COVID-19 in Patients With Neuromyelitis Optica Spectrum Disorders and Myelin Oligodendrocyte Glycoprotein Antibody Disease in North America

From the COViMS Registry

Scott D. Newsome, DO, Anne H. Cross, MD, Robert J. Fox, MD, June Halper, MSN, APN-C, Pamela Kanellis, PhD, Bruce Bebo, PhD, David Li, MD, Gary R. Cutter, PhD, Kottil W. Rammohan, MD, and Amber Salter, PhD

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Abstract

Background and Objective
To describe the impact of coronavirus disease 2019 (COVID-19) on people with neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody disease (MOGAD).

Methods
The COVID-19 Infections in Multiple Sclerosis (MS) and Related Diseases (COViMS) Registry collected data on North American patients with MS and related diseases with laboratory-positive or highly suspected SARS-CoV-2 infection. Deidentified data were entered into a web-based registry by health care providers. Data were analyzed using t-tests, Pearson χ² tests, or Fisher exact tests for categorical variables. Univariate logistic regression models examined effects of risk factors and COVID-19 clinical severity.

Results
As of June 7, 2021, 77 patients with NMOSD and 20 patients with MOGAD were reported in the COViMS Registry. Most patients with NMOSD were laboratory positive for SARS-CoV-2 and taking rituximab at the time of COVID-19 diagnosis. Most patients with NMOSD were not hospitalized (64.9% [95% CI: 53.2%–75.5%]), whereas 15.6% (95% CI: 8.3%–25.6%) were hospitalized only, 9.1% (95% CI: 3.7%–17.8%) were admitted to the ICU and/or ventilated, and 10.4% (95% CI: 4.6%–19.5%) died. In patients with NMOSD, having a comorbidity was the sole factor identified for poorer COVID-19 outcome (OR = 6.0, 95% CI: 1.79–19.98). Most patients with MOGAD were laboratory positive for SARS-CoV-2, and almost half were taking rituximab. Among patients with MOGAD, 75.0% were not hospitalized, and no deaths were recorded; no factors were different between those not hospitalized and those hospitalized, admitted to the ICU, or ventilated.

Discussion
Among the reported patients with NMOSD, a high mortality rate was observed, and the presence of comorbid conditions was associated with worse COVID-19 outcome. There were no deaths reported in the patients with MOGAD, although these observations are limited due to small sample size.
The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) raised concerns about the risks of COVID-19 in those with neuroimmunologic disorders that affect the CNS. Risk factors associated with worse COVID-19 outcomes in multiple sclerosis (MS) include increased hospitalizations with B cell–depleting therapies, recent treatment with glucocorticoid use, and Black or African American race. However, little data have been reported on how COVID-19 affects people with neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody disease (MOGAD).

NMOSD and MOGAD are distinct disorders that have a spectrum of presentations and unique autoantibodies that differentiate them from MS and other diseases. Disability levels vary in NMOSD and MOGAD, with the former often associated with a greater disability. However, outcomes of COVID-19 in people with NMOSD or MOGAD are largely unknown, especially in those with preexisting medical comorbidities and/or taking specific disease-modifying therapies (DMTs).

The rarity of coexisting SARS-CoV-2 and these autoantibody-associated disorders make them well suited to a registry-based study. The COVID-19 Infections in MS and Related Diseases (COViMS) Registry was designed to collect information on COVID-19 in people with MS, NMOSD, and MOGAD from North American health care professionals. Here, we aimed to describe the clinical characteristics, risk factors for severe course of COVID-19, and overall COVID-19 outcomes in patients with NMOSD and MOGAD.

Methods

Study Design

The COViMS Registry collected data on patients in North America who had a laboratory positive or highly suspected infection with SARS-CoV-2 with MS and other related diseases, including NMOSD and MOGAD. Highly suspected patients for SARS-CoV-2 infection were identified by a health care professional based on typical COVID-19 symptoms and signs (e.g., anosmia, ageusia, shortness of breath, and pneumonia) with no better explanation for their symptoms/signs. Health care professionals were asked to report patients after a minimum of 7 days from initial infectious symptom onset and when sufficient time had passed to observe the COVID-19 disease course through resolution of acute illness or death.

The COViMS Registry is jointly supported by the Consortium of MS Centers, the National MS Society USA, and the MS Society of Canada.

Data collection was de-identified, cross-sectional, and entered into a secure, online database on the COViMS Registry website (COViMS.org) using the REDCap system (project-redcap.org). The Registry was determined to be not human subject research by the WUSTL Institutional Review Board. Data use agreements govern the use of some data that were contributed, and thus, access to individual level data is not permitted by outside researchers. Data collection began April 1, 2020, and is ongoing. The study herein used data collected from April 1, 2020, through June 7, 2021.

COVID-19 Clinical Outcome

Health care professionals indicated whether the patient was hospitalized, admitted to the intensive care unit (ICU), required ventilator support, and/or died during their COVID-19 clinical course, with response options of “yes,” “no,” or “unknown” to each. Unknown responses were considered as not having the outcome. These separate outcomes were used to characterize COVID-19 severity, with the following levels: not hospitalized, hospitalization alone, ICU admission and/or ventilation and death where if more than 1 event was indicated, the patient was assigned to the highest level of event that occurred.

Demographic and Clinical Characteristics

Demographic factors collected were sex (male, female, and nonbinary), age, race (White; Black or African American [Black]; Asian; American Indian, Alaska Native, or Indigenous Canadian; Native Hawaiian or Other Pacific Islander; other; or unknown), and ethnicity (Hispanic/Latino, not Hispanic/Latino, other, or unknown). Clinical characteristics collected include disease type (if NMOSD, NMO-IgG or aquaporin-4 antibody status noted), disease duration, and ambulation milestones (fully ambulatory, walks with assistance, and nonambulatory). Comorbid conditions were indicated by selecting all applicable including cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, chronic neurologic and/or neuromuscular disease, diabetes, hypertension, immunodeficiency disease, and morbid obesity. Comorbid conditions were also summed to categorize the count as 0 (reference), 1, 2, and ≥3 comorbidities. Cigarette use history was captured as never, past, current, or unknown. Glucocorticoid treatment during the prior 2 months was ascertained. Current DMT at the time of SARS-CoV-2

Glossary

COVID-19 = coronavirus disease 2019; COViMS = COVID-19 Infections in MS and Related Diseases; DMT = disease-modifying therapy; ICU = intensive care unit; MOGAD = myelin oligodendrocyte glycoprotein antibody disease; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorders; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
infection was reported by the provider as one of the following: alemtuzumab, azathioprine, cladribine, daclizumab, dimethyl fumarate, diroximel fumarate, eculizumab, fingolimod, glatiramer acetate, hematopoietic stem cell transplant, interferon-beta, intravenous immunoglobulin, methotrexate, mitoxantrone, mycophenolate, natalizumab, ocrelizumab, ofatumumab, ozanimod, rituximab, satralizumab, tocilizumab, siponimod, teriflunomide, other, none, and unknown.1

Statistical Analysis
The analyses were limited to patients with NMOSD and MOGAD who were laboratory positive or highly suspected for SARS-CoV-2 infection and reported by a health care professional in North America. Cohort characteristics were summarized using mean (SD) for continuous variables, median (interquartile range) for ordinal variables, and frequencies (%) for categorical variables.1 Comparisons between groups were made using χ² tests, Fisher exact tests, and Student t-tests, as appropriate, and reported descriptive statistics and p values.1

A description of the demographic and clinical characteristics of those 8 patients with NMOSD who died of COVID-19 is reported in Table 2. All deceased patients with NMOSD had at least 1 medical comorbidity. Five of the 8 (62.5%) fatal NMOSD cases were aquaporin-4 IgG positive, and 4 (50%) were Black or African American. Six (75.0%) of the 8 patients with NMOSD who died of COVID-19 were on rituximab, but the proportion of deaths among those taking rituximab was not statistically different than the proportion among those not on rituximab (6/46 = 13.0% compared with 2/31 = 6.5%, p = 0.46). No significant differences were found among those taking rituximab vs those not on rituximab among patients with NMOSD who were hospitalized or worse (6/18 = 33.3% taking rituximab compared with 2/9 = 29.0% not taking rituximab, p = 0.68).

Results

demographic and clinical characteristics of patients with NMOSD
As of June 7, 2021, there were 77 patients with NMOSD reported in the COViMS Registry. Most patients were female (81.6%) and in the United States at the time of COVID-19 (97.2%), with a mean age (SD) of 48.1 (14.1) years (Table 1). Race and ethnicity of patients were diverse with 38.2% Black, 25.0% non-Hispanic White, 17.1% Hispanic or Latino, and 19.7% other racial groups. The average NMOSD disease duration was 9.1 (7) years, and 67.2% were aquaporin-4 IgG seropositive. Although the majority of patients with NMOSD were fully ambulatory (75.7%), some required assistance with ambulation (14.9%), and 9.4% were nonambulatory. At the time of COVID-19 diagnosis, most patients with NMOSD were on rituximab (62.2%), and 9.5% were not on a DMT. Sixty percent had a comorbidity, with hypertension (20.8%), diabetes (15.6%), and morbid obesity (14.3%) being the most frequent comorbidities reported. Only 4 (5.6%) patients with NMOSD were current cigarette smokers.

Almost all (89.6%) patients with NMOSD were laboratory positive for SARS-CoV-2. Fever (57.1%) and dry cough (40.3%) were commonly reported symptoms of COVID-19, whereas 2.6% of patients with NMOSD reported being asymptomatic. Seven patients reported having neurologic symptoms from COVID-19, with motor dysfunction occurring in 3 of the 7 and cognitive and sensory dysfunction each in 2 of

COVID-19 outcomes in patients with NMOSD
Most patients with NMOSD were not hospitalized (64.9% [95% CI: 53.3%–75.5%]), whereas 15.6% (95% CI: 8.3%–25.6%) were hospitalized only, and 9.1% (95% CI: 3.7%–17.8%) were admitted to the ICU and/or ventilated. Over 10% (10.4%; 95% CI: 4.6%–19.5%) died. No demographic characteristics were statistically significantly different between those not hospitalized and those hospitalized, admitted to the ICU, ventilated, or died of COVID-19. Having a medical comorbidity was the only statistically significant difference observed; those with a comorbidity were 6-fold more likely to have a poor clinical COVID-19 outcome compared with those with no comorbidity (OR = 6.0, 95% CI: 1.79–19.98).

A description of the demographic and clinical characteristics of patients with MOGAD with COVID-19 is reported in Table 2. All deceased patients with MOGAD had at least 1 medical comorbidity. Of the 20 patients with MOGAD, 14 (70%) had 1 or more medical comorbidities, whereas 6 (30%) did not have any medical comorbidities. Of the 14 patients with MOGAD and 1 or more medical comorbidities, 13 (92.9%) had 1 medical comorbidity. The most common medical comorbidities were hypertension (40.3%) and diabetes (28.6%). The median hospital stay was 6 days (range: 0–62). Six patients (30.0%) were admitted to the ICU, and 2 patients (10.0%) required ventilation. Five patients (25.0%) died. No demographic characteristics were statistically significantly different between those not hospitalized and those hospitalized, admitted to the ICU, ventilated, or died of COVID-19. Having a medical comorbidity was the only statistically significant difference observed; those with a comorbidity were 6-fold more likely to have a poor clinical COVID-19 outcome compared with those with no comorbidity (OR = 6.0, 95% CI: 1.79–19.98).

COVID-19 outcomes in patients with MOGAD
The demographic and clinical characteristics of patients with MOGAD with COVID-19 are reported in Table 2. All deceased patients with MOGAD were on rituximab at the time of their COVID-19 diagnosis. The most common symptoms from COVID-19 reported in these patients with MOGAD were fever (57.1%), dry cough (45.0%), and shortness of breath (40.3%). The symptom duration was 0–6 days in 13.3% of patients with NMOSD, 7–13 days for 22.2%, 14–20 days for 20.0%, and 21 days or longer in 44.4% of patients. Of the 77 patients with NMOSD, 15.6% had pneumonia.

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Table 1 COViMS NMOSD Overall and by Clinical Outcome

| Factor                  | Total (N = 77) | Not hospitalized (n = 50) | Hospitalized, ICU admission/ventilation/death (n = 27) | p Value |
|-------------------------|----------------|----------------------------|---------------------------------------------------|---------|
| Female                  | 62 (81.6)      | 43 (86.0)                  | 19 (73.1)                                         | 0.17b   |
| Age                     | 48.1 (14.1)    | 46.9 (14.1)                | 50.3 (14.2)                                       | 0.33a   |
| Race                    |                |                            |                                                   | 0.13b   |
| Non-Hispanic White      | 19 (25.0)      | 11 (22.4)                  | 8 (29.6)                                          |         |
| Black or African American| 29 (38.2)     | 18 (36.7)                  | 11 (40.7)                                         |         |
| Hispanic or Latino      | 13 (17.1)      | 12 (24.5)                  | 1 (3.7)                                           |         |
| Other/unknown           | 15 (19.7)      | 8 (16.3)                   | 7 (25.9)                                          |         |
| Disease duration<sup>c</sup> | 9.1 (7.0)  | 8.6 (6.5)                  | 10.2 (7.9)                                        | 0.37a   |
| NMOSD type              |                |                            |                                                   | 0.47b   |
| NMO-IgG/aquaporin-4 antibody (+) | 43 (55.8) | 28 (56.0)                  | 15 (55.6)                                         |         |
| NMO-IgG/aquaporin-4 antibody (−) | 15 (19.5) | 8 (16.0)                   | 7 (25.9)                                          |         |
| Unknown                 | 19 (24.7)      | 14 (28.0)                  | 5 (18.5)                                          |         |
| Ambulatory status       |                |                            |                                                   | 0.21d   |
| Fully ambulatory        | 56 (75.7)      | 40 (81.6)                  | 16 (64.0)                                         |         |
| Walk with assistance    | 11 (14.9)      | 6 (12.2)                   | 5 (20.0)                                          |         |
| Nonambulatory           | 7 (9.5)        | 3 (6.1)                    | 4 (16.0)                                          |         |
| Glucocorticoid during the last 2 months? |             |                            |                                                   | 0.67d   |
| No                      | 56 (72.7)      | 36 (72.0)                  | 20 (74.1)                                         |         |
| Yes                     | 6 (7.8)        | 5 (10.0)                   | 1 (3.7)                                           |         |
| Unknown                 | 15 (19.5)      | 9 (18.0)                   | 6 (22.2)                                          |         |
| DMT at the time of COVID-19<sup>c</sup> |             |                            |                                                   | 0.63d   |
| Azathioprine            | 5 (6.8)        | 4 (8.5)                    | 1 (3.7)                                           |         |
| Eculizumab              | 5 (6.8)        | 4 (8.5)                    | 1 (3.7)                                           |         |
| Mycophenolate           | 5 (6.8)        | 4 (8.5)                    | 1 (3.7)                                           |         |
| Ocrelizumab             | 1 (1.4)        | 0 (0.0)                    | 1 (3.7)                                           |         |
| Rituximab               | 46 (62.2)      | 28 (59.6)                  | 18 (66.7)                                         |         |
| Other                   | 5 (6.8)        | 2 (4.3)                    | 3 (11.1)                                          |         |
| None                    | 7 (9.5)        | 5 (10.6)                   | 2 (7.4)                                           |         |
| Length of time on current DMT<sup>c</sup> |             |                            |                                                   | 0.49b   |
| <6 months               |                |                            |                                                   | 0.32b   |
| 6 or more months        | 9 (13.8)       | 7 (17.1)                   | 2 (8.3)                                           |         |
| Have comorbidities?     | 56 (86.2)      | 34 (82.9)                  | 22 (91.7)                                         |         |
| No                      |                |                            |                                                   | 0.004b  |
| Yes                     | 29 (38.7)      | 25 (52.1)                  | 4 (14.8)                                          |         |
| Cancer                  | 5 (6.5)        | 2 (4.0)                    | 3 (11.1)                                          | 0.34d   |
| Cardiovascular disease  | 6 (7.8)        | 4 (8.0)                    | 2 (7.4)                                           | 0.99d   |
| Cerebrovascular disease | 1 (1.3)        | 1 (2.0)                    | 0 (0.0)                                           | 0.99d   |

Continued
hospitalized, and 15.0% (95% CI: 3.2%–37.9%) were admitted to the ICU and/or ventilated. No deaths were recorded as of June 7, 2021. A full listing of individual MOGAD patient clinical characteristics, COVID-19 clinical outcome, and COVID-19 treatments is provided in Table 3. No demographic characteristic or clinical COVID-19 outcome was statistically different between those not hospitalized and those hospitalized, admitted to the ICU, or ventilated (data not shown and available on request). Notably, these comparisons were limited due to the small number of patients with MOGAD who were reported.

**Differences in COVID-19 Deaths Among Patients With NMOSD and MS**

Seventy-four patients with MS and 8 patients with NMOSD died during the study time period. There were a few differences in demographic and clinical characteristics between these groups worth noting (Table 4). Specifically, the NMOSD cohort who died were younger (50 ± 19.2 vs 62.1 ± 12.3, p = 0.016), had shorter disease duration (9.3 ± 7.4 vs 20.6 ± 12.1, p = 0.012), and a greater percentage of patients were on rituximab compared with the patients with MS who died (75% vs 5.4%, p < 0.001).

**Discussion**

The COViMS Registry has provided a platform for collecting clinician-reported data on patients with MS and related disorders who developed COVID-19. These Registry data provide clinicians with useful information about how SARS-CoV-2 infection affects patients with NMOSD and MOGAD and indicate those who might be at greatest risk for more severe COVID-19 outcomes. NMOSD and MOGAD are uncommon, and this study represents the largest cohort of patients with NMOSD and MOGAD with COVID-19 reported to date. A French study of 15 total patients with NMOSD and MOGAD (5 seropositive NMOSD, 5 seronegative NMOSD, and 5 with MOGAD) with COVID-19 reported an association of older age and more disability with hospitalization, but no deaths.3

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**Table 1 COViMS NMOSD Overall and by Clinical Outcome (continued)**

| Factor                  | Total (N = 77) | Not hospitalized (n = 50) | Hospitalized, ICU admission/ventilation/death (n = 27) | p Value |
|-------------------------|---------------|--------------------------|------------------------------------------------------|---------|
| Chronic kidney disease  | 2 (2.6)       | 0 (0.0)                  | 2 (7.4)                                              | 0.12d   |
| Chronic liver disease   | 0 (0.0)       | 0 (0.0)                  | 0 (0.0)                                              |         |
| Chronic lung disease    | 7 (9.1)       | 3 (6.0)                  | 4 (14.8)                                             | 0.23d   |
| Chronic neurologic disease | 4 (5.2)   | 1 (2.0)                  | 3 (11.1)                                             | 0.12d   |
| Diabetes                | 12 (15.6)     | 7 (14.0)                 | 5 (18.5)                                             | 0.60a   |
| Hypertension            | 16 (20.8)     | 9 (18.0)                 | 7 (25.9)                                             | 0.41b   |
| Immunodeficiency disease| 2 (2.6)       | 1 (2.0)                  | 1 (3.7)                                              | 0.99d   |
| Morbid obesity          | 11 (14.3)     | 4 (8.0)                  | 7 (25.9)                                             | 0.032b  |
| Other                   | 12 (15.6)     | 8 (16.0)                 | 4 (14.8)                                             | 0.89b   |
| Comorbid conditions count |          |                          |                                                      | 0.027b  |
| 0                       | 32 (41.6)     | 27 (54.0)                | 5 (18.5)                                             |         |
| 1                       | 24 (31.2)     | 12 (24.0)                | 12 (44.4)                                            |         |
| 2                       | 10 (13.0)     | 5 (10.0)                 | 5 (18.5)                                             |         |
| ≥3                      | 11 (14.3)     | 6 (12.0)                 | 5 (18.5)                                             |         |
| Type of COVID-19 diagnosis |          |                          |                                                      | 0.028b  |
| Laboratory positive     | 69 (89.6)     | 42 (84.0)                | 27 (100.0)                                           |         |
| Suspected COVID-19, not confirmed | 8 (10.4) | 8 (16.0)                | 0 (0.0)                                              |         |

Abbreviations: COVID-19 = coronavirus disease 2019; COViMS = COVID-19 Infections in MS and Related Diseases; DMT = disease-modifying therapy; ICU = intensive care unit; NMOSD = neuromyelitis optica spectrum disorders. Values presented as mean ± SD, median (P25, P75) or N (column %).

a Pearson $\chi^2$ test.
b ANOVA.
c Data not available for all patients. Missing values: sex = 1, age = 1, disease duration = 5, DMT at the time of COVID-19 = 2, and length of time on current DMT = 10.
d Fisher exact test.
e Kruskal-Wallis test.
| Sex | Age | Race | US state at the time of COVID-19 onset | Disease duration (y) | NMOSD antibody serostatus | Ambulatory status | DMT at the time of COVID-19 | Comorbidities | Pneumonia | Length of hospital stay | COVID-19 treatments |
|-----|-----|------|---------------------------------------|---------------------|--------------------------|------------------|-----------------------------|---------------|-------------|----------------------|----------------------|
| Female | 73 | Non-Hispanic White | Colorado | 2 | Positive | Walk with assistance | None | Cancer, cardiovascular disease, and chronic lung disease | Yes | 4–6 d | | Hydroxychloroquine, azithromycin, and oxygen therapy |
| Female | 30 | Black or African American | Florida | 2 | Negative | Fully ambulatory | Rituximab | Diabetes and morbid obesity | Yes-bilateral | 19–21 d | | Antiviral and other antibiotic, convalescent plasma, tocilizumab, and oxygen therapy |
| Female | 55 | Other/unknown | Unknown | 9 | Positive | Walk with assistance | Rituximab | Hypertension | Unknown | 30+ d | | |
| Female | 39 | Black or African American | Washington | 10 | Positive | Nonambulatory | Other | Chronic kidney disease and morbid obesity | Unknown | 4–6 d | | |
| Female | 26 | Black or African American | California | 5 | Positive | Fully ambulatory | Rituximab | Diabetes and morbid obesity | Yes | Unknown | | |
| Male | 80 | Non-Hispanic White | Missouri | 25 | Negative | Nonambulatory | Rituximab | Hypertension | No | 7–9 d | | |
| Female | 46 | Non-Hispanic White | Vermont | 8 | Negative | Fully ambulatory | Rituximab | Diabetes, hypertension, and morbid obesity | Yes-bilateral | 30+ d | | Antiviral, systemic glucocorticoids, other anti-inflammatory agents, oxygen therapy, IVIG, and convalescent plasma |
| Female | 52 | Black or African American | Kentucky | 13 | Positive | Fully ambulatory | Rituximab | Chronic lung disease and hypertension | Yes-bilateral | 30+ d | | Systemic glucocorticoids, azithromycin, other antibiotics, oxygen therapy, and IVIG |

Abbreviations: COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; IVIG = intravenous immunoglobulin; NMOSD = neuromyelitis optica spectrum disorders.
| Sex | Age | Race | US state at the time of COVID-19 onset | Disease duration | Ambulatory status | DMT at the time of COVID-19 | Comorbidities | COVID-19 clinical severity outcome | Pneumonia | Length of hospital stay | COVID-19 treatments |
|-----|-----|------|----------------------------------------|------------------|-------------------|-----------------------------|---------------|----------------------------------|-----------|----------------------|-------------------|
| Female | 67 | Black or African American | Unknown | 15 | Fully ambulatory | Mycophenolate | Cancer, chronic lung disease, and diabetes | Admitted to the ICU and/or ventilated | No | 13-15 d | Hydroxychloroquine and systemic glucocorticoids |
| Male | 54 | Non-Hispanic White | Kansas | 3 | Fully ambulatory | Rituximab | Hypertension | Admitted to the ICU and/or ventilated | Yes-bilateral | 7-9 d | Chloroquine, azithromycin, and oxygen therapy |
| Female | 19 | Non-Hispanic White | California | 3 | Fully ambulatory | Mycophenolate | No | Hospitalization only | Yes-bilateral | 4-6 d | Hydroxychloroquine, azithromycin, and other antibiotics |
| Female | 26 | Non-Hispanic White | Unknown-United States | 2 | Fully ambulatory | Rituximab | Obesity | Not hospitalized | No | — | None |
| Female | 58 | Hispanic or Latino | Missouri | 7 | Fully ambulatory | None | No | Not hospitalized | No | — | Systemic glucocorticoids |
| Female | 32 | Other/unknown | California | 3 | Fully ambulatory | Rituximab | Morbid obesity | Not hospitalized | No | — | Azithromycin |
| Female | 43 | Non-Hispanic White | Kentucky | 2 | Walk with assistance | Azathioprine | Diabetes, hypertension, and morbid obesity | Not hospitalized | Yes-unilateral | — | Azithromycin |
| Female | 20 | Hispanic or Latino | Unknown-United States | 8 | Fully ambulatory | Fingolimod | Migraines | Not hospitalized | No | — | None |
| Female | 62 | Other/unknown | California | 2 | Fully ambulatory | Rituximab | None | Not hospitalized | No | — | Tylenol |
| Female | 26 | Non-Hispanic White | Rhode Island | 2 | Fully ambulatory | Rituximab | No | Not hospitalized | No | — | Unknown |
| Female | 64 | Other/unknown | Unknown-United States | 0 | Walk with assistance | Rituximab | Diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea | Not hospitalized | No | — | None |
| Female | 25 | Non-Hispanic White | Nebraska | 15 | Fully ambulatory | IVIG | None | Not hospitalized | No | — | Bamlanivimab |
| Male | 69 | Other/unknown | Canada | 4 | Fully ambulatory | None | Cancer and hypertension | Not hospitalized | No | — | None |
| Male | 58 | Non-Hispanic White | Ohio | 2 | Fully ambulatory | Rituximab | Hypertension and morbid obesity | Admitted to the ICU and/or ventilated | Yes-bilateral | 1-3 d | Unknown monoclonal antibody infusion |
| Female | 27 | Non-Hispanic White | Canada | 4 | Fully ambulatory | Azathioprine | None | Not hospitalized | No | — | None |
| Male | 27 | Other/unknown | Canada | Unknown | Unknown | Unknown | None | Not hospitalized | No | — | Unknown |

Continued
Approximately two-thirds of patients with NMOSD in the COViMS Registry did not require hospitalization; however, 10.4% of the entire cohort died (8/77). This mortality rate is notable for being 4 times the rate than what was seen with patients with MS in COViMS and almost 6 times greater than that reported for the general population in the United States. However, a 95% CI ranging from 4.6% to 19.5% leaves some uncertainty as to the level of excess risk. A large percentage of the NMOSD cohort were Black and on rituximab, both of which are known risk factors for severe COVID-19 in other populations. The sole factor that identified statistically poorer COVID-19 outcome in NMOSD was the presence of a medical comorbidity, which resulted in 6-fold greater odds of worse COVID-19 outcomes. The most common medical comorbidities in this cohort were hypertension, diabetes, and morbid obesity, which have also been observed to increase risks of poor outcome from COVID-19 in the general population.

In the MS population within the COViMS Registry and in other registries/surveys, common risk factors for severe COVID-19 outcomes included older age, male sex, Black race, higher disability level, recent corticosteroid use, and use of B cell–depleting therapies. No demographic or DMT differences were observed in relation to NMOSD outcomes, although our statistical power to identify differences was limited. Overall, almost 60% of patients with NMOSD with COVID-19 in COViMS were treated with B cell–depleting therapies (46/77), and the proportion of NMOSD taking rituximab with fatal outcomes was nominally higher compared with those not taking rituximab (13.0% vs 6.5%). In addition, a large proportion of NMOSD were of Black race (29/77), and 4 of the 8 deaths were in NMOSD of Black race. Hence, with a larger sample size, rituximab and Black race could prove to be additional risk factors for severe COVID-19 in NMOSD. In fact, to achieve an 80% power to detect a difference in more severe outcomes between these groups, it would require over 200 patients per group. Thus, precautions to prevent exposure to SARS-CoV-2 in patients with NMOSD are recommended. Moreover, COVID-19 vaccination has been strongly encouraged by infectious disease experts and the Centers for Disease Control and Prevention, especially for those who are at high risk for more severe COVID-19 disease, and thus COVID-19 vaccination in NMOSD may be particularly important.

None of the 20 patients with MOGAD with COVID-19 in the COViMS Registry died, and only 5 required hospitalization. Patients with MOGAD in this cohort had similar comorbidities as those with NMOSD, and almost half were taking rituximab. Not identifying specific risks factors of poorer outcomes with COVID-19 in MOGAD is likely due to the small size of the cohort.

Altering B cell–depleting therapy dosage and/or frequency of administration during the COVID-19 pandemic has been
| Factor                                      | Total (N = 82) | MS (n = 74) | NMO (n = 8) | p Value |
|---------------------------------------------|---------------|-------------|-------------|---------|
| **Sex**                                     |               |             |             | 0.21b   |
| Male                                        | 35 (42.7)     | 34 (45.9)   | 1 (12.5)    |         |
| Female                                      | 46 (56.1)     | 39 (52.7)   | 7 (87.5)    |         |
| Nonbinary                                   | 1 (1.2)       | 1 (1.4)     | 0 (0.0)     |         |
| **Age**                                     |               |             |             | 0.016a  |
| Male                                        | 60.9 (13.5)   | 62.1 (12.3) | 50.1 (19.2) |         |
| Female                                      | 61.2 (13.6)   | 61.3 (13.1) | 50.5 (19.2) |         |
| **Race**                                    |               |             |             | 0.18b   |
| Non-Hispanic White                          | 54 (65.9)     | 51 (68.9)   | 3 (37.5)    |         |
| Black or African American                   | 20 (24.4)     | 16 (21.6)   | 4 (50.0)    |         |
| Hispanic or Latino                          | 2 (2.4)       | 2 (2.7)     | 0 (0.0)     |         |
| Other/unknown                               | 6 (7.3)       | 5 (6.8)     | 1 (12.5)    |         |
| **Country at the time of COVID-19 onset**   |               |             |             | 0.99b   |
| United States                               | 77 (97.5)     | 70 (97.2)   | 7 (100.0)   |         |
| Canada                                      | 1 (1.3)       | 1 (1.4)     | 0 (0.0)     |         |
| Other                                       | 1 (1.3)       | 1 (1.4)     | 0 (0.0)     |         |
| **Disease duration**                        | 19.3 (12.2)   | 20.6 (12.1) | 9.3 (7.4)   | 0.012a  |
| **Ambulatory status**                       |               |             |             | 0.075b  |
| Fully ambulatory                            | 15 (20.5)     | 11 (16.9)   | 4 (50.0)    |         |
| Walk with assistance                        | 20 (27.4)     | 18 (27.7)   | 2 (25.0)    |         |
| Nonambulatory                               | 38 (52.1)     | 36 (55.4)   | 2 (25.0)    |         |
| **Glucocorticoid during the last 2 months?**|               |             |             | 0.45a   |
| No                                          | 54 (76.1)     | 48 (75.0)   | 6 (85.7)    |         |
| Yes                                         | 6 (8.5)       | 5 (7.8)     | 1 (14.3)    |         |
| Unknown                                     | 11 (15.5)     | 11 (17.2)   | 0 (0.0)     |         |
| **DMT at the time of COVID-19**             |               |             |             | 0.002b  |
| Alemtuzumab                                 | 1 (1.3)       | 1 (1.5)     | 0 (0.0)     |         |
| Dimethyl fumarate                           | 4 (5.3)       | 4 (5.9)     | 0 (0.0)     |         |
| Glatiramer acetate                          | 2 (2.6)       | 2 (2.9)     | 0 (0.0)     |         |
| Interferon-beta                             | 1 (1.3)       | 1 (1.5)     | 0 (0.0)     |         |
| Mycophenolate                               | 1 (1.3)       | 1 (1.5)     | 0 (0.0)     |         |
| Natalizumab                                 | 3 (3.9)       | 3 (4.4)     | 0 (0.0)     |         |
| Ocrelizumab                                 | 19 (25.0)     | 19 (27.9)   | 0 (0.0)     |         |
| Rituximab                                   | 10 (13.2)     | 4 (5.9)     | 6 (75.0)    |         |
| Siponimod                                   | 2 (2.6)       | 2 (2.9)     | 0 (0.0)     |         |
| Teriflunomide                                | 5 (6.6)       | 5 (7.4)     | 0 (0.0)     |         |
| Other                                       | 2 (2.6)       | 1 (1.5)     | 1 (12.5)    |         |
| None                                        | 26 (34.2)     | 25 (36.8)   | 1 (12.5)    |         |
| **Rituximab use**                           |               |             |             | <0.001a |
| No                                          | 72 (87.8)     | 70 (94.6)   | 2 (25.0)    |         |

Continued
Table 4 Differences in COVID-19 Deaths Among Patients With MS and NMO in COViMS (continued)

| Factor                                | Total (N = 82) | MS (n = 74) | NMO (n = 8) | p Value |
|---------------------------------------|---------------|-------------|-------------|---------|
| Length of time on current DMT<sup>a</sup> |               |             |             | 0.99<sup>b</sup> |
| <6 months                             | 1 (2.1)       | 1 (2.4)     | 0 (0.0)     |         |
| 6 or more months                      | 46 (97.9)     | 40 (97.6)   | 6 (100.0)   |         |
| Have comorbidities?                   |               |             |             | 0.99<sup>b</sup> |
| No                                    | 6 (7.3)       | 6 (8.1)     | 0 (0.0)     |         |
| Yes                                   | 72 (87.8)     | 64 (86.5)   | 8 (100.0)   |         |
| Unknown                               | 4 (4.9)       | 4 (5.4)     | 0 (0.0)     |         |
| Cancer                                | 7 (8.5)       | 6 (8.1)     | 1 (12.5)    | 0.67<sup>a</sup> |
| Cardiovascular disease                | 22 (26.8)     | 21 (28.4)   | 1 (12.5)    | 0.34<sup>a</sup> |
| Cerebrovascular disease               | 1 (1.2)       | 1 (1.4)     | 0 (0.0)     | 0.99<sup>b</sup> |
| Chronic kidney disease                | 7 (8.5)       | 6 (8.1)     | 1 (12.5)    | 0.67<sup>a</sup> |
| Chronic liver disease                 | 3 (3.7)       | 3 (4.1)     | 0 (0.0)     | 0.99<sup>b</sup> |
| Chronic lung disease                  | 7 (8.5)       | 5 (6.8)     | 2 (25.0)    | 0.079<sup>a</sup> |
| Chronic neurologic disease            | 9 (11.0)      | 8 (10.8)    | 1 (12.5)    | 0.88<sup>a</sup> |
| Diabetes                              | 17 (20.7)     | 14 (18.9)   | 3 (37.5)    | 0.22<sup>a</sup> |
| Hypertension                          | 43 (52.4)     | 39 (52.7)   | 4 (50.0)    | 0.99<sup>b</sup> |
| Immunodeficiency disease              | 4 (4.9)       | 4 (5.4)     | 0 (0.0)     | 0.99<sup>b</sup> |
| Morbid obesity                        | 19 (23.2)     | 15 (20.3)   | 4 (50.0)    | 0.058<sup>a</sup> |
| Other                                 | 26 (31.7)     | 25 (33.8)   | 1 (12.5)    | 0.22<sup>a</sup> |
| Pneumonia                             | 27 (32.9)     | 22 (29.7)   | 5 (62.5)    | 0.061<sup>a</sup> |
| Emergency department visited?         |               |             |             | 0.18<sup>a</sup> |
| Yes                                   | 59 (72.0)     | 51 (68.9)   | 8 (100.0)   |         |
| No                                    | 8 (9.8)       | 8 (10.8)    | 0 (0.0)     |         |
| Unknown                               | 15 (18.3)     | 15 (20.3)   | 0 (0.0)     |         |
| Hospitalized?                         |               |             |             | 0.30<sup>b</sup> |
| Yes                                   | 70 (85.4)     | 63 (85.1)   | 7 (87.5)    |         |
| No                                    | 9 (11.0)      | 9 (12.2)    | 0 (0.0)     |         |
| Unknown                               | 3 (3.7)       | 2 (2.7)     | 1 (12.5)    |         |
| Admitted to the ICU?                  |               |             |             | 0.27<sup>a</sup> |
| Yes                                   | 51 (62.2)     | 45 (60.8)   | 6 (75.0)    |         |
| No                                    | 18 (22.0)     | 18 (24.3)   | 0 (0.0)     |         |
| Unknown                               | 13 (15.9)     | 11 (14.9)   | 2 (25.0)    |         |
| Ventilation?                          |               |             |             | 0.21<sup>b</sup> |
| Yes                                   | 41 (50.0)     | 38 (51.4)   | 3 (37.5)    |         |
| No                                    | 22 (26.8)     | 21 (28.4)   | 1 (12.5)    |         |
| Unknown                               | 19 (23.2)     | 15 (20.3)   | 4 (50.0)    |         |

Continued
considered in patients with MS because of the mounting evidence that these agents increase the risk of infections, including COVID-19, in MS.1-3,8 Some studies have suggested that patients with MS can achieve similar suppression of new inflammatory disease activity with lower doses and/or extended intervals between doses of rituximab or ocrelizumab.9-12 It is unclear whether these treatment approaches would be applicable to NMOSD but may be of interest especially because the main difference in clinical characteristics between patients with NMOSD and MS in COViMS was the use of rituximab. Of interest, 2 small case series in NMOSD have shown that it might be possible to prevent future clinical NMOSD relapses along with reducing the risk of infections by using lower doses of rituximab and/or with a decrease in frequency of rituximab infusions.13,14 Moreover, it may be reasonable in some patients (e.g., NMOSD with medical comorbidities and NMOSD with hypogammaglobulinemia) to consider tailoring their treatment regimen in hopes to minimize infectious risks.15

Last, in the COViMS Registry, 7 patients with NMOSD who were alive reported having neurologic symptoms in relation to COVID-19 including motor dysfunction (42.9%) and cognitive and sensory dysfunction (28.6%). Because of the nature of data collection in the COViMS Registry, it is unclear whether these symptoms were due to a provoked relapse, pseudorelapse, or neurologic complications from COVID-19 as has been seen in other patient populations.16 Neurologic symptoms were not reported in the patients with MOGAD in this registry.

Limitations of this study include the small sample size relative to more common diseases (e.g., MS). This study is not population-based, as has been a limitation in many COVID-19 studies. Reporting biases may be present; reporting is voluntary, and more severe outcomes might have been disproportionately captured. Additional risk factors for more severe COVID-19 outcomes might be uncovered with a larger sample size, with studies from areas of the world where NMOSD and MOGAD are particularly prevalent, or when combining data from different registries.

**Conclusions**

Among the reported patients with NMOSD, a high mortality rate was observed, and the presence of comorbid conditions was associated with worse COVID-19 outcome. There were no deaths reported in the patients with MOGAD, an observation that was limited due to small sample size.

Overall, these results suggest that it is of utmost importance for people with NMOSD to be especially vigilant and avoid exposure and adopt measures to minimize the risk of infection by SARS-CoV-2. Data will continue to be collected via the COViMS Registry to help enhance our understanding of how infection by SARS-CoV-2 affects both NMOSD and MOGAD.

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Appendix Authors

| Name                  | Location                                      | Contribution                                                                 |
|-----------------------|-----------------------------------------------|------------------------------------------------------------------------------|
| Scott D. Newsome, DD  | Johns Hopkins University School of Medicine, Baltimore, MD | Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data |
| Anne H. Cross, MD     | Washington University in St. Louis School of Medicine, MO | Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data |
| Robert J. Fox, MD     | Mellen Center for MS, Cleveland Clinic, OH     | Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data |
| June Halper, MSN, APN-C | Consortium of MS Centers, Hackensack, NJ  | Drafting/revision of the manuscript for content, including medical writing for content |
| Pamela Kanellis, PhD  | MS Society of Canada, Toronto, Ontario, Canada | Drafting/revision of the manuscript for content, including medical writing for content |
| Bruce Bebo, PhD       | National Multiple Sclerosis Society (USA), New York, NY | Drafting/revision of the manuscript for content, including medical writing for content |
| David Li, MD          | University of British Columbia, Vancouver, British Columbia, Canada | Drafting/revision of the manuscript for content, including medical writing for content |
| Gary R. Cutter, PhD   | The University of Alabama at Birmingham      | Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data |
| Kottil W. Rammohan, MD | University of Miami School of Medicine, FL    | Drafting/revision of the manuscript for content, including medical writing for content |
| Amber Salter, PhD     | Washington University in St. Louis School of Medicine, MO | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data |

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