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Clinical Features of COVID-19 on Patients With Neuromyelitis Optica Spectrum Disorders

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Abstract

Background and Objectives

To describe the clinical features and disease outcomes of coronavirus disease 2019 (COVID-19) in patients with neuromyelitis optica spectrum disorder (NMOSD).

Methods

The Neuroimmunology Brazilian Study Group has set up the report of severe acute respiratory syndrome (SARS-CoV2) cases in patients with NMOSD (pwNMOSD) using a designed web-based case report form. All neuroimmunology outpatient centers and individual neurologists were invited to register their patients across the country. Data collected between March 19 and July 25, 2020, were uploaded at the REDONE.br platform. Inclusion criteria were as follows:

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Glossary

AQP4 = aquaporin 4; **CBA** = cell-based assay; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **DMT** = disease-modifying therapy; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorders; **OR** = odds ratio; **pwNMOSD** = patients with NMOSD; **RT-PCR** = reverse transcription-polymerase chain reaction; **SARS** = severe acute respiratory syndrome.

(1) NMOSD diagnosis according to the 2015 International Panel Criteria and (2) confirmed SARS-CoV2 infection (reverse transcription-polymerase chain reaction or serology) or clinical suspicion of COVID-19, diagnosed according to Center for Disease Control / Council of State and Territorial Epidemiologists (CDC/CSTE) case definition. Demographic and NMOSD-related clinical data, comorbidities, disease-modifying therapy (DMT), COVID-19 clinical features, and severity were described.

Results

Among the 2,061 pwNMOSD followed up by Brazilian neurologists involved on the registry of COVID-19 in pwNMOSD at the REDONE.br platform, 34 patients (29 women) aged 37 years (range 8–77), with disease onset at 31 years (range 4–69) and disease duration of 6 years (range 0.2–20.5), developed COVID-19 (18 confirmed and 16 probable cases). Most patients exhibited mild disease, being treated at home (77%); 4 patients required admission at intensive care units (severe cases); and 1 patient died. Five of 34 (15%) presented neurologic manifestations (relapse or pseudoexacerbation) during or after SARS-CoV2 infection.

Discussion

Most NMOSD patients with COVID-19 presented mild disease forms. However, pwNMOSD had much higher odds of hospitalization and intensive care unit admission comparing with the general Brazilian population. The frequency of death was not clearly different. NMOSD disability, DMT type, and comorbidities were not associated with COVID-19 outcome. SARS-CoV2 infection was demonstrated as a risk factor for NMOSD relapses. Collaborative studies using shared NMOSD data are needed to suitably define factors related to COVID-19 severity and neurologic manifestations.

Coronavirus disease 2019 (COVID-19), as an unprecedented challenge to global public health, requires international data collection to address the effect of the disease in groups at potential increased risk.[1] Brazil, one of the main epicenters of the COVID-19 pandemic, reached the unfortunate milestone of more than 2 million severe acute respiratory syndrome (SARS-CoV2) infection cases and more than 100k deaths (accessed on August 8, Johns Hopkins COVID19 resource center). The international community has rapidly launched several patient registries to ascertain the overall effect of the COVID-19 in neuroimmunologic diseases, particularly multiple sclerosis (MS).[2] Notwithstanding, some series of MS patients have been recently reported.[3–6] Scarce data are available about the effect of SARS-CoV2 infection on patients with neuromyelitis optica spectrum disorders (NMOSD), a severe CNS autoimmune astrocytopathy treated with immunosuppressant therapy.[7,8]

Compared with MS, patients with NMOSD (pwNMOSD) are older at disease onset and present higher disability, higher rate of hospitalization, and early-age risk of mortality.[8] Because NMOSD prognosis is relapse-related, it is mandatory to start disease-modifying therapy (DMT) soon after the index clinical event.[9] Many of the commonly used DMTs for NMOSD are cell-depleting immunosuppressants, which may potentially increase the risk of viral and bacterial infections.[10] The effect of SARS-CoV2 infection on pwNMOSD is a gap of knowledge. The purpose of this study was to describe the frequency and clinical features of COVID-19 in a cohort of patients with NMOSD.

Methods

Study Design and Participants

This was a prospective observational cohort study developed by the Brazilian Academy of Neurology using the REDONE.br (Brazilian Registry of Neurological Diseases) platform, starting on March 19, 2020, and punctually closed on July 25, 2020, to be resumed afterward. REDONE.br invited 51 neuroimmunology university and private centers distributed across all 27 Brazilian states. Forty-seven of 51 centers (92%) from 19 states (70%) participated in this study. Each referral center received a link to register all flu-like symptoms among pwNMOSD using a web-based case report form. Neurologists have continuously updated the REDONE.br database reporting the longitudinal follow-up of patients during the SARS-CoV-2 pandemic. Inclusion criteria: (1) patients diagnosed according to the 2015 International Panel for NMOSD criteria[10] and (2) flu-like illness presenting a SARS-CoV2 positive test classified as a confirmed case (reverse transcription-polymerase chain reaction [RT-PCR] and/or IgA/IgM or IgG seropositivity), or clinical suspicion of COVID-19 diagnosed according to CDC/CSTE case definition,[9] classified as a possible case. The cell-based assay (CBA) test to detect antibodies against aquaporin 4 (AQP4-IgG) was performed in most

patients. Exclusion criteria for this study included confirmed infections by H1N1, H3N2, or influenza B and myelin oligodendrocyte protein (MOG)-IgG seropositivity. The anti-MOG IgG was detected using an in-house CBA in live human embryonic kidney (HEK)-293 cells as described elsewhere.[11]

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Ethics Committee of the "Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (Unesp)" under the internal review board number CAAE 31021220.2.0000.5411. All participants signed a written informed consent form before enrollment. This study was conducted according to the latest Declaration of Helsinki.

NMOSD Characteristics

Data collection was related to specific variables such as sex, comorbidities, age at disease onset, disease duration, disability at the last follow-up evaluated by Expanded Disability Status Scale (EDSS), previous use of DMT, maintenance or not during the pandemic, and relapse after infection.

COVID-19 Features

Data regarding COVID-19 included diagnostic criteria (confirmed or probable) and clinical presentation. Chest CT data were recorded when available.

Clinical Outcome

Clinical outcome and disease severity of COVID-19 were evaluated in the pwNMOSD considering the variables: treatment at home (mild cases) or at hospital (moderate cases) and the development of critical conditions (severe cases), such as sepsis, septic shock, acute respiratory syndrome, and need of ventilatory support. In addition, demographic and clinical features of COVID-19 in pwNMOSD were compared with those reported for the general Brazilian population, using similar features as observed for patients with NMOSD (home treatment, hospital admission, intensive care unit [ICU] admission, death, sex, age range [15–59 years], and comorbidity). Data from the Brazilian population were obtained at official national sources at antigo.saude.gov.br/images/pdf/2020/July/30/Boletim-epidemiologico-COVID-24.pdf and opendatasus.saude.gov.br/dataset/bd-srag-2020.[12] Data collection from both groups started from the beginning of the pandemics in Brazil till the closure date of this study (July 25, 2020). For both groups, we considered patients who exhibited positive results for SARS-CoV2 by RT-PCR or serology (as defined by the Brazilian Ministry of Health) from the beginning of the pandemics in Brazil till the closure date of this study (July 25, 2020).

Statistical Analysis

Demographic data, NMOSD clinical and disability profile, COVID-19 clinical features, and outcome were descriptively reported. The comparison of means between groups' home treatment and hospital admission was made using the Student *t* test. The comparison of the proportions between groups for the categorized variables was performed by the test of difference of proportions, analogous to the χ^2 test. The odds ratio (OR) and the 95% confidence interval (95% CI) were obtained through the contingency table of the association between groups and the categorized variables of interest. In addition, the clinical outcome of COVID-19 in patients with NMOSD was compared with the Brazilian general population, using the 2-tailed Fisher's exact test, estimating the OR and the 95% CI. Considering the exploratory nature of the study, no adjustment for multiple comparison was made, and p values ≤ 0.05 were significant. All analyzes were performed using the SAS for the Windows v9.4 program.

Data Availability

Anonymized patient data are available on request.

Results

A total of 34 cases of SARS-CoV2 infection, classified as confirmed (n = 18) or probable (n = 16), were identified in a cohort of 2,061 pwNMOSD, distributed among all 5 Brazilian regions (north = 82 patients, northeast = 643, midwest = 140, southeast = 1,119, and south = 77). Most COVID-19 probable or confirmed cases were from the southeast region (n = 15; 44%), followed by northeast (n = 13; 38%) and north (n = 6; 18%) regions.

Demographic, clinical, and laboratory features of NMOSD patients exhibiting COVID-19 are summarized in Table 1. The women:men ratio was of 6:1. The mean age was 37 years old (range 8–77), and only 3 of 34 patients were older than 50. The mean age at NMOSD diagnosis was 31 years (range 4–69), and disease duration was 6 years (range 0.2–20.5). The median EDSS was 3.5, ranging from 0 to 8.5. Fifteen of 27 patients (56%) exhibited AQP4-IgG, 12 patients did not exhibit anti-AQP4 IgG, and 7 patients were not tested; however, all patients fulfilled the 2015 International Panel Criteria.

More than half of patients (56%) had no comorbidity, whereas 24% of patients exhibited more than 1 comorbidity. Hypertension (21%), obesity (24%), diabetes (15%), and dyslipidemia (15%) were the most common comorbidities. Nine patients presented lymphopenia, which was severe in 2 patients (364 and 600/mm^3), and none of these patients needed to be hospitalized for COVID-19 treatment.

General COVID-19 characteristics in pwNMOSD are listed in Table 2. Main symptoms included fever or chill (79%), dry cough (56%), myalgia (65%), fatigue (53%), coryza (47%), and dyspnea (38%). Gastrointestinal symptoms that occurred in 7 of 34 patients are diarrhea (7; 21%) and abdominal pain (3; 9%). Neurologic symptoms included headache (62%), anosmia (50%), ageusia (24%), and delirium (3%). Most patients (77%) exhibited mild COVID-19 forms being treated at home, and 8 patients (23%) needed to be hospitalized (moderate and severe cases). No differences were observed

Table 1 Demographic, Clinical, and Treatment Features of Patients With Neuromyelitis Optica Spectrum Disorders Who Developed COVID-19

	Total (n = 34)	Home treatment (n = 26)	Hospital admission (n = 8)	*p* Value or (95% CI)
Age (mean, range)	37 (8–77)	42 (8–56)	36 (16–77)	0.72
Age of NMOSD onset (mean, range)	31 (4–69)	35 (4–54)	31 (14–69)	0.89
Disease duration–y (mean, range)	6 (0.2–20.5)	6 (0.2–20.5)	5 (2–8.5)	0.41
EDSS (median, range)	3.5 (0–8.5)	3 (0–8.5)	4 (1–8.5)	0.25
Sex (n, %)				
Female	29 (85)	22 (85)	7 (87.5)	0.84; 0.8 (0.1–8.2)
Male	5 (15)	4 (15)	1 (12.5)	
Color (n, %)				
White	9 (27)	6 (23)	3 (37)	0.73; 0.5 (0.1–2.7)
African descent	23 (67)	19 (73)	4 (50)	0.43; 2.7 (0.5–13.9)
Asian descent	1 (3)	1 (4)	0	1.00
Not informed	1 (3)	0	1 (13)	1.00
No. of comorbidities (n, %)				
No comorbidities	19 (56)	15 (58)	4 (50)	1.00; 1.4 (0.3–6.7)
1 comorbidity	7 (21)	5 (19)	2 (25)	1.00; 0.71 (0.1–4.7)
>1 comorbidity	8 (23)	6 (23)	2 (25)	1.00; 0.9 (0.1–5.7)
Comorbidities (n, %)				
Obesity	8 (24)	6 (23)	2 (25)	1.00; 0.9 (0.1–5.7)
Hypertension	7 (21)	5 (19)	2 (25)	1.00; 0.7 (0.1–4.7)
Diabetes	5 (15)	3 (12)	2 (25)	0.71; 0.4 (0.1–2.9)
Dyslipidemia	5 (15)	2 (8)	3 (38)	0.13; 0.1 (0.02–1.1)
Cardiomyopathy	1 (3)	0	1 (13)	1.00
Neoplasm	1 (3)	1 (4)	0	1.00
Other autoimmune disease	3 (9)	3 (12)	0	0.77
Smoking	1 (3)	1 (4)	0	1.00
Treatment (n, %)				
No treatment	2 (6)	1 (4)	1 (13)	0.96; 0.3 (0.02–5.1)
AZT	10 (30)	9 (35)	1 (13)	0.45; 3.7 (0.3–35)
MTX	1 (3)	1 (4)	0	1.00
MMF + PD	1 (3)	0	1 (13)	1.00
RTX	12 (35)	9 (35)	3 (38)	1.00; 0.9 (0.2–4.6)
AZT + RTX	1 (3)	0	1 (13)	1.00
AZT + PD	5 (15)	4 (15)	1 (13)	1.00; 0.9 (0.1–10)
RTX + PD	2 (6)	2 (8)	0	1.00

Abbreviations: AD = autoimmune disease; AZT = azathioprine; CI = confidence interval; MTX = methotrexate; MMF = mycophenolate mofetil; NMOSD = neuromyelitis optica spectrum disorders; PD = prednisone; RTX = rituximab.

Table 2 Clinical and Neurologic Features, and Outcome of COVID-19 in Patients With Neuromyelitis Optica Spectrum Disorders (NMOSD), Encompassing Confirmed (n = 18) and Probable (n = 16) Cases

	Total (n = 34)
COVID-19 laboratory diagnosis	
Real-time reverse transcription-polymerase chain reaction severe acute respiratory syndrome-CoV2	18 (53%)
General symptoms (n, %)	
Fever	23 (68)
Chill	14 (41)
Dry cough	19 (56)
Myalgia	22 (65)
Fatigue	18 (53)
Arthralgia	5 (15)
Coryza	16 (47)
Sore throat	10 (29)
Diarrhea	7 (21)
Abdominal pain	3 (9)
Nausea	3 (9)
Dyspnea	13 (38)
Neurologic symptoms (n, %)	
Headache	21 (62)
Anosmia	17 (50)
Ageusia	8 (24)
Delirium	1 (3)
Severity (n, %)	
Hospitalization	8 (24)
Intensive care unit (ICU)	4 (12)
Death	1 (3)

Only the frequency of ageusia was different in these groups, being more frequent in confirmed cases (44% vs 6%, $p = 0.02$).

regarding demographic and clinical features comparing confirmed and probable COVID-19 cases, except for ageusia, which was more frequent in confirmed cases (44% vs 6%, $p = 0.02$).

Considering the hospitalized patients, 6 of 8 patients exhibited ground glass opacity, and 4 of 8 patients presented 1 or more comorbidities and used immunosuppressive drugs. Among the 8 hospitalized patients, (1) 4 patients required intensive care support (severe cases); (2) 2 women without comorbidities (16 years old, EDSS 3.5, rituximab and 32 years old, EDSS 4.0, azathioprine) and 1 patient with dyslipidemia (46 years old, EDSS 7.0, azathioprine and prednisone) needed mechanical ventilation; (3) 1 patient needed ICU but no mechanical ventilation, and although patient was treated with rituximab, she was also an elderly patient (77 years old) exhibiting multiple comorbidities, including hypertension, diabetes, dyslipidemia, and cardiomyopathy; and (4) a 46-year-old patient with EDSS 7.0 using azathioprine plus prednisone and presenting dyslipidemia died after evolving SARS, sepsis, and shock septic. Clinical characteristics of hospitalized and critical patients are summarized in eTable 1, links.lww.com/NXI/A540.

NMOSD treatment was suspended in 1 patient during the pandemic and in another during the active COVID-19. Fifteen patients (44%) used rituximab either as a monotreatment (12; 35%) or combined with other oral immunosuppressive drugs (3; 9%). Sixteen of 34 patients (56%) used azathioprine as monotherapy (10; 29%) or combined with prednisone (5; 15%) or rituximab (1; 3%). Four of 8 hospitalized patients and 11 of 26 patients treated at home were in use of rituximab. Among the hospitalized patients, 2 patients used prednisone (with mycophenolate or azathioprine) and 1 used only azathioprine. One patient did not use any immunosuppressive drugs.

Five of 34 patients (15%) with NMOSD presented neurologic manifestations (relapse or pseudoexacerbation) during or after SARS-CoV2 infection. A 48-year-old patient, EDSS 3.0, using rituximab, presented a new right optic neuritis 7 days after the viral infection onset, being treated with oral corticosteroids, with complete recovery (patient 1). A 25-year-old patient, EDSS 5.0, who had a previous optic neuritis, evolved with flu-like syndrome and visual acuity worsening, being treated with IV methylprednisolone with good recovery (patient 2). A 16-year-old patient, EDSS 3.5, also had optic neuritis and presented total recovery after therapy with corticosteroids (patient 3). A 22-year-old patient had myelitis, being treated with IV methylprednisolone with poor recovery (EDSS 8.5) (patient 4). A 32-year-old patient exhibited a 1-point increase in EDSS (EDSS 4.0 to 5.0), even after 50 days after being discharged from the intensive care unit (patient 5). These patients who presented neurologic manifestations requiring hospital admission are given in eTable 1, links.lww.com/NXI/A540.

No associations were observed regarding EDSS (≤4.0 or >4.0) and the duration (≤17 or >17 days) of COVID-19 and its outcomes (home treatment, hospital admissions, ICU, cure, and death) in pwNMOSD. Similarly, no associations were observed between DMT type (azathioprine or rituximab) and comorbidities (without or at least 1 comorbidity) with COVID-19 outcomes (home treatment, hospital admission, ICU, cure, or death) (all p values > 0.05, data not shown).

Demographics and clinical features of COVID-19 in pwNMOSD were compared with those reported for the general Brazilian

Table 3 Demographic and Clinical Features of COVID-19 in 18 PCR-Confirmed Patients With NMOSD Compared With Those Reported for the General Brazilian Population

	NMOSD	General Brazilian population	*p* Value	OR (CI)
Severe acute respiratory syndrome-CoV2 infection by PCR testing or serology (confirmed COVID-19)	n = 18	n = 2,394,513	—	—
Home treatment	12 (67%)	2,157,661 (90%)[a]	—	—
Hospital treatment	6 (33%)	236,852 (11%)	0.01	4.6 (1.6–12.0)
Hospital-ICU	4 (22%)	71,826 (3%)[a]	0.002	9.2 (2.6–26.8)
Death	1 (6%)	86,449 (4%)	0.62	1.6 (0.1–8.7)
Hospitalized patients				
Men	0	134,468 (57%)	—	—
Women	6 (100%)	102,317 (43%)	0.01	2.0-undefined
Age <60 y (15–59)	5 (83%)	101,707 (43%)[a]	0.06	0.9–158.1
At least 1 comorbidity	2 (33%)	138,499 (58%)[a]	0.25	0.05–2.0

Abbreviations: CI = confidence interval; ICU = intensive care unit; NMOSD = neuromyelitis optica spectrum disorders; OR = odds ratio; PCR = polymerase chain reaction.
[a] antigo.saude.gov.br/images/pdf/2020/July/30/Boletim-epidemiologico-COVID-24.pdf and opendatasus.saude.gov.br/dataset/bd-srag-2020

population (Table 3). pwNMOSD presented with a higher frequency of hospital treatment (33% vs 11% OR 4.6 [95% CI 1.6–12.0] $p = 0.01$) and a higher frequency of ICU treatment (22% vs 3% OR 9.2 [95% CI 2.6–26.8] $p = 0.002$). An increased risk of death was not seen.

Discussion

To date, this study included the greatest number of probable and confirmed cases of COVID-19 among pwNMOSD. The estimated prevalence of NMOSD in Latin America is 5 of 100,000 inhabitants.[13] Taking account that the Brazilian population is estimated to have 210,147,125 inhabitants by July 25, 2020, the total number of Brazilian patients with NMOSD may be roughly estimated to 10,590. Therefore, the coverage of the REDONE.br registry was approximately 20% of national cases, a number that can be considered a representative sample. The distribution of COVID-19 in patients with NMOSD was heterogeneous among the 5 major Brazilian regions, agreeing with the more populated areas exhibiting higher COVID-19 incidence rates in the general population.[14]

The preponderance of women and African descents in pwNMOSD with COVID-19 is in accordance with the known demographic profile of the disease.[13] Although male sex and older age have been associated with severity of COVID-19,[1] it is possible that the female preponderance and low median age (only 1 of 34 patient was aged >60 years) as observed in this cohort may be responsible for the predominance of mild COVID-19 cases in pwNMOSD.

Chronic diseases such as hypertension, diabetes mellitus, heart disease, asthma, and obesity are already known to increase COVID-19 severity.[15] The prevalence of known risk factors associated with severe COVID-19, such as hypertension and obesity, is also high in patients with MS and NMOSD.[16,17] Although obesity, hypertension, dyslipidemia, and diabetes were observed in this series, more than half (56%) of pwNMOSD did not present comorbidities. Although comorbidities play an important role in COVID-19 outcome, this scenario is multifaceted and cannot be resolved by this case series.[18]

Besides underlying disorders, patients with NMOSD have an additional morbidity factor associated with DMT and disability related to NMOSD (EDSS). Scarce and inconclusive theoretical efforts based on the use of immunosuppressive drugs in autoimmune disorders during the pandemic or during the SARS-CoV2 infection have challenged neurologists on the decision to maintain or suspend the NMOSD treatment.[19] In this series, 97% (33/34) of patients maintained immunosuppressive drugs during the pandemic and even 97% (32/33) during the infection. Almost half of the patients were treated with rituximab and the other half with azathioprine in mono or combined treatment.

To understand the effect of COVID-19 on pwNMOSD, we compared the NMOSD demographic and clinical features with those reported for the general Brazilian population exhibiting COVID-19, using data available at the Brazilian Ministry of Health Databank. As given in Table 3, pwNMOSD presented a higher rate of hospitalization and of ICU admission than the general population. By contrast, the frequency of death was not

clearly higher between pwNMOSD (n = 1; 6%) and the general Brazilian population (n = 86,449; 4%). On the search for factors that could contribute to higher severity of COVID-19 in pwNMOSD, we analyzed variables such as sex, adjusted age range (15–59 years), and comorbidities between the 2 groups. A difference was observed regarding women having a higher frequency of hospital admission, which could be explained by known disease-associated incidence in women and a low number of cases included in this study. Further studies are needed to confirm this result (Table 3).

Because of the low prevalence of NMOSD,[13] it is understandable that only case report[8] and small sample size[7] have been reported. Considering that there are expectations about the potential risk of interrupt treatment on patients with NMOSD[20] and pondering the conflicting data regarding the use of anti-CD20,[7,8,21] collaborative studies with sharing data are needed to clarify the effect of immunosuppressive drugs on COVID-19 severity and clinical outcome in these patients.[22]

Neurologic symptoms reported in this series included headache, anosmia, ageusia, and delirium, which were already described as neurologic manifestations in recently published articles.[23] Another important issue refers to the effect of SARS-CoV2 infection on NMOSD features. Among the patients who exhibited neurologic manifestations during COVID-19, 2 patients presented new neurologic manifestations and increased EDSS and poorly responded to methylprednisolone treatment. An additional patient exhibited a new episode of optic neuritis 7 days after COVID-19 recovery. These patients may be classified as NMOSD relapses. The other 2 patients exhibited exacerbation of their previous neurologic manifestations and presented a good response to methylprednisolone therapy. Whether these 2 patients exhibited relapse or pseudoexacerbation during COVID-19 is challenging because imaging procedures were not performed. Despite the small number of patients, the coincidence between SARS-CoV2 infection and NMOSD neurologic manifestations (e.g., relapse and pseudoexacerbation) deserves further investigation to ascertain whether the virus itself or the host inflammation associated with COVID-19 may contribute to impair previous or promote new neurologic findings.[24]

Major methodological limitations of this study included the following: (1) the low number of tests for COVID-19 diagnosis at the time of the study and (2) the electronic communication between patients and their neurologists. Despite these limitations, this is the first data collection on patients with NMOSD in the context of the superimposed COVID-19 infection in a severely affected country.

In conclusion, most NMOSD patients with COVID-19 presented mild disease forms, particularly among women. However, pwNMOSD had much higher odds of hospitalization and ICU admission comparing with the general Brazilian population. The frequency of death was not clearly different. NMOSD disability, DMT type, and comorbidities were not associated with COVID-19 outcome. SARS-CoV2 infection was demonstrated as a risk factor for NMOSD relapses. Collaborative studies using shared NMOSD data are needed to suitably define factors related to COVID-19 severity and neurologic manifestations.

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Disclosure

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Continued

Appendix *(continued)*

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Appendix *(continued)*

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