Original research

COVID-19 has no impact on disease activity, progression and cognitive performance in people with multiple sclerosis: a 2-year study

Federico Montini ,[1] Agostino Nozzolillo,[1] Nicolò Tedone,[2,3] Damiano Mistri,[2,3] Paola MV Rancoita,[4] Chiara Zanetta,[1] Alessandra Mandelli,[5] Roberto Furlan,[5] Lucia Moiola,[1] Vittorio Martinelli ,[1] Maria A Rocca ,[1,2,3] Massimo Filippi ,[1,2,3,6,7] On behalf of the Clinical SanRaf MS Study Group

[1]Neurology Unit, IRCCS Ospedale San Raffaele, Milano, Italy
[2]Neuroimaging Research Unit, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milano, Italy
[3]Vita-Salute San Raffaele University, Milano, Italy
[4]University Centre for Statistics in the Biomedical Sciences (CUSSB), Vita-Salute San Raffaele University, Milano, Italy
[5]Clinical Neuroimmunology Unit, Institute of Experimental Neurology, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milano, Italy
[6]Neurorehabilitation Unit, IRCCS Ospedale San Raffaele, Milano, Italy
[7]Neurophysiology Service, IRCCS Ospedale San Raffaele, Milano, Italy

Correspondence to
Professor Massimo Filippi, Neuroimaging Research Unit, Division of Neuroscience; Neurology Unit; Neurorehabilitation Unit; and Neurophysiology Unit, IRCCS Ospedale San Raffaele, Milano, 20132, Italy; filippi.massimo@hsr.it

Received 22 June 2023
Accepted 25 September 2023

To cite: Montini F, Nozzolillo A, Tedone N, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2023-332073

ABSTRACT

Background Sequelae of COVID-19 in people with multiple sclerosis (PwMS) have not been characterised. We explored whether COVID-19 is associated with an increased risk of disease activity, disability worsening, neuropsychological distress and cognitive dysfunction during the 18–24 months following SARS-COV-2 infection.

Methods We enrolled 174 PwMS with history of COVID-19 (MS-COVID) between March 2020 and March 2021 and compared them to an age, sex, disease duration, Expanded Disability Status Scale (EDSS), and a line of treatment-matched group of 348 PwMS with no history of COVID-19 in the same period (MS-NCOVID). We collected clinical, MRI data and SARS-CoV2 immune response in the 18–24 months following COVID-19 or baseline evaluation. At follow-up, PwMS also underwent a complete neuropsychological assessment with brief repeatable battery of neuropsychological tests and optimised scales for fatigue, anxiety, depression and post-traumatic stress symptoms.

Results 136 MS-COVID and 186 MS-NCOVID accepted the complete longitudinal evaluation. The two groups had similar rate of EDSS worsening (15% vs 11%, p=1.00), number of relapses (6% vs 5%, p=1.00), disease-modifying therapy change (7% vs 4%, p=0.81), patients with new T2-lesions (9% vs 11%, p=1.00) and gadolinium-enhancing lesions (7% vs 4%, p=1.00) on brain MRI. 22% of MS-COVID and 23% MS-NCOVID were cognitively impaired at 18–24 months evaluation, with similar prevalence of cognitive impairment (p=1.00). The z-scores of global and domain-specific cognitive functions and the prevalence of neuropsychiatric manifestations were also similar. No difference was detected in terms of SARS-CoV2 cellular immune response.

Conclusions In PwMS, COVID-19 has no impact on disease activity, course and cognitive performance 18–24 months after infection.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several factors associated with multiple sclerosis can lead to a severe COVID-19 outcome, but less is known regarding the long-term consequences after infection.

WHAT THIS STUDY ADDS

⇒ The study shows that despite the experience of COVID-19 triggering autoimmune conditions in healthy individuals, it does not seem to increase the risk of clinicoradiological disease activity nor motor and cognitive worsening in people with multiple sclerosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This finding supports the lightening of COVID-19-preventive policies also in this fragile population.

INTRODUCTION

Since early 2020, significant efforts were made to better understand how SARS-CoV-2 affects people with multiple sclerosis (PwMS) and identify risk factors for adverse outcomes with COVID-19. Older age,[1 2] more severe disability[1 2] and obesity[1] emerged as major risk factors for severe COVID-19 infection, with additional risk factors comprising black ethnicity,[2] cardiovascular comorbidities[2] and recent treatment with corticosteroids.[2] Although a significant association between disease-modifying therapy (DMT) exposure and COVID-19 severity was not found at the beginning,[1] subsequent studies showed that rituximab or ocrelizumab was associated with a twofold increased risk of severe COVID-19,[3] with a 4.5 and 1.63-fold increased risk of hospitalisation,[2] respectively, and with a twofold increased risk of intensive-care unit admission.[4]

The postacute long-term sequelae and complications of COVID-19 infection in terms of increased risk of disease activity, disability worsening and treatment changes have not been characterised yet among PwMS. Additionally, patients may suffer from increased neuropsychological distress due to COVID-19 pandemic, with psychological trauma following quarantine, infection and eventual hospitalisation. These conditions may trigger or worsen psychological symptoms frequently described in PwMS, including anxiety, fatigue and depression, and also post-traumatic stress. Neuropsychiatric sequalae emerged among COVID-19 survivors in the general population.[5] In particular, patients who

suffered from a more severe COVID-19 infection could be at a higher risk of long-term consequences.

A recent study in PwMS showed that COVID-19 is not associated with increased risk of relapses or disability at a 6 months of follow-up.[6] In this study, 94% of patients had a complete recovery 1 year after COVID-19 infection, and a mild initial COVID-19 disease course was the only predictor of a full resolution.[6] Fatigue, hyposmia and dyspnoea were residual COVID-19 symptoms at months 3 and 6 postinfection, but not after 1 year.[6] Emerging data suggest that COVID-19 may determine detrimental immunologic, neurologic and neuropsychiatric effects that may persist several months after the resolution of the infection.[7] The literature showed that individuals recovering from COVID-19 infection may suffer from persistent symptoms, a condition known as long COVID or postacute sequelae of COVID-19.[8] RNA sequencing analysis showed significant perturbations to gene expressions in COVID-19 survivors, persisting at least 6 months after infection, possibly explaining long COVID as immune consequence of COVID-19 infection.

Given these premises, this study evaluated a well-characterised cohort of PwMS who suffered from COVID-19 in comparison with a cohort of PwMS with no history of COVID-19. We explored whether COVID-19 is associated with an increased risk of clinical and MRI activity, disability worsening and treatment changes during the 18–24 months following SARS-COV-2 infection. We also evaluated the presence and severity of cognitive impairment and neuropsychiatric manifestations (depression, anxiety, fatigue and post-traumatic stress symptoms) 18–24 months after SARS-COV-2 infection. Finally, we assessed whether COVID-19 had an impact on the cellular immune response to SARS-COV-2 at follow-up.

METHODS

For this case–control study, we enrolled patients afferent to the Multiple Sclerosis Center of the IRCCS San Raffaele Hospital, who had a diagnosis of MS according to 2017 McDonald Criteria.[9] The study started in March 2020 and ended in December 2022. We expanded a previously enrolled cohort of PwMS,[10] enrolling a total of 174 PwMS who had a confirmed COVID-19 infection between March 2020 and March 2021 (PwMS with history of COVID-19 (MS-COVID)). Inclusion criteria were typical clinical symptoms of COVID-19, such as fever, cough and dyspnoea, and a positive nucleic acid amplification test for SARS-CoV-2 at the time of experiencing symptoms, or a positive IgG or IgM SARS-CoV-2 serology within 3 months following typical COVID-19 symptoms. The majority of patients suffered from a mild COVID-19 infection. Only seven of them suffered from a severe COVID-19 infection requiring hospitalisation.

A separate group of 348 PwMS who did not have a history of COVID-19 symptoms or diagnosis between March 2020 and March 2021 (MS-NCOVID) were randomly selected from the Multiple Sclerosis Center cohort. The MS-COVID and MS-NCOVID groups were matched at a ratio of 1:2 by age (within 4 years), sex, Expanded Disability Status Scale (EDSS, within 0.5), disease duration (within 3 years) and line of treatment (first or second line). First-line treatments included glatiramer acetate, interferon, teriflunomide and dimethyl fumarate, whereas second-line treatments included fingolimod, natalizumab, cladribine, rituximab, ocrelizumab and alemtuzumab. All participants were unvaccinated against SARS-CoV-2 due to the historical moment of the study.

Both MS-COVID and MS-NCOVID patients were enrolled within 1 year after the infection (MS-COVID) or initial evaluation (MS-NCOVID). This initial evaluation, performed at enrolment between March 2020 and March 2021, will be called 'baseline evaluation'. Data collection was obtained by direct patient interview during a scheduled neurological evaluation.

We included patients who agreed (1) to have their longitudinal clinical data collected, (2) to undergo a neuropsychological assessment 8–24 months after the initial evaluation and (3) who performed at least one brain MRI during this period.

Clinical assessment

In both groups, we retrospectively collected the same clinical data of our previous study done at baseline evaluation.[10] During the following 18–24 months, patients underwent regular neurological follow-up with scheduled outpatient visits every 3–6 months. During the visits, we collected the EDSS,[11] disease phenotype and its changes (relapsing-remitting, primary progressive, secondary progressive), number of relapses, DMT and its change, occurrence and number of new/enlarging T2 lesions on brain MR imaging, occurrence and number of enhancing lesions on postgadolinium T1-weighted images, occurrence and number of COVID-19 infections from baseline evaluation. Brain MR imaging was performed as per clinical practice using different scanners and protocols of acquisition, limiting the possibility to perform quantitative analysis of lesion volumes.

At follow-up, EDSS worsening was defined by an EDSS score increase ≥1.5, 1.0 or 0.5, confirmed after a 3-month relapse-free period, when baseline EDSS score was 0, ≤5.5 or ≥6.0, respectively.

Neuropsychological assessment and neuropsychiatric manifestations

18–24 months after COVID-19 infection or initial evaluation, PwMS underwent a neuropsychological evaluation using the Brief Repeatable Battery of Neuropsychological Tests (BRB-N).[12] Specifically, the selective recall test was used to evaluate verbal memory, the 10/36 spatial recall test was used to evaluate visual memory, the symbol digit modalities test was used to evaluate information processing speed, the Paced Auditory Serial Addition Test 2" and 3" per digit version was used to evaluate attention, and the word list generation was used to evaluate verbal fluency. Z-scores for all BRB-N tests were calculated using sex-adjusted, age-adjusted and education-adjusted regression models according to the normative data from an Italian representative sample.[13] Then z-scores for specific cognitive domains were quantified by averaging z-scores of tests belonging to the previous cognitive domains, as previously described.[14] Finally, z-scores of global cognitive functions (obtained by averaging *z*-scores of cognitive domains) were quantified.[14] Test failure was defined as a score 1.5 SD below normative values.[15] Cognitive impairment was defined as failure on tests in at least two different cognitive domains.[15]

In addition, the Modified Fatigue Impact Scale (MFIS)[16] was used to assess fatigue, and MS patients with a score ≥38 were considered fatigued.[17] The Hospital Anxiety and Depression Scale (HADS)[18] was used to assess anxiety and depression, and MS patients with a score ≥8 in one of the two subscales exhibited clinically relevant anxiety or depression symptoms.[17] The Pittsburgh Sleep Quality Index (PSQI)[19] was used to assess sleep quality, and a PSQI score >5 indicated poor sleep quality.[19] Finally, we administered the Impact of Event Scale-Revised (IES-R)[20] to assess the psychological effects of a prior COVID-19 infection or the COVID-19 pandemic event as well as the potential existence of post-traumatic stress symptoms. The presence

Table 1 Main demographic and clinical characteristics of the two study groups at baseline

Variable	MS-COVID (n=136)	MS-NCOVID (n=186)	P-value
Sex male, number (%)	55 (40.4%)	59 (31.7%)	0.13*
Median age (IQR)	41 (33; 49)	45 (35; 52)	0.07†
Median disease duration at baseline (IQR)	9.44 (5.11; 16.44)	12.35 (3.77; 20.22)	0.32†
Median EDSS at baseline (IQR)	1.5 (1;3)	1.5 (1.5;2.5)	0.50†
Phenotype at baseline, number (%)			0.09*
RR	4 (2.9%)	2 (1.1%)	
SP	130 (95.6%)	174 (93.6%)	
PP	2 (1.5%)	10 (5.9%)	
Ongoing treatment at baseline, number (%)			0.50*
First-line	76 (55.9%)	96 (51.6%)	
Second-line	60 (44.1%)	90 (48.4%)	

*Fisher's exact test.
†Mann-Whitney U test.
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PP, primary progressive; RR, relapsing-remitting; SP, secondary progressive.

of post-traumatic stress disorder symptoms was indicated by a score ≥33.[20]

Assessment of immune response to SARS-CoV2 (ELISPOT assay)

T-cell responses to SARS-CoV-2 were measured using Human IFN-γ ELISpot PRO kit (Mabtech) 18–24 months after COVID-19 infection or initial evaluation.

Cryopreserved peripheral blood mononuclear cells were rapidly thawed, viability was assessed by 0.4% trypan blue dye exclusion, and cells were rested in 10% human serum-Iscove's Modified Dulbecco Medium with 20 U/mL IL-2 at 37°C in a humidified 5% CO2 incubator for 2 hours before stimulation. 4×10^5 cells/well were added to strip-plate precoated with anti-IFN-γ (mAb 1-D1K) and stimulated with a pool of combined peptides to cover the domains of the entire spike protein 'S' (PepTivator SARS-CoV-2 Prot_S, S1 and S+, Miltenyi) and the nucleocapsid phosphoprotein 'N' (PepTivator SARS-CoV-2 Prot_N, Miltenyi). The final concentration of each peptide in the cell suspension was 1 µg/mL. Anti-CD3 was used as a positive control. All stimulation conditions were performed in the presence of anti-CD28 (1 µg/mL). Plates were incubated for 18 hours at 37°C with 5% CO2. Spot-forming cells were detected according to the antibody manufacturer's instructions and counted using an automated ELISpot Reader System (CTL software). The number of spots was expressed as spots/4×10^5 cells.

Statistical analysis

Disease duration at baseline was computed at COVID onset for MS-COVID patients and at interview for MS-NCOVID patients. Continuous variables were reported as median and IQR, while categorical variables as absolute and relative frequencies. For baseline characteristics, continuous variables were compared between the two groups (MS-COVID and MS-NCOVID) by using the Mann-Whitney test, while categorical variables with the Fisher's exact test. For outcome variables, continuous variables (neuropsychological/ neuropsychiatric scores and ELISPOT variables) were compared between the two groups (MS-COVID and MS-NCOVID) by using the median regression adjusted for age and sex, while categorical variables (change in clinical characteristics and categorised neuropsychological/neuropsychiatric scores) with the logistic regression adjusted for age and sex. When needed, in all the analyses, p values were adjusted with Bonferroni's correction to account for multiple testing.

For sensitivity analysis, all the analyses were performed also by excluding patients of the MS-NCOVID group who got the COVID during the follow-up.

For all statistical analyses, the significant level was 0.05. All statistical analyses were performed using R V.3.6.2 (http:// www.R-project.org/).

RESULTS

Study population

Amidst the 174 PwMS with a history of COVID-19 and the 348 PwMS with no such history, 136 and 186, respectively, fulfilled the criteria. The two groups, MS-COVID and MS-NCOVID, were comparable in terms of age, sex, disease duration, EDSS, disease phenotype and type of DMTs used (table 1).

Clinical and MRI assessment at follow-up

Median EDSS at follow-up was 1.5 (IQR=1.0–2.63) in the MS-COVID group and 2.0 (IQR=1.5–3.38) in the MS-NCOVID group (p=0.1074). During follow-up, four patients (2.94%) from the MS-COVID group and four patients (2.15%) from the MS-NCOVID group had a change of disease clinical phenotype. Table 2 summarises results of associations between MS group and change in disease/patient characteristics. During follow-up, 21 PwMS from MS-COVID group and 20 from MS-NCOVID group had EDSS worsening (adjusted p=0.71). Percentage of patients with relapses (6.6% vs 5.4%, adjusted p=1.00), need for DMT change (7.4% vs 3.8%, adjusted p=0.99), new/enlarging brain T2-hyperintense lesions (8.8% vs 10.2%, adjusted p=1.00) and gadolinium-enhancing lesions (6.7% vs 3.9%, adjusted p=1.00) were similar between the two groups. Type of ongoing DMT among patients with any evidence of disease activity was similar among the two groups (data not shown).

Table 2 Clinical and MRI characteristics of the two study groups at follow-up

Patients experiencing	MS-COVID (n=136)	MS-NCOVID (n=186)	OR of MS-COVID vs MS-NCOVID (95% CI)*	P-value*
EDSS worsening, number (%)	21 (15.4%)	20 (10.8%)	1.66 (0.84 to 3.29)	0.71
Relapses, number (%)	9 (6.6%)	10 (5.4%)	1.21 (0.47 to 3.12)	1.00
DMT change, number (%)	10 (7.4%)	7 (3.8%)	1.93 (0.72 to 5.48)	0.99
New/enalarging T2 lesions, number (%)	12 (8.8%)	19 (10.2%)	0.78 (0.35 to 1.66)	1.00
Gadolinium-enhancing lesions, number (%) (six missing)	9 (6.7%)	7 (3.9%)	1.66(0.60 to 4.80)	1.00

*ORs and p values from univariate logistic regression analyses were adjusted for age and sex. P values were adjusted with Bonferroni's correction to account for multiple testing.
DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

Table 3 Comparison of neuropsychological and neuropsychiatric variables between MS-COVID and MS-NCOVID patients at follow-up

Variable	N	MS-COVID (n=136)	MS-NCOVID (n=186)	P-value*
Median Z Verbal Memory, median (IQR)	302	0.58 (–1.15; 0.08)	0.86 (–1.58; –0.07)	0.18†
Median Z Visual Memory, median (IQR)	301	0.06 (–0.75; 0.68)	0.18 (–0.86; 0.55)	1.00†
Median Z IPS, median (IQR)	299	0.25 (–0.78; 1.11)	0.15 (–0.91; 0.48)	1.00†
Median Z Attention, median (IQR)	222	0.33 (–0.94; 0.31)	0.61 (–0.99; –0.02)	1.00†
Median Z Verbal fluency, median (IQR)	300	0.21 (–0.90; 0.48)	0.38 (–1.07; 0.18)	1.00†
Median Z Global, median (IQR)	222	0.12 (–0.61; 0.28)	0.27 (–0.66; 0.08)	1.00†
Cognitive impairment, number (%)	301	28 (22.1%)	40 (23.0%)	1.00‡
MFIS Fatigue, number (%)	308	45 (34.6%)	67 (37.6%)	1.00‡
Median MFIS score, median (IQR)	308	31 (16.25; 41)	30 (17.25; 44.75)	1.00†
HADS Anxiety, number (%)	306	45 (35.2%)	65 (36.5%)	1.00‡
Median HADS Anxiety score, median (IQR)	306	6 (3;9)	5.5 (3;9)	1.00†
HADS Depression, number (%)	306	18 (14.1%)	29 (16.3%)	1.00‡
Median HADS Depression score, median (IQR)	306	3 (1;6)	3 (2;6)	1.00†
PSQI Poor quality sleep, number (%)	309	78 (60.0%)	103 (57.5%)	1.00‡
Median PSQI score, median (IQR)	309	7 (4;9.75)	6 (4;9)	1.00†
IES_R PTSD, number (%)	308	18 (13.9%)	26 (14.6%)	1.00‡
Median IES_R score, median (IQR)	308	8 (2;19)	11 (3;24.75)	1.00†

*P-values were adjusted with Bonferroni's correction to account for multiple testing.
†Median regression adjusted for age and sex.
‡Logistic regression adjusted for age and sex.
HADS, Hospital Anxiety and Depression Scale; IES_R, Impact of Event Scale-Revised; IPS, information processing speed; MFIS, Modified Impact Fatigue Scale; MS, multiple sclerosis; PSQI, Pittsburgh Sleep Quality Index; PTDS, post-traumatic stress disorder.

The analysis was repeated by excluding the 58 MS-NCOVID patients who developed COVID-19 infection during the 18–24 months after baseline and results were similar (data not shown).

Neuropsychological and neuropsychiatric assessments at follow-up

Table 3 summarises the results of neuropsychological and neuropsychiatric assessments. Twenty-eight (22.05%) MS-COVID and 40 (22.99%) MS-NCOVID patients were cognitively impaired, with no between-group significant difference in the prevalence of cognitive impairment (adjusted p=1.00). The z-scores of global cognitive functions, verbal and visual memory, information processing speed, attention and verbal fluency did not significantly differ between the two groups of patients (see table 3).

No significant differences in MFIS, HADS anxiety, HADS depression, PSQI and IES-R scores nor in the prevalence of fatigue, anxiety, depression, poor sleep quality and post-traumatic stress disorder symptoms were found between MS-COVID and MS-NCOVID patients (all adjusted p=1.00).

Also in this case, the results of the between-group comparisons were similar when excluding MS-NCOVID who developed COVID-19 infection during the 18–24 months after baseline (data not shown).

Assessment of immune response to SARS-CoV2

No significant difference emerged in terms of CD3 spots, spike spots, nucleocapsid spot between MS-COVID and MS-NCOVID patients (all adjusted p=1.00) (table 4). The results were similar after exclusion of MS-NCOVID who developed COVID-19 infection during the 18–24 months after baseline (data not shown).

DISCUSSION

This study aimed to evaluate the impact of SARS-CoV-2 infection on disease activity, disability progression, cognitive impairment, neuropsychiatric manifestations and cellular immune response in PwMS during 18–24 months after infection. We found no statistically significant differences in terms of clinical and MRI disease activity, disability progression and treatment change between the MS-COVID and MS-NCOVID groups during the follow-up period, consistent with the results of a previous study, with shorter follow-up.[6] In addition, the MS-COVID group did not have a higher prevalence of cognitive impairment or neuropsychiatric symptoms, such as depression, anxiety, fatigue and stress compared with the MS-NCOVID group. These findings are consistent with those of a meta-analysis that showed that pandemic-related restrictions had no significant impact on the

Table 4 Comparison of ELISPOT variables between MS-COVID and MS-NCOVID patients at follow-up

Variable	N	MS-COVID (n=136)	MS-NCOVID (n=186)	P-value*
Median CD3 spots/400.000 cells (IQR)	222	1506 (1158; 1810)	1544 (1076; 1828.5)	1.00†
Median Spike spots/400.000 cells (IQR)	239	307 (142.5; 491.5)	292 (94; 432)	1.00†
Median Nucleocapsid spots/400.000 cells (IQR)	251	156.5 (44.75; 337.25)	133 (25; 291)	1.00†

*P-values were adjusted with Bonferroni's correction to account for multiple testing.
†Median regression adjusted for age and sex.
MS, multiple sclerosis.

mental health of PwMS, although they frequently experienced anxiety and depression during the pandemic.[5]

Elispot assays showed no difference in term of cellular immune response to SARS-CoV-2 between MS-COVID and MS-NCOVID patients. This was not unexpected, considering that almost all MS-NCOVID patients were vaccinated during the follow-up period, likely interfering with the assay results.

In the general population, patients with COVID-19 are at risk for different post-COVID-19 conditions.[21] Risk factors for post-COVID-19 sequelae are female sex, older age, higher BMI, active smoking status and comorbidities (asthma, chronic obstructive pulmonary disease, diabetes, immunosuppression). Among the post-COVID-19 conditions, researchers observed cases of post-COVID-19 autoimmune and inflammatory diseases in individuals who had recovered from the virus.[22] Two large retrospective cohort studies[23 24] were conducted to better understand this connection. The studies found that the incidence of autoimmune conditions, including rheumatoid arthritis, systemic lupus erythematosus, vasculitis, inflammatory bowel disease and type 1 diabetes, was higher in individuals who had COVID-19 compared with those who did not. Another study[25] revealed a higher likelihood of acquiring an autoimmune condition after COVID-19 compared with a non-COVID-19 group. Although these studies do not prove a causal link, they provide compelling evidence of an increased risk of diverse autoimmune diseases following SARS-CoV-2 infection, enhancing the need to investigate this possible association in PwMS. Although no longitudinal case–control study investigated whether patients with previous autoimmune conditions are at higher risk of exacerbation after COVID-19 infection, some relapses have been described among patients with systemic lupus erythematosus[26] and autoimmune haemolytic anaemia.[27]

PwMS needed a longer time to recover from COVID-19 than healthy controls in this study.[28] Although case reports[29 30] initially suggested a possible association between COVID-19 and MS disease activity as well as other CNS autoimmune conditions,[31] a previous study did not detect an increased frequency of relapses during the pandemic period.[32] This negative finding was unexpected. As mentioned above, autoimmune sequelae of COVID-19 have been abundantly described as well as in PwMS following systemic infections.[33 34]

In the general population, fatigue and cognitive impairment have been described ≥6 months after COVID-19,[35] especially in older patients. However, our patients were relatively young (41 years), had low disability (EDSS 1.5), the majority had a mild form of COVID-19 infection. Overall, these factors might explain the relatively low percentage of cognitively impaired MS patients and the lack of consequences from COVID-19 on cognitive functioning and fatigue.

Despite these encouraging results, longer term impact of COVID-19 among PwMS must be further investigated, particularly among PwMS with a previous severe COVID-19 infection. Magnitude and type of immune system response are known to be influenced by an individual's exposure history, which includes previous infections, vaccinations and microbial metabolites.[36] For instance, measles infection could reduce preinfective antibody repertoire and alter immune response to future new infective events.[37] In general, infective events can either enhance or hinder future immune response.

PwMS have a complex alteration of the immune system with altered immune homeostasis.[38] A recent study showed that patients who developed mild COVID-19 (as most of our patients) had increased response to immune stimuli, such as influenza vaccination.[39]

However, among our patients, no difference was detected in terms of disease activity or disease-related outcomes. Similar single-cell whole-transcriptomic approaches[39] could be useful to better understand the long-term impact of COVID-19 on the immune system in PwMS.

Based on these findings, it may be appropriate to suggest that PwMS can begin to return to their normal lives with less fear of COVID-19. This is in line with the policy adopted by most governments as a result of the conclusion of the COVID-19 pandemic. Of course, caution and good hygiene practices should still be encouraged, as the virus can still pose a risk to anyone, regardless of their immune status, particularly because future variants can have a different spectrum of neurological symptoms.[40]

Our study is not without limitations. Most patients from both groups were vaccinated 18–24 months after the baseline evaluation, significantly reducing the likelihood of detecting a difference in terms of T-cell response between them. COVID-19 severity was generally mild, with only seven patients requiring inpatient admission for severe COVID-19 infection. Further studies should investigate the presence of sequelae among PwMS with severe COVID-19 infection. Nevertheless, our findings are still reassuring. First, our patients were not vaccinated at the time of COVID-19 infection, and the severity of infection has decreased significantly since the beginning of the pandemic and the commencement of vaccination efforts. Other limitations are the relatively short follow-up period and the relatively small sample. Future studies with longer follow-up periods and larger sample sizes are needed to confirm these findings and shed more light on the long-term impact of COVID-19 in PwMS. Finally, PwMS did not undergo a neuropsychological assessment at baseline, thus not allowing us to identify possible worsening of cognition during the study. However, considering the relatively small and almost identical percentage of patients with cognitive deficits at follow-up in the two groups, which were well matched for all disease-related features at baseline, we do not expect any influence of COVID-19 infection on this aspect in our study.

Twitter Nicolò Tedone @Nico_Ted1 and Lucia Moiola @lucia65243896

Acknowledgements We are grateful to Cinzia Pozzoni for the support in data collection and management.

Collaborators Clinical SanRaf MS Study Group: Matteo Azzimonti, Bruno Colombo, Giulia D'Amore, Federica Esposito, Laura Ferrè, Angela Genchi, Antonino Giordano, Simone Guerrieri, Mor Gueye, Irene Gattuso, Maria Sofia Martire, Paolo Preziosa and Martina Rubin.

Contributors Study concept: MF, MAR. Data acquisition and analysis: FM, AN, NT, DM, PMVR, CZ, AM, RF, LM, VM. Interpretation of data: FM, PMVR, AM, RF, MAR, MF. Statistical analysis: PMVR. Drafting of the manuscript: FM, MAR. Revision of the manuscript: all authors. Guarantor of the study: MF.

Funding This study has been partially supported by FISM—Fondazione Italiana Sclerosi Multipla—cod. 2021/C19-R-Single/005 and financed or cofinanced with the '5 per mille' public funding.

Competing interests FM, AN, NT, DM, PMVR, CZ, AM and RF have nothing to disclose. LM received compensation for speaking activities, and/or consulting services from Merck, Biogen, Novartis, Roche, Sanof, and TEVA. VM received compensation for speaking and/or for consultancy and support for travel expenses and participation in Congresses from Biogen, Merck-Serono, Novartis, Genzyme and Teva Pharmaceutical Industries. MAR received consulting fees from Biogen, Bristol Myers Squibb, Eli Lilly, Janssen, Roche; and speaker honoraria from AstraZeneca, Biogen, Bristol Myers Squibb, Bromatech, Celgene, Genzyme, Horizon Therapeutics Italy, Merck Serono SpA, Novartis, Roche, Sanofi and Teva. She receives research support from the MS Society of Canada, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. She is Associate Editor for Multiple Sclerosis and Related Disorders. MF is Editor-in-Chief of the Journal of Neurology, Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology; received compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, Roche, Sanofi; speaking activities from

Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; participation in Advisory Boards for Alexion, Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, Takeda; scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, Sanofi-Genzyme; he receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by ethical standards committee on human experimentation of IRCCS Ospedale San Raffaele, Milan (Protocol ID. 101/INT/2020). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

ORCID iDs
Federico Montini http://orcid.org/0000-0002-8367-0741
Vittorio Martinelli http://orcid.org/0000-0002-5987-5739
Maria A Rocca http://orcid.org/0000-0003-2358-4320
Massimo Filippi http://orcid.org/0000-0002-5485-0479

REFERENCES

1 Louapre C, Collongues N, Stankoff B, *et al*. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. *JAMA Neurol* 2020;77:1079–88.
2 Salter A, Fox RJ, Newsome SD, *et al*. Outcomes and risk factors associated with SARS-CoV-2 infection in a North American Registry of patients with multiple sclerosis. *JAMA Neurol* 2021;78:699–708.
3 Sormani MP, De Rossi N, Schiavetti I, *et al*. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. *Ann Neurol* 2021;89:780–9.
4 Simpson-Yap S, De Brouwer E, Kalincik T, *et al*. Associations of disease-modifying therapies with COVID-19 severity in multiple sclerosis. *Neurology* 2021;97:e1870–85.
5 Rogers JP, Lewis G. Neuropsychiatric sequelae of COVID-19: long-lasting, but not uniform. *Lancet Psychiatry* 2022;9:762–3.
6 Bsteh G, Assar H, Gradl C, *et al*. Long-term outcome after COVID-19 infection in multiple sclerosis: a nation-wide multicenter matched-control study. *Eur J Neurol* 2022.
7 Lopez-Leon S, Wegman-Ostrosky T, Perelman C, *et al*. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021;11:16144.
8 Ryan FJ, Hope CM, Masavuli MG, *et al*. Long-term perturbation of the peripheral immune system months after SARS-CoV-2 infection. *BMC Med* 2022;20:26.
9 Thompson AJ, Banwell BL, Barkhof F, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17:162–73.
10 Montini F, Nozzolillo A, Rancoita PMV, *et al*. Modifiable risk factors of COVID-19 in patients with multiple sclerosis: a single-centre case-control study. *J Neurol* 2023;270:1835–42.
11 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–52.
12 Rao SM, and the Cognitive Function Study Group of the National Multiple Sclerosis Society. *A manual for the brief repeatable battery of neuropsychological test in multiple sclerosis*. Milwaukee, WI: Medical College of Wisconsin, 1990.
13 Amato MP, Portaccio E, Goretti B, *et al*. The Rao's brief repeatable battery and Stroop test: normative values with age, education and gender corrections in an Italian population. *Mult Scler* 2006;12:787–93.
14 Sepulcre J, Vanotti S, Hernández R, *et al*. Cognitive impairment in patients with multiple sclerosis using the brief repeatable battery-neuropsychology test. *Mult Scler* 2006;12:187–95.
15 Amato MP, Morra VB, Falautano M, *et al*. Cognitive assessment in multiple sclerosis-an Italian consensus. *Neurol Sci* 2018;39:1317–24.
16 Fisk JD, Ritvo PG, Ross L, *et al*. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* 1994;18 Suppl 1:S79–83.
17 Marchesi O, Vizzino C, Meani A, *et al*. Fatigue in multiple sclerosis patients with different clinical phenotypes: a clinical and magnetic resonance imaging study. *Eur J Neurol* 2020;27:2549–60.
18 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
19 Curcio G, Tempesta D, Scarlata S, *et al*. Validity of the Italian version of the Pittsburgh sleep quality index (PSQI). *Neurol Sci* 2013;34:511–9.
20 Craparo G, Faraci P, Rotondo G, *et al*. The impact of event scale - revised: psychometric properties of the Italian version in a sample of flood victims. *Neuropsychiatr Dis Treat* 2013;9:1427–32.
21 Tsampasian V, Elghazaly H, Chattopadhyay R, *et al*. Risk factors associated with post–COVID-19 condition: a systematic review and meta-analysis. *JAMA Intern Med* 2023;183:566–80.
22 Rojas M, Rodríguez Y, Acosta-Ampudia Y, *et al*. Autoimmunity is a hallmark of post-COVID syndrome. *J Transl Med* 2022;20:129.
23 Chang R, Yen-Ting Chen T, Wang S-I, *et al*. Risk of autoimmune diseases in patients with COVID-19: a retrospective cohort study. *EClinicalMedicine* 2023;56:101783.
24 Tesch F, Ehm F, Vivirito A, *et al*. Incident autoimmune diseases in association with a SARS-CoV-2 infection: a matched cohort study. *Clin Rheumatol* 2023;42:2905–14.
25 Syed U, Subramanian A, Wraith DC, *et al*. Incidence of immune-mediated inflammatory diseases following COVID-19: a matched cohort study in UK primary care. *BMC Med* 2023;21:363.
26 Khalid MZ, Rogers S, Fatima A, *et al*. A flare of systemic lupus erythematosus disease after COVID-19 infection: a case of lupus cerebritis. *Cureus* 2021;13:e16104.
27 Finkenthal TA, Aldaher Z, Ahmed S, *et al*. Autoimmune hemolytic anemia exacerbation associated with COVID-19 infection and markedly elevated inflammatory markers. *Cureus* 2021;13:e20416.
28 Garjani A, Middleton RM, Nicholas R, *et al*. Recovery from COVID-19 in multiple sclerosis: a prospective and longitudinal cohort study of the United Kingdom multiple sclerosis register. *Neurol Neuroimmunol Neuroinflamm* 2022;9:e1118.
29 Giordano A, Cetta I, Orrico M, *et al*. Stress related to COVID-19 pandemic as a trigger for disease activity in multiple sclerosis: a case report. *Neurol Sci* 2021;42:3969–71.
30 Finsterer J. SARS-CoV-2 triggered relapse of multiple sclerosis. *Clin Neurol Neurosurg* 2022;215:107210.
31 Montini F, Martinelli V, Sangalli F, *et al*. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) after SARS-CoV-2 pneumonia. *Neurol Sci* 2021;42:4373–5.
32 Babtain F, Bajafar A, Nazmi O, *et al*. The disease course of multiple sclerosis before and during COVID-19 pandemic: a retrospective five-year study. *Mult Scler Relat Disord* 2022;65:103985.
33 Correale J, Fiol M, Gilmore W. The risk of relapses in multiple sclerosis during systemic infections. *Neurology* 2006;67:652–9.
34 Confavreux C. Infections and the risk of relapse in multiple sclerosis. *Brain* 2002;125:933–4.
35 Hartung TJ, Neumann C, Bahmer T, *et al*. Fatigue and cognitive impairment after COVID-19: a prospective multicentre study. *EClinicalMedicine* 2022;53:101651.
36 Arneth B. Trained innate immunity. *Immunol Res* 2021;69:1–7.
37 Mina MJ, Kula T, Leng Y, *et al*. Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens. *Science* 2019;366:599–606.
38 Monteiro A, Rosado P, Rosado L, *et al*. Alterations in peripheral blood monocyte and dendritic cell subset homeostasis in relapsing-remitting multiple sclerosis patients. *J Neuroimmunol* 2020;350:577433.
39 Sparks R, Lau WW, Liu C, *et al*. Influenza vaccination reveals sex dimorphic imprints of prior mild COVID-19. *Nature* 2023;614:752–61.
40 Sahin A, Karadag-Oncel E, Buyuksen O, *et al*. The diversity in the clinical features of children hospitalized with COVID-19 during the nonvariant, alpha (B.1.1.7), Delta (B.1.617.2), and Omicron (B.1.1.529) variant periods of SARS CoV-2: caution for neurological symptoms in Omicron variant. *J Med Virol* 2023;95:e28628.