



Characteristics and management of multiple sclerosis patients during the Omicron era: is there a concern about the MS course in the face of the new variant of COVID-19?

Sepideh Paybast¹ · Mohammad Amin Habibi¹ · Abdorreza Naser Moghadasi¹

Received: 12 July 2022 / Accepted: 6 October 2022
© Fondazione Società Italiana di Neurologia 2022

Abstract

Introduction The Omicron variant of COVID-19 is highly transmissible, triggering unprecedented infection rates. The present study aimed to investigate the course of multiple sclerosis (MS) in the Omicron era among Iranian patients with MS.

Methods This observational study was designed on MS patients of the national MS registry of Iran through a self-designed online questionnaire. A questionnaire was prepared as a Google Form for MS patients during the Omicron outbreak from 1 March to 30 April 2022.

Results One hundred seventy-four patients with a mean age of 37.3 ± 9.04 were enrolled. Of the patients, 95.97% used DMT, the most common of which were rituximab and fingolimod. Of the patients, 77.58% were fully vaccinated for COVID-19. Regardless of the COVID-19 vaccination status, 76 patients developed COVID-19, which was mild to moderate. Except for recent corticosteroid therapy and secondary progressive MS (SPMS), other demographic and MS characteristics were not significantly associated with the severity of COVID-19. There was also a marginal association between the Expanded Disability Status Scale (EDSS) and the severity of COVID-19. In addition, 17.10% of patients reported MS relapse following COVID-19 leading to escalation therapy in eight patients.

Conclusion Our study demonstrated that in the Omicron era, most patients developed mild COVID-19. Although the predominant COVID-19 variant in this period was Omicron, we could not separate the pathogenic variants. The risk factors for COVID-19 during the Omicron era were not different from other pandemic waves. Our preliminary results revealed that the MS relapse following COVID-19 was higher than in previous waves.

Keywords Multiple sclerosis · COVID-19 · Omicron variant

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS CoV2) is developed by coronavirus, which is heterogeneous in variances of interest (VOIs) and variants of concern (VOCs). Early variants, including alpha, beta, and gamma, were revealed to have a preserved immune response by vaccination and natural infection. Moreover, the mutations in early variants slightly affected immune evasion and infectivity. Omicron variant (B.1.1.529) was initially reported in November 2021 in Africa and nominated as a novel VOC

[1]. Compared with the original Wuhan strain, at least 60 mutations have been found in the Omicron variant, 39 related to the spike proteins. The high number of mutations on the spike protein make Omicron highly transmissible via the immune system's escaping, particularly against neutralizing antibodies produced by vaccines and previous infections [2, 3], which increase concerns about immunity against Omicron variants. As a result, given the distinguishing features of Omicron VOC, the management of Omicron-type COVID-19 is of particular note.

Multiple sclerosis (MS), a central nervous system (CNS) disorder with an autoimmune origin, attracted particular attention during the COVID-19 pandemic. Regarding the nature of immunosuppressive or immune-modulatory agents in MS patients, the therapeutic approaches need to be adjusted during the COVID-19 pandemic [4, 5]. Moreover, some DMTs, especially immunosuppressive agents in

✉ Abdorreza Naser Moghadasi
abdorrezamoghadasi@gmail.com

¹ Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

patients with lymphopenia, should be held within active COVID-19 infection. Likewise, the vaccination schedule for MS patients differs slightly from the general population. Those treated with fingolimod or B-cell depleting therapies should receive a booster dose of the COVID-19 vaccine [6]. It should be noted that there are few reports regarding the possible increased risk of CNS demyelinating syndromes and MS relapse in vaccinated individuals.

As far as we know, there is no report of the therapeutic challenges in MS patients since the advent of the Omicron outbreak. In the present study, we aimed to investigate the MS characteristics of Iranian MS patients to illustrate the crucial points in managing COVID-19-infected MS patients in the Omicron era.

Material and methods

Study design

This observational study was designed on MS patients of the national MS registry of Iran through a self-designed online questionnaire from March to April 2022. We created a primary questionnaire, which three MS patients completed, to evaluate the intelligibility of questions. Then, the intelligible questions were edited. Next, the questionnaire was sent to four MS expert neurologists and one epidemiologist to comment on the content of the questions. After the corrections were made, the final version of the questionnaire was formatted as a Google Form, and the link was made available for MS patients on social networks for 2 months. In addition, the study was approved by the university's local ethics committee (Code of Ethics: IR.TUMS.NI.REC.1400.024).

Study population

All patients diagnosed with MS based on McDonald Criteria 2017 and aged over 18 years who fulfilled the Google Form questionnaire were enrolled. We included patients who replied to the questionnaire in the Omicron era from 1 March 2022 to 30 April 2022. Patients with a recent history of COVID-19, which was not confirmed by polymerase chain reaction (PCR) assays, were excluded. Eventually, 174 patients met the eligibility criteria.

Study measures

The questionnaire was developed to investigate the patients' characteristics: [1] demographic data; (b) MS characteristics; (c) COVID-19 infection data, including the history of COVID-19 before and during the Omicron era; (d)

vaccine-related data; (e) the protocol adopted to regulate MS treatment during the Omicron outbreak.

Based on the WHO recommendation, COVID-19 was categorized into three stages: [1] moderate to severe: requiring hospitalization, [2] mild to moderate: requiring home admission along with medical treatment; and [3] mild: when it did not affect the patient's daily activity [7].

MS relapse was defined as a monophasic clinical episode with objective findings typical of MS, which was developed acutely or subacutely, with duration of at least 24 h [8]. We considered 6 weeks as the period attributed to MS relapse associated with COVID-19 infection or vaccination. In addition, if a patient recorded an MS attack in the questionnaire, the relevant data from the MS registry system were also checked to eliminate a pseudo-relapse case.

Statistical analysis

Statistical analysis was conducted using SPSS 26.0 (SPSS Inc, Chicago, IL) software. Data were expressed as mean \pm SD for quantitative variables and counts (%) for categorical variables. For data analysis, one-sample *t*-test, Kolmogorov–Smirnov, chi-square, and Whitney–Mann statistical tests were used; multinomial and ordinal regression model was used to evaluate the association between the patient and disease characteristics and the probability or severity of Omicron-type COVID-19. The significant difference was considered *P*-value < 0.05.

Results

One hundred seventy-four patients were enrolled in this study. The minimum and maximum ages of patients were 19 and 66 years old, respectively, and the mean age of patients was 37.3 ± 9.04 . Thirteen patients (7.5%) were categorized as elderly patients (> 50 years old). In sex distribution, 133 patients (76.4%) were female and 41 patients (23.6%) were male with a 3.24:onefold (female/male) ratio. The habitual profile, including cigarette smoking, was positive in 17 patients (9.8%). Additionally, three patients (1.72%) mentioned opioid addiction (one with a transient consumption of tramadol to attenuate spasticity associated with MS, and two with a history of at least five year of opium addiction, unrelated to MS). Forty-eight patients (26.4%) had one or more comorbidity, in which hypothyroidism was most frequently reported. Moreover, comorbidities were more common in elderly patients.

In terms of MS type, 126 patients (72.4%) were relapse-remitting MS (RRMS), 10 (5.7%) were primary progressive MS (PPMS), 26 (14.9%) were secondary progressive MS

(SPMS), and 12 (6.9%) were clinically isolated syndrome (CIS). The mean duration of MS was 10.62 ± 6.86 , and the minimum and maximum were 1 and 35 years, respectively. The mean EDSS score was estimated to be 2.43 ± 1.94 . One hundred one patients (59.8%) noted no significant limitation in their daily activities ($EDSS \leq 2$). Twenty-eight patients (16.1%) had $EDSS \leq 4$, and 22 patients (12.6%) reported they needed aid to walk ($EDSS \geq 6$).

Out of 174 patients, 167 patients (95.97%) used DMT, the most common of which were rituximab (33.9%) and fingolimod (10.3%). The demographic and MS characteristics of patients are summarized in Table 1.

Regarding the COVID-19 vaccination status, the most frequently used vaccine against COVID-19 was the Sinopharm vaccine ($n = 151$, 85.7%). Two patients were fully vaccinated with four doses of the Sinopharm COVID-19 vaccine. One hundred thirty-three (76.4%) received three doses of the COVID-19 vaccines. Thirty-six patients were not fully vaccinated, as 31 (17.8%) were immunized with two doses of the COVID-19 vaccine, and five received only one dose. Moreover, 3 (1.72%) were not vaccinated, one of whom developed moderate to severe COVID-19. In terms of vaccine safety, no one reported significant adverse events after the COVID-19 vaccination. However, 11 patients (6.43%) experienced MS relapse following COVID-19 vaccination, which improved significantly with pulse steroid therapy. Myelitis ($n = 4$) and brain stem syndromes ($n = 3$) were the most frequent relapse phenotype after immunization. Seven patients with post-COVID-19 vaccination relapse required escalation to a high-efficacy DMT (Table 2).

As shown in Tables 2 and 3, 76 patients (43.7%) developed COVID-19, of whom 29 patients (38.1%) had a history of early variants of COVID-19 before the Omicron wave. In addition, 72 (41.1%) were infected only in the earlier waves. Seventy-seven patients (44.3%) did not experience any types of COVID-19, 66 (37.9%) developed COVID-19 at least once, 25 (14.4%) were infected twice, four (2.3%) were infected three times, and one was infected four and the other five times. To evaluate the association between demographic/MS characteristics and the risk of developing COVID-19 in the Omicron era, our results revealed that, except for MS type ($P = 0.004$), other demographic and MS characteristics were not associated with developing COVID-19 ($P > 0.05$). SPMS were the most susceptible group to developing COVID-19 infection. In addition, COVID-19 occurred regardless of the COVID-19 vaccination status, whereas 57 patients developed COVID-19 after receiving the third dose of the COVID-19 vaccine.

In terms of COVID-19 severity, 70 patients had mild upper respiratory tract symptoms. Only six patients (7.89%) were hospitalized, none requiring invasive oxygenation. Two patients with moderate to severe COVID-19 had a recent

Table 1 Demographic and MS characteristics of the MS patients

Variables	N (%)
Age (mean \pm SD) (year)	37.3 \pm 9.04
Age > 50	13 (7.5%)
Age \leq 50	161 (92.5%)
Sex	
Female	133 (76.4%)
Male	41 (23.6%)
Addiction	
Yes	17 (9.8%)
No	157 (90.2%)
Underlying Disease	
Cancer	3 (1.7%)
Hypothyroidism	3 (1.7%)
Hypertension	5 (2.9%)
Heart disease	1 (0.6%)
Diabetes mellitus	1 (0.6%)
Allergic reactions	7 (4%)
Others	19 (10.9%)
EDSS score (mean \pm SD)	2.43 \pm 1.94
Type of MS	
CIS	12 (6.9%)
RRMS	126 (72.4%)
PPMS	10 (5.7%)
SPMS	26 (14.9%)
Duration of MS (mean \pm SD) (year)	10.62 \pm 6.86
Minimum	1
Maximum	35
DMT class	
Rituximab	59 (33.9%)
Ocrelizumab	16 (9.2%)
Fingolimod	18 (10.3%)
Dimethyl fumarate	13 (7.5%)
Teriflunomide	3 (1.7%)
INF β -1a IM	8 (4.6%)
INF β -1a SC	14 (8%)
INF β -1b SC	8 (4.6%)
Glatiramer acetate	17 (9.8%)
Azathioprine	4 (2.3%)
Others	7 (4%)
None	7 (4%)

MS multiple sclerosis, CIS clinically isolated syndrome, RRMS relapse-remitting MS, SPMS secondary progressive MS, PPMS primary progressive MS, DMT disease-modifying treatment, INF β interferon beta, IM intramuscular, SC subcutaneous

history of pulse steroid therapy. The results did not demonstrate a significant association between the severity of the COVID-19 and any of the demographic and MS characteristics, including age ($P = 0.22$), sex ($P = 0.456$), habitual profile ($P = 0.589$), duration of MS ($P = 0.112$), DMT class

Table 2 The COVID-19-related data among MS patients in the Omicron era

Variables	N (%)
History of COVID-19 in the Omicron era	
Yes	76 (43.7%)
No	98 (56.3%)
History of COVID-19 in the earlier waves of COVID-19	
Yes	72 (41.4%)
No	102 (58.6%)
Time of COVID-19 after COVID-19 vaccination	
After 1 st dose	4 (5.4%)
After 2 nd dose	16 (21.62%)
After 3 rd dose	54 (72.97%)
The severity of COVID-19	
Required hospitalization	6 (6.97%)
Required home care	63 (73.25%)
No treatment required	17 (19.76%)
COVID-19 vaccination	
0	3 (1.7%)
1	5 (2.9%)
2	31 (17.8%)
3	133 (76.4%)
4	2 (1.1%)
Relapse after receiving the COVID-19 vaccine	
Yes	11 (6.43%)
No	160 (93.57%)

MS multiple sclerosis

($P=0.815$), previous history of COVID-19 ($P=0.492$), and COVID-19 vaccination ($P=0.546$). However, a significant correlation was observed with recent pulse steroid therapy ($P=0.018$) and MS type ($P=0.007$). SPMS was the most susceptible group to developing severe COVID-19 infection. Notably, none of the PPMS patients were infected in the Omicron era. Moreover, a marginal association ($P=0.058$) was found between EDSS and COVID-19 severity.

Eventually, we assessed the disease activity after COVID-19 infection. Out of 76 patients, 13 (17.10%) experienced clinical relapse after COVID-19 (Table 4). Like vaccine-associated relapses, myelitis ($n=4$) and brain stem syndromes ($n=2$) were the most prevalent relapse phenotypes. Eight patients had to switch their DMTs to higher efficacy ones. Totally, during the Omicron outbreak, one hundred sixty-five patients (94.8%) remained on their DMT. A female patient withdrew her DMT by herself. Eight patients (4.6%) were escalated to a high-efficacy DMT, mainly B

Table 3 Basic characteristics of MS patients with and without COVID-19 infection during the Omicron wave

Variables	Number (%)		P-value
	Patients who developed COVID-19	Patients who did not develop COVID-19	
Number	76	98	–
Age (mean \pm SD)	36.7 \pm 8.5	37.7 \pm 9.4	0.501
Age > 50	3 (3.9%)	10 (10.2%)	
Age \leq 50	73 (96.1%)	88 (89.8%)	
Sex			0.077
Female	63 (82.9%)	70 (71.4%)	
Male	13 (17.1%)	28 (28.6%)	
Addiction			0.185
Yes	10 (13.2%)	7 (7.1%)	
No	66 (86.8%)	91 (92.9%)	
Type of MS			0.004
CIS	4 (5.3%)	8 (8.2%)	
RRMS	55 (72.4%)	71 (72.4%)	
PPMS	0 (0%)	10 (10.2%)	
SPMS	17 (22.4%)	9 (9.2%)	
Duration of MS (mean \pm SD) (year)	11.25 \pm 7.22	10.13 \pm 6.56	0.292
Minimum	1	1	
Maximum	31	35	
DMTs			0.821
Rituximab	30 (39.5%)	29 (29.6%)	
Ocrelizumab	6 (7.9%)	10 (10.2%)	
Fingolimod	9 (11.8%)	9 (9.2%)	
Dimethyl fumarate	6 (7.9%)	7 (7.1%)	
Teriflunomide	2 (2.6%)	1 (1%)	
INF β -1a IM	3 (3.9%)	5 (5.1%)	
INF β -1a SC	4 (5.3%)	10 (10.2%)	
INF β -1b SC	2 (2.6%)	6 (6.1%)	
Glatiramer acetate	6 (7.9%)	11 (11.2%)	
Azathioprine	2 (2.6%)	2 (2%)	
Other	2 (2.6%)	5 (5.1%)	
None	4 (5.3%)	3 (3.1%)	
Underlying disease			0.105
Cancer	0 (0%)	3 (3.1%)	
Hypothyroidism	3 (3.9%)	0 (0%)	
Hypertension	4 (5.3%)	1 (1%)	
Heart disease	1 (1.3%)	0 (0%)	
Diabetes mellitus	1 (1.3%)	0 (0%)	
Allergic reactions	2 (2.6%)	5 (5.1%)	
Others	9 (11.8%)	10 (10.2%)	

MS multiple sclerosis, CIS clinically isolated syndrome, RRMS relapse-remitting MS, SPMS secondary progressive MS, PPMS primary progressive MS, DMT disease-modifying treatment, INF β interferon beta, IM intramuscular, SC subcutaneous

cell-depleting agents. No one reported a history of progression after COVID-19.

Table 4 The characteristics of MS patients who experienced MS relapse after COVID-19 during the Omicron wave

Variables	Number (%)		P-value
	Relapse	Non-relapse	
Number	13	63	
Age (mean ± SD)	37.07 ± 8.34	36.73 ± 8.59	
Age > 50	1 (7.7%)	2 (3.17%)	0.894
Age ≤ 50	12 (92.3%)	61 (96.83%)	0.446
Sex			
Female	8 (61.54%)	55 (87.3%)	0.025
Male	5 (38.46%)	8 (12.7%)	
Duration of MS (mean ± SD)	8.61 ± 5.56	11.80 ± 7.44	0.149
EDSS	3.42 ± 1.95	2.32 ± 1.97	0.072
Type of MS			
CIS	2 (15.38%)	2 (3.17%)	0.10
RRMS	10 (76.92%)	45 (71.43%)	
PPMS	0	0	
SPMS	1 (7.7%)	16 (25.4%)	

MS multiple sclerosis, CIS clinically isolated syndrome, RRMS relapse-remitting MS, SPMS secondary progressive MS, PPMS primary progressive MS, DMT disease-modifying treatment, *INFβ* interferon beta, IM intramuscular, SC subcutaneous

Discussion

The Omicron variant of COVID-19 emerged as a novel VOI, initially in Africa. Genetic research demonstrated the most mutations in the genome of Omicron compared to early variants; several spike protein mutations provided an immune escape mechanism in the Omicron variant. Accordingly, it has a considerable growth advantage over other variants, leading to rapid spread with higher incidence levels. Several studies have investigated the immunological response against Omicron excited by the COVID-19 vaccine or natural immunity, revealing that recognizing spike protein receptor-binding domains by memory B cells is reduced when comparing Omicron VOI with early variants. However, immune responses provided by T cells remain preserved against Omicron variants [6].

Although MS patients are theoretically at higher risk for infections than the general population, this increased risk has not been the case in the COVID-19 pandemic [7, 8]. In the present study, during the Omicron era, 76 patients (43.7%) developed COVID-19, of whom 29 patients (38.1%) had a history of COVID-19 in the earlier waves. Based on the results, while the prevalence of COVID-19 was higher in the Omicron era than in other waves, it was comparable to the general population. However, the risk factors for developing COVID-19 during the Omicron era were not different from other pandemic waves. We revealed SPMS as the main contributor to developing COVID-19, and other

demographic and MS characteristics, including DMT type, did not increase the risk of developing COVID-19. It should be noted that, in this line, previous pre-Omicron outbreak meta-analyses did not exhibit whether a specific DMT significantly modifies the progression of SARS-CoV-2 in the MS population [12, 13].

In terms of COVID-19 severity, COVID-19 was primarily found to be mild, as only six patients (7.89%) were hospitalized without a need for invasive oxygenation. Our results were in line with previous reports on MS patients and the general population infected with the Omicron variant, which revealed less respiratory tract involvement and a reduced probability of hospital admission and invasive oxygenation in the Omicron pandemic [9–11]. In addition, the severity of COVID-19 was associated with recent pulse steroid therapy ($P=0.018$) and MS type ($P=0.007$), and no significant association was observed with other demographic or MS characteristics except for a margination association for EDSS ($P=0.058$).

A recent review highlighted the older age, male gender, EDSS score of > 3, cardiac comorbidities, obesity, progressive MS course, and recent administration of high doses of corticosteroid as the significant risk factors for developing severe COVID-19 [14]. Likewise, an Iranian multicenter study recommended recent pulse steroid therapy and probably anti-CD20 monoclonal antibodies as substantial contributors to severe COVID-19 [8].

The results revealed that the COVID-19 occurred regardless of the COVID-19 vaccination, as 75% of the infected patients were fully vaccinated. In contrast, an Italian report revealed that three doses of COVID-19 immunization led to a 56% reduction in the risk of the Omicron variant [11]. We assume that this difference might be due to several factors: [1] most of our patients (85.7%) were vaccinated with the Sinopharm COVID-19 vaccines. Previous reports have shown that the Sinopharm vaccines were relatively less effective than the mRNA vaccines [15]; [2] rituximab and fingolimod were the most frequently used DMTs, which have previously been shown to reduce the effectiveness of the vaccines [16]; [3] regarding the significant burden of COVID-19 in Iran and the urgent need for national vaccination, the optimal time interval between DMT infusion and vaccine might not have been applied leading to a possible reduction in the vaccine efficacy. What is more, the main goal of vaccination is not to prevent infections but rather to prevent severe diseases. In this regard, none of our patients experienced severe to critical COVID-19.

On the other hand, given the changes in the immune response against the Omicron variant compared to early variants of coronavirus [17], it might be suggested that the Omicron variant might have a different course in MS patients. On this subject, we demonstrated that 13 patients (17.10%) experienced MS relapse after COVID-19 in the Omicron

era. Eight patients were escalated to a high-efficacy DMT, particularly B cell–depleting agents.

While the exact pathology of relapse associated with COVID-19 remains ambiguous, the expression of peripheral pro-inflammatory mediators in COVID-19, which leads to dysfunction of the blood–brain barrier, appears to be the most hypothetical mechanism that facilitates the migration of autoreactive lymphocytes (particularly Th1/17 cells) to the CNS and consequently leads to irreversible demyelinating damage [18–20]. This pro-inflammatory profile occurs mainly in the cytokine storm syndrome in patients with severe to critical COVID-19. However, none of our patients reported severe to critical COVID-19. Consistent with our findings, *Josef Finsterer* reported a case of MS relapse following mild COVID-19 [21]. Similarly, a case series of four patients with MS relapse associated with COVID-19 did not show a statistical correlation between the severity of COVID-19 and clinical relapse (19).

It should be noted that establishing a secure causal link between Omicron and MS relapse is not feasible. First, we did not isolate the pathogenic variants of COVID-19, making it impossible to attribute the higher relapse rates to the Omicron variant alone. However, given that Omicron was the predominant variant of COVID-19 at that time, we assume that most cases of COVID-19 were of the Omicron type. Second, the COVID-19 pandemic has placed a debilitating psychological burden on MS patients, which might be considered an independent risk factor for relapse. Therefore, attributing the MS relapse only to COVID-19 is unsophisticated. However, considering the possible overestimated rate, a frequency of 17.10% relapse in the present study highlights the importance of the need for a greater understanding of Omicron immunopathology.

Our study has some limitations. First, we did not isolate our patients' pathogenic variants of COVID-19. As a result, along with the predominant Omicron variant, other variants, such as delta, might exist, making it difficult to interpret the data correctly. Second, the study's questionnaire-based nature and the small sample size limited the precise analysis and interpretation. Additionally, a selection bias might have occurred (i.e., patients with more severe diseases were less likely to participate in the study, which resulted in an improper impression of the COVID-19 patients). Third, we did not have access to the patients' MRI information. Fourth, the lack of a control group did not allow to effectively state that MS does not influence the course of COVID-19 in the "Omicron era" with respect to a control population. Extensive multicenter studies are required to understand better the MS course in association with the Omicron variant to optimize the best practice in MS management.

Conclusion

The present study shows that 43.7% of MS patients in the Omicron era developed COVID-19 regardless of the COVID-19 vaccination, which was mild to moderate in severity. The risk factors for COVID-19 during the Omicron era were not different from other pandemic waves. Except for recent pulse steroid therapy and SPMS, no other demographic and MS characteristics were associated with the severity of COVID-19. In addition, 17.10% of our patients reported MS relapse after COVID-19. Our preliminary results suggest that the Omicron variant could trigger MS exacerbation. However, more extensive studies are needed to confirm our findings.

Acknowledgements We thank the MS patients who participated in the present study.

Author contribution All the authors accepted full responsibility for the work and contributed to the writing and correction of the manuscript. SP and AN had the idea for the manuscript. SP and MH wrote the initial draft. MH did the statistical analysis. AN revised the manuscript critically for important intellectual content. All the authors made suggestions contributing to the final article.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval None.

References

1. Karim SSA, Karim QA (2021) Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. *The Lancet* 398(10317):2126–2128
2. Greaney AJ, Starr TN, Gilchuk P, Zost SJ, Binshtein E, Loes AN et al (2021) Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition. *Cell Host Microbe* 29(1):44–57.e9
3. Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM et al (2021) SARS-CoV-2 variants, spike mutations and immune escape. *Nat Rev Microbiol* 19(7):409–424
4. Reyes S, Cunningham AL, Kalincik T, Havrdová EK, Isobe N, Pakpoor J et al (2021) Update on the management of multiple sclerosis during the COVID-19 pandemic and post-pandemic: an international consensus statement. *J Neuroimmunol* 357:577627
5. Reder AT, Centonze D, Naylor ML, Nagpal A, Rajbhandari R, Altincatal A et al (2021) COVID-19 in patients with multiple sclerosis: associations with disease-modifying therapies. *CNS Drugs* 35(3):317–330
6. Take A, Coelho CH, Zhang Z, Dan JM, Yu ED, Methot N et al (2022) SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron. *Cell* 185(5):847–59.e11
7. Luna G, Alpine P, Burman J, Fink K, Fogdell-Hahn A, Gunnars-son M et al (2020) Infection risks among patients with multiple

- sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. *JAMA Neurol* 77(2):184–191
8. Ghadiri F, Sahraian MA, Shaygannejad V, Ashtari F, GhalyanchiLangroodi H, Baghbanian SM et al (2022) Characteristics of COVID-19 in patients with multiple sclerosis. *Mult Scler Relat Disord* 57:103437
 9. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B (2022) Characteristics and outcomes of hospitalized patients in south africa during the COVID-19 omicron wave compared with previous waves. *JAMA* 327(6):583–584
 10. Ulloa AC, Buchan SA, Daneman N, Brown KA (2022) Estimates of SARS-CoV-2 omicron variant severity in Ontario. *Canada Jama* 327(13):1286–1288
 11. Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A et al (2022) Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance. A Prospective Observational Study from the ZOE COVID Study 399(10335):1618–24
 12. Möhn N, Konen FF, Pul R, Kleinschnitz C, Prüss H, Witte T et al (2020) Experience in multiple sclerosis patients with COVID-19 and disease-modifying therapies: a review of 873 published cases. *J Clin Med* 9(12):4067
 13. Diaz de la Fe A, Peláez Suárez AA, Fuentes Campos M, Cabrera Hernández MN, Goncalves CA, Schultz S et al (2021) SARS-CoV-2 infection and risk management in multiple sclerosis. *Diseases* 9(2):32
 14. Immovilli P, Morelli N, Terracciano C, Rota E, Marchesi E, Vol-laro S et al (2022) Multiple sclerosis treatment in the COVID-19 era: a risk-benefit approach. *Neurol Int* 14(2):368–377
 15. Fan YJ, Chan KH, Hung IF (2021) Safety and efficacy of COVID-19 vaccines: a systematic review and meta-analysis of different vaccines at phase 3. *Vaccines (Basel)* 9(9):989
 16. Golshani M, Hrdý J (2022) Multiple sclerosis patients and disease-modifying therapies: impact on immune responses against COVID-19 and SARS-CoV-2 vaccination. *Vaccines* 10(2):279
 17. Sospedra M (2018) B cells in multiple sclerosis. *Curr Opin Neurol* 31(3):256–262
 18. Dzedzic A, Saluk-Bijak J, Miller E, Niemcewicz M, Bijak M (2021) The impact of SARS-CoV-2 infection on the development of neurodegeneration in multiple sclerosis. *Int J Mol Sci* 22(4):1804
 19. Michelena G, Casas M, Eizaguirre MB, Pita MC, Cohen L, Alonso R et al. (2022) ¿ Can COVID-19 exacerbate multiple sclerosis symptoms? A case series analysis. *Mult Scler Relat Disord* 57:103368
 20. Barzegar M, Vaheb S, Mirmosayyeb O, Afshari-Safavi A, Nehzat N, Shaygannejad V (2021) Can coronavirus disease, 2019 (COVID-19) trigger exacerbation of multiple sclerosis? A retrospective study. *Mult Scler Relat Dis* 52
 21. Finsterer J (2022) SARS-CoV-2 triggered relapse of multiple sclerosis. *Clin Neurol Neurosurg* 215:107210

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.