COVID-19 outcomes in patients with multiple sclerosis: understanding changes from 2020 to 2022

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ABSTRACT

Background: Epidemiologic studies on COVID-19 in patients with multiple sclerosis (pwMS) have focused on the first waves of the pandemic until early 2021. We aimed to extend these data from the onset of the pandemic to the global coverage by vaccination in summer 2022.

Methods: This retrospective, multicenter observational study analyzed COVISEP registry data on reported COVID-19 cases in pwMS between January 2020 and July 2022. Severe COVID-19 was defined as hospitalization or higher severity.

Results: Among 2584 pwMS with confirmed/highly suspected COVID-19, severe infection rates declined from 14.6% pre-omicron wave to 5.7% during omicron wave ($p<0.001$). Multivariate analysis identified age (OR 1.43, 95CI[1.25-1.64] per 10 years), male sex (OR 2.01, 95CI[1.51-2.67]), obesity (OR 2.36, 95CI[1.52-3.68]), cardiac comorbidities (OR 2.36, 95CI[1.46-3.83]), higher EDSS scores (OR 2.09, 95CI[1.43-3.06] for EDSS 3-5.5 and OR 4.53, 95CI[3.04-6.75] for EDSS $\geq$ 6) and anti-CD20 therapies (OR 2.67, 95CI[1.85-3.87]) as risk factors for COVID-19 severity. Vaccinated individuals experienced less severe COVID-19, whether on (risk ratio (RR) 0.64, 95CI[0.60-0.69]) or off (RR 0.32, 95CI[0.30-0.33]) anti-CD20.

Discussion: In pwMS, consistent risk factors were anti-CD20 therapies and neurological disability, emerging as vital drivers of COVID-19 severity regardless of wave, period, or vaccination status.

INTRODUCTION

The COVID-19 pandemic has profoundly changed global healthcare structure. Patients with multiple sclerosis (MS) were particularly at risk for severe COVID-19 in the context of a disabling inflammatory disease with immunomodulating or immunosuppressive disease-modifying therapies (DMT). Commonly accepted risk factors for severe COVID-19 in the general population, such as older age, cardiac comorbidities, obesity and male sex[1] have also been identified as risk factors in patients with MS (pwMS).[2] Moreover, progressive disease course,[3] high Expanded-Disability Status Scale (EDSS) scores and disease duration[4] have been shown to be independent determinants of COVID-19 lethality in pwMS.

Treatment strategies in MS now include early initiation of highly effective DMT, inducing a higher risk of infection.[5] Patients on anti-CD20 therapies or recent (<1 month) methylprednisolone have a higher risk of severe COVID-19, independently of other factors such as age, EDSS score, male sex and disease duration.[6] Additionally, pwMS on anti-CD20 therapies have lower immune responses to SARS-CoV-2 infection.[7] Patients with MS can present lower immune responses to vaccination,[8] particularly with anti-CD20 and fingolimod.[9,10]

However, most epidemiological studies investigating COVID-19 severity in pwMS are based on data from the first waves of the pandemic in 2020 or early 2021. [6,11–17] The emergence of new SARS-CoV-2 variants of varying severity,[18] the development of vaccines with efficacy against symptomatic infections[19,20] and the subsequent massive vaccination campaigns launched in 2021 to stop the pandemic have changed the epidemiology, risk factors, and outcomes for COVID-19. COVID-19 severity was reduced during the delta and omicron waves, likely reflecting the effect of vaccination and modified severity of these variants.[21]

In this study, we aimed to describe the evolution of COVID-19 presentations in pwMS over time, from the beginning of the pandemic to global vaccination coverage at the end of summer 2022, using data from the COVISEP database, an extensive multicenter declarative registry on COVID-19 infections in pwMS from MS centers belonging to the French MS Society. We analyzed whether risk factors for severe COVID-19 changed with successive SARS-CoV-2 variants and widespread access to vaccination.

METHODS

Population. The COVISEP registry is a multicenter, retrospective, observational study collecting data on confirmed or highly suspected COVID-19 in pwMS. Forty-nine centers including MS expert centers, general hospitals and private practice neurologists from the French MS Society (Société Francophone de la SEP, SFSEP) participated in data collection. Data from the COVISEP registry collected between March 1, 2020 and May 21, 2020 have been previously reported.[14] This study focuses on data from the COVISEP registry between January 1, 2020 and July 31, 2022.

Inclusion criteria. Patients with MS and at least one of the following criteria were included: (1) positive result of a SARS-CoV-2 polymerase chain reaction (PCR) test on a nasopharyngeal swab; (2) typical thoracic computed tomography (CT)-scan abnormalities (namely, ground-glass opacities in epidemic areas); (3) sudden onset of anosmia or ageusia in the absence of rhinitis or nasal obstruction; or (4) COVID-19 symptoms (cough, fever and asthenia) in an epidemic area. Only first SARS-CoV-2 infections were considered. The non-inclusion criterion was the patient's refusal to have their medical information used.

Collected data. Data were collected from patient's medical records using an electronic clinical record form on RedCap (https://www.project-redcap.org/). Collected data included age and disease course, EDSS score before COVID-19, comorbidities, current DMT, chest CT-scan, PCR data for SARS-CoV-2, COVID-19 symptoms and severity.

Endpoints. The primary endpoint was COVID-19 severity on a seven-point ordinal scale,[22] referred to as the COVID-19 severity score: a score of 1 indicated no hospitalization or limitations on activities; 2 indicated no hospitalization but limitation of activities; 3 indicated hospitalization without supplemental oxygen requirement; 4 indicated hospitalization and supplemental oxygen requirement; 5 indicated hospitalization and non-invasive ventilation or high-flow oxygen requirement; 6 indicated

hospitalization and invasive mechanical ventilation or extracorporeal membrane oxygenation; and 7 meant death from COVID-19. A score of 3 was considered the threshold for severe COVID-19.

Ethics. The study protocol is registered on ClinicalTrials.gov (NCT04355611) and at the Institut National des Données de Santé for confidential electronically processed patient data. The ethics committee of Sorbonne University approved the study. Patients were informed of the purpose of the study, and the collection of non-opposition (consent) to the use of medical data was carried out according to French law, good clinical practice, and the General Data Protection Regulation. Data were managed by the STROBE Statement Checklist (https://www.strobe-statement.org/checklists/).

Statistical analysis. Descriptive results were expressed as counts and frequencies for categorical variables and medians [interquartile range, IQR] or mean (standard deviation) for quantitative variables. Group comparisons were performed using Mann-Whitney U-test for numerical and ordinal variables, and Fisher or chi-square tests when appropriate for categorical variables. Two-sided $p < .05$ was considered statistically significant. Differences in COVID-19 severity rates between subgroups were estimated by risk ratios (RR). Multivariate logistic regression models assessed the association of selected variables with COVID-19 severity, defined as COVID-19 severity score ≥3. Selected variables were chosen based on previous studies investigating risk factors of COVID-19 severity in pwMS.[11,14,23] Age was considered as a continuous variable, EDSS was divided into three bins (<3, 3-5.5, and ≥6), DMTs were categorized into 4 classes: no DMT, anti-CD20 (*i.e.* ocrelizumab, rituximab, ofatumumab), fingolimod, other DMT. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). McFadden pseudo-R^2 values were calculated for each variable to quantify the proportion of total outcome variability accounted for by the model. Missing data were not imputed and only complete datasets were analyzed for multivariate models. After a qualitative analysis of COVID-19 severity according to the date of infection between 2020 and 2022, we pre-specified period and subgroup analyses for logistic regression models to determine risk factors associated with severe COVID-19 as follows: i) before omicron wave from 01/01/2020 until 20/12/2021; ii) after omicron wave, from 21/12/2021 until 31/07/2022; iii) after the onset of generalized vaccination

campaign, from 01/07/2021 until 31/07/2022; iv) within vaccinated patients only, with ≥2 injections of anti-SARS-CoV-2 vaccine. Data analyses were performed in Python version 3.9.12 (Python Software Foundation) using Pandas package version 1.4.2, Scipy version 1.7.3, and Statsmodels version 0.13.2.

RESULTS

Patients' characteristics

Patients' characteristics and COVID-19 data are represented in **Table 1**. A total of 2584 pwMS with confirmed or highly suspected COVID-19 were reported to the COVISEP registry between January 1st, 2020 and July 31st, 2022. The mean age at the time of SARS-CoV-2 infection was 43.9 (SD 12.6) years and 1879 (72.7%) patients were female. The main disease course was relapsing-remitting MS (RRMS) in 1982 (76.7%) patients, followed by secondary progressive MS (SPMS) in 367 (14.2%), primary progressive MS (PPMS) in 197 (7.6%) and clinically isolated syndrome (CIS) in 27 (1.0%) patients. A total of 669 (25.9%) patients received anti-CD20 therapy, including ocrelizumab in 476 (18.5%), rituximab in 187 (7.3%) and ofatumumab in 6 (0.2%). Other DMTs included fingolimod in 292 (11.3%), natalizumab in 271 (10.5%), platform DMT in 748 (28.9%) and no ongoing DMT in 518 (20.1%). Cardiovascular comorbidities were found in 112 (4.3%) and obesity in 168 (6.5%) patients. Of 2273 SARS-CoV-2 PCR performed, 2187 (96.2%) were positive, and 224/460 (48.7%) patients had ground-glass opacities on chest CT scans. The majority of COVID-19 were not severe (*i.e.* score of 1-2 on the COVID-19 severity scale), 286 (11.1%) patients reached the severity grade of 3 indicating hospitalization, 21 (0.8%) were on invasive mechanical ventilation or ECMO and 22 (0.9%) died from COVID-19. Overall, 604 (23.3%) patients received at least two injections of SARS-CoV-2 vaccine.

Number and severity of COVID-19 cases over time

The number of COVID-19 cases in the COVISEP registry and the proportion of severe cases according to SARS-CoV-2 waves and variants in France are shown in **Figure 1.** The number of cases increased consistently with the presence of an epidemic wave; the proportion of severe cases was highest during the original (17.8% during the 1st wave) and delta (19.8%) variants. The proportion of severe infections decreased from 14,6% (254/1735) before the omicron wave to 5.7% (32/563) during the omicron wave ($p<0.001$), and started to decrease steadily from October 2021, corresponding to 4 months after the availability of SARS-CoV-2 vaccination for all pwMS in France (i.e., July 2021).

Throughout the data collection period, most severe COVID-19 (severity score ≥3) were found in patients treated with ocrelizumab (61/476, 12.8%), rituximab (61/187, 32.6%), and in patients without ongoing DMT (81/518, 15.6%), as illustrated in **Figure 2A and B**.

Multivariate logistic regression models of severe COVID-19 (2020-2022)

Figure 3A shows the results of the multivariate analysis estimating the association between demographic or clinical variables and COVID-19 severity for the entire cohort (from January 2020 to July 2022), and **Figure 3B** shows the cumulative variance for significantly associated risk factors (see **Suppl. Table 1** for detailed values). Among the studied variables, older age was associated with higher COVID-19 severity (OR 1.43, 95CI[1.25-1.64] per 10 years), as were male sex (OR 2.01, 95CI[1.51-2.67]), obesity (OR 2.36, 95CI[1.52-3.68]), and cardiac comorbidities (OR 2.36, 95CI[1.46-3.83]). Higher EDSS scores were positively associated with severe COVID-19 (OR 2.09, 95CI[1.43-3.06] for EDSS of 3-5.5 and OR 4.53, 95CI[3.04-6.75] for EDSS ≥ 6). Anti-CD20 therapies was associated with a higher risk of severe COVID-19 (OR 2.67, 95CI[1.85-3.87]) versus other DMTs, in contrast to fingolimod (OR 0.99, 95CI[0.56-1.76] or no DMT (OR 1.26, 95CI[0.84-1.89]). Vaccination (with ≥2 injections) was associated with a lower risk of severe COVID-19 (OR 0.45, 95CI[0.31-0.65]). EDSS showed the highest variance accounting for COVID-19 severe outcome ($R^2_{McFadden} = 0.139$).

Multivariate logistic regression models of severe COVID-19 in different periods and subgroups

Figure 4 presents multivariate analyses of variables associated with severe COVID-19 in different periods and subgroups of patients as pre-specified. Before the omicron wave, from January 2020 to December 2021, including 1735 cases (**Figure 4A**), risk factors associated with COVID-19 severity were similar to those observed in the whole period, including age (OR 1.48, 95CI[1.28-1.71]), male sex (OR 1.79, 95CI[1.31-2.43]), obesity (OR 2.13, 95CI[1.31-3.45]), cardiac comorbidities (OR 2.65, 95CI[1.59-4.42]), higher EDSS scores (OR 2.32, 95CI[1.55-3.48] for EDSS of 3-5.5 and OR 4.45, 95CI[2.9-6.81] for EDSS ≥6), and treatment with anti-CD20 therapies (OR 2.72, 95CI[1.88-2.73]). Two-dose vaccination was not associated with a lower risk of severe COVID-

19 in this specific period (OR 0.79 95CI[0.46-1.34]). During the omicron wave, from January 2022 to July 2022, including 563 cases (**Figure 4B**), male sex (OR 3.46, 95CI[1.52-7.86]), obesity (OR 3.76, 95CI[1.13-12.47]), EDSS scores ≥6 (OR 6.56, 95CI[1.90-22.67]) and anti-CD20 therapies (OR 3.55, 95CI[1.11-11.36]) were associated with severe COVID-19. Sensitivity analyses conducted on biologically confirmed cases only (n=2282) yielded results consistent with the entire cohort. Similarly, during the period starting from the global vaccination campaigns (July 2021 to July 2022), including 892 cases (**Figure 4C**), age (OR 1.34, 95CI[1.03-1.74]), male sex (OR 3.08, 95CI[1.75-5.42]), obesity (OR 4.46, 95CI[1.95-10.24]), EDSS scores ≥6 (OR 3.70, 95CI[1.63-8.36]) and treatment with anti-CD20 therapies (OR 4.20, 95CI[1.98-8.89]) were associated with higher COVID-19 severity, while vaccination was associated with lower severity (OR 0.49, 95CI[0.27-0.88]).

COVID-19 severity in vaccinated patients

In the subgroup of patients with ≥2 injections of anti-SARS-CoV-2 vaccine, including 604 cases (**Figure 4D**), age (OR 1.34, 95CI[1.03-1.74]), male sex (OR 3.08, 95CI[1.75-5.42]) and anti-CD20 therapies (OR 4.20, 95CI[1.98-8.89]) were the only factors associated with higher COVID-19 severity. **Supplementary Table 2** presents the number of severe cases in unvaccinated and vaccinated patients according to DMT subgroups. Severe COVID-19 cases were more frequent in patients receiving anti-CD20 compared to those not receiving anti-CD20, both in unvaccinated (21.3% versus 9.8%, p <0.001) and vaccinated patients (13.6% versus 2.8%, p <0.001). Severe COVID-19 was less frequent in vaccinated patients versus unvaccinated patients, both in patients receiving anti-CD20 (relative reduction = 36.1%, risk ratio (RR) = 0.64, 95CI = 0.60–0.69, p <0.001) and in patients not receiving anti-CD20 (relative reduction = 71.4%, RR = 0.32, 95CI = 0.30–0.33, p <0.001).

DISCUSSION

In this large multicenter, observational, retrospective study based on the COVISEP registry, we present the evolution of COVID-19 severity in 2584 pwMS from the first original variants through the vaccination campaigns and omicron wave. We observed a significant decrease of severe COVID-19 from the onset of the omicron wave. Importantly, regardless of the time period, even during the omicron wave, anti-CD20 and neurological disability were consistently associated with COVID-19 severity. Similarly, among vaccinated patients, the use of anti-CD20 was still associated with increased severity. Vaccination was associated with a risk reduction of severe COVID-19 in patients on anti-CD20 and not on anti-CD20, but with a lower magnitude for patients on anti-CD20.

The first original viruses and the delta variant were responsible for the largest peaks of severe infections, while the omicron wave showed a significant increase in case reports but milder infections, as observed in the general population.[24,25] In France, patients on anti-CD20 therapies were targeted for priority SARS-CoV-2 vaccination before extension to all pwMS and the general population. Afterwards, severe cases decreased drastically, probably due to immunity acquired from previous infections and vaccination.

The risk factors for severe infection evolved with successive variants and the development of vaccines. Our multivariate analysis found that risk factors for severe COVID-19 in the general population were also found in pwMS, including age, male gender, obesity and cardiovascular comorbidities.[1] In our study, anti-CD20 therapies remained independent risks factors for COVID-19 severity during all periods of interest, including those with an absolute lower severity risk. Several studies have described the association between COVID-19 severity and anti-CD20.[6,11,15,26,27] Additionally, in the subgroup analysis of patients vaccinated in 2021-2022, anti-CD20 exposure was the only factor associated with a more severe outcome, along with age and male sex. This is in line with the efficacy of vaccination campaigns in decreasing viral transmission and reducing severe infections in the general population, but with a modest efficacy in immunocompromised patients, especially those receiving B-cell depleting treatments. This modest efficacy is probably due to the poor humoral responses to vaccines with anti-CD20 therapies, as previously reported.[28,29] However, despite a lower vaccine efficacy in pwMS on anti-CD20, we could estimate a mild but significant

reduction in the risk of severe COVID-19 in vaccinated versus unvaccinated patients. Given the overlap between the period of vaccination and the omicron wave, it remains difficult to estimate the contribution of these 2 factors in the observed lower severity in vaccinated patients on anti-CD20 versus unvaccinated patients. Our data did not allow us to disentangle these effects as the number of unvaccinated patients on anti-CD20 during the omicron wave needed to be higher. Intriguingly, treatment with sphingosine-1-phosphate receptor modulator (S1PRM) was not associated with COVID-19 severity, despite initial fear among neurologists.[30,31] No other study has reported an increased COVID-19 severity in patients treated with S1PRM, which is however associated with a poor humoral and cellular vaccine response against SARS-CoV-2. Unlike B cell depletion therapies, we could speculate that lymphocyte trapping does not limit the standard immune response to SARS-CoV-2.

In patients with high EDSS scores, it can be difficult to distinguish between the risk of severe COVID-19 linked to disability and that linked to the type of DMT used. Indeed, among DMT, studies showed that patients on rituximab therapy had a higher risk of severe COVID-19 compared with other types of treatments, including ocrelizumab.[32] However, patients on rituximab often present with older age, progressive disease course and higher EDSS scores. A recent study[23] confirmed that in patients treated with anti-CD20 therapies, patients with progressive MS had a higher risk of severe COVID-19 than patients with RRMS; however, the use of anti-CD20 therapies was not responsible for this increased COVID-19 severity in patients with progressive MS, suggesting a key role for disability. In addition, in a systematic review of COVID-19 in pwMS conducted during the first year of the pandemic, patients with no DMT, who often suffer from progressive MS, had the highest hospitalization and mortality rates.[33] Consistently with these data, our study showed that neurological disability remained a key variable associated with COVID-19 severity in all the studied periods. Interestingly, high EDSS was not significantly associated with COVID-19 severity among vaccinated patients in our multivariate model, highlighting the importance of vaccination in patients with high disability. Finally, the absence of DMT was not associated with more severe infections in our multivariate analysis, which included age and EDSS scores as potential confounders, suggesting that the absence of treatment itself was not associated with severity.

Our study has several limitations. Firstly, the declarative case ascertainment may not perfectly reflect the epidemiology of SARS-CoV-2 in pwMS. The large number of cases during the omicron wave may have made it difficult for physicians to update the declarations, many infections may have remained asymptomatic (especially with vaccination) and the advent of antigenic self-testing may have led physicians to miss infections. Secondly, the retrospective design exposes to missing data. For instance, while the delay between the last anti-CD20 infusion and vaccine dose has been shown to influence vaccine response, all the dates of anti-CD20 infusions were not collected in our study, and we only had records of the last infusion before the onset of a COVID-19 infection. We we did not collect serology data to assess responses to vaccination, therefore we cannot assess if the higher rates of COVID-19 among patients on anti-CD20 therapies were linked to poor vaccine response, as studies have suggested lower antibody rates in these patients. Moreover, we considered proven (with a positive PCR for SARS-CoV-2) or probable (with CT-scan abnormalities or highly suggestive clinical symptoms) SARS-CoV-2 infections for inclusion in the COVISEP registry. Thirdly, our study lacks information on long-term outcomes after COVID-19, such as residual symptoms, possible disease reactivation, or disability status.

Our study is a large, multicenter observational study of 2584 patients with multiple sclerosis who presented with COVID-19 from the first waves in January 2020 to the end of vaccination campaigns in July 2022, describing a comprehensive history of COVID-19 epidemiology and the evolution of severity factors in this population. Severe cases decreased with the omicron wave and mass vaccination. Regardless of the wave or period, consistent risk factors were treatment with anti-CD20 therapies and disability, making these elements important drivers of COVID-19 severity.

Authors contributions

Dr Louapre has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Louapre, Papeix

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Jeantin, Louapre

Critical revision of the manuscript for important intellectual content: All authors

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Data availability: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of interests

Lina Jeantin reports no disclosure.

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Bruno Stankoff reports research support from Roche, Sanofi, and Merck and personal fees for lectures or advisory boards from Novartis, Sanofi, Biogen, Janssen, and Merck

Pierre Clavelou reports receiving personal fees for board participation from Janssen and Novartis and for board participation and travel from Sanofi and Merck outside the submitted work.

Eric Thouvenot reports receiving personal fees from Biogen, BMS, Janssen, Horizon, Merck, Novartis, and Sanofi outside the submitted work.

Eric Manchon reports no disclosure.

Thibault Moreau reports receiving travel grants and fees for advisory boards from Biogen, Roche, Novartis, Sanofi, and Teva outside the submitted work.

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Mickaël Zedet reports receiving expert testimony from Alexion and Novartis, and travel grants from Merck, Roche and Sanofi Aventis France.

Caroline Papeix receiving honoraria and consulting fees from Alexion, Biogen, Merck, Horizon, and Roche outside the submitted work and serving as president of the Francophone Multiple Sclerosis Society from 2021 to 2024.

Celine Louapre has received consulting or travel fees from Biogen, Novartis, Roche, Sanofi, Teva and Merck Serono, and research grant from Biogen.

Appendix: COVISEP Study group

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CH Libourne	Arnaud Gagnol
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Table 1: Patients characteristics and COVID-19 data.

Variable	n = 2584
Age – mean (SD) *	43.9 (12.6)
Female gender – no. (%) **	1879 (72.7)
Disease duration – mean (SD)	12.7 (9.9)
Disease course – no. (%) †	
RRMS	1982 (76.7)
SPMS	367 (14.2)
PPMS	197 (7.6)
CIS	27 (1.0)
EDSS – median [range] ††	2.0 [0.0-9.5]
Disease-modifying therapies – no. (%) ‡	
Ocrelizumab	476 (18.5%)
Fingolimod	292 (11.3%)
Natalizumab	271 (10.5%)
Dimethylfumarate	262 (10.2%)
Teriflunomide	202 (7.8%)
Rituximab	187 (7.3%)
Interferon beta	135 (5.2%)
Glatiramer	135 (5.2%)
Cladribine	14 (0.5%)
Ofatumumab	6 (0.2%)
Alemtuzumab	4 (0.2%)
Other ‡‡	72 (2.8%)
No DMT	518 (20.1%)
Comorbidities – no. (%)	
Smoking	239 (9.2%)
Obesity (BMI >30 kg/m^2)	168 (6.5%)
Cardiovascular disease	112 (4.3%)
Pulmonary disease	67 (2.6%)
Diabetes	54 (2.1%)
COVID-19 diagnosis – no. (%)	
Positive SARS-CoV-2 rt-PCR	2187/2273 (96.2%)
Ground glass opacity on thoracic CT scan	224/460 (48.7%)
COVID-19 symptoms – no. (%)	
Asthenia	2020 (78.2)
Fever	1536 (59.4)
Cough	1514 (58.6)
Headache	1269 (49.1)
Anosmia/agueusia	1171 (45.3)
Dyspnea	749 (29.0)
Digestive disorders	560 (21.7)
Dizziness	353 (13.7)
COVID-19 severity – no. (%)	
Grade 1: Not hospitalized, no limitations on activities	1064 (41.2)
Grade 2: Not hospitalized, limitation on activities	1234 (47.6)
Grade 3: Hospitalized, not requiring supplemental oxygen	70 (2.7)
Grade 4: Hospitalized, requiring supplemental oxygen	121 (4.7)
Grade 5: Hospitalized, or noninvasive ventilation or high-flow oxygen devices	52 (2.0)
Grade 6: Hospitalized, on invasive mechanical ventilation or ECMO	21 (0.8)
Grade 7: Death	22 (0.9)
Vaccination (at least 2 injections) – no. (%)	604 (23.3)
Type of vaccine §	
BNT162b2	460/604 (71.1)
mRNA-1273	85/604 (14.1)
ChAdOx1 nCoV-19	28/604 (4.6)

Data missing for: * 7 patients, ** 2 patients, † 11 patients, †† 91 patients, ‡ 10 patients, § 31 patients

‡‡ Other treatments included: mycophenolate mofetil (n = 16), azathioprine (n = 14), methotrexate (n = 13), biotin (n = 3), cyclophosphamide (n = 2), mitoxantrone (n = 1), methylprednisolone (n = 1) and phase 2 or phase 3 pharmacological protocols (n = 22).
Abbreviations: DMT (Disease-modifying therapy), EDSS (Expanded Disability Status Scale)

Figure 1: Number of cases of COVID-19 in the COVISEP registry and proportion of severe cases according to SARS-CoV-2 waves and variants in France.

The figure represents the data from the COVISEP registry about declared COVID-19 in patients with MS between January 2020 and July 2022. The five waves of COVID-19 in France and the main circulating variants are represented. The bar plots represent the number of COVID-19 cases in the COVISEP registry (in blue) and the number of severe COVID-19 (i.e. severity score of 3 or over, indicated hospitalization, in orange). The yellow line graph represents the proportion of patients with severe COVID-19 among cases and its fluctuations with COVID-19 variants, calculated over 45 rolling days before and after the considered date.

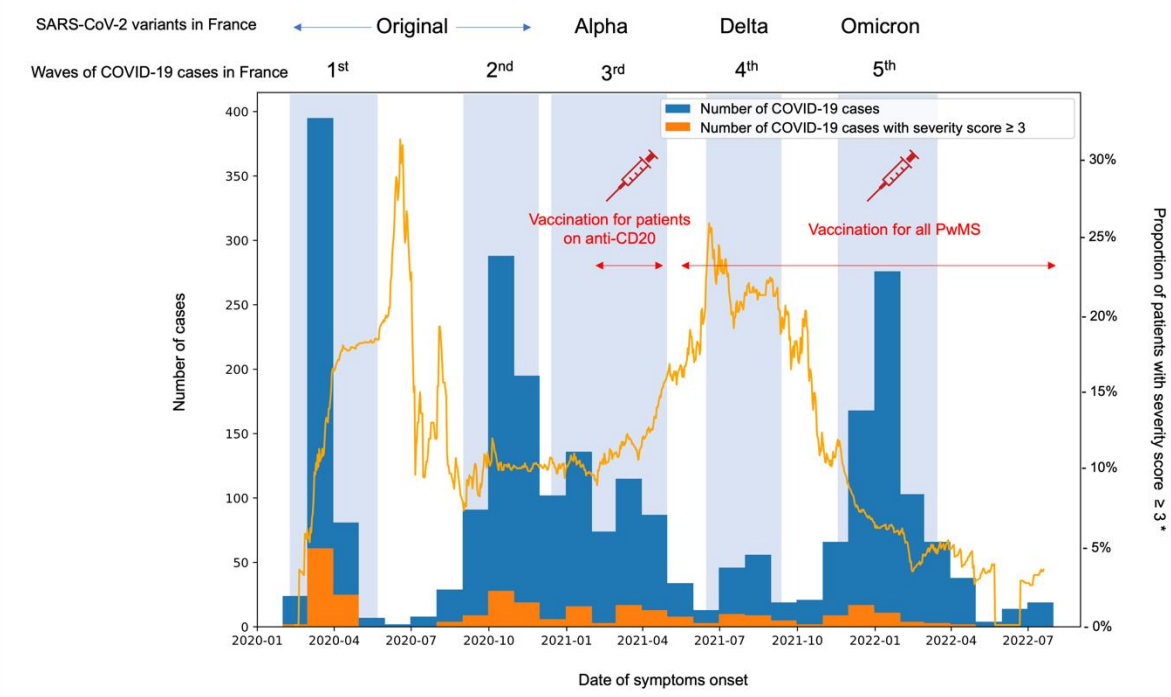


Figure 2: COVID-19 number of cases and severity according to treatment groups.

A: COVID-19 number of cases according to treatment groups. The ratio on top of each bar represents the number of severe cases (*i.e.* COVID-19 severity score of 3 or more) out of the total number of cases.

B: Percentage of severe COVID-19 cases according to treatment groups.

Other treatments included: mycophenolate mofetil (n = 16), azathioprine (n = 14), methotrexate (n = 13), biotin (n = 3), cyclophosphamide (n = 2), mitoxantrone (n = 1), methylprednisolone (n = 1) and phase 2 or phase 3 pharmacological protocols (n = 22).

COVID-19 severity score: a score of 1 indicated no hospitalization or limitations on activities; 2 indicated no hospitalization but limitation of activities; 3 indicated hospitalization without supplemental oxygen requirement; 4 indicated hospitalization and supplemental oxygen requirement; 5 indicated hospitalization and noninvasive ventilation or high-flow oxygen requirement; 6 indicated hospitalization and invasive mechanical ventilation or extracorporeal membrane oxygenation; and 7 indicated death from COVID-19. A score of 3 was considered the threshold for severe COVID-19 (requiring hospitalization).

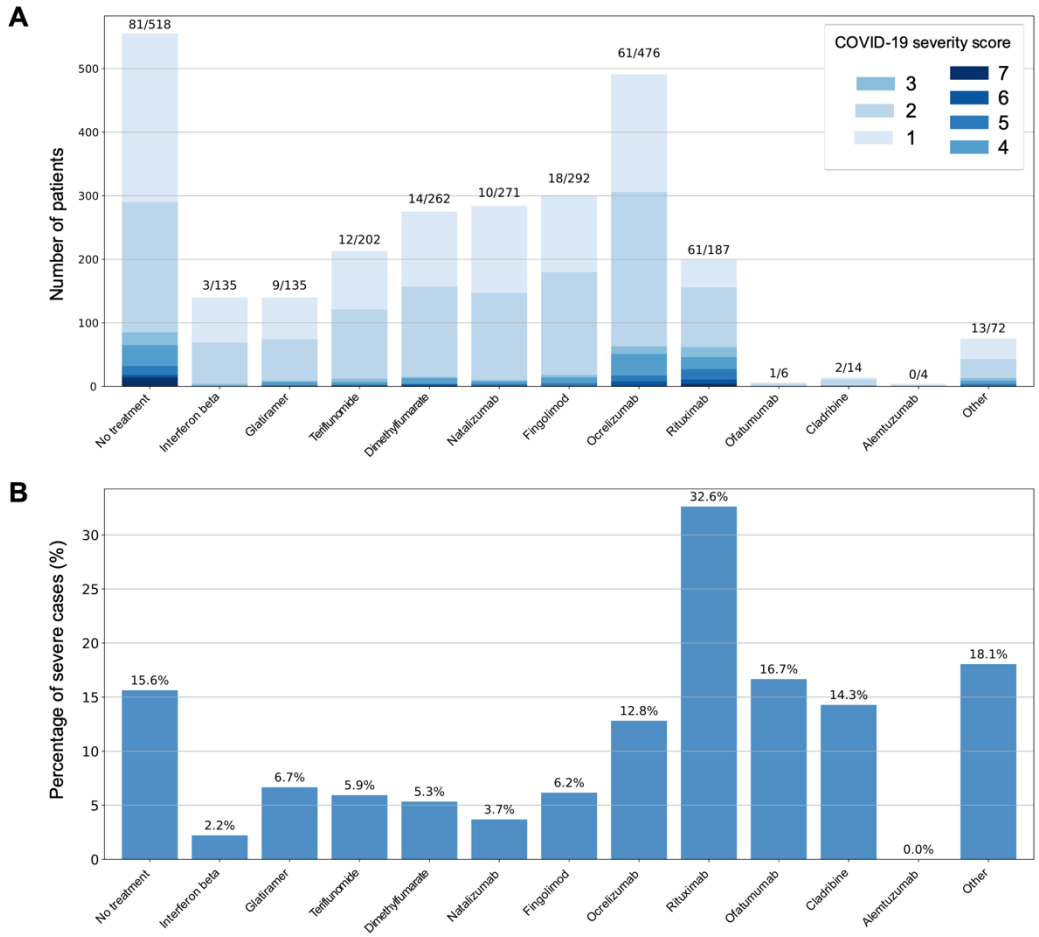


Figure 3: multivariate analysis for clinical factors associated with COVID-19 severity in patients with MS for the whole cohort.

A: multivariate analysis for clinical factors associated with COVID-19 severity (*i.e.* severity score of 3 or more, indicating hospitalization).

B: Cumulative R^2 for COVID-19 severity including EDSS, age, treatment with anti-CD20, vaccination, sex, cardiopathy and obesity.

Abbreviations: DMT (Disease-modifying therapy), EDSS (Expanded Disability Status Scale)

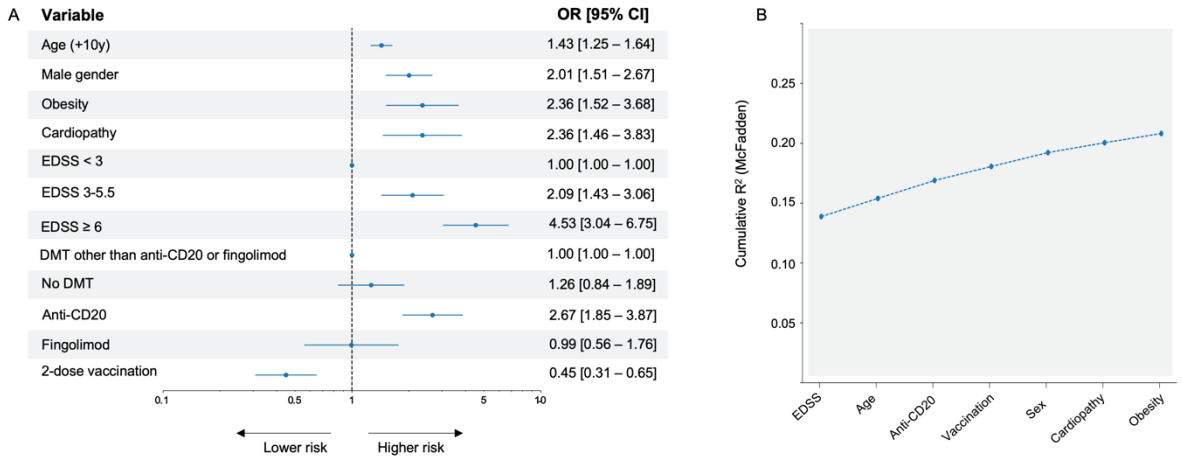


Figure 4: Multivariate analyses of factors associated with COVID-19 severity in patients with MS before and after omicron wave, during vaccination campaigns, and among vaccinated patients

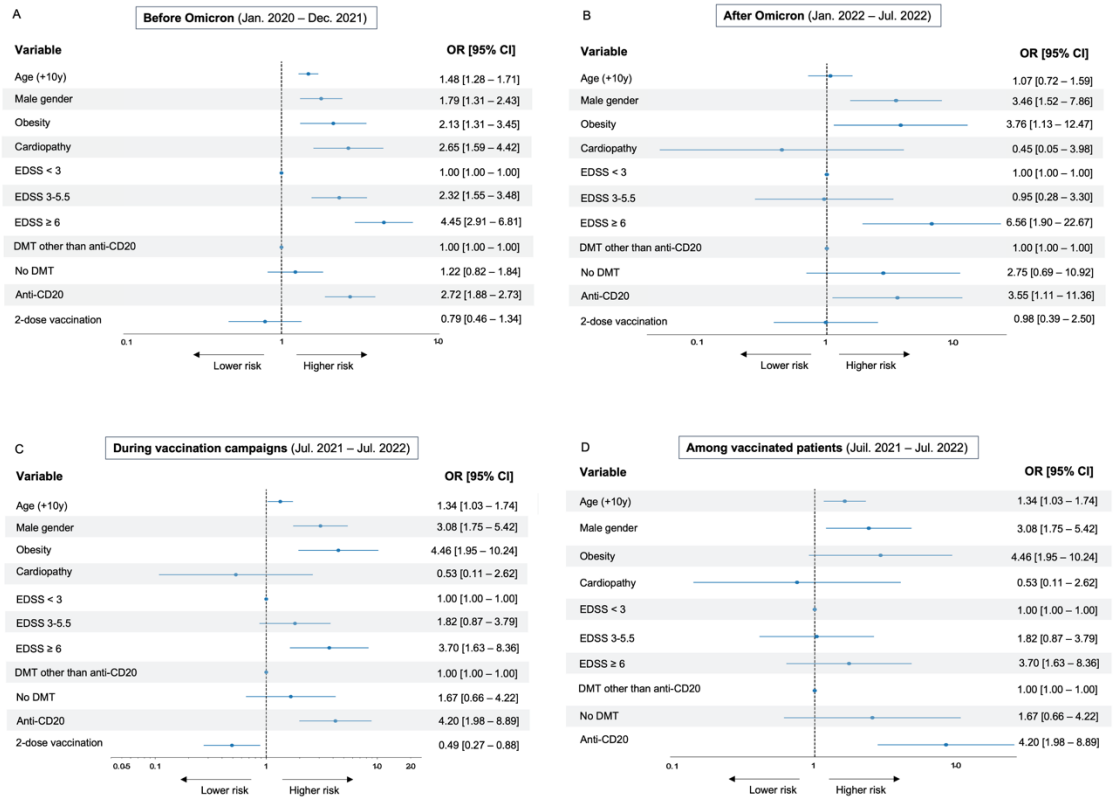
A: Multivariate analysis of clinical factors associated with COVID-19 severity before the omicron wave (from January 2020 to December 2021), n=1735

B: Multivariate analysis of clinical factors associated with COVID-19 severity during the omicron wave (from January 2022 to July 2022), n=563

C: Multivariate analysis of clinical factors associated with COVID-19 severity during vaccination campaigns (from July 2021 to July 2022), n=892

D: Multivariate analysis of clinical factors associated with COVID-19 severity among vaccinated patients only (from July 2021 to July 2022), n=604

Abbreviations: DMT (Disease-modifying therapy), EDSS (Expanded Disability Status Scale)



Suppl. Table 1: Cumulative variance values in the multivariable analysis for COVID-19 severity in the whole cohort.

Variables	Cumulative variance
EDSS	0.139
EDSS + Age	0.154
EDSS + Age + Anti-CD20	0.169
EDSS + Age + Anti-CD20 + Vaccination	0.181
EDSS + Age + Anti-CD20 + Vaccination + Gender	0.192
EDSS + Age + Anti-CD20 + Vaccination + Gender + Cardiopathy	0.200
EDSS + Age + Anti-CD20 + Vaccination + Gender + Cardiopathy + Obesity	0.208

Abbreviations: EDSS (Expanded Disability Status Scale)

Suppl. Table 2: Number of severe COVID-19 cases according to vaccination status and anti-CD20 exposure

DMT	Vaccination	Number (%) of severe COVID-19 / COVID-19 cases
No DMT or DMT other than anti-CD20	No	153 / 1565 (9.8%)
	Yes	10 / 350 (2.8%)
Anti-CD20	No	88 / 413 (21,3%)
	Yes	35 / 256 (13,6%)

Abbreviations: DMT (Disease Modifying therapy)