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Evaluation of comorbidities and health care resource use among patients with highly active neuromyelitis optica

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ABSTRACT

Background: Neuromyelitis optica (NMO) is characterized by unpredictable attacks on the optic nerves and spinal cord, causing accumulations of neurological disability that may lead to blindness and paralysis. We examined comorbidities and health care use among patients with highly active NMO, defined as at least two relapses within 12 months of the patient's first NMO encounter in the database.

Methods: This retrospective study of a US administrative claims database compared patients with highly active NMO to matched individuals without NMO. All outcomes, including Charlson Comorbidity Index (CCI) score, hospitalizations, and emergency department visits, were measured over the 12-month period following the patient's first NMO encounter in the database.

Results: A total of 1349 patients with NMO were identified. Of these, 134 had highly active NMO (80% female, mean age 45.6 years) and were matched to 670 non-NMO controls. Patients with highly active NMO had significantly greater comorbidity burden than non-NMO controls (mean CCI score: 4.1 versus 0.6; $P < 0.0001$) and greater proportions of hospitalization (53.7% versus 4.0%; $P < 0.0001$) and emergency department visits (60.5% versus 9.7%; $P < 0.0001$).

Conclusions: High occurrence of several acute and chronic conditions and extensive health care use highlight the significant medical burden among patients with highly active NMO.

1. Introduction

Neuromyelitis optica (NMO) is a life-threatening, rare, autoimmune disease of the central nervous system. It is characterized by acute optic neuritis and longitudinally extensive transverse myelitis resulting in an accumulation of substantial, and often permanent, neurologic deficits and disability, including blindness and paralysis [1,2]. Population-based studies from a number of countries suggest worldwide prevalence rates of 0.5 to 4.4 per 100,000 individuals [3]. In the United States (US), the estimated prevalence of NMO is 4000 to 8000 patients [3]. Women are much more commonly affected than men, with a 3:1 female-to-male ratio [4]. The median age of onset is generally in the late 30s, but a wide range is reported [4,5].

The clinical presentation of NMO can be quite variable, which, when combined with the rarity of the condition, can lead to delayed diagnosis and treatment. Unilateral or bilateral optic neuritis, including central visual loss with ocular pain, is often the initial event of relapsing NMO. Clinical manifestations of myelitis may include severe paraplegia, sensory loss, bladder dysfunction, spasms, and pain. Brainstem involvement may manifest with nausea, vomiting, hiccups, vertigo, hearing loss, facial weakness, trigeminal neuralgia, diplopia, ptosis, or nystagmus [6]. Myelitis that extends into the brainstem may cause respiratory failure and death [7].

It is estimated that 80% to 90% of NMO cases follow a relapsing, rather than monophasic, disease course [4,8]. The prognosis of relapsing NMO is poor, particularly among patients with frequent relapses [9,10]. NMO relapses have been associated with long-term visual and motor disability. A prior study among 106 patients with NMO found that relapsing NMO resulted in 34% of patients with permanent motor disability, 23% patients with wheelchair dependency, and 18% with permanent blindness during the 6 years of follow-up. Moreover, 9% of patients had died by the end of follow-up [11]. Another study that used

Abbreviations: AQP4, aquaporin 4; AQP4-IgG, aquaporin 4–immunoglobulin G; CCI, Charlson Comorbidity Index; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IQR, interquartile range; MS, multiple sclerosis; NMO, neuromyelitis optica; Q1, first quartile; Q3, third quartile; SD, standard deviation; Th, T-helper; US, United States.

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predictive models among patients with NMO concluded that greater relapse frequency was associated with a 20% increased risk of mortality per attack (relative risk, 1.21) [9]. Unlike multiple sclerosis (MS), where a secondary progressive phase is common later in the disease for those who initially present with relapsing remitting disease and serves as a major predictor of disability, in NMO, the disability accumulation is stepwise and directly associated with the sequelae of acute attacks [9–12]. Therefore, relapse prevention is paramount for successful treatment of relapsing NMO.

No therapies are currently approved for the treatment of NMO. High-dose intravenous corticosteroids are typically used for the treatment of acute relapses, with plasma exchange often used as rescue therapy for patients who do not respond to corticosteroids. Immunosuppressant therapies such as azathioprine, mycophenolate mofetil, and rituximab are commonly used for long-term stabilization and prevention of relapse [13]. Despite these treatments, more than half of patients will continue to experience acute attacks resulting in additional and potentially permanent neurologic disability [13–15].

In addition to the burden associated with acute relapses and the residual and accumulated disability that results from these attacks, patients with NMO also tend to have a variety of comorbid conditions. A recent systematic review of comorbid conditions associated with NMO suggests that several autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and myasthenia gravis co-occur with NMO [16]. Evidence also exists regarding the greater expression of AQP4 antibodies among patients with NMO and possible co-occurrence with neoplastic conditions [17]. In addition, a study conducted in the United Kingdom suggests substantial cognitive and psychiatric comorbidities among patients with NMO [18]. Although previous studies have provided evidence regarding high prevalence of comorbid conditions among patients with NMO, no prior study has comprehensively examined the prevalence using data from patients treated in real-world settings.

To gain a fuller appreciation of the medical burden of NMO, particularly among patients with frequent relapses and for whom the need for effective treatment is most urgent, we sought to measure the prevalence of comorbidities and proportions of clinical event-driven health care resource use in the US using a large, administrative insurance claims database.

2. Methods

2.1. Study design

We conducted a retrospective case-control study designed to examine incremental comorbidity and health care resource use burden among patients with highly active NMO, defined as at least two relapses within 12 months of the patient's first NMO encounter in the database, compared with the overall NMO population and with age- and sex-matched individuals without NMO.

2.2. Data source

For the purposes of this study, we used multiple years (2009–2014) of the MarketScan Commercial Claims and Encounters database and the MarketScan Medicare Supplemental database. In the US, insurance providers include government-sponsored plans such as Medicare (covering elderly individuals aged 65 years or older and disabled beneficiaries), Medicaid (covering individuals below a certain threshold of the poverty line), and nongovernment commercial plans that are generally provided by employers. These databases contain employer- and health-plan–sourced information on medical and drug utilization of beneficiaries enrolled in privately insured fee-for-service plans, such as preferred and exclusive provider organizations, point-of-service plans, indemnity plans, health maintenance organizations, consumer-directed health plans, and capitated health plans [19]. Complete payment and charge information, dates and place of service (e.g., inpatient, outpatient, emergency), diagnoses, procedures, and detailed information on hospitalizations, including admission and discharge dates, can be retrieved from medical claims within these databases. Pharmacy claims in these databases include complete outpatient prescription drug information, which consists of patient co-payments, mail-order drugs, injectables, drugs from specialty pharmacies, and all standardized prescription-level fields collected on a typical pharmacy claim (e.g., date of fill/refill, drug name and class, strength, quantity, days' supply).

These databases also contain medical (i.e., inpatient, outpatient, physician office, and ancillary services) and pharmacy claims for Medicare-eligible retirees with employer-sponsored Medicare supplemental plans. Since de-identified unique patient numbers were used to tracked patients longitudinally and no patient consent forms were required, the institutional review board at RTI International determined this study to be exempt.

2.3. Eligibility criteria

2.3.1. Patients with NMO

Enrollees were identified as having NMO if they met either of the following criteria between January 1, 2009, and June 30, 2013: (1) had at least one inpatient or two outpatient visits for an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of NMO (ICD-9-CM code 341.0), or (2) had at least two visits ($\geq$ 6 months apart) for a diagnosis of transverse myelitis (ICD-9-CM code 341.2x or 323.82) in combination with at least one visit for an inflammatory optic-related condition (most commonly ICD-9-CM code 377.3). Due to the lack of laboratory data, and unavailability of aquaporin 4–immunoglobulin G (AQP4-IgG) test to identify patients with NMO, we relied on ICD-9-CM diagnostic codes to identify patients with NMO. Although, these tests may have lower accuracy than biomarker tests, we included ICD-9-CM codes for NMO and allied conditions (transverse myelitis and optic-related conditions) to obtain a pool of patients with possible NMO. To avoid classifying patients with MS with certain similar symptoms as having NMO, we excluded enrollees who had been treated with beta-interferon therapy or other MS-related treatments (i.e., glatiramer acetate, natalizumab, dimethyl fumarate, teriflunomide, and fingolimod). Finally, individuals with a diagnosis of MS after the initial NMO, transverse myelitis, or optic neuritis diagnosis were excluded from the study population. The first date of an NMO, transverse myelitis, or optic neuritis event was considered to be the *index date*.

2.3.2. Patients with highly active NMO

To identify the highly active relapsing NMO population, we further restricted our NMO population to those with at least two relapses in the 12 months following the index date. A relapse event was defined as either (1) an inpatient visit with a principal discharge diagnosis of NMO, transverse myelitis, optic neuritis, or other associated neurological condition (identified by clinical expert); (2) an inpatient/outpatient visit for intravenous methylprednisolone (five administrations); or (3) an inpatient/outpatient visit for plasma exchange or intravenous immunoglobulin. Relapse events occurring within 28 days of each other were part of a single relapse.

For all patients with NMO, the first month (i.e., first 30 days) following the index date was not used for assessment of outcome measures in order to eliminate the bias of counting the health care encounter that led to their identification. Thus the 12-month follow-up period for cases was month 2 through month 13 after their index date. Patients with NMO with $<$ 13 months of continuous enrollment after their index date were excluded from the study.

2.3.3. Non-NMO controls

We obtained a 5% random sample of the MarketScan databases for the purposes of analyzing non-NMO enrollees (control cohort). Patients

with no medical encounter with the following ICD-9-CM codes were selected as non-NMO controls: 34x.xx (other disorder of the central nervous system), 323.82 (transverse myelitis), 377.3x (optic neuritis). Unlike patients with NMO, no specific diagnosis codes could be used for the purpose of identifying an index date. Therefore, a random date between July 1, 2009, and December 31, 2013, was selected and termed the study index date for those in the control cohort. The rationale for assessing comorbidity burden and resource utilization for the NMO group in months 2 through 13 after the index date was not applicable for the control group. Therefore, all outcome measures for the control group were assessed in the 12-month period immediately following their randomly chosen index date (i.e., months 1 through 12). Controls with < 12 months of continuous health plan enrollment following their index date were excluded from the study.

2.4. Study measures

All outcome measures, including comorbidity burden, hospitalizations, and emergency department visits, were measured over a 12-month, post-index date, follow-up period.

Comorbidity burden was measured by calculating a Charlson Comorbidity Index (CCI) score during the 12-month post-index date period. The CCI is a measure of patients' overall comorbidity burden and includes 20 categories of comorbidities, as defined by ICD-9-CM diagnosis and procedure codes, with associated weights corresponding to the severity of the comorbid condition of interest [20]. A higher CCI score represents a greater overall comorbidity burden. We also reported the proportion of patients with a recorded diagnosis for each of the Charlson comorbidities during the designated post-index date period.

In addition, frequencies of specific comorbidities highlighted in previously published literature were also tabulated. These included mental health disorders (e.g., depression and anxiety); autoimmune diseases, including myasthenia gravis, systemic lupus erythematosus, Sjögren syndrome, celiac disease, sarcoidosis, mixed connective tissue disease, hypothyroidism, polyarteritis nodosa, pernicious anemia, ulcerative colitis, primary sclerosing cholangitis, and idiopathic thrombocytopenic purpura; and steroid-related complications, including diabetes, hypertension, and osteoporosis. Certain NMO symptom–related conditions, including neuropathic pain and bladder/bowel dysfunction, were also assessed.

For each comparator group, all-cause inpatient hospital and emergency department resource use was aggregated over the 12-month follow-up period. We calculated the percentage of patients in each group with at least one inpatient admission, the average length of stay per admission among those with at least one admission, and the average total time in hospital over the 1-year study period among those with at least one admission. In addition, we calculated the percentage of patients in each group with at least one emergency department visit, as well as the average number of emergency department visits over the 12-month follow-up period among patients with at least one emergency department visit.

2.5. Statistical analysis

2.5.1. Case-control matching

Outcomes for patients with highly active relapsing NMO were compared with outcomes for all patients with NMO and for non-NMO controls. Because patients with highly active relapsing NMO were included in the all-NMO group, these two groups were not mutually exclusive. A direct covariate-matching method was used to obtain greater balance between the two comparator groups of primary interest: patients with highly active NMO and controls without NMO. Matching was conducted at a 1:5 ratio (i.e., 5 controls for each patient with highly active NMO) based on a set list of variables, including patient age at the index date (in 10-year increments), sex, insurance payer (commercial or Medicare), year of index date, and geographic location (US census region).

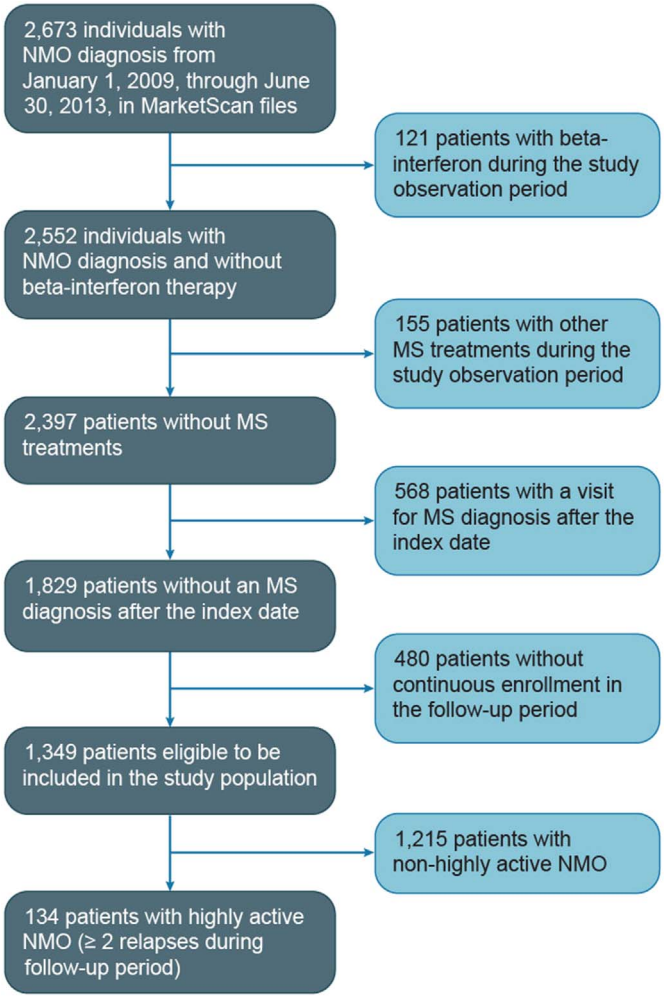

Fig. 1. Algorithm describing selection of study population. MS = multiple sclerosis; NMO = neuromyelitis optica.

2.5.2. Descriptive analysis

All demographic characteristics, comorbidity measures, and health care resource use measures were analyzed descriptively through the tabular display of mean values, medians, ranges, and standard deviations of continuous variables and frequency distributions for categorical variables. The statistical significance of descriptive, unadjusted differences between cohorts were measured using appropriate statistical tests (i.e., chi-square tests, nonparametric *t*-tests, Wilcoxon rank sum tests), with the significance of differences in results reported with *P* values. No statistical comparisons were made between patients with highly active NMO and all patients with NMO.

3. Results

Overall, 1349 patients met the NMO diagnostic and continuous enrollment criteria and constituted the all-NMO cohort. Of these patients, 134 met the study inclusion criteria for highly active NMO (Fig. 1). In addition, 2,628,966 individuals were identified as potential controls, 670 of whom were matched with patients with highly active NMO based on 1:5 direct covariate matching.

3.1. Demographic characteristics

Table 1 shows the comparison of demographic characteristics across

Table 1
Baseline characteristics after matching.

	All NMO (n = 1349)		Highly active NMO (n = 134)		Control cohort (n = 670)		*P* value	
							Highly active vs. controls	All NMO vs. controls
Age at index date								
Mean (SD)	46.48 (17.15)		45.62 (14.70)		44.86 (15.47)		0.6009	0.039
Median	50		46.5		46			
Range (min, max)	(0.00, 91.00)		(11.00, 78.00)		(0.00, 79.00)			
Distribution (n, %)								
0–17	110	8.15%	5	3.73%	25	3.73%	1.000	< 0.001
18–24	72	5.34%	12	8.96%	60	8.96%	1.000	0.003
25–34	120	8.90%	12	8.96%	60	8.96%	1.000	1.000
35–44	216	16.01%	30	22.39%	150	22.39%	1.000	0.001
45–54	345	25.57%	39	29.10%	195	29.10%	1.000	0.098
55–64	345	25.57%	27	20.15%	135	20.15%	1.000	0.008
65–69	55	4.08%	2	1.49%	10	1.49%	1.000	0.002
70–74	43	3.19%	4	2.99%	20	2.99%	1.000	0.892
75–79	28	2.08%	3	2.24%	15	2.24%	1.000	0.870
80–84	10	0.74%	–	0.00%	–	0.00%	1.000	0.036
85 +	5	0.37%	–	0.00%	–	0.00%	1.000	0.177
Sex (n, %)								
Male	433	32.10%	27	20.15%	135	20.15%	1.000	< 0.001
Female	916	67.90%	107	79.85%	535	79.85%	1.000	< 0.001
Year of index date (n, %)								
2009	327	24.24%	27	20.15%	135	20.15%	1.000	0.043
2010	327	24.24%	30	22.39%	150	22.39%	1.000	0.374
2011	346	25.65%	31	23.13%	155	23.13%	1.000	0.229
2012	245	18.16%	33	24.63%	165	24.63%	1.000	0.001
2013[a]	104	7.71%	13	9.70%	65	9.70%	1.000	0.147
Geographic region (n, %)								
Northeast	305	22.61%	31	23.13%	155	23.13%	1.000	0.822
Northcentral	300	22.24%	33	24.63%	165	24.63%	1.000	0.239
South	461	34.17%	48	35.82%	240	35.82%	1.000	0.487
West	247	18.31%	20	14.93%	100	14.93%	1.000	0.060
Unknown	36	2.67%	2	1.49%	10	1.49%	1.000	0.113
Insurance plan type (n, %)								
Commercial	1164	86.29%	120	89.55%	600	89.55%	1.000	0.039
Medicare	185	13.71%	14	10.45%	70	10.45%	1.000	0.039

NMO = neuromyelitis optica; SD = standard deviation.
[a] Since only half of 2013 data were used to identify patients with NMO, the total number of patients identified in the year 2013 is lower than in other years.

cohorts. Prior to matching, patients with highly active NMO were significantly older than controls (mean age: 45.6 years versus 38.0 years for controls; $P < 0.0001$) and were more likely to be female (79.8% for patients with highly active NMO versus 50.6% for controls; $P < 0.0001$). The distribution of geographic region and insurance plan type did not differ between highly active NMO cases and controls. Patients with highly active NMO and controls were well balanced after 1:5 direct covariate matching. However, patients in the all-NMO cohort remained significantly older than controls (46.5 versus 44.9; $P = 0.039$), were significantly less likely to be female than and controls (67.9% versus 79.9%; $P < 0.001$), and were significantly more likely than controls to be in a Medicare advantage plan rather than a commercial insurance plan (13.71% versus 10.45%, $P = 0.039$) (Table 1). Patients with highly active NMO had, on average, 2.9 relapses, with several patients (n = 16) having ≥ 5 relapses during the 12-month follow-up period (data not represented in tabular form).

3.2. Comorbidity burden

Comorbidity burden was significantly greater among patients with highly active NMO compared with controls (mean CCI score: 4.1 versus 0.6; $P < 0.001$) (Table 2). Although, no statistical tests were performed to compare patients with highly active NMO with all patients with NMO, comorbidity burden was observed to be greater among patients with highly active disease compared with the overall NMO population. A gradient was seen across all three cohorts for each of the specific reported comorbidities, with the greatest prevalence of comorbidities observed in patients with highly active NMO and the lowest observed in the control cohort.

Hypertension was the most prevalent comorbidity in all three cohorts, with prevalence among highly active NMO cases being almost three times higher versus those in matched controls (43.3% for patients with highly active NMO versus 15.4% for controls; $P < 0.001$). The second and third most common comorbidities for both NMO cohorts were hemiplegia/paraplegia (41.79% for highly active NMO versus 30.91% for all NMO) and bladder dysfunction (29.9% for highly active NMO versus 22.8% for all NMO). These conditions can be considered as direct sequelae of NMO; however, due to no clear definition or consensus regarding them, we grouped them as comorbidities of NMO. No patients in the control group were reported to have either of those conditions. Depression prevalence was also highest in patients with highly active NMO, and over five times greater than the prevalence reported among controls (25.37% versus 4.63%; $P < 0.001$).

Autoimmune conditions were generally highest among patients with highly active NMO and lowest among matched controls. For example, 19.4% of highly active NMO cases had rheumatic disease, compared with 9.5% of all patients with NMO and 2.1% of patients in the control cohort ($P < 0.001$). Similarly, > 8% of the patients with highly active NMO had Sjögren syndrome compared with 3.1% of all patients with NMO and < 1% in the control group ($P < 0.001$). The prevalence of hypothyroidism was more than five times greater in patients with highly active NMO (22.4%) compared with non-NMO controls (4.3%; $P < 0.001$). Similar results were observed for other autoimmune comorbidities, including mixed connective tissue disease and myasthenia gravis.

Conditions that can be linked to chronic steroid use were also more

Table 2
Comorbidities during 12-month post-index date period reported in ≥ 2% of patients with highly active NMO.

	All NMO (n = 1349)		Highly active NMO (n = 134)		Control cohort (n = 670)		*P* value	
							Highly active NMO vs. controls	All NMO vs. controls
Charlson Comorbidity Index								
Mean (SD)	2.85 (2.99)		4.06 (3.33)		0.64 (1.37)		< 0.001	< 0.001
Median	2		3		0			
Range (min, max)	(0.00, 20.00)		(0.00, 14.00)		(0.00, 12.00)			
Comorbidity[a] (n, %)								
Hypertension	464	34.40%	58	43.28%	103	15.37%	< 0.001	< 0.001
Hemiplegia/paraplegia	417	30.91%	56	41.79%	0	0.00%	< 0.001	< 0.001
Bladder dysfunction	307	22.76%	40	29.85%	0	0.00%	< 0.001	< 0.001
Depression	241	17.87%	34	25.37%	31	4.63%	< 0.001	< 0.001
Hypothyroidism	195	14.46%	30	22.39%	29	4.33%	< 0.001	< 0.001
Diabetes without complications	217	16.09%	28	20.90%	42	6.27%	< 0.001	< 0.001
Skin ulcers/cellulitis	198	14.68%	28	20.90%	30	4.48%	< 0.001	< 0.001
Anxiety	166	12.31%	28	20.90%	26	3.88%	< 0.001	< 0.001
Chronic pulmonary disease	220	16.31%	27	20.15%	34	5.07%	< 0.001	< 0.001
Rheumatic disease	128	9.49%	26	19.40%	14	2.09%	< 0.001	< 0.001
Cerebrovascular disease	169	12.53%	25	18.66%	6	0.90%	< 0.001	< 0.001
Moderate or severe liver disease	111	8.23%	22	16.42%	16	2.39%	< 0.001	< 0.001
Neuropathic pain	116	8.60%	20	14.93%	3	0.45%	< 0.001	< 0.001
Mild liver disease	51	3.78%	12	8.96%	6	0.90%	< 0.001	< 0.001
Malignancy[b]	105	7.78%	11	8.21%	17	2.54%	0.001	< 0.001
Sjögren syndrome	42	3.11%	11	8.21%	4	0.60%	< 0.001	< 0.001
Peripheral vascular disease	100	7.41%	10	7.46%	8	1.19%	< 0.001	< 0.001
Osteoporosis	84	6.23%	10	7.46%	6	0.90%	< 0.001	< 0.001
Congestive heart failure	57	4.23%	9	6.72%	4	0.60%	< 0.001	< 0.001
Diabetes with complications	57	4.23%	8	5.97%	9	1.34%	0.001	< 0.001
Systemic lupus erythematosus	43	3.19%	7	5.22%	3	0.45%	< 0.001	< 0.001
Sarcoidosis	28	2.08%	6	4.48%	1	0.15%	< 0.001	< 0.001
Renal disease	45	3.34%	4	2.99%	2	0.30%	0.001	< 0.001
Myocardial infarction	19	1.41%	4	2.99%	2	0.30%	0.001	0.019
Metastatic solid tumor	19	1.41%	3	2.24%	1	0.15%	0.002	0.007

NMO = neuromyelitis optica; SD = standard deviation.
[a] Comorbidities measured in the 12-month post-index date period. Only comorbidities with ≥ 2% prevalence in the highly active NMO group are presented in the table.
[b] Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin and metastatic solid tumor.

prevalent among patients with highly active NMO compared with all patients with NMO and with matched controls. The proportion of patients with diabetes among highly active NMO cases was more than three times greater than it was among matched controls (26.9% for patients with highly active NMO versus 20.3% for all patients with NMO and 7.6% for controls; $P < 0.001$ for both NMO cohorts versus controls). Similarly, the prevalence of other diseases associated with steroid use (e.g., osteoporosis) was greatest for highly active NMO cases and significantly greater than those reported for matched controls (7.5% for highly active NMO versus 6.2% for all patients with NMO and 0.9% for controls; $P < 0.001$ for highly active NMO versus controls). Several conditions that can be linked with NMO symptoms, including neuropathic pain, were also more prevalent among highly active NMO cases compared with matched controls.

3.3. Hospitalizations and emergency department visits

As with comorbidity burden, resource use patterns revealed a gradient of greatest resource use among patients with highly active NMO and lowest resource use among non-NMO controls. More than half of patients with highly active NMO (53.7%) had at least one inpatient stay in the 12-month follow-up period, compared with 22.4% of all patients with NMO and only 4.0% of patients in the control cohort ($P < 0.001$ for all comparisons) (Table 3). Average length of stay per hospitalization among those with at least one admission was significantly greater for patients with highly active NMO versus controls (9.6 days versus 4.5 days, $P = 0.027$) and approached significance for all patients with NMO compared with controls (7.8 days versus 4.5 days; $P = 0.06$). Total time in hospital over 12 months of follow-up averaged 26.9 days among patients with highly active NMO with at least one admission compared with 18.0 days for all patients with NMO and 6.5 days among controls with at least one admission ($P < 0.05$ for all comparisons). The proportion of patients with highly active NMO with at least one emergency department visit was almost twice as great as that reported for all patients with NMO and approximately six times greater than that reported for matched controls (60.5% versus 34.9% versus 9.7%; $P < 0.001$ for all comparisons). The average number of emergency department visits during the follow-up period was 5.2 for patients with highly active NMO versus 2.8 for all patients with NMO and 0.5 for non-NMO controls ($P < 0.05$ for all comparisons).

4. Discussion

Using data from MarketScan commercial claims and Medicare supplemental files, we conducted a retrospective observational study to identify patients with highly active NMO. In addition, we examined comorbidity and health care resource use burden among patients with highly active NMO compared with all patients with NMO and non-NMO matched controls. To the best of our knowledge, this is the first study to identify patients with highly active NMO using an administrative claims database in the US. More importantly, it is the first study to examine the prevalence of comorbidities and describe the extent of health care resource use among patients with NMO and the subset of patients with highly active NMO in a real-world setting.

The overall NMO cohort, including highly active and non-highly active NMO cases, had 1349 patients. Previous estimates from academic medical centers extrapolated a prevalence of NMO in the US of about 4000 to 8000 patients [3]. As MarketScan data contain information on 66 million covered lives in the US (i.e., approximately 20% of the overall US population), our estimate of 1349 patients with NMO falls

Table 3
Hospitalizations and emergency department visits.

	All NMO (n = 1349)	Highly active NMO (n = 134)	Control cohort (n = 670)	*P* value	
				Highly active NMO vs. controls	All NMO vs. controls
Patients with any inpatient admission (n, %)	302 22.38%	72 53.73%	27 4.03%	< 0.001	< 0.001
Average number of admissions					
Mean (SD)	0.43 (1.06)	1.36 (1.98)	0.05 (0.28)	< 0.001	0.065
Median	0.00	1.00	0.00		
IQR (Q1, Q3)	(0.00, 0.00)	(0.00, 2.00)	(0.00, 0.00)		
Average length of stay of those with an admission (days)					
Mean (SD)	7.80 (8.99)	9.55 (11.29)	4.49 (5.01)	0.027	0.060
Median	4.62	5.00	3.00		
IQR (Q1, Q3)	(2.00, 9.00)	(3.00, 12.25)	(2.00, 5.00)		
Total time in hospital of those with an admission (days)					
Mean (SD)	18.03 (28.46)	26.92 (36.12)	6.48 (7.63)	0.005	0.037
Median	6.5	10.00	3.00		
IQR (Q1, Q3)	(3.00, 18.00)	(4.00, 33.50)	(2.00, 7.00)		
Patients with emergency department visits (n, %)	471 34.91%	81 60.45%	65 9.70%	< 0.001	< 0.001
Number of emergency department visits					
Mean (SD)	2.77 (8.60)	5.21 (10.45)	0.49 (2.10)	< 0.001	0.034
Median	0.00	1.00	0.00		
IQR (Q1, Q3)	(0.00, 2.00)	(0.00, 5.00)	(0.00, 0.00)		

IQR = interquartile range; NMO = neuromyelitis optica; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

within the previously estimated prevalence range. The prevalence of NMO has been reported to be greater among females, with a female-to-male ratio > 3:1 [4]. We observed a similar ratio among the highly active NMO cases in our study (3.95:1); however, the female-to-male ratio was about 2:1 for the overall NMO population. Previous evidence suggests that female-to-male ratio among NMO patients is about 8:1 for AQP4-seropositive patients, whereas, it is 2:1 for seronegative patients. We believe that our study is limited by lack of AQP4 testing (as discussed previously) and therefore our sex distribution drifts toward previous studies that have had similar issues [21]. The mean age of our study population was consistent with previous studies [4,5].

Although, no prior study using real-world data has examined the prevalence of comorbidities among patients with NMO, several studies have documented the potential co-occurrence of many of the conditions. Existing evidence suggests that the most common conditions that coexist with NMO are autoimmune conditions, including systemic lupus erythematosus [22,23], Sjögren syndrome [24,25], psoriasis [26], rheumatoid arthritis [27], and many others. Our findings also suggest that the prevalence of several autoimmune disorders was greater among patients with highly active and non-highly active NMO compared with their matched control counterparts. A recent systematic review indicated that the presence of a host of autoantibodies among patients with NMO may be linked with greater co-occurrence of autoimmune conditions [16].

These autoimmune diseases lie on the spectrum between Th2 and Th17, defined by the characteristic T-helper (Th) response [28]. NMO pathology exhibits evidence of both Th2 and Th17 disease, consistent with our findings of overlap with other Th2 diseases such as lupus and Th17 diseases such as psoriasis.

High frequency of cancer among patients with NMO can also be linked to greater expressions of antibodies. A study among patients with NMO in a neurology clinical practice reported that 8 of 26 patients included in the study had malignancies [17]. The research concludes that in some patients with NMO, AQP4 antibodies may indicate a “paraneoplastic immune response.” [17] Indeed, several studies have suggested that NMO relapse has co-occurred with metastasis of tumors, and the relapses have subsided with appropriate management of tumors [29–31]. While no direct links have yet been established between specific neoplastic conditions and NMO, certain cancers are known to trigger immunological reactions that have bystander inflammatory effects in the central nervous system. The prevalence of malignancies in our current real-world study highlights the need for further investigation.

In addition to increased inflammation and autoantibody production among patients with NMO, we identified comorbidities among patients with NMO due indirectly to the disease and its treatments. First, greater prevalence of several comorbidities can be linked to use of treatment approaches to manage relapses. For example, corticosteroids used to suppress inflammation [32] have been associated with hyperglycemia leading to diagnosis of diabetes mellitus [33–35]. Similarly, other immunosuppressive therapies have been linked to the presence of cardiovascular diseases. Other conditions can also be due to spinal cord injury among patients with NMO, including osteoporosis, skin ulcer, and cellulitis, especially in patients with limited mobility [36–37]. Finally, anxiety and stress due to constant relapses among patients with NMO may be potential reasons for frequent occurrences of psychiatric comorbidities. Findings from our study reveal that the prevalence of depression was more than five times greater among patients with highly active NMO compared with matched controls.

Apart from providing a detailed assessment of comorbidity burden associated with highly active NMO, the study findings also highlight the extensive health care resource use among patients with highly active NMO. More than 50% of patients with highly active NMO had at least one inpatient admission during the study follow-up period compared with less than 5% of the non-NMO control population. The average length of stay among patients with highly active NMO (9.6 days) with an inpatient admission was significantly longer than among controls (4.5 days). These findings are comparable to another population-based study that assessed length of stay across different racial groups with NMO [38]. The average length of stay for hospitalizations with a diagnosis of NMO varied from 8.6 days for whites to 10.5 days for African Americans [38]. In addition to increased inpatient admission-related resource use, the current study's findings showed that use of emergency department services was significantly greater among cases than among controls. It is plausible that both inpatient and emergency department use may be associated with the greater number of relapses among patients with NMO in the study population. Because disease-related and treatment-related comorbidities and NMO relapses and their sequelae

can lead to substantial health care resource use, including emergency department visits and hospitalizations, it is imperative that effective new therapies reduce the risk of relapses in NMO and help minimize the comorbidity burden experienced by these patients.

The current study has several limitations that should be noted. Due to the lack of laboratory data and unavailability of an AQP4-IgG test to identify patients with NMO, we relied on ICD-9-CM diagnostic codes; such codes may have a lower accuracy than biomarker tests. Moreover, no previous study has examined the validity and reliability of the ICD-9-CM diagnostic codes to identify patients with NMO. Therefore, we may have misclassified some non-NMO patients with similar profiles, such as optico-spinal demyelination, and MS as having NMO. Nevertheless, to reduce the diagnostic errors, we employed rigorous patient-selection criteria, such as excluding patients who either had a diagnosis of MS or received MS-related treatment post-NMO diagnosis. Moreover, for the main study analysis, we included only highly active NMO cases with at least two relapses of NMO during the follow-up period.

Despite using data from a large administrative claims database, our study was limited by the NMO case sample size. Furthermore, we were not able to compare demographic, clinical, and health care resource use characteristics from the period prior to initial NMO diagnosis, as lengthening the required time horizon would have further restricted the study population. In addition, as the study included only 134 patients with highly active NMO, we did not observe cell sizes that were large enough for individual comorbidities to be able to compare comorbidity burden between cohorts with and without highly active NMO.

Despite these limitations, this is the first study to assess comorbidity and health care resource use burden among patients with NMO and the subset of patients with highly active NMO and compare them with non-NMO matched controls. Co-occurrence of several acute and chronic conditions, along with extensive health care resource use, highlights the elevated medical burden among patients with highly active NMO. The current study emphasizes the high medical and economic burden associated with NMO. Future research should be directed toward development of disease-modifying and curative treatments for patients with NMO, especially patients with frequent relapses, to reduce the overall disease burden.

Declaration of interest

Mayank Ajmera, Josephine Mauskopf, and Sean Candrilli are employees of RTI Health Solutions. Audra Boscoe was an employee of Alexion Pharmaceuticals when this study was conducted. Michael Levy is an employee of Johns Hopkins University. This study was conducted by RTI Health Solutions under the direction of Alexion Pharmaceuticals.

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