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Association of Smoking with Disease Progression in Persons with Multiple Sclerosis Undergoing Autologous Hematopoietic Cell Transplantation: A Single-Center Experience

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ABSTRACT

Background: Smoking remains a significant issue that increases the prevalence of multiple sclerosis (MS) and its progression to secondary progressive forms. **Objectives:** The goal is to identify the relationship between smoking and disease progression in MS patients who have undergone autologous hematopoietic stem cell transplantation (auto-HSCT) at the Centro de Hematología y Medicina Interna, Clínica Ruiz, Puebla, Mexico. **Methods:** This retrospective study involved MS patients treated with auto-HSCT, followed for 12 months. The response to transplantation was measured using the difference in Expanded Disability Status Scale (EDSS) scores before and 12 months after the transplant. A difference of −0.5 or greater indicated a good response, while a difference below 0.5 indicated a poor response. **Results:** The study included 419 patients, with a median age of 47 years (IQR: 40-53). The majority were non-smokers (315) compared to smokers/ex-smokers (104). In patients with PMSS, EDSS stabilization at 12 months was observed in both smokers/ex-smokers (median 6, interquartile range (IQR) = 1 vs. 6, IQR = 1, p = 0.466) and non-smokers (median 6, IQR = 1 vs. 6, IQR = 1.5, p = 0.001), although non-smokers showed a statistically significant difference. **Conclusion:** Smoking may negatively impact MS progression, especially in its progressive forms. (REV INVEST CLIN. 2024;76(5):223-9)

Keywords: Multiple sclerosis. Smoking. Auto-HSCT. Disease progression.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease leading to demyelination and neurodegeneration in the central nervous system (CNS). It primarily affects individuals aged 20-40 and is the leading cause of non-traumatic disability among young adults in the West[1]. The disease's origin is complex and involves environmental factors, particularly in genetically predisposed individuals, which abnormalize immune system activation against CNS components, causing myelin inflammation and neuronal degeneration[2]. Key risk factors include Vitamin D, sun exposure, smoking, herpes virus, obesity, salt intake, intestinal dysbiosis and diet; caffeine, alcohol, consumption of salt[3].

Charcot described MS's clinical manifestations in the mid-19th century, highlighting the disease's heterogeneity through its varying forms and inflammatory mechanisms[1,4,5]. MS is typically classified into three forms: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS).

The Expanded Disability Status Scale (EDSS), developed by John Kurtzke in 1983, is widely used to assess disease progression. It ranges from 0 to 10, with 0.5-unit increments indicating increased disability, based on neurological examination[6]. The EDSS is a reliable tool for monitoring disease progression and guiding clinical interventions, making it the most commonly used disability scale internationally[7].

Smoking, despite a global decline in prevalence, remains a significant health risk and is linked to increased MS prevalence and progression to secondary forms[8-11]. Cigarette smoke acts as a pulmonary irritant, promoting chronic inflammation and potentially triggering autoimmune diseases. Genetic factors also contribute to MS susceptibility. Neurotoxic elements in cigarette smoke can exacerbate disease activity, brain atrophy, and disability in MS patients[12-15]. Therefore, smoking is a critical factor in MS progression, highlighting the need for cessation to improve long-term disease management. This study aims to explore the relationship between smoking and disease progression in MS patients undergoing autologous hematopoietic cell transplantation at the Centro de Hematología y Medicina Interna, Clínica Ruiz, Puebla, Mexico.

METHODS

This retrospective study was based on the MS patient database of patients treated with auto-HSCT at Clínica Ruiz. Patients diagnosed with any of the three MS subtypes (RRMS, PPMS, SPMS), without regard to age, who had an EDSS <8.0, provide a Brain and full spinal magnetic resonance imaging no older than 3 months from scheduled treatment date, had stopped all immunosuppressive or modulation drugs 3 months prior, and could travel to Puebla, Mexico, were accepted for treatment. The EDSS score was measured in all patients by a neurologist from the program's specialist team prior to transplantation. Subset selection was determined by convenience, with data obtained from the follow-up records of patients that provides us their EDSS scores measured by neurologists from their countries at 12 months post-transplantation. Patients with a smoking history before undergoing hematopoietic cell transplantation were included, but the number of cigarettes smoked and the duration of smoking were not considered. All patients included in the study signed a consent form to use their data for research and this work was approved by the internal research ethics committee. Response to transplantation was defined based on the difference between the pre-transplant EDSS score and 12 months post-transplant: a difference ≥0.5 was defined as a good response to transplantation, a difference equal to 0 was defined as a disease stabilization and a difference below −0.5 was defined as a poor response. The total number of patients included in this study was 419 (277 women and 142 men), with a median age of 47 years (interquartile range [IQR]: 40-53). In terms of MS type, 201 patients had RRMS, 130 had SPMS, and 88 had PPMS. Table 1 summarizes the patients' clinical characteristics. The HSCT procedure followed the "Mexican method" (Fig. 1).

The Kolmogorov-Smirnov test was used to evaluate the normality of the data distribution. The parameters of this study did not conform to a normal distribution; therefore, between-group comparisons were analyzed analyze categorical variables, and $p < 0.05$ were considered statistically significant. Statistical analysis was performed using SPSS 25 software (IBM Corp. Published 2017. IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) and GraphPad Prism 9 (GraphPad Prism version 9 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com).

Table 1. Clinical characteristics of 419 patients with an EDSS score, 12 months post-HSCT, and grouped by smoking history

Clinical characteristics	Never-smoker		Smokers /ex-smokers		p
	Count	Median (IQR)	Median (IQR)	Count	
Sex					
F	209			68	0.857[a]
M	106			36	
Age (years)		46 (13)	48 (11.5)		0.27[b]
Weight (kg)		72 (22.4)	72 (21.5)		0.448[b]
Height (m)		1.69 (0.14)	1.7 (0.125)		0.308[b]
BMI		24.4 (6.8)	25.05 (6.5)		0.505[b]
Years of evolution		9 (13)	6 (11.5)		0.335[b]
MS type					
RRMS	155			46	0.25[a]
SPMS	100			30	
PPMS	60			28	
Hemoglobin (g/dL)		14.2 (1.5)	14.2 (1.8)		0.992[b]
White blood cell count ($\times 10^3/\mu L$)		6 (2.2)	6.7 (2.6)		0.1[b]
Platelet count ($\times 10^3/\mu L$)		260 (86)	241 (72)		0.161[b]
EDSS pre-transplant		5.5 (3)	5.5 (3)		0.891[b]
EDSS 12 months after transplant		5.0 (4)	5 (4)		0.639[b]
Origin					
Asia	1			0	
Eastern Europe	2			1	
North America	184			48	
Northern Europe	97			47	
Oceania	8			5	
Southeastern Europe	1			1	
Western Europe	22			2	

[a]Chi-squared.
[b]Mann-Whitney U test.
EDSS: Expanded Disability Status Scale, HSCT: hematopoietic stem cell transplantation, IQR: interquartile range, MS: multiple sclerosis, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis, PPMS: primary progressive multiple sclerosis, BMI: body mass index.

RESULTS

Analysis of the main characteristics of the study groups showed that there were a greater number of patients in the group with a non-smoking history (315 vs. 104). When analyzing whether smoking is related to gender, we found that the total number of patients with no history of smoking, 209 patients (60%) were women; this relationship was maintained in the group with a history of smoking (65% were women). However, the Chi-square test results showed no statistically significant differences.

The number of years of evolution in the group with a history of smoking was greater (median 9 vs. 6), but the difference was not statistically significant.

The most prevalent type of MS was RRMS. The percentage of patients with a history of smoking by MS type was 20% for RRMS, 23% for PPMS, and 31% for

Figure 1. Schematic representation of the Mexican conditioning regimen employed for autografting persons with autoimmune disorders.

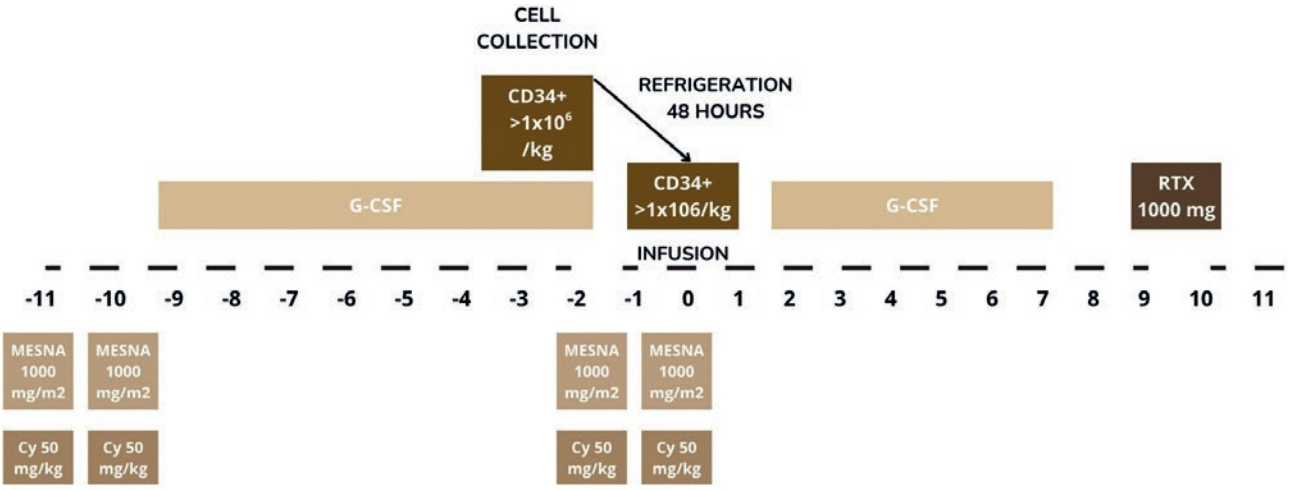
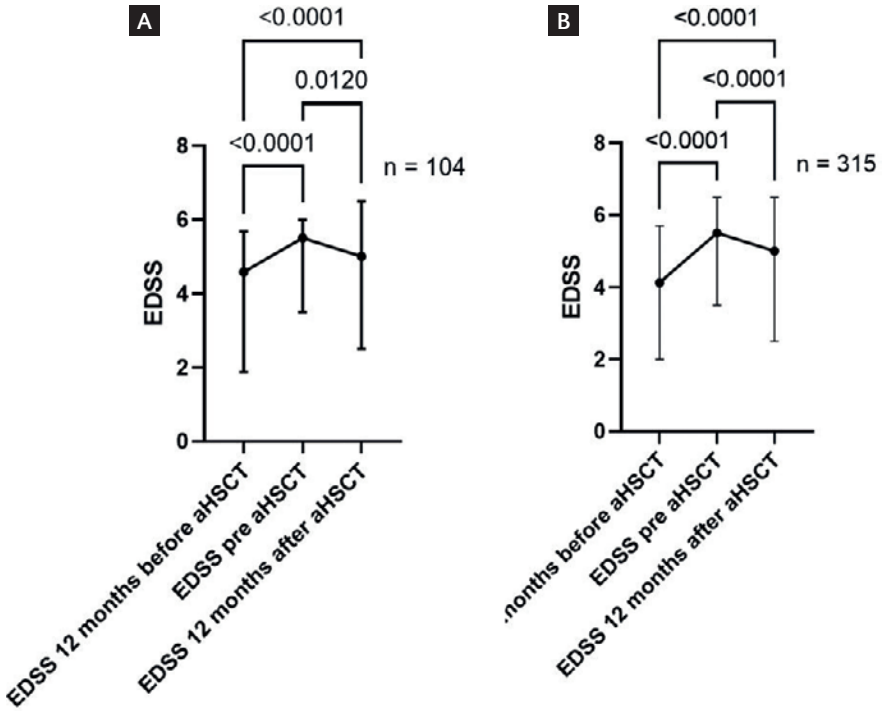


Figure 2. **A:** multiple sclerosis progression in patients treated with hematopoietic stem cell transplantation 12 months before and after hematopoietic stem cell transplantation measured using the Expanded Disability Status Scale scale in patients who were smokers or former smokers. **B:** multiple sclerosis progression in patients treated with hematopoietic stem cell transplantation 12 months before and after hematopoietic stem cell transplantation, assessed using the Expanded Disability Status Scale scale in never-smoking patients.



PPMS. According to the Chi-square test, there was no association between the type of MS and smoking.

No statistically significant differences were found in terms of age, weight, height, body mass index, hemoglobin level, leukocyte count, or platelet count.

When analyzing the response to transplantation and evaluating the change in the EDSS score before and 12 months after transplantation, a decrease in the EDSS score was observed in both study groups (Fig. 2). The EDSS score decreased or stabilized in 74% of the entire cohort, and by MS type, 155 (77%)

patients had RRMS, 96 (74%) had SPMS, and 60 (73%) had PPMS.

The response to transplantation by type of MS did not show a statistically significant difference. Similarly, there were no EDSS score differences at 12 months post-transplantation in the PPMS group when compared with the pre-transplant scores (median 6, IQR = 3 vs. 6 IQR = 2, p = 0.270).

When evaluating the response to transplantation by MS type (Fig. 3) we found a numerical difference in the response of patients with PPMS. In the group of patients with no smoking history, the pre-transplant EDSS score was 6, which remained at 12 months after transplantation. In the group with a history of smoking, the score at 12 month increased (6-6.25). In the group of patients with SPMS, stabilization of the EDSS score at 12 months was observed in the group of smokers and ex-smokers (Median 6, IQR = 1 vs. 6 IQR = 1, p = 0.466), as well as in the group of never smokers (median 6, IQR = 1 vs. 6 IQR = 1.5, p = 0.001).

The relationship between the response to transplantation and smoking was explored, and per the Chi-squared results, no significant relationship was detected in the entire cohort. The same analysis according to the type of MS showed that in patients with PPMS, there was a relationship between the presence of a smoking habit and the response to transplantation.

DISCUSSION

In this study, we analyzed the relationship between smoking history and auto-HSCT response in patients with MS. The results showed that all patients with MS who underwent auto-HSCT had favorable results, reflected in a decrease or stabilization in disease progression, as assessed by the EDSS score. Regardless of the study group evaluated, both groups (smokers and never-smokers) responded favorably 12 months after transplant. In both groups, the median EDSS score at 12 months was significantly lower than the pre-transplant EDSS score. This indicates that in our cohort, auto-HSCT effectively slowed the progression of MS, regardless of patients' smoking history.

In an MS animal model, an exploratory study by Enzmann et al.[16] established that cigarette smoke exposure affects the course of actively induced experimental autoimmune encephalitis differently (EAE) in various strains of mice[16]. Furthermore, different studies have reported that the application of nicotine in an EAE animal model significantly improves symptoms, suggesting that nicotine has a protective effect in an animal model of MS[17,18]. However, it is important to consider the genetic background that influences the effect of cigarette smoke on neuroinflammation of autoimmune origin. Briggs (2021) analyzed whether gene variations in the genes encoding the α7 and α9 nAChR (alpha nicotinic alpha 7 [CHRNA7] cholinergic receptor and alpha 9 [CHRNA9]) modify the risk of MS attributed to smoking. Their results suggest that CHRNA7 and CHRNA9 variants modify the risk of MS conferred by tobacco smoke, whereby the risk among smokers was increased in carriers of the CHRNA9 minor haplotype and in non-carriers of the CHRNA7 minor haplotype[19].

When analyzing the data according to the type of MS, the results were interesting. In both RRMS study groups, there was a statistically significant decrease in the EDSS score at 12 months after transplantation. In patients with PPMS, the EDSS score stabilized at 12 months when compared with the pre-transplant EDSS score in both smoking and non-smoking patients, suggesting stabilization in disease progression as a result of auto-HSCT. However, in non-smoking patients, the EDSS score pre-transplant and at 12 months post-transplant remained stable, whereas in smoking patients, the EDSS score increased at 12 months. According to the Chi-squared results, there was a relationship between PPMS and smoking history.

Although there is no statistically significant difference, this finding suggests that in non-smoking patients with PPMS, transplantation proves to be more effective in curbing disease progression than in patients with a history of smoking, and according to the EDSS scores, MS progression appears to continue. It's crucial to consider that these results might be constrained by the duration of the study or the size of the sample.

CONCLUSION

The results of this study suggest that smoking could be a factor that negatively influences MS progression,

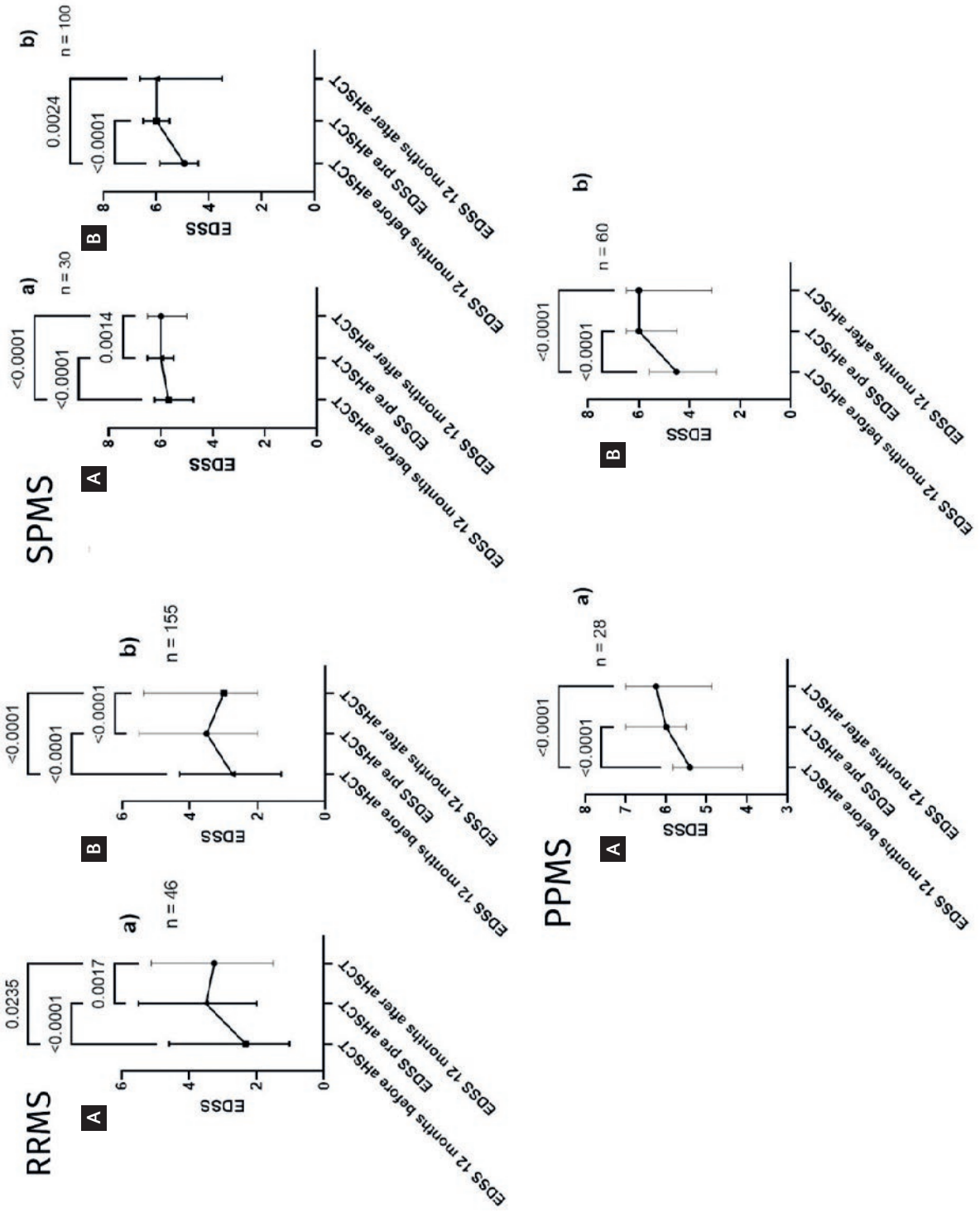


Figure 3. Multiple sclerosis progression in relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis, and primary progressive multiple sclerosis patients treated with hematopoietic stem cell transplantation, 12 months before and after hematopoietic stem cell transplantation, assessed using the Expanded Disability Status Scale in **A:** smoker or ex-smoker patients, and **B:** never-smoker patients.

particularly in individuals with progressive forms of MS. Smoking should be considered an important antecedent when selecting auto-HSCT candidates. Further studies on the association between smoking and response to auto-HSCT in the setting of MS are required.

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