ORIGINAL ARTICLE

Risk Factors and Outcomes of COVID-19 in Thai Patients with Neuromyelitis Optica Spectrum Disorder: A Single Center Study

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Background: Long-term immunotherapy use in patients with neuromyelitis optica spectrum disorder (NMOSD) raised concerns about the increased risk and severity of infection during the coronavirus disease 2019 (COVID-19) pandemic. Real-world data exploring the risks and outcomes of COVID-19 in NMOSD patients are warranted.

Materials and Methods: A retrospective medical chart review of NMOSD patients at a tertiary care center in Thailand during the COVID-19 pandemic was performed. Patients with and without COVID-19 were compared using descriptive statistics. Among infected patients, those with asymptomatic-to-mild infection and severe-to-critical infection were compared. Univariate and multivariate logistic regression analyses for risk factors of infection were performed.

Results: Of the 175 NMOSD, 24 (13.7%) patients had COVID-19. The risk factors for COVID-19 were type 2 diabetes mellitus (T2DM) (OR 14.72, 95% CI 3.17 to 68.43), rituximab use (OR 3.45, 95% CI 1.29 to 9.19), and younger age during the pandemic (OR 0.95, 95% CI 0.91 to 0.99). Four patients (16.7%) had a severe-to-critical disease, leading to one death. The more severe patients more commonly had comorbid T2DM, hypertension, and lymphopenia.

Conclusion: NMOSD patients in Thailand had a higher infection rate than the general Thai population. In addition to the general risk factors of COVID-19, such as T2DM, NMOSD patients had an increased risk of infection from rituximab use.

Keywords: Neuromyelitis optica; NMOSD; COVID-19; Risk factor; Outcome

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Neuromyelitis optica spectrum disorder (NMOSD) is a rare antibody-mediated central nervous system inflammatory demyelinating disease with an unclear etiology. The biomarker for NMOSD is the aquaporin 4 (AQP4) antibody[1]. Long-term immunotherapy is required for all AQP4-IgG-positive NMOSD patients to prevent further attacks and thus limit cumulative disability. The use of immunotherapy in AQP4-IgG-positive NMOSD patients has raised concerns about the potential increased susceptibility to infection and lower response to vaccination during the coronavirus disease 2019 (COVID-19) pandemic.

Theoretically, patients receiving immunotherapy could be more susceptible to viral infection compared to the general population, but study results have not been consistent[2,3]. Although the Food and Drug Administration (FDA)-approved monoclonal antibody therapies are available for AQP4-IgG-positive NMOSD, the high costs limit their accessibility to patients in lower- and middle-income countries. The main options available in Thailand are azathioprine and mycophenolate mofetil (MMF), which deplete both T- and B-lymphocytes, and rituximab an anti-CD20 therapy[4]. As the number of B cells is reduced by these immunotherapies, patients are at risk of having a more severe viral infection.

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Disease characteristics in NMOSD have some interracial differences[5], and treatment options in lower- and middle-income countries are limited, as previously mentioned. Therefore, real-world data on COVID-19 in NMOSD patients from different settings are warranted. The authors aimed to study the risk factors and outcomes of COVID-19 in Thai NMOSD patients over the past three years.

Materials and Methods

Study design

A retrospective medical chart review of patients in the Multiple Sclerosis and Related Disorders Clinic at a tertiary care hospital in Thailand between January 1, 2020 and July 31, 2022, was performed[4]. The included patients were: 1) diagnosed with NMOSD according to the 2015 International Panel for NMO Diagnosis[6] and 2) actively followed at the clinic or by telephone during the pandemic. Every patient had undergone brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and serum AQP4-IgG testing by cell-based assays (Euroimmun, Lübeck, Germany) for diagnosis. Patients with incomplete data between 2020 and 2022 were excluded. Siriraj Institutional Review Board approved the present study (COA No. Si. 235/2022), and all patients gave written informed consents. Data on the COVID-19 situation in Thailand were obtained from the Department of Disease Control, Ministry of Public Health of Thailand.

Variables

Demographic data of patients consisted of sex, age at onset, current age, comorbidities, number of attacks, disease activity, current immunotherapy, ambulatory status, absolute lymphocyte count (ALC) at the start of the observation, and the last Expanded Disability Status Scale (EDSS) score[7]. Disease activity was determined to be active if there was at least one attack within 2 years prior to having COVID-19 for infected patients or between 2018 and 2020 for non-infected patients. Details pertaining to COVID-19 and COVID-19 vaccination were collected.

The SARS-CoV-2 infection had to be proven by either a reverse transcription-polymerase chain reaction (RT-PCR) or an antigen test kit. A standardized infection ratio (SIR) of NMOSD patients compared to the general population was calculated. The severity of COVID-19 was classified into two groups: asymptomatic-to-mild disease (fever, upper respiratory tract symptoms, mild pneumonia not requiring oxygen supplement), and severe-to-critical disease (dyspnea, desaturation, acute respiratory failure, organ failure, death)[8,9]. During the data collection period, government regulations regarding COVID-19 in Thailand were loosened in the later period which may affect the infection rate and patient susceptibility.

Statistical analysis

Statistical analysis was performed on PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, including frequency and percentage, were used for categorical variables. Continuous variables were reported as median (interquartile range, IQR). Normality of distribution of variables was examined by Kolmogorov-Smirnov test. Comparison of factors between NMOSD patients with and without COVID-19 was made using Pearson's chi-squared test or Fisher's exact tests for categorical variables and Mann-Whitney U test for continuous variables. Univariate logistic regression analyses were performed to determine risk factors for COVID-19 and reported as odds ratio (OR) and 95% confidence interval (CI). Variables with a p-value less than 0.25 on univariate analysis were further analyzed by multivariate logistic regression to determine the independent predictors of COVID-19[10]. Risk factors for severe COVID-19 were also determined by comparing asymptomatic-to-mild and severe-to-critical disease patients. A p-value less than 0.05 was considered significant.

Results

Overall characteristics of NMOSD patients

A total of 175 patients were included, with 161 (92.0%) being AQP4-IgG seropositive. The majority of patients were female (93.1%), and the median age during the COVID-19 pandemic was 50.8 (IQR 41.2 to 59.9) years. Most patients (91.4%) received immunotherapy, with 76 patients (43.4%) receiving azathioprine, 45 (25.7%) MMF, 35 (20.0%) rituximab, 3 (1.7%) satralizumab, 1 (0.6%) inebilizumab, and 1 (0.6%) cyclophosphamide. The median duration of immunotherapy use was 5.4 (IQR 2.4 to 8.7) years. About 6.9% had the most recent ALC of less than 1,000 cells/mm^3. The majority (72.6%) were fully ambulatory, and 57.1% only had a mild disability with EDSS scores of 0 to 2.5. Sixty-seven percent had at least one of the following comorbidities: obesity, dyslipidemia, hypertension, type 2 diabetes mellitus (T2DM), systemic autoimmune disease,

Table 1. Demographic data of NMOSD patients with and without COVID-19

Variables	All NMOSD patients (n=175)	Non-COVID-19 patients (n=151)	COVID-19 patients (n=24)	p-value
Female; n (%)	163 (93.1)	143 (94.7)	24 (100)	0.063
Age at onset (year); median (IQR)	37.3 (27.0 to 43.3)	37.3 (27.4 to 47.6)	37.3 (24.1 to 43.8)	0.689
Age during the study period (year); median (IQR)	50.8 (41.2 to 59.9)	51.7 (41.4 to 59.9)	44.6 (38.0 to 59.6)	0.132
AQP4-IgG positive; n (%)	161 (92.0)	137 (90.7)	24 (100)	0.222
Disease duration[a] (year); median (IQR)	11.4 (7.1 to 18.1)	11.7 (7.5 to 18.9)	10.0 (4.6 to 14.2)	0.096
Number of attacks; n (%)				0.793
1 to 5	119 (68.0)	102 (67.5)	17 (70.8)	
6 to 10	37 (21.1)	33 (21.9)	4 (16.7)	
>10	19 (10.9)	16 (10.6)	3 (12.5)	
Active disease[b]; n (%)	83 (47.4)	69 (45.7)	14 (58.3)	0.249
Recent use of corticosteroid[c]; n (%)	83 (47.4)	70 (46.4)	13 (54.2)	0.477
Current immunotherapy	160 (91.4)	136 (90.1)	24 (100)	0.229
Azathioprine; n (%)	76 (43.4)	68 (45.0)	8 (33.3)	0.283
Azathioprine dose (mg/day); median (IQR)	75.0 (62.5 to 100)	75.0 (62.5 to 100)	75.0 (50.0 to 100)	0.331
MMF; n (%)	45 (25.7)	39 (25.8)	6 (25.0)	0.931
MMF dose (mg/day); median (IQR)	1,250 (1,000 to 2,000)	1,250 (1,000 to 2,000)	1,500 (1,000 to 2,000)	0.723
Rituximab; n (%)	35 (20.0)	25 (16.6)	10 (41.7)	0.011
Immunotherapy duration (n=160) (year); median (IQR)	5.4 (2.4 to 8.7)	5.9 (2.6 to 8.8)	2.6 (1.5 to 6.4)	0.019
Ambulatory status; n (%)				0.725
Fully ambulatory	127 (72.6)	108 (71.5)	19 (79.2)	
Assistance required	40 (22.9)	36 (23.8)	4 (16.7)	
Bedbound	8 (4.6)	7 (4.6)	1 (4.2)	
EDSS; n (%)				0.864
0.0 to 2.5	100 (57.1)	84 (55.6)	16 (66.7)	
3.0 to 5.5	29 (16.6)	26 (17.2)	3 (12.5)	
6.0 to 8.0	37 (21.1)	33 (21.9)	4 (16.7)	
8.5 to 10.0	8 (4.6)	7 (4.6)	1 (4.2)	
Comorbidities[d] (n=170); n (%)	114 (67.1)	96 (65.8)	18 (75.0)	0.372
T2DM (n=169)	19 (11.2)	13 (9.0)	6 (25.0)	0.033
Hypertension (n=169)	32 (18.9)	25 (17.2)	7 (29.2)	0.167
Dyslipidemia (n=169)	40 (23.7)	33 (22.8)	7 (39.2)	0.494
Obesity (n=159)	60 (37.7)	50 (37.0)	10 (41.7)	0.666
Absolute lymphocyte count <1,000[e] (n=160); n (%)	11 (6.9)	9 (6.6)	2 (8.7)	1.000
Received COVID-19 vaccine; n (%)	148 (84.6)	130 (86.1)	18 (75.0)	0.219
Number of doses; median (IQR)	2 (2 to 3)	2 (2 to 3)	2 (1 to 3)	0.531
Types of vaccine[f]; n (%)				
Inactivated (n=136)	63 (46.3)	57 (47.9)	6 (35.3)	0.330
Viral vector (n=136)	77 (56.6)	63 (52.9)	14 (82.4)	0.022
mRNA[g] (n=142)	66 (46.5)	59 (47.6)	7 (38.9)	0.490

EDSS=Expanded Disability Status Scale; MMF=mycophenolate mofetil; NMOSD=neuromyelitis optica spectrum disorder; T2DM=type 2 diabetes mellitus; IQR=interquartile range

[a] Disease duration was calculated from the date of initial NMOSD symptom onset to the date of the last follow-up during the study period. [b] Active disease was defined as having at least one NMOSD attack within two years before having COVID-19 or before the COVID-19 outbreak for non-COVID-19 patients. [c] Recent use of corticosteroid was considered if the patient had received steroids equal to or more than prednisolone equivalent dose of 20 mg/kg/day or intravenous methylprednisolone within two months before contacting COVID-19 or the COVID-19 outbreak began. [d] Other important comorbidities (n=169) included 6 (3.6%) patients with cancer [5 (3.4%) in the non-COVID-19 group and 1 (4.2%) in the COVID-19 group; p-value=1.000] and 13 (7.7%) patients with other autoimmune diseases [11 (7.6%) in non-COVID-19 group and 2 (8.3%) in COVID-19 group; p-value=1.000]. [e] The most recent absolute lymphocyte count before infection or the most recent value during the follow-up period for non-COVID-19 patients was used. [f] The vaccines included were: 1) inactivated vaccine: CoronaVac (Sinovac®), BBIBP-CorV (Sinopharm®); 2) viral-vector vaccine: ChAdOx1 nCoV-19 (Oxford-Astrazeneca®); 3) mRNA vaccine: BNT162b2 (Pfizer®), mRNA-1273 (Moderna®). [g] Some patients did not have the types of prior doses of COVID-19 vaccination recorded.

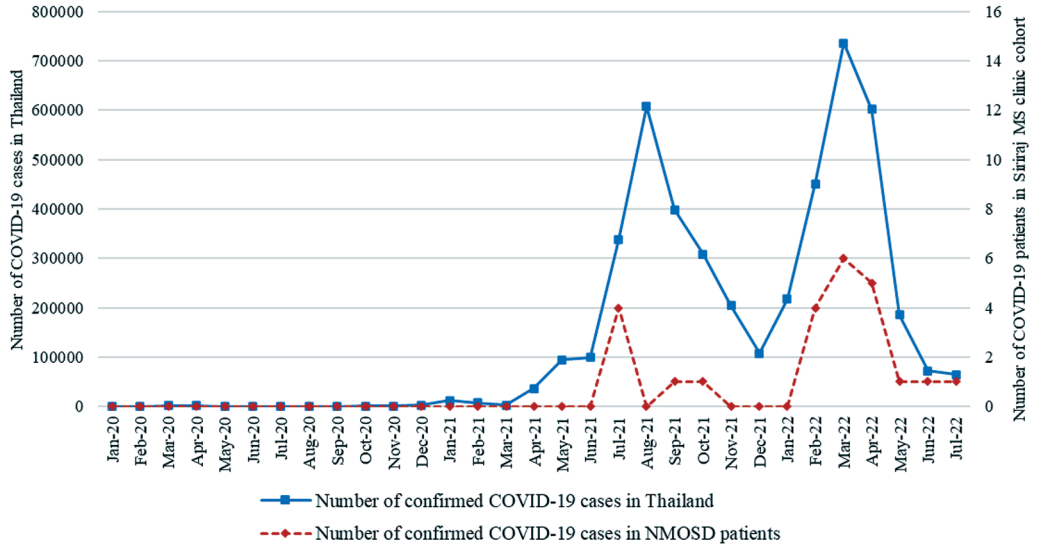

Figure 1. Comparison of the incidence of COVID-19 in NMOSD patients in the clinic and the general population of Thailand.

NMOSD=neuromyelitis optica spectrum disorder

The most widespread COVID-19 waves in Thailand were the fourth wave from June to December 2021 and the fifth wave from January 2022 onwards, which were predominated by the B.1.617.2 (delta) and the B.1.1.529 (omicron) variants, respectively. All the infected NMOSD patients contacted the virus during these two periods, with a higher infection rate during the omicron wave at 2.6 cases/month. The infection rate in NMOSD patients began to fall after May 2022, similar to the trends of the national outbreak. However, from June 2022, the number of confirmed COVID-19 cases in Thailand might be under-reported due to the loosened regulation and reporting criteria for COVID-19.

or malignancy. Baseline demographic and patient characteristics were summarized in Table 1.

NMOSD patients in the present cohort had received one or more types of the following COVID-19 vaccines: 1) inactivated vaccine: CoronaVac (Sinovac®), BBIBP-CorV (Sinopharm®), 2) viral-vector vaccine: ChAdOx1 nCoV-19 (Oxford-Astrazeneca®), and 3) mRNA vaccine: BNT162b2 (Pfizer®) and mRNA-1273 (Moderna®). Eighty-four percent of NMOSD patients received at least one dose of the COVID-19 vaccine, with a median number of doses of 2 (IQR 2 to 3). The most commonly used type of vaccine was viral vector (56.6%), followed by inactivated (46.8%), and mRNA vaccines (46.5%). The mRNA vaccines were mainly used as boosters. Those who refused vaccination reported vaccine hesitancy due to fear of disease relapse and vaccination side effects.

Incidence of COVID-19 among NMOSD patients

From January 2020 to July 2022, 24 (13.7%) AQP4-IgG-positive NMOSD patients had COVID-19. Compared to the 6% infection rate in the general population[11], the SIR was 2.3. Twenty patients had an asymptomatic-to-mild infection, and four had severe-to-critical disease. Among the severe cases, one resulted in death.

The COVID-19 pandemic in Thailand peaked in 5 distinct waves. The most widespread waves were the fourth wave (B.1.617.2 [delta] variant-predominated) from June to December 2021 and the fifth wave (B.1.1.529 [omicron] variant-predominated) from January 2022 onwards. All infected NMOSD patients contacted the virus during those two periods (Figure 1), with a higher infection rate during the omicron-predominated wave at 3 cases/month (Table 2).

Risk factors of COVID-19 in NMOSD patients

Comorbid T2DM was more common among NMOSD patients with COVID-19 than non-infected NMOSD patients (25.0% versus 9.0%, p=0.033). All COVID-19 patients were treated with immunotherapy during the time of infection. Rituximab was more frequently used in the COVID-19 group (41.7% versus 16.6%, p=0.011). However, infected patients had a shorter duration of immunotherapy (2.6 versus 5.9 years, p=0.019). Vaccination status was not different between infected and non-infected patients.

Among the 35 patients (20.0%) receiving rituximab in the present cohort, 10 had COVID-19. Nine of those were infected during the fifth wave, and eight had received at least one dose of the COVID-19 vaccine prior to the infection.

Table 2. Comparison between asymptomatic-to-mild disease and severe-to-critical COVID-19 in NMOSD patients

Factors	All COVID-19 cases (n=24)	Asymptomatic-to-mild (n=20)	Severe-to-critical (n=4)	p-value
Female; n (%)	20 (83.3)	16 (80.0)	4 (100)	1.000
Age onset (year); median (IQR)	37.3 (24.1 to 43.8)	37.3 (24.1 to 42.7)	44.4 (27.0 to 54.7)	0.505
Age during the study period (year); median (IQR)	44.6 (38.0 to 59.6)	43.3 (38.0 to 53.1)	61.5 (45.3 to 65.8)	0.136
AQP4-IgG positive; n (%)	24 (100)	20 (100)	4 (100)	-
Disease duration[a] (year); median (IQR)	10.0 (4.5 to 14.2)	10.0 (4.4 to 13.4)	12.2 (8.2 to 21.1)	0.278
Number of attacks; n (%)				0.118
1 to 5	17 (70.8)	13 (65.0)	4 (100)	
6 to 10	4(16.7)	4 (20.0)	0 (0.0)	
>10	3 (12.5)	3 (15.0)	0 (0.0)	
Active disease[b]; n (%)	14 (58.3)	14 (70.0)	0 (0.0)	0.020
Recent use of corticosteroid[c]; n (%)	13 (54.2)	13 (65.0)	0 (0.0)	0.031
Current immunotherapy	24 (100)	20 (100)	4 (100)	-
Azathioprine; n (%)	8 (33.3)	7 (35.0)	1 (25.0)	1.000
Azathioprine dose (mg/day); median (IQR)	75 (50 to 100)	75 (50 to 100)	37.5 (37.5 to 37.5)	0.139
MMF; n (%)	6 (25.0)	3 (15.0)	3 (75.0)	0.035
MMF dose (mg/day); median (IQR)	1,500 (1,000 to 2,000)	1,500 (1,000 to 1,500)	2,000 (1,000 to 2,000)	0.422
Rituximab; n (%)	10 (41.7)	10 (50.0)	0 (0.0)	0.114
Immunotherapy duration (year); median (IQR)	2.6 (1.5 to 6.4)	2.4 (1.4 to 3.9)	6.4 (3.8 to 9.5)	0.141
Ambulatory status; n (%)				0.083
Fully ambulatory	19 (79.2)	17 (85.0)	2 (50.0)	
Assistance required	4 (16.7)	3 (15.0)	1 (25.0)	
Bedbound	1 (4.2)	0 (0.0)	1 (25.0)	
EDSS; n (%)				0.229
0.0 to 2.5	16 (66.7)	14 (70.0)	2 (50.0)	
3.0 to 5.5	3 (12.5)	3 (15.0)	0 (0.0)	
6.0 to 8.0	4 (16.7)	3 (15.0)	1 (25.0)	
8.5 to 10.0	1 (4.2)	0 (0.0)	1 (25.0)	
Comorbidities[d]; n (%)	18 (75.0)	14 (70.0)	4 (100.0)	0.323
T2DM	6 (25.0)	3 (15.0)	3 (75.0)	0.035
Hypertension	7 (29.2)	3 (15.0)	4 (100.0)	0.003
Dyslipidemia	7 (29.2)	4(20.0)	3 (75.0)	0.059
Obesity	10(41.7)	8(40.0)	2 (50.0)	1.000
Absolute lymphocyte <1,000[e]; n (%)	2 (8.7)	0 (0.0)	2 (50.0)	0.024
Infection rates in different periods; n (%)				0.539
June to December 2021, rate of infection (patients/month)	6 (25.0), 1.0	4 (20.0), 0.7	2 (50.0), 0.3	
January to July 2022, rate of infection (patients/month)	18 (75.0), 2.6	16 (80.0), 2.3	2 (50.0), 0.3	
Received COVID-19 vaccine; n (%)	18 (75.0)	15 (75.0)	3 (75.0)	1.000
Types of vaccine[f]; n (%)				
Inactivated (n=21)	6 (35.3)	6 (42.9)	0 (0.0)	0.515
Viral vector (n=21)	14 (82.4)	11 (78.6)	3 (100.0)	1.000
mRNA (n=22)	7 (38.9)	5 (33.3)	2 (66.7)	0.528

EDSS=Expanded Disability Status Scale; MMF=mycophenolate mofetil; NMOSD=neuromyelitis optica spectrum disorder; T2DM=type 2 diabetes mellitus; IQR=interquartile range

[a] Disease duration was calculated from the date of initial NMOSD symptom onset to the date of the last follow-up during the study period. [b] Active disease was defined as having at least one NMOSD attack within two years before having COVID-19 or before the COVID-19 outbreak for non-COVID-19 patients. [c] Recent use of corticosteroid was considered if the patient had received steroids equal to or more than prednisolone equivalent dose of 20 mg/kg/day or intravenous methylprednisolone within two months before contacting COVID-19 or the COVID-19 outbreak began. [d] Other important comorbidities included 1 (4.2%) patient with cancer, who had asymptomatic-to-mild disease (p=1.000) and 2 (8.3%) patients with other autoimmune diseases (1 patient in each group; p=0.312). [e] The most recent absolute lymphocyte count before infection or the most recent value during the follow-up period for non-COVID-19 patients was used. [f] The vaccines included were: 1) inactivated vaccine: CoronaVac (Sinovac®), BBIBP-CorV (Sinopharm®); 2) viral-vector vaccine: ChAdOx1 nCoV-19 (Oxford-Astrazeneca®); 3) mRNA vaccine: BNT162b2 (Pfizer®), mRNA-1273 (Moderna®).

Table 3. Univariate and multivariate logistic regression analyses for factors associated with COVID-19

Factors	Univariate analysis; OR (95% CI)	p-value	Multivariate analysis[a]; OR (95% CI)	p-value
Male	2.37 (0.69 to 8.14)	0.171	-	-
Age at study period	0.98 (0.95 to 1.01)	0.143	0.95 (0.91 to 0.99)	0.011
Disease duration	0.94 (0.89 to 1.00)	0.052	-	-
Active disease[b]	1.16 (0.52 to 2.55)	0.720	-	-
Recent use of corticosteroid[c]	1.01 (0.46 to 2.22)	0.986	-	-
Azathioprine	0.65 (0.28 to 1.48)	0.299	-	-
Mycophenolate mofetil	0.91 (0.36 to 2.28)	0.837	-	-
Rituximab	3.25 (1.37 to 7.71)	0.007	3.45 (1.29 to 9.19)	0.013
Immunotherapy duration	0.87 (0.77 to 0.99)	0.037	-	-
Absolute lymphocyte count <1,000	1.15 (0.23 to 5.61)	0.867	-	-
Expanded Disability Status Scale	0.92 (0.78 to 1.08)	0.287	-	-
Any comorbidities	1.97 (0.76 to 5.15)	0.165	-	-
Type 2 diabetes mellitus	3.76 (1.41 to 10.03)	0.008	14.72 (3.17 to 68.43)	<0.001
Hypertension	2.81 (0.89 to 5.33)	0.087	-	-
Obesity	1.57 (0.70 to 3.50)	0.273	-	-
No vaccination	1.97 (0.75 to 5.15)	0.168	-	-

OR=odds ratio; CI=confidence interval

[a] Backward stepwise multivariate logistic regression was performed using variables with a p-value less than 0.25 in the univariate analysis, which included sex, age at study period, disease duration, rituximab, immunotherapy duration, having any comorbidities, type 2 diabetes mellitus, hypertension, and vaccination status. Only age, rituximab, and type 2 diabetes remained independently significant in the model. [b] Active disease was defined as having at least one NMOSD attack within two years before contacting COVID-19 or the COVID-19 outbreak. [c] Recent use of corticosteroid was considered if the patient had received steroids equal to or more than prednisolone equivalent dose of 20 mg/kg/day or intravenous methylprednisolone within two months before contacting COVID-19 or the COVID-19 outbreak began.

Univariate logistic regression analysis demonstrated that T2DM (OR 3.39, 95% CI 1.14 to 10.02) and rituximab use (OR 3.60, 95% CI 1.44 to 9.02) were associated with higher odds of COVID-19. Longer duration of immunotherapy was associated with lower odds of infection (OR 0.87, 95% CI 0.76 to 0.99). After adjusting for sex, age at study period, disease duration, rituximab, immunotherapy duration, having any comorbidities, T2DM, hypertension, and vaccination status, the multivariate analysis revealed that comorbid T2DM (OR 14.72, 95% CI 3.17 to 68.43), rituximab use (OR 3.45, 95% CI 1.29 to 9.19), and younger age during the pandemic (OR 0.95, 95% CI 0.91 to 0.99) were independent risk factors of COVID-19 in the present NMOSD cohort (Table 3).

Outcomes of COVID-19 in NMOSD patients

Most COVID-19 cases in the present cohort (20/24) resulted in asymptomatic or mild diseases. However, four patients (16.7%) required hospitalization due to severe infections causing dyspnea and desaturation, and one required mechanical ventilation. The critically ill patient later died from severe respiratory failure. These severe-to-critical patients more frequently had lymphopenia (50.0% versus 0%, p=0.024), comorbid T2DM (75.0% versus 15.0%, p=0.035) and hypertension (100.0% versus 15.0%, p=0.003) compared to asymptomatic-to-mild patients (Table 2). None of the severe-to-critical patients had active NMOSD. The deceased case was a 61-year-old bedbound AQP4-IgG-positive NMOSD patient with multiple comorbidities, including T2DM, hypertension, dyslipidemia, obesity, and lymphopenia.

Discussion

The present study was a retrospective cohort study that found 13.7% of Thai NMOSD cohort had COVID-19 during the three years of the pandemic, higher than the 6% cumulative incidence in the general population[11]. The infection rate followed the national trend with all the NMOSD patients being infected during the delta and omicron variants-predominated waves, which were more widespread compared to the previous waves. The risk factors of COVID-19 included T2DM, rituximab use, and younger age during the pandemic. Nearly one-fifth of patients developed severe-to-critical COVID-19 requiring hospitalization and respiratory support.

Although all NMOSD patients with COVID-19 were on immunotherapy during the time of infection, only rituximab was found to be an independent risk factor for the infection. The use of rituximab was also more common in infected patients in some

other studies[12,13]. Rituximab mainly depletes B cells, which in turn reduces the production of neutralizing antibodies against viruses[3]. Lower antibody response after vaccination was also observed in patients taking rituximab. Therefore, the higher risk of COVID-19 persists even after immunization[14,15].

Whether the use of rituximab increases the risk of having severe COVID-19 remains controversial. Many studies suggested that decreased humoral immune response from rituximab increased the severity of COVID-19[16,17], but the correlation was inconsistent[18,19]. The present study might be underpowered for this analysis due to the low rate of rituximab use[4]. Anyhow, the rationale for rituximab use should be weighed against the risk of NMOSD relapse[20]. Strategic timing of rituximab and vaccination is required for maximal antibody response while maintaining disease control[21].

As in the general population, T2DM was also a risk factor of COVID-19 in the present cohort[22]. However, infected patients in the present cohort tended to be younger. In contrast to other studies[23], the authors suspected that behavior could be a confounding factor. Younger NMOSD patients could be more socially engaged and thus had a higher risk of exposure to the virus.

T2DM along with hypertension and lymphopenia were also risk factors for severe COVID-19, which was similar to the general population[24,25]. Studies from large cohorts of COVID-19 in CNS inflammatory demyelinating disease patients in Europe and the US also supported that atherosclerotic risk factors increased the risk of severe infection[7,26].

Interestingly, lack of vaccination did not increase the risk of COVID-19 in NMOSD patients. The majority of patients were infected during the omicron-predominated outbreak. The lower vaccine coverage against the omicron variant could explain this finding in parts. The type of vaccines and a number of doses had no effect either. However, even with decreased vaccine efficacy against the omicron variant, a booster with mRNA vaccine is still recommended[27]. Vaccination remains an effective prevention measure in NMOSD patients taking immunotherapy[21].

The limitations of the present study were: 1) the small number of COVID-19 among NMOSD patients, 2) missing data from the retrospective study design could yield reporting bias, 3) uncontrolled behavioral factors, which could modify the risk of infection, 4) lack of a matched control group from the general population, preventing determination of disease-specific risk factors, and 5) heterogeneity of variants of SARS-CoV-2 and COVID-19 vaccine. A prospective multicentre study should improve the power of the present study on COVID-19 in NMOSD.

Conclusion

NMOSD patients in Thailand had a higher rate of infection than the general Thai population. Among patients with NMOSD, the risk of COVID-19 was higher in patients with younger age, rituximab use, and T2DM. Further studies are warranted to demonstrate the outcomes of COVID-19 in NMOSD patients.

What is already known on this topic?

Atherosclerotic cardiovascular risk factors, such as T2DM, are associated with increased risk and severity of COVID-19. However, the role of NMOSD-specific risk factors, such as the use of immunotherapy, including rituximab, is still controversial.

What this study adds?

This study found the incidence of COVID-19 was higher in NMOSD patients than in the general Thai population. Rituximab was associated with an increased risk of COVID-19 in NMOSD patients. Moreover, T2DM and younger age during the pandemic were also associated with a higher risk of COVID-19 in Thai NMOSD patients.

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Conflicts of interest

The authors declare no conflict of interest.

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