Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Outcomes of COVID-19 infection in multiple sclerosis and related conditions: One-year pandemic experience of the multicenter New York COVID-19 Neuroimmunology Consortium (NYCNIC)

Sylvia Klineova [a,1,*], Asaff Harel [b,1,*], Rebecca Straus Farber [c], Tracy DeAngelis [d], Yinan Zhang [a], Roland Hentz [e], Tung Ming Leung [e], Kathryn Fong [c], Tyler Smith [f], Richard Blanck [d], Lana Zhovtis-Ryerson [f]

[a] The Corinne Goldsmith Dickinson Center for MS at Icahn School of Medicine at Mount Sinai Hospital New York, USA
[b] Division of Neuro-Immunology, Department of Neurology, Lenox Hill Hospital, North Shore University Hospital, Zucker School of Medicine at Hofstra/Northwell, New York, USA
[c] Columbia University Multiple Sclerosis Center, Columbia University Irving Medical Center, New York, USA
[d] Neurological Associates of Long Island, USA
[e] Biostatistics Unit, Feinstein Institutes for Medical Research, Great Neck, New York, USA
[f] NYU Multiple Sclerosis Comprehensive Care Center, NYU Langone Health, New York, New York, USA

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ABSTRACT

Objective: To determine outcomes of COVID-19 in patients with Multiple Sclerosis (MS) and related conditions, and to determine predictors of these outcomes.
Methods: This was a multicenter, observational cohort study of patients with MS or related CNS autoimmune disorders who developed confirmed or highly suspected COVID-19 infection from 2/1/2020 to 12/31/2020.
Main outcome and measure: The primary outcome measure was hospitalization status due to COVID-19. Severity of infection was measured using a 4-point ordinal scale: 1. home care; 2. hospitalization without mechanical ventilation; 3. hospitalization and mechanical ventilation, and 4. death.
Results: Of 474 patients in the study, 63.3% had confirmed COVID-19 infection and 93.9% were diagnosed with an MS phenotype. Mean age was 45 ± 13 (mean±SD) years, 72% were female, and 86% were treated with a DMT at the time of infection. 58 patients (12.2%) were hospitalized. 24 patients (5.1%) were critically ill (requiring ICU care or outcome of death), of which 15 patients (3.2%) died. Higher neurological disability and older age independently predicted hospitalization. 85% (102/120) of patients with known antibody results not treated with anti-CD20 therapies were seropositive while only 39.5% (17/43) of patients treated with anti-CD20 demonstrated seropositivity ($p < 0.0001$). Only 25% (2/8) of patients with PCR-confirmed COVID-19 being treated with anti-CD20 therapies demonstrated seropositivity.
Conclusions: Neurological disability and older age independently predicted hospitalization due to COVID-19. Additionally, the results demonstrate that anti-CD20 therapies significantly blunt humoral responses post-infection, a finding that carries implications with regards to natural or vaccine-mediated immunity.

1. Introduction

In early March 2020, New York State became the earliest epicenter of the COVID-19 pandemic in the United States. What started as a novel viral disease in December 2019 in Wuhan, China, rapidly spread across continents, exerting unprecedented impact on our lives. While infection rates have oscillated between peaks and troughs, the current scientific opinion is that COVID-19 will remain relevant in the long term. Over 90% of scientists recently surveyed stated their belief that the disease will become endemic (Phillips, 2021).

While there are now comprehensive reviews describing clinical course, prognosis, and risk factors for poor COVID-19 outcomes in the

* Corresponding authors.
E-mail address: sylvia.klineova@mssm.edu (S. Klineova).
[1] These authors contributed equally to this work.

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general population (Pascarella et al., 2020; Wiersinga et al., 2019) there is relatively limited data regarding COVID-19 in people with autoimmune diseases such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) (Safavi et al., 2020; Louapre et al., 2020; Chaudhry et al., 2020; Zabalza et al., 2020; Parrotta et al., 2020; Sormani et al., 2021; 10; Evangelou et al., 2021). Over 2.2 million people worldwide and more than 700,000 people in the US have MS (Wallin et al., 2016; Wallin et al., 2019). As complex differences in immune function related to the disease or to its treatment could impact COVID-19 risk factors and outcomes, there exist a myriad of questions regarding care and guidance for patients. One year into pandemic, with novel vaccines available, questions are arising regarding the potential of disease modifying therapies (DMTs) to impact the adequacy and longevity of natural or vaccine-mediated immunity. Several observational studies evaluating COVID-19 in MS patients have been recently conducted, though many are limited by small sample size (Chaudhry et al., 2020; Zabalza et al., 2020; Parrotta et al., 2020; REDONE.br – Neuroimmunology Brazilian Study Group Focused on COVID-19 and MS 2019), methodology based on patient self-report (Safavi et al., 2020; Evangelou et al., 2021) or online reporting tools (Salter et al., 2021) and lack of formal diagnostic testing (Louapre et al., 2020; Evangelou et al., 2021). To the best of our knowledge, no large, multi-center US cohort data have yet been published.

Recognizing the current need for large collaborative studies, we established the New York COVID-19 Neuroimmunology Consortium (NYCNIC), a partnership between five MS centers in New York City and Long Island. This collaboration enabled analysis of a large number of COVID-19 cases and ensured a diverse study population, while at the same time maintained data integrity. We conducted an observational study of patients with MS and related conditions who developed COVID-19 infection, aiming to characterize COVID-19 disease course and risk factors for hospitalization. As a novel aspect of our work, we also assessed antibody production in COVID-19 patients stratified by DMT.

2. Methods

2.1. Data collection

We conducted a multicenter, observational cohort study of patients with MS or related CNS autoimmune inflammatory disorders with confirmed or highly suspected COVID-19 diagnosis (The NYCNIC registry). Five MS centers in New York City and surrounding vicinity participated: the MS centers at Columbia University Irving Medical Center, Icahn School of Medicine at Mount Sinai, New York University Langone Medical Center, Northwell Health Partners, and Neurological Associates of Long Island.

The study was approved by Institutional Review Boards at each participating institution. Using an electronic clinical record form on RedCap (https://www.project-redcap.org/), data were collected from medical records of patients diagnosed with COVID-19 between February 1, 2020, and December 31, 2020.

2.2. Population of interest

Adults (≥18 years) with MS (Thompson et al., 2018), NMOSD (Wingerchuk et al., 2015), Myelin oligodendrocyte glycoprotein associated disease (MOGAD), neurosarcoidosis, or autoimmune encephalomyelitis who reported being diagnosed with COVID-19 infection by a healthcare provider (based on symptoms, course, radiographic findings consistent with CDC COVID-19 criteria (Coronavirus, 2021) and/or positive COVID-19 PCR when available). Patients that exhibited positive COVID-19 PCR/serology, were considered to have "confirmed COVID-19" and all others were considered to have "suspected COVID-19". The sample size of this study was determined by convenience and feasibility, with each site documenting all known cases of COVID-19 infection in their patients during the review period. All

Table 1
Baseline Demographic and Clinical Characteristics

Age, n (%)	
<40 yo	174 (37)
40- <60 yo	237 (50)
60- <80 yo	63 (13)
Female sex, n (%)	339 (72)
COVID-19 Infection, n (%)	
Confirmed	300 (63)
Suspected	174 (37)
Disease Type, n (%)	
MS	
RRMS	353 (74)
SPMS	58 (12)
PPMS	20 (4)
CIS	8 (2)
RIS	5 (1)
Unknown	1 (0.2)
NMOSD	14 (3)
MOGAD	3 (0.6)
Neurosarcoidosis	4 (0.8)
Autoimmune Encephalitis	3 (0.6)
Other	5 (1)
Disease Duration, median (IQR) (years)	9 (5-16)
BMI, n (%)	
≤30	302 (64)
30-40	131 (28)
≥40	26 (5)
Unknown	15 (3)
Ambulation Status, n (%)	
Fully Ambulatory	347 (73)
Impaired but ambulates without assistance	34 (7)
Ambulates with Cane	37 (8)
Ambulates with walker	29 (6)
Non-ambulatory	27 (6)
Current DMT Class, n (%)	
Anti-CD20 Therapies	165 (35)
Fumarates	80 (17)
S1P Receptor Agents	38 (8)
Natalizumab	54 (11)
Teriflunomide/leflunomide	9 (1.9)
Platform agents	49 (10)
Other	14 (3)
None	65 (14)
Comorbidities, n (%)	
Hypertension	94 (20)
Cardiovascular disease	14 (3)
Cerebrovascular disease	5 (1)
Diabetes	36 (8)
Hyperlipidemia	56 (12)
Chronic Lung disease	44 (9)
Smoking Status, n (%)	
Never	343 (72)
Current or Former	127 (27)
Unknown	4 (1)
Race, n (%)	
White	279 (59)
Black or African American	107 (23)
Other/unknown	88 (19)
Ethnicity, n (%)	
Not Hispanic or Latino	303 (64)
Hispanic or Latino	88 (19)
Unknown Ethnicity	83 (18%)
Insurance Status, n (%)	
Private	319 (67)
Medicaid	59 (12)
Medicare	50 (11)
Public not otherwise specified	44 (9)
Unknown	2 (0.4)

Abbreviations: yo = years old, MS = multiple sclerosis, PPMS = primary progressive MS, RRMS = relapsing remitting MS, SPMS = secondary progressive MS, CIS = clinically isolated syndrome, RIS = radiologically isolated syndrome,

NMOSD = neuromyelitis optica spectrum disorder, MOGAD = myelin oligodendrocyte glycoprotein associated disease, IQR = interquartile range, BMI = body mass index, DMT = disease modifying therapy.
Platform agents: Glatiramer acetate, Interferons
Other therapies: Mycophenolate mofetil (3), Cladribine (1), Oral steroids (3), Azathioprine (1), Intravenous immunoglobulins (4), Infliximab (1) Vedolizumab (1)

COVID-19 serology tests were EUA approved.

2.3. Definition of study end points

The primary outcome measure was hospitalization status of patients for COVID-19. Severity of COVID-19 infection was measured on a 4-point ordinal scale: 1. home care; 2. hospitalization without mechanical ventilation; 3. hospitalization and mechanical ventilation, and 4. death. Patient demographics and neuroimmune disease-specific data including duration of disease, current DMT use, and baseline ambulatory status (measured along a 5-point ordinal scale: 1. fully ambulatory, 2. limited ambulation with no assistance, 3. unilateral assistance, 4. bilateral assistance and 5. wheelchair/bedbound) were collected. DMT's were grouped by mechanism of action (see Table 1).

Regarding COVID-19, we collected data relating to symptoms, diagnostic testing including SARS-CoV-2 nasopharyngeal swab results (NAAT or antigen testing) and SARS-CoV-2 serologic status. Data regarding potential risk factors and comorbidities was obtained.

DMT utilization rates in our COVID-19 cohort were compared to estimates of general utilization of DMTs across the 5 centers. Each center calculated internal raw estimates of utilization of fumarates, teriflunomide/leflunomide, natalizumab, and anti-CD20 therapies using electronic medical records, and these were then compiled together.

2.4. Statistical analysis

Descriptive statistics (frequency distribution for categorical variables and mean, SD, median, interquartile range, minimum, and maximum for continuous variables) were calculated. Univariable logistic regression was used to screen variables with a p-value criterion of $pp < < 0.05$ for entry into the model selection procedure. Stepwise selection was used with variable entry and retention criteria of $pp < < 0.05$ to select the final multivariable model. Variables that were specified for clinical relevance were retained in the model at each selection step. Firth's correction was used in cases where quasi-separation was present in the model due to categorical levels with low frequencies. Descriptive statistics and Chi-Square/Fischer test results were used for exploratory analyses.

3. Results

3.1. Patient characteristics

We reviewed 479 patient records. Three patients with insufficient time to follow-up and 2 patients with missing data were excluded. A total of 474 patients with MS and related conditions were included in final analysis. Three-hundred subjects had confirmed COVID-19 infection based on positive PCR or serology, and 174 had suspected COVID-19 infection. 445 patients had a diagnosis within the MS spectrum (clinically definite MS, clinically isolated syndrome, or radiologically isolated syndrome), 14 had NMOSD, 3 had MOGAD, 4 had neurosarcoidosis, and 8 had other neuroimmune conditions. The average subject age was 45 ± 13 (mean±SD) years old, the median of disease duration was 9 years (IQR: 5–16), 72% were female, and 86% were treated with a DMT at the time of COVID-19 infection. 59% were white and 23% were black or African American. 19% were Hispanic or Latino. 27% were current or former smokers. 67.30% had private health insurance, 12% had Medicaid, and 11% had Medicare. See Table 1 for full patient demographics and clinical characteristics.

3.2. COVID-19 infection outcomes

A total of 58 patients (12.2%) were hospitalized for treatment of COVID-19. 24 patients (5.1%) were critically ill (ICU care or outcome of death), of which 15 patients (3.2%) died. Though most patients had a mild to moderate COVID-19 course, 49 patients (10.3%) had exacerbation of existing neurological symptoms related to primary neurological condition, and 2 patients developed true disease activity in the form of new-onset sensory myelitis approximately 1 week and 3 weeks following resolution of mild COVID-19 respiratory symptoms. Other

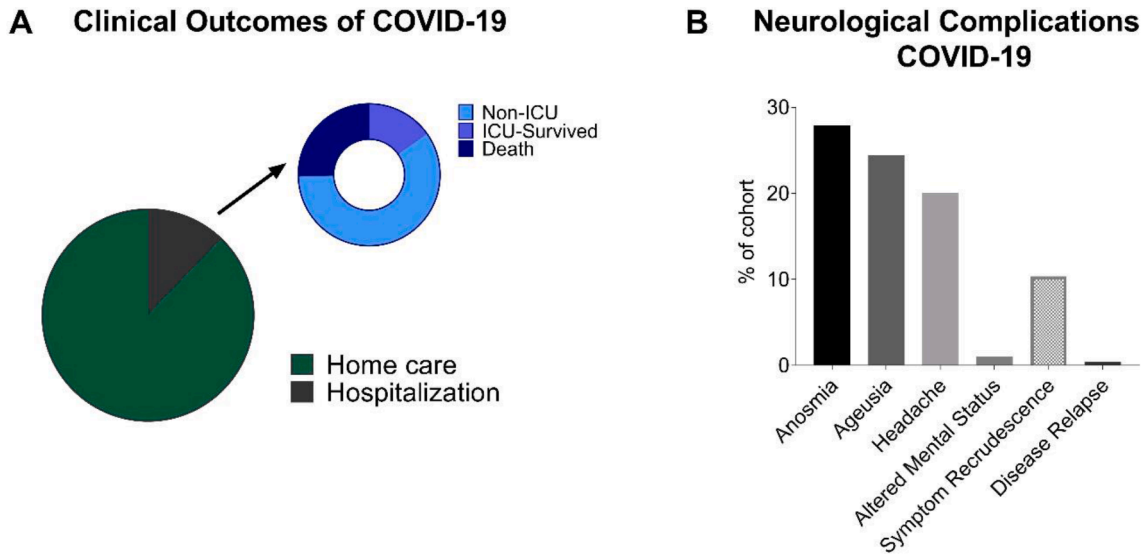

Fig. 1. Clinical outcomes and neurological complications of COVID-19 Infection. (A) A large majority of patients had mild infection and did not require hospitalization. Rates of critical illness and death were low. 58 patients (12.2%) were hospitalized. 24 patients (5.1%) were critically ill (requiring ICU care or outcome of death), out of which 15 patients (3.2%) died. (B) Neurological complications occurred in a sizeable minority of patients, with 49 patients (10.3%) suffering worsening of existing neurological symptoms and 2 patients developing disease relapse. ICU = intensive care unit.

Table 2
Prognostic factors of hospitalization due to COVID-19 infectionl.

Univariable analysis			
Prognostic factor	OR	95% CI	p value
Age	1.052	1.028, 1.076	<0.0001
Disease Duration	1.051	1.024, 1.079	0.0002
Sex (Male vs Female)	1.94	1.101, 3.416	0.0218
Insurance Type			0.0001
Public-Medicaid vs Private	2.269	1.008, 5.109	0.0479
Public- Medicare vs Private	4.342	2.048, 9.208	0.0001
Public (NOS) vs Private	4.639	2.130, 10.101	0.0001
Unknown vs Private	2.409	0.057, 101.748	0.6453
Obesity			0.0186
BMI >=30-40 vs BMI<30	1.975	1.083, 3.602	0.0264
BMI >=40 vs BMI<30	3.606	1.395, 9.322	0.0081
Unknown vs BMI < 30	0.699	0.089, 5.515	0.7340
Ambulation Status			<0.0001
Impaired but No Assistance vs Fully Ambulatory	1.103	0.317, 3.835	0.8780
Cane vs Fully Ambulatory	1.381	0.456, 4.179	0.5678
Walker vs Fully Ambulatory	6.962	2.995, 16.187	< 0.0001
Non-Ambulatory Wheelchair/Bedbound vs Fully Ambulatory	9.114	3.889, 21.361	< 0.0001
Number of CV Comorbidities	1.701	1.290, 2.242	0.0002
Pulmonary Disease	0.912	0.344, 2.416	0.8529
Race			0.1454
Black or African American vs White	1.792	0.960, 3.344	0.0669
Other/Unknown vs White	0.946	0.431, 2.077	0.8891
Ethnicity			0.3355
Hispanic or Latino vs. Not Hispanic or Latino	1.360	0.698, 2.649	0.3659
Other/Unknown vs. Not Hispanic or Latino	0.662	0.284, 2.649	0.3402
Smoking			0.2629
Current/Former vs Never	1.546	0.860, 2.780	0.1457
Unknown vs Never	2.757	0.280, 27.190	0.3851
Disease modifying therapy			0.3147
Teriflunomide/leflunomide vs No DMT	0.313	0.014, 6.788	0.4593
Platform Therapies vs No DMT	0.588	0.177, 1.950	0.3855
S1P Receptor Agents vs No DMT	0.586	0.158, 2.174	0.4246
Anti-CD20 Therapies vs No DMT	1.285	0.578, 2.859	0.5382
Fumarates vs No DMT	0.790	0.299, 2.087	0.6347
Natalizumab vs No DMT	0.283	0.066, 1.214	0.0894
Other Therapies vs No DMT	1.190	0.248, 5.700	0.8280
Rituximab treatment			0.0425
Other DMT vs Rituximab	0.396	0.191, 0.820	0.0127
No DMT vs Rituximab	0.549	0.212, 1.425	0.2179
Multivariable Analysis			
	OR	95% CI	P value
Age (unit of 1 year)	1.029	1.002, 1.058	0.0365
Age (unit of 10 years)	1.336	1.1018, 1.753	0.0365
Ambulation Status			0.0005
Impaired Without Assistance vs Fully Ambulatory	0.932	0.265, 3.284	0.9132
Cane vs Fully Ambulatory	0.821	0.252, 2.672	0.7436
Walker vs Fully Ambulatory	4.259	1.705, 10.637	0.0019
Non-Ambulatory vs Fully Ambulatory	5.032	1.975, 12.820	0.0007
Sex (Male vs Female)	1.749	0.945, 3.237	0.0751
Number of CV Comorbidities	1.201	0.861, 1.673	0.2804
Pulmonary Disease	0.993	0.350, 2.820	0.9902

Abbreviations: NOS = not otherwise specified, BMI = Body Mass Index, CI = confidence interval, CV = cardiovascular, DMT = disease modifying therapy.

COVID-19 neurological complications included 132 (27.8%) with anosmia, 116 (24.5%) with ageusia, 96 (20.3%) with headache, and 5 (1.0%) with altered mental status. (Fig. 1)

3.3. Risk factors for severe COVID-19 infection

Univariable analysis showed that age, disease duration, sex, insurance type, obesity status, ambulation status, and number of CV comorbidities were associated with hospitalization (Table 2). Notably, we demonstrated no association between DMT class and risk of hospitalization. However, in an exploratory univariable analysis that compared rituximab ($N = 53$) to other DMT treatments ($N = 356$) or no treatment ($N = 65$), rituximab use was associated with a higher risk of hospitalization for COVID-19 ($p = 0.0425$) when compared to other treatments. This association was not observed with ocrelizumab.

Next, a stepwise logistic regression was performed to assess potential risk factors associated with hospitalization. The final logistic regression model showed that ambulation status ($p = 0.0005$) and age ($p = 0.0365$) were significantly associated with hospitalization after adjusting for the other covariates in the model (Table 2). The estimated odds of being hospitalized were 4.259 higher for individuals requiring assistance with a walker (95% CI: 1.705-–10.637) and 5.032 higher for those who are non-ambulatory (95% CI: 1.975, 12.820) as compared to fully ambulatory patients. The estimated odds of being hospitalized for a patient at a given age were 1.029 times the odds of a patient one year younger (95% CI: 1.002-–1.058) and 1.336 times the odds of a patient ten years younger (95% CI: 1.018-–1.753). There was no association between DMT class, or specific DMTs, and risk for hospitalization from COVID-19.

3.4. SARS-CoV-2 serology after COVID-19 infection

To investigate the effect of DMT on antibody production after infection, we identified 163 patients who had available results of SARS-CoV-2 antibody testing. While most patients who were not treated with anti-CD20 therapies were seropositive (102 out of 120), only a minority of patients treated with anti-CD20 therapies demonstrated antibody production (17 out of 43). This association of anti-CD20 therapy use and serum antibody results was statistically significant ($p < 0.0001$). (Fig. 2)

To increase the validity of our findings, we next limited analysis to only the 41 patients with both a PCR-confirmed COVID-19 infection and recorded SARS-CoV-2 serum antibody results. Out of this subset, only 25% (2 of 8) patients treated with anti-CD20 therapies exhibited a positive antibody test. Conversely, amongst the other 33 patients that were not treated with anti-CD20 therapies, 94% (31) exhibited positive antibodies. The association between anti-CD20 therapy use and serum antibody results in this subset remained statistically significant ($p = 0.0002$). (Fig. 2) To evaluate whether timing could confound the results, the time interval between PCR and serum testing was obtained in 7 of 8 patients on anti-CD20 therapies and 27 of 33 patients not on anti-CD20 therapies. The median time interval between PCR testing and serum antibody testing was shorter in the non-anti-CD20 therapy group (8 weeks) compared to the group being treated with anti-CD20 therapies (12 weeks). However, 67% of patients on anti-CD20 therapy with seronegative status but PCR-confirmed COVID-19 infection underwent antibody testing within 12 weeks, suggesting that timing was not a major confounder.

Limited sample size precluded formal statistical analysis to conclusively determine whether serostatus was associated with COVID-19 outcome. However, only one of eight SARS-CoV-2 PCR-confirmed but antibody-negative patients necessitated hospitalization, a 54 year-old woman on ocrelizumab with comorbid diabetes. Our findings suggest that lack of antibody production is likely not a prominent factor driving COVID-19 severity.

3.5. DMT representation in COVID-19 cohort

While our study was not designed to evaluate associations between DMT class and incidence of symptomatic COVID-19 infection, there was a substantial under-representation of teriflunomide in our cohort, accounting for only 9 patients out of 474. The proportion of teriflunomide use in the COVID-19 cohort was only 25% of the expected proportion based on our internal estimates of DMT utilization. Rates of anti-CD20 therapies, natalizumab, and fumarates in the COVID-19 cohort were

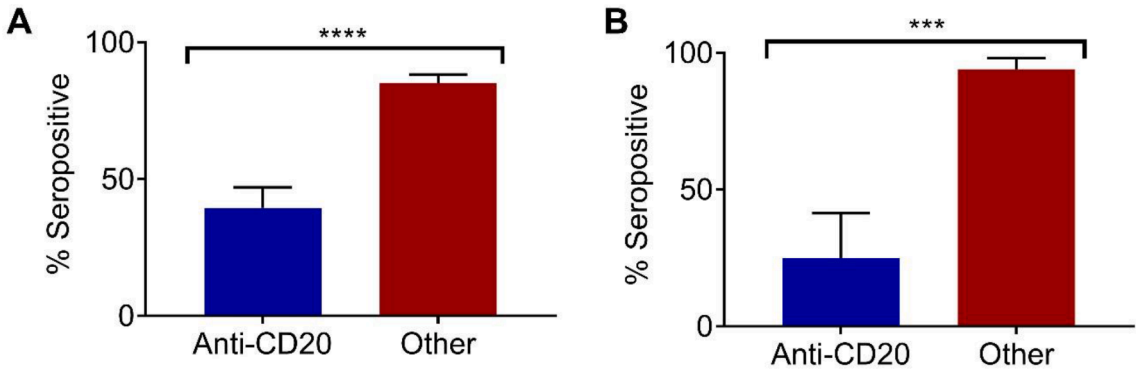

Fig. 2. SARS-CoV-2 Serology after COVID-19 Infection. (A) Percent seropositivity amongst the entire cohort (ie. both suspected and PCR-confirmed COVID-19) ($N = 163$). (B) Percent seropositivity within a subset of patients with PCR-confirmed COVID-19 and known SARS-CoV-2 antibody results ($N = 41$). Anti-CD20 therapy use was associated with a lower rate of seropositivity compared to use of other or no treatments. ****$p < 0.0001$, ***$p = 0.0002$.

all within 35% above or below our internal estimates of overall utilization. The fact that most sites could not obtain information about other DMT classes or patients not on DMT significantly limited further analysis.

4. Discussion

Differences in immune function, driven by neuroimmune conditions themselves or their treatments, triggered initial concern that patients with such diseases have increased risk for severe COVID-19 infection. We have shown that the majority of patients with MS and related conditions did not require hospitalization, despite treatment with DMTs. In our cohort, 12.2% of patients were hospitalized and 3.2% died, a rate that is comparable to COVID-19 outcomes described in the general population (Pascarella et al., 2020; Wiersinga et al., 2019; Thompson et al., 2020). This is also in line with all other observational studies regarding COVID-19 outcomes in MS. (Safavi et al., 2020; Louapre et al., 2020; Chaudhry et al., 2020; Zabalza et al., 2020; Parrotta et al., 2020; Sormani et al., 2021; REDONE.br – Neuroimmunology Brazilian Study Group Focused on COVID-19 and MS 2019; Evangelou et al., 2021; Salter et al., 2021).

While COVID-19 outcomes in our patients did not appear worse from a cardiorespiratory standpoint when compared to the general population, more than 10% of patients exhibited worsening of pre-existing neurological symptoms consistent with pseudo-exacerbation. We additionally found two patients who appeared to have true exacerbations within several weeks after infection. While intriguing, these findings are not likely to be specific to COVID-19 itself, as viral infections are well-known triggers of both pseudo-exacerbations and post-viral true exacerbations. (Correale et al., 2006).

The strongest predictor of hospitalization due to COVID-19 in our cohort was disability status, measured by ambulatory ability. This is in agreement with recently published findings from a large North American registry utilizing an online reporting tool. (Salter et al., 2021). While we found associations with age, neuroimmune disease duration, sex, insurance type, obesity, ambulation status, and number of CV comorbidities in univariable analyses, only ambulation status and age were significant in our multivariable model. This likely stems from the strength of disability status as a predictor of COVID-19 outcome in our cohort, as it may overpower other potentially related variables. We have shown unadjusted association between rituximab treatment and hospitalization, an observation previously reported by some registries, (Safavi et al., 2020; Zabalza et al., 2020; Parrotta et al., 2020) but our final model did not demonstrate association between any DMT or DMT class and increased risk of hospitalization. Furthermore, we found no disease-specific risk factor for hospitalization. The relationship between the level of neurological disability and COVID-19 severity is likely not specific to COVID-19, as it has been reported with other infections. (Rogers et al., 2008). However, this finding provides valuable information in counseling patients with varying degrees of neurological disability.

A major strength and novel aspect of our study is the inclusion of SARS-CoV-2 antibody data for a substantial percentage (34.4%) of our cohort. Of the patients with known serology, the majority (73%) exhibited positive antibodies. This demonstrates a high rate of true COVID-19 infections in our cohort, despite the lack of confirmatory PCR testing due to low testing availability early in the pandemic. Though most patients in our cohort were seropositive after infection, only 40% of patients on anti-CD20 therapies were seropositive, compared to 85% of those not on anti-CD20 therapies. Confirmatory analysis limited to only patients with PCR-confirmed COVID-19 infection further strengthened this relationship (25% seropositive in anti-CD20 therapy group and 94% seropositive in non-anti-CD20 therapy group). Although median timing interval of antibody testing was slightly different between the two groups, this did not appear to be a major confounder, as the majority of both groups underwent testing within 12 weeks of PCR (75% of anti-CD20 and 65% of non-anti-CD20 group). Furthermore, 67% of patients on anti-CD20 therapy with seronegative but PCR-confirmed COVID-19 infection underwent antibody testing within 12 weeks, a time frame during which seropositivity should persist (Ibarrondo et al. 2020).Although the antibody testing assays used were not consistent in our cohort, sensitivity is typically high for all assays granted "EUA" by the FDA (Maillart et al. 2020). A smaller observational study (Zabalza et al., 2020) and isolated reports (Maillart et al., 2020; Thornton and Harel, 2020) also suggested that patients on anti-CD20 therapies may have a blunted humoral response to COVID-19 infection. This is in line with previous studies evaluating response to conventional vaccines in those on anti-CD20 therapies (Baker et al., 2020; Ciotti et al., 2020; Stokmaier et al., 2018; Bar-Or et al., 2020), and a more recent Israeli study evaluating responses to Pfizer COVID-19 vaccine. (Achiron et al., 2021). However, it is important to note that blunting of the humoral response may not necessarily mean a lack of functional immunity, and there is immense interest in memory *T*-cell--mediated adaptive immune response (Le Bert et al., 2020). Such questions are of paramount importance as anti-CD20 therapies comprise one of the most frequently used DMT classes for patients with MS and related conditions.

In comparison to already published COVID-19 disease data in MS patients, our work has several additional strengths. New York State houses one of the most diverse populations in the world and is the second-largest COVID-19 epicenter in the United States with regards to mortality (Covid.cdc.gov, 2021). Analysis of patients from the 5 NYCNIC centers, each serving a heterogeneous patient population, ensured not only a large sample size but also diversity. To our knowledge, there has

been only one larger multi-center cohort of this type, housed in Italy, which differs substantially in patient demographic. (Sormani et al., 2021). In the US, there has been no similar large multi-center initiative to date. (Chaudhry et al., 2020). While the National MS Society, Consortium for MS Centers, and Multiple Sclerosis Society of Canada have recently published results of a joint online-reporting database of COVID-19 infections in patients with neuroimmune conditions like MS, (Salter et al., 2021), the online reporting design is open to substantial cofounding due to factors like sampling bias and potential duplication of entries.

The relative under-representation of teriflunomide in our cohort is notable given recent evidence that teriflunomide and other dihydroorotate dehydrogenase (DHODH) inhibitors impede SARS-CoV-2 replication in cell culture. (Xiong et al., 2020). This class of medications exhibits broad antiviral effects, (Edwards et al., 2017), thought to be related to impedance of viral replication secondary to DHODH inhibition. A novel high potency DHODH inhibitor is currently being studied as a treatment of COVID-19 infection. (https://clinicaltrials.gov/ct2/-show/NCT04439071 03/04/2021). Our results are intriguing within this context but given the reliance on internal estimates amongst the five centers, the data has to be interpreted with caution. In order to obtain an additional source of information regarding DMT utilization for comparison, we used market-share data from Sanofi Genzyme (unpublished data). As of January 2021, teriflunomide utilization in NY State accounted for 6.7% of all FDA-approved DMTs, while teriflunomide only accounted for 3.0% of all FDA-approved DMTs in our COVID- 19 cohort. This further suggests that teriflunomide was indeed under-represented in our cohort. It is important to note that this observation is open to potential confounders and further research is necessary to conclusively determine potential protective properties of teriflunomide.

Our study has several limitations owing to the real-world nature of the study. Inclusion of confirmed and suspected COVID-19 cases poses a risk of including patients with infections other than COVID-19. This stems from the pragmatic nature of this study and the fact that early during the pandemic, formal testing of mild COVID-19 cases was not recommended by NYS authorities, or available. We increased our diagnostic certainty by only including patients with symptoms strongly suggestive of COVID-19. The initial identification of research participants was based on self-reporting to physicians rather than contacting patients proactively, which could cause under ascertainment bias (albeit less than with an online-reporting tool). Use of a variety of EUA designated serological tests in our cohort could have altered observed results.

5. Conclusions

We have shown that neurological disability and age are the main hospitalization risk factors in a large number of diverse patients with MS and related conditions from the NYCNIC cohort. We have also demonstrated that treatment with anti-CD20 therapies was associated with a substantially lower humoral immune response after COVID-19. While future studies will be aimed at elucidating the intricacies of the immune response in these patients, the present results will aide in counseling of patients and development of future treatment strategies.

CRediT authorship contribution statement

Sylvia Klineova: Conceptualization, Visualization, Data curation, Writing – original draft. **Asaff Harel:** Conceptualization, Visualization, Data curation, Writing – original draft. **Rebecca Straus Farber:** Conceptualization, Visualization, Data curation. **Tracy DeAngelis:** Conceptualization, Visualization, Data curation. **Yinan Zhang:** Data curation, Formal analysis. **Roland Hentz:** Formal analysis. **Tung Ming Leung:** Formal analysis. **Kathryn Fong:** Data curation. **Tyler Smith:** Data curation. **Richard Blanck:** Data curation. **Lana Zhovtis-Ryerson:** Conceptualization, Visualization, Data curation.

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Sylvia Klineova reports personal fees from Biogen, Alexion Pharmaceuticals and Genentech.

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References

Phillips, N., 2021. The coronavirus is here to stay - here's what that means. Nature 590 (7846), 382–384. *https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas*.

Pascarella, G., et al., 2020. COVID-19 diagnosis and management: a comprehensive review. J. Intern. Med. 288 (2), 192–206.

Wiersinga, W.J., et al., 2020. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 324 (8), 782–793.

Safavi, F., Nourbakhsh, B., Azimi, A.R., 2020. B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with multiple sclerosis during the early COVID-19 epidemic in Iran. Mult. Scler. Relat. Disord. 43, 102195.

Louapre, C., et al., 2020. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. JAMA Neurol. 77 (9), 1079–1088.

Chaudhry, F., et al., 2020. COVID-19 in multiple sclerosis patients and risk factors for severe infection. J. Neurol. Sci. 418, 117147.

Zabalza, A., Cárdenas-Robledo, S., Tagliani, P., Arrambide, G., Otero-Romero, S., Carbonell-Mirabent, P., Rodriguez-Barranco, M., Rodríguez-Acevedo, B., Restrepo Vera, J.L., Resina-Salles, M., Midaglia, L., Vidal-Jordana, A., Río, J., Galan, I., Castillo, J., Cobo-Calvo, Á., Comabella, M., Nos, C., Sastre-Garriga, J., Tintore, M., Montalban, X., 2020. COVID-19 in multiple sclerosis patients: susceptibility, severity risk factors and serological response. Eur. J. Neurol. https://doi.org/10.1111/ene.14690.

Parrotta, P., Kister, I., Charvet, L., Sammarco, C., Saha, V., Charlson, R.E, Howard, J., Gutman, J.M., Gottesman, M., Abou-Fayssal, N., Wolintz, R., Keilson, M., Fernandez-Carbonell, C., Krupp, L.B., Zhovtis Ryerson, L., 2020. COVID-19 outcomes in MS: Observational study of early experience from NYU Multiple Sclerosis Comprehensive Care Center. Neurol Neuroimmunol Neuroinflamm 7 (5), e835. https://doi.org/10.1212/NXI.0000000000000835.

Sormani, M.P., De Rossi, N., Schiavetti, I., Carmisciano, L., Cordioli, C., Moiola, L., Radaelli, M., Immovilli, P., Capobianco, M., Trojano, M., Zaratin, P., Tedeschi, G., Comi, G., Battaglia, M.A., Patti, F., Salvetti, M., 2021. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. Ann. Neurol. 89 (4), 780–789. https://doi.org/10.1002/ana.26028.

REDONE.br – Neuroimmunology Brazilian Study Group Focused on COVID-19 and MS, 2021. Incidence and clinical outcome of Coronavirus disease 2019 in a cohort of 11,560 Brazilian patients with multiple sclerosis. Mult. Scler. https://doi.org/10.1177/1352458520978354.

Evangelou, N., et al., 2021. Self-diagnosed COVID-19 in people with multiple sclerosis: a community-based cohort of the UK MS register. J. Neurol. Neurosur. Psychiatry 92 (1), 107–109.

Wallin, M.T., et al., 2016. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the global burden of disease study. Lancet Neurol. 18 (3), 269–285, 2019.

M.T. Wallin, et al., The prevalence of MS in the United States. A population-based estimate using health claims data, 2019. 92(10): p. e1029–e1040.

Salter, A., et al., 2021. Outcomes and risk factors associated With SARS-CoV-2 infection in a North American registry of patients with multiple sclerosis. JAMA Neurol.

Thompson, A.J., et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.

Wingerchuk, D.M., et al., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85 (2), 177–189.

17 Coronavirus, https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html. March 2021.

Thompson, C.N., et al., 2020. COVID-19 outbreak - New York City, February 29-June 1. MMWR Morb. Mortal. Wkly. Rep. 69 (46), 1725–1729, 2020.

Correale, J., Fiol, M., Gilmore, W., 2006. The risk of relapses in multiple sclerosis during systemic infections. Neurology 67 (4), 652–659.

Rogers, M.A., et al., 2008. Mobility and other predictors of hospitalization for urinary tract infection: a retrospective cohort study. BMC Geriatr. 8, 31.

Ibarrondo, F.J., et al., 2020. Rapid decay of anti–SARS-CoV-2 antibodies in persons with mild Covid-19. N. Engl. J. Med. 383 (11), 1085–1087.

Maillart, E., et al., 2020. Beyond COVID-19: DO MS/NMO-SD patients treated with anti-CD20 therapies develop SARS-CoV2 antibodies? Mult. Scler. Relat .Disord. 46, 102482.

Thornton, J.R., Harel, A., 2020. Negative SARS-CoV-2 antibody testing following COVID-19 infection in two MS patients treated with ocrelizumab. Mult. Scler. Relat. Disord. 44, 102341.

Baker, D., et al., 2020. COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. Clin. Exp. Immunol. 202 (2), 149–161.

Ciotti, J.R., Valtcheva, M.V., Cross, A.H., 2020. Effects of MS disease-modifying therapies on responses to vaccinations: a review. Mult. Scler. Relat. Disord. 45, 102439.

Stokmaier, D., et al., 2018. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis (S36.002). Neurology 90 (15), S36.002. Supplement.

Bar-Or, A., et al., 2020. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. Neurology 95 (14), e1999–e2008.

Achiron, A., et al., 2021. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther. Adv. Neurol. Disord. 14, 17562864211012835.

Le Bert, N., et al., 2020. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature 584 (7821), 457–462.

30 Covid.cdc.gov, https://covid.cdc.gov/covid-data-tracker/#datatracker-home. April 2021.

Xiong, R., et al., 2020. Novel and potent inhibitors targeting DHODH are broad-spectrum antivirals against RNA viruses including newly-emerged coronavirus SARS-CoV-2. Protein Cell 11 (10), 723–739.

Edwards, K.R.T., Able, R.A., Mandel, M., 2017. Potential antiviral properties of teriflunomide: a consideration for optimizing MS treatment sequencing. ACTRIMS, 2017.

https://clinicaltrials.gov/ct2/show/NCT04439071. A study to evaluate efficacy and safety of PTC299 in hospitalized participants with coronavirus (COVID-19) (FITE19). 03/04/ 2021.