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The Turkish experience of COVID-19 infection in people with NMOSD and MOGAD: A milder course?

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ABSTRACT

Background: COVID-19 is a multisystemic infection with variables consequences depending on individual and comorbid conditions. The course and outcomes of COVID-19 during neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disorders (MOGAD) are not clearly known.

Objective/methods: The aim of this study was to examine the features and outcomes of COVID-19 infection in NMOSD and MOGAD patients. The patients' demographic and clinical factors, disease modifying treatment

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(DMT) used and disease information of COVID-19 infection were recorded. Conditions leading to hospitalization and severe exposure to COVID-19 infection were also analyzed.

Results: The study included 63 patients from 25 centers. Thirty-two patients (50.8%) belong to AQP-4 seropositive group, 13 (20.6%) and 18 (28.6%) were in MOG-positive and double-seronegative groups, respectively. Risk factors for severe COVID-19 infection and hospitalization were advanced age, high disability level and the presence of comorbid disease. Disease severity was found to be high in double-seronegative NMOSD and low in MOGAD patients. No statistically significant effect of DMTs on disease severity and hospitalization was found.

Conclusion: In NMOSD and MOGAD patients, advanced age, high disability and presence of comorbid disease pose risks for severe COVID-19 infection. There was no direct significant effect of DMTs for COVID-19 infection.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic was recognized in February 2020. The infection spread rapidly among millions of people. On May 2021 there were more than 150 million people infected and nearly 3 million lives lost (http 2021a). The first case and related death in Turkey was seen in March 2020. As of April 2021, when our study data collection was completed, there were 3357,988 cases and 31,713 deaths in Turkey (https://ourworldindata.org/coronavirus/country/turkey)(http 2021b).

COVID-19 is a multisystemic infection with a variety of outcomes (Vakili et al., 2021). The primary and secondary consequences of this systemic infection in people with immune-mediated neurological diseases have been reported with a spectrum of outcomes (Vakili et al., 2021; Camelo-Filho et al., 2020; Anand et al., 2020). Most of these are observational studies on large multiple sclerosis (MS) cohorts (C Louapre et al., 2020; Sormani et al., 2021; Simpson-Yap et al., 2021; Sen et al., 2021; Zabalza et al., 2020; Loonstra et al., 2020; Parrotta et al., 2020). However, the information of COVID-19 infection on neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disorders (MOGAD) are limited with only case reports or small case series (Louapre et al., 2020a,b; Zeidan et al., 2021; Fan et al., 2020; De Ruijter et al., 2020; Alonso et al., 2021; Cabal-Herrera and Mateen. 2021; Creed et al., 2020; Sahraian et al., 2020; Yin et al., 2021; Apostolos-Pereira et al., 2021; Newsome et al., 2021; Louapre et al., 2020b). The objective of this study was to describe the demographic, clinical, and therapeutic characteristics and outcomes of NMOSD and MOGAD patients infected with SARS-CoV-2 in a large national cohort.

2. Methods

2.1. Data collecting

The study was initiated by the Turkish Neurological Society MS Study Group. Turkish Neurological Association MS Study Group is an organization where all active MS and NMOSD-MOGAD patients in Turkey are followed up. This study was open to all specialized centers volunteering to contribute data on NMOSD and MOGAD patients with COVID-19 infection. Twenty-five centers participated in the study.

Demographic and clinical data for each patient, including age, gender, body mass index, job status, smoking, comorbid diseases were recorded. Inclusion criteria for patients with NMOSD diagnosis was defined according to International Consensus Diagnostic Criteria (Wingerchuk et al., 2015). Patients were classified as seropositive for apuaporin-4 antibody (AQP-4 seropositive), seropositive for MOG antibody (MOGAD) and seronegative both for AQP-4 and MOG antibodies (double seronegative). The information such as duration of illness, disability level as EDSS score, previous treatments, current treatment at the last visit and corticosteroid use in the previous 3 months were recorded. The approvals were obtained from the Republic of Turkey Ministry of Health and Kocaeli University Ethics Committees (E-29,549, 770–903.02.01–4007). Our data entry forms are modified for NMOSD patients from the database used for the Musc-19 study (Sormani et al., 2021; Sen et al., 2021).

2.2. Study population

In this study, NMOSD and MOGAD patients diagnosed with COVID-19 between March 11 2020, and April 1 2021, were included. Only patients with a complete follow-up through COVID-19 infection were included in this analysis. Included patients had at least one positive PCR test for COVID-19 or had clinical (cough, fever, bone-joint-muscle pain, weakness, loss of smell and taste, etc.) and radiological findings (confirmed by computed tomography) that were highly suggestive for COVID-19 and being in close contact with COVID-19 seropositive infected people and/or were serologically positive despite of negative PCR results. Patients were assessed either face to face or with telephone interview. Patients with negative PCR results had close contact with a patient infected with COVID-19, elevated acute phase reactants and symptoms compatible with COVID-19.

Baseline MOG-IgG testing was performed by the Euroimmun kit that utilizes a cell-based assay employing formalin-fixed HEK293 cells transfected with full-length human MOG (reactivity at a dilution of 1:10 is positive). For AQP4 IgG analysis, Euroimmune transfected cells (EU 90) (serum reactivity at a dilution of 1:10 is positive) was used. The majority of the patients were studied in the same center.

According to the WHO classification, the severity of COVID-19 disease was categorized into four groups, as mild, moderate, severe, and critical. The mild group included patients with no evidence of pneumonia and/or hypoxia, asymptomatic or minimally affected. Patients with signs and symptoms of pneumonia but no signs of severe pneumonia were included in the moderate group. Third group included patients with severe disease; with pneumonia and one of the following findings: >30 breaths/min; severe respiratory distress; or $SpO_2 < 90\%$ on room air. Patients were considered critical if they had acute respiratory distress syndrome or other respiratory failure requiring mechanical ventilation or septic shock and/or organ failure requiring intensive care unit (ICU) follow-up (http 2021c).

2.3. Statistical analysis

Demographic and clinical data were given as mean ± standard deviation, median, minimum-maximum and number (%). COVID-19 severity was divided into two subclasses as “mild” or “moderate/severe/critical”. Initially, the associations of the factors with severe COVID-19 or hospital admission were assessed by univariate and multivariate (enter method) logistic methods. Then, the independent variables: age, gender, BMI, smoking, disease type (AQP-4-Ab-seropositive, MOGAD and double seronegative), disease duration, last EDDS, presence of comorbidities, steroid use (within the last three months), and disease-modifying treatment (DMT) (none, rituximab, azathioprine, other) were analyzed with the stepwise multivariate model (backward: Wald method). Since there may be independent variables affecting infection severity and hospitalization they were also separately analyzed and then correlated. Factors affecting the severity of the disease were compared between patients with mild disease as one group and for patients with moderate-severe and critical disease as another group. The

strength of the results was presented as Odds ratio (OR) and corresponding 95% confidence intervals (Cl). Pearson's or Spearman's test were performed, as applicable, for correlations.

A chi-Square test was used to determine the presence of a significant difference between the treatments of rituximab (single dose vs multiple doses) or azathioprine (less than 6 months vs more than 6 months) to the severity of COVID-19 or hospital admission. The significance level was taken as $p < 0.05$. Data were analyzed with IBM SPSS V25.

3. Results

3.1. Study population

Sixty-three patients from 25 centers in 14 cities were included in the study. Fifty-eight (92.1%) patients had COVID-19 PCR positivity. The remaining five patients were those with a definite diagnosis of COVID-19 with clinical, imaging, contact conditions and serological evidence as mentioned above.

3.2. Clinical and demographics features

The age distribution of the patients varied between 18 and 80, with an average age of 39.1. In terms of gender distribution, 46 patients (73.0%) were female. Twenty-seven (42.9%) patients remained isolated in their homes during the pandemic. Six patients (9.5%) were healthcare workers. The number of patients with at least one comorbidity was 14 (22.2%). The most common comorbid diseases were hypertension, hyperlipidemia, and thyroid disease. None of the patients had obstructive sleep apnea. Two patients had a previously diagnosed and cured malignancy (ovary and thyroid), further data is shown in Table 1.

Thirty-two patients (50.8%) were in AQP-4 seropositive group, 13 patients (20.6%) and 18 patients (28.6%) were in double-seronegative and MOG-positive groups respectively. In the whole group the median disease duration was 2.5 years and final EDSS was 2.0 (Table 2). Mean EDSS values by subgroups was recorded for AQP-4 seropositive group as 2.36, for MOG-seropositive group as 1.12 and for double-seronegative group as 2.0.

We analyzed the age and disability status of our patients. We divided the patients into 4 groups in terms of age distribution. The first group composed patients with 18–30 years old, the second one had patients between 31 and 45 years old, the third group had patients between 46 and 60 years and the last group composed patients over 61 years old. The patients who were older than 61 years had significantly higher EDSS when compared with the patients 18–30 years and 31- 45 years age group ($p = 0.006$, $p = 0{,}042$ respectively). Furthermore, there was a significant correlation between age and EDSS when age used as a continuous variable ($r = 0.5060$; $p < 0.001$). However, the effect of duration of the disease was not included in these statistics.

Table 1
Baseline demographic and clinical characteristics of the study cohort ($N = 63$).

Age, years		39.1 (18.0–80.0)
Sex	Female	46 (73.0)
Body Mass Index		24.2 (18.4–38.8)
Employment	Not employed/Housewife	27 (42.9)
	Workman	12 (19.0)
	Office clerk	11 (17.5)
	Student	4 (6.3)
	Other	9 (14.3)
Healthcare workers	Yes	6 (9.5)
Smoking	Never smoked	44 (69.8)
	Current smoker	11 (17.5)
	Former smoker	8 (12.7)
Presence of at least one comorbidity		14 (22.2)
Comorbidities	Hypertension	3 (4.8)
	Thyroid Disease	3 (4.8)
	Hyperlipidemia	3 (4.8)
	Coronary Heart Disease	2 (3.2)
	History of malignancy	2 (3.2)
	Diabetes	1 (1.6)
	Other	4 (6.3)

Date are reported as mean (range) and n (%)

Table 2
Clinical and theuropathic characteristics of the study cohort ($N = 63$).

Clinical phenotype	AQP-4 seropositive	32 (50.8)
	MOG seropositive	13 (20.6)
	Double seronegative	18 (28.6)
Disease duration, years		2.5 (0.3–10.5)
Last available EDSS		2.0 (0.0–8.0)
In treatment		54 (85.7)
Treatment duration, months		15.0 (0.17–10.35)
Treatment	Rituximab	26 (41.3)
	Azathioprine	23 (36.5)
	None	9 (14.3)
	Maintenance steroid	3 (4.8)
	Eculizumab	1 (1.6)
	Tocilizumab	1 (1.6)
Patients not on treatment		9/63 (14.3)
Reason for not being on treatment	Patient's decision	4/9 (44.4)
	Treatment not started	2/9 (22.2)
	Ineffectives	1/9 (11.1)
	Side effect	1/9 (11.1)
	Treatment stopped*	1/9 (11.1)
Use of pulse methylprednisolone previous 3 months	Yes	5 (7.9)

Please note that data are reported as median (IQR) and n(%) within the table, whereas in the main manuscript data are reported with minimum and maximum values.
* Treatment stopped as a result of disease being stable for a long time.

The vast majority of patients (85.7%) were on treatment at the time of their COVID-19 infection. Rituximab (41.3%) and azathioprine (36.5%) were the most common treatments. Nine patients were not on treatment at the time of the study. Three patients were receiving maintenance doses of corticosteroids. There was one patient on eculizumab and one on tocilizumab (Fig. 1). Five patients (7.9%) had received high-dose corticosteroids (1000 mg of methylprednisolone, 5–7 days followed with or without oral taper) for an acute exacerbation within the last three months.

Regarding COVID-19 symptoms, five patients remained asymptomatic (7.9%). The most common symptoms were fatigue (58.7%), cough (39.7%), bone pain (34.9%), loss of taste (31.7%), and loss of smell (30.2%). Detailed symptom information is given in Fig. 2. The most common findings were congestion in the throat (22.2%) and tonsil swelling (9.5%). There were 14 (22%) patients with fever.

Radiological and/or clinical pneumonia was detected in 15 patients (23.8%). Among them, 9 patients were receiving rituximab (60%), 5 (33.3%) azathioprine and 1 (6.7%) was a drug-free patient.

3.3. Disease modifying treatments

Rituximab was the first-line treatment in 15 patients. Eleven patients had previously used azathioprine and then were switched to rituximab due to ineffectiveness or side effects. There were 23 patients on azathioprine (Table 3). Two patients receiving azathioprine were also using oral corticosteroids at a dose of 4 and 8 mg/day. During the COVID-19 infection period, 3 patients were using only oral corticosteroids. The duration of this medication for each patient was 46 months, 14 months, and 7 months respectively. Corticosteroid doses were 16 mg/day in two and 8 mg on alternative days in the other. There was one patient on tocilizumab and one on eculizumab who were both stable at

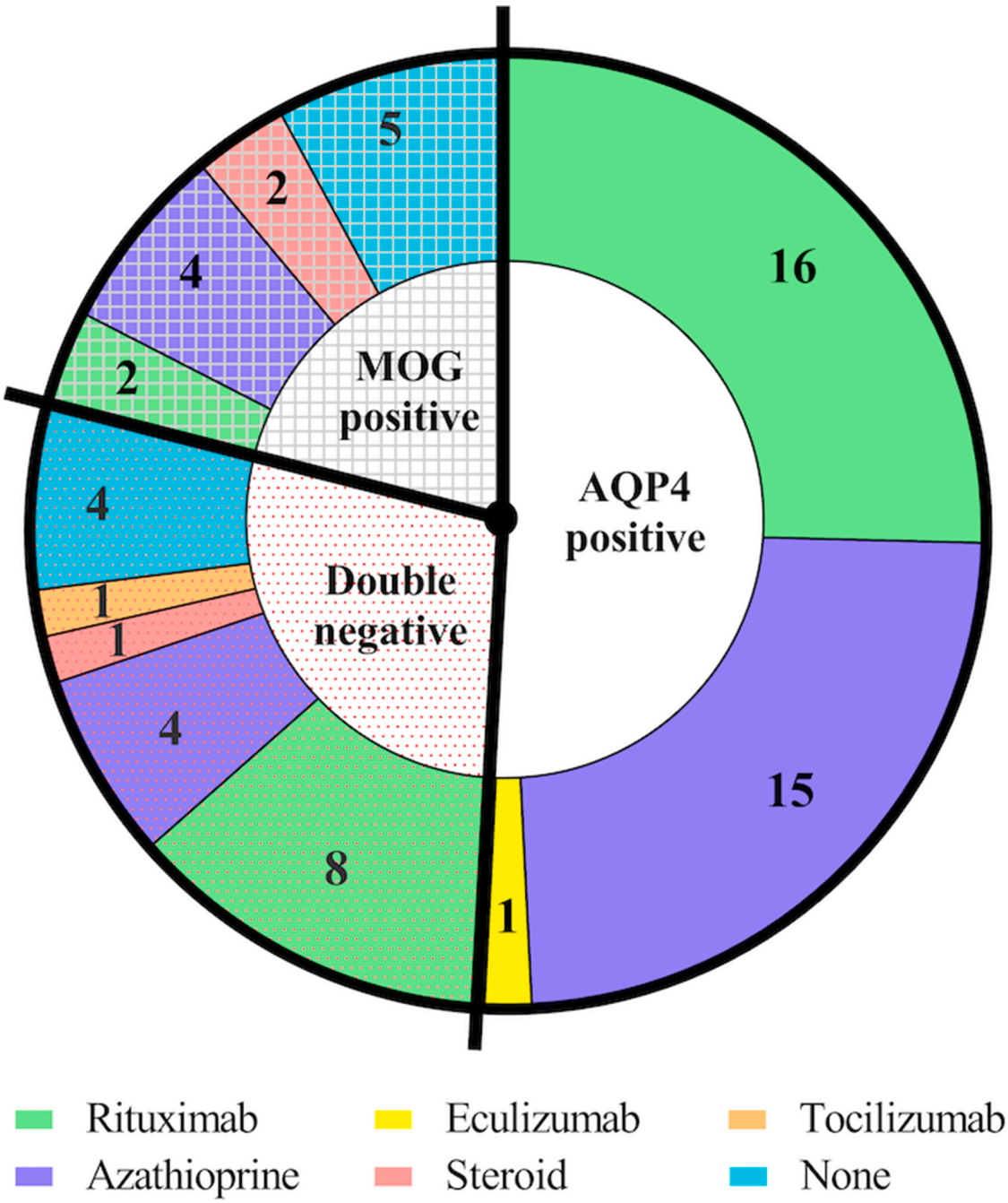

Fig. 1. Distribution of treatments used by clinical phenotype

the time of the COVID-19 infection.

Nine patients were not on any treatment at the time of their COVID-19 infection. Four of these patients had previously used azathioprine, and their treatments were discontinued 7–48 months before COVID-19 infection. One was treated with cyclophosphamide for a year, approximately three years before COVID-19. One used mycophenolate mofetil treatment for a year and discontinued it 15 months prior to COVID-19 infection. Two patients had never used any DMTs.

COVID-19 severity and hospitalization status were evaluated according to the duration of rituximab and azathioprine use of the patients. The patients were grouped as those using rituximab and azathioprine for less than 6 months or more. For each drug there was no relationship between the duration of DMTs use and hospitalization and COVID-19 severity (Table 4).

The mean time between rituximab infusion and COVID-19 infection of 26 patients was 3.1 (0.4–7.2) months. The time between B cell depleting treatment and COVID-19 infection was divided as 0–2 months, 2–4 months, and longer than 4 months. No significant different was found between different duration groups and COVID-19 severity. On the other hand, no correlation was found between time from rituximab infusion to COVID-19 infection and COVID-19 infection severity.

3.4. Relationship of COVİD-19 infection with relapses

In our study, we evaluated the relationship between COVID-19 infection and relapse. Relapse developing 3 months before and 3 months after COVID-19 infection were examined. Relapses were seen in 7 patients during this period. 3 patients had a relapse before COVID-19 infection, 3 patients had a relapse after COVID-19 infection, and one patient experienced relapse on the same day as COVID-19 infection. Two

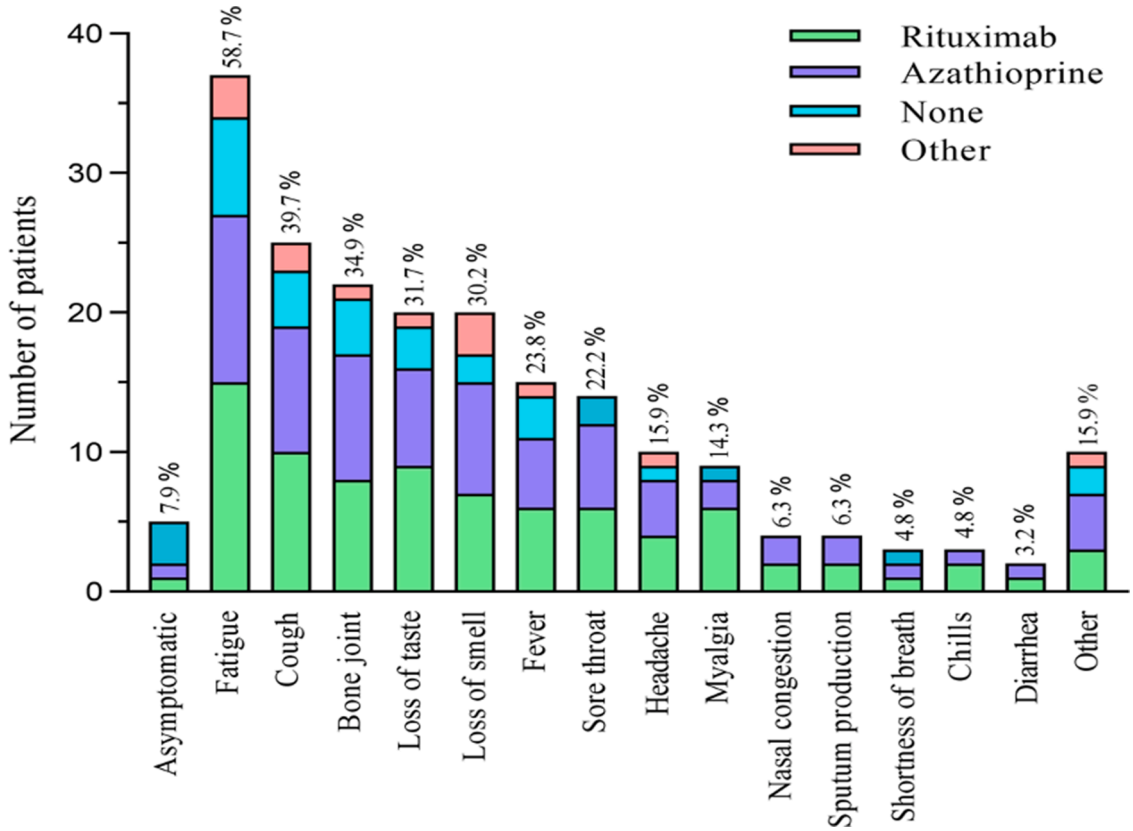

Fig. 2. Distribution of COVID-19 symptoms by treatments

Table 3
Demographic and clinical characteristics according to disease modifying treatments.

	Number of patients	F/M	Age	Disease duration years ± SD (Range)	Last EDSS	Previous DMT use
Rituximab	26	3.33	41.3 (15.9)	3.27 ± 2.02 (0.3–6.2)	2.54 (0.0–8.0)	15 None 11 Azathioprine
Azathioprine	23	2.83	40.2 (14.9)	2.92 ± 2.54 (0.9–10.5)	1.87 (0.0–5.0)	23 None
None	9	1.25	29.9 (9.5)	3.13 ± 2.37 (0.4–7.1)	1.28 (0.0–4.0)	4 Azathioprine 2 Oral steroid 1 Cyclophosphamide 2 None
Other	5	4.00	40.0 (10.8)	3.35 ± 2.87 (0.7–6.9)	2.30 (1.0–3.0)	5 None
Total	63	46/16	39.1 (18.0–80.0)	3.13 ± 2.44 (0.3–10.5)	2.10 (0.0–8.0)	

Table 4
Disease modifying treatments usage time.

DMTs		COVID-19 disease severity			Hospitalization		
Rituximab	Total	Mild	Modere/ severe/ critical	P value	Yes	No	*P* Value
Single dose	13	5	8	0.680	4	9	0.786
Two or more doses	13	4	9		4	9	
Azathioprine							
Less than six months	7	4	3	0.999	1	6	0.996
More than six months	16	8	8		3	13	

of these patients were untreated. One patient was using rituximab. The other 4 patients were under azathioprine treatment. Detailed information is given in the Table 5. With these data it is difficult to conclude a certain relationship between the COVID-19 infection and NMOSD and MOGAD relapses. The number of relapses is nearly equal before and after COVID-19.

3.5. *Severe illness and death associated with COVID-19*

Patients were divided into four groups according to the severity of COVID-19 disease. Twenty-eight patients (44.4%) had mild disease. Thirty patients (47.6%) experienced moderate severity whereas 4 (6.3%) patients were severe, and one patient (1.6%) developed a critical illness and died.

Older age, being double seronegative for AQP4-IgG and MOG-IgG, high EDSS, and having a comorbid disease were associated with severe COVID-19 infection by univariate analysis. Older age and double seronegative disease type were associated with severe COVID-19 infection in multivariate analysis. The type of the DMTs used was not associated with the severity of COVID-19 infection (Table 6).

Table 5
Relationship of COVID-19 infection with relapses.

Age	Gender	Serology for disease subtype	Time of relapse in association with COVID-19 infection	Relapse pattern	DMTs
35	Female	Double seronegative	30 days earlier	Optic neuritis	None
34	Male	Double seronegative	18 days earlier	Optic neuritis	Azathioprine
19	Female	MOG seropositive	9 days earlier	Spinal	None
53	Female	AQP-4 seropositive	Same day	Spinal	Rituximab
34	Female	AQP-4 seropositive	10 days later	Optic neuritis	Azathioprine
46	Female	AQP-4 seropositive	50 days later	Optic neuritis	Azathioprine
71	Female	AQP-4 seropositive	70 days later	Optic neuritis	Azathioprine

3.6. Risk factors for hospitalization

Fourteen (22.2%) of the patients were hospitalized. Older age, high EDSS value, and a comorbid disease were associated with hospitalization by univariate analysis. Multivariate analysis showed that high EDSS was associated with hospitalization. Although the hospitalization rate of patients using rituximab was high, there was no statistically significant difference in terms of hospitalization for any drug. (Table 7).

3.7. Subgroup of patients with higher EDSS

In the study cohort, 4 patients had an EDSS score of ≥ 5 three females (aged 45, 53, and 67) and fourth one being and 80 years old male. One female patient was double-seronegative and the other patients were AQP-4 seropositive. Final EDSS values were 8 in two patients, 7 in one patient, and 5 in one patient. In all, their first and last episodes were myelitis. A 45-year-old female patient was on azathioprine, and the other three patients were on rituximab. All were hospitalized with pneumonia and had at least one comorbidity. COVID-19 infection severity was moderate in two, severe in one patient and critical in one patient who later died. Mortality developed in the 80-year-old male patient who had an EDSS of 8. The disease duration of this patient was 3 months. He had received his first rituximab treatment cycle prior to 1 month of COVID-19 infection. He was hospitalized in ICU with signs of severe lung infection. He had developed renal failure in intensive care and died on the 12th day after the onset of COVID-19 symptoms.

3.8. COVID-19 treatment

Three patients did not receive any treatment for COVID-19 infection. Antiviral therapy (favipiravir) was used in 56 patients (88.9%). Four patients only received chloroquine. Five patients used chloroquine in addition to antiviral therapy. Antibacterial therapy was used in addition to antiviral therapy in 9 patients. Low molecular weight heparin was used in 5 patients, and corticosteroids were used in 2 patients.

Table 6
Factors affecting COVID-19 severity.

	COVID-19 Severe		**Univariate**		**Multivariate[1]**		**Multivariate[2]**	
	Mild	**Moderate / Severe / Critical**	**OR (%95 CI)**	**p**	**OR (%95 CI)**	**p**	**OR (%95 CI)**	**p**
Gender	28 (44.4)	35 (56.6)						
Female	20 (43.5)	26 (56.5)	Ref.					
Male	8 (47.1)	9 (52.9)	0.731 (0.244–2.189)	0.731	1.161 (0.206–6.550)	0.866		
Age	33.04 (±9.16)	44.11 (±16.36)	1.066 (1.019–1.114)	**0.005**	1.075 (1.001–1.154)	**0.046**	1.070 (1.008–1.137)	**0.027**
Body mass index	23.64(±3.42)	24.82 (±3.95)	1.096 (0.945–1.272)	0.224	0.951 (0.741–1.219)	0.689		
Smoking								
No	24 (46.2)	28 (53.8)	Ref.					
Yes	4 (36.4)	7 (63.6)	1.5 (0.391–5.752)	0.554	1.361 (0.152–12.174)	0.783		
Disease type								
AQP-4 positive	14 (43.8)	18 (56.2)	Ref.					
MOG positive	11 (84.6)	2 (15.4)	0.141 (0.027–0.744)	**0.021**	0.241 (0.023–2.498)	0.233	0.305 (0.050–1.871)	0.200
Double seronegative	3 (16.7)	15 (83.3)	3.889 (0.937–16.134)	**0.046**	9.833 (1.399–69.119)	**0.022**	10.908 (2.059–57.779)	**0.005**
Disease duration	2.82 (0.3–8.1)	3.38 (0.5–10.5)	1.018 (0.816–1.269)	0.875	0.884 (0.629–1.243)	0.518		
Last EDSS	1.48 (0.0–4.5)	2.59 (0.0–8.0)	1.590 (1.072–2.36)	**0.021**	1.102 (0.617–1.967)	0.743		
Comorbidity								
No	26 (53.1)	23 (46.9)	Ref.					
Yes	2 (14.3)	12 (85.7)	6.783 (1.371–33.548)	**0.019**	6.397 (0.834–49.069)	0.074		
Steroid use in the last months								
No	26 (44.8)	32 (55.2)	Ref.					
Yes	2 (40.0)	3 (60.0)	1.219 (0.189–7.849)	0.835	0.677 (0.038–12.147)	0.791		
Disease-modifying therapy								
None	5 (55.6)	4 (44.4)	Ref.					
Rituximab	9 (34.6)	17 (65.4)	2.361 (0.505–11.049)	0.275	0.862 (0.063–11.723)	0.911		
Azathioprine	12 (52.2)	11 (47.8)	1.146 (0.244–5.391)	0.863	0.406 (0.028–5.902)	0.519		
Other	3 (60.0)	2 (40.0)	0.833 (0.108–5.980)	0.872	0.942 (0.036–24.966)	0.972		

[1] Enter Method.
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Table 7
Factors affecting hospital admissions.

	Hospital admissions		Univariate		Multivariate[1]		Multivariate[2]	
	No	Yes	OR (%95 CI)	p	OR (%95 CI)	p	OR (%95 CI)	p
Gender	49 (77.8)	14 (22.2)	1.108 (0.295–4.153)	0.879	1.395 (0.183–10.609)	0.748		
Female	36 (78.3)	10 (21.7)						
Male	13 (76.5)	4 (23.5)						
Age	36.8 (±13.0)	47.6 (±17.4)	1.052 (1.001–1.087)	**0.021**	1.094 (0.956–1.251)	0.191		
Body mass index	23.7 (3.2)	26.3 (4.9)	1.126 (0.969–1.308)	0.121	1.222 (0.952–1.568)	0.115		
Smoking			1.350 (0.256–7.117)	0.723	1.353 (0.133–13.757)	0.798		
No	40 (76.9)	12 (23.1)						
Yes	9 (81.8)	2 (18.2)						
Disease type								
AQP-4 positive	23 (71.9)	9 (28.1)	Ref.		Ref.			
MOG positive	12 (92.3)	1 (7.7)	0.213 (0.024–1.885)	0.165	0.882 (0.035–22.007)	0.939		
Double seronegative	14 (77.8)	4 (22.2)	0.730 (0.189–2.823)	0.649	1.407 (0.168–11.818)	0.753		
Disease duration	3.2 (0.4–8.2)	2.9 (0.4–10.6)	0.933 (0.707–1.230)	0.621	1.045 (0.725–1.505)	0.814		
Last EDSS	1.7 (0.0–4.5)	3.6 (1.0–8.0)	1.975 (1.253–3.113)	**0.003**	1.760 (0.970–3.192)	**0.043**	1.908 (1.211–3.006)	**0.005**
Comorbidity								
No	42 (85.7)	7 (14.3)	Ref.					
Yes	7 (50.0)	7 (50.0)	6.000 (1.606–22.421)	**0.008**	3.426 (0.421–27.887)	0.250		
Steroid use in the last months								
No	47 (81.0)	11 (19.0)	Ref.					
Yes	2 (40.0)	3 (60.0)	6.409 (0.953–43.101)	0.056	6.534 (0.341–125.115)	0.213		
Disease-modifying therapy								
None	8 (87.5)	1 (12.5)	Ref.					
Rituximab	18 (69.2)	8 (30.8)	3.556 (0.379–33.381)	0.267	2.645 (0.126–55.443)	0.531		
Azathioprine	19 (82.6)	4 (17.4)	1.684 (0.162–17.516)	0.663	0.652 (0.025–17.263)	0.798		
Other	4 (80.0)	1 (20.0)	2.000 (0.098–41.003)	0.653	1.463 (0.044–48.371)	0.831		

[1] Enter Method.
[2] Backward:Wald method.

4. Discussion

A number of studies reported the risk and outcomes of COVID-19 in patients with MS, but only limited series and a few case reports on NMOSD and MOGAD patients were reported (Zeidan et al., 2021; Fan et al., 2020; De Ruijter et al., 2020; Alonso et al., 2021; Cabal-Herrera and Mateen. 2021; Creed et al., 2020; Sahraian et al., 2020; Yin et al., 2021; Apostolos-Pereira et al., 2021; Newsome et al., 2021; Louapre et al., 2020b). Depending on antibody seropositivity and the type of antibody, our cohort included a spectrum of patients covering NMOSD and MOGAD. Most of the patients in our cohort had PCR confirmed COVID-19 positivity. All common symptoms of COVID-19, as fatigue, cough, bone-joint pain, loss of taste-smell and fever in our study cohort were similar with those in the normal population and patients with MS (C Louapre et al., 2020; Sormani et al., 2021; Simpson-Yap et al., 2021; Sen et al., 2021; Zabalza et al., 2020; Loonstra et al., 2020; Parrotta et al., 2020).

In their cohort, Fan et al., mentioned two patients with relapsing NMOSD were diagnosed with COVID-19 related pneumonia (Fan et al., 2020). In the French cohort 75 patients were questioned by phone about COVID-19 infection and 5 of them was documented as being COVID-19 positive. In the İranian cohort COVID-19 positivity was found in 5 of 130 patients (Sahraian et al., 2020). Alonso et al., reported 16 NMOSD patients in a common cohort of COVID-19 positive MS/NMOSD patients from 15 countries (Alonso et al., 2021). Yin et al., reported that none of the NMOSD patients were diagnosed with COVID-19 during the pandemic, regardless of their AQP4-IgG positivity in a Chinese cohort. This cohort demonstrated a large survey of patients with a very low risk of COVID-19 (Yin et al., 2021).

Louapre et al., identified the antibody status in their total of 15 patients with 5 as being AQP-4 seropositive, 5 with MOGAD and 5 being double seronegative (Louapre et al., 2020b). Depending on antibody positivity and the type of antibody, our cohort includes AQP4-IgG seropositive NMOSD, MOGAD and double seronegative NMOSD patients. Nearly half of the patients had AQP4-IgG positivity whereas 18 patients were double-seronegative. Double seronegative group was found to be associated with severe COVID-19 infection by univariate and multivariate analysis. A strong side of our study is the subclassification and evaluation of NMOSD and MOGAD patients according to their antibody status. This subgroup analysis allowed us to define the COVID-19 severity and outcomes in this selected patient population. In our study, information about 13 patients with a diagnosis of MOGAD is also included and we observed that the severity of COVID-19 in these patients was mild and there were fewer hospitalizations. Similar with the data of the study by Newsome et al., we could not identify any specific risk factors for MOGAD patients with COVID-19, it can be due to the small numbers in this group (Newsome et al., 2021).

In different studies, clinical determinants of the severity of COVID-19 were studied and patients with older ages were shown to require intensive medical care, and men were more susceptible to have severe disease than women (Zhang et al., 2021; Zheng et al., 2020; Yang et al., 2020). Alonso et al., specifically reported their clinical data for COVID-19 in MS and NMOSD patients in Latin America. Their study included 16 NMOSD patients, of whom 9 (56%) required hospitalization/ICU admission and 5 of them (31.2%) died from COVID-19 (Alonso et al., 2021). The hospitalized/ICU admitted patients were older, had a higher EDSS and longer disease duration compared to patients that did not required hospitalization. Our study has also confirmed the main factors affecting the severity of the disease as advanced age, high EDSS and comorbid diseases.

High disability status is one of the most determinant factors on quality of life in central nervous system demyelinating diseases. In our study, high EDSS was found to be associated with only in univariate analyzes for severity and both in univariate and multivariate analyzes for hospitalization in NMOSD/MOGAD patients. For individual examination in the total group 4 patients had an EDSS 5 and above. All developed pneumonia and were hospitalized. These patients also had comorbid diseases. In our cohort neurologists had the tendency to hospitalize the patients with higher EDSS levels regardless of their initial COVID-19 infection severity. In the Turkish MS&COVID-19 cohort the severity of COVİD-19 was found to be higher in the patient group with high EDSS (Sormani et al., 2021). The LATAM group reported the older age, increased EDSS and longer disease duration to be significantly associated with hospitalization (Alonso et al., 2021).

In a recent study, 15 patients with NMOSD or MOGAD from 11 centers were analyzed for the outcomes of COVID-19 infection () (Louapre et al., 2020b). Similar to our design, they also included five patients with aquaporin-4 (AQP4) seropositivity, five with MOG antibodies and five patients without either antibody (double--seronegativity). These patients received commonly Anti-CD 20 therapy. In their cohort, all patients requiring hospitalization were on rituximab, and time to last infusion was shorter compared to patients with milder COVID-19. Sahraian et al., reported that rituximab did not increase the incidence of infection in their group, but that it may increase the severity of COVID-19 (Sahraian et al., 2020). In our study 94.1% of the NMOSD patients with COVID-19 infection were under DMTs. Despite that the disease-modifying treatments used by the patients were not associated significantly with disease severity and hospitalization, the majority of hospitalized patients were under rituximab treatment, but this didn't reach statistical significance. The duration of treatment, whether it was less than 6 months or more also didn't have affected the outcome. The mean age of patients under rituximab was not higher than other treatment groups and their mean EDSS was not markedly higher, however, the treating neurologists had a tendency to hospitalize earlier and more the patients treated with rituximab.

It appears that the behavior of COVID-19 infection in NMOSD & MOGAD patients is like the rest of the general population with patients who are older and have comorbidities experience a more severe disease. Similarly, disease-specific advanced disability level as it's in people with MS is also a risk factor for more severe course of COVID-19 infection in NMOSD & MOGAD patients. Despite that the use of CD-20 depleting DMTs such as Rituximab in people with MS and some other immune-mediated diseases who get the COVID-19 infection has been reported to have a worst outcome (Sormani et al., 2021; Simpson-Yap et al., 2021; Sparks et al., 2021). In our cohort of patients with NMOSD and MOGAD we have not observed such a significant association. In our cohort MOGAD patients had a tendency to have a milder course. Whether these observations are by chance or may be explained by a number of other variables are subject to be shown in further studies with other large cohorts.

5. Conclusion

According to the results of our study, older age, presence of comorbid conditions and advanced EDSS are the main risk factors for severe COVID-19 infection and hospitalization in NMOSD and MOGAD patients. MOGAD patients have a better outcome. There was no direct significant effect of the type of DMTs used by the patients on the severity of the infection.

Limitations

The detailed complete blood count, biochemistry and serologic testing for COVID-19 IgG of the patients included in our study were not adequately available. Therefore, we cannot present results on the immunological profiles of our cohort. Despite that our cohort was relatively large, when the study subjects were subclassified according to their disease-serostatus and severity of COVID-19 the comparative groups had some limitations. Lack of well documented data for people within the Turkish general population with COVID-19 infection didn't allow us to compare the outcomes of our NMOSD/MOGAD cohort with the ones on national basis.

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Declaration of Competing Interest

S. Sen has received honoraria or consultancy fees for participating to advisory boards, giving educational lectures and/or travel and registration coverage for attending scientific congresses or symposia from F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Merck-Serono, Novartis, Teva, Biogen Idec/Gen Pharma.

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References

Alonso, R., Silva, B., Garcea, O., et al., 2021. COVID-19 in multiple sclerosis and neuromyelitis optica spectrum disorder patients in Latin America COVID-19 in MS and NMOSD patients in LATAM. Mult. Scler. Relat. Disord. 51, 102886.

Anand, P., Slama, M.C., Kaku, M., et al., 2020. COVID-19 in patients with myasthenia gravis. Muscle Nerve 62 (2), 254–258. Aug.

Apostolos-Pereira, S.L., Ferreira, L.C., Boaventura, M., et al., 2021. Clinical features of COVID-19 on patients with neuromyelitis optica spectrum disorders. Neurol. Neuroimmunol. Neuroinflamm. 8 (6), e1060. Aug 26.

Cabal-Herrera, A.M., Mateen, F.J., 2021. COVID-19 in a patient treated with eculizumab for aquaporin-4 neuromyelitisoptica. J. Neurol. 1–4. https://doi.org/10.1007/s00415-021-10578-7. Online ahead of print.

Camelo-Filho, A.E., Silva, A.M., Estephan, E.P., et al., 2020. Myasthenia Gravis and COVID-19: clinical characteristics and outcomes. Front. Neurol. 11, 1053. Sep 11.

Creed, M.A., Ballesteros, E., Greenfield Jr, L.J., et al., 2020. Mild COVID-19 infection despite chronic B cell depletion in a patient with T aquaporin-4 positive neuromyelitis optica spectrum disorder. Mult. Scler. Relat. Disord. 44, 102199.

De Ruijter, N.S., Kramer, G., Gons, R.A.R., et al., 2020. Neuromyelitis optica spectrum disorder after presumed coronavirus (COVID-19) infection: a case report. Mult. Scler. Relat. Disord. 46, 102474.

Fan, M., Qiu, W., Bu, B., et al., 2020. Risk of COVID-19 infection in MS and neuromyelitis optica spectrum disorders. Neurol. Neuroimmunol. Neuroinflamm. 7 (5), e787.

https, 2021a, https://covid19.who.int.

http, 2021b, https://ourworldindata.org/coronavirus/country/turkey.

http, 2021c, https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. WHO COVİD-19 severe scala.

Loonstra, F.C., Hoitsma, E., Kempen, Z.L.V., et al., 2020. COVID-19 in multiple sclerosis: the Dutch experience. Mult. Scler. 26 (10), 1256–1260.

Louapre, C., Collongues, N., Stankoff, B., et al., 2020a. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and Multiple Sclerosis. JAMA Neurol. 77 (9), 1079–1088.

Louapre, C., Maillart, E., Papeix, C., et al., 2020b. Outcomes of coronavirus disease 2019 in patients with neuromyelitis optica and associated disorders. Eur. J. Neurol. https://doi.org/10.1111/ene.14612.

Newsome, S.D., Cross, A.H., Fox, R.J., et al., 2021. COVID-19 in patients with neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody disease in North America: from the COVIMS registry. Neurol. Neuroimmunol. Neuroinflamm. 8 (5), e1057. Aug 24.

Parrotta, E., DO, Kister I, Charvet, L., et al., 2020. COVID-19 outcomes in MS. Neurol. Neuroimmunol. Neuroinflamm. 7 (5), e835.

Sahraian, M.A., Azimi, A., Navardi, S., et al., 2020. Evaluation of COVID-19 infection in patients with Neuromyelitis optica spectrum disorder (NMOSD): a report from Iran. Mult. Scler. Relat. Disord. 44, 102245.

Sen, S., Karabudak, R., Schiavetti, I., et al., 2021. The outcome of a national MS-COVID-19 study: what the Turkish MS cohort reveals? Mult. Scler. Relat. Disord. 52, 102968.

Simpson-Yap S., De Brouwer E., Kalincik T., et al., Associations of DMT therapies with COVID-19 severity in multiple sclerosis. medRxivPreprint 2021.doi: 10.1101/2021.02.08.21251316.

Sormani, M.P., Rossi, N.D., Schiavetti, I., et al., 2021. Disease modifying therapies and COVID-19 severity in multiple sclerosis. Ann. Neurol. https://doi.org/10.1002/ana.26028.

Sparks, J.A., Wallace, Z.S., Seet, A.M., et al., 2021. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: results from the COVİD-19 Global Rheumatology Alliance physician registry. Ann. Rheum. Dis. 1137–1146. May 28annrheumdis-2021-220418, 80(9).

Vakili, K., Fathi, M., Hajiesmaeili, M., 2021. Neurological symptoms, comorbidities, and complications of COVID-19: a literature reviewand meta-analysis of observational studies. Eur. Neurol. 1–18. https://doi.org/10.1159/000516258. Online ahead of print.

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

Yang, J., Zheng, Y., Gou, X., et al., 2020. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta analysis. Int. J. Infect. Dis. 94, 91–95.

Yin, H., Zhang, Y., Xu, Y., et al., 2021. The impact of COVID-19 on patients with neuromyelitis optica spectrum disorder beyond infection risk. Front. Neurol. 12, 657037. Mar 22.

Zabalza, A., Cardenas-Robledo, S., Tagliani, P., et al., 2020. COVID-19 in multiple sclerosis patients: susceptibility, severity risk factors and serological response. Eur. J. Neurol. https://doi.org/10.1111/ene.14690. Online ahead of print.

Zeidan, S., Maillart, E., Louapre, C., et al., 2021. COVID-19 infection in NMO/SD patients: a French survey. J. Neurol. 268 (4), 1188–1190.

Zhang, N., Xie, T., Ning, W., et al., 2021. The Severity of COVID-19 and its determinants: a systematic review and meta-analysis in China. Sustainability 13, 5305.

Zheng, Z., Peng, F., Xu, B., et al., 2020. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect 81 (2), e16–e25.