

**Research Article**
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# Effect of COVID-19 Lockdown on Patients with Multiple Sclerosis: an Italian Survey

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### ABSTRACT

**Background:** Italy was one of the first affected countries by coronavirus disease 2019 (COVID-19) pandemic. Public health measures like quarantine or national lockdown were adopted, with negative psychological and clinical effects on patients with chronic diseases. To investigate the impact of lockdown on patients with multiple sclerosis (MS), we developed a 36 items self-report questionnaire.

**Methods:** Questionnaires were emailed to 120 patients with MS and 100 with chronic migraine (CM) as a control group, matched for age, sex, and education. The questionnaire was divided into five domains, evaluating concerns about 1) MS and therapy during COVID-19 pandemic, 2) personal and family caregiving, 3) working activities, 4) general and disease-related emotions during the lockdown, 5) future expectations concerning health status, social life, and working activity.

**Results:** patients with MS had higher scores than those with CM in domains 4 and 5, investigating respectively general and disease-related emotions and future expectations ( $p=0.05$  and  $0.02$  respectively). About half of the patients with MS expressed some concern about the need to continue their therapy during the pandemic compared to people with CM ( $p=0.0002$ ).

**Conclusions:** Covid-19 pandemic had a more negative impact on psychological status of patients with MS compared with those with CM.

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**Received:** May 18, 2021; **Accepted:** May 26, 2021; **Published:** May 31, 2021

**Keywords:** COVID-19 Pandemic, Multiple Sclerosis, Emotions, Disease-Modifying Therapy

### Introduction

Due to the COVID-19 pandemic infection, on March 2020 Italy entered a lockdown that lasted until the summer.

During that period, all non-essential elective medical and surgical procedures were stopped. Consequently, patients with multiple sclerosis (MS) discontinued their outpatient activities such as neurological consultations, physiotherapy, occupational therapy, and radiological follow-ups. Also, patients with MS had to face alone a number of difficulties such as shopping, looking after loved ones, going to work, organize remote teaching for their children. Neurologists had to weigh up the need to start or continue disease-modifying treatments against the risk of infection and MS activity. Being an unprecedented situation, most decisions were made based on a theoretical approach.

As a consequence, a moderate to severe psychological impact of the outbreak has been reported. Being a female, a student, or

having specific physical symptoms (including coughs, myalgia, chills, and poor self-rated health status) were factors associated with the pandemic's psychological impact, anxiety, and depression [1]. Patients with MS were found to be specifically vulnerable to the neuropsychiatric impacts of the COVID-19 pandemic. Besides, people with MS are known to undertake maladaptive coping strategies, which will make them even more susceptible to the detrimental neuropsychiatric effects of the outbreak [2]. To investigate quarantine's impact due to the COVID-19 pandemic on patients with MS, we developed a 36 items self-report questionnaire divided into five domains.

### Materials and Methods

From March 15 to May 4 2020, 120 questionnaires were emailed to the patients with MS most recently visited at the MS Center of the Policlinico Umberto I, Sapienza University of Rome. As a control group, the same questionnaire was emailed to 100 patients with chronic migraine (CM) visited at the same hospital's headache center, matched for age, sex, and education. We chose patients with CM as it is a very disabling neurologic condition. In terms of associated disability expressed with "years lived with disability,"

Migraine ranked first in the subgroup of people under the age of 50, the age group deeply involved in family and work duties. In addition, among people with frequent migraine, the chronic form causes the highest degree of disability and costs, both direct and indirect [3, 4].

Patients diagnosed with psychiatric comorbidity or taking antidepressants (i.e., amitriptyline as prophylactic medication for migraine or SSRI for fatigue) were excluded.

The questionnaire consisted of 36-items self-reported, divided into five domains. Each item was scored on a Likert scale ranging from 0-4: 0= never, 1= rarely, 2= sometimes, 3= often, 4= almost always. In the first domain, we evaluated any concerns about MS and therapy in relation to the COVID-19 pandemic (score 0-28); in the second, we asked about personal and family caregiving (score 0-16); in the third, we investigated working activities (score 0-16); in the fourth, we evaluated general (4G score 0-32) and disease-related (4 DR, score 0-32) emotions during the lockdown; in the fifth, we assessed future expectations concerning health status, social life, and working activity (score 0-20). We evaluated both the total score (0-144) and the impact on patients of each domain (none, mild, and high impact) using cut-off values (table 1). For each dimension the cut-offs were calculated on the basis of the scores obtained for the individual answers. In particular, three levels have been identified:

**Table 1: NeuroCOVID-19 test**

0	1	2	3	4
Never	Rarely	Sometimes	Often	Almost always

0-1: low frequency

2-4: medium-high frequency

<b>Domain 1: concerns about MS in relation to COVID 19, score 0-28 ,cut-off no impact <math>\leq 7</math> , cut-off mild impact <math>8 \leq x \leq 14</math>, cut-off high impact <math>15 \leq x \leq 28</math></b>
How many times did you think that your disease could predispose you to SARS-COV-2 infection?
How many times did you think that a worsening of your disease in this period could be more probable?
How many times have you felt worried about the management of a possible worsening of your disease (for example: can I go for a check-up visit?)
How many times did you think that drug therapy for your disease could increase the risk of being infected with the virus?
How many times have you thought about stopping drug therapy fearing that it could increase the risk of infection?
Did the management of your disease change during this period (e.g. going for outpatient visits, do blood tests, physiotherapy)?
Did you have any difficulty in finding the drugs you usually use for the treatment of your disease (for example: going to the pharmacy or to the attending physician; problems related to prescriptions and / or therapeutic plans)?
<b>Domain 2: family and personal caregiving, score 0-16, cut-off no impact <math>\leq 4</math> , cut-off mild impact <math>5 \leq x \leq 8</math>, cut-off high impact <math>9 \leq x \leq 16</math></b>
Did you have difficulties in being assisted by your family members/caregiver (e.g., due to the restrictions imposed by the government, they could not come home often)?
Did you have more difficulties than usual in taking care of family members (for example, I couldn't use babysitting help, or I couldn't grocery shop for my parents, etc.)?
Did you have more difficulties than usual in obtaining basic necessities as a result of the restrictions decided by the government (e.g., I gave up in-store shopping because of the long waiting times and my difficulty in standing for a long time)?
Did you have more difficulties than usual in managing your daily activities (e.g., housework)?
<b>Domain 3: working activity, score 0-16, cut-off no impact <math>\leq 4</math> , cut-off mild impact <math>5 \leq x \leq 8</math>, cut-off high impact <math>9 \leq x \leq 16</math></b>
Have you been given the opportunity to work from home or in "smart-working" mode or study and follow lessons from home?
Do you think that the "smart-working" mode / remote study can represent an advantage for you even when the COVID-19 emergency has returned?
Did the emergency create more problems in your work management (e.g., forced you to use days of annual leave because your company doesn't apply the "smart-working" mode, reduction of the hours of the public transportations, no company shuttle?)
<b>Domain 4: general emotions and disease-related emotions, score 0-32, cut-off no impact <math>\leq 8</math>, cut-off mild impact <math>9 \leq x \leq 16</math>, cut-off high impact <math>17 \leq x \leq 32</math>,</b>
In relation to the COVID-19 emergency period
How many times have you felt worried?
How many times have you felt anxious?
How many times have you felt angry?
How many times have you felt irritated?
How many times have you felt useless?

How many times have you felt scared?
How many times have you felt sad?
How many times have you felt frustrated?
In relation to the migraine
How many times have you felt worried?
How many times have you felt anxious?
How many times have you felt angry?
How many times have you felt irritated?
How many times have you felt useless?
How many times have you felt scared?
How many times have you felt sad?
How many times have you felt frustrated?
<b>Domain 5: future, score 0-20, cut-off no impact <math>\leq 5</math>, cut-off mild impact <math>6 \leq x \leq 10</math>, cut-off high impact <math>11 \leq x \leq 20</math></b>
Are you currently worried about your working condition/study (e.g., I'm afraid of losing it / I'm afraid of being left behind with exams)?
Did you have negative thoughts and emotions (mistrust, fear, distress, anger) about the economic consequences of this period?
Did you have / still have negative thoughts and emotions (distrust, fear, distress, anger) about the social consequences of this period?
Did you have / still have negative thoughts and emotions (distrust, fear, distress, anger) about the management of your disease following this period?
Did you have negative thoughts and emotions (mistrust, fear, distress, anger) about the consequences related to social relationships following this period of isolation (e.g., hugging, shaking hands, going to the cinema, going out with friends, start a relationship)?
<b>Total score: 0-144, cut-off no impact <math>\leq 36</math>, cut-off mild impact <math>37 \leq x \leq 74</math>, cut-off high impact <math>75 \leq x \leq 144</math></b>

-**No impact:** given by the sum of the maximum number of answers never/rarely with a score of 0/1.

-**Medium impact:** given by the sum of the maximum number of answers sometimes with a score of 2.

-**High impact:** given by the sum of the maximum number of answers often/always with a score of 3/4.

Taking the first dimension (disease management) as an example: it consists of 7 questions for which the maximum score of the “no impact” level is given by multiplying the number of questions by the maximum value attributed to the answers never/rarely:  $7 \times 1 = 7$ . All scores between 0 and 7 for this dimension will fall into the “non-impact” category.

Similarly, the “medium impact” level is given by multiplying the number of questions by the maximum of the value attributed to the answers “sometimes”:  $7 \times 2 = 14$ . All scores between 8 and 14 for this dimension will fall into the “medium impact” category; finally, the “high impact” level is given by multiplying the number of questions by the maximum of the value attributed to the “often/always” answers:  $7 \times 4 = 28$ . All scores between 15 and 28 for this dimension will fall into the “high impact” category.

The same questionnaire applied in patients with CM had already been published elsewhere [5].

The questionnaire was completed voluntarily, all patients gave their written informed consent, and all subjects’ privacy rights were observed. The work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by our local ethical committee.

### Statistical Analysis

All statistical analyses were performed using the software SPSS, v 25.0 (IBM Co., Armonk, NY). Data were analyzed for normality of distribution using the Kolmogorov-Smirnov test and were expressed as mean ( $\pm$  standard deviation (SD)) for continuous variables or as frequencies (n, %) for categorical variables. Group comparisons (MS vs. CM) were performed using the Fisher test or  $\chi^2$  test when appropriate for categorical variables. Any 2-sided  $P < .05$  was considered statistically significant.

### Results

Out of 120 questionnaires emailed to patients with MS, 104 replied (87%) (68 F, mean age 45 years,  $\pm 12$ , education 15 years  $\pm 3$ ). Conversely, out of the 100 sent to people with CM, only 68 answered (45 F, age years 46,  $\pm 13$  years, education 14  $\pm 4$  years). In the total sample (172 patients) 85 were employed as clerks, 38 were white-collar workers, 44 were unemployed or homemaker, and 5 were students; 83 were married, 69 were unmarried, and 20 were divorced or widowed (Table 2).

Twenty-two patients spent the lockdown alone, 40 with another person, and 110 with two or more people. We found no differences between people with MS and CM concerning demographic and general variables (education, marital status, employment, and the number of cohabitants).

Among patients with MS, 71 had a relapsing-remitting 20 a secondary progressive, and 13 a primary progressive form of MS. Mean EDSS was  $2.0 \pm 1.5$  (table 2).

**Table 2: Demographic and clinical characteristics of patients with MS and CM**

	MS (#104)	CM (#68)	P<0.05
Age (mean, SD)	45 ± 12	46 ± 13	NS
Sex F, %	68 (65.3)	45 (66)	NS
Education (mean, SD)	15 ± 3	14 ± 4	NS
Marital status, %			
Married	46 (44.2)	37 (54)	
Divorced or separated	10 (9.6)	10 (14.7)	
Single	48 (46.2)	21 (30.8)	
Cohabitants # (%)			NS
1	27 (26)	13 (19.1)	
>1	63 (60.5)	47 (69)	
none	14 (13.4)	8 (11.7)	
Employment # (%)			NS
Clerk	56 (53.8)	29 (42.6)	
White-collar	21 (20)	17 (25)	
Unemployed/homemaker	24 (23)	20 (29.4)	
student	3 (2.8)	2 (2.9)	
MS clinical features			
EDSS (mean, SD)	2 ± 1.5		
EDSS >2.5 (%)	29 (27.8)		
Type of MS, %			
RR	71 (68.2)		
SP	20 (19.2)		
PP	13 (12.5)		
DMTs, %			
Interferons	10 (9.6)		
Glatiramer acetate	6 (5.7)		
Dimethyl fumarate	19 (18.2)		
Teriflunomide	18 (17.3)		
Fingolimod	16 (15.3)		
Natalizumab	14 (13.4)		
Ocrelizumab	14 (13.4)		
Alemtuzumab	2 (1.9)		
Cladribine	5 (4.8)		
First-line therapy	53 (51)		
CM drugs, %			
Topiramate		12 (17.64)	
Erenumab		5 (7.35)	
Fremanezumab		10 (14.7)	
Flunarizine		7 (10.3)	
Atenolol		15 (22)	
Botulinum toxin		4 (5.9)	
Valproate		15 (22)	

Considering the degree of impact for each domain, the highest frequencies of “high-impact” scores were detected in domains 4 and 5, investigating respectively general and disease-related emotions and future expectations. In particular, about 37% and 45% of patients with MS manifested problems in the emotional sphere. They were worried about future health status, social life, and working activities compared to patients with CM ( $p=0.05$  and  $0.02$ , respectively). About half of the people with MS expressed some concerns about MS and therapy in relation to the COVID-19 pandemic ( $p=0.0002$ , see table 3). The frequency of response and the degree of impact for each area in people with MS and CM is showed in figure 1.

**Table 3: Frequencies of the impact of each domain in patients with MS and CM (level of significance p<0.05).**

	MS (#104)	CM (#68)	P<0.05
<b>Domain 1</b>			0.0002
No impact	44 (42.3)	50 (73.5)	
Mild impact	42 (40.38)	14 (20.5)	
High impact	18 (17.3)	4 (5.8)	
<b>Domain 2</b>			NS
No impact	67 (64.4)	51 (75)	
Mild impact	29 (27.8)	12 (17.64)	
High impact	8 (7.7)	5 (7.35)	
<b>Domain 3</b>			NS
No impact	67 (64.4)	37 (54.4)	
Mild impact	20 (19.2)	21(30.8)	
High impact	16 (15.38)	10 (14.7)	
<b>Domain 4 G</b>			0.05
No impact	38 (36.5)	18 (26.4)	
Mild impact	36 (34.6)	18 (26.4)	
High impact	30 (28.84)	32 (47)	
<b>Domain 4 DR</b>			NS
No impact	49 (47.1)	22 (28.2)	
Mild impact	31 (29.8)	25 (22.2)	
High impact	23 (22.1)	21 (17.5)	
<b>Domain 5</b>			0.02
No impact	26 (25)	9 (13.2)	
Mild impact	42 (40.38)	22 (32.3)	
High impact	36 (34.6)	37 (54.4)	

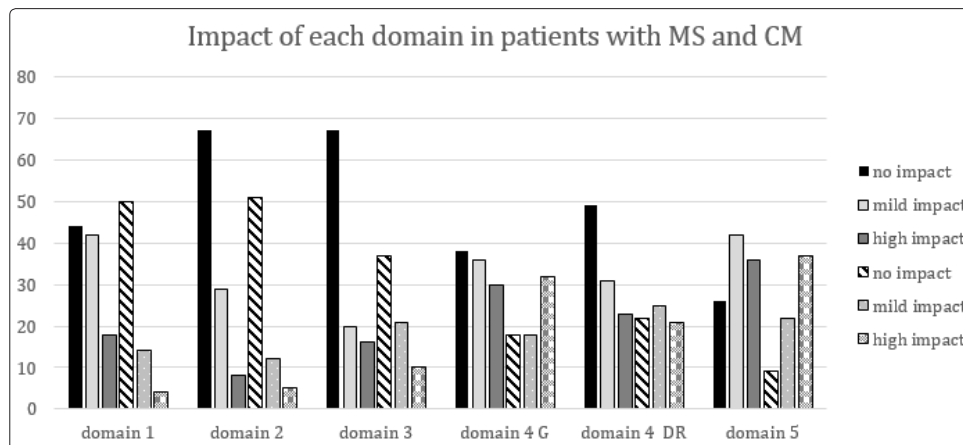
**Domain 1:** Concerns about MS and drug therapy.

**Domain 2:** Concerns about family and personal caregiving.

**Domain 3:** Concerns about the working activity.

**Domain 4:** G and DR: Both general and disease-related emotions during the lockdown.

**Domain 5:** Future expectations concerning health status, social life, and working activity.



**Figure 1:** Frequency of response and the degree of impact for each area in patients with MS (in bold) and CM (light shades).

**Domain 1:** Concerns about MS and drug therapy

**Domain 2:** Concerns about family and personal caregiving

**Domain 3:** Concerns about the working activity

**Domain 4:** G and DR: Both general and disease-related emotions during the lockdown

**Domain 5:** Future expectations concerning health status, social life, and working activity



## Discussion

In this study, we developed a self-report questionnaire to evaluate the clinical and emotional impact of lockdown on people with MS. At the beginning of the pandemic, neurologists were confronted with how to advise their patients regarding immunosuppressive treatment. National professional bodies (e.g., Italian Society of Neurology and Association of British Neurologists) and patient organizations have responded by issuing guidelines for the COVID-19 pandemic, primarily focused on MS disease-modifying therapies (DMTs) [6-8]. The MS International Federation published global advice to the MS community addressing measures to reduce infection risk and general implications related to DMTs use [7]. The National MS Society endorsed the MS International Federation global advice and published broad DMT guidelines on its COVID-19 web page [8].

Our questionnaire was sent in February 2020 when Europe was at the beginning of the pandemic, and many uncertainties existed concerning DMTs exposure. People were scared (still they are), and the media gave (and give) conflicting information. In this scenario, it is not surprising that about half of the people with MS expressed some concerns about MS and therapy during the COVID-19 pandemic. A recent multicenter observational study describing the clinical characteristics and outcomes in patients with MS and COVID-19 found that age, EDSS, and obesity were independent risk factors for severe COVID-19; no association was evident between DMTs exposure and COVID-19 severity [9]. These data are in line with other recent reports, but, in the beginning, we were not aware of it [10]. An Australian survey, evaluating the perspective of people with MS on their DMT about the COVID-19 pandemic, found that a large proportion of patients had some concern regarding the impact of their DMT on COVID-19, whether the overall level of concern on their risk of contracting COVID-19 or on a theoretical risk for more severe disease in most cases was at most mild [11].

Patients appeared to be concerned about the emotional side of the pandemic also. About 30% of patients with MS stated that quarantine has a strong impact on general and disease-related emotions, and about 40% were worried about the future. People with chronic migraines also complained of emotional distress but to a lesser extent.

Many studies reported negative psychological effects during quarantine, including post-traumatic stress symptoms, confusion, and anger [2]. Stressors included longer quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma [2]. Therefore, quarantine's potential benefits need to be weighed against the possible psychological costs [12-14].

Our patients had no psychiatric comorbidity, but they still showed anxiety and concern about the pandemic and future expectations. In a recent study, patients with MS were more anxious, stressed, and depressed during the COVID-19 pandemic than their caregivers and people without MS [15]. Given that our patients were not assessed for psychiatric symptoms with the formal psychometric test, adjustments for level of anxiety and depression were not performed. Therefore, we can only identify the presence of symptoms suggestive of emotional distress. Moreover, since we excluded individuals with pre-existing psychiatric difficulties, our results may underestimate the psychological impact of the pandemic on the MS population, given that those already suffering from depression/anxiety are likely more vulnerable to additional pandemic-related distress.

Very few patients with MS and CM were worried about personal and family caregiving and work activities. It is possible that the prolongation of the pandemic, and the consequent quarantine, could lead to greater repercussions also on these two aspects. There is evidence that the effect on the psychological and everyday life of quarantine can still be detected months or years later, suggesting the need to carry out effective mitigation measures as part of the quarantine planning process [16]. In this regard, we have planned a longer follow-up of these patients to evaluate any new problems arising after the end of the lockdown.

In conclusion, the lockdown's emotional impact has been particularly meaningful in patients with MS, even higher than that observed in patients with other chronic diseases, such as CM.

## Author Contributions

Conceptualization: Dr Altieri and Dr Fratino, methodology: Dr Fratino, formal analysis: Dr Altieri, investigations: Dr Altieri, Pauri, Conte, Frontoni, Dr Merluzzo and Dr Criusafulli, writing—original draft preparation: Dr Altieri, writing—review and editing: Dr Altieri, Conte, Di Piero.

All authors have read and agreed to the published version of the manuscript.

**Funding:** this research received no external funding

**Declarations of Interest:** none

**Acknowledgements:** Editorial assistance was provided by Francesca Cappellini

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