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Risk of Getting COVID-19 in People With Multiple Sclerosis

A Case-Control Study

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Abstract

Background and Objectives

Several studies have assessed risk factors associated with the severity of COVID-19 outcomes in people with multiple sclerosis (PwMS). The potential role of disease-modifying therapies (DMTs) and demographic and clinical factors on the risk of acquiring SARS-CoV-2 infection has not been evaluated so far. The objective of this study was to assess risk factors of contracting SARS-CoV-2 infection in PwMS by using data collected in the Italian MS Register (IMSR).

Methods

A case-control (1:2) study was set up. Cases included PwMS with a confirmed diagnosis of COVID-19, and controls included PwMS without a confirmed diagnosis of COVID-19. Both groups were propensity score–matched by the date of COVID-19 diagnosis, the date of last visit, and the region of residence. No healthy controls were included in this study. COVID-19 risk was estimated by multivariable logistic regression models including demographic and clinical covariates. The impact of DMTs was assessed in 3 independent logistic regression models including one of the following covariates: last administered DMT, previous DMT sequences, or the place where the last treatment was administered.

Results

A total of 779 PwMS with confirmed COVID-19 (cases) were matched to 1,558 PwMS without COVID-19 (controls). In all 3 models, comorbidities, female sex, and a younger age were significantly associated ($p < 0.02$) with a higher risk of contracting COVID-19. Patients receiving natalizumab as last DMT (OR [95% CI]: 2.38 [1.66–3.42], $p < 0.0001$) and those who underwent an escalation treatment

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Italian MS Register coinvestigators are listed in Appendix 2.

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Glossary

DMT = disease-modifying therapy; **EC** = ethical committee; **EDSS** = Expanded Disability Status Scale; **IMSR** = Italian MS Register; **IQR** = interquartile range; **MedDRA** = Medical Dictionary for Regulatory Activities; **MoA** = mechanisms of action; **MS** = multiple sclerosis; **PS** = propensity score; **PwMS** = people with multiple sclerosis.

strategy (1.57 [1.16–2.13], $p = 0.003$) were at significantly higher COVID-19 risk. Moreover, PwMS receiving their last DMT requiring hospital access (1.65 [1.34–2.04], $p < 0.0001$) showed a significant higher risk than those taking self-administered DMTs at home.

Discussion

This case-control study embedded in the IMSR showed that PwMS at higher COVID-19 risk are younger, more frequently female individuals, and with comorbidities. Long-lasting escalation approach and last therapies that expose patients to the hospital environment seem to significantly increase the risk of SARS-CoV2 infection in PwMS.

Classification of Evidence

This study provides Class III evidence that among patients with MS, younger age, being female individuals, having more comorbidities, receiving natalizumab, undergoing an escalating treatment strategy, or receiving treatment at a hospital were associated with being infected with COVID-19. Among patients with MS who were infected with COVID-19, a severe course was associated with increasing age and having a progressive form of MS, whereas not being on treatment or receiving an interferon beta agent was protective.

In 2019, a new coronavirus—the SARS-CoV-2 responsible for COVID-19—appeared and quickly became pandemic.[1] As the number of COVID-19 cases increased over time, many questions have arisen about the risk of COVID-19 for individuals with autoimmune disease and the management of patients who need immunotherapies.[2] Up to 70% of people with multiple sclerosis (PwMS) are treated with disease-modifying therapies (DMTs) that affect the immune response; in turn, these therapeutic agents may expose the patient to increased risk of developing COVID-19 and experiencing worse COVID-19 outcomes[3] than individuals not receiving these agents. Several national and international initiatives have been set up to rapidly collect data about potential risk factors associated with the severity of COVID-19 in PwMS.[4-6] Most studies have consistently demonstrated male sex, an older age, the presence of comorbidities, and higher disability as risk factors for a more severe disease course.[4-9] The potential critical role of MS immunotherapies in the COVID-19 severity has also been investigated with conflicting results. Several studies showed an increased risk of a severe course for PwMS with a recent use of methylprednisolone[4-7] and a last therapy with depletive anti-CD20 drugs[4,6,7]; others did not find any association between DMT exposure and COVID-19 severity,[5,8,9] whereas some researchers reported a protective role of interferon beta agents.[4,5,7]

Therefore, recommendations have emerged regarding the management of DMT exposure based on respective mechanisms of action (MoA).[10] However, such an approach must be carefully evaluated to balance the temptation to stop or delay specific DMTs to reduce the risk of severe COVID-19 outcomes and the potential impact on MS reactivation and disability progression that such a treatment choice could imply.[11,12] Choice of treatment strategy, in general and particularly during the COVID-19 pandemic, should take into account differences in MoA and duration of the immunologic effects of each therapy, which can vary and may be short-lasting or persist for some years.[13] The cumulative effect of DMT sequencing on the immune system must also be carefully evaluated.[14]

So far, factors increasing the risk of acquiring SARS-CoV-2 infection in PwMS have not been evaluated. MS registers, however, offer a unique tool for the provision of denominators for answering this question and afford the possibility of analyzing data regarding the complete MS history in patients with and without SARS-CoV-2 infection, including information on DMT exposure duration and treatment sequencing.

In this article, using data collected from the Italian MS Register (IMSR), we conducted, for the first time, a case-control study aimed at investigating factors associated with the risk of getting COVID-19. We focused not only on the role of the last administered therapy but also on the potential cumulative effect of previous DMT sequences and on the location where the last treatment was administered (i.e., hospital-based or home-based treatment). As a secondary objective, we further assessed the risk factors associated with the severity of COVID-19 outcomes.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was conducted using longitudinal, prospectively acquired clinical data extracted from the IMSR.[15] The IMSR

was approved by the ethical committee (EC) of the Azienda Ospedaliero-Universitaria – Policlinico of Bari (Study REGISTRO SM001, approved on August 7, 2016) and the local EC of all participating centers. All patients signed informed consent allowing the use of demographical and clinical data for research purposes.

Data Extraction

In 2020, health-care professionals who contributed data to the IMSR were asked to report all MS cases with laboratory confirmed (i.e., using PCR or serology test) diagnosis of COVID-19 using the adverse event module of the IMSR web-based data collection tool. This module enables the collection of the following information: COVID-19 diagnosis according to the Medical Dictionary for Regulatory Activities (MedDRA),[16] date of event, severity of the infection (mild, moderate, severe, or critical), and date of resolution (with or without sequelae) or date of death. To prevent patients with suspected COVID-19 from being included among the controls, we excluded the patients for whom the adverse event module included a MedDRA code for suspected COVID-19 without a confirmation of the diagnosis by PCR or a positive result for serologic anti–SARS-CoV2 test from the data set.

The decision regarding what level of COVID-19 severity to assign was left to the neurologist's judgment. Patients who had an asymptomatic course or only mild general symptoms were classified as mild; patients who presented with more prominent general symptoms, with possible need for oxygen supplementation, but who did not require hospitalization were defined as moderate; and finally, patients who required hospitalization and/or who eventually died of Covid-19 were defined as severe/critical cases. By the end of December 2020, when anti–COVID-19 vaccines were made available in Italy, the collection of information regarding vaccination status (date, type, and number of doses) was also collected in the IMSR.

Comorbidities, codified according to *International Classification of Diseases-9* codes, were extracted from the data set of the IMSR. Comorbidities included the following: allergy, autoimmune diseases, cardiovascular diseases, epilepsy, headache, tumors, psychiatric disorders, thyroid dysfunctions, and others.

In Italy, all IV immunotherapies are administered at hospital infusion centers in accredited MS centers.

Study Design

To evaluate the demographic and clinical factors associated with the risk of COVID-19 in PwMS, a case-control study (1:2) was established. Cases were defined as PwMS with confirmed COVID-19, as reported in the adverse event module of the IMSR web-based application. Controls were selected from the IMSR data set from PwMS without a diagnosis of COVID-19 using propensity score (PS) matching based on the date of the last visit and locality. Patients who received the anti–COVID-19 vaccination and who had not experienced COVID-19 infection before vaccination were excluded from the analysis, thus avoiding the possibility of being selected as controls.

Statistical Analysis

Between-group comparisons were performed by using the Student test, Mann-Whitney test, Kruskal-Wallis test, or χ^2 test, as appropriate. Controls were identified using a logistic regression model including COVID-19 diagnosis date/date of last visit and region of residence as covariates to predict the probability (PS) of developing COVID-19. An 8-to-1 greedy matching algorithm was used to identify 2 matched controls for each positive case according to the PS. Adequacy of balance for the covariates in the matched sample was assessed using standardized mean difference between the 2 groups, considering differences of less than 10% as good balance, and graphical methods.[17-19]

Multivariable logistic regression models were used to assess the association between risk factors and COVID-19 occurrence. The following covariates were included in the models: sex (male vs female individuals), age, disease duration (≤10, 11–20, >20 years), course of disease (progressive vs relapsing), presence of one or more of the following comorbidities: allergy, autoimmune diseases, cardiovascular diseases, epilepsy, headache, tumors, psychiatric disorders, thyroid dysfunctions and others (yes/no), Expanded Disability Status Scale (EDSS) score at the last visit, and relapses in the previous year (yes/no). The impact of DMT exposure was assessed in 3 independent logistic regression models in which one of the following, mutually exclusive, covariates was added: (1) last administered DMT, (2) type of previous DMT sequences administered from disease onset (only moderate efficacy DMT, only high efficacy DMT, and moderate efficacy DMT, followed by high efficacy DMT) or (3) the place where the last treatment was administered (hospital-based or home-based treatment).

Specifically, high efficacy DMT included natalizumab, fingolimod, cyclophosphamide, mitoxantrone, cladribine, alemtuzumab, methotrexate, rituximab, and/or ocrelizumab; moderate efficacy DMTs included interferon beta products, glatiramer acetate, teriflunomide, dimethyl fumarate, and/or azathioprine; treatments administered at hospital included natalizumab, cyclophosphamide, mitoxantrone, alemtuzumab, rituximab, or ocrelizumab; treatments self-administered at home included fingolimod, cladribine, methotrexate, interferon beta products, glatiramer acetate, teriflunomide, dimethyl fumarate, or azathioprine.

To ensure that results were sufficiently robust, only treatments that were started at least 30 days before COVID-19 diagnosis were included to account for intermittently dosed DMTs and to prevent assigning risk to a DMT started only a few days before COVID-19 diagnosis. For the secondary objective of our study, which was the identification of risk factors associated with a severe course of COVID-19, a Poisson regression model with correction for overdispersion

was built using the same covariates included in the case-control analysis. A 2-sided p value of < 0.05 was deemed significant. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC) and R, version 3.2.0.

Data Availability

The data analyzed in this study are the property of the individual contributing centers. They can be made available on reasonable request for the purpose of replication of the analyses included in this study and at the discretion of the principal investigators.

Results

Risk Factors for Acquiring COVID-19 in PwMS

As of March 31, 2021, data from 779 PwMS with confirmed COVID-19 (96.3% confirmed by PCR, 3.7% confirmed by a serologic anti–SARS-CoV2 test) and 1,558 PS-matched controls were extracted from the IMSR.

The demographic and disease characteristics of cases and controls are reported in Table 1. Cases were younger (median [IQR] age: 42.40 [33.00–50.80] vs 46.90 [37.50–55.70] years, $p < 0.0001$), less disabled (median [interquartile range (IQR)] EDSS: 2.00 [1.00–3.50] vs 2.00 [1.00–4.50], $p = 0.0006$), more frequently female individuals (69.83% vs 64.18% $p = 0.0066$), with comorbidities (8.22% vs 5.26%, $p = 0.0054$), with a disease duration ≤10 years (44.16% vs 38.83%, $p = 0.0054$), with a relapsing disease course (86.26% vs 78.95%, $p < 0.0001$), and with at least 1 relapse in the last year (12.20% vs 8.28%, $p = 0.0024$) in comparison with controls.

Regarding DMT exposure, cases were less frequently treated with interferon beta products (13.35% vs 19.26%, $p < 0.0001$), with DMT being self-administered at home (55.71% vs 63.41%, $p < 0.0001$) and more frequently treated during the course of the disease with only high efficacy DMT or moderate efficacy DMTs followed by high efficacy DMT strategies (18.23% vs 15.60%, 30.17% vs 23.11%, $p < 0.0001$, respectively) in comparison with controls (Figure).

In all the 3 primary logistic regression models (Tables 2-4), the presence of comorbidities (ranging between 69% and 74% of increased risk) and female sex (ranging between 25% and 27% of increased risk) were found to be significantly and consistently associated with a higher risk of acquiring COVID-19, whereas age was associated with a lower risk of acquiring COVID-19 (each year of current age was associated with a decreased risk ranging from 10% to 11%).

Regarding the impact of DMTs, we found, in the first model (Table 2), based on the last DMT, a significantly higher risk of COVID-19 infection in patients who received natalizumab (OR [95% CI]: 2.38 [1.66–3.42]). In the second model (Table 3), based on the evaluation of treatment strategies received during the whole disease course, patients who underwent an escalation strategy from moderate efficacy DMTs followed by high efficacy DMTs were at significantly higher risk of getting COVID-19 (1.57 [1.16–2.13]) in comparison with patients never treated and those exposed only to first-line DMTs. Finally, in the third model (Table 4), which considered the place of treatment administration of the last DMT, a significantly higher risk of getting COVID-19 was found in patients who received treatment at the hospital and needed more frequent access to the MS center (1.65 [1.34–2.04]) in comparison with those who took self-administered DMT at home.

Risk Factors for Developing Severe COVID-19 in PwMS

Among the 779 PwMS with a confirmed diagnosis of COVID-19, 643 (82.5%) were reported as affected by a mild, 116 (14.9%) by a moderate, and only 20 (2.6%) by a severe disease course. Five patients died (4 men; mean age: 60.6 years; mean disease duration: 14 years; mean EDSS: 4.8), 3 experienced a relapsing course, and 2 experienced a progressive course. Each of them received a different last DMT (glatiramer acetate, ocrelizumab, azathioprine, natalizumab, and fingolimod).

The main clinical and demographic characteristics of PwMS with COVID-19 are summarized in Table 5. PwMS exhibiting a severe COVID-19 course were significantly older ($p < 0.0001$), more frequently male individuals ($p = 0.04$), more disabled ($p = 0.0003$), and more frequently with a progressive form ($p < 0.0001$) in comparison with those affected by a mild or moderate COVID-19 disease course.

The multivariable Poisson regression model showed that older age ($p = 0.0004$) and a progressive disease course ($p = 0.0067$) were the most significant risk factors of a severe COVID-19 course, whereas being treated with interferon beta products ($p = 0.0476$) and not treated at all ($p = 0.0356$) were associated with a lower risk (Table 6).

Classification of Evidence

This study provides Class III evidence that among patients with MS, younger age, being female, having more comorbidities, receiving natalizumab, undergoing an escalating treatment strategy, or receiving treatment at a hospital was associated with being infected with COVID. Among patients with MS who were infected with COVID-19, a severe course was associated with increasing age and experiencing a progressive form of MS, whereas not being on treatment or receiving an interferon beta agent was protective.

Discussion

Unlike most articles published so far during the COVID-19 pandemic,[4-9,20] which focus on the identification of factors associated with the severity of COVID-19 outcomes in

Table 1 Demographic and Clinical Characteristics of PwMS With COVID-19 (Cases) and PwMS Without COVID-19 (Controls)

Variable	PwMS with COVID-19 (n = 779)	PwMS without COVID-19 (n = 1,558)	*p* Value
Age, median (IQR), y	42.40 (33.00–50.80)	46.90 (37.50–55.70)	<0.0001
Patients with comorbidities, n (%)	64 (8.22)	82 (5.26)	0.0054
Disease duration, classes			
≤10	344 (44.16)	605 (38.83)	0.0054
11–20	272 (34.92)	525 (33.70)	
>20	147 (18.87)	388 (24.90)	
Missing	16 (2.05)	40 (2.57)	
Female sex, n (%)	544 (69.83)	1,000 (64.18)	0.0066
EDSS score, median (IQR)	2.00 (1.00–3.50)	2.00 (1.00–4.50)	0.0006
Number of EDSS scores, median (IQR)	10.00 (5.00–20.00)	10.00 (5.00–20.00)	0.8316
Patients with at least 1 relapse in the previous year, n (%)	95 (12.20)	129 (8.28)	0.0024
Disease course			
Relapsing	672 (86.26)	1,230 (78.95)	<0.0001
Progressive	78 (10.01)	260 (16.69)	
Missing	29 (3.72)	68 (4.36)	
Last DMT recorded, n (%)			
Alemtuzumab	16 (2.05)	24 (1.54)	<0.0001
Teriflunomide	33 (4.24)	87 (5.58)	
Azatioprine	15 (1.93)	34 (2.18)	
Dimethyl fumarate	117 (15.02)	197 (12.64)	
Glatiramer acetate	56 (7.19)	165 (10.59)	
Cyclophosphamide	4 (0.51)	9 (0.58)	
Fingolimod	83 (10.65)	164 (10.53)	
Methotrexate	5 (0.64)	16 (1.03)	
Natalizumab	137 (17.59)	120 (7.70)	
Mitoxantrone	3 (0.39)	12 (0.77)	
Interferon beta products	104 (13.35)	300 (19.26)	
Rituximab	18 (2.31)	36 (2.31)	
Ocrelizumab	70 (8.99)	131 (8.41)	
Cladribine	21 (2.70)	25 (1.60)	
Never treated	97 (12.45)	238 (15.28)	
Last DMT recorded classified on the basis of the place of administration, n (%)			
At hospital	248 (31.84)	332 (21.31)	<0.0001
At home	434 (55.71)	988 (63.41)	
Never treated	97 (12.45)	238 (15.28)	
DMT sequences, n (%)			
Never treated	111 (14.25)	258 (16.56)	0.0001

Continued

Table 1 Demographic and Clinical Characteristics of PwMS With COVID-19 (Cases) and PwMS Without COVID-19 (Controls) *(continued)*

Variable	PwMS with COVID-19 (n = 779)	PwMS without COVID-19 (n = 1,558)	*p* Value
Only high efficacy DMTs	142 (18.23)	243 (15.60)	
Moderate efficacy DMTs followed by high-efficacy DMTs	235 (30.17)	360 (23.11)	
Only moderate efficacy DMTs	291 (37.36)	697 (44.74)	

Abbreviations: DMT = disease-modifying therapy; PwMS = people with multiple sclerosis.

PwMS, we have built a case-control study embedded in a national MS registry to evaluate the risk factors associated with becoming infected by SARS-CoV-2. The use of a disease registry has allowed us to analyze data about the whole disease and treatment history, including crucial information on the exposure duration to each DMT and the type of treatment sequencing received, in patients with and without COVID-19.

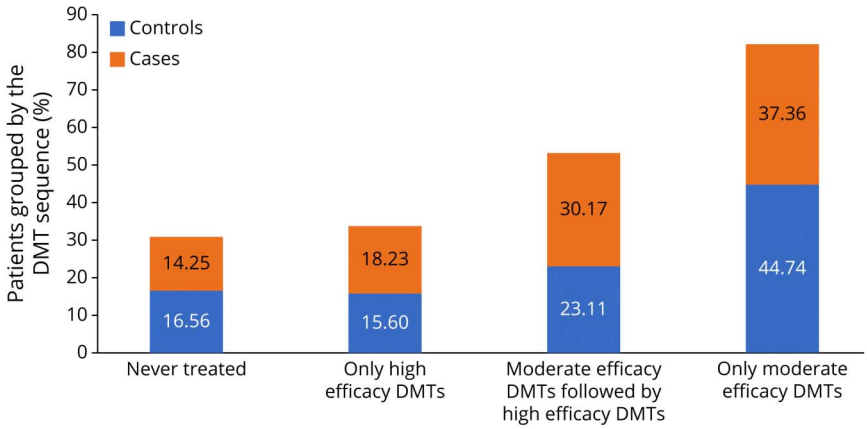
In our case-control study, PwMS who developed COVID-19 were younger, more frequently female individuals, less disabled, and with more active disease in comparison with PwMS who did not develop COVID-19. These findings suggest that younger PwMS with lower levels of disability might have had a higher number of social interactions and those with a higher disease activity an increased need to attend clinics for corticosteroid therapy or for changes in therapy, both of which exposed individuals to higher risk of SARS-CoV-2 infection.

Moreover, our results highlight that patients who received natalizumab are at high risk of acquiring COVID-19. We can speculate that PwMS who need to periodically visit the MS clinic to receive DMT, as for the monthly administration of natalizumab, and/or who need to undergo more frequent blood examinations might have a greater number of environmental (hospital) exposures that are undoubtedly one of the major risk factors for developing a highly contagious viral respiratory disease.[21]

Since the pandemic spread in March 2020, many changes have been implemented in an attempt to reduce the risk of SARS-CoV-2 infection associated with indoor environments such as hospital waiting rooms.[22] This has included the use of telemedicine.[23] However, patients receiving infusion DMT or treatment requiring periodic monitoring have had to attend the hospital for drug administration, the laboratory for blood testing, or the radiology unit for MRI. The risk of acquiring COVID-19 during outpatient consultations or while receiving an infusion therapy has not been reported so far but is a matter of active investigation.[24]

Of most importance, we found the risk of getting COVID-19 was higher in those who underwent an escalation treatment strategy with a history of multiple exposures to immunotherapy, which may have chronically modified the immune system and overall susceptibility to infection.[14] Some DMTs, indeed, are associated with long-lasting effects on the immune system,[25-28] which can combine with the effects of subsequent therapies. These results prompt a safety evaluation of escalation therapy in the context of the potential risk of infection associated with previous or sequential immunosuppression during any treatment decision.[14]

Figure Histogram Shows the Percentages of PwMS Exposed to the Different Treatment Sequences



Blue bars represent controls, and orange bars represent cases. PwMS = people with multiple sclerosis.

Table 2 ORs for Risk of COVID-19 Infection Among People With Multiple Sclerosis—Logistic Regression Model Including the Last Recorded DMT

Covariate	OR	95% CI	*p* Value
Female sex	**1.25**	**1.03–1.51**	**0.02**
Presence of comorbidities	**1.69**	**1.18–2.40**	**0.004**
Patients with at least 1 relapse in the previous year	1.25	0.93–1.69	0.14
Progressive disease course	0.87	0.61–1.24	0.45
Disease duration, classes (≤10 years as reference)			
11–20	1.19	0.95–1.48	0.13
>20	1.17	0.88–1.56	0.27
Age	**0.9**	**0.86–0.95**	**<0.0001**
EDSS score	0.95	0.90–1.01	0.11
Last DMT recorded, never treated as reference			
Alemtuzumab	1.47	0.73–2.93	0.28
Azatioprine	1.58	0.79–3.14	0.19
Cladribine	1.68	0.89–3.20	0.11
Cyclophosphamide	1.42	0.42–4.85	0.57
Dimethyl fumarate	1.31	0.93–1.84	0.12
Fingolimod	1.21	0.84–1.75	0.31
Glatiramer acetate	0.87	0.59–1.29	0.49
Interferon beta products	0.84	0.60–1.17	0.30
Methotrexate	1.36	0.47–3.97	0.57
Mitoxantrone	1.03	0.28–3.84	0.96
Natalizumab	**2.38**	**1.66–3.42**	**<0.0001**
Ocrelizumab	1.39	0.94–2.06	0.10
Rituximab	1.4	0.74–2.64	0.30
Teriflunomide	0.97	0.60–1.56	0.90

Abbreviation: DMT = disease-modifying therapy.
Covariates found to be significant in the model are marked in bold.

Various limitations of this study deserve discussion. We did not collect data regarding socioeconomic or worker status that might contribute to the risk of COVID-19 infection. Furthermore, reporting of COVID-19 cases by health-care professionals was voluntary, which may have biased the results toward patients who more frequently attended clinics to receive the DMT infusions, which would overestimate the risk among patients receiving DMT at the hospital. Nevertheless, the study design we chose, which allowed us to randomly select controls from the entire IMSR database based on the region of residence and date of the last recorded visit, enabled us to mitigate the effect of such bias.

As the secondary objective, we replicated previous studies in assessing the risk factors associated with COVID-19 severity in PwMS. We confirmed the clinical characteristics, the distribution of clinical outcomes, and the main risk factors associated with the severity of COVID-19, which have been consistently reported in previous studies, despite the definitions of COVID-19 severity differing between them.[4-9] Most (n = 643, 82.5%) of our patients reported a mild COVID-19 course, which is consistent with findings from the Italian program[4] and the Spanish registry[8] in which 85% and 76% of patients, respectively, presented with mild infection. In keeping with previous studies,[4-9] PwMS experiencing a severe COVID-19 course were significantly older, more often male individuals, more disabled, and more frequently found to have a progressive form of MS in comparison with patients affected by a mild or moderate COVID-19 disease course. The multivariable Poisson regression model revealed older age, a

Table 3 ORs for Risk of COVID-19 Infection Among People With Multiple Sclerosis—Logistic Regression Model Including the DMT Sequences

Covariate	OR	95% CI	*p* Value
Female sex	**1.27**	**1.04–1.51**	**0.02**
Presence of comorbidities	**1.72**	**1.22–2.44**	**0.002**
Patients with at least 1 relapse in the previous year	1.25	0.93–1.68	0.14
Progressive disease course	0.83	0.59–1.17	0.29
Disease duration, classes (≤10 years as reference)			
11-20	1.12	0.90–1.40	0.32
>20	1.07	0.80–1.43	0.64
Age	**0.89**	**0.85–0.93**	**<0.0001**
EDSS score	0.96	0.91–1.02	0.19
DMT sequences, never treated as reference			
Only high efficacy DMTs	1.33	0.97–1.83	0.08
Moderate efficacy DMTs followed by high efficacy DMTs	**1.57**	**1.16–2.13**	**0.004**
Only moderate efficacy DMTs	0.99	0.75–1.30	0.93

Abbreviation: DMT = disease-modifying therapy.
Covariates found to be significant in the model are marked in bold.

progressive course, and the presence of comorbidities (even if the latter did not reach statistical significance) as being the most important factors associated with a higher risk of severe course of COVID-19, whereas interferon beta treatment and no treatment were associated with a lower risk of infection, as previously reported.[4,5,7] We did not confirm the association between a severe COVID-19 outcome and anti-CD20 drug exposure, as reported in other studies.[4,6,7] An explanation of these different results may be because the percentage of patients receiving anti-CD20 drugs was lower in our cohort (8.99%) in comparison with that reported in studies that found the association of these drugs with severe COVID-19 (11.1%,[4] 35.8%[6]). Moreover, in our study, we used a more rigorous criterion of treatment exposure; indeed, only anti-

Table 4 ORs for Risk of COVID-19 Infection Among People With Multiple Sclerosis—Last DMT Recorded Classified on the Basis of the Place of Administration

Covariate	OR	95% CI	*p* Value
Female sex	**1.25**	**1.03–1.51**	**0.02**
Presence of comorbidities	**1.74**	**1.22–2.46**	**0.002**
Patients with at least 1 relapse in the previous year	1.26	0.94–1.69	0.13
Progressive disease course	0.83	0.59–1.16	0.27
Disease duration, classes (≤10 years as reference)			
11–20	1.18	0.95–1.47	0.73
>20	1.16	0.88–1.54	0.13
Age	**0.89**	**0.85–0.93**	**<0.0001**
EDSS score	0.96	0.90–1.02	0.13
Last DMT recorded classified on the basis of the place of administration, never treated as reference			
At hospital	**1.65**	**1.34–2.04**	**<0.0001**
At home	0.94	0.71–1.24	0.65

Abbreviation: DMT = disease-modifying therapy.
Covariates found to be significant in the model are marked in bold.

Table 5 Demographic and Clinical Characteristics by the Clinical Course of COVID-19

Variable	COVID-19 symptoms severity			*p* Value
	Mild (n = 643)	Moderate (n = 116)	Severe (n = 20)	
Age, median (IQR), y	41.80 (32.70–50.60)	43.20 (33.20–50.30)	59.10 (53.25–63.55)	<0.0001
Patients with comorbidities, n (%)	53 (8.24)	7 (6.03)	4 (20.00)	0.1099
Disease duration, y	11.20 (5.15–17.80)	10.80 (4.70–19.60)	15.70 (5.80–24.35)	0.2676
Male sex, n (%)	193 (30.02)	31 (26.72)	11 (55.00)	0.0385
EDSS score, median (IQR)	2.00 (1.00–3.50)	2.00 (1.00–3.50)	4.50 (2.75–6.50)	0.0003
Number of EDSS scores, median (IQR)	11.00 (5.00–21.00)	8.00 (4.00–17.00)	9.50 (5.00–21.00)	0.0782
Patients with at least 1 relapse in the previous year, n (%)	77 (11.98)	17 (14.66)	1 (5.00)	0.4379
Disease course				
Relapsing	560 (87.09)	102 (87.93)	10 (50.00)	<0.0001
Progressive	56 (8.71)	12 (10.34)	10 (50.00)	
Missing	27 (4.20)	2 (1.72)	0 (0.00)	
Last DMT recorded, n (%)				
Alemtuzumab	13 (2.02)	3 (2.59)	0 (0.00)	0.1758
Teriflunomide	27 (4.20)	4 (3.45)	2 (10.00)	
Azatioprine	11 (1.71)	3 (2.59)	1 (5.00)	
Dimethyl fumarate	94 (14.62)	19 (16.38)	4 (20.00)	
Glatiramer acetate	48 (7.47)	6 (5.17)	2 (10.00)	
Cyclophosphamide	3 (0.47)	1 (0.86)	0 (0.00)	
Fingolimod	68 (10.58)	13 (11.21)	2 (10.00)	
Methotrexate	2 (0.31)	2 (1.72)	1 (5.00)	
Natalizumab	120 (18.66)	15 (12.93)	2 (10.00)	
Mitoxantrone	1 (0.16)	2 (1.72)	0 (0.00)	
Interferon beta products	92 (14.31)	11 (9.48)	1 (5.00)	
Rituximab	14 (2.18)	4 (3.45)	0 (0.00)	
Ocrelizumab	55 (8.55)	11 (9.48)	4 (20.00)	
Cladribine	19 (2.95)	2 (1.72)	0 (0.00)	
Never treated	76 (11.82)	20 (17.24)	1 (5.00)	

Abbreviation: DMT = disease-modifying therapy.

CD20 drugs administered for a minimum of 30 days were considered in the analysis to prevent the possibility of assigning an increased risk of Sars-Cov-2 infection to a DMT administered only for a few days.

In conclusion, data from the IMSR seem to suggest that the risk of contracting COVID-19 in PwMS may be more linked to the cumulative effect of sequences of different immunotherapies than to the type of the last administered treatment. Furthermore, patients with MS treated with DMT administered at MS clinics, who are more often younger and with higher disease activity, are at higher risk of being infected by COVID-19 compared with those taking oral or injectable therapies at home. Further studies assessing the safety of the escalation therapy approach and the risk of infections associated with previous or sequential immunosuppression are needed to improve treatment decision-making in clinical practice.

Studies of alternative administration routes for some drugs currently requiring a higher frequency of hospital attendance are also needed. In fact, 2 studies suggested that natalizumab

Table 6 Multivariable Poisson Regression Model for Severe COVID-19 Infection

Risk factor	IRR	95% CI	*p* Value
Male sex	1.92	0.73–5.05	0.1889
Presence of comorbidities	3.12	0.98 10.00	0.0556
Patients with at least 1 relapse in the previous year	1.20	0.17–8.68	0.8539
Progressive disease course	**5.32**	**1.59–17.79**	**0.0067**
Disease duration, classes (≤10 years as reference)			
11–20	0.43	0.13–1.42	0.168
>20	0.30	0.08–1.22	0.0932
Age	**1.09**	**1.04–1.15**	**0.0004**
EDSS score	1.23	0.93–1.64	0.1503
Last DMT recorded, dimethyl fumarate treated as reference			
Azatioprine	0.21	0.02–2.11	0.5375
Fingolimod	0.89	0.17–4.52	0.8867
Glatiramer acetate	0.63	0.12–3.43	0.5941
Interferon beta products	**0.11**	**0.01–0.97**	**0.0476**
Methotrexate	0.17	0.02–1.78	0.1404
Natalizumab	0.63	0.12–3.26	0.5796
Ocrelizumab	0.35	0.07–1.63	0.1801
Teriflunomide	0.52	0.08–3.40	0.4939
Never treated	**0.09**	**0.01–0.85**	**0.0356**

Abbreviations: DMT = disease-modifying therapy; IRR = incidence rate ratio.
Covariates found to be significant in the model are marked in bold.

administered subcutaneously was comparable with IV dosing regarding efficacy, pharmacokinetics/pharmacodynamics, and safety, while needing a shorter time of hospital attendence.[29,30] An increased use of telemedicine[23] and greater attention to the safety of indoor environments,[22] such as hospital waiting rooms, could contribute to minimizing the risk of COVID-19.

Finally, this study does not confirm a critical role of current MS therapies in the severity of COVID-19. The study supports earlier findings that older PwMS with progressive disease and greater disability are at a higher risk of severe COVID-19 and that interferon beta exposure decreases this risk.[4-9] A more correct assessment of the relationship between DMT exposure duration and the risk of contracting COVID-19, and of COVID-19 severe outcomes, especially now that new variants of coronavirus are emerging, remains a crucial goal.

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Continued

Appendix 1 *(continued)*

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