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Development and validation of a claims-based algorithm to identify patients with Neuromyelitis Optica Spectrum disorder☆

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ABSTRACT

Introduction: No validated algorithm exists to identify patients with neuromyelitis optica spectrum disorder (NMOSD) in healthcare claims data. We developed and tested the performance of a healthcare claims–based algorithm to identify patients with NMOSD.

Methods: Using medical record data of 101 adults with NMOSD, multiple sclerosis (MS), or myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD), we tested the sensitivity and specificity of claims-based algorithms developed through interviews with neurologists. We tested the best-performing algorithm's face validity using 2016–2019 data from IBM MarketScan Commercial and Medicare Supplemental databases. Demographics and clinical characteristics were reported.

Results: Algorithm inclusion criteria were age ≥ 18 years and (≥1 NMO diagnosis [or ≥ 1 transverse myelitis (TM) and ≥ 1 optic neuritis (ON) diagnosis] and ≥ 1 NMOSD drug) or (≥2 NMO diagnoses ≥90 days apart). Exclusion criteria were MS diagnosis or use of MS-specific drug after last NMO diagnosis or NMOSD drug; sarcoidosis diagnosis after last NMO diagnosis; or use of ≥1 immune checkpoint inhibitor. In medical record billing data of 50 patients with NMOSD, 30 with MS, and 21 with MOGAD, the algorithm had 82.0% sensitivity and 70.6% specificity. When applied to healthcare claims data, demographic and clinical features of the identified cohort were similar to known demographics of NMOSD.

Conclusions: This clinically derived algorithm performed well in medical records. When tested in healthcare claims, demographics and clinical characteristics were consistent with previous clinical findings. This algorithm will enable a more accurate estimation of NMOSD disease burden using insurance claims datasets.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD), previously known as neuromyelitis optica (NMO) or Devic disease, is an inflammatory disorder of the central nervous system (CNS) characterised by acute attacks on the optic nerves, spinal cord, brain, or brainstem. These unpredictable attacks follow a stepwise deterioration pattern, have a relapsing course in ≥90% of cases, and often lead to

Abbreviations: AQP4-IgG−, aquaporin-4 seronegative; AQP4-IgG+, aquaporin-4 seropositive; CNS, central nervous system; *ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification*; IRB, institutional review board; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; TM, transverse myelitis.

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permanent neurological deficits and disability, including blindness and paralysis [1]. In general, distinguishing between patients with multiple sclerosis (MS), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), and NMOSD (either aquaporin-4 seropositive [AQP4-IgG+] or aquaporin-4 seronegative [AQP4-IgG−]) is challenging as all of these conditions can present in similar ways clinically (i.e., transverse myelitis [TM] and optic neuritis [ON]) and radiologically (i.e., similarities in magnetic resonance imaging [MRI] findings) [2,3]. Misdiagnosis of NMOSD as other demyelinating disorders is common, with previous studies reporting MS misdiagnosis rates ranging from 29% to 42.5% [4] and > 70% of participants receiving an initial diagnosis other than NMOSD, including MS [5].

NMOSD affects approximately 0.5 to 10 per 100,000 people [6]. AQP4-IgG+ NMOSD affects mostly females (female-to-male ratio of up to 9:1) [7], with a mean age at onset of approximately 40 years, which is a later age of onset than is typically seen with MS. MOGAD, in contrast, has a nearly 1:1 female-to-male ratio and is more prevalent in children than in adults [7].

Although NMOSD has been described in the literature for over a century, the first modern diagnostic criteria were developed only 20 years ago and have been revised twice, most recently in 2015 [6,8]. Currently, a diagnosis of NMOSD is made based on an inflammatory attack of the optic nerves, spinal cord, brainstem, or brain in the context of positive serology for AQP4 antibody. The threshold is higher with negative serology for AQP4 antibody: at least 2 inflammatory attacks disseminated across the optic nerves, spinal cord, area postrema, brainstem, diencephalon, or cerebrum (one of which must be optic neuritis, acute myelitis, or area postrema syndrome), plus supportive criteria including signal abnormality extending over ≥3 vertebral segments or more than half the length of the optic nerve on spinal cord or brain MRI, respectively [4,7].

Real-world data sources have allowed for the expansion of health outcomes research, but that research relies on the assumption that patients are being accurately identified in those data sources [10,11]. Multiple expert panels and the US Food and Drug Administration have recommended validating the algorithms used to identify patients when using real-world data sources for health outcomes research. However, as of 2011, fewer than 5% of real-world data studies used validated codes [11–14]. While studies have assessed the comorbidity and healthcare resource use burden among patients with NMOSD using various combinations of diagnosis codes, including that for NMO [9,15–17], they have not used a validated algorithm or presented algorithm performance assessments. The extent to which these studies may be misidentifying patients in healthcare claims with other conditions is unknown. These discrepancies highlight the need for a validated algorithm to identify patients with NMOSD in healthcare claims data. Being able to identify patients with NMOSD and to distinguish them from patients with MS, MOGAD, and other CNS inflammatory disorders would improve cohort identification in future studies using healthcare claims data and ensure that the correct population is being studied. Improvements in patient identification would not only provide more accurate epidemiology estimates but would also enable a more precise estimation of the humanistic burden, healthcare resource utilisation, and cost of NMOSD. Our objective was to develop, test, and validate the performance of a healthcare claims–based algorithm to identify patients with NMOSD.

2. Methods

2.1. Algorithm development

Through structured cognitive interviews with 3 expert neurologists (SC, BG, ML) with extensive experience in diagnosing and treating patients with NMOSD, MOGAD, and MS, we developed 21 candidate algorithms that use data available in healthcare claims datasets to identify patients with NMOSD (Fig. 1). We conducted 2 structured interviews with each neurologist: one to review physician coding practices for the diagnoses of interest, (from which we developed the algorithm logic,) and a second to elicit the physicians' opinions on this logic. These interviews included information on NMOSD diagnosis, routine and acute management, and management of chronic complications or conditions. We also discussed relevant inclusion and exclusion criteria to avoid including patients with MOGAD or MS. Several criteria were considered but ultimately not included in the candidate algorithms based on expert consensus that these criteria would not improve the algorithm's performance.

2.2. Testing internal validity of candidate algorithms using clinic billing data

We tested the performance of each candidate algorithm using patient medical records composed of clinic billing data containing only *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes and medications. We collected data between November 1, 2016, and October 19, 2021, from a purposive sample of 101 adults with NMOSD, MOGAD, or MS. The collected data included diagnosis dates, medications used, *ICD-10-CM* codes for NMOSD and MS from the outpatient clinic (MOGAD has no *ICD-10-CM* code), and patient demographics. The latest physician-determined diagnosis of NMOSD (including AQP4 IgG serostatus), MS, or MOGAD based on published clinical criteria was considered the criterion standard diagnosis [6,18,19]. Internal validity was assessed by comparing available billing data, as a proxy for insurance claims, to the physician's diagnosis derived from medical records.

These data were collected from 5 geographically diverse neurology clinics across the United States (OR, MA, PA, TX, and WA), including 3 neurology clinics affiliated with the previously mentioned experts. The medical record review portion of this study was approved by a central institutional review board (IRB; Western IRB, tracking number

Fig. 1. Methods.
MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder.
[a] Assessed by comparing available billing data to the latest physician-determined diagnosis of NMOSD, MOGAD, or MS.

20202935) and met the requirements for a waiver of consent under 45 CFR 46.116 (d). Eligible patients were adults treated at their site for at least 2 years prior to their most recent visit date, which had to be within 2 years of study end (i.e., the site's IRB approval date). Patients were required to have at least 1 visit per 12-month period (Appendix Fig. 1).

Given their clinical similarities, we recognised that it would be difficult to distinguish patients with MOGAD from those with NMOSD. Thus, we included a larger proportion of patients with MOGAD than would be expected based on known prevalence to ensure that we would be able to assess the algorithm's performance in distinguishing the MOGAD and NMOSD populations.

We calculated algorithm sensitivity and specificity. The best-performing algorithm was chosen based on a combination of high specificity and sensitivity. Given our purposely oversampled MOGAD population, we also performed a subgroup analysis to test performance excluding the MOGAD population.

2.3. Testing face validity of best-performing algorithm using healthcare claims data

We tested the best-performing algorithm's face validity using administrative claims data from the IBM® MarketScan® Commercial and Medicare Supplemental Databases from January 1, 2016, to December 31, 2019. The MarketScan® data have information on health services for over 37.9 million patients through privately insured fee-for-service, point-of-service, or capitated health plans and the healthcare experience of individuals with Medicare supplemental insurance paid for by employers. These databases contain enrolment information and administrative claims data with healthcare utilisation information (e.g., inpatient and outpatient services, prescription drug claims). The administrative claims portion of the study used deidentified patient records and did not involve the collection, use, or transmittal of individually identifiable data; therefore, IRB review was not necessary.

Prevalent (existing or newly diagnosed) adult patients with NMOSD who were identified using the algorithm were required to have ≥1 year of continuous enrolment after a qualifying *ICD-10-CM* diagnosis code (NMO: G36.0; TM: G37.3; ON: H46.1×, H46.8, H46.9) during the study period. Patient demographics, health insurance type, and clinical characteristics (including the Charlson Comorbidity Index score, concurrent diagnoses, medications, and diagnostic testing) were assessed [20,21].

To the extent possible, we followed the modified Standards for Reporting of Diagnostic Accuracy criteria [10]. All statistical analyses were performed using SAS, version 9.4 (Cary, NC).

3. Results

3.1. Algorithm development

We developed 21 algorithms, including a primary algorithm and 20 iterations with all possible combinations of the inclusion and exclusion criteria. The neurology experts reported that all patients with NMOSD would be taking a chronic immunosuppressive drug for prevention of NMOSD attacks and that 1 instance of an NMOSD drug code when paired with a diagnosis code of NMO (G36.0) would be sufficient to identify patients with NMOSD. They proposed that a diagnosis code for TM or ON alone when paired with an NMOSD drug could indicate uncertainty regarding the patient's diagnosis and thus would not be reliable in identifying patients with NMOSD. Instances of NMOSD diagnosis codes separated by at least 90 days were included to capture the rare occasions when a patient's medications may not be available in claims data. The exclusion criteria were MS diagnosis or use of an MS-specific drug after the last NMO diagnosis or NMOSD drug, sarcoidosis diagnosis after the last NMO diagnosis, or use of ≥1 immune checkpoint inhibitor. As the algorithm was designed for adults, a prerequisite for inclusion was an age of ≥18 years. The inclusion criteria consisted of (≥1 NMO diagnosis [or ≥ 1 TM and ≥ 1 ON diagnosis] and ≥ 1 NMOSD drug) or (≥2 NMO diagnoses ≥90 days apart). The best-performing algorithm is outlined in Fig. 2.

3.2. Testing internal validity of candidate algorithms using clinic billing data

We tested the algorithm's performance using the medical records of 50 patients who met consensus criteria for NMOSD, 30 with MS, and 21 with MOGAD. The mean (SD) age of patients with NMOSD was 50.1 (16.5) years, and 78.0% were female (Table 1). Of the patients with NMOSD, 40 were AQP4-IgG+ and 10 were AQP4-IgG−. No patients with a history of sarcoidosis or immune checkpoint inhibitor use were identified, likely due to the relative rarity of patients with these characteristics, which were included in the final algorithm due to clinical recommendations of the practicing neurologists. Most patients (96.0%) with NMOSD had a diagnosis code for NMO, all patients with MS had a diagnosis code for MS, and 85.7% and 23.8% of patients with MOGAD had diagnosis codes for NMOSD and MS, respectively (Table 1).

The algorithm demonstrated 82.0% sensitivity and 70.6% specificity in the medical record data (Table 2). In the subgroup analysis excluding the MOGAD cohort, the sensitivity was 82.0% and the specificity was 96.7%. We identified 9 false-negative patients. Among them, 3 did not meet criteria for the algorithm numerator (i.e., ≥1 NMO diagnosis [or ≥ 1 TM and ≥ 1 ON diagnosis] and ≥ 1 NMOSD drug; or ≥ 2 NMO diagnoses ≥90 days apart) and 6 met the numerator criteria but were excluded due to either a diagnosis of MS or taking an MS drug after the last NMO diagnosis or NMOSD drug (Supplemental Table 1).

3.3. Testing face validity of best-performing algorithm using healthcare claims data

In the administrative healthcare claims data, 960 patients with commercial or Medicare supplemental insurance met the inclusion criteria based on the diagnosis in their claim. Among them, 382 patients met the remaining algorithm criteria and were identified as having NMOSD (Appendix Fig. 2). The mean (SD) age of patients in the sample was 46.2 (13.3) years, and 83.0% were female (Table 3). Nearly all patients (99.2%) had at least 1 claim for NMO. Clinical characteristics defining or reported to be associated with NMOSD were observed with variable frequency (Table 4). MRI was performed in over half of the patients identified (52.9%), and less than half of patients (42.9%) had evidence of receiving at least 1 medication for NMOSD (Table 5).

4. Discussion

While prior studies assessed comorbidities and healthcare resource use in patients with NMOSD [15], they did not use a validated diagnostic algorithm. We tested algorithms, developed through a series of cognitive interviews with neurologists, using 2 data sources. In medical records (a proxy for administrative claims data), the algorithms developed in this study performed well, with a sensitivity of 82.0% and specificity ranging from 70.6% when considering patients with NMOSD, MS, and MOGAD to 96.7% when considering only patients with NMOSD and MS. In healthcare claims data, sex, age, and other key clinical characteristics of patients identified as having NMOSD aligned with those reported in the literature [22]. The initial tests suggested that the best-performing algorithm is capable of accurately identifying patients with NMOSD. This algorithm was developed with clinical input from expert neurologists. It included patients with (≥1 NMO diagnosis [or ≥ 1 TM and ≥ 1 ON diagnosis] and ≥ 1 NMOSD drug) or (≥2 NMO diagnoses ≥90 days apart) and excluded those with an MS diagnosis or use of an MS-specific drug after the last NMO diagnosis or NMOSD drug, a sarcoidosis diagnosis after the last NMO diagnosis, or use of ≥1 immune checkpoint inhibitor.

Validation is recognised as a key component of research using health administrative data [10]. The results of this validation study may allow

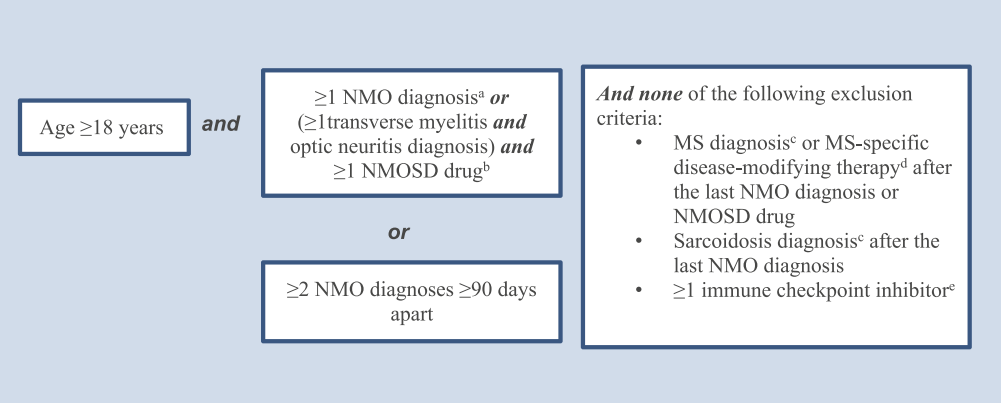

Fig. 2. NMOSD algorithm.
ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis; TM = transverse myelitis.
[a] All inclusion diagnosis codes are from *ICD-10-CM* (NMO: G36.0; TM: G37.3; ON: H46.1×, H46.8, H46.9).
[b] Azathioprine, bortezomib, eculizumab, inebilizumab, mycophenolate mofetil, rituximab, satralizumab, and tocilizumab.
[c] All exclusion diagnosis codes are from *ICD-10-CM* (MS: G35; sarcoidosis: D86.xx).
[d] Alemtuzumab, interferon beta, cladribine, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, siponimod, and teriflunomide.
[e] Atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, and pembrolizumab.

Table 1
Demographic and clinical characteristics of patients in medical record sample.

	NMOSD	MS	MOGAD	All patients
Patients, n (%)	50 (49.5)	30 (29.7)	21 (20.8)	101 (100)
Age at last clinic visit, mean (SD), years	50.1 (16.5)	49.5 (11.9)	41.4 (11.4)	48.1 (14.6)
Female, n (%)	39 (78.0)	22 (73.3)	11 (52.4)	72 (71.3)
Race, n (%)				
White	26 (52.0)	29 (96.7)	15 (71.4)	70 (69.3)
Black or African American	11 (22.0)	0 (0)	3 (14.3)	14 (13.9)
Asian	1 (2.0)	0 (0)	0 (0)	1 (1.0)
Unclear or unknown	12 (24.0)	1 (3.3)	3 (14.3)	16 (15.8)
Hispanic, Latino, or Spanish origin, n (%)	2 (4.0)	0 (0)	4 (19.0)	6 (5.9)
Follow-up/study period, mean (SD), days	874 (144.7)	871 (133.0)	857 (112.6)	870 (134.0)
ICD-10 CM code, n (%)[a]				
NMO	48 (96.0)	1 (3.3)	18 (85.7)	67 (66.3)
MS	11 (22.0)	30 (100.0)	5 (23.8)	46 (45.5)
TM	8 (16.0)	3 (10.0)	2 (9.5)	13 (12.9)
ON	7 (14.0)	2 (6.7)	12 (57.1)	21 (20.8)
Use of any NMOSD drug[b]	44 (88.0)	5 (16.7)	19 (90.5)	68 (67.3)
Use of any MS-specific disease-modifying therapy[c]	1 (2.0)	22 (73.3)	1 (4.8)	24 (23.8)

ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis; TM = transverse myelitis.
[a] Includes all *ICD-10-CM* codes during the study period.
[b] Azathioprine, eculizumab, mycophenolate mofetil, rituximab, and tocilizumab. Inebilizumab and satralizumab were approved by the US Food and Drug Administration after the study period and therefore had no observed use in the NMOSD cohort, as expected. Bortezomib also had no observed use in the cohort.
[c] Alemtuzumab, interferon beta, cladribine, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, siponimod, and teriflunomide.

researchers who use this algorithm in the future to better estimate the accuracy of their results in healthcare claims. The sensitivity of this algorithm was higher than that of many published algorithms. We are unaware of any other validated algorithm for NMOSD to which we could compare our results. Quan et al. investigated the sensitivity of *ICD-10-CM* codes using medical records as a criterion standard for 32 conditions and found that sensitivity ranged from 12.7% for weight loss to 80.8% for metastatic cancer [23]. The sensitivity of 82% measured with this algorithm was higher than that of the highest condition in the Quan et al. study. While we used the latest physician-determined diagnosis of NMOSD (including AQP4 IgG serostatus), MS, or MOGAD, among the 9 false-negative patients, 6 met the algorithm numerator criteria (i.e., ≥1 NMO diagnosis [or ≥ 1 TM and ≥ 1 ON diagnosis] and ≥ 1 NMOSD drug; or ≥ 2 NMO diagnoses ≥90 days apart) but were excluded due to either having a diagnosis of MS or taking an MS drug after the last NMO diagnosis or NMOSD drug (Supplemental Table 1). Non-physicians

Table 2
Algorithm performance using medical records including and excluding patients with MOGAD.

	Total patients, n	Sensitivity, %	Specificity, %
Medical records[a]			
All patients	101	82.0	70.6
Excluding patients with MOGAD	80	82.0	96.7

MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease.
[a] Proxy for healthcare claims datasets.

Table 3
Demographics of patients in healthcare claims data.

	Patients with NMOSD $n = 382$
Age, mean (SD), years	46.2 (13.3)
Female, n (%)	317 (83.0)
Region, n (%)	
Midwest	74 (19.4)
Northeast	79 (20.7)
South	177 (46.3)
West	51 (13.4)
Insurance type	
Commercial	357 (93.5)
Medicare	25 (6.5)

NMOSD = neuromyelitis optica spectrum disorder.

Table 4
Clinical characteristics of patients in healthcare claims data.

	Patients with NMOSD n = 382
Charlson comorbidity index, mean (SD)	1.2 (2.0)
No. of chronic conditions, mean (SD)	4.6 (2.4)
Concurrent diagnoses observed, n (%)	
Neuromyelitis optica	379 (99.2)
Optic neuritis	107 (28.0)
Acute myelitis	65 (17.0)
Cerebrospinal fluid abnormalities	1 (0.3)
Microcystic macular oedema	4 (1.0)
Hiccups or nausea/vomiting	47 (12.3)
Symptomatic narcolepsy	1 (0.3)
Type I diabetes	5 (1.3)
Rheumatoid arthritis	19 (5.0)
Sjogren's syndrome	17 (4.5)
Systemic lupus erythematosus	23 (6.0)
Autoimmune thyroiditis	7 (1.8)
Myasthenia gravis	7 (1.8)
Ulcerative colitis	2 (0.5)

NMOSD = neuromyelitis optica spectrum disorder.

Table 5
NMOSD diagnostic testing and treatment in claims data.

	Patients with NMOSD, n (%) n = 382
Magnetic resonance imaging use	202 (52.9)
Received high-dose IV methylprednisolone	142 (37.2)
Oral corticosteroid use	158 (41.4)
Plasma exchange	24 (6.3)
Intravenous immunoglobulin	10 (2.6)
NMOSD medication use[a]	164 (42.9)
Azathioprine	44 (11.5)
Eculizumab	2 (0.5)
Mycophenolate mofetil	69 (18.1)
Rituximab	60 (15.7)
Tocilizumab	5 (1.3)

FDA = US Food and Drug Administration; IV = intravenous; NMOSD = neuromyelitis optica spectrum disorder.

[a] Inebilizumab and satralizumab were approved by the FDA after the study period and therefore had no observed use in the NMOSD cohort, as expected. Eculizumab was approved by the FDA in June 2019 and subsequently had little use in the NMOSD cohort.

commonly perform the coding for billing in offices, which could explain this inconsistency. Positive predictive value and negative predictive value were not included in the analysis given that the sample was non-random.

We included 7 patients with MOGAD for every 10 with MS; this is a much higher ratio than would be seen in a random sample. The incidence and prevalence of MOGAD are largely unknown, although studies in Europe suggest that the incidence is between 1.6 and 3.4 per 1,000,000 person-years and tends to be higher in children [24,25]. The 2020 global prevalence of MS was 35.9 per 100,000 people [26]. The overrepresentation of the MOGAD population in our sample reduced the algorithm's specificity but allowed us to judge its performance in a key population. Unsurprisingly, given the clinical similarities and lack of an *ICD* diagnosis code for MOGAD, NMOSD and MOGAD could not be distinguished with *ICD* codes alone. We recommend using claims enriched with laboratory data (e.g., cell-based assays for anti–AQP4-IgG and anti–MOG-IgG). We estimated that the algorithm's true performance will likely be closer to that in the subgroup analysis without the MOGAD population because of the relative rarity of MOGAD in the general population.

Given the lack of a previously validated algorithm for NMOSD, there is no direct comparison for the claims validation results. However, to assess the algorithm's face validity when comparing to the literature more broadly, patient demographics, clinical characteristics, and diagnostic testing and treatment among patients with NMOSD identified in claims were consistent with reported results in studies where the condition was identified by clinicians. For example, we found that 83% of our study sample was female (i.e., a sex ratio of 4.8 to 1), which reflects the higher prevalence among females compared to males (2.3–7.6× higher) reported in a global systematic review [27] and is consistent with the ratio of >3:1 reported globally [28]. Further, patients with NMOSD in our study had a mean age of 46 years, consistent with the global peak prevalence of NMOSD, reported to be between 40 and 49 years of age [27].

The mean age observed in our study was consistent with the range of 42 to 47 years in other claims analyses using unvalidated algorithms, while the proportion of female patients was higher than the range of 58% to 77% [15,17,29–32]. The variation in observations emphasises the need to use a validated algorithm to identify NMOSD in claims. In addition, core clinical characteristics of ON and TM were frequently observed in our claims-identified NMOSD cohort, and an NMO diagnosis itself was found in nearly all (>99%) patients. The high prevalence of co-existing autoimmune diseases is also consistent with the prevalence in the literature [33–35]. In addition, we observed steroid use to be common and consistent with its use as a treatment for disease exacerbations [30,36]. However, use of NMOSD medication, while present in more than two-fifths of patients, would be indicated for all patients with NMOSD. There are a few possible explanations for this discrepancy. First, patients may have received medications in the inpatient setting, which may not be identified in the bundled billing of inpatient stays [37], or through patient assistance programs [38]. Second, this patient population reflects a mix of patients with different stages of NMOSD, some of whom may have been newly diagnosed and not yet begun treatment. Third, the medical record review, which demonstrated that 88% of patients with NMOSD were on an NMOSD medication, was conducted at clinics led by NMOSD experts who are more likely to provide evidence-based care. In a population-based sample, fewer patients may be receiving the appropriate medications to treat NMOSD [39].

4.1. Study implications for NMOSD claims research

In health economics and outcomes claims research, misclassification and misidentification of patients have important consequences. For example, when applying the algorithm to an exploratory analysis of the economic burden in patients with NMOSD, we estimated that 44.2% of patients experienced hospitalisation in the year after diagnosis while another study, using a different, unvalidated algorithm, found that 22.4% of patients were hospitalised [15]. Similarly, a more recent claims study using data from 2014 to 2018 found that the mean total cost in the year after NMOSD diagnosis was $29,054 compared with $94,945 in our study [31]. Another recent NMOSD study that analysed 2014–2019 claims data, using a different algorithm that was also unvalidated, estimated a mean total annualised cost of $60,599 in patients with NMOSD [30]. Thus, the use of multiple unvalidated algorithms can lead to widely different estimates of the clinical and economic burden in patients with NMOSD.

4.2. Limitations

This study has limitations. First, in developing and testing the algorithm, we used data from outpatient clinics only. Therefore, we were unable to capture information from inpatient or other settings. Off-site care, including imaging studies, procedures, and laboratory tests, may not have been thoroughly documented in the patient charts at the study sites. The algorithm's true performance could be better when using a full healthcare claims record. Second, we did not represent the full range of demyelination conditions. Other causes of CNS inflammation, including infectious, autoimmune, and paraneoplastic phenomena, were not excluded in the algorithm; some may mimic NMOSD, potentially leading

to false positives. Third, since medication data were collected from medical records and not from pharmacy claims when pharmacy claims were less comprehensive (e.g., when a patient paid for medication out-of-pocket), accuracy could be overstated.

Fourth, this study includes a purposive sample of patients rather than a random sample; as a result, positive predictive value and negative predictive value were not included in the analysis. Additionally, the specificity of the algorithm will be affected by the inclusion of a higher relative proportion of patients with MOGAD versus MS. If the MS population were larger, as would be expected in a random sample, the number of both false positives and false negatives might also be higher. However, we decided to oversample rare conditions (NMOSD and MOGAD) to have a reasonable sample size of these patients to test our algorithms, rather than to match the real-world prevalence of the 3 conditions. Furthermore, given the clinical similarities and lack of an *ICD* diagnosis code for MOGAD, NMOSD and MOGAD could not be distinguished using *ICD* codes alone. In certain geographic areas, the prevalence of MOGAD is higher than that of NMOSD, which could lead to more false positives [7,40]. A random sample would provide more accurate validation statistics, but it would require a larger sample size than we were able to include in the study. We do not plan to repeat the medical record review with a larger sample size.

Additionally, this study tested the proposed algorithm using both medical records and healthcare claims data. We had access to the standard diagnostic criteria in medical records but not in healthcare claims data. In the healthcare claims analysis, we could not identify true positive or negatives, so we instead assessed the algorithm's face validity by comparing the demographic and clinical characteristics of the identified population to those of known NMOSD populations. This method was limiting given that age at peak prevalence was difficult to estimate and had a high standard deviation (13.3%). Furthermore, only 28% of patients had a claim for ON and 17% for TM, and relatively few patients (<50%) were on an immunosuppressant. Finally, the care provided and coding practices at the 5 highly specialized centres from which our data were derived may not be broadly representative of US practices; this may falsely inflate the sensitivity and specificity of our NMOSD algorithm.

5. Conclusions

This clinically-derived algorithm performed well in identifying true AQP4-IgG+ and AQP4-IgG− patients with NMOSD. When tested using healthcare claims data, demographics and clinical characteristics were consistent with previous clinical findings. When used in an insurance claims database, this algorithm will enable a more accurate estimation of NMOSD disease burden, including a better understanding of related cost, healthcare resource utilisation, and disease-modifying treatment patterns.

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Anisha M. Patel: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Alex Exuzides:** Writing – review & editing, Methodology, Conceptualization. **Irina Yermilov:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Hannah Dalglish:** Writing – review & editing, Writing – original draft, Project administration. **Sarah N. Gibbs:** Writing – review & editing, Formal analysis. **Sheila R. Reddy:** Writing – review & editing, Methodology, Formal analysis. **Eunice Chang:** Writing – review & editing, Formal analysis. **Caleb Paydar:** Writing – review & editing, Formal analysis. **Stanley Cohan:** Writing – review & editing, Methodology, Formal analysis. **Benjamin Greenberg:** Writing – review & editing, Methodology, Formal analysis. **Michael Levy:** Writing – review & editing, Methodology, Formal analysis.

Declaration of competing interest

The authors declare financial and other relationships that may be considered potential competing interests. These are also reflected in the completed ICMJE forms.

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References

[1] Mayo Clinic Staff, Neuromyelitis optica - Symptoms and causes. https://www.mayoclinic.org/diseases-conditions/neuromyelitis-optica/symptoms-causes/syc-20375652, 2024 (accessed 15 December 2022).

[2] H. Yokote, H. Mizusawa, Multiple sclerosis and neuromyelitis optica spectrum disorders: some similarities in two distinct diseases, Neural Regen. Res. 11 (2016) 410–411, https://doi.org/10.4103/1673-5374.179048.

[3] Neuromyelitis Optica Spectrum Disorder & MOG Associated Disease, MS Aware. Clevel. Clin. Abu Dhabi. https://multiplesclerosis.clevelandclinicabudhabi.ae/nmo-and-mogad/, 2024 (accessed 15 December 2022).

[4] M.A. Mealy, S.E. Mossburg, S.-H. Kim, S. Messina, N. Borisow, R. Lopez-Gonzalez, J.P. Ospina, M. Scheel, A.K. Yeshokumar, A. Awad, M.I. Leite, J.A. Jimenez Arango, F. Paul, J. Palace, H.J. Kim, M. Levy, Long-term disability in neuromyelitis optica spectrum disorder with a history of myelitis is associated with age at onset, delay in diagnosis/preventive treatment, MRI lesion length and presence of symptomatic brain lesions, Mult. Scler. Relat. Disord. 28 (2019) 64–68, https://doi.org/10.1016/j.msard.2018.12.011.

[5] W. Huang, J. ZhangBao, X. Chang, L. Wang, C. Zhao, J. Lu, M. Wang, X. Ding, Y. Xu, L. Zhou, D. Li, M.K. Behne, J.M. Behne, M.R. Yeaman, E. Katz, C. Lu, C. Quan, Neuromyelitis optica spectrum disorder in China: quality of life and medical care experience, Mult. Scler. Relat. Disord. 46 (2020) 102542, https://doi.org/10.1016/j.msard.2020.102542.

[6] D.M. Wingerchuk, B. Banwell, J.L. Bennett, P. Cabre, W. Carroll, T. Chitnis, J. de Seze, K. Fujihara, B. Greenberg, A. Jacob, S. Jarius, M. Lana-Peixoto, M. Levy, J. H. Simon, S. Tenembaum, A.L. Traboulsee, P. Waters, K.E. Wellik, B. G. Weinshenker, International consensus diagnostic criteria for neuromyelitis optica spectrum disorders, Neurology 85 (2015) 177–189, https://doi.org/10.1212/WNL.0000000000001729.

[7] J. Yung Hor, N. Asgari, I. Nakashima, S.A. Broadley, M.I. Leite, N. Kissani, A. Jacob, R. Marignier, B.G. Weinshenker, F. Paul, S.J. Pittock, J. Palace, D. M. Wingerchuk, J.M. Behne, M.R. Yeaman, K. Fujihara, Epidemiology of neuromyelitis optica spectrum disorder and its prevalence and incidence worldwide, Front. Neurol. 11 (2020) 501, https://doi.org/10.3389/fneur.2020.00501.

[8] D.M. Wingerchuk, V.A. Lennon, S.J. Pittock, C.F. Lucchinetti, B.G. Weinshenker, Revised diagnostic criteria for neuromyelitis optica, Neurology 66 (2006) 1485–1489, https://doi.org/10.1212/01.wnl.0000216139.44259.74.

[9] D.M. Wingerchuk, W.F. Hogancamp, P.C. O'Brien, B.G. Weinshenker, The clinical course of neuromyelitis optica (Devic's syndrome), Neurology 53 (1999) 1107–1114, https://doi.org/10.1212/wnl.53.5.1107.

[10] E.I. Benchimol, D.G. Manuel, T. To, A.M. Griffiths, L. Rabeneck, A. Guttmann, Development and use of reporting guidelines for assessing the quality of validation studies of health administrative data, J. Clin. Epidemiol. 64 (2011) 821–829, https://doi.org/10.1016/j.jclinepi.2010.10.006.

[11] C. van Walraven, C. Bennett, A.J. Forster, Administrative database research infrequently used validated diagnostic or procedural codes, J. Clin. Epidemiol. 64 (2011) 1054–1059, https://doi.org/10.1016/j.jclinepi.2011.01.001.

[12] C. De Coster, H. Quan, A. Finlayson, M. Gao, P. Halfon, K.H. Humphries, H. Johansen, L.M. Lix, J.-C. Luthi, J. Ma, P.S. Romano, L. Roos, V. Sundararajan, J. V. Tu, G. Webster, W.A. Ghali, Identifying priorities in methodological research using ICD-9-CM and ICD-10 administrative data: report from an international consortium, BMC Health Serv. Res. 6 (2006) 77, https://doi.org/10.1186/1472-6963-6-77.

[13] P. Huston, C.D. Naylor, Health services research: reporting on studies using secondary data sources, CMAJ Can. Med. Assoc. J. 155 (1996) 1697–1709.

[14] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Oncology Center of Excellence, Real-world data: assessing electronic health records and medical claims data to support regulatory decision-making for drug and biological products. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory, 2021 (accessed 15 December 2022).

[15] M.R. Ajmera, A. Boscoe, J. Mauskopf, S.D. Candrilli, M. Levy, Evaluation of comorbidities and health care resource use among patients with highly active neuromyelitis optica, J. Neurol. Sci. 384 (2018) 96–103, https://doi.org/10.1016/j.jns.2017.11.022.

[16] C. Costantino, Identifying patients with neuromyelitis optica spectrum disorder in US insurance claims database from 2001 To 2007 (2019) Poster Presented at ECTRIMS September 2019, Stockholm, Sweden, Poster, 2024, p. 408.

[17] A. Exuzides, N. Wu, D. Sheinson, C. Flores Avile, C. Costantino, P. Sidiropoulos, Identification and temporal trends of patients with neuromyelitis optica spectrum disorder in a US insurance claims database, J. Med. Econ. 24 (2021) 581–588, https://doi.org/10.1080/13696998.2021.1917421.

[18] A.J. Thompson, B.L. Banwell, F. Barkhof, W.M. Carroll, T. Coetzee, G. Comi, J. Correale, F. Fazekas, M. Filippi, M.S. Freedman, K. Fujihara, S.L. Galetta, H. P. Hartung, L. Kappos, F.D. Lublin, R.A. Marrie, A.E. Miller, D.H. Miller, X. Montalban, E.M. Mowry, P.S. Sorensen, M. Tintoré, A.L. Traboulsee, M. Trojano, B.M.J. Uitdehaag, S. Vukusic, E. Waubant, B.G. Weinshenker, S.C. Reingold, J. A. Cohen, Diagnosis of multiple sclerosis: 2017 Revisions of the McDonald criteria, Lancet Neurol. 17 (2018) 162–173, https://doi.org/10.1016/S1474-4422(17)30470-2.

[19] S. Jarius, F. Paul, O. Aktas, N. Asgari, R.C. Dale, J. De Seze, D. Franciotta, K. Fujihara, A. Jacob, H.J. Kim, I. Kleiter, T. Kümpfel, M. Levy, J. Palace, K. Ruprecht, A. Saiz, C. Trebst, B.G. Weinshenker, B. Wildemann, MOG encephalomyelitis: international recommendations on diagnosis and antibody testing, J. Neuroinflammation 15 (2018) 134, https://doi.org/10.1186/s12974-018-1144-2.

[20] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (1987) 373–383.

[21] R.A. Deyo, D.C. Cherkin, M.A. Ciol, Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases, J. Clin. Epidemiol. 45 (1992) 613–619.

[22] C. Glisson, F. Gonzalez-Scarano, J. Dashe, Neuromyelitis optica spectrum disorders (NMOSD): Clinical features and diagnosis. https://www.uptodate.com/contents/neuromyelitis-optica-spectrum-disorder-nmosd-clinical-features-and-diagnosis, 2022.

[23] H. Quan, B. Li, L. Duncan Saunders, G.A. Parsons, C.I. Nilsson, A. Alibhai, W.A., Ghali, for the IMECCHI investigators, assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database: assessing validity of ICD-9-CM and ICD-10, Health Serv. Res. 43 (2008) 1424–1441, https://doi.org/10.1111/j.1475-6773.2007.00822.x.

[24] K. O'Connell, A. Hamilton-Shield, M. Woodhall, Prevalence and incidence of neuromyelitis optica spectrum disorder, aquaporin-4 antibody-positive NMOSD and MOG antibody-positive disease in Oxfordshire, UK, J. Neurol. Neurosurg. Psychiatry 91 (2020) 1126–1128, https://doi.org/10.1136/jnnp-2020-323158.

[25] C. de Mol, Y. Wong, E. van Pelt, B. Wokke, T. Siepman, R. Neuteboom, D. Hamann, R. Hintzen, The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults, Mult. Scler. Houndmills Basingstoke Engl. 26 (2020) 806–814, https://doi.org/10.1177/1352458519845112.

[26] C. Walton, R. King, L. Rechtman, W. Kaye, E. Leray, R.A. Marrie, N. Robertson, N. La Rocca, B. Uitdehaag, I. van der Mei, M. Wallin, A. Helme, C. Angood Napier, N. Rijke, P. Baneke, Rising prevalence of multiple sclerosis worldwide: insights from the atlas of MS, third edition, Mult. Scler. Houndmills Basingstoke Engl. 26 (2020) 1816–1821. doi:https://doi.org/10.1177/1352458520970841.

[27] V. Papp, M. Magyari, O. Aktas, T. Berger, S.A. Broadley, P. Cabre, A. Jacob, J. Kira, M.I. Leite, R. Marignier, K. Miyamoto, J. Palace, A. Saiz, M. Sepulveda, O. Sveinsson, Z. Illes, Worldwide incidence and prevalence of NMO: A systematic review, Neurology (2020) 59–77, https://doi.org/10.1212/WNL.0000000000011153.

[28] D.M. Wingerchuk, Neuromyelitis optica: effect of gender, J. Neurol. Sci. 286 (2009) 18–23, https://doi.org/10.1016/j.jns.2009.08.045.

[29] A. Exuzides, D. Sheinson, P. Sidiropoulos, F. Magrini, S. Gholizadeh, A. Surinach, L. Cook, C.S. Meyer, M. Yeaman, Burden and cost of comorbidities in patients with neuromyelitis optica spectrum disorder, J. Neurol. Sci. 427 (2021) 117530, https://doi.org/10.1016/j.jns.2021.117530.

[30] M. Royston, A. Kielhorn, D. Weycker, M. Shaff, L. Houde, I. Tanvir, S. Bhattacharyya, M. Levy, Neuromyelitis optica spectrum disorder: clinical burden and cost of relapses and disease-related care in US clinical practice, Neurol. Ther. 10 (2021) 767–783, https://doi.org/10.1007/s40120-021-00253-4.

[31] A. Exuzides, D. Sheinson, P. Sidiropoulos, S. Gholizadeh, F. Magrini, A. Surinach, L. Cook, C.S. Meyer, M.R. Yeaman, The costs of care from a US claims database in patients with neuromyelitis optica spectrum disorder, J. Neurol. Sci. 427 (2021) 117553, https://doi.org/10.1016/j.jns.2021.117553.

[32] R.K. Knapp, F. Hardtstock, T. Wilke, U. Maywald, B. Deiters, S. Schneider, J. Mouchet, Evaluating the economic burden of relapses in neuromyelitis optica spectrum disorder: a real-world analysis using German claims data, Neurol. Ther. 11 (2022) 247–263, https://doi.org/10.1007/s40120-021-00311-x.

[33] M.I. Leite, E. Coutinho, M. Lana-Peixoto, S. Apostolos, P. Waters, D. Sato, L. Melamud, M. Marta, A. Graham, J. Spillane, A.M. Villa, D. Callegaro, E. Santos, A.M. da Silva, S. Jarius, R. Howard, I. Nakashima, G. Giovannoni, C. Buckley, D. Hilton-Jones, A. Vincent, J. Palace, Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients, Neurology 78 (2012) 1601–1607, https://doi.org/10.1212/WNL.0b013e31825644ff.

[34] A. Iyer, L. Elsone, R. Appleton, A. Jacob, A review of the current literature and a guide to the early diagnosis of autoimmune disorders associated with neuromyelitis optica, Autoimmunity 47 (2014) 154–161, https://doi.org/10.3109/08916934.2014.883501.

[35] S.J. Pittock, V.A. Lennon, J. de Seze, P. Vermersch, H.A. Homburger, D. M. Wingerchuk, C.F. Lucchinetti, H. Zéphir, K. Moder, B.G. Weinshenker, Neuromyelitis optica and non organ-specific autoimmunity, Arch. Neurol. 65 (2008) 78–83, https://doi.org/10.1001/archneurol.2007.17.

[36] J. Beekman, A. Keisler, O. Pedraza, M. Haramura, A. Gianella-Borradori, E. Katz, J. N. Ratchford, G. Barron, L.J. Cook, J.M. Behne, T.F. Blaschke, T.J. Smith, M. R. Yeaman, Neuromyelitis optica spectrum disorder: patient experience and quality of life, Neurol. Neuroimmunol. Neuroinflammation 6 (2019) e580, https://doi.org/10.1212/NXI.0000000000000580.

[37] Billing and Coding, Rituximab (A56380). https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56380&ver=44&, 2024 (accessed 21 December 2023).

[38] Inc Genentech, Explore Rituxan financial assistance programs | Rituxan immunology access solutions. https://www.genentech-access.com/hcp/brands/rituxan-ra/find-patient-assistance.html, 2024. (Accessed 21 December 2023).
[39] J.K. Elrod, J.L. Fortenberry, Centers of excellence in healthcare institutions: what they are and how to assemble them, BMC Health Serv. Res. 17 (2017) 425, https://doi.org/10.1186/s12913-017-2340-y.
[40] R. Orlandi, S. Mariotto, A. Gajofatto, Prevalence, incidence, and season distribution of MOG antibody-associated disease in the province of Verona, Italy, Mult. Scler. Relat. Disord. 63 (2022) 103884, https://doi.org/10.1016/j.msard.2022.103884.