antidepressant use (reference was no), use of fatigue medications (reference as no). N = 483. Coefficient = 3.13. [a]The *p* value represents the statistical significance of the relationship between the predictor variable(s) and the outcome variable (fatigue outcome). $p \leq 0.05$ was considered significant. The coefficient (aOR) represents the change in the outcome variable associated with a one-unit increase in the predictor variable(s), holding all other variables constant.

The best predictive equation for negative fatigue outcomes could therefore be written as, y = 3.13–0.41 (subtype) − 0.34 (depression outcome) − 0.23 (pain outcome) + 1.61 (antidepressant use) + 4.23 (fatigue medication use). The use of fatigue medications and pain outcomes are the biggest predictors of fatigue prognosis.

Discussion

This study of 483 patients with MS analyzed the effect of demographic, behavioral, clinical, and medication-related factors on fatigue progression. The strength of this study is in its longitudinal design. We were able to investigate the course of fatigue over a 2-year period and thus the factors that contribute to its outcomes, in order to identify the factors that contribute to a better control of fatigue in MS patients in Lebanon.

Consistent with the literature, we found that the predictors for fatigue outcomes included MS subtype, depression outcomes, antidepressant use, pain outcomes, and fatigue medication use[2,5–7,14]. Our data shows that patients with progressive forms of MS were linked with worse fatigue, which is in line with the current literature. These correlations are likely multifactorial and may be bi-directional, caused by factors such as decreased mobility that can lead to increased fatigue, while fatigue itself can decrease mobility and thus worsen disability. Similarly, depression and chronic pain can lead to feelings of decreased energy, exacerbating patient fatigability. Our study did not show a relation between the number of relapses and the progression of fatigue. This study excluded the effect of worsening disability on fatigue. However, one study showed that changes in depression, or mood, had a positive relation to fatigue progression over time, whereas worsening disability or the number of relapses did not, which is consistent with our findings[15]. In contrast, another study reported that patients experiencing acute relapses showed a worsening fatigue status[16].

Subjects with persistent or new onset depression at the follow up visit were more likely to have persistent or worsened fatigue, highlighting the relationship between depression and fatigue. Depression is a common comorbid condition in MS patients, suggesting that optimizing the treatment of depression may be significant in fatigue management[17]. Indeed, commonly used antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been correlated with alleviating other MS symptoms[18]. Surprisingly, we found that patients taking antidepressants were more likely to have negative fatigue outcomes. It is possible that subjects taking antidepressants had more severe symptoms of depression at presentation. Alternatively, the antidepressants may be causing fatigue as a side effect. Further research is needed to fully understand the relationship between antidepressant use and its impact on fatigue outcomes in patients with MS[19].

Another unexpected finding was among patients taking fatigue medications. These patients more likely to have negative fatigue outcomes, which could suggest that these patients have more severe symptoms overall or that these medications are not entirely effective in completely alleviating fatigue of multifactorial etiology. A randomized, double blinded, crossover trial has shown that the use of fatigue medications amantadine and modafinil has no advantage over placebo in improving fatigue symptoms MS patients based on MFIS scores. Rather, use of these medications caused more frequent adverse events, including pulmonary embolism and myocarditis due to amantadine, and hospitalizing MS exacerbations due to modafinil[20]. Therefore, this could be an explanation to the negative impact these medications have to the patients in our study on their fatigue outcome.

Patients with persistent pain or worsening pain at follow up more likely to have negative fatigue outcomes, suggesting a relationship between pain and fatigue. Indeed, the experience of chronic pain is disproportionally high in patients with MS and is associated with higher levels of fatigue[21]. Additionally, the outcome of fatigue can also be mediated by pain, and the relationship is likely bidirectional[21]. Given the impact of pain on quality of life in MS patients, both physically and psychosocially, addressing pain is crucial in the holistic management of patients with MS, especially considering its impact on fatigue.

Limitations

The outcomes were measured over a 2-year period, so it is plausible that some variables would have been revealed to be correlated to fatigue outcomes had more time elapsed. A study based on the NARCOMS database reported fatigue worsening over time but required a long-follow up time to detect[22]. The variability in the length of time interval between first and last visit for different patients in this study introduces challenges when comparing

fatigue outcomes over time and may obscure trends in fatigue progression, making it difficult to draw consistent conclusions across patients. This is because some patients may have had more time to experience changes in their symptoms, whereas others may have been followed up in a shorter time frame, affecting the ability to assess changes in fatigue accurately. Furthermore, the absence of information on whether patients were in relapse or remission at the time of assessment was a notable limitation. Fatigue assessment of some patients during a relapse complicates the interpretation of results, as the data collected may not represent a patient's typical fatigue levels outside of relapse periods. This could have led to inflated fatigue scores for these patients and introduced variability in the data that affects accuracy of identifying associations between fatigue and the other variables being studied. The impact of social isolation or exposure to COVID-19 may have also played a role as the study period overlapped with the pandemic. Additionally, the patient population is from a single tertiary care center in Beirut, and thus may not be generalizable to the broader MS population due to the single center study design.

Recall bias could affect the results as patients had to recall their symptoms during clinic visits. Further research is necessary to provide a more comprehensive understanding of the relationship between fatigue and variables such as MS subtype, depression outcomes, pain outcomes, and antidepressant use, as well as additional variables not included in our study such as anxiety and sleep quality.

Conclusions and practical implications

In conclusion, this study links longitudinal fatigue progression with MS subtype, depression, pain, use of antidepressants, and fatigue medications. Fatigue is one of the major symptoms of MS, and its management could require addressing these points in order to better optimize the patient's care and improve quality of life.

With our findings, certain practical implications can be made. *(1) Identification of associations:* this study highlights that MS type, depression outcomes, pain outcomes, and antidepressant and fatigue medication use are associated with fatigue outcomes in MS patients. While these associations do not imply causation, they can still be useful for healthcare providers in identifying patients who may be at higher risk of experiencing fatigue and for considering preventive measures accordingly. *(2) Targeted interventions:* understanding the associations between depression, pain, and fatigue outcomes in MS patients may help healthcare providers design targeted interventions to reduce the impact of these symptoms and help improve the fatigue outcomes and enhance patients' overall quality of life. *(3) Importance of comprehensive care:* This study highlights the importance of a comprehensive approach to care for MS patients, with a focus on addressing not just the physical symptoms of the disease but also the mental and emotional well-being of the patient, which can positively affect patient outcomes. (4) *Need for further research:* While this study provides important insights into the relationship between various factors and fatigue outcomes in MS patients, further research is needed to fully understand the underlying mechanisms and to develop more effective interventions to reduce the impact of fatigue on MS patients.

Received: 10 October 2023; Accepted: 22 November 2024
Published online: 30 December 2024

References

1. Lerdal, A., Celius, E. G. & Moum, T. Fatigue and its association with sociodemographic variables among multiple sclerosis patients. *Mult. Scler.* **9**(5), 509–514 (2003).
2. Rooney, S., Wood, L., Moffat, F. & Paul, L. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of multiple sclerosis. *Mult. Scler. Relat. Disord.* **28**, 276–282 (2019).
3. Manjaly, Z. M. et al. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* **90**(6), 642–651 (2019).
4. Kister, I., Bacon, T. & Cutter, G. R. A longitudinal study of symptom botheration in multiple sclerosis. *Mult. Scler. Relat. Disord.* **46**, 102585 (2020).
5. Ghajarzadeh, M. et al. Fatigue in multiple sclerosis: Relationship with disease duration, physical disability, disease pattern, age and sex. *Acta neurologica Belgica* **113**(4), 411–414 (2013).
6. Fiest, K. M. et al. Fatigue and comorbidities in multiple sclerosis. *Int. J. MS Care* **18**(2), 96–104 (2016).
7. Forwell, S. J. et al. Primary and nonprimary fatigue in multiple sclerosis. *Int. J. MS Care* **10**(1), 14–20 (2008).
8. Yamout, B. et al. Multiple sclerosis in the Levant: A regional consensus statement. *Int. J. Neurosci.* **124**(5), 377–382 (2014).
9. Zeineddine, M. et al. Epidemiology of multiple sclerosis in Lebanon: A rising prevalence in the middle east. *Mult. Scler. Relat. Disord.* **52**, 102963 (2021).
10. Meca-Lallana, V. et al. Assessing fatigue in multiple sclerosis: Psychometric properties of the five-item Modified Fatigue Impact Scale (MFIS-5). *Mult. Scler. J. Exp. Transl. Clin.* **5**(4), 2055217319887987 (2019).
11. Tustumi, F. Choosing the most appropriate cut-point for continuous variables. *Rev. Col. Bras. Cir.* **49**, e20223346 (2022).
12. DeCoster, J., Gallucci, M. & Iselin, A.-M.R. Best practices for using median splits, artificial categorization, and their continuous alternatives. *J. Exp. Psychopathol.* **2**(2), 197–209 (2011).
13. Derogatis, L. R. et al. The Hopkins symptom checklist (HSCL): A self-report symptom inventory. *Behav. Sci.* **19**(1), 1–15 (1974).
14. Valentine, T. R., Alschuler, K. N., Ehde, D. M. & Kratz, A. L. Prevalence, co-occurrence, and trajectories of pain, fatigue, depression, and anxiety in the year following multiple sclerosis diagnosis. *Mult. Sclerosis J.* **28**(4), 620–631 (2022).
15. Téllez, N. et al. Fatigue in multiple sclerosis persists over time: A longitudinal study. *J. Neurol.* **253**(11), 1466–1470 (2006).
16. Hanken, K. et al. Fatigue in Multiple Sclerosis is related to relapses, autonomic dysfunctions and introversion: A quasi-experimental study. *Mult. Sclerosis Relat. Disord.* **36**, 101401 (2019).
17. Tarasiuk, J. et al. Co-occurrence of fatigue and depression in people with multiple sclerosis: A mini-review. *Front. Neurol.* **12**, 817256 (2021).
18. Stamoula, E., et al. Antidepressants on multiple sclerosis: A review of in vitro and in vivo models. *Front. Immunol.* **12** (2021).
19. Koch, M. W. et al. Pharmacologic treatment of depression in multiple sclerosis. *Cochrane Database Syst. Rev.* **2**, cd007295 (2011).
20. Nourbakhsh, B. et al. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. *Lancet Neurol.* **20**(1), 38–48 (2021).
21. Amtmann, D. et al. Pain affects depression through anxiety, fatigue, and sleep in multiple sclerosis. *Rehabil. Psychol.* **60**(1), 81–90 (2015).
22. Salter, A. et al. Severity and worsening of fatigue among individuals with multiple sclerosis. *Mult. Scler. J. Exp. Transl. Clin.* **9**(2), 20552173231167080 (2023).

Acknowledgements
The data provided to us was through the EPIC database documented from from November 2018- November 2020. The Modified Fatigue Impact Scale 5 (MFIS-5) was the fatigue metric that was used to assess fatigue level for all patients included in this study. Access to the dataset generated for this study will be provided upon reasonable request from the corresponding author.

Author contributions
D.M.: Formal analysis, Investigation, Writing—Original Draft, Project administration. C.F.: Formal analysis, Investigation, Writing—Original Draft, Project administration. H.S.: Investigation, Data Curation, Writing—Original Draft. M.A.: Methodology, Formal analysis, Data Curation. R.N.: Investigation, Writing—Original Draft. J.C.: Investigation, Writing—Original Draft. R.J.: Investigation, Writing—Original Draft. R.T.: Investigation, Writing—Original Draft. S.A.: Methodology, Writing—Review & Editing, Supervision. S.K.: Writing—Review & Editing, Supervision.

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to S.J.K.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.