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COVID-19 susceptibility and outcomes among patients with neuromyelitis optica spectrum disorder (NMOSD): A systematic review and meta-analysis

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ABSTRACT

Background: We conducted this systematic review and meta-analysis to assess the risk of coronavirus disease (COVID-19), clinical features and outcome among patients with neuromyelitis optica spectrum disorder (NMOSD).

Methods: We systematically searched PubMed, Scopus, Web of Science, and Embase from December 1, 2019, to July 2, 2021. The gray literature including the references of original studies, review studies, conference abstracts, and WHO COVID-19 database was also searched. We included any type of studies that reported NMOSD patients with COVID-19, prevalence of COVID-19 among NMOSD patients or the infection outcome (hospitalization, intensive care unit [ICU] admission, or mortality).

Results: Out of 540 records, a total of 23 studies (19 published articles and 4 conference abstracts) including 112 NMOSD patients with COVID-19 met the inclusion criteria. Nine studies reporting risk of COVID-19 and nine studies on outcome were included in a quantitative synthesis. The pooled prevalence of COVID-19 was 1.2% (95% CI: 0.001%–0.030%; $I^2 = 92%$, $p < 0.001$), with hospitalization of 33.7% (95% CI: 23.3–44.8%; $I^2 = 9.1%$, $p = 0.360$) with 52.9% on rituximab treatment. ICU admission was 15.4% (95% CI: 7.6%–24.7%; $I^2 = 20.7%$, $p = 0.272$) and mortality was 3.3% (95% CI: 0–9.7%; $I^2 = 21.3%$, $p = 0.253$). Thirty-eight patients (48.7%) reported at least one comorbidity. The mean age of the included patients was 40.8 (10.63) years, female/male ratio was 3.35:1. The most common COVID-19 symptom was fever (54.5%), followed by fatigue/asthenia (42.9%), headache (41.6%), and cough (40.3%). Four patients developed neurological worsening. The Begg's and Egger's tests showed no evidence of publication bias.

Conclusion: The analysis suggests that comorbidity and treatment with rituximab may be risk factors for COVID-19 infection in NMOSD patients.

1. Introduction

The outbreak of Coronavirus Disease 2019 (COVID-19), which is caused by Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2), has led to the tragic loss of over 4 million people as of June 23, 2021 with more than 18 million infected cases worldwide (World Health Organization, 2021). From the early stages of the outbreak, it has been suggested that patients with suppressed immune systems may be at an elevated risk of contracting the virus, experiencing more severe forms of

the disease (World Health Organization, 2020).

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disease of the central nervous system (CNS) that mainly presents with optic neuritis and myelitis (Wingerchuk et al., 2007). For many years, NMOSD was considered as a variant of multiple sclerosis (MS) (Wingerchuk et al., 2007). However, the discovery of anti-aquaporin 4 antibody (AQP4 Ab) and further immunological and pathological evidence characterised it a distinct entity different from MS, and defined NMOSD as an autoimmune astrocytopathy (Lennon

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et al., 2004; Lucchinetti et al., 2014). The disabling nature of NMOSD and the treatment with immunosuppressive therapies (e.g., azathioprine [AZA], mycophenolate mofetil [MMF], rituximab [RTX], and corticosteroids) predispose these patients to bacterial and viral infections (Luna et al., 2020; Ritter and Pirofski, 2009; Seksik et al., 2009). This raised a concern about the risk of severe COVID-19 in patients with NMOSD.

Available data suggests that mortality and hospitalization rates of COVID-19 among MS patients could be slightly higher than the general population (Barzegar et al., 2021b; Prosperini et al., 2021). Findings in patients with MS strengthen the assumption that NMOSD patients also may be at an increased risk of developing severe COVID-19. Current evidence on the effects of COVID-19 infection on NMOSD mostly is found in case reports and small observational studies. A systematic review by Sharifian-Dorche summarized the cases of COVID-19 with MS and NMOSD (Sharifian-Dorche et al., 2021). However, this study was conducted in the early stage of the pandemic, limited to a relatively small sample size, and did not include a meta-analysis. Moreover, the authors only searched the database PubMed and did not determine the risk of the infection in the NMOSD population.

Therefore, we conducted this systematic review and meta-analysis to bring together the existing evidence on the characteristics of COVID-19 infection in patients with NMOSD. The purposes of our systematic review were to characterize NMOSD patients with COVID-19, and to estimate the risk of COVID-19 and the outcomes of the infection among NMOSD patients.

2. Methods

2.1. Literature search

We searched PubMed, Scopus, web of science, and Embase from December 1, 2019, to July 2, 2021. We also searched the gray literature including the references of the included studies, review studies, conference abstracts, and WHO COVID-19 database. The following search strategy was used: (("NMO Spectrum Disorder" OR NMOSD OR NMO OR "Devic Disease" OR "Devic Syndrome" OR neuromyelitis optica" OR "neuromyelitis optica spectrum disorder" AND ("COVID 19" OR "COVID-19 Virus Disease" OR "COVID 19 Virus Disease*" OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease" OR "2019 nCoV Disease" OR "2019-nCoV Diseases" OR "COVID-19 Virus Disease*")). We customized our search syntax (query) for each data bank. This study was carried out following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Moher et al., 2015). The PRISMA check list is documented in Supplementary file.

2.2. Inclusion and exclusion criteria

All types of studies including case report/series, cross-sectional, case-control, and cohort studies that reported COVID-19 in patients with a previous NMOSD diagnosis were included. The outcomes were demographic and clinical characteristics of infected patients, COVID-19-related symptoms, susceptibility to COVID-19, COVID-19 outcomes (hospitalization, intensive care unit [ICU] admission, and mortality) in infected patients, and hospitalization status by different therapies. Cross-sectional, case-control, and cohort studies that reported COVID-19 susceptibility or outcomes (hospitalization, intensive care unit [ICU] admission, or death) were included in the meta-analysis. The exclusion criteria were as follows: (a) preprinted articles, (b) studies pertaining to other demyelinating diseases such as MS and myelin oligodendrocyte glycoprotein antibody disorders (MOGAD), (c) reviews, animal studies, hypotheses, *in-vitro* studies, (d) SARS or MERS related articles, and (e) inability to extract data on NMOSD in studies reporting a mixed sample of NMOSD with other inflammatory demyelinating disorders of CNS.

2.3. Study selection and data extraction

Two researchers (NE and MB) independently screened the articles. If there was a disagreement between the reviewers, it was addressed by a senior researcher (AAS). Two authors independently extracted the data (SB, AM). Extracted data included author, date of first publication, study type, location of study, study sample, number of patients with suspected/confirmed COVID-19, age, sex, comorbidities (heart diseases, hypertension, diabetes mellitus, pulmonary diseases, malignancies, obesity, smoking, and autoimmune diseases), aquaporin-4 antibody (AQP4-Ab) status, COVID-19 symptoms (fever, cough, dyspnea/shortness of breath, fatigue/asthenia, cough, headache, nausea/vomiting, diarrhea, anosmia, and ageusia), expanded disability status scale (EDSS), maintenance therapies (rituximab, azathioprine, mycophenolate mofetil, corticosteroid, ofatumumab, tocilizumab, inebilizumab, eculizumab, methotrexate, no therapy), and the number of patients who required hospitalization, ICU admission, and died of COVID-19. Corresponding authors were contacted to retrieve demographical and clinical data of patients.

2.4. Quality assessment

Two authors (MB and OM) independently assessed the quality of the included published articles (cross-sectional and cohort studies) using the Newcastle-Ottawa scale (NOS) quality tests (Stang, 2010). We rated the quality of included studies by giving stars to the three parameters selection, comparability, and outcome according to the NOS guidelines. Each star meant one score. To calculate overall quality, all scores were summed. Studies with score less than 5 were considered low quality, score 5–7 were considered moderate quality, and studies with score more than 7 were considered high quality. Any disagreement between researchers was resolved by a senior researcher (AAS).

2.5. Statistical analysis

Descriptive analysis including mean (standard deviation [SD]) for continuous variables and frequency (%) for categorical variables was used to report demographic and clinical characteristics of patients. The data was weighted when we combined aggregated data with those reported individually. Meta-analysis was conducted with Stata software (version 14, Stata Corporation, College station, Texas, USA). Statistical heterogeneity across the included studies was assessed using chi-square-based Q statistics and I-square (I^2) index. Fixed effect model was used to estimate the rates of hospitalization, ICU admission, and death. Because of high heterogeneity ($I^2 \geq 50\%$), the random effect model using DerSimonian-Laird method was conducted to estimate the prevalence of COVID-19 among NMOSD patients. To estimate the prevalence of COVID-19 among NMOSD patients, we pooled the proportions of NMOSD patients with the infection among people with NMOSD. To estimate the rates of hospitalization, ICU admission, and death, we pooled the proportion of NMOSD patients in need of hospitalization, ICU, and death among NMOSD patients with the infection. We used Forest plots to visually evaluate the prevalence of COVID-19, the rate of hospitalization, and the rate of death in each study and the pooled estimate of each prevalence with their 95% confidence intervals (95% CI). Funnel plot, Begg's test, and Egger's test were used to investigate the publication bias. Begg's and Egger's tests $P < 0.05$ indicate potential publication bias. However, some possible publication bias may remain undetected, because these tests have low statistical power when the number of included studies is small.

3. Results

3.1. Study characteristics

PRISMA flow chart is shown in Fig. 1. The literature search found

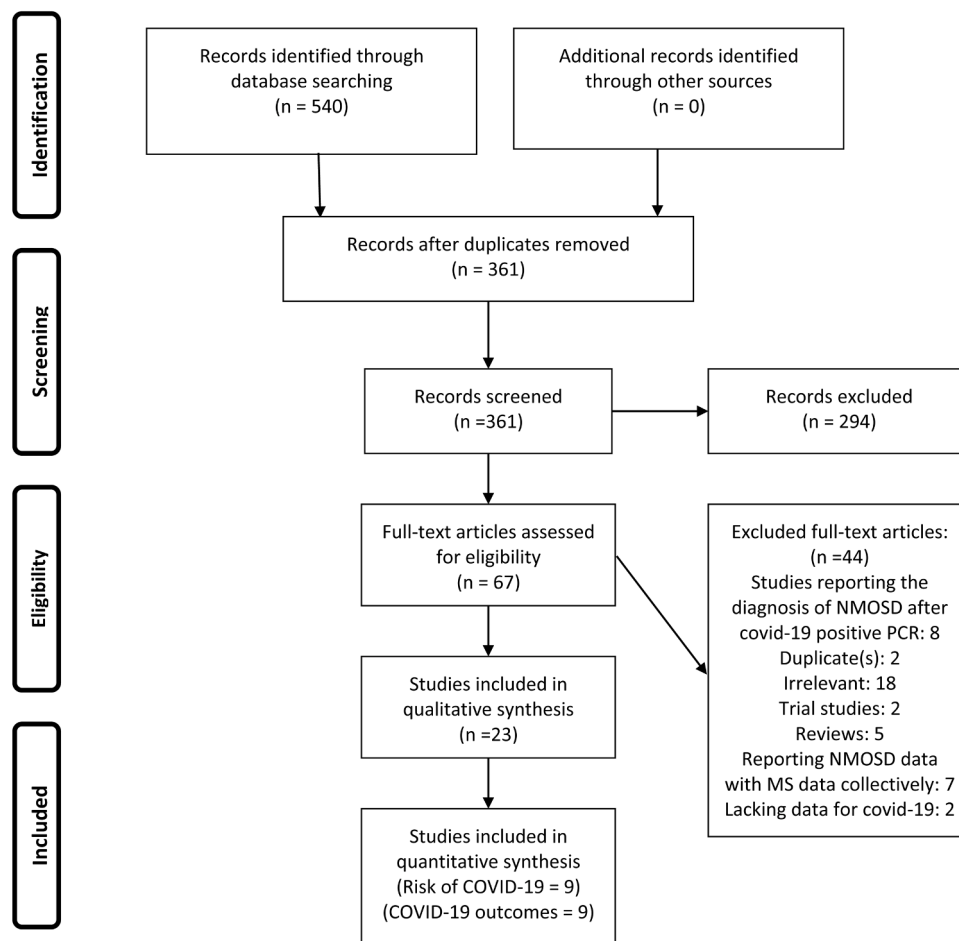


Fig. 1. Study selection.

540 studies. After eliminating duplicates, we screened 361 records. Of these, 67 studies were assessed with full-text review. Finally, 23 studies met the inclusion criteria including 19 published articles (Alonso et al., 2021; Cabal-Herrera and Mateen, 2021; Ciampi et al., 2020; Creed et al., 2020; Fan et al., 2020; Friedli et al., 2021; Louapre et al., 2020b; Maillart et al., 2020; Mantero et al., 2020; Mirmosayyeb et al., 2020; Montero-Escribano et al., 2020; Parrotta et al., 2020; Sahraian et al., 2020; Stastna et al., 2021; Tomczak and Han, 2020; Viswanathan, 2020; Woo et al., 2021; Yin et al., 2021; Zeidan et al., 2021) and 4 conference abstracts (Boaventura et al., 2020; Graham et al., 2020; Kurihara and Bharat, 2021; Mehdipour and Ashtari, 2020) reporting 112 NMOSD patients with COVID-19. The search included nine studies on risk of COVID-19 and nine studies on outcome, with a total of 6243 NMOSD patients. Characteristics of each included study is summarized in Table 1. Regarding type of studies, 11 were case report/series (Cabal-Herrera and Mateen, 2021; Ciampi et al., 2020; Creed et al., 2020; Friedli et al., 2021; Graham et al., 2020; Kurihara and Bharat, 2021; Maillart et al., 2020; Mantero et al., 2020; Montero-Escribano et al., 2020; Parrotta et al., 2020; Woo et al., 2021), 6 were cross sectional studies (Mehdipour and Ashtari, 2020; Mirmosayyeb et al., 2020; Sahraian et al., 2020; Tomczak and Han, 2020; Yin et al., 2021; Zeidan et al., 2021), and six were cohort studies (Alonso et al., 2021; Boaventura et al., 2020; Fan et al., 2020; Louapre et al., 2020b; Stastna et al., 2021; Viswanathan, 2020). Six studies were from North America (Cabal-Herrera and Mateen, 2021; Creed et al., 2020; Graham et al., 2020; Kurihara and Bharat, 2021; Parrotta et al., 2020; Tomczak and Han, 2020), 3 from France (Louapre et al., 2020b; Maillart et al., 2020; Zeidan et al., 2021) and Iran (Mehdipour and Ashtari, 2020; Mirmosayyeb et al., 2020; Sahraian et al., 2020), two from China (Fan et al., 2020; Yin

et al., 2021) and one each from Spain (Montero-Escribano et al., 2020), Brazil (Boaventura et al., 2020), Germany (Woo et al., 2021), Italy (Mantero et al., 2020), Switzerland (Friedli et al., 2021), Chile (Ciampi et al., 2020), Czechia (Stastna et al., 2021), Latin America (Alonso et al., 2021), and Malaysia (Viswanathan, 2020). Quality assessment of each published article is documented in Supplementary Tables 2–3.

3.2. COVID-19 prevalence among patients with NMOSD

Night studies (7 published articles and 2 conference abstracts) reported the prevalence of COVID-19 (Boaventura et al., 2020; Fan et al., 2020; Mehdipour and Ashtari, 2020; Mirmosayyeb et al., 2020; Sahraian et al., 2020; Tomczak and Han, 2020; Viswanathan, 2020; Yin et al., 2021; Zeidan et al., 2021). The lowest prevalence of COVID-19 was 0% in China (based on 535 samples), 0% in USA (based on 14 samples), and 0% (based on 71 samples) in Malaysia and the highest prevalence was 6.7% in France (based on 75 samples). The pooled estimate of the prevalence of COVID-19 was 1.2% (95% CI: 0.001%–0.030%; $I^2=92\%$, $p<0.001$) in a total sample of 6243 NMOSD patients (Fig. 2). The Begg's ($p=0.602$) and Egger's ($p=0.116$) tests showed no evidence of publication bias (Fig. 1 in the Supplementary appendix).

3.2.1. Hospitalization of NMOSD patients with COVID-19

Seven studies reported hospital admission data (Alonso et al., 2021; Boaventura et al., 2020; Louapre et al., 2020b; Mirmosayyeb et al., 2020; Sahraian et al., 2020; Stastna et al., 2021; Zeidan et al., 2021). Of 89 NMOSD patients, 31 cases needed hospitalization with a pooled rate of 33.7% (95% CI: 23.3%–44.8%; $I^2=9.1\%$, $p=0.360$) (Fig. 3). We did not observe potential publication bias in Begg's ($p=0.879$) and Egger's

Table 1
Characteristics of included studies.

Refs.	Location	Type of publishing	Date of first publication	Type of study	Sample size	Suspected/confirmed COVID-19	Quality score
(Montero-Escribano et al., 2020)	Spain	Published article	05./07/2020	Case report/series	5	1	–
(Creed et al., 2020)	USA	Published article	05/19/2020	Case report/series	1	1	–
(Mantero et al., 2020)	Italy	Published article	07/07/2020	Case report/series	1	1	–
(Graham et al., 2020)	USA	Conference abstract	12/07/2020	Case report/series	2	2	–
(Maillart et al., 2020)	France	Published article	09/03/2020	Case report/series	1	1	–
(Woo et al., 2021)	Germany	Published article	07/11/2020	Case report/series	1	1	–
(Cabal-Herrera and Mateen, 2021)	USA	Published article	04/27/2021	Case report/series	1	1	–
(Ciampi et al., 2020)	Chile	Published article	07/12/2020	Case report/series	5	4	–
(Kurihara and Bharat, 2021)	USA	Conference abstract	05/20/2021	Case report/series	1	1	–
(Friedli et al., 2021)	Switzerland	Published article	05/18/2020	Case report/series	1	1	–
(Parrotta et al., 2020)	USA	Published article	07/09/2020	Case report/series	1	1	–
(Mirmosayyeb et al., 2020)	Iran	Published article	09/14/2020	Cross sectional	157	6	6/10
(Mehdipour and Ashtari, 2020)	Iran	Conference abstract	12/07/2020	Cross sectional	140	6	–
(Sahraian et al., 2020)	Iran	Published article	06/01/2020	Cross sectional	130	5	7/10
(Yin et al., 2021)	China	Published article	03/22/2021	Cross sectional	535	0	8/10
(Tomczak and Han, 2020)	USA	Published article	06/30/2020	Cross sectional	14	0	4/10
(Zeidan et al., 2021)	France	Published article	09/12/2020	Cross sectional	75	5	7/10
(Boaventura et al., 2020)	Brazil	Conference abstract	12/07/2020	Cohort	2061	34	–
(Alonso et al., 2021)	USA	Published article	05/07/2021	Cohort	16	16	3/9
(Louapre et al., 2020b)	France	Published article	10/26/2020	Cohort	10	10	3/9
(Fan et al., 2020)	China	Published article	06/04/2020	Cohort	3060	2	6/9
(Stastna et al., 2021)	Czechia	Published article	06/23/2021	Cohort	13	13	5/9
(Viswanathan, 2020)	Malaysia	Published article	07/03/2020	Cohort	71	0	7/9

($p = 0.427$) tests (Fig. 2 in the Supplementary appendix).

3.2.2. ICU admission of NMOSD patients with COVID-19

Seven studies reported the prevalence of ICU admission ranging from 0 to 43.8% (Alonso et al., 2021; Boaventura et al., 2020; Louapre et al., 2020b; Mehdipour and Ashtari, 2020; Mirmosayyeb et al., 2020; Stastna et al., 2021; Zeidan et al., 2021). The pooled rate of ICU admission was 15.4% (95% CI: 7.6%–24.7%; $I^2=20.7%$, $p = 0.272$) (Fig. 4). We did not observe potential publication bias in Begg's ($p = 1.000$) and Egger's ($p = 0.835$) tests (Fig. 3 in the Supplementary appendix).

3.2.3. Mortality of NMOSD patients with COVID-19

Nine studies reported mortality, with a range from 0 to 31.3% (Alonso et al., 2021; Boaventura et al., 2020; Fan et al., 2020; Louapre et al., 2020b; Mehdipour and Ashtari, 2020; Mirmosayyeb et al., 2020; Sahraian et al., 2020; Stastna et al., 2021; Zeidan et al., 2021). The overall rate of death was estimated as 3.3% (95% CI: 0–9.7%; $I^2 = 21.3%$, $p = 0.253$) (Fig. 5). The Begg's ($p = 0.466$) and Egger's ($p = 0.544$) tests showed no evidence of publication bias (Fig. 4 in the Supplementary appendix).

3.3. Patients' characteristics and COVID-19 related symptoms

Table 2 presents demographic and clinical data of NMOSD patients with COVID-19 included in this study. The mean age of NMOSD patients with COVID-19 was 40.8 (SD 10.6) years, female/male ratio was 3.35:1, disease duration was 8.1 (SD 4.6) years and mean EDSS score was 3.39 (1.24). The most common COVID-19-related symptom was fever (54.5%), following by fatigue/asthenia (42.9%), headache (41.6%), shortness of breath/dyspnea (31.2%), and anosmia (31.9%). Ageusia

was found in 12.5% of patients, diarrhea in 13.0%, and nausea/vomiting in 5.2%. Four of 26 (15.4%) infected patients had neurological worsening (Boaventura et al., 2020; Mantero et al., 2020). One developed pseudo-relapse with worsening of paresthesias in the lower limbs, without other serious complications (Mantero et al., 2020). Two patients needed hospitalization and another one required admission to ICU (Boaventura et al., 2020). All four patients recovered. Thirty-eight patients (out of 78, 48.7%) reported at least one comorbidity. The most common comorbidities were hypertension (14.1%) and autoimmune diseases (14.1%), followed by diabetes mellitus (8.9%), pulmonary diseases (6.4%), and malignancy (3.8%). Data on autoimmune diseases in 8 patients were reported in detail. Myasthenia gravis and psoriasis were reported in two patients and each of the following comorbidities was reported in one patient: autoimmune hepatitis, autoimmune myositis, systemic lupus erythematosus, Sjögren's disease, myositis, rheumatoid arthritis, and pernicious anemia. Obesity was reported in 20 (21.3%) patients, 5 patients were smokers (5.3%). Patients' characteristics according to hospitalization status is presented in Table 3.

3.4. NMOSD treatment and the risk of COVID-19

Information on therapies was available for 106 patients. The most commonly used therapies was rituximab (54.7%), followed by azathioprine (23.6%), long-term corticosteroid (16.0%), and mycophenolate mofetil (8.5%). Hospitalization was needed in 27 of 51 (52.9%) patients who received RTX, 6 of 25 (24.0%) patients who received AZA, 4 (44.5%) of 9 patients on MMF, and 3 (20.0%) of 15 patients treated with long-term corticosteroid. Demographic and clinical features of patients separated by therapies are documented in Table 4. Six out of nine patients who died of COVID-19 were on RTX (Alonso et al., 2021; Stastna

Table 2
Demographic and clinical features of NMOSD patients with COVID-19.

Characteristics	N (%) or Mean (SD)	Number of patients with determined status
Demographic and clinical		
Age, mean (SD)	40.80 (10.63)	106
Sex, female/male, n (ratio)	77/23 (3.35: 1)	100
Disease duration, mean (SD)	8.09 (4.63)	99
EDSS, mean (SD)	3.39 (1.24)	70
AQP4-Ab, positive, n (%)	39 (54.2)	72
COVID-19 symptoms		
Fever	42 (54.5)	77
Cough	31 (40.3)	
Fatigue/asthenia	33 (42.9)	
Shortness of breath/ Dyspnea	24 (31.2)	
Headache	32 (41.6)	
Nausea/vomiting	4 (5.2)	
Diarrhea	10 (13.0)	
Anosmia	23 (31.9)	72
Ageusia	9 (12.5)	
Neurological worsening	4 (15.4)	26
Comorbidity		
At least one comorbidity	38 (48.7)	78
Hypertension	11 (14.1)	
Heart diseases	2 (2.6)	
Diabetes mellitus	7 (8.9)	
Pulmonary disease	5 (6.4)	
Malignancy	3 (3.8)	
Autoimmune diseases	11 (14.1%)	
Smoking	5 (5.3)	94
Obesity	20 (21.3)	
Treatment		
Rituximab	58 (54.7)	106
Corticosteroid	17 (16.0)	
Mycophenolate mofetil	9 (8.5)	
Azathioprine	25 (23.6)	
Ofatumumab	2 (1.9)	
Tocilizumab	1 (0.9)	
Inebilizumab	1 (0.9)	
Ecilizumab	1 (0.9)	
Methotrexate	1 (0.9)	
No treatment	5 (4.7)	

N: number; SD: standard division; EDSS: expanded disability status scale; AQP4-Ab: aquaporin-4 antibody.

et al., 2021), two were on prednisone (Ciampi et al., 2020; Stastna et al., 2021), and one was on combination therapy of AZA and prednisone (Boaventura et al., 2020). The mean age of deceased cases was 58.2 (SD 7.04) years, 7 (77.8%) were female, and mean of disease duration and EDSS score were 13.0 (SD 7.0) years and 4.5 (1.8), respectively. Information on the comorbidity of the deceased was available for four patients in detail. All four deceased cases had comorbidity including hypertension in three patients, and one case each had a cardiovascular condition, diabetes mellitus, dyslipidemia, malignancy, and rheumatoid arthritis. Regarding the other five cases, obesity and diabetes mellitus was each reported by two patients.

4. Discussion

In this systematic review and meta-analysis, we comprehensively assessed available studies on NMOSD patients infected with COVID-19. The pooled prevalence of COVID-19 was 1.2% (95% CI: 0.001%–0.030%), based on a total of 6243 NMOSD patients with female predominance. Of those 33.7% needed hospitalization, 15.4% ICU admission and the mortality was 3.3%. More than half of rituximab-treated patients needed hospital admission and 2/3 of those died. Approximately half of the NMOSD patients with COVID-19 had at least one comorbidity. The data suggest that comorbidity and treatment with rituximab are risk factors for COVID-19 infection in NMOSD patients.

Table 3
Characteristics of NMOSD patients with COVID-19 based on hospitalization status.

Characteristics	Hospitalized	Non-hospitalized
Age, mean (SD)	n = 37 46.54 (14.87)	n = 55 37.36 (8.57)
Sex, female, n (%)	n = 35 25 (71.4)	n = 55 46 (83.6)
Disease duration, mean (SD)	n = 34 9.35 (6.70)	n = 55 7.57 (3.12)
EDSS, mean (SD)	n = 21 4.50 (1.97)	n = 47 2.94 (0.89)
AQP4-Ab, positive, n (%)	n = 10 9 (90)	n = 13 6 (46.1)
Comorbidity		
At least one comorbidity, n (%)	n = 24 13 (54.2)	n = 48 23 (47.9)
Hypertension, n (%)	6 (25.0)	5 (10.4)
Heart diseases, n (%)	2 (8.3)	1 (2.1)
Diabetes mellitus, n (%)	4 (16.7)	3 (6.2)
Pulmonary disease, n (%)	2 (8.3)	3 (6.2)
Malignancy, n (%)	1 (4.2)	2 (4.2)
Autoimmune diseases, n (%)	4 (16.7)	5 (10.4)
Obesity, n (%)	n = 25 9 (37.5)	n = 55 11 (20.0)
Smoking, n (%)	n = 25 1 (4.0)	n = 55 3 (5.4)
Treatment		
Rituximab, n (%)	n = 37 26 (70.3)	n = 55 22 (40.0)
Corticosteroid, n (%)	4 (10.8)	11 (20.0)
Mycophenolate mofetil, n (%)	4 (10.8)	5 (9.1)
Azathioprine, n (%)	6 (16.2)	19 (34.5)
Ofatumumab, n (%)	0	1 (1.8)
Inebilizumab, n (%)	0	1 (1.8)
Ecilizumab, n (%)	0	1 (1.8)
Methotrexate, n (%)	0	1 (1.8)
No treatment, n (%)	1 (2.7)	3 (5.4)

n: number; SD: standard division; EDSS: expanded disability status scale; AQP4-Ab: aquaporin-4 antibody.

The most common COVID-19-related symptom was fever (54.5%), followed by fatigue/asthenia (42.9%), headache (41.6%), and cough (40.3%). Anosmia and dyspnea were found in about 30%. These data are in accordance with the findings in the general population (Boaventura et al., 2020; Salter et al., 2021) and in MS patients (Louapre et al., 2020a; Salter et al., 2021). Neurological worsening was reported by 15.4% of infected NMOSD patients (Boaventura et al., 2020; Mantero et al., 2020). Recent evidence suggests that COVID-19 may trigger exacerbation of MS (Barzegar et al., 2021d; Garjani et al., 2021). However, due to short follow-up and absence of control group, it could not be possible to determine the probable association between COVID-19 and risk of relapse in NMOSD patients.

This meta-analysis provided an estimation on the prevalence of COVID-19 of NMOSD patients. Three studies from China, USA, and Malaysia found no NMOSD patients with COVID-19 (Tomczak and Han, 2020; Viswanathan, 2020; Yin et al., 2021). The highest risk of COVID-19 was found in studies from France (6.7%). This discrepancy could be attributed to the differences in study settings, health policies, level of adherence to preventive protocols, and the phase of the pandemic in which the study had been conducted. Our estimated prevalence is not inconsistent with the prevalence of COVID-19 reported by a systematic review and meta-analysis in MS patients 1–13% (Moghadasi et al., 2021) and in other autoimmune diseases 1.1% (Akiyama et al., 2021), respectively. A higher prevalence of COVID-19 among patients with autoimmune disease was observed (Akiyama et al., 2021). As the pandemic continue to spread, the prevalence of COVID-19 among NMOSD population could be changed. Therefore, it is possible that the prevalence of the infection in the countries with low prevalence would increase.

The rate of hospitalization that was estimated in this study (33.7%) is higher than 20.7% reported in a systematic review on MS patients

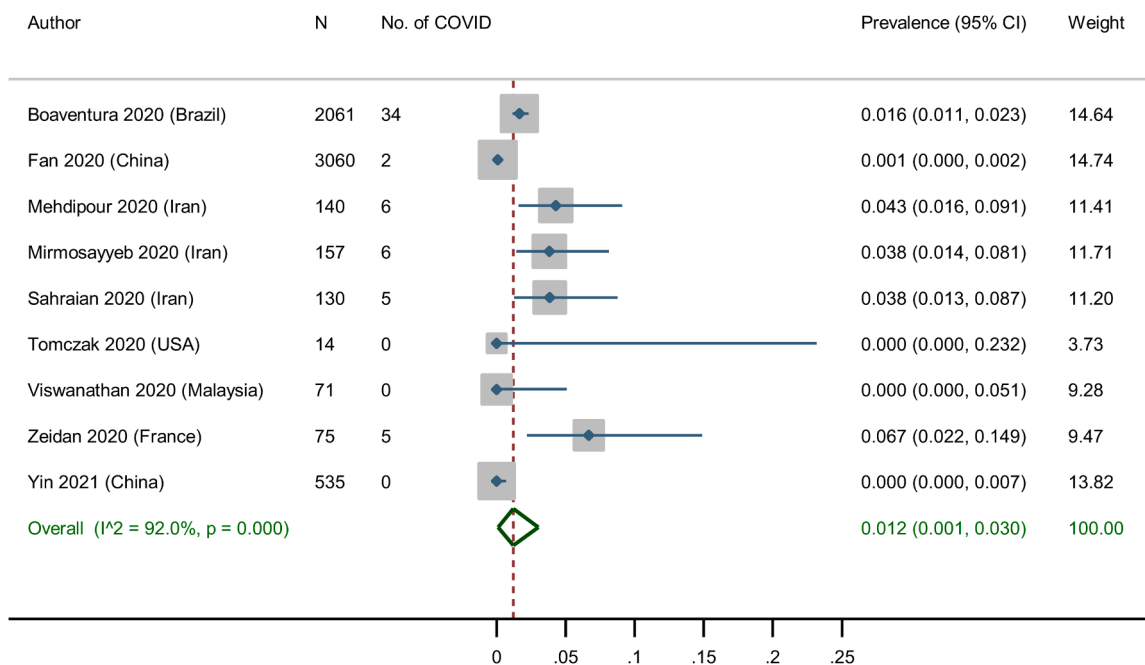


Fig. 2. COVID-19 prevalence among patients with NMOSD.

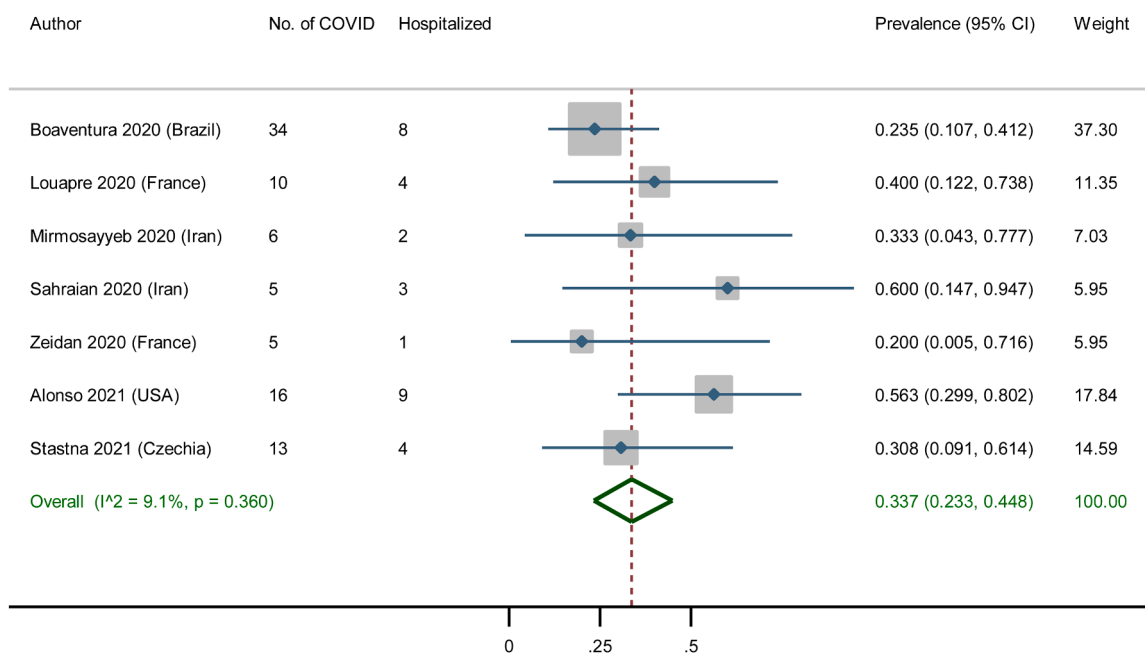


Fig. 3. Rate of hospitalization among NMOSD patients with COVID-19.

(Barzegar et al., 2021b). There is a large variation in the rate of hospitalization in primary studies, even between studies from a same country. The hospitalization rates in two surveys from Iran reported 33.3% (Mirmosayyeb et al., 2020) and 60% (Sahraian et al., 2020), in two studies from France were 40% (Louapre et al., 2020b) and 20.0% (Zeidan et al., 2021), in studies from Latin America were 23.5% (Boaventura et al., 2020) and 56% (Alonso et al., 2021), and in a study from Czechia was 30.8% (Stastna et al., 2021). The reasons for this variation are similar with those mentioned for variation in the prevalence of COVID-19.

The risk of hospitalization due to COVID-19 increases with age, with hospitalization rate being 7.4% in adults between 18 and 64 years of age, but 13.8% at age 65 years and above (Garg et al., 2020). The rate of

ICU admission reported from 0 to 43.8%, with a pooled rate of 15.4%. Risk of ICU admission among adults 20–54 years of age was reported from 2 to 10.4%, increasing to 31% in adults aged 75–84 years (Statista, 2021). The mortality in our study (3.3%) is in accordance with a mortality rate of 3.0 reported in MS patients with COVID-19 (Barzegar et al., 2021b). A broad range has been reported for the risk of death due to COVID-19 in NMOSD patients. A multi-centric registry study from LATAM with 16 NMOSD patients reported the risk of death as 31.2% (Alonso et al., 2021). The COVID-19 mortality rate among NMOSD patients in the Brazilian registry was 2.9%, (Boaventura et al., 2020). On the contrary, the French Covisep registry and other observational studies found no cases of death due to the infection (Louapre et al., 2020b). In adults aged 25–55 years, the infection fatality rate (IFR) was in a range

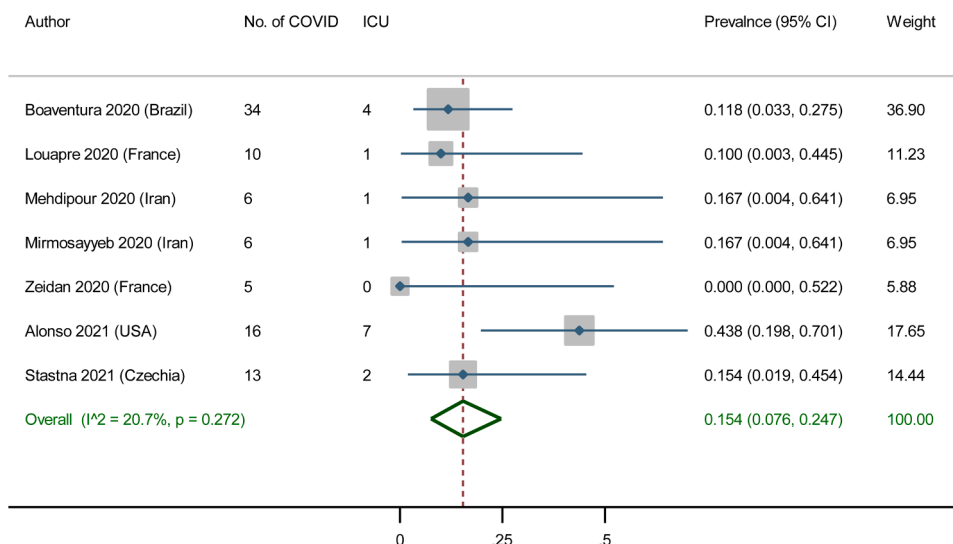


Fig. 4. Rate of ICU admission among NMOSD patients with COVID-19.

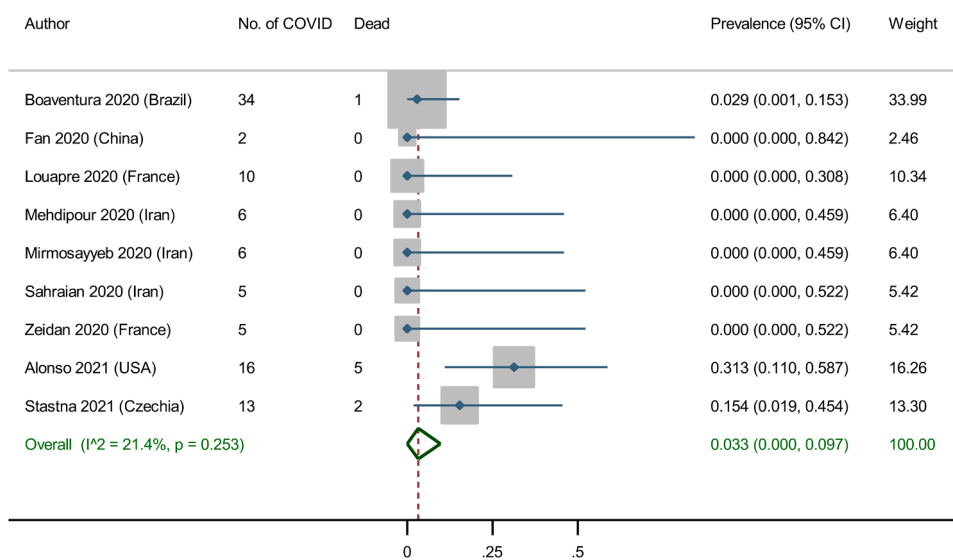


Fig. 5. Rate of death among NMOSD patients with COVID-19.

Table 4

Characteristics of patients were treated with rituximab, azathioprine, mycophenolate mofetil, or corticosteroids.

	RTX		AZA		MMF		Corticosteroids	
	All	Hospitalized	All	Hospitalized	All	Hospitalized	All	Hospitalized
Age, mean (SD)	n = 41 41.6 (15.1)	n = 22 46.3 (16.8)	n = 10 34.8 (10.4)	n = 5 39.6 (11.7)	n = 7 39.8 (12.5)	n = 3 41.3 (14.0)	n = 9 47.1 (15.6)	n = 2 46.6 (16.7)
Sex, female, n (%)	n = 35 25/35 (71.4)	n = 22 17 (77.3)	n = 10 9 (90.0)	n = 5 4 (80.0)	n = 7 6 (85.7)	n = 3 2 (66.7)	n = 9 5 (55.6)	n = 2 0
EDSS score, mean (SD)	n = 25 3.5 (1.5)	n = 18 3.9 (1.5)	n = 10 3.3 (1.9)	n = 5 4.3 (1.8)	n = 5 2.1 (1.0)	n = 1 1.0	n = 6 3.7 (2.2)	n = 2 3.7 (2.2)
Disease duration, mean (SD)	n = 38 8.1 (5.4)	n = 20 8.9 (6.4)	n = 10 7.5 (5.8)	n = 5 5.8 (3.6)	n = 5 5.8 (5.3)	n = 1 2.0	n = 7 5.9 (7.1)	n = 2 5.9 (7.1)
Comorbidity, n (%)	n = 27 12 (44.4)	n = 15 8 (53.3)	n = 10 2 (20.0)	n = 5 2 (40.0)	n = 7 6 (85.7)	n = 3 2 (66.7)	n = 7 6/7 (85.7)	n = 2 2 (100)

n: number; SD: standard division; EDSS: expanded disability status scale; RTX: rituximab; AZA: azathioprine; MMF: mycophenolate mofetil.

of 0.0% to 0.4% and raised to 1.4% in adults aged ≥ 65 years (Levin et al., 2020).

It is expected that female predominance and age of infected patients and those needed hospitalization (40 and 45 years, respectively) put

them at a decreased risk of poor COVID-19 outcome (Galbadage et al., 2020; Levin et al., 2020). However, when we compare the COVID-19 outcomes between NMOSD patients and general population, it seems that risk of severe COVID-19 in NMOSD patients may be higher than that

of general population at the same age. The possible increased risk could be related to the high prevalence of comorbidities, the dysregulated immune system and the maintenance therapies used.

Our findings are in the line with studies on MS population, which showed that older age, male sex, greater EDSS, and having comorbidities are associated with increased risk of COVID-19 severity and mortality (Alonso et al., 2021; Barzegar et al., 2021a; Louapre et al., 2020b; Salter et al., 2021). In the present study comorbidity was common. The most common comorbidity among all patients was obesity, followed by hypertension, autoimmune diseases, and diabetes mellitus. These conditions are highly prevalent in NMOSD patients (Ajmera et al., 2018; Barzegar et al., 2021c; Shahmohammadi et al., 2019), and also independently associated with worse COVID-19 outcomes (Gupta et al., 2020; Sanyaolu et al., 2020). Aging is known as an important risk factor for being hospitalized, ICU admission, and death from COVID-19 (Grasselli et al., 2020; Gupta et al., 2020). There is also an increasing trend in hospitalization and mortality rates with higher age groups in infected patients with comorbidity (Thakur et al., 2021; Tisminetzky et al., 2020).

Race and ethnicity have been suggested as contributing factors to COVID-19 outcomes (Mathur et al., 2021; Sze et al., 2020). African Americans are at an increased risk of developing severe NMOSD relapse and mortality (Mealy et al., 2018; Zhao-Fleming et al., 2021). However, no study has attempted to investigate the effect of race-ethnicity on infection outcome among NMOSD population. Therefore, we could not provide data to elucidate the impact of race-ethnicity on COVID-19 outcome among NMOSD patients. Current data suggest as an explanation that race-ethnicity minority populations experience social and financial inequity and have inadequate access to healthcare services (Kabarriti et al., 2020; Ogedegbe et al., 2020).

One of the greatest challenges physicians are facing during the pandemic is managing immunosuppressive therapies in patients with autoimmune diseases. NMOSD in most cases follows a relapsing course and may lead to neurological disability and morbidity as a consequence of cumulative sequelae of attacks, justifying early initiation of immunosuppressive treatment (Kim et al., 2021; Zhao-Fleming et al., 2021). Azathioprine and mycophenolate mofetil are two common immunosuppressive agents used for the treatment of NMOSD patients. About 22% and 44.5% of NMOSD patients who were on azathioprine and mycophenolate mofetil needed hospitalization. The effect of MMF and AZA on COVID-19 outcome is currently a subject of debate. Although a study in myasthenia gravis patients found no association between MMF and severity of COVID-19 (Michala et al., 2021), another in liver transplant patients found that MMF increased the risk of severe infection, especially at doses higher than 1 g/day (Colmenero et al., 2021). Since a limited number of patients are being treated with AZA and MMF, a definitive conclusion on the effect of these drugs on COVID-19 outcomes in NMOSD patients awaits further research.

Long-term oral corticosteroid as monotherapy or combination therapy is occasionally used to manage NMOSD in the chronic phase. Two reported deceased cases were on prednisone and one was treated with a combination of prednisone and AZA. Previous studies on MS patients have shown that the use of corticosteroids prior to COVID-19 can increase the risk of severe infection (Sormani et al., 2021b). However, it could be associated with better outcome when used in critically ill patients (Sterne et al., 2020). Few published data exist on the outcome of COVID-19 in NMOSD patients treated with monoclonal antibodies targeting interleukin (IL)-6 receptor (such as tocilizumab and satralizumab) and the complement system (eculizumab). Primary observational studies reported that tocilizumab can control cytokine storm in the COVID-19 patients and therefore can be used as a therapy in infected patients, especially in those with severe illness (Luo et al., 2020; Xu et al., 2020). Further clinical trial studies verified the safety of tocilizumab in COVID-19 patients; however, the effectiveness of this agent still remains unclear (Gordon et al., 2021; Rosas et al., 2021; Veiga et al., 2021).

We found that more than half of rituximab-treated patients needed hospital admission. Six out of 9 deceased cases were also treated with rituximab. These findings, while preliminary, suggest that NMOSD patients treated with rituximab may be more vulnerable to develop severe forms of COVID-19 infection. This is in accordance with studies on MS and other autoimmune diseases that have shown an increased risk of severe COVID-19 in patients using rituximab (Avouac et al., 2021; Michala et al., 2021; Salter et al., 2021; Sormani et al., 2021a). This possible relation could be related to general practice that patients treated with rituximab are usually older and have more disability, which increase the risk of serious infection. However, the mean of age and EDSS score of patients treating with rituximab was not substantially different with other NMOSD patients. The role of rituximab could be due to the B cell-depleting effect of rituximab that attenuates antibody responses, resulting in compromised antiviral immunity. It also diminishes T-cell counts, mainly CD4+ and to a lesser degree CD8+ (Lioussis and Sfikakis, 2008; Mélet et al., 2013), which have crucial role in the response to SAR-CoV2 (Cao, 2020).

Of particular concern is the effect of disease-modifying therapies (DMTs) and immunosuppressive therapies on vaccine effectiveness. Studies show poor antibody production following the COVID-19 infection and administration of mRNA vaccine in MS and NMOSD patients treated with anti-CD20 agents (Apostolidis et al., 2021; Bigaut et al., 2021; Brill et al., 2021; Louapre et al., 2021). On the other hand these patients generated robust SARS-CoV-2 specific T-cell responses following the vaccination (Apostolidis et al., 2021; Brill et al., 2021). Treatment with DMTs has not been linked to an impaired response to SARS-CoV-2 vaccine (Jena et al., 2021). Notwithstanding the aforementioned disadvantages, the efficacy of rituximab is higher than azathioprine and MMF (Huang et al., 2019; Nikoo et al., 2017). Moreover, drug discontinuation could predispose NMOSD patients to potentially-life-threatening attacks (Kim et al., 2021; Zhao-Fleming et al., 2021). Therefore, the administration of rituximab should be weighed against the risk of severe infection on a case-by-case basis.

Our study has some limitations. First, none of the included patients were asymptomatic. Therefore, we could not determine the rate of asymptomatic COVID-19 infection among NMOSD patients. This could also confound our interpretation of COVID-19 severity among NMOSD patients. Second, we included case report/series which are not representative of the NMOSD population. However, we did not include these studies in quantitative synthesis. Third, some of included studies in meta-analysis on COVID-19 outcome reported small number of infected patients which can affect our estimation. Fourth, a small group of patients were treated with therapies rather than rituximab and azathioprine. As such, we were unable to draw any conclusion on the impact of the aforementioned agents on COVID-19 outcomes. The fifth limitation of our study is the inclusion of conference abstracts with insufficient data, whose validity was not assessed carefully. However, including conference abstracts reduced publication bias and made our study more comprehensive. Sixth, the articles from languages other than English were not included. It should be noticed that none of primary studies has enrolled an age-sex-comorbidity matched control group from general population. Therefore, it is impossible to precisely illustrate the effect of NMOSD on COVID-19 susceptibility and outcomes. Caution should be applied in comparison of COVID-19 outcomes (risk of hospitalization, ICU admission, and mortality) between NMOSD patients and the general population.

In conclusion, our systematic review and meta-analysis suggests that NMOSD patients, particularly those who were treated with rituximab and had comorbidity need more attention. Further studies with an age-sex-comorbidity-matched control group from the general population are needed to determine whether NMOSD patients are at increased risk of contracting COVID-19 and developing severe infection.

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Ethical considerations

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

All data will be available for secondary analysis in necessary cases from the corresponding author through an email address.

CRedit authorship contribution statement

Mahdi Barzegar: Conceptualization, Formal analysis, Investigation, Validation, Writing – original draft, Writing – review & editing. **Omid Mirmosayyeb:** Data curation, Methodology, Visualization, Writing – review & editing. **Narges Ebrahimi:** Investigation, Methodology, Writing – review & editing. **Sara Bagherieh:** Investigation, Methodology, Writing – original draft, Writing – review & editing. **Alireza Afshari-Safavi:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **Ali Mahdi Hosseinabadi:** Investigation, Methodology, Writing – review & editing. **Vahid Shaygannejad:** Conceptualization, Project administration, Writing – review & editing. **Nasrin Asgari:** Conceptualization, Project administration, Writing – review & editing.

Declaration of Competing Interest

The Authors declare that there is no conflict of interest relevant to the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.msard.2021.103359](https://doi.org/10.1016/j.msard.2021.103359).

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