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SARS-CoV-2 Infection in Multiple Sclerosis

Results of the Spanish Neurology Society Registry

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Abstract

Objective

To understand COVID-19 characteristics in people with multiple sclerosis (MS) and identify high-risk individuals due to their immunocompromised state resulting from the use of disease-modifying treatments.

Methods

Retrospective and multicenter registry in patients with MS with suspected or confirmed COVID-19 diagnosis and available disease course (mild = ambulatory; severe = hospitalization; and critical = intensive care unit/death). Cases were analyzed for associations between MS characteristics and COVID-19 course and for identifying risk factors for a fatal outcome.

Results

Of the 326 patients analyzed, 120 were cases confirmed by real-time PCR, 34 by a serologic test, and 205 were suspected. Sixty-nine patients (21.3%) developed severe infection, 10 (3%) critical, and 7 (2.1%) died. Ambulatory patients were higher in relapsing MS forms, treated with injectables and oral first-line agents, whereas more severe cases were observed in patients on pulsed immunosuppressors and critical cases among patients with no therapy. Severe and critical infections were more likely to affect older males with comorbidities, with progressive MS forms, a longer disease course, and higher disability. Fifteen of 33 patients treated with

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Glossary

ANOVA = analysis of variance; **CI** = confidence interval; **DMT** = disease-modifying treatment; **EDSS** = Expanded Disability Status Scale; **ICU** = intensive care unit; **IQR** = interquartile range; **IVMP** = IV pulses of methylprednisolone; **MS** = multiple sclerosis; **OR** = odds ratio; **RT** = real time; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2.

rituximab were hospitalized. Four deceased patients have progressive MS, 5 were not receiving MS therapy, and 2 were treated (natalizumab and rituximab). Multivariate analysis showed age (OR 1.09, 95% CI, 1.04–1.17) as the only independent risk factor for a fatal outcome.

Conclusions

This study has not demonstrated the presumed critical role of MS therapy in the course of COVID-19 but evidenced that people with MS with advanced age and disease, in progressive course, and those who are more disabled have a higher probability of severe and even fatal disease.

The COVID-19 pandemic is representing a challenge for the care of patients with immune-mediated diseases such as multiple sclerosis (MS) requiring immunomodulatory or immunosuppressive disease-modifying treatments (DMTs).

For coronaviruses, the aberrant host immune response is responsible for the severe respiratory failure during infection[1] that may lead 21% of patients with MS to be hospitalized and 3.5% to die.[2] A key issue is identifying inherent factors of MS that may put patients at an increased risk of severe COVID-19 beyond the well-established older age and comorbid diseases in the general population.[3] Theoretically, the repression of immune hyperactivation underlying the efficacy of immunosuppressants is precisely what could confer on patients a worse prognosis by allowing viral replication, which, in turn, may also prevent them from developing an acute respiratory distress syndrome by limiting the aberrant inflammatory response. Anti-CD20 drugs are speculated to confer protection[4-6] despite minimal B cell involvement at the initial viral response,[7] but also susceptibility.[8] S1P modulators and DMTs inducing pronounced lymphopenia such as cladribine, alemtuzumab, and dimethyl fumarate have been found to be involved in both severe[9-12] and uncomplicated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[13,14] However, to date, there are no conclusive data in this regard. This article describes the cases entered in the Spanish registry of patients with MS with suspected or confirmed COVID-19 between March and June 2020. We believe in its potential to reinforce—or question—previous data and offer new insights in the clinical management of patients with MS more likely to experience fatal outcomes from COVID-19.

Methods

This is a national, multicenter and observational study of adult patients with MS who tested positive for SARS-CoV-2 on a real-time (RT)-PCR (on nasopharyngeal swabs) or serologic test, or with highly suspected COVID-19 based on clinical (fever, persistent cough and/or sore throat, dyspnea, and diarrhea) and radiologic features (chest x-ray or chest CT findings of pneumonia), although no confirmatory test was performed. All patients included had available information on the COVID-19 outcome (recovery or death), and data were retrospectively collected from symptom onset. The Spanish Neurology Society created a web-based platform and invited member sites in Spain to participate in the collection of the data. The database is still open for neurologists to continue submitting cases.

Standard Protocol Approvals, Registrations, and Patient Consents

The Ethics Committee of Hospital Virgen de la Arrixaca (Murcia, Spain) approved the study, and all patients gave their oral or written informed consent for the use of medical data following the Declaration of Helsinki and local regulations.

Data Collection

Data collection included demographics, MS course and duration, the last Expanded Disability Status Scale (EDSS) score before COVID-19 infection, current—and time on—DMT, decisions over DMTs during COVID-19 (delaying, interrupting, keeping, or switching treatment), exposure to IV pulses of methylprednisolone (IVMP) in the last 2 months, and comorbidities at the time of infection. As for COVID-19, we collected any neurologic symptom highly suggestive of SARS-CoV-2 infection (hyposmia/anosmia, dysgeusia, headache, and myalgia), treatment, lymphocyte count during the infection, and COVID-19 course and outcome (recovery or death). Clinical evolution of COVID-19 was grouped into the following severity of illness categories: mild (ambulatory patients), severe (patients who were hospitalized), and critical illness (patients who were admitted in the intensive care unit [ICU] or died).

Statistical Analysis

Descriptive statistics were used to summarize data; quantitative variables were described with measures of central tendency and dispersion (mean ± SD or median [interquartile

Table 1 Demographic and Clinical Characteristics of Patients With MS and COVID-19 in the Spanish Registry (n = 326)

	Value
Age, y	
Mean ± SD	44.8 ± 11.5
Median (IQR)	43.5 (37–51)
Sex, female	221 (67.8)
Time since MS diagnosis, y	
Mean ± SD	11.0 ± 8.0
Median (IQR)	9 (5–17)
Disease course	
RRMS	263 (80.7)
SPMS	43 (13.2)
PPMS	20 (6.1)
EDSS score	
Mean ± SD	2.6 ± 2.2
Median (IQR)	2.0 (1.0–3.5)
Grouped DMTs	
Injectables	49 (15.0)
Oral first-line agents	78 (24)
Reversible immunosuppressive therapy	53 (16.2)
Pulsed immunosuppressive therapy	80 (24.5)
Other	7 (2.1)
None	59 (18.1)
Time on current DMT	
<6 mo	18/266 (6.8)
6–24 mo	77/266 (29.0)
>24 mo	171/266 (64.0)
IVMP pulses in the last 2 mo	7 (2.1)
COVID-19 diagnosis[a]	
Confirmed by RT-PCR	120 (36.8)
Confirmed by a serologic test	34 (10.4)
Highly suspected based on clinical and/or radiologic features	205 (62.9)
Lymphocyte levels during infection[b]**, cells/μL**	145 (44.5)
Mean ± SD	1,233.4 ± 742.2

Abbreviations: BMI = body mass index; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IQR = interquartile range; IVMP = IV methylprednisolone; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; RT-PCR = real-time PCR; SPMS = secondary progressive multiple sclerosis.
Data are n (%) unless otherwise indicated. Injectables (interferons, n = 36, and glatiramer acetate, n = 13); oral first-line agents (dimethyl fumarate, n = 41, and teriflunomide, n = 37); reversible immunosuppressive therapy (fingolimod, n = 27, and natalizumab, n = 26); pulsed immunosuppressive therapy (rituximab, n = 33, cladribine, n = 6, ocrelizumab, n = 23, and alemtuzumab, n = 18).
[a] Multiresponse variable.
[b] Calculated on patients with the available blood lymphocyte count at the date of examination.

range [IQR]) and qualitative variables with absolute (n) and relative (%) frequencies. Statistical comparisons between continuous variables were performed with independent *t* tests for the analysis of 2 groups and with the analysis of variance (ANOVA) for more than 2 groups. The χ^2 test or Fisher exact test was applied to categorical variables. The significance level of 0.05 was used for statistical testing, and missing data were not imputed.

For the analysis of variables associated with the clinical course of COVID-19, DMTs were categorized as follows: (1) injectable (interferons and glatiramer acetate); (2) oral first-line agents (teriflunomide and dimethyl fumarate); (3) reversible immunosuppressants (natalizumab and fingolimod); (4) pulsed immunosuppressants (alemtuzumab, ocrelizumab, rituximab, and cladribine), and (5) other drugs. To identify risk factors for critical COVID-19 course and death, the independent variables age, sex, comorbidities, MS phenotype, EDSS score, DMTs, IVMP in the last 2 months, and treatment for COVID-19 were analyzed using the univariate logistic regression model. The phenotype of MS was grouped as relapsing vs progressive, and DMTs were grouped by level of immunosuppression as injectables + oral first-line agents vs the rest of treatments. Comorbidities, IVMP use, and treatment for COVID-19 were treated as categorical variables (yes vs no).

A multivariate regression model was performed via automated forward stepwise selection of variables with p values <0.2. Results are expressed as ORs and 95% CIs. An exploratory analysis was performed to assess the disease course in patients treated with B cell–depleting therapy for less or more than 24 months, assuming that the immunosuppressive effect is stabilized after 24 months of exposure despite the different administration regimens adopted with ocrelizumab and rituximab. Analyses were performed with the Statistical Package for the Social Sciences version 22.0 (SPSS Inc, Chicago).

Data Availability

All data collected in this study are available following data availability policy in an effort to promote data transparency.

Results

As of 15 June 2020, a total of 336 cases were entered in the registry, 9 of whom were still active, whereas another corresponded to a patient younger than 18 years. The number of cases evaluable in the analysis was 326, 120 (36.8%) of whom tested positive for SARS-CoV-2 by RT-PCR, 34 (10.4%) by a serologic test, and 205 (62.8%) were highly suspected cases with clinical symptoms and/or radiologic findings compatible with SARS-CoV-2 infection. The mean age of patients was 44.8 ± 11.5 years; most were female (n = 221; 67.8%) and had a relapsing course of MS (n = 263; 80.7%). The mean MS duration was 11.0 ± 8.0 years, and the median EDSS score at COVID-19 infection was 2.0 (IQR: 1.0 to 3.5). One hundred

Table 2 Patient Characteristics by the Clinical Course of COVID-19

	Clinical course[a]			
	Mild (ambulatory) (n = 244)	Severe (hospitalization) (n = 69)	Critical (ICU admission/death) (n = 10)	*p* Value
Age, y				<0.001[c]
Mean ± SD	42.7 ± 10.3	51.1 ± 12.7	55 ± 12.4	
Median (IQR)	42 (36–49)	49 (42–61)	56.5 (47–68)	
Sex, female	175 (71.7)	39 (56.5)	4 (40)	<0.05[d]
MS duration, y				<0.05[c]
Mean ± SD	10.3 ± 7.6	13.6 ± 8.9	14 ± 9.6	
Median (IQR)	9 (4–16)	12 (7–20)	13 (5–25)	
MS course				<0.001[d]
RRMS	218 (89.3)	37 (53.6)	5 (50)	
SPMS/PPMS	26 (10.6)	32 (46.4)	5 (50)	
EDSS score				<0.001[c]
Mean ± SD	2.2 ± 1.9	4.1 ± 2.4	4.4 ± 2.7	
Median (IQR)	1.5 (1–3)	3.5 (2–6.5)	3.7 (2–6.5)	
Current DMT				
Interferon beta	31 (12.7)	5 (7.2)	0 (0)	NS
Glatiramer acetate	12 (4.9)	1 (1.4)	0 (0)	NS
Teriflunomide	28 (11.4)	7 (10.1)	1 (10)	NS
Dimethyl fumarate	40 (16.3)	0 (0)	1 (10)	<0.001[d]
Natalizumab	21 (8.6)	3 (4.3)	1 (10)	NS
Fingolimod	24 (9.8)	3 (4.3)	0	NS
Alemtuzumab	16 (6.5)	1 (1.4)	1 (10)	NS
Ocrelizumab	15 (6.1)	8 (11.6)	0	NS
Rituximab	17 (6.9)	15 (21.7)	1 (10)	<0.05[d]
Cladribine	6 (2.4)	0 (0)	0	NS
Other	4 (1.6)	1 (1.4)	0	NS
Time on current DMT				NS
<6 mo	15 (6.1)	3 (4.3)	0	
6–24 mo	60 (24.5)	15 (21.7)	1 (10)	
>24 mo	139 (57.0)	27 (39.1)	4 (40)	
IVMP in the last 2 mo	3 (1.2)	4 (5.8)	0 (0)	NS
Patients with comorbidities[b]	105 (43)	39 (56.5)	8 (80)	<0.05[d]
Smoking	39 (15.9)	7 (10.1)	0 (0)	NS
Obesity (BMI >30 kg/m^2)	21 (8.6)	15 (21.7)	3 (30)	<0.001[d]
Arterial hypertension	16 (6.5)	14 (20.2)	3 (30)	<0.001[d]
Diabetes mellitus	7 (2.8)	4 (5.8)	5 (50)	<0.001[d]
Bronchopathy	5 (2.0)	3 (4.3)	1 (10)	NS
Ischemic cardiomyopathy	0 (0)	2 (2.9)	1 (10)	<0.05[d]

Continued

Table 2 Patient Characteristics by the Clinical Course of COVID-19 *(continued)*

	Clinical course[a]			
	Mild (ambulatory) (n = 244)	Severe (hospitalization) (n = 69)	Critical (ICU admission/death) (n = 10)	*p* Value
Health care personnel	19 (7.7)	0 (0)	1 (10)	<0.05[d]
Lymphocyte levels[e] during infection, cells/μL	84 (34.4)	49 (71.0)	10 (100)	
Mean ± SD	1,474.93 ± 774.9	916.5 ± 545.8	650.1 ± 345.6	0.001[c]
COVID-19 treatment	41 (16.8)	65 (94.2)	8 (80)	<0.001[d]

Abbreviations: BMI = body mass index; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; ICU = intensive care unit; IQR = interquartile range; IVMP = IV methylprednisolone; NS = not significant; NTZ = natalizumab; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.
Data are n (%) unless otherwise indicated.
[a] Clinical course of COVID-19 was available for 323 patients of the total included.
[b] Multiresponse variable.
[c] *p* Value for ANOVA comparison.
[d] *p* Value for Fisher test comparison.
[e] Calculated on patients with the available blood lymphocyte count at the date of examination.

thirty-three patients (40%) were receiving reversible or pulsed immunosuppressive therapy, and 171 (64%) were treated with the current DMT for at least 2 years. Baseline characteristics are presented in table 1. Continuing the current DMT was the most common approach, regardless of their level/type of immunosuppression (injectables, 43 [91.5%]; oral first-line agents, 57 [80.3%]; reversible immunosuppressants, 32 [65.3%]; and pulsed immunosuppressants, 49 [65.3%]. The next planned dose was delayed in 13 (34.2%) patients on rituximab, 12 (31.6%) on natalizumab, and 9 (23.7%) on ocrelizumab.

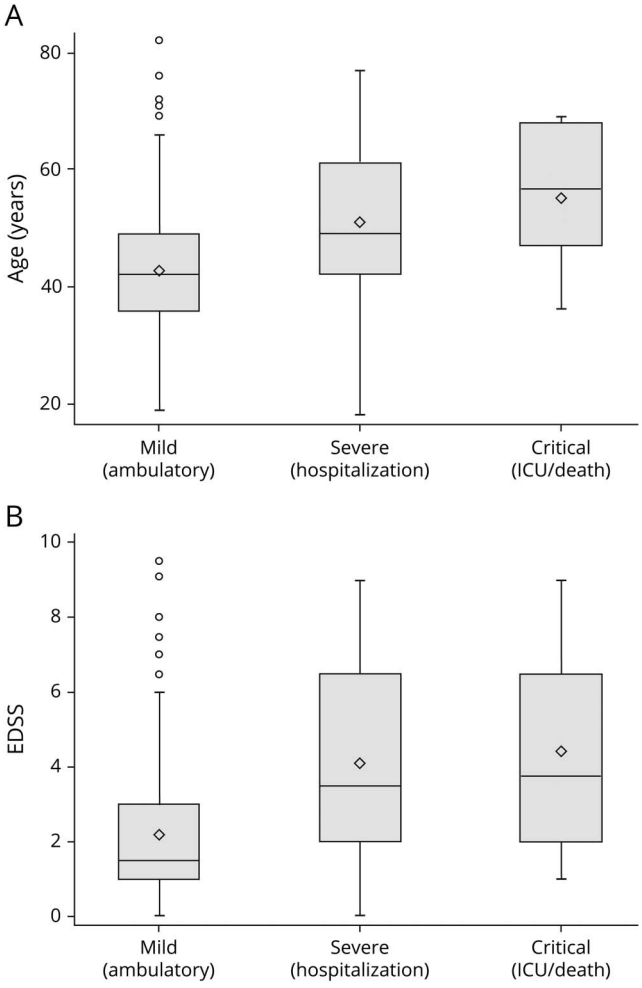
Clinical Course of COVID-19

Common neurologic symptoms at onset included hyposmia/anosmia in 95 (29.5%) patients and dysgeusia in 71 (21.8%). Headaches and myalgia were observed in 14 (4.6%) and 8 (2.45%) patients, respectively. Most cases (244/323; 75.5%) were ambulatory, 69/323 (21.3%) were severe, and 10 (3%) were critical. Of the 326 patients with MS and COVID-19 included in this cohort, 7 (2.1%) patients died, of which 4 were admitted to the ICU. The median length of hospital stay was 10 days (IQR, 6–15 days), and the median length of ICU stay was 10 days (IQR, 9–16 days). Compared with ambulatory cases, patients with severe or critical disease were more likely to be older, male, have a longer MS duration, higher EDSS scores, and a progressive MS course (table 2 and figure 1). Patients with critical infection were more likely to have at least 1 comorbidity, with diabetes, obesity, hypertension, and ischemic heart disease being the most common. The proportion of health care personnel was 10% (1/10) among patients with critical course and 7.7% (19/244) among ambulatory cases (table 2). Having received IVMP in the last 2 months was not significantly associated with the infection's clinical course (table 2).

Most patients with relapsing MS (83.8%) were ambulatory, and half of the patients with progressive forms (50.8%) developed severe COVID-19 (figure 2A). High rates of ICU/deaths (8.6%) and hospitalizations (41.4%) were observed in patients who were not receiving DMTs (figure 2B), and we found statistical differences in the percentage of patients on different COVID-19 courses according to DMT (Fisher exact test p value < 0.001). Ambulatory cases were particularly higher in patients receiving injectables (87.8%), oral first-line agents (88.3%), and reversible immunosuppressors (86.5%), whereas a higher rate of hospitalization was found in patients on pulsed immunosuppressive therapy (30.0%) (figure 2B). Dimethyl fumarate and rituximab were the only DMT significantly associated with the course of infection. Forty patients of the 41 receiving dimethyl fumarate were ambulatory (p < 0.001), and 15 of the 33 patients on rituximab were hospitalized (p < 0.05). Patients treated with rituximab were on average 49.3 (8.5) years old (median 47 [43–54]), and 60% (20/33) presented progressive MS. When disease course was analyzed according to B cell–depleting therapy and time of exposure, results showed that treatment with rituximab/ocrelizumab for less than 24 months was significantly associated with the course of the infection (Fisher p = 0.002), with almost half of patients (48.3%) hospitalized.

The median age of 7 fatal cases was 61 (IQR, 52–68) years, 4 were female, 4 had secondary progressive course, and the median EDSS score was 4.5 (IQR, 3.5–8.5) (table 3). Five of the 7 patients who died of COVID-19 were not receiving DMTs, and the remaining 2 were on immunosuppressive agents (one in each natalizumab and rituximab) for >24 months. These 2 patients had their treatment dose temporarily delayed. None of the deceased patients was a smoker, and obesity, diabetes, and hypertension were reported in 3 patients (43%). One deceased patient was a health care worker. Three (43%) of the 7 deceased patients showed neurologic symptoms compatible with COVID-19. Age, MS duration, MS course, and EDSS score were observed to be significantly associated with the COVID-19 outcome (table 3). A significant relationship was found between

Figure 1 COVID-19 Course by MS Characteristics: (A) Age; (B) EDSS Score



Box plots show medians and IQRs. Means are shown with a rhombus. Outliers are shown with small circles. Differences in age and EDSS score between groups reached statistical significance (ANOVA comparison p values < 0.001). EDSS = Expanded Disability Status Scale; ICU = intensive care unit; IQR = interquartile range; MS = multiple sclerosis.

not being treated with DMTs and mortality from COVID-19 compared with treated patients (n = 5, [71.4%] and n = 2 [28.6%], respectively, Fisher exact test p value < 0.001). Patients not treated with DMTs had a mean age of 53.5 (13.2) years (median 53 [43–65]) and a mean EDSS score of 3.75 (2.8) (median: 3 [1.5–6.5]).

Risk Factors for Critical COVID-19 Course and Mortality

Univariate analyses revealed that age, COVID-19 treatment, MS phenotype, and EDSS score were all significantly associated with an increased risk of critical course and mortality (table 4). Multivariate analysis confirmed a significant association of mortality and older age (OR, 1.09, 95% CI, 1.04–1.17; $p = 0.001$, per year increase), whereas levels of lymphocytes were identified as significantly associated with a reduced risk of critical course (OR 0.99, 95% CI 0.996–1; $p = 0.015$).

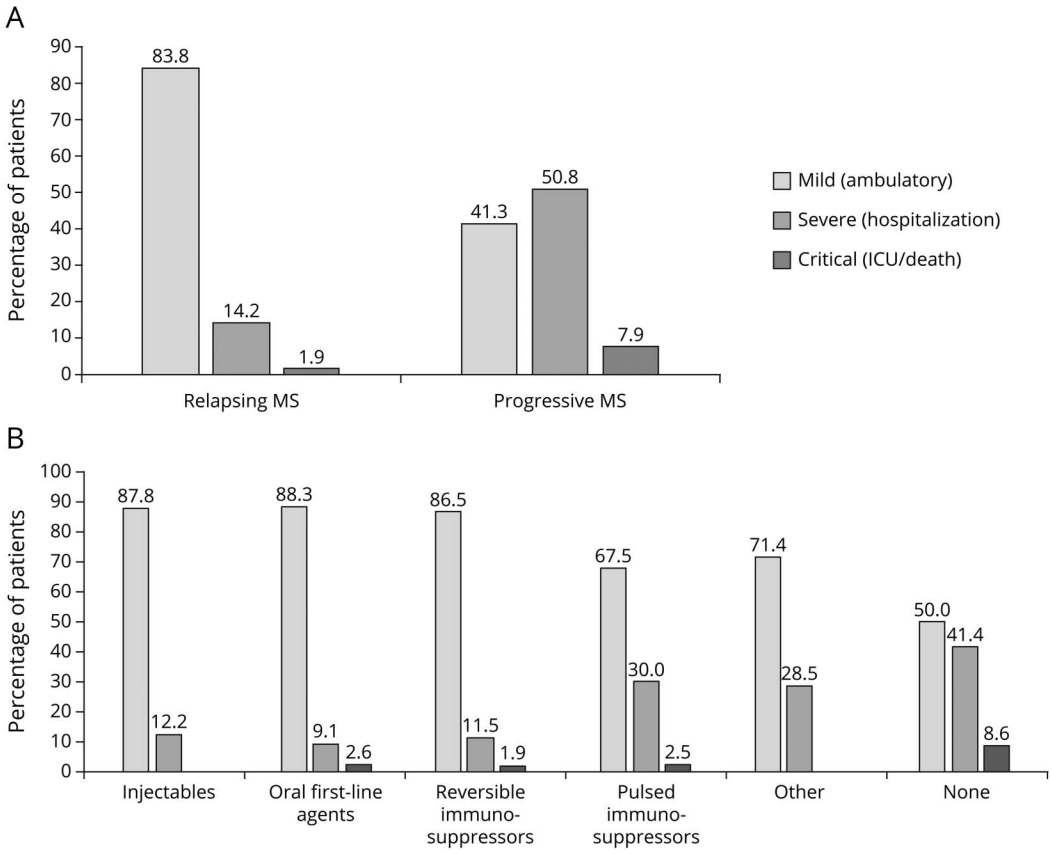
Discussion

This large series describing COVID-19 course in people with MS shows that most patients developed a mild/moderate disease, which is in line with findings from the Italian program in which 85% of patients presented a mild infection.[15] We confirm an overall mortality rate of 2.1%, which is lower than that in the French registry (3.5%)[2] and that reported among individuals from the general population aged <65 (4.5%–11.2%) in European countries.[16] Although patients without a confirmed positive COVID-19 test may have contributed to lowering the rates of hospitalization and deaths attributed to the coronavirus, our data altogether suggest that patients with MS do not seem to be at a higher risk of life-threatening complications from SARS-CoV-2 compared with the general population. These results may be influenced by the hypothetical more rigorous confinement measures adopted by immunosuppressed patients, determining a lower risk of COVID-19 infection, especially those most vulnerable because of older age and greater disability, which is supported by the median EDSS score of 2.0 in our population.

In general, our data show that patients of older age, with longer disease duration and progressive forms of MS, were more likely to be admitted to the ICU and die. Mortality was particularly high in patients older than 52 years. An increased admission rate to the ICU was observed in patients aged 47 years and older, with comorbidities and higher EDSS scores, which normally correspond to progressive courses of MS. Patients with diabetes, obesity, ischemic heart disease, and hypertension were linked to more hospitalizations and ICU admissions. Altogether, these findings reflect the undoubted consequences of age and the contribution of aging-related factors in a more severe evolution of the infection. In this MS cohort, health care personnel accounted for 6.1% (20/326) of all infections, and although we are limited in drawing conclusions because the number of patients, this study suggests that health care workers with MS may be at a high risk of evolving critically.

Of interest, we could not demonstrate any association between the immunosuppressive therapy and the severity of COVID-19 as the vast majority of patients receiving immunosuppressants recovered from disease. Of note, patients on DMTs were mostly ambulatory, patients without MS treatment reported the higher admission rates to hospital and ICU admission in this study, and 5 of the 7 patients who died were not receiving DMTs. Similar to what is observed in clinical practice, we observed an elevated proportion of progressive MS forms among untreated patients with MS (44%), which accounted for 19.3% of the whole cohort. Therefore, the unfavorable COVID-19 course in this particularly susceptible group is not surprising.[2,17] In addition, although limited by the very small number of deceased patients, our results are in line with those from the French cohort in which the proportion of hospitalized/deceased patients was higher in the group not receiving MS treatment.[2] Similarly, in this Spanish cohort, the exposure to DMTs, regardless of type, was not found to be a

Figure 2 MS Phenotype (A) and DMT (B) Distribution



Differences in the percentage of patients with different COVID-19 courses by MS phenotype and DMT reached statistical significance (Fisher exact test *p* value < 0.001). Injectables (interferons and glatiramer acetate); oral first-line agents (dimethyl fumarate and teriflunomide); reversible immunosuppressors (natalizumab and fingolimod); pulsed immunosuppressors (alemtuzumab, ocrelizumab, rituximab, and cladribine). COVID-19 = coronavirus disease 2019; DMT = disease-modifying treatment; ICU = intensive care unit; MS = multiple sclerosis.

predictor of critical COVID-19 in the multivariate model. However, the relationship that we observed between rituximab and the course of infection deserves attention given the association with a higher risk of a severe COVID-19 course seen in the Italian cohort of 784 patients.[15] It is also unclear why 15 patients treated with rituximab were hospitalized, but it may be related to the drug's mechanism of action, the strong immunosuppressive effect, and its routine use in progressive forms of MS and older patients. The finding that being treated with B cell–depleting therapy for less than 24 months led to a more severe clinical course of infection may be cautiously assumed to be a delayed immunosuppressive effect of treatment during the first 24 months and a greater systemic inflammatory response in these patients compared with those treated for more than 24 months. Such results will be highlighted in the forthcoming updated registry data. If common features in deceased patients of having a higher EDSS score and progressive MS led to a critical outcome, this also merits further studies. Based on our data, we did not find the course of MS and disability as risk factors for critical course and death in multivariate analysis as other studies showed,[2] possibly because of the limited number of patients and sample distribution.

Although our patients shared baseline characteristics with the French and Italian cohorts, the limitation that data are likely to be biased by incomplete case ascertain in particular patients with very mild or mild COVID-19 has to be considered. They were a mean of 10 years older and had a longer MS duration than that of the Iranian cohort reported by Safavi et al.,[8] in which all patients suspected of having COVID-19 had full recovery even if they were on B cell–depleting agents. The fact that in our study the patients hospitalized had a reference lymphocyte count and that critical patients showed lymphopenia regardless of whether they had been exposed to MS treatments is only presumed to the virus but might question again the role of maintenance immunosuppression in the spectrum of disease severity in SARS-CoV-2.

A similar percentage of patients reported here were treated with immunomodulatory and immunosuppressive therapies for more than 2 years in the majority of cases. The general trend in decisions regarding treatment was toward maintaining medication regardless of the type of DMT, but in several cases, neurologists considered temporarily delaying the restart of treatment of natalizumab, rituximab, and ocrelizumab, probably due to the uncertainty surrounding the pandemic. Nevertheless, and

Table 3 Patient Characteristics by COVID-19 Outcome

	Patients deceased from COVID-19 (n = 7)	Patients recovered from COVID-19 (n = 319)	*p* Value
Age, y			<0.001[a]
Mean ± SD	60.7 ± 8.6	44.5 ± 11.4	
Median (IQR)	61 (52–68)	43 (37–50)	
Sex, female	4 (57.1)	217 (98.2)	NS
MS duration, y			<0.05[a]
Mean ± SD	17.4 ± 9.2	10.9 ± 7.9	
Median (IQR)	15 (11–27)	9 (5–17)	
MS course			<0.001[b]
RRMS	2 (28.5)	261 (81.8)	
SPMS	4 (57.1)	39 (12.2)	
PPMS	1 (14.3)	19 (5.9)	
EDSS score			<0.001[a]
Mean ± SD	5.4 ± 2.6	2.6 ± 2.2	
Median (IQR)	4.5 (3.5–8.5)	2 (1–3)	
DMT			<0.001[b]
Yes	2 (28.6)	265 (83.0)	
None	5 (71.4)	54 (16.9)	
IVMP in the last 2 mo	0 (0)	7 (2.2)	NS
Presence of comorbidities			NS
Yes	6 (85.7)	147 (46.0)	
No	1 (14.3)	172 (54.0)	
Lymphocyte levels[c] during infection, cells/μL	n = 7	n = 138	
Mean ± SD	704.4 ± 396.6	1,260.31 ± 746.46	NS

Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IQR = interquartile range; IVMP = IV methylprednisolone; NS = not significant; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis. Data are n (%) unless otherwise indicated.
[a] *p* Value for *t* test comparison.
[b] *p* Value for Fisher test comparison.
[c] Calculated on patients with the available blood lymphocyte count at the date of examination.

despite patients on rituximab tending to have a severe course in our study, we consider this moment difficult to advocate for any management approach owing to the continuously update advice,[18] except recommending prescribers to carefully balance the particular risks to each patient and educate them on preventive measures.

A criticism of the study could be the lack of a clear definition of severe COVID-19 infection. Hospitalization data were limited to admissions but no complications on hospitalization such as the need for supplemental oxygen or the use of ventilators (noninvasive and mechanical) were recorded, nor presenting respiratory symptoms (dyspnea, hypoxia, pneumonia, and acute respiratory distress syndrome). Therefore, this study cannot distinguish between moderate and severe forms of COVID-19 infection in patients with MS hospitalized, except the critical cases resulting in ICU admission or death. This is important as not all deaths occurred among patients admitted to ICU and not all patients admitted to ICU died. Data were also lacking on the time to the ICU from the time of hospital admission and on laboratory and radiologic findings on admission. A further limitation would be the incomplete ascertain in some cases of patients with very mild or mild COVID-19. The limited access to RT-PCR tests at the beginning of the pandemic in Spain explains the low percentage of patients tested for RT-PCR. As is common in all registries, selection bias and the lack of systematic assessment of patients cannot be ruled out, nor that the hypothetical more rigorous compliance with confinement measures by

Table 4 Univariate Analyses of Risk Factors for Critical COVID-19 Course and Mortality

	Critical COVID-19 course		Mortality	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age (y)	1.07 (1.01–1.12)	0.007[a]	1.11 (1.04–1.17)	0.001[a]
Sex (male vs female)	3.24 (0.90–11.75)	0.073	0.62 (0.13–2.85)	0.546
MS phenotype (RRMS[b] vs PMS)	0.23 (0.06–0.81)	0.022[a]	0.09 (0.02–0.47)	0.046[a]
DMT (injectable + oral first-line[b] vs other therapies)	0.38 (0.08–1.82)	0.227	[c]	0.938
EDSS score	1.33 (1.05–1.69)	0.018[a]	1.55 (1.15–2.08)	0.003[a]
IVMP (yes[b] vs no)	[c]	0.983	[c]	0.999
Comorbidities (yes[b] vs no)	4.69 (0.98–22.46)	0.050	7.02 (0.84–58.9)	0.072
COVID-19 treatment (yes[b] vs no)	7.81 (1.63–37.44)	0.010[a]	4.82 (0.92–25.23)	0.062
Lymphocyte levels (cells/μL)	0.99 (0.99–1)	0.014[a]	0.99 (0.99–0.99)	0.060

Abbreviations: EDSS = Expanded Disability Status Scale; IVMP = IV methylprednisolone; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; PMS = progressive multiple sclerosis.
[a] Significant variables.
[b] Reference category.
[c] Nonestimable because of sample distribution.

immunosuppressed patients, even during the de-escalation phase, may have favored our results. Differences in clinicians' awareness of the infection may have resulted in differences in monitoring, prevention, and advising measures with regard to patients.

In conclusion, this study confirms the absence of a critical role of MS DMTs in the evolution of SARS-CoV-2 infection. Instead, older patients, with a progressive course of MS, higher disability, and comorbidities, might be more vulnerable to severe outcomes of COVID-19, and the surveillance of this group should continue. Importantly, we observed a probability of critical course among health care personnel with MS that has not been addressed in previous studies. There is an urgent need for more research to be done to confirm these preliminary findings and allow refinement of guidelines on the management of patients with MS during the COVID-19 pandemic. The cases of new variants of coronavirus and patients vaccinated entering the registries that are active worldwide will offer an update that probably changes the main conclusions drawn from our results and other studies published in the MS population with COVID-19.

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SARS-CoV-2 Infection in Multiple Sclerosis: Results of the Spanish Neurology Society Registry

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