New onset or relapsing neuromyelitis optica temporally associated with SARS-CoV-2 infection and COVID-19 vaccination: A systematic review

Tamar Harel, MD[1,2], Emily F. Gorman, MLIS[3], Mitchell T. Wallin, MD, MPH[1, 2]

[1] Department of Veterans Affairs Multiple Sclerosis Center of Excellence (VA MSCoE), Baltimore VA Medical Center, Baltimore, MD, United States, [2] Department of Neurology, University of Maryland Medical Center, Baltimore, MD, United States, [3]Health Sciences and Human Services Library, University of Maryland, Baltimore, MD, United States

UNIVERSITY of MARYLAND SCHOOL OF MEDICINE

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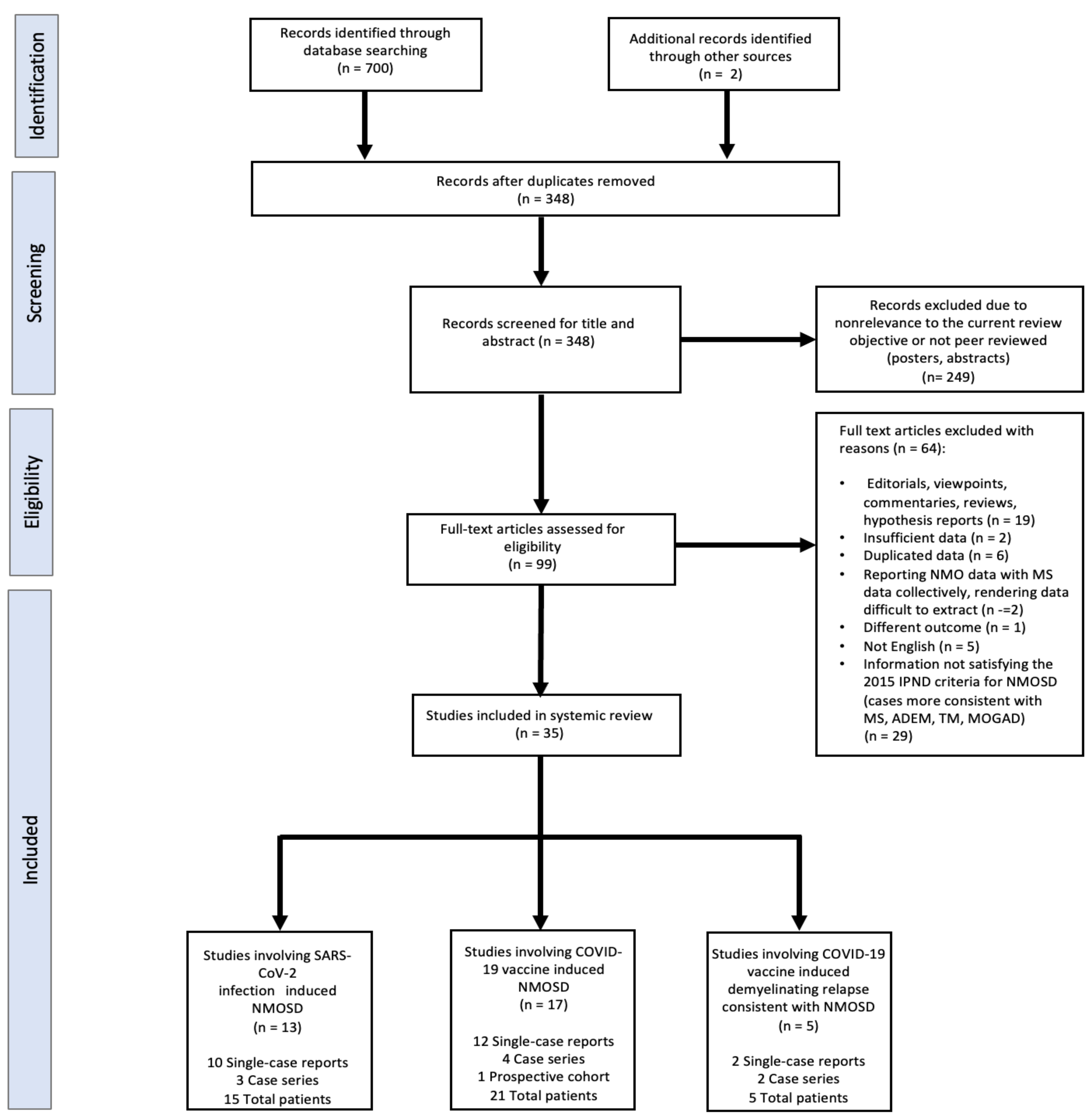
Introduction

- Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has the ability to dysregulate the host immune system, producing various autoantibodies. This can induce a cascade of immune-mediated central nervous system (CNS) damage from either direct inoculation of the CNS or a systemic autoimmune response towards the virus.[1,2,3] It has been shown that the SARS-CoV2 can traverse the blood brain barrier and provoke CNS demyelination.[1]
- Case reports have associated SARS-CoV-2 infection with an array of CNS autoimmune demyelinating disorders such as transverse myelitis, acute demyelinating encephalomyelitis, multiple sclerosis (MS), and neuromyelitis optica spectrum disorder (NMOSD).[4]
- Mounting evidence suggests that there is an intricate interplay between environmental factors, such as vaccines and viral infection, and genetic susceptibility that leads to CNS inflammation.[5]
- Through this systematic review, we will assess the association between SARS-CoV-2 infections and the para and post-infectious manifestations of NMOSD. We will also investigate the potential association between COVID-19 vaccination and the development of de novo or relapsing NMOSD.

Methods

- A Boolean search of the medical literature was conducted between December 1, 2019 to September 1, 2022, utilizing Medline, Cochrane Library, Embase, Trip Database, Clinicaltrials.gov, Scopus, and Web of Science databases.
- Articles were collated and managed on Covidence® software.
- The authors independently appraised the articles for meeting study criteria and followed PRISMA guidelines.
- The literature search included all case reports and case series that met study criteria and involved NMOSD following either the SARS-CoV-2 infection or the COVID-19 vaccination.

Figure 1. Flow chart of literature inclusion in accordance with PRISMA guidelines



Results

New Onset NMOSD Following SARS-CoV-2 Infection

- Median age 37.5 years (range 7.5 – 71 years)
- Latency period from the onset of COVID-19 symptoms to the first neurological manifestations followed a dual distribution:
  - *(i) Short latency:* 3 to 14 days in 53% of patients
  - *(ii) Long latency* (60 to 120 days) in 20% of patients.
- Median time interval between the initial SARS-CoV-2 infection symptoms and NMOSD symptom onset 4 days (range 3 – 120 days).
- 13% had a history of a previously diagnosed immune-mediated condition
- 40% had comorbidities
- Transverse myelitis was the most common neurological phenotype occurring in 67% patients
- 67% AQP4 antibody positive, 27% AQP4 antibody negative
- 84% had complete or partial recovery following treatment, 15% died

New Onset and Relapsing NMOSD Following COVID-19 Vaccination

- 81% of cases experienced an initial relapse of NMOSD following the COVID-19 vaccination and 19% of cases had a recurrent exacerbation
- 54% of cases involved an mRNA vaccine, 31% of cases involved a viral vector vaccine, 15% of cases involved an inactivated COVID-19 vaccine
- The median duration between vaccination and onset of NMOSD related clinical symptoms was 10 days (range 1 to 97 days)
- 31% had a history of a previously diagnosed immune-mediated condition
- 15% has family history of an immune-mediated condition
- Transverse myelitis was the most common phenotype, occurring in 65% of patients.
- 8% tested positive for AQP4 antibody,12% were AQP4 antibody negative.
- 88% experienced complete or partial recovery following treatment, 8% did not improve with treatment, 4% died

Figure 2. Duration from vaccination to symptom onset for each vaccine

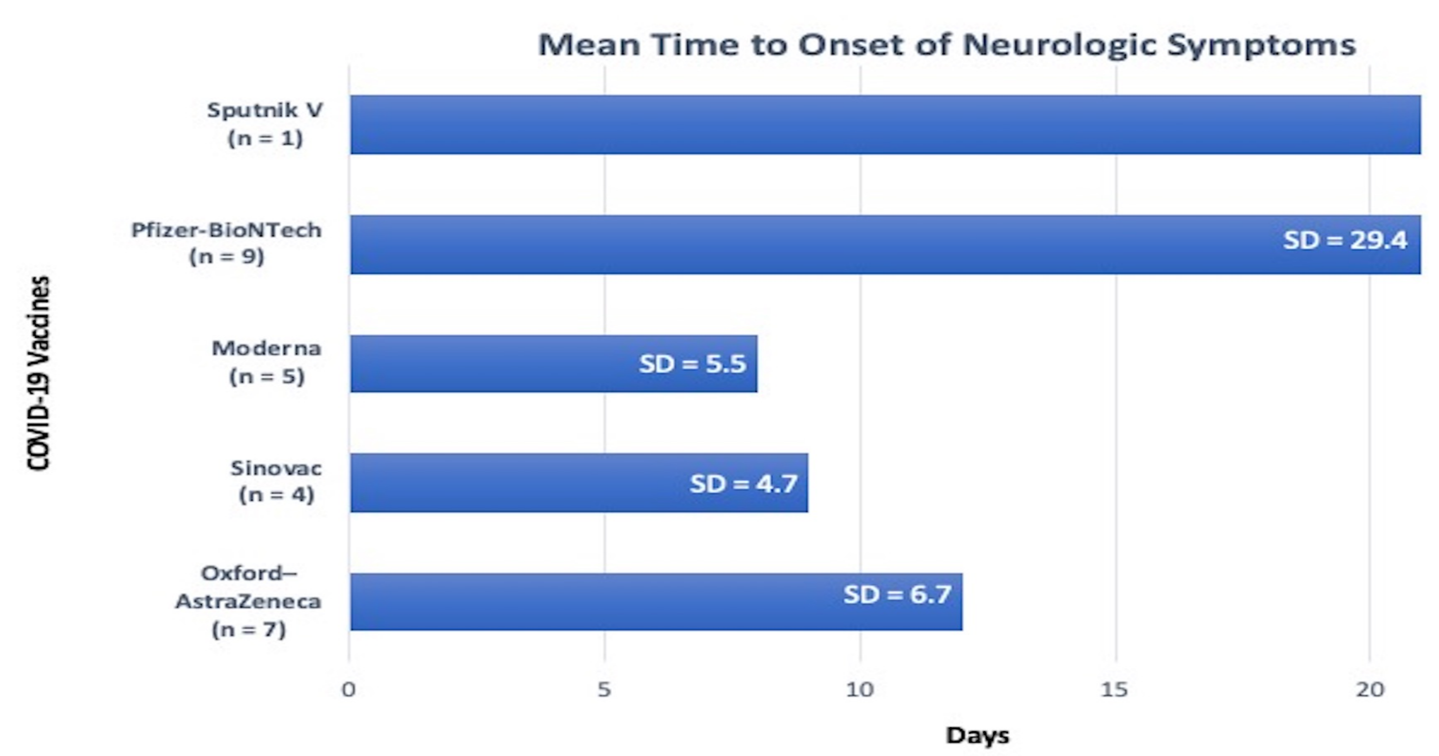


Table 1: Comparison of demographic and disease characteristics of patients with SARS-CoV-2 post-infection and COVID-19 post-vaccination NMOSD

Characteristics	NMOSD following a SARS-CoV-2 infection	De novo and relapsing NMOSD following COVID-19 vaccination
Age in years, Mean (SD)	37.5 (21)	50 (16)
Sex		
- Female (%)	11 (73%)	20 (77%)
- Male (%)	3 (20%)	6 (33%)
- Not reported (%)	1 (7%)	0 (0%)
Patients with a reported comorbid autoimmune condition (%)	2 (13`%)	8 (31%)
Patients with a comorbid condition (%)	6 (40%)	12 (46%)
Days between exposure to SARS-CoV-2 infection vs COVID-19 vaccination & NMOSD onset (range)	14 (3 – 120)	10 (1 - 97)
Neurological Manifestations		
- Transverse myelitis (TM) (%)	10 (67%)	17 (65%)
- Short-segment TM (%)	2 (13%)	4 (15%)
- Longitudinally extensive TM (%)	8 (53%)	13 (50%)
- Optic neuritis (%)	7 (47%)	5 (19%)
- Area postrema syndrome (%)	2 (13%)	3 (12%)
- Brainstem involvement (%)	5 (33%)	3 (12%)
AQP-4 antibody status		
- Positive (%)	10 (67%)	22 (85%)
- Negative (%)	4 (27%)	3 (12%)
- Unknown (%)	1 (7%)	1 (4%)
Outcome		
- Complete or partial recovery (%)	11 (73%)	22 (85%)
- No recovery (%)	0 (0%)	2 (8%)
- Death (%)	2 (13%)	1 (4%)
- Not reported (%)	2 (13%)	1 (4%)

Conclusions

This systematic review suggests that there is an association between NMOSD and SARS-CoV-2 infections and COVID-19 vaccinations. This association requires further study using quantitative epidemiological assessments in a large population to better quantify the risk.

References

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