Risk and outcomes of COVID-19 in patients with multiple sclerosis

RISK AND OUTCOMES OF COVID-19 IN PATIENTS WITH MULTIPLE SCLEROSIS

Authors: Irene Moreno-Torres, MD PhD[1]; Virginia Meca Lallana, MD[2]; Lucienne Costa-Frossard, MD[3]; Celia Oreja-Guevara, MD PhD[4]; Clara Aguirre, MD[2]; Elda María Alba Suárez, MD[5]; Mayra Gómez Moreno, MD PhD[6]; Laura Borrega Canelo, MD[7]; Julia Sabín Muñoz, MD[8]; Yolanda Aladro, MD[9]; Alba Cárcamo Fonfría, MD[9] ; Elena Rodríguez García, MD PhD[10]; Juan Pablo Cuello, MD[11]; Enric Monreal, MD[3]; Susana Sainz de la Maza, MD[3]; Fernando Pérez Parra, MD[12]; Francisco Valenzuela Rojas, MD[13]; Carlos López de Silanes de Miguel, MD PhD[14]; Luis Ignacio Casanova Peño, MD PhD[14]; María Luisa Martínez Ginés, MD[11]; María Rosario Blasco Quílez, MD PhD[8]; Aida Orviz García, MD[1]; Luisa María Villar-Guimerans, PhD[3]; Guillermo Fernández-Dono, MsC[15]; Víctor Elvira; PhD[16]; Carmen Santiuste, MSC[3]; Mercedes Espiño PhD[3]; José Manuel García Domínguez, MD[11]

Affiliations: [1]Unidad de Enfermedades Desmielinizantes, Hospital Universitario Fundación Jiménez Diaz, Madrid, Spain; [2]Unidad de Enfermedades Desmielinizantes, Hospital Universitario la Princesa, Madrid, Spain; [3]Unidad de Esclerosis Múltiple, Hospital Universitario Ramón y Cajal, Madrid, Spain; [4]Department of Neurology, Hospital Clínico San Carlos, Departamento de Medicina, Facultad de Medicina, Universidad Complutense de Madrid (UCM) and IdISSC, Madrid, Spain; [5]Unidad de Neuroinmunología y Esclerosis Múltiple, Hospital Universitario la Paz, Madrid, Spain; [6]Hospital Universitario Infanta Leonor, Madrid, Spain; [7]Hospital Universitario Fundación Alcorcón, Madrid, Spain; [8]Unidad de Neuroinmunología, Hospital Universitario Puerta de Hierro, Madrid, Spain; [9]Unidad de Enfermedades Desmielinizantes, Hospital Universitario de Getafe, Madrid, Spain; [10]Hospital Universitario Severo Ochoa, Madrid, Spain; [11]Unidad de Enfermedades Desmielinizantes, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [12]Hospital Universitario

del Henares, Madrid, Spain; [13]Hospital Central de la Defensa "Gómez Ulla", Madrid, Spain; [14]Hospital Universitario de Torrejón, Madrid, Spain; [15]Universidad Complutense de Madrid, Madrid, Spain; 16 University of Edinburgh, Edinburgh, Scotland.

Corresponding author: Jose Manuel García Domínguez, MD, Unidad de Enfermedades Desmielinizantes, Hospital General Universitario Gregorio Marañón, Calle Doctor Esquerdo, 46, 28007 Madrid, Spain.

Email address: jgarciadominguez@salud.madrid.org

Phone: +34 915868339

Fax: +34 915868339

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Email addresses for all authors:

Irene Moreno-Torres: irene.morenot@quironsalud.es

Virginia Meca Lallana: virmeca@hotmail.com

Lucienne Costa-Frossard: lufrossard@yahoo.es

Celia Oreja-Guevara: orejacbn@gmail.com

Clara Aguirre: claraguih@hotmail.com

Elda María Alba Suárez: eldamaselda@gmail.com

Mayra Gómez Moreno: mayragomezmoreno@yahoo.es

Laura Borrega Canelo: lborregoc@fhalcorcon.es

Julia Sabín Muñoz: julia.sabin.m@gmail.com

Yolanda Aladro: yolanda.aladro@salud.madrid.org

Alba Cárcamo Fonfría albacarcamof@gmail.com

Elena Rodríguez García: ergarcia@salud.madrid.org

Juan Pablo Cuello: cuellojp@yahoo.es

Enric Monreal: penry02@hotmail.com

Susana Sainz de la Maza: susanasmc85@hotmail.com

Fernando Pérez Parra: perezparra.fernando@gmail.com

Francisco Valenzuela Rojas: fvalenzuelarojas5@gmail.com

Carlos López de Silanes de Miguel: carlosdesilanes@yahoo.es

Luis Ignacio Casanova Peño: i.casanovap@gmail.com

María Luisa Martínez Ginés: marisamgines@hotmail.com

María Rosario Blasco Quílez: charoblascoquilez@yahoo.es

Aida Orviz García: aida.orviz@gmail.com

Luisa María Villar-Guimerans: lvillar.hrc@salud.madrid.org

Guillermo Fernández-Dono: guillermofd_@hotmail.com

Víctor Elvira: victor.elvira.arregui@gmail.com

Carmen Santiuste: mariadelcarmen.santiuste@salud.madrid.org

Mercedes Espiño: mespino.hrc@salud.madrid.org

José Manuel García Domínguez: jgarciadominguez@salud.madrid.org

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Abstract

Background: Limited information is available on incidence and outcomes of COVID-19 in patients with multiple sclerosis (MS). This study investigated the risks of SARS-CoV-2 infection and COVID-19–related outcomes in patients with MS, and compared these with the general population.

Methods: A regional registry was created to collect data on incidence, hospitalization rates, intensive care unit (ICU) admission and death in patients with MS and COVID-19. National government outcomes and seroprevalence data were used for comparison. The study was conducted at 14 specialist MS treatment centers in Madrid, Spain, between February and May 2020.

Results: Two-hundred nineteen patients were included in the registry, 51 of whom were hospitalized with COVID-19. The mean age ± standard deviation was 45.3 ± 12.4 years and the mean duration of MS was 11.9 ± 8.9 years. The infection incidence rate was lower in patients with MS than the general population (adjusted incidence rate ratio 0.78; 95% confidence interval: 0.70–0.80), but hospitalization rates were higher (relative risk 5.03 [3.76–6.62]). Disease severity was generally low, with only one admission to an intensive care unit and five deaths. Males with MS had higher incidence rates and risk of hospitalization than females. No association was found between the use of any disease-modifying treatment and hospitalization risk.

Conclusion: Patients with MS do not appear to have greater risks of SARS-CoV-2 infection or severe COVID-19 outcomes compared with the general population. The decision to start or continue disease-modifying treatment should be based on a careful risk-benefit assessment.

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Introduction

Patients with multiple sclerosis (MS) are at increased risk of infection and infectious complications, due to the effects of both the disease and disease-modifying treatments (DMTs).[1] Infections are an important cause of hospitalization in patients with MS,[2, 3] with almost 8% of those hospitalized requiring intensive care.[3] Several factors are associated with an increased risk of infection-related hospitalization in patients with MS, including older age, longer disease duration, comorbidities, immunosuppression, prior hospital admission, obesity, and diabetes.[2, 4, 5]

In December 2019, the first cases of pneumonia caused by an unknown virus were reported in Wuhan, China.[6] The pathogen causing the infection was subsequently identified and named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), and on 11 March 2020 the World Health Organization declared a pandemic.[7]

SARS-CoV-2 is a zoonotic RNA virus similar to SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus). In infections caused by those coronaviruses, immunosuppression does not appear to be associated with an increased risk of severe disease or death.[8] To date, no increase in the development of clinical or severe lung disease has been reported in patients with SARS-CoV-2 infection who have undergone solid organ transplantation or received chemotherapy.[8, 9] Specific data on outcomes in treated patients with MS and coronavirus infection are, however, scarce.

We performed an observational study to quantify the risks of infection, hospitalization, admission to intensive care and death due to SARS-CoV-2 infection (henceforth referred to as COVID-19, except where the virus itself is being discussed) among patients with MS relative to the general population, and to identify factors associated with risk of

hospitalization.

Methods

Design

The study was conducted in the Madrid region of Spain. A regional COVID-19 registry was set up by members of the Study Group for Demyelinating Diseases, representing 14 MS centers across the region.

Between 9 February and 29 May 2020, all patients who were treated for MS at one of these centers and in whom COVID-19 was confirmed or highly suspected were included in the registry, regardless of whether they were admitted to hospital. Clinical and demographic data, laboratory test results, MS-specific information, and details of treatment for COVID-19 were entered into the registry.

This study was conducted according to the principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee at the Fundación Jiménez Díaz University Hospital, Madrid; all patients gave informed consent to be included in the registry. Patient data were anonymized, and measures were implemented to prevent re-identification or access by unauthorized parties. Follow-up was until recovery from COVID-19 or death.

Definitions and outcomes

Confirmed COVID-19 was defined as a positive reverse transcriptase–polymerase chain reaction (RT-PCR) nasopharyngeal swab or serologic (enzyme-linked immunosorbent assay [ELISA]) test for SARS-CoV-2. COVID-19 was highly suspected in patients who had at least two cardinal symptoms of COVID-19 (e.g. persistent dry cough, difficulty breathing, anosmia/ageusia, and fever) and/or positive radiologic findings, and a high circumstantial probability of infection in a pandemic setting (e.g. a positive test in a close family member),

in the absence of a confirmatory test result.

The outcomes of interest were number of cases of COVID-19; COVID-19–related hospitalization; admission to an intensive care unit (ICU); and death.

Statistical analysis

Data on clinical variables, laboratory test results, COVID-19 treatment, and MS-related information were analyzed descriptively. Laboratory data from patients with MS were compared with corresponding data from matched (hospitalized) patients with COVID-19 but without MS; the latter were from a registry created by Dr Luisa Maria Villar and colleagues at the Ramón y Cajal University Hospital, Madrid.

Binary and categoric variables were analyzed using contingency 2 × 2 tables, and significance was calculated using the chi-squared test. For continuous variables, a non-parametric Wilcoxon rank-sum test was performed to compare subgroups (hospitalized vs non-hospitalized patients; hospitalized MS patients vs hospitalized non-MS patients from the Villar *et al.* registry). Binary uni- and multivariable logistic regression was used to identify factors predictive of hospitalization. We use a penalized version of the multivariable logistic regression model, with L1 penalty (Lasso regression), in order to avoid the separation problem.[10] The penalized model also helps to enhance the interpretability of the results by excluding irrelevant variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed for each variable, with $P < 0.05$ considered significant.

In addition, we calculated the incidence rate (IR; defined as the number of cases divided by the total population at risk) of COVID-19 for both the MS population and the general Spanish population aged 15–79 years; this range was chosen because it corresponds to the age distribution of the MS population. IRs for patients with MS were derived from registry and local data on the MS population, while data from the ongoing National Study of Serological

Epidemiology of COVID-19 (NSSE-C19)[11] were used to generate IRs for the general Spanish population. In NSSE-C19, the percentage of the Spanish population infected with SARS-COV-2 was estimated by measuring the prevalence of antibodies to the new virus. The size of the MS population for the 14 centers was estimated from local pharmacy registries, and increased by 10% to account for untreated patients. IRs were then used to calculate incidence rate ratios (IRRs), defined as the IR for the MS population divided by the IR for the general population, to allow for comparison between populations.

The risk of hospitalization in patients with MS and COVID-19, relative to the general COVID-19 population in Spain,[12] was calculated by comparing the ratios of hospitalizations to cases in both populations. Lastly, the case-fatality rate (number of deaths divided by number of reported cases) for the registry (COVID-19/MS) population was compared with national data.[12]

Results

Study population

Of 5641 patients with MS treated at the 14 participating centers, 219 (3.9%) had confirmed or highly suspected COVID-19, and were entered into the registry. COVID-19 was confirmed in 101 (46.1%) patients (RT-PCR: 88 patients [40.2%]; ELISA: 13 patients [5.9%]), and highly suspected in 118 (53.9%) patients.

The demographic and MS-related characteristics of patients are summarized in **Table 1**. Most (82.2%) patients had relapsing-remitting MS (RRMS), and most had stable disease: 182 (83.0%) patients experienced no relapses in the previous year. The mean age of MS cases was 45.3 years. Compared with the Spanish MS population,[11, 13] the registry had a higher percentage of patients aged 30–50 years; however, no significant difference was found in the percentage of cases by age group in the MS and general populations (eFigure 1 in the

supplement). Consistent with this, comorbidities of interest were uncommon in the COVID-19/MS population; among patients with PCR-confirmed disease, diabetes, pulmonary disease, and cardiovascular disease were all significantly less prevalent than in the corresponding general Spanish COVID-19 population (**Table 2**). Lymphopenia was absent in most patients for whom data were available (152/177; 85.9%). Patients with MS had broadly similar symptoms of COVID-19 to the general population, but had a significantly higher incidence of pneumonia, colds, and diarrhea (**Table 2**).

In our study population, 63% of COVID-19 cases were in females, similar to the general Spanish COVID-19 population ($P = 0.12$). However, after adjusting for the approximately three-fold greater prevalence of MS in females than in males,[14] the risk of developing COVID-19 was found to be 1.67-fold higher in males versus females with MS.

Outcome of COVID-19 in MS patients

Fifty-one patients (23.3%) were hospitalized due to COVID-19. One patient (0.45%) was admitted to ICU, but did not require mechanical ventilation. This patient, a 36-year-old male, had been diagnosed with RRMS 2 years previously, had an EDSS score of 2.0, and was receiving alemtuzumab.

Sequential Organ Failure Assessment (SOFA) and CURB-65 scores were available for 71 and 57 patients, respectively; only one patient had a SOFA score >4 and two patients had CURB-65 scores ≥3.

Five patients died: 4 males aged 48–61 years and 1 female aged 57 years (eTable 1 in the supplement). Their median EDSS score was 8.0 (range 4.0–9.0), and time since diagnosis ranged from 3–27 years. All of those who died had secondary progressive MS, and all except one had known bilateral pneumonia and lymphopenia. Only one of the deceased patients was taking DMT (rituximab).

The outcome of COVID-19 by DMTs is shown in **Figure 1**. Most of the MS patients who were hospitalized for COVID-19 were receiving teriflunomide, ocrelizumab, rituximab or no treatment. MS patients receiving anti-CD20 monoclonal antibodies or not receiving DMT were more likely to have SPMS or PPMS compared with those receiving other treatments (**Figure 1)**.

Factors influencing hospitalization risk

Compared with non-hospitalized patients, hospitalized patients in our registry were significantly older (mean age ± standard deviation [SD]: 51.2 ± 13.7 vs 43.4 ± 11.4; $P < 0.01$) and had higher EDSS scores (mean ± SD score 4.26 ± 2.87 vs 2.27 ± 1.85; $P < 0.01$), as shown in **Figure 2** and eTable 2 in the supplement. In addition, hospitalized patients had significantly lower lymphocyte counts, and significantly higher C-reactive protein and fibrinogen levels, than non-hospitalized patients. Compared with patients in the Villar *et al.* registry (hospitalized patients with COVID-19, but without MS), hospitalized patients from the study population were significantly younger and had lower C-reactive protein levels.

In the univariable logistic regression analysis, the relapsing-remitting phenotype was associated with a reduced risk of hospitalization, whereas progressive forms of MS, an EDSS >3.0, and a history of smoking, diabetes or arterial hypertension were associated with an increased risk of hospitalization (**Figure 2** and eTable 3 in the supplement). However, in multivariable logistic regression, the only variable confirmed to reduce the risk of hospitalization was the relapsing-remitting phenotype (**Figure 2**; OR, 0.18; 95% CI, 0.08–0.41; $P < 0.001$). No variable or specific DMT was associated with an increased risk of hospitalization in the multivariable analysis.

Incidence of COVID-19 in MS patients

Using estimated IRs obtained from NSSE-C19,[11] the IRR for the registry population was 0.78

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1.For consistency with the text, use an upper case italicized *P* for the *P*-value
2. In panel C the data point representing the OR for diabetes is missing – please correct (the x-axis scale will need to be adjusted in order to show this)
3. In panel D relapsing-remitting MS is represented with the Spanish abbreviation 'EMRR'. Please change to the English language version 'RRMS'

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Perfect. Thank you for the observations. I will send you the new version:
1. p-value was replaced by *P*-value
2. The point representing the OR is now present and we adjusted the x-axis
3.EMRR was replaced by RRMS

(95% CI, 0.70–0.80). IRRs were <1 for all subgroups defined by age, except for patients aged 15–29 years (**Table 3;** IRR, 1.04; 95% CI, 0.79–1.28). Compared with the general population, infection probability was lower for female patients with MS and higher for male patients with MS.

The likelihood of hospitalization due to COVID-19 was significantly higher in MS patients compared with the general Spanish population (**Table 4**; RR, 5.03; 95% CI, 3.76–6.62). Among those with MS, males were 1.5–3.0 times more likely to be hospitalized than females.

Five patients with MS died, giving a case-fatality ratio of 0.023. This was significantly lower than in the Madrid region overall (0.062; 4258 deaths/68 984 cases; $P = 0.024$), but not compared with Spain overall (0.041; 7678 deaths/187 703 cases; $P < 0.23$).

Discussion

We present outcomes and incidence data from a registry of patients with MS diagnosed with COVID-19 at 14 centers in Madrid, one of the cities most affected during the first wave of the 2020 pandemic. Patients with MS in Madrid are in regular contact with neurologists, and are instructed to seek medical advice whenever they suspect infection. This allows for the greater detection of positive cases. Additionally, the organization of MS care in Madrid, with specialist clinics in each hospital, allowed us to accurately estimate the incidence of MS in our population.

In the general population, older age is a clear risk factor for diagnosis of COVID-19.[15-17] However, data from NSSE-C19 show that the distribution of antibodies to SARS-CoV-2 by age group is consistent with the population pyramid for Spain.[11] Thus, increasing age does not augment the risk of SARS-CoV-2 infection *per se*; however, it does increase the risk of a more severe clinical course, hospitalization, and death.[16] In agreement with this, we found

that patients with MS who were hospitalized with COVID-19 were significantly older than those who were not hospitalized.

Because of a lack of published data specific to the Spanish population, we were not able to adequately adjust our results for both age and comorbidities. Patients in our population had a lower prevalence of relevant comorbidities compared with the general Spanish COVID-19 population, probably because they were, on average, younger. These factors may partly explain the low rates of severe infection in our population, as measured by SOFA and CURB-65 scores; only one patient in our registry was admitted to an ICU. Interestingly, however, patients with MS were more likely to be hospitalized because of COVID-19 versus the general population. We postulate that this may be due to the use of admission criteria that prioritized patients with chronic comorbidities and/or taking immunosuppressive medication. Thus, despite having low disease severity, patients with MS may have been hospitalized as a precaution rather than because of risk to life, although the higher rates of pneumonia among MS patients may also have been a factor.

In agreement with the observations of other researchers,[18-21] we also believe that the low disease severity in many of our patients may be related to a protective effect of therapeutic immunosuppression against cytokine storm. Cytokine storm is associated with increased morbidity and mortality in COVID-19,[15, 22] and has been described as a consequence of lymphocyte dysregulation leading to over-activity in other parts of the immune response.[22, 23] Most DMTs used in MS either deplete or modulate these over-active cells, and there is therefore a mechanistic basis for protection against cytokine storm in DMT-treated patients with MS.

Some authors have proposed that DMT-treated patients with MS are at a higher risk of infection with SARS-CoV-2 or of having a more severe outcome due to their immune

status.[24-27] However, in our study, none of the DMTs used in MS were associated with an increased risk of hospitalization. Our results are similar to those reported by the Dutch group,[35] and indicate that no apparent difference exists in DMT use and COVID-19 disease course.

In contrast to the Italian group,[28] we did not find an association between the use of anti-CD20 monoclonal antibodies, interferon or corticosteroids and the outcome of COVID-19 in MS patients. With regard to anti-CD20 monoclonal antibodies, we found a higher percentage of hospitalized patients taking these drugs, but these patients were also more likely to have SPMS or PPMS. For this reason, we did not find an increased risk of hospitalization for patients taking anti-CD20 monoclonal antibodies in multivariable analysis. We believe that treatment in this case acts as a dependent factor, and that the *true* factor involved in the risk of hospitalization is the MS phenotype.

The small number of patients who died or were admitted to ICU does not permit correlation analysis, but our findings suggest that the course of COVID-19 in patients with MS is, overall, no worse than in the general population.

Some DMTs can induce sustained lymphopenia. In our study, there were no differences in the need for hospitalization between patients who had or did not have lymphopenia before SARS-CoV-2 infection. The only characteristic found to have a significant impact on hospitalization risk in our population was relapsing-remitting disease, which was associated with a lower risk of hospitalization for COVID-19. This finding may be explained by better functional status and less disability in RRMS patients compared to those with progressive forms of the disease. Indeed, all five of the deaths in our registry were in patients with SPMS; patients with this form of MS have a longer duration of disease, and might be more immunologically senescent than patients with RRMS. This may predict a worse outcome of

COVID-19.

Comparing our data with estimates based on data from the ongoing NSSE-C19 study allows for a more realistic calculation of the risk of COVID-19 in the MS population. In our analysis, patients with MS had a lower COVID-19 infection risk than the general Spanish population. However, to confirm this, we believe there is a need for an antibody prevalence study in the MS population to establish the exact risk of SARS-CoV-2 infection in MS patients compared with the general population.

Although men and women appear to have an equal risk of SARS-CoV-2 infection,[29, 30] the probability of a severe disease outcome or death is higher for men, both in Spain[12] and globally.[29-31] Our results in patients with MS are consistent with these findings. We found that the probability of COVID-19 (relative to the general population) was higher for male than female patients with MS. Additionally, the risk of hospitalization for COVID-19 (again, relative to the general population) was higher for males with MS than for females. Four of the five deaths in our study population were in men. The reasons for sex-based differences in disease course and outcome are not yet clear.

Our study has limitations that are common to many registry studies. Definitive cause-and-effect relationships can only be verified through well-designed prospective studies, and we cannot discount the influence of confounding factors on our findings. Moreover, although the study was conducted across multiple sites within the region, the results cannot necessarily be generalized to other settings within Spain or indeed to other countries. Nevertheless, our findings make an important contribution to knowledge at this early stage in our understanding of COVID-19 and its interaction with MS, and should be viewed in that context.

Conclusions

The risk of COVID-19 appears to be no greater in patients with MS than in the general Spanish population. We found a low risk of severe outcomes (ICU admission and death) in patients with MS and COVID-19, and a lower risk of COVID-19–related hospitalization for patients with RRMS versus other forms of MS. Our findings also suggest that outcomes of COVID-19 may be more severe in men, patients with SPMS, and those with greater disability. We did not find an association between the use of specific DMTs and an increased risk of hospitalization. MS is a debilitating disease, and the potential risks and benefits of starting or continuing DMTs must be carefully considered, alongside other factors such as age and comorbidities, in the context of the current pandemic.

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Author Contributions

I.M.T., L.C.F., J.M.G., and V.M.L. designed the study and the registry, enrolled patients, analyzed the data, and wrote and reviewed drafts of the manuscript. I.M.T. wrote the first draft. I.M.T., G.F.D., and V.E. performed the statistical analyses. C.O.J., C.A., E.M.A.S., M.G.M., L.B.C., J.S.M., Y.A., A.C.F., E.R.G., J.P.C., F.P.P., F.V.R., C.L.S.M., L.I.C.P., M.L.M.G., R.B.Q., S.S.M., E.M., M.L.V.G., C.S., M.E., and A.I.O.G. enrolled patients, and reviewed drafts of the manuscript.

All authors approved the final version for submission.

Conflict of Interest/Disclosures

I. Moreno-Torres. has received honoraria for lecturing or assistance for conference attendance from Bayer, Biogen, Merck, Teva, Novartis, Roche, and Genzyme, and research grants from Novartis; V. Meca-Lallana has received consulting or speaking fees from Almirall, Biogen, Genzyme, Merck Serono, Novartis, Roche, Terumo, Sanofi, Teva, and Celgene; L. Costa-Frossard has received funding for research projects or in the form of conference fees, mentoring, and assistance for conference attendance from Bayer, Biogen,

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Data availability statement

The original data presented in this article are available to download (in .xlsx format) from: http://dx.doi.org/10.17632/cczx45n32y.1

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Table captions

Table 1. Baseline characteristics of the study population (N = 219)

Table 2. Comorbidities, risk factors and symptoms†

Table 3. Incidence rates (IR) and incidence rate ratio (IRR) of COVID-19 in MS patients

Table 4. Relative risk (RR) of hospitalization for COVID-19 in MS patients

Figure captions

Figure 1. Outcome of COVID-19 in MS patients according to DMTs.

The bars show the number of patients who were not hospitalized (blue), hospitalized (orange), admitted to an ICU (green) or died (red) for each treatment. On the right, age, EDSS and MS phenotype are shown for each treatment. Continuous variables are presented as mean ± standard deviation.

COVID-19, coronavirus disease 2019; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; Hosp, hospital; ICU, intensive care unit; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; y, years.

Figure 2. Risk factors for hospitalization in MS patients with COVID-19. **Panels A and B:** comparison of median age (A) and EDSS (B) between non-hospitalized patients and hospitalized patients (*P* values from Wilcoxon rank-sum test). Horizontal lines within each colored box indicate the median and interquartile range, while the whiskers indicate the range of values. Outliers are indicated by diamond symbols. **Panels C and D:** risk factors for hospitalization, with odds ratios and 95% confidence intervals. Univariable logistic regression is shown in panel C, and multivariable logistic regression with L1 penalty (Lasso regression) is shown in panel D. Complete logistic regression data are shown in eTable 3 in the supplement. Additional notes on panel D: lymphocyte counts are $\times 10^9$/L; alemtuzumab, cladribine, fingolimod, glatiramer acetate, ocrelizumab and rituximab were penalized in the Lasso regression, and are thus excluded. Lymphocyte counts in panel C are in cells/µL.

COVID-19, coronavirus disease 2019; DMTs, disease-modifying treatments; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary progressive

multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.