Multiple Sclerosis and Related Disorders 37 (2020) 101488

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Validation of claims-based diagnoses of adult and pediatric neuromyelitis optica spectrum disorder and variations in diagnostic evaluation and treatment initiation

Sabrina Gmuca[a,b,c,d,*], Duriel I Hardy[e], Sona Narula[b,e], Sharon Stoll[f,g], Julia Harris[h,i], Yongdong Zhao[j,k], Rui Xiao[l], Pamela F. Weiss[a,b,c], Amy T. Waldman[b,e], Jeffrey S. Gerber[b,m]

[a] Department of Pediatrics, Division of Rheumatology, Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia, PA, 19104, United States
[b] Perelman School of Medicine at University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA, 19104, United States
[c] Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Roberts Center for Pediatric Research, Philadelphia, PA,19146, United States
[d] PolicyLab, Children's Hospital of Philadelphia, Roberts Center for Pediatric Research, Philadelphia, PA, 19146, United States
[e] Department of Pediatric, Division of Neurology, Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia PA, 19104, United States
[f] Department of Neurology, Yale New Haven Hospital, 20 York St. New Haven, CT, 06519, United States
[g] Yale School of Medicine, 333 Cedar St, New Haven, CT, 06510, United States
[h] University of Missouri-Kansas City School of Medicine, 2411 Holmes St, Kansas City MO, 64108, United States
[i] Department of Pediatrics, Division of Rheumatology, Children's Mercy Kansas City, 2401 Gillham Road, Kansas City MO, 64108, United States
[j] Department of Pediatrics, Division of Rheumatology, Seattle Children's Hospital, 4800 Sand Point Way NE, Seattle, Washington, 98105, United States
[k] University of Washington School of Medicine, 1959 NE Pacific Street, Seattle, WA 98195, United States
[l] Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine at University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA,19104, United States
[m] Department of Pediatrics, Division of Infectious Disease, Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia PA, 19014, United States

ARTICLE INFO

Keywords:
Neuromyelitis optica
Neuromyelitis optica spectrum disorder

ABSTRACT

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a rare demyelinating disease in need of more studies to determine effective treatment regimens. The rarity of the disorder, however, makes large randomized-controlled trials challenging. Validation of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code for NMO could facilitate the use of large healthcare claims data for future research. We aimed 1) to determine the positive predictive value (PPV) of the ICD-9-CM code for NMO as well as evaluate case-finding algorithms for the identification of patients with NMO/NMOSD and 2) to compare the evaluation of and treatment for pediatric versus adult patients.

Methods: This was a multicenter retrospective cohort study of patients with ≥ 1 ICD-9 code for NMO seen at 3 pediatric and 2 adult United States medical centers from 2001–2016. Using a standardized data entry form, pediatric and adult neurologists and rheumatologists reviewed patients' medical records to determine whether patients fulfilled the 2006 criteria for NMO and/or the 2015 criteria for NMOSD in order to determine the positive predictive value (PPV) for the ICD-9-CM code. Demographic and clinical information was abstracted from patient medical records to ascertain variables then evaluated in case-based finding algorithms for further identification of patients with true NMO/NMOSD. We also evaluated differences in clinical characteristics between pediatric and adult patients using chi-squared or Fisher's exact tests, as appropriate, to assess for treatment variation.

Results: A single code for NMO had a PPV of 47% across all sites, with significant site variation (0–77%). The best case-finding algorithm included at least 5 codes as well as a documented hospitalization (PPV = =90% for children and PPV = 92% for adults). Children were more likely to be evaluated by a rheumatologist or

Abbreviations: ADHD, attention-deficit hyperactivity disorder; AQP4-IgG, aquaporin-4 immunoglobulin G; CHOP, The Children's Hospital of Philadelphia; CMKC, Children's Mercy Kansas City; CNS, central nervous system; CT, computed tomography; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10, International Classification of Diseases, 10th Revision, Clinical Modification (ICD-9-CM); MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; PPV, positive predictive value; REDCap, Research Electronic Data Capture; SCH, Seattle Children's Hospital; UPHS, University of Pennsylvania Health System; YNHH, Yale New Haven Hospital

* Corresponding author at: Children's Hospital of Philadelphia, Roberts Center for Pediatric Research, 2716 South Street, 11214, Philadelphia, PA 19146, United States.
E-mail address: gmucas@email.chop.edu (S. Gmuca).

https://doi.org/10.1016/j.msard.2019.101488
Received 23 September 2019; Received in revised form 28 October 2019; Accepted 29 October 2019
2211-0348/ Published by Elsevier B.V.

ophthalmologist, undergo magnetic resonance imaging of the orbits, and receive immunosuppressive and biologic agents than their adult counterparts. Rituximab was administered similarly among the two groups.
Conclusion: The ICD-9 code for neuromyelitis optica (NMO) is inaccurate for identification of NMO/NMOSD. Using case-finding algorithms increases the PPV. The initial diagnostic evaluation and treatment of NMOSD differs significantly between children and adults.

1. Introduction

Neuromyelitis optica (NMO), recently renamed neuromyelitis optica spectrum disorder (NMOSD), is rare autoimmune mediated demyelinating disease of the central nervous system (CNS) that preferentially targets the optic nerves and spinal cord, resulting in severe and potentially devastating sequelae. NMOSD is distinct from other neuroinflammatory conditions in that it can be associated with serum aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies. Prior diagnostic criteria for NMO (Wingerchuk et al., 2006) required optic nerve and spinal cord involvement; however, in 2015, new diagnostic criteria were created using nomenclature that defines the unifying term NMO spectrum disorders (NMOSD) and stratifies patients by serologic testing (NMOSD with and without AQP4-IgG) (Wingerchuk et al., 2015). The advent of biologic treatments has provided promising new medications for the treatment of NMOSD, however, further research is warranted to develop evidence-based treatment guidelines.

The rarity of NMOSD makes conducting research in this field challenging. Incidence rates in the general population have ranged from 0.053 to 0.4 per 100,000 per year (Etemadifar et al., 2015; Cabre et al., 2009; Cabrera-Gomez et al., 2009; Asgari et al., 2011; Jacob et al., 2013). Worldwide prevalence of NMOSD ranges from 0.5 to 4.4 cases per 100,000 (Pandit et al., 2015). Given the small number of patients with NMOSD, the feasibility of controlled trials and prospective studies is limited. Retrospective chart reviews of large healthcare databases offer a more practical method for studying this patient cohort. However, in order to effectively use retrospective data, the validation of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) for NMO is imperative. There have been no prior reports of validated methods to accurately identify patients, adult or pediatric, with NMO/NMOSD in electronic medical records.

The primary objective of this study was to determine the proportion of study subjects with at least one documented ICD-9-CM code for NMO (341.0) who met the 2006 and/or 2015 NMO and NMOSD criteria, respectively, in order to validate the ICD-9-CM code via retrospective chart review. Secondary objectives were 1) to determine a case-finding algorithm for identification of patients with NMO/NMOSD, and 2) to compare clinical characteristics (including diagnostic tests, consultations, treatments and co-morbidities) between adult and pediatric patients with a confirmed diagnosis of NMO/NMOSD. Accurate identification of NMOSD would help to describe the clinical epidemiology of this condition, monitor quality of care, and evaluate interventions when using administrative data to this study this patient population.

2. Material and methods

This study received approval by the respective Institutional Review Boards (IRB), with the Children's Hospital of Philadelphia's review board serving as the supervising IRB. We conducted a retrospective cohort study that included medical record review at three pediatric medical centers and two adult medical centers: Children's Hospital of Philadelphia (CHOP), Seattle Children's Hospital (SCH), Children's Mercy Kansas City (CMKC), the University of Pennsylvania Health System (UPHS), and Yale-New Haven Hospital (YNHH). Data included both inpatient and outpatient encounters and eligible patients included all children and adults with at least one ICD-9-CM code indicating "Neuromyelitis optica" (341.0) documented in the electronic medical record between May 1, 2001 and January 1, 2016. Study investigators from each site abstracted medical records using a data abstraction form developed by the principal investigator on the secure, password-protected, web-based application REDCap (Research Electronic Data Capture). Key information extracted from the medical records included demographics (age, gender and year of diagnosis), medications received, clinically relevant co-existing medical conditions and co-morbidities (using ICD-9-CM diagnoses codes), available laboratory results (e.g. aquaporin 4 antibody results) and imaging study results. Each of the criteria of the 2006 and 2015 definitions for NMO and NMOSD were evaluated. The investigators determined which of the 2006 (Wingerchuk et al., 2006) and 2015 criteria (Wingerchuk et al., 2015) for NMO and NMOSD, respectively, each individual patient met. If a patient fulfilled the requisite number of criteria to meet a diagnosis of NMO and/or NMOSD, they were then deemed to have "true NMO/NMOSD."

Validation metrics included positive predictive value (PPV), defined as the proportion of confirmed cases ("true positives") of all patients identified by a test ("test positives"). In this case, our "test" was the ICD-9-CM code for NMO. We evaluated the accuracy of the NMO ICD-9-CM code by calculating the PPV stratified by individual study site. Demographics were summarized by standard descriptive statistics including frequencies and percentages for categorical variables (e.g. sex, race) and by range, median, and interquartile range (IQR) for continuous or count variables. We also determined the additive predictive value of other covariates in addition to the ICD-9-CM code for the identification of NMO/NMOSD. Other covariates included 1) receipt of

Table 1
Identified Subjects with at Least One ICD-9-CM Code for NMO.

	All (n = 219)	CHOP (n = 34)	CMKC (n = 16)	SCH (n = 4)	UPHS (n = 143)	YNHH (n = 22)
Demographics and clinical characteristics						
Age, median (IQR)	39 (17,52)	12 (6,14)	8 (5,13)	12 (11,14)	44 (32, 56)	44 (27,54)
Female, n (%)	167 (76%)	22 (65%)	11 (69%)	4 (100%)	110 (77%)	20 (9%)
White race, n (%)	104 (51%)	18 (53%)	12 (75%)	1 (25%)	63 (44%)	10 (45%)
Positive predictive values						
PPV for NMO/NMOSD	47%	41%	13%	0%	48%	77%
PPV for 2006 NMO criteria	22%	24%	6%	0%	21%	41%
PPV for 2015 NMOSD criteria	44%	41%	13%	0%	45%	73%
PPV for physician diagnosis	67%	41%	25%	50%	75%	91%

Legend. Gold standard is medical chart review demonstrating fulfillment of criteria for NMO and/or NMOSD respectively. IQR = interquartile range. PPV = positive predictive value. CHOP = The Children's Hospital of Philadelphia. SCH = Seattle Children's Hospital. CMKC = Children's Mercy Kansas City. YNHH = Yale-New Haven Hospital. UPHS = the University of Pennsylvania Health System. NMO = neuromyelitis optica. NMOSD = neuromyelitis optica spectrum disorder.

glucocorticoids (oral and/or intravenous within 30 days after the first documented code for NMO), 2) hospitalization at the time of diagnosis (defined as patient being hospitalized within either 30 days before or after the initial code for NMO), 3) encounter with a subspecialist (neurologist, ophthalmologist, and rheumatologist within 6 months prior to or 6 months after the first documented code for NMO), and 4) imaging of the central nervous system (CNS), including computed tomography (CT) scan of the brain, brain magnetic resonance imaging (MRI), spine MRI, or MRI of the orbits. We identified algorithms with the highest PPV for NMO/NMOSD for the overall cohort and also stratified for adults and pediatric patients. In cases where more than one algorithm was found to have a high average PPV, the algorithm with the least number of variables was favored. We used chi-squared tests or Fisher's exact tests, as appropriate, to compare demographic and clinical variables between pediatric and adult patients who met criteria for NMO/NMOSD. We considered $p < 0.05$ statistically significant. All data analyses were performed using STATA 14 (STATA Corp, College Station TX).

3. Results

Data were abstracted for a total of 224 subjects across all 5 sites. Five subjects were excluded from analyses due to missing data. Therefore, a total of 219 subjects with at least one documented ICD-9-CM code for NMO were identified during the study interval across all 5 sites. The proportion of subjects who had ≥ 2 codes was 58% (128/219). Table 1 shows patient demographics, stratified by site. The majority of patients were female (76%), non-Hispanic (96%), and Caucasian (51%). There were 165 adult patients (143 from UPHS and 22 from Yale New-Haven), and 54 pediatric patients (34 from CHOP, 16 from CMKC, and 4 from SCH).

Of the included 219 subjects with at least one documented ICD-9-CM code for NMO, 102 subjects fulfilled the 2006 criteria for NMO and/or the 2015 criteria for NMOSD, for a total PPV of 47% (Table 1). The PPV for NMO/NMOSD was 52% for adult centers, and 30% for pediatric centers ($p < 0.01$). The PPV for fulfillment of the 2006 criteria for NMO was 22% and the PPV for fulfillment of the 2015 criteria for NMOSD was 44%. These PPVs varied significantly based on center ($p < 0.01$). In contrast, upon review of the medical records, 147 subjects had a physician documented diagnosis of NMO/NMOSD for a PPV of 67%.

The majority of subjects who met clinical criteria for NMO/NMOSD were AQP4-IgG positive (74%). For those subjects who did not meet criteria for NMO/NMOSD, 27% ($n = 31$) were AQP4-IgG positive. Regarding PPV stratified AQP4-IgG status, for patients that were AQP4-IgG positive ($n = 120$), the PPV of the code for NMO/NMOSD was 74% (89/120) and for those who were found to be AQP4-IgG negative, the PPV was only 13% (13/99).

We evaluated a number of coding algorithms based on information typically evaluable from administrative healthcare claims data in order to better identify subjects with NMO/NMOSD (Table 2). For both pediatric and adult patients, an increasing number of ICD-9-CM codes

Table 2
Positive predictive value (PPV) for case-finding algorithms for NMO/NMOSD clinical criteria.

	Combined PPV ($n = 219$)	Pediatric PPV ($n = 54$)	Adult PPV ($n = 165$)
ICD-9 code 341.0			
≥ 2 codes	59% (76/128)	52% (14/27)	61% (62/101)
≥ 3 codes	66% (65/98)	69% (11/16)	66% (54/82)
≥ 4 codes	72% (57/79)	83% (10/12)	70% (47/67)
≥ 5 codes	73% (54/74)	83% (10/12)	71% (44/62)
ICD-9 + no MS code			
≥ 2 codes + +no MS	63% (50/79)	57% (13/23)	66% (37/56)
≥ 3 codes + no MS	75% (41/55)	71% (10/14)	76% (31/41)
≥ 4 codes + no MS	80% (35/44)	82% (9/11)	79% (26/33)
≥ 5 codes + no MS	81% (33/41)	82% (9/11)	80% (24/30)
ICD-9 + corticosteroids			
≥ 2 codes + corticosteroids	64% (55/86)	58% (14/24)	66% (41/62)
≥ 3 codes + corticosteroids	70% (45/64)	73% (11/15)	69% (34/49)
≥ 4 codes + corticosteroids	77% (41/53)	91% (10/11)	74% (31/42)
≥ 5 codes + corticosteroids	78% (39/50)	91% (10/11)	74% (29/39)
Codes + Hospitalized			
≥ 2 codes + hospitalized	61% (48/79)	59% (13/22)	61% (35/57)
≥ 3 codes + hospitalized	65% (39/60)	77% (10/13)	62% (29/47)
≥ 4 codes + hospitalized	69% (34/49)	90% (9/10)	64% (25/39)
≥ 5 codes + hospitalized	71% (32/45)	90% (9/10)	92% (23/35)
Codes + Subspecialist			
≥ 2 codes + subspecialist	62% (70/113)	54% (14/26)	64% (56/87)
≥ 3 codes + subspecialist	68% (60/88)	73% (11/15)	67% (49/73)
≥ 4 codes + subspecialist	75% (53/71)	91% (10/11)	72% (43/60)
≥ 5 codes + subspecialist	76% (50/66)	91% (10/11)	73% (40/55)
Codes + CNS imaging			
≥ 2 codes + CNS imaging	62% (72/117)	54% (13/24)	63% (59/93)
≥ 3 codes + CNS imaging	67% (61/91)	67% (10/15)	67% (51/76)
≥ 4 codes + CNS imaging	73% (55/75)	83% (10/12)	71% (45/63)
≥ 5 codes + CNS imaging	74% (52/70)	83% (10/12)	72% (42/58)
Codes + corticosteroids + CNS imaging			
≥ 2 codes + corticosteroids + CNS imaging	65% (52/80)	57% (13/23)	68% (39/57)
≥ 3 codes + corticosteroids + CNS imaging	71% (42/59)	71% (10/14)	71% (32/45)
≥ 4 codes + corticosteroids + CNS imaging	78% (39/50)	91% (10/11)	74% (29/39)
≥ 5 codes + corticosteroids + CNS imaging	79% (37/47)	91% (10/11)	75% (27/36)

CNS = central nervous system and imaging includes any one of the following: computed tomography of the head, magnetic resonance imaging of the brain, magnetic resonance imaging of the orbits or magnetic resonance imaging of the spine. Corticosteroids includes either oral and/or intravenous corticosteroids. Hospitalization includes any hospitalization for any indication within 30 days prior to or 30 days after the first documented ICD-9-CM code for NMO. MS = multiple sclerosis and no codes for MS indicates there were no documented ICD-9-CM codes for MS (340) at any time in the patient's medical record. Subspecialist indicates that the patient was seen by either a rheumatologist, ophthalmologist and/or neurologist within 6 months prior to or 6 months after the initial documented ICD-9 code for NMO. The number of codes indicates the minimum number of codes for NMO (341.0) documented at any point throughout the patient's medical record.

resulted in an increased PPV of the code. We found that the best PPV for both pediatric and adult patients resulted from the algorithm of at least 5 ICD-9-CM codes for NMO and hospitalization within either 30 days prior to or after the initial documented ICD-9-CM code (pediatric PPV: 90%; adult PPV: 92%). However, this significantly reduced the overall sample sizes of the two cohorts (pediatric $n = 9$; adult $n = 23$). For the pediatric centers, the algorithm of "≥ 4 codes + corticosteroids + CNS imaging" also resulted in a high PPV of 91% and a similar evaluable sample size ($n = 10$) as did the algorithms of "≥ 4 codes + corticosteroids" and "≥ 4 codes + subspecialist." For the adult subjects, all of the other algorithms resulted in PPVs < 80%. Of the subjects who did not meet criteria for NMO/NMOSD, the most common alternative diagnoses documented included transverse myelitis ($n = 4$), optic neuritis ($n = 3$), attention-deficit hyperactivity disorder (ADHD) ($n = 2$), acute disseminated encephalomyelitis ($n = 2$), systemic lupus erythematosus ($n = 2$) and Sjögren syndrome ($n = 2$). It is interesting to note that the ICD-9-CM code for ADHD (341.01) is quite similar to the code for NMO (341.0) and therefore patients may have been accidentally incorrectly coded.

We also obtained data regarding demographic and clinical characteristics of patients with confirmed diagnoses of NMO/NMOSD ($n = 102$) to compare pediatric and adult patients (Table 3). We found that pediatric patients were more likely to be evaluated by an ophthalmologist (88% vs. 21%; $p < 0.001$) and rheumatologist (44% vs. 7%; < 0.001) within 6 months prior to or 6 months after their first ICD-9-CM code. Pediatric patients were also more likely to be hospitalized (94% vs. 55%; $p < 0.01$) and to undergo magnetic resonance imaging (MRI) of the orbits (44% vs. 11%; $p < 0.01$) within ± 30 days of their diagnosis. Furthermore, patients with NMO/NMOSD seen at pediatric centers were more commonly prescribed oral corticosteroids, intravenous corticosteroids, plasmapheresis, intravenous immunoglobulin, and cyclophosphamide than their adult counterparts within ± 30 days of their diagnosis (all $p < 0.01$). There was no statistically significant difference in the proportion of adults who received rituximab compared to children ± 30 days of their diagnosis (56% vs. 33%; $p = 0.07$).

4. Discussion

Using a multicenter, chart review-based validation, we found that a single ICD-9-CM code for NMO inaccurately identifies patients with NMO/NMOSD. However, the use of a case-finding algorithm significantly improves the PPV for accurate identification of both pediatric and adult patients with NMO/NMOSD. The best identified algorithm includes at least 5 documented ICD-9-CM codes for NMO as well as a hospitalization with a resultant PPV of 90% in pediatric patients and 92% in adult patients. However, it is important to note that while adding variables to the case-finding algorithm increases the PPV, the sensitivity of that algorithm decreases as fewer patients fulfill these criteria.

In this study, there were also notable differences among pediatric and adult patients who fulfilled criteria for NMO/NMOSD regarding their initial diagnostic evaluation as well as medications prescribed. Pediatric patients diagnosed with NMO/NMOSD were much more likely to see subspecialists, be hospitalized and receive more immunotherapies. Given that affected children will inherently have more time to potentially have a relapse, aggressive treatment upfront may be warranted. Nonetheless, our study findings highlight the ongoing needed for further standardization of care for patients with NMOSD.

Our study has some limitations. First, we did not examine ICD-10-CM codes in this study. ICD-10-CM was introduced in the United States in 2015 and at the start of our study, given the rarity of NMO/NMOSD in the general population, we were concerned we would have insufficient data to examine the ICD-10-CM code. Also, since there is one single ICD-10-CM code (G36.0) for NMO it is likely that the ICD-9-CM code maps successfully onto the ICD-10 code. Nonetheless, separate studies are needed to determine the accuracy of the ICD-10-CM code (G36.0) for identification of patients with NMOSD. Second, we were unable to calculate the negative predictive value (NPV) of the code because there was no master list at each site for all of the known patients receiving care for NMOSD. A third limitation is that a few patients were excluded from the analysis because of an unclear diagnosis or insufficient data to confirm or refute the diagnosis which may have resulted in an under- or over- estimation of the PPV in this study. Fourth, while the initial treatment and evaluation of children with NMOSD significantly differed from that of adults, the impact of these differences on long-term clinical outcomes warrants further exploration. Last, our findings may be limited to the hospital centers included in this study, however, at the same time, the multicenter design of this study as well as the inclusion of both pediatric and adult centers is a great strength of the study. This is further strengthened by the fact that medical chart reviews were performed by both pediatric and adult neurologists and rheumatologists with expertise in neuro-inflammatory disorders.

While we ascertained case-finding algorithms using data typically available in healthcare claims, these algorithms will first need to be validated in large healthcare claims databases prior to appropriate use

Table 3
Demographics, clinical characteristics and prescribed first-line medications for patients fulfilling clinical criteria for NMO/NMOSD.

	Total Cohort ($n = 102$)	Pediatric Centers ($n = 16$)	Adult centers ($n = 86$)	p-value
Demographics and Clinical Characteristics				
Age, median (IQR)	44 (24, 56)	12 (11,15)	47 (30,58)	< 0.001*
Female, n (%)	89 (87)	12 (75)	77 (90)	0.12
White race, n (%)	37 (36)	5	32	0.78
Hospitalized, n (%)	62 (61)	15 (94)	47 (55)	< 0.01*
Consultations				
Neurology consult, n (%)	94 (92)	16 (100)	78 (91)	0.35
Ophthalmology consult, n (%)	32 (31)	14 (88)	18 (21)	< 0.001*
Rheumatology consult, n (%)	13 (13)	7 (44)	6 (7)	< 0.001*
Imaging				
MRI brain, n (%)	94 (92)	14 (88)	80 (93)	0.61
MRI spine, n (%)	86 (84)	14 (88)	72 (84)	1.00
MRI orbits, n (%)	16 (16)	7 (44)	9 (11)	< 0.01*
CT head, n (%)	2 (2)	1 (6)	1 (1)	0.29
Co-morbid Diagnoses				
Sjögren syndrome, n (%)	13 (13)	4 (25)	9 (11)	0.12
SLE, n (%)	6 (6)	0 (0)	6 (7)	0.59
Sarcoidosis, n (%)	1 (1)	0 (0)	1 (1)	1.00
Anti-phospholipid antibody syndrome, n (%)	1 (1)	0 (0)	1 (1)	1.00
Mixed-connective tissue disease, n (%)	1 (1)	0 (0)	1 (1)	1.00
Medications				
Intravenous corticosteroids, n (%)	58 (57)	15 (94)	43 (50)	< 0.01*
Oral corticosteroid, n (%)	55 (54)	15 (94)	40 (47)	< 0.01*
PLEX, n (%)	17 (17)	7 (44)	10 (12)	< 0.01*
IVIg, n (%)	5 (5)	4 (25)	2 (1)	< 0.001*
DMARDS, n (%)	14 (14)	4 (25)	10 (12)	0.23
Cyclophosphamide, n (%)	2 (2)	2 (13)	0 (0)	< 0.01*
Rituximab, n (%)	37 (36)	9 (56)	28 (33)	0.07

Patients were considered to have NMO/NMOSD if they met either then 2006 criteria for neuromyelitis optica or the 2015 criteria for neuromyelitis optica spectrum disorder (NMOSD). Pediatric: CHOP ($n = 14$); KCMC ($n = 2$); adult: UPHS ($n = 59$) and YNHH ($n = 17$). MRI = magnetic resonance imaging. IQR: interquartile range. CT = computed tomography. SLE= systemic lupus erythematosus. PLEX = plasma exchange. IVIg = intravenous immunoglobulin. DMARDs = disease modifying anti-rheumatic drugs including at least one of the following: methotrexate, sulfasalazine, azathioprine, mycophenolate mofetil, leflunomide, plaquenil, or tacrolimus.

of them to identify diagnoses of NMOSD. Other future research efforts should address recent advancements in the field of neurology. First, future work should examine the role of documented testing and reporting of myelin oligodendrocyte glycoprotein (MOG) antibodies as MOG antibody disease is a distinct, yet similar entity to NMO/NMOSD, most commonly presenting as acute demyelinating encephalomyelitis in children (Narayan et al., 2018; Armangue et al., 2016). Based on our findings of the PPV of the ICD-9-CM code performing better for subjects who were AQP4-IgG positive, we hypothesize that a proportion of patients who received a code for NMO but did not fulfill clinical criteria for NMO/NMOSD were, in fact, MOG positive. MOG testing, however, was not commercially available at the time of the clinical chart reviews performed in this study, therefore, it is unclear how many patients could have, in fact, been diagnosed with MOG-associated disease. However, laboratory testing results are not usually available in healthcare claims data and therefore would not be of practical use when creating an algorithm for identifying subjects with NMOSD. In addition, there is currently no available ICD-9-CM or ICD-10-CM code for MOG-associated disorders. Future revisions to the ICD-CM classification system may consider incorporation of a code indicating the presence of MOG antibodies. However, until this is available, one might consider limiting use of the code for NMO to those who are AQP4-IgG positive and applying the code "Demyelinating disease of the central nervous system, unspecified" (341.9 or G37.9) to all other individuals. Lastly, with the recent approval of eculizumab by the US Food and Drug Administration (FDA) for the treatment of NMOSD, future studies should examine the frequency of use of this medication among pediatric versus adult patients as a first-line agent (Pardo et al., 2019; Pittock et al., 2019).

5. Conclusions

A single ICD-9-CM code for NMO/NMOSD has a low positive predictive value for identification of the condition in both children and adults. Using a case finding algorithm, however, one can improve the PPV of the code to identify cases of pediatric and adult NMO/NMOSD in the electronic medical record. Further work is needed to validate this algorithm in a healthcare claims database as well as examine the PPV value of the more recent ICD-10-CM code for NMO/NMOSD. Our study findings also suggest significant variation in the initial diagnostic evaluation and treatment of pediatric versus adult patients and therefore a need to further standardize treatment for NMO/NMOSD.

Funding source declaration

Dr. Gmuca was funded by NIAMS NIH grant T32-AR007442-29 during the initial design of this study as well as during data abstraction.

Declaration of Competing Interest

Dr. Zhao receives research support from Childhood Arthritis and Rheumatology Research Alliance (CARRA) and Bristol-Myers Squibb. The remaining authors have no financial interests to disclose.

References

Wingerchuk, D.M., Lennon, V.A., Pittock, S.J., Lucchinetti, C.F., Weinshenker, B.G., 2006. Revised diagnostic criteria for neuromyelitis optica. Neurology 66 (10), 1485–1489.
Wingerchuk, D.M., Banwell, B., Bennett, J.L., et al., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85 (2), 177–189.
Etemadifar, M., Nasr, Z., Khalili, B., Taherioun, M., Vosoughi, R., 2015. Epidemiology of neuromyelitis optica in the world: a systematic review and meta-analysis. Mult. Scler. Int. 2015, 174720.
Cabre, P., Gonzalez-Quevedo, A., Bonnan, M., et al., 2009. Relapsing neuromyelitis optica: long term history and clinical predictors of death. J. Neurol. Neurosurg. Psychiatr. 80 (10), 1162–1164.
Cabrera-Gomez, J.A., Kurtzke, J.F., Gonzalez-Quevedo, A., Lara-Rodriguez, R., 2009. An epidemiological study of neuromyelitis optica in Cuba. J. Neurol. 256 (1), 35–44.
Asgari, N., Lillevang, S.T., Skejoe, H.P., Falah, M., Stenager, E., Kyvik, K.O., 2011. A population-based study of neuromyelitis optica in Caucasians. Neurology 76 (18), 1589–1595.
Jacob, A., Panicker, J., Lythgoe, D., et al., 2013. The epidemiology of neuromyelitis optica amongst adults in the Merseyside county of United Kingdom. J. Neurol. 260 (8), 2134–2137.
Pandit, L., Asgari, N., Apiwattanakul, M., et al., 2015. Demographic and clinical features of neuromyelitis optica: a review. Mult. Scler. 21 (7), 845–853.
Narayan, R., Simpson, A., Fritsche, K., et al., 2018. MOG antibody disease: a review of MOG antibody seropositive neuromyelitis optica spectrum disorder. Mult. Scler. Relat. Disord. 25, 66–72.
Armangue, T., Yeshokumar, A.K., Sepúlveda, M., Graus, F., Saiz, A., 2016. Antibodies in acquired demyelinating disorders in children. Mult. Scler. Demyelinating Disord. 1 (1), 5.
Pardo, S., Giovannoni, G., Hawkes, C., Lechner-Scott, J., Waubant, E., Levy, M., 2019. Editorial on: eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. Mult. Scler. Relat. Disord. 33, A1–A2.
Pittock, S.J., Berthele, A., Fujihara, K., et al., 2019. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. New Eng. J. Med. 381 (7), 614–625.