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REVIEW ARTICLE

Optic neuritis associated with COVID-19 vaccine: a systematic review for clinical characteristics of an uncommon side effect

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Abstract

To characterize the clinical presentation of optic neuritis (ON) associated with COVID-19 vaccination. Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement, a search was performed in PUBMED, Google Scholar, and SciELO database using the keywords "COVID-19 vaccination" AND "optic neuritis." Only articles written in English were included. A total of 126 articles were retrieved, of which 33 corresponded to cases of ON. Because 15 (13 patients) of the 33 articles had comorbidities, these were excluded. The mean age of the included patients was 42 years, the incidence was 79% in women versus 29% in men, and 27 of the cases were unilateral versus 17 bilateral. Treatment consisted of steroids in 37 of the cases, steroids plus plasmapheresis in 7 cases. Vaccines associated with ON were vector type in 18 of the cases, genetic type in 22 cases, and inactivated type in 4 cases; no association with ON was reported for viral and protein attenuated vaccine types. As in the case reported by our group, evidence in the literature indicates that bilateral ON is rare but requires prompt plasmapheresis as an adjunct to intravenous methylprednisolone to reduce neurological sequels.

Keywords: *COVID-19. Vaccine. Optic neuritis.*

Neuritis optica asociada a vacunas COVID-19: características clínicas de un efecto secundario poco común

Resumen

Caracterizar la presentación clínica de la neuritis óptica asociada a la vacunación con COVID-19. Siguiendo la declaración Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) se realizó una búsqueda en PUBMED y Google Scholar utilizando las palabras clave «COVID-19 vaccination» y «optic neuritis». Se incluyeron solo artículos escritos en inglés. Se recuperó un total de 126 artículos, de los cuales 33 correspondían a casos de neuritis óptica (ON). Se excluyeron 15 (13 pacientes) de los 33 artículos porque presentaban comorbilidades. La edad media de los pacientes incluidos fue de 42 años, la incidencia fue del 79% en mujeres frente al 29% en hombres, y 27 de los casos fueron unilaterales frente a 17 bilaterales. El tratamiento consistió en esteroides en 37 de los casos, esteroides más plasmaféresis en 7 casos. Las vacunas asociadas a la ON fueron de tipo vectorial en 18 de los casos, de tipo genético en 22 casos y de tipo inactivado en 4 casos; no se observó ninguna asociación con la ON en los tipos de vacuna vírica y proteica atenuada.

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Al igual que en el caso reportado por nuestro grupo, la evidencia en la literatura indica que la ON bilateral es rara, pero requiere plasmaféresis rápida como complemento de metilprednisolona intravenosa para reducir las secuelas neurológicas.

Palabras clave: *COVID-19. Vacuna. Neuritis óptica.*

Introduction

Since its emergence and rapid global spread, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with high rates of hospitalization and mortality. Efforts to control the disease have included the development of specific antiviral drugs and safe vaccines. Since the mid-2020s, several clinical trials of antiviral drugs and vaccines have been announced. CanSino Biologics was the first vaccine to be approved by a national authority in China for limited use in military personnel. BioNTech/Pfizer, Moderna, the Gamaleya Institute, and Oxford University reported promising results in vaccine trials by November 2020, and several countries approved the use of Pfizer-BioNTech's COVID-19 vaccine for emergency use by December 2020. Other vaccines were approved by the World Health Organization shortly thereafter[1,2].

Mexico was the first country in Latin America to import and apply vaccines against COVID-19, following a five-stage vaccination program[3-34]. Health care workers and the elderly were the first to be vaccinated. As vaccination progressed globally, several adverse reactions, including neurologic disorders, were reported[35]. Several studies in this regard have also been published in Mexico[36-40]. According to these reports, the most common adverse events were headache, fatigue, and myalgia. Neuro-ophthalmic complaints, although rare, have been reported both in SARS-CoV-2 infection and after vaccination against COVID-19[41,42].

Optic neuritis (ON) is an inflammatory condition that affects one or both optic nerves. Typical ON is a clinical manifestation of central nervous system (CNS) inflammation, usually characterized by unilateral pain on ocular movement, mild to moderate decrease in visual acuity (VA), and dyschromatopsia in young adults. Atypical ON (AON), more common in patients older than 50 years or younger than 12 years, is characterized by bilateral involvement, severe visual loss (20/200), and severe optic disc inflammation[43]. Considering that ON is a rare side effect of COVID-19 vaccines, we present a review of cases of ON after COVID-19 vaccination reported in the literature is also presented.

Epidemiology

A subset demonstrated the incidence of neuro-ophthalmic sequelae after COVID-19 disease is far greater than after vaccination against the virus[44,45]. ON was the neuro-ophthalmic sequelae most frequently reported after COVID-19 infection and vaccination, and before the onset of the pandemic, it is known to occur at a stable rate in the general population[46].

Associated

The neurotropism of SARS-CoV-2 virus is poorly elucidated; access of the virus to the CNS through the olfactory bulb, crossing the blood–brain barrier following viremia, transport through infected leukocytes is a probable mechanisms[47].

While the phenomenon is poorly studied, previous studies have suggested molecular mimicry between myelin basic protein and viral proteins, epitope spreading, bystander activation, and superantigen activation as potential mechanisms[48].

Materials and methods

A systematic search was conducted in PubMed, Google Scholar using the terms using the keywords "COVID-19 vaccination" AND "optic neuritis." Two clinicians (C.G. and M.A.R.D.) conducted a full-text review of the articles and extracted all relevant data on ON associated with COVID-19 vaccination. Inclusion criteria included a complete clinical characterization of ON, identification of vaccines administered, and time of onset of clinical symptoms in adult patients. Only articles written in English were included. Articles with insufficient data to confirm clinical ON were excluded.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences 23 (IBM Inc., Somers, NY, USA). Qualitative variables were reported as percentages and compared using the Chi-squared (χ^2) test with Yates

Table 1. Characteristics of studies included in our systematic review corresponded to cases of isolated ON

Author	Publication type	Age	Gender	Time*	Vaccine associated	Affected eye	Type of ON	Treatment
Arnao et al., 2022[3]	LE	ND	Female	2.00	Vector-based vaccine	Both	Bilateral	Steroids
Estrada et al., 2022[4]	CR	19	Female	1.00	Vector-based vaccine	Left	Unilateral	Steroids
		27	Female	1.28	Vector-based vaccine	Left	Unilateral	Steroids
Roy et al., 2022[5]	CS	48	Female	0.71	Vector-based vaccine	Left	Unilateral	Steroids
		40	Male	1.71	Vector-based vaccine	Right	Bilateral	Steroids
Tarcha et al., 2023[6]	CR	22	Male	1.42	Genetic	Both	Bilateral	Steroids and immunoglobulin
Elnahry et al., 2023[7]	CR	69	Female	2.28	Genetic	Both	Bilateral	Steroids
		32	Female	0.85	Vector-based vaccine	Left	Unilateral	Steroids
Shemer et al., 2023[8]	CR	54	Male	24.00	Genetic	Right	Unilateral	Steroids
		38	Female	8.00	Genetic	Left	Unilateral	Steroids
		42	Female	3.00	Genetic	Left	Unilateral	Steroids
		14	Male	9.00	Genetic	Left	Unilateral	Steroids
Saluja et al., 2023[9]	LE	35	Male	0.28	Vector-based vaccine	Both	Bilateral	Steroids
Pirani et al., 2023[10]	CR	31	Female	0.85	Genetic	Right	Unilateral	Steroids
		46	Female	1.14	Genetic	Right	Unilateral	Steroids
Shah et al., 2022[11]	CR and review	39	Female	4 weeks (first doses)	Genetic	Right	Unilateral	Steroids with plasmapheresis
1 week (second doses)								
Motegi et al., 2022[12]	CR	86	Male	1.14	Genetic	Right	Unilateral	Steroids
Wang et al., 2022[13]	CR	21	Female	3.00	Inactivated	Right	Unilateral	Steroids
		38	Female	3.00	Inactivated	Right	Unilateral	Steroids
Tugizova et al., 2023[14]	CC	65	Female	0.71	Genetic	Right	Unilateral	Steroids and immunoglobulin
		67	Male	0.14	Genetic	Left	Bilateral	Steroids
Lee, 2022[15]	CR	28	Female	0.28	Vector-based vaccine	Right	Unilateral	Steroids
Liu and Lee 2022[16]	CR	49	Female	2.00	Vector-based vaccine	Both	Bilateral	Steroids

(Continues)

Table 1. Characteristics of studies included in our systematic review corresponded to cases of isolated ON *(continued)*

Author	Publication type	Age	Gender	Time*	Vaccine associated	Affected eye	Type of ON	Treatment
Saxton et al., 2023[17]	CR	28	Female	1.00	Genetic	Right	Unilateral	Steroids
Zhang et al., 2023[18]	CR	58	Female	0.01	Genetic	Left	Unilateral	Steroids
Natung et al., 2023[19]	CR	44	Female	0.57	Vector-based vaccine	Both	Bilateral	Steroids
Badeeb et al., 2024[20]	CC	66	Female	1.42	Genetic	both	Bilateral	Steroids
Katayama et al., 2022[21]	CR	63	Male	1.50	Genetic	Both	Bilateral	Steroids
Donaldson and Margolin, 2023[22]	CC	54	Male	3.00	Vector-based vaccine	Right	Bilateral	Steroids
Raxwal et al., 2022[23]	CR	47	Female	1.14	Genetic	Left	Unilateral	Steroids
Huang et al., 2023[24]	CC	47	Female	4.00	Vector-based vaccine	Both	Bilateral	Steroids

*Time between vaccination and optic neuritis development (weeks).
CP: case report; LE: letter to the editors; CC: clinical correspondence, ON: optic neuritis.

correction. Differences between continuous variables were assessed using Student's t-test; $p < 0.05$ was considered significant.

Results

A total of 126 articles were retrieved. Of these, only 14 (32 patients) corresponded to cases of isolated ON (Table 1); 6 articles (12 patients) reported ON associated with autoimmune diseases, optic neuromyelitis, encephalomyelitis, and other causes (Table 2). The PRISMA flow chart is presented in figure 1.

General characteristics of patients

A total of 44 patients (32 with isolated ON and 12 with ON associated with autoimmune disease) were included in this analysis. Considering that bilateral optic nerve involvement or AON are more severe conditions, a descriptive analysis was performed comparing bilateral versus unilateral optic nerve involvement. Female patients were more frequently affected (33/44) than males (11/44) (χ^2, $p = 0.056$). Unilateral ON was more frequent in the included patients (27/44). According to the logarithm of the minimum angle of resolution (LogMAR chart) values, the left eye was most affected (non-parametric test, $p = 0.004$). The mean time between vaccination and onset of symptoms was 1.72 ± 1.07 weeks for AON and 4.7 ± 6.7 weeks for unilateral ON; no significant differences were found between the two groups (Table 3).

Association to vaccines

Generic messenger ribonucleic acid (mRNA) vaccines were most associated with ON (22 cases), 62.9% of which were unilateral ON, followed by vector-based vaccine (18 cases), which accounted for 64.7% of bilateral ON cases. Finally, inactivated vaccines were most frequently associated with bilateral involvement.

Treatment administered

Intravenous corticosteroids were the most common treatment, used in 37 cases. All other patients received combined treatment with corticosteroids and plasma exchange (PLEX) (Table 3)[3-34].

Bivariate correlations were found between ON type (unilateral or bilateral) and sex ($p = 0.04$, $R = -0.367$), and severity of vision loss in the left eye ($p = 0.005$, $R = -0.511$).

Table 2. Characteristics of studies included in our systematic review corresponded to cases with autoimmune disease

Author	Publication type	Age	Gener	Time*	Vaccine associated	Affected eye	Type of ON	Treatment
Shemer et al., 2023[8]	CR	38	Male	18.00	Genetic	Left	Unilateral	Previous retrobulbar ON
		29	Female	24.00	Genetic	Right	Unilateral	Esclerosis múltiple
		45	Female	6.00	Genetic	Right	Unilateral	Disclosed MS with 2 episodes of ON
Leber et al., 2021[25]	CR	32	Female	0.07	Inactivated	Both	Bilateral	Tiroiditis
Shirah et al., 2023[26]	CR	31	Female	2.00	Genetic	Left	Unilateral	Lupus
Nagaratnam et al., 2022[27]	CR	36	Female	2.00	Vector-based vaccine	Both	Bilateral	Encefalomielitis aguda
Kang et al., 2023[28]	CR	42	Female	1.00	Genetic	Left	Unilateral	SLE
Yildiz 2022[29]	CR	32	Male	2.00	Inactivated	Right	Unilateral	1. Tumor
								2. Graves' disease
Richardson-May et al., 2022[30]	CR	71	Female	1.00	Vector-based vaccine	Right	Unilateral	Guillain-Barre syndrome
Chu et al., 2023[31]	CR	60	Female	2.14	Vector-based vaccine	Left	Unilateral	Stem cell transplant
Shukla et al., 2022[32]	CR	56	Female	1.71	Vector-based vaccine	Both	Bilateral	Sarcoidosis
Helmchen et al., 2022[33]	LE	40	Female	2.00	Vector-based vaccine	Both	Bilateral	Esclerosis Múltiple
Levi-Strauss et al., 2022[34]	LE	72	Female	3.00	Genetic	ND	ND	Neuromielitis

*Time between vaccination and optic neuritis development (weeks).
CR: case report; LE: letter to the editors, ON: optic neuritis, SLE: systemic lupus erythematosus.

Clinical report

A 59-year-old female patient, previously healthy, reported receiving the COVID-19 vaccine 22 days before the onset of clinical symptoms. The patient progressively developed moderate to severe left hemicrania with periorbital involvement; over the next 48 h, left VA decreased to amaurosis. Bilateral ON was observed over the next 72 h. The patient consulted a physician, and magnetic resonance imaging was performed. Patchy inflammatory hyperintensities were observed in the optic nerves, with greater anterior (papillary) involvement. Cerebrospinal fluid cytochemistry (glucose, 57 mg/dL; protein, 23 mg/dL, 3 cells mm^3) and cytology were performed, along with determination of oligoclonal bands and detection of AQP4 and anti-myelin oligodendrocyte glycoprotein antibodies (both negative), as well as microbiological culture and staining. AON was considered at diagnosis and the patient received a bolus of methylprednisolone for 5 days, followed by 5 sessions of PLEX. At the end of treatment, bilateral VA was 20/70. Additional tests included a rheumatologic profile (anti-Smith, antinuclear, anti-DNAdc, anti-SSA, anti-SSB, and anticardiolipin Immunoglobulin G and Immunoglobulin M, C3 and C4 proteins, rheumatoid factor, and *Mycobacterium tuberculosis* GenXpert) with negative results.

Discussion

Vaccine side effects have been extensively reported (especially with viral agents), including ocular side effects. In such cases, it is imperative to assume an association between vaccination and the development

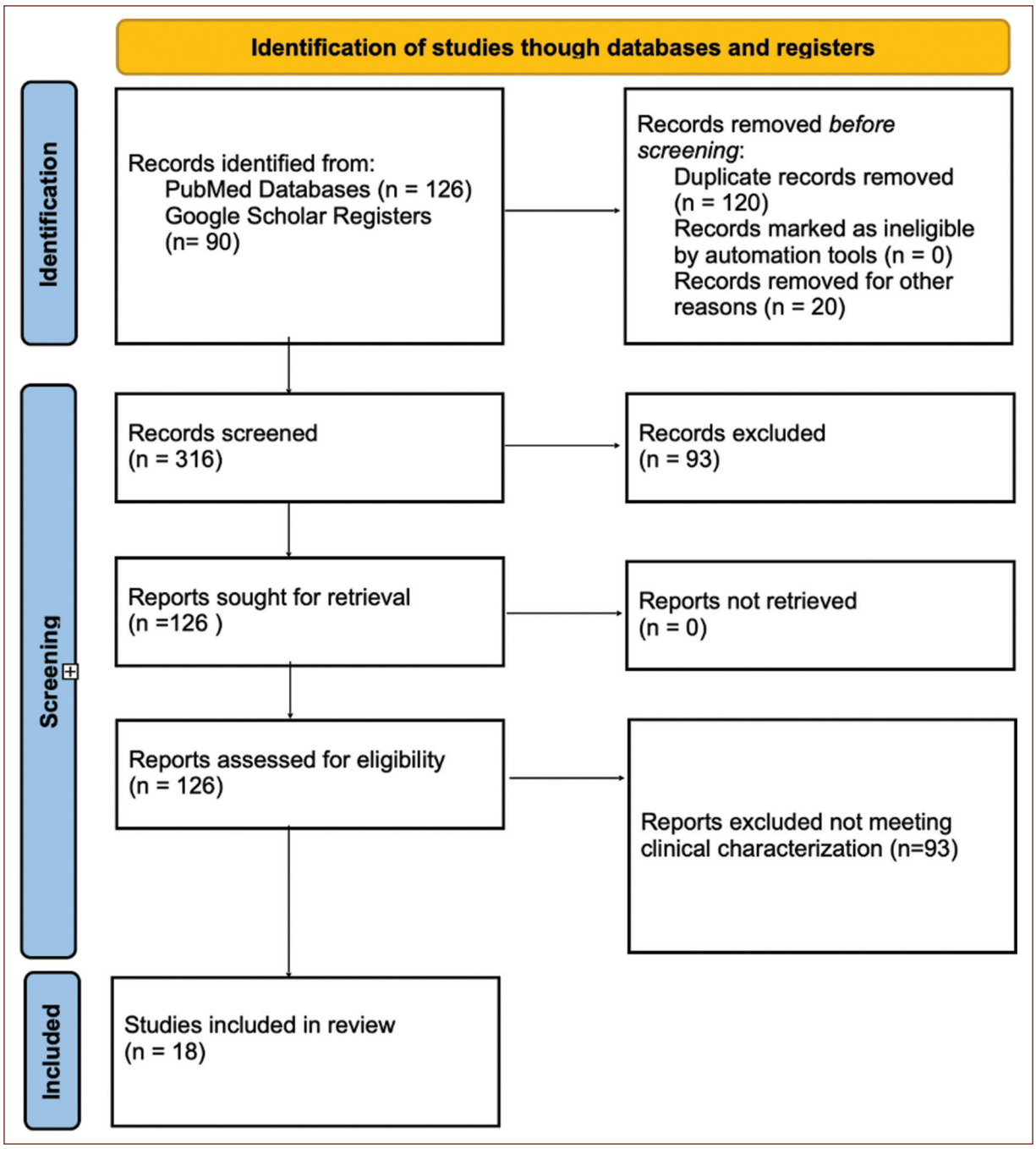

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram depicting the flow of information through the different phases of a systematic review.

of complications to establish causality[48,49]. ON, one of the most serious ocular diseases can be caused by a variety of inflammatory and infectious conditions. According to their clinical presentation, cases of ON can be classified as typical (unilateral visual loss, retroorbital pain on extraocular movement, dyschromatopsia, and higher prevalence in younger patients) or atypical (bilateral onset, refractory to corticosteroid treatment, and optic nerve head/peripapillary hemorrhage)[43].

In this study, we present a case of ON associated with COVID-19 vaccination (ChAdOx1-2 vaccine) and a literature review of ON cases reported as associated with COVID-19 vaccination in the PUBMED and Google

Table 3. General characteristics of the included patients

General data	Bilateral optic neuritis (n = 17)	Unilateral optic neuritis (n = 27)	p
Age (years)	48.6 ± 14	41.07 ± 16.1	0.07
Time elapsed between vaccination and ON onset (weeks)	1.72 ± 1.07	4.5 ± 6.7	0.6
Isolated ON, n (%)	13 (40.6)	19 (59.4)	0.7
ON plus autoimmune disease, n (%)	4 (33.3)	8 (66.7)	
Female, n (%)	11 (33.3)	22 (66.7)	0.2
Male, n (%)	6 (54.5)	5 (45.5)	
Type of vaccine administered, n (%) Vector-based vaccine Genetic Inactivated	 11 (61.1) 5 (22.7) 1 (25)	 7 (38.9) 17 (77.3) 3 (75)	 0.03
Abnormal fundoscopy, n (%)	12 (46.2)	14 (53.8)	0.1
Visual acuity, n (%) Mild to moderate Severe	 5 (23.8) 10 (52.6)	 16 (76.2) 9 (47.4)	 0.1
LogMAR score Right eye Left eye	 0.66 ± 0.8 0.98 ± 0.9	 0.51 ± 0.73 0.3 ± 0.65	 0.3 0.004
Serum antibodies, n (%) AQP4 MOG	 2 (50) 3 (50)	 20 (50) 3 (50)	 1
Treatment, n (%) Corticosteroid monotherapy Corticosteroids plus PLEX	 14 (37.8) 3 (42.9)	 23 (62.2) 4 (57.1)	 1

ON: optic neuritis; PLEX: plasma exchange; MOG: myelin oligodendrocyte glycoprotein.

Scholar databases. Our results suggest that the incidence of ON associated with SARS-CoV-2 vaccines is low (only 44 patients were retrieved); moreover, a significant proportion of these patients (38.6%) had autoimmune diseases associated with ON. The vaccines most frequently associated with ON were those of genetic origin (mRNA), and females were the most affected sex.

To date, the mechanism of vaccine-related ON is not clearly understood, but some hypotheses have been proposed, such as molecular mimicry with viral proteins, immune cross-reactivity with human tissues, activation of NLRP3 inflammation, and/or microthromboembolism formation[44-47].

Despite limitations related to the small sample size and its retrospective design, our work showed interesting results. We suggest long-term follow-up of these patients, especially those with associated autoimmune disease, to prevent visual dysfunction.

Conclusion

Clinicians should be aware of the risk of ocular side effects of COVID-19 vaccines, especially in patients with functional neurological compromise, to promptly initiate immunomodulatory treatment (corticosteroids plus PLEX) and prevent further complications.

Limitations of the study

It is important to consider that only two databases were used: PubMed and Google Scholar. A third database, SciELO, could not be included, mainly because this database contains studies reported in languages other than English. Another important limitation is that only one neurological referral center was included: the National Institute of Neurology and Neurosurgery, a public neurological referral center. During the period of preparation of this manuscript, the number of cases of NO has increased considerably; however, many of the reported cases have been attributed to the COVID-19 Omicron variant.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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