VALUE IN HEALTH ▮ (2018) ▮▮▮–▮▮▮

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Identifying Patients with Relapsing-Remitting Multiple Sclerosis Using Algorithms Applied to US Integrated Delivery Network Health Care Data

Hoa Van Le, MD, PhD[1], *Chi Thi Le Truong, MD, PhD*[2], *Aaron W.C. Kamauu, MD, MS, MPH*[1,3], *John Holmén, PhD, MS*[4], *Christopher Fillmore, MD, MS*[4], *Monica G. Kobayashi, PhD, MBMA*[1], *Canter Martin, MBA*[1], *Meritxell Sabidó, MD, MS*[5], *Schiffon L. Wong, MPH*[6,*]

[1]*PAREXEL Int., Durham, NC, USA;* [2]*MedCodeWorld, Mississauga, ON, Canada;* [3]*Anolinx LLC, Salt Lake City, UT, USA;* [4]*Intermountain Healthcare, Murray, UT, USA;* [5]*Merck KGaA, Darmstadt, Germany;* [6]*EMD Serono, Inc., Billerica, MA, USA*

ABSTRACT

Background: Relapsing-remitting multiple sclerosis (RRMS) has a major impact on affected patients; therefore, improved understanding of RRMS is important, particularly in the context of real-world evidence. **Objectives:** To develop and validate algorithms for identifying patients with RRMS in both unstructured clinical notes found in electronic health records (EHRs) and structured/coded health care claims data. **Methods:** US Integrated Delivery Network data (2010–2014) were queried for study inclusion criteria (possible multiple sclerosis [MS] base cohort): one or more MS diagnosis code, patients aged 18 years or older, 1 year or more baseline history, and no other demyelinating diseases. Sets of algorithms were developed to search narrative text of unstructured clinical notes (EHR clinical notes–based algorithms) and structured/coded data (claims-based algorithms) to identify adult patients with RRMS, excluding patients with evidence of progressive MS. Medical records were reviewed manually for algorithm validation. Positive predictive value was calculated for both EHR clinical notes–based and claims-based algorithms. **Results:** From a sample of 5308 patients with possible MS, 837 patients with RRMS were identified using only the EHR clinical notes–based algorithms and 2271 patients were identified using only the claims-based algorithms; 779 patients were identified using both algorithms. The positive predictive value was 99.1% (95% confidence interval [CI], 94.2%–100%) for the EHR clinical notes–based algorithms and 94.6% (95% CI, 89.1%–97.8%) to 94.9% (95% CI, 89.8%–97.9%) for the claims-based algorithms. **Conclusions:** The algorithms evaluated in this study identified a real-world cohort of patients with RRMS without evidence of progressive MS that can be studied in clinical research with confidence.

Keywords: algorithm, claims, electronic health records, multiple sclerosis, relapsing-remitting multiple sclerosis.

Introduction

Multiple sclerosis (MS) is a chronic, degenerative neurological condition associated with neurological impairment and disability progression. Because there is currently no cure, MS persists throughout the lives of those affected [1]. Globally, in 2008, the median incidence of MS was estimated to be 2.5 cases per 100,000 population and the median prevalence was 30 per 100,000 [2]. By 2013, the median global prevalence of MS had increased to 33 per 100,000 [3].

Clinical subtypes of MS include relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and primary progressive multiple sclerosis (PPMS) [4]. RRMS, characterized by relapse events followed by partial or complete remission without disease progression during remission, is the most common MS subtype and accounts for approximately 85% of cases at diagnosis [5]. Over the clinical course, RRMS may be assessed as active (relapses or magnetic resonance imaging [MRI] activity indicating gadolinium-enhancing lesions, additions, or growth of T2 lesions) or not active, and worsening (progression of disability over time) or not worsening (without disability progression) [4]. Relapse rates have been shown to have an influence on disease and disability progression [6,7]. Over time, most patients with RRMS develop SPMS, 50% within 10 years and 80% within 20 years [5,8]. SPMS is associated with sustained disability progression and loss of discrete relapse events. Given the impact of RRMS on affected patients, improved understanding of RRMS is important, in particular in the context of real-world evidence.

Electronic health record (EHR) databases are being used increasingly in the study of MS and its management [9]. MS subtype is clinically relevant for treatment and health care utilization decision making. Identifying MS subtypes from EHR clinical notes–based or claims-based data has been explored in some published studies, often using natural language processing (NLP) to create algorithms [10–12]. Studies using EHR data showed good validity with a positive predictive value (PPV) of 80% or more [10,11], but claims-based algorithms were not validated [12].

* *Address correspondence to:* Schiffon Letitia Wong, EMD Serono, Inc., 45A Middlesex Turnpike, Billerica, MA 01821.
E-mail: schiffon.wong@emdserono.com.

1098-3015$36.00 – see front matter

https://doi.org/10.1016/j.jval.2018.06.014

This study aimed to develop and validate EHR clinical notes–based algorithms (hereafter referred to as "EHR-based algorithms") and claims-based algorithms for identifying patients with RRMS (without evidence of progressive disease), and therefore expand the pharmacoepidemiological resources for MS studies using real-world data. The cohort of patients with RRMS was the focus, because this patient population had clinical characteristics close to those of the target population of clinical trial studies for disease-modifying therapies (DMTs), particularly novel DMTs, of interest. As such, the cohort may be beneficial for future epidemiological studies and studies of comparative effectiveness.

The primary objective was to develop case ascertainment EHR-based algorithms for patients with RRMS subtype using NLP and to validate these algorithms using medical record clinical note reviews. The RRMS cohort excluded patients with evidence of progressive MS subtypes. The secondary objective was to develop corresponding case ascertainment health insurance claims–based algorithms for patients with RRMS. Because there is no diagnosis code for MS subtype, the claims-based algorithm identified the RRMS cohort as patients with MS, excluding patients with evidence of progressive disease or disability progression, as assessed by several options. Validation for the claims-based algorithms was conducted using medical chart reviews of clinical notes and patient profiles from random samples of patients with RRMS.

Methods

The design is a validation study using unstructured and structured medical records to validate EHR- and claims-based algorithms for case ascertainment of a retrospective cohort of patients with RRMS without evidence of progressive MS. The identified cohort for the EHR-based algorithm was composed of patients with RRMS, excluding patients with progressive MS subtypes. The identified cohort for the claims-based algorithms was composed of patients with MS, excluding patients with progressive MS or evidence of disability progression.

EHR data in the study period from January 1, 2010, to December 31, 2014, were extracted from Intermountain Healthcare, an integrated provider-payer delivery network covering more than 5 million patients across 22 hospitals, 185 clinics, and 750 physicians in Utah and Idaho. Intermountain Healthcare collects EHR data of inpatient and outpatient encounters, diagnoses, procedures, medication orders, laboratory results, and clinical notes from all general and specialty types, including primary care physicians, neurologists, and MS specialists.

A base cohort of eligible patients with possible MS was aged at least 18 years, had been enrolled in the database for at least 12 months before the index date, had no documented pregnancy during the study period or the 12-month pre-index period, and had no other demyelinating disease diagnoses (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 341.xx). Pregnant women were excluded because pregnancy can have an impact on MS activity and treatment [13]. Symptoms and use of DMTs were part of the definition for identification of patients with MS. Data were collected until the earliest of loss to follow-up, death, or end of the study period.

The index date was defined as the first MS diagnosis code (*ICD-9-CM* 340) or DMT record during the study period. The DMT record had to be preceded by at least one MS diagnosis code (*ICD-9-CM* 340) any time before the study period.

Algorithms

The EHR-based algorithms used NLP to identify key terms and phrases in the narrative text of unstructured clinical notes. The claims-based algorithms used only structured/coded data, which provided a comparison of the information available via unstructured notes versus structured claims records.

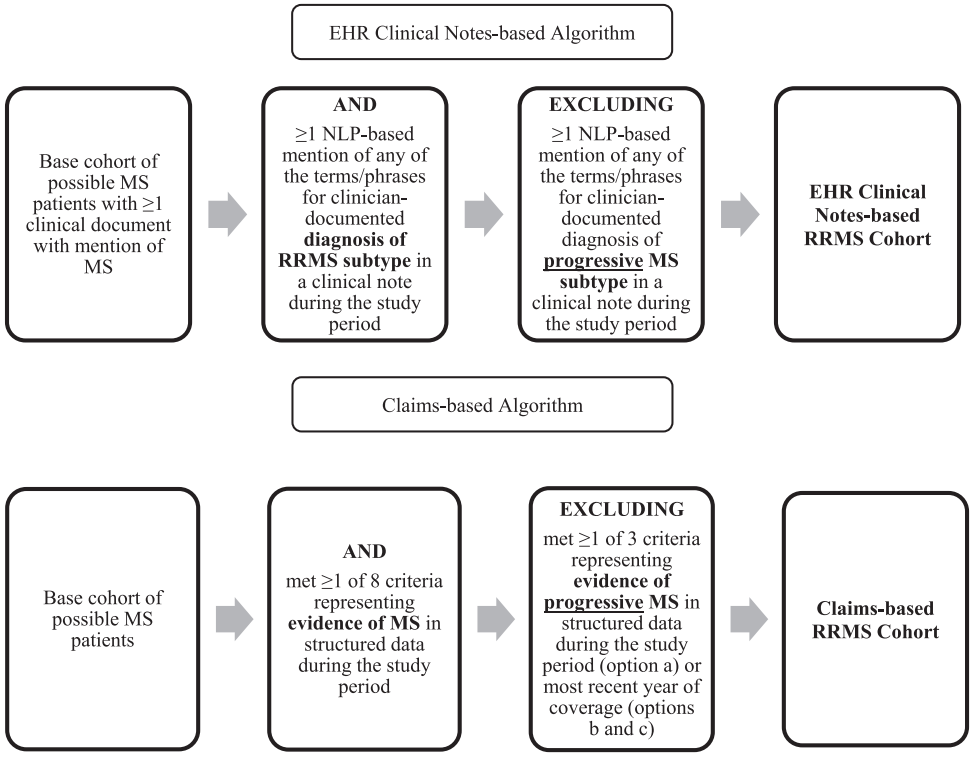

Fig. 1 – RRMS study population cohort development. EHR, electronic health record; MS, multiple sclerosis; NLP, natural language processing; RRMS, relapsing-remitting multiple sclerosis.

Two algorithms were used in combination to identify patients with RRMS without evidence of progressive disease (Fig. 1). Algorithm 1 was first used as inclusion criteria, and algorithm 2 was used as exclusion criteria; patients with RRMS were positive for algorithm 1 and negative for algorithm 2. An EHR-based and a claims-based algorithm 2 were applied to the results of the respective claims-based and EHR-based algorithm 1. In addition, the EHR- and claims-based algorithms 2 were applied to the combined results of the EHR- and claims-based algorithms 1. To be considered a patient with RRMS without evidence of progressive disease on the basis of the combined EHR- and claims-based algorithms, results of either, or both, algorithms 1 needed to be positive and no option for algorithm 2 could be positive.

Algorithm 1 (inclusion criteria)

The EHR-based algorithm analysis was restricted to patients in the base MS cohort with at least one clinical document with mention of MS. The algorithm used key terms and phrases, such as ["multiple, sclerosis"] and ["relapsing" and/or "remitting"], that potentially indicated RRMS subtype (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.014). Iterations of algorithm development and manual verification were conducted to refine the algorithm.

The claims-based algorithm searched for combinations to identify patients with evidence of MS: presence of MS *ICD-9-CM* diagnosis codes, MS-related symptom codes recorded as a part of a neurology visit, prescribed MS DMT codes, and codes signifying brain/spinal MRI performed (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.014; the full list of *ICD-9-CM* codes is available on request). The DMTs of interest included alemtuzumab, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, natalizumab, peginterferon beta-1a, and teriflunomide.

Algorithm 2 (exclusion criteria)

The EHR-based algorithm used key terms and phrases that relied on finding the term "progressive" near the phrase "multiple sclerosis" to potentially indicate progressive MS subtypes at any time during the study period (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.014). The algorithm was as follows: "contains (document_text,' NEAR((progressive, multiple, sclerosis) , 6, FALSE) ' ,18)." This NLP-based algorithm searched the clinical notes text for instances where the terms "progressive," "multiple," and "sclerosis" were within six words of each other, in any order in relation to each other. Iterations of this algorithm did not include evidence of negation (e.g., "no" or "not" near the term "progressive"). Manual review found a low incidence of negation. It was therefore not included in the final algorithm because of the potential for finding false negatives.

Three options were assessed for the claims-based algorithm 2 to identify patients with progressive MS (see Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.014). Three options used claims-based algorithm 1 inclusions. Option A added medications more commonly used for progressive cases (mitoxantrone, cyclophosphamide, or methotrexate) at any time during the study period [14]. Option B used a claims-based algorithm using the Kurtzke Functional System Score (KFSS) adapted from *ICD-9-CM* codes to generate Expanded Disability Status Scale (EDSS) scores. For each KFSS component, cross-mapping of *ICD-9-CM* codes was performed as closely as possible by an experienced clinician. Using the pyramidal functions system as an example, a KFSS of 1 for abnormal signs without disability was mapped to *ICD-9-CM* code 781.2 (abnormality of gait), and a KFSS of 6 for quadriplegia was mapped to *ICD-9-CM* codes 344.00 (quadriplegia unspecified), 344.09 (other quadriplegia), and V49.84 (bed confinement status). "Unknown" (value = 9) was not mapped for the KFSS, and "Normal" (value = 0) was defined by an absence of a sign or symptom. The EDSS score was calculated twice (in the 7th to the 12th month before the end of the patient's most recent year of care coverage and in the 1st to the 6th month before and at the end of the most recent year of coverage). Disease progression was defined as an increase of 1.0 or more if the previous EDSS score was 0 to less than 5.5, or 0.5 or more if the previous EDSS score was 5.5 or more [15]. Option C applied an algorithm modified from Gilden et al. [12] in which progressive MS was defined as 12 months or more of recorded MS history during the patient's most recent year of coverage, with either 10 or more of the last 12 months at the exacerbation level or the last 12 months at the plateau/stable level with a final therapy type of nursing home, home health, or selected rehabilitation/durable medical equipment [12]. The most recent year of coverage was defined by at least one documented medical encounter (of any kind) for any given 12-month period, with no more than 365 days between any documented medical encounter for the patient, after the index date and during the study period. If the patient did not have a gap of 365 days, then the last date of the study period (i.e., December 31, 2014) was the end of the "most recent 1-year period of care coverage."

Patients who received mitoxantrone, cyclophosphamide, or methotrexate at any time during the study period were excluded to be conservative and exclude any patients who may have had progressive disease. Options B and C were assessed during the most recent year of coverage to allow for relapses during the study period, but these exclude patients who may be transitioning or have already progressed to SPMS. As with medications, this was a conservative approach designed to exclude patients who may have had progressive disease so as to maximally isolate patients with RRMS.

Medical Chart Review for Algorithm Validation

Two random samples of approximately 100 patients with RRMS, identified by each pair of the EHR- and claims-based algorithms, were manually validated by a single physician review. Consistent with typical NLP validation [16–18], validation of the EHR-based algorithms consisted of physician review of all available clinician-written clinical notes, including outpatient clinic notes, inpatient progress reports, and brain/spinal MRI reports, to find explicit evidence confirming MS subtype. Each review was categorized as "yes/certain," "likely," "possible," "no," or "unknown" for RRMS. Unknown was assigned when the clinician's impressions of MS subtype was not included in the EHR notes and therefore could not be determined. Definitive evidence was defined as explicit documentation of MS, RRMS, and/or progressive MS by the patient's treating physician(s), and was used to calculate PPV for the EHR-based algorithms. Further details of this validation process are presented in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.014.

Validation of claims-based algorithms consisted of physician review of comprehensive patient profiles, including all diagnoses (*ICD* codes), medication (names and Healthcare Common Procedure Coding System codes), procedure (Current Procedural Terminology codes), and brain/spinal MRI records, and all clinical notes (of any type) to find evidence confirming MS subtype. Each review was categorized as "yes/certain," "likely," "possible," "no," or "unknown" for RRMS. Evidence was defined as documentation across the comprehensive patient profile consistent with MS, RRMS, and/or progressive MS, and was used to calculate the PPV for claims-based algorithms.

Statistical Analysis

Descriptive statistics are reported for demographic and clinical characteristics of the MS patient population eligible for the study

and the cohorts identified. The baseline characteristics reported include the Charlson Comorbidity Index score and resource utilization (e.g., hospitalizations and emergency visits).

PPVs, with 95% confidence intervals (CIs) (defining positive as "yes/certain," "likely," or "possible"; negative as "no"; and excluding "unknown" cases), were calculated from medical chart review results (criterion standard) and output from each algorithm as part of the validation process. PPV was defined as the proportion of patients who were identified by the algorithms as having the condition and whose medical chart review indicated had the condition ("true positive") divided by the total number of patients identified with the condition by the algorithms: PPV = (true positives)/(true positives + false positives).

Sensitivity analyses were also conducted to determine upper and lower bounds and to estimate the extent to which "unknown" cases would influence the PPV. In these analyses, positive was defined as 1) "yes/certain" or "likely" (with "possible" and "unknown" excluded); 2) "yes/certain" (with "likely," "possible," and "unknown" excluded); 3) "yes/certain," "likely," or "possible" (including "unknown" cases as negative); and 4) "yes/certain," "likely," "possible," or "unknown."

Results

A total of 12,011 patients were identified with at least one MS diagnosis (*ICD-9-CM* code 340) at any time during the study period. After applying additional inclusion and exclusion criteria, 5308 patients with possible MS were included in the base cohort (Fig. 2). For the EHR-based algorithm, 4623 (87.1%) patients were identified with at least one clinical document mention of MS.

Algorithm Results

Of the 5308 patients with possible MS, 3111 (58.6%) patients were positive for the EHR- or claims-based algorithm 1 (Table 1). A total of 990 (18.7%) patients were positive for the EHR-based algorithm 1, and 2960 (55.8%) patients were positive for the claims-based algorithm 1 (Table 2). The number of patients positive for both the claims- and EHR-based algorithms 1 was 839 (15.8%). A total of 2121 patients were positive for only the claims-based algorithm 1, and 151 were positive for only the EHR-based algorithm 1.

Algorithm 2 was applied to identify patients with progressive MS among the 3111 patients who were positive for either or both algorithms 1 (Table 2). Most patients identified with progressive MS by the claims-based algorithm were identified by option B (n = 608), compared with fewer than 100 patients identified by option A (n = 61) or C (n = 45). A total of 898 patients were identified by any algorithm 2, out of the 3111 patients who were identified by any algorithm 1. The 898 patients include 56 patients identified by the EHR-based algorithm 1 and the claims-based algorithm 2, 689 patients identified by the claims-based algorithms 1 and 2, and 153 patients identified by the EHR-based algorithms 1 and 2.

The final RRMS study cohort (patients positive for any algorithm 1 [3111] but not positive for any algorithm 2 [898]) therefore contained 2213 patients. A total of 837 patients from the pool of 990 patients identified using the EHR-based algorithm 1 and 2271 patients from the pool of 2960 patients identified using the claims-based algorithm 1 remained in the final cohort after algorithm 2 exclusion criteria were applied.

The 2213 patients had similar demographic characteristics to the base cohort. Use of DMT in the 12 months before the index date appeared more commonly in patients with MS (positive for algorithm 1) or RRMS than in those with possible MS (Table 1).

When the baseline characteristics of patients with RRMS identified by each pair of algorithms were considered, a numerically higher proportion of those identified using claims-based algorithms had diagnoses of cerebrovascular disease, hypertension, myocardial infarction, peripheral vascular disease, and psychosis (data not shown); a higher mean Charlson Comorbidity Index score; accident and emergency visits; and use of supportive therapy; a numerically lower proportion had brain or spinal MRI in the 12 months before the index date (Table 1).

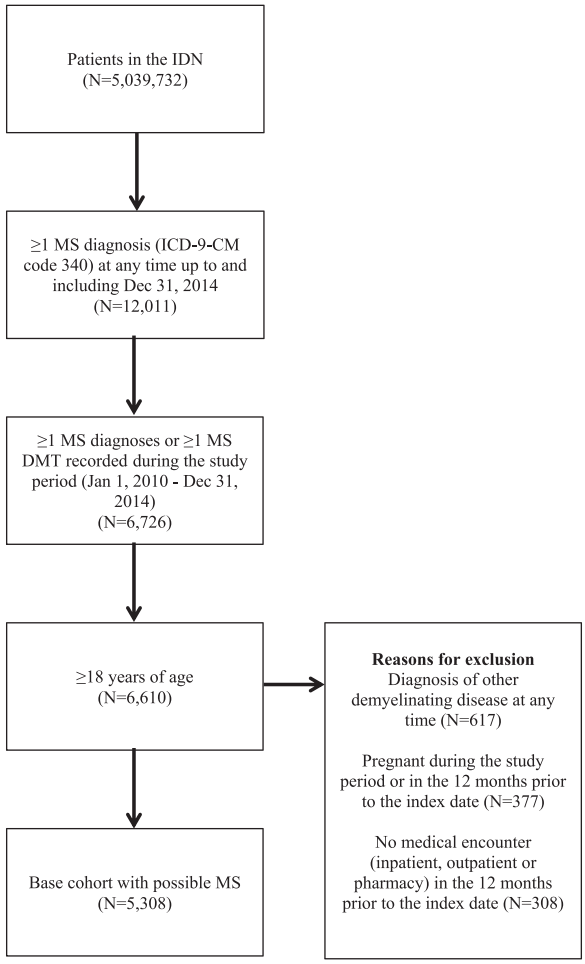

Fig. 2 – Base cohort patient disposition. DMT, disease-modifying therapy; EHR, electronic health record; *ICD-9-CM, International Classification of Diseases, Ninth Edition, Clinical Modification*; MS, multiple sclerosis.

Algorithm Validation

Results of the manual chart review to validate a random sample of patients with RRMS identified by each pair of the EHR-based (n = 111) and claims-based (n = 137) algorithms are presented in Tables 3 and 4, respectively.

PPV was 99.1% (95% CI 94.2%–100%) for the EHR-based algorithms, when unknown cases were excluded from the analyses (Table 3). Of a sample of 111 patients identified by the EHR-based algorithms, 1 patient was negative (no evidence of MS) and 3 patients were unknown (MS subtype was not explicitly recorded). For the three unknown results, one reported the terms "relapsing" and "remitting" as part of the note template and not the clinician's actual impression or documentation, one reported the term "remitting" in the context of "history of chronic remitting depression," and one reported the term "remitting" in the context of "Clinical history: Multiple sclerosis. Remitting vision disturbance."

Table 1 – Baseline demographic and clinical characteristics of patients with inclusion criteria (positive for algorithm 1) and patients with RRMS according to either the EHR- and/or claims-based algorithms 1 and 2.

Characteristic	Patients meeting algorithm inclusion criteria* (N = 3111)	Patients with RRMS†		
		Combined (claims-based or EHR-based) algorithms [N = 2213])	Claims-based (N = 2271)‡	EHR-based (N = 837)‡
Sex: female, n (%)	2320 (74.6)	1666 (75.3)	1694 (74.6)	647 (77.3)
Age at index date (y), mean ± SD	48.0 ± 13.4	47.2 ± 13.2	47.5 ± 13.3	46.0 ± 19.6
Race/ethnicity, n (%)				
White	2930 (94.2)	2085 (94.2)	2140 (94.2)	791 (94.5)
Other§	54 (1.7)	41 (1.9)	41 (1.8)	16 (1.9)
Unknown	127 (4.1)	87 (3.9)	90 (4.0)	30 (3.6)
Charlson Comorbidity Index score				
Mean ± SD	1.32 ± 2.1	1.16 ± 1.9	1.19 ± 1.9	0.99 ± 1.6
0, n (%)	1478 (47.5)	1126 (50.9)	1127 (49.6)	443 (52.9)
1, n (%)	728 (23.4)	528 (23.9)	550 (24.2)	207 (24.7)
2, n (%)	369 (11.9)	248 (11.2)	262 (11.5)	87 (10.4)
>3, n (%)	536 (17.2)	311 (14.1)	332 (14.6)	100 (12.0)
Hospitalizations‖, n (%)	469 (15.1)	273 (12.3)	293 (12.9)	98 (11.7)
A&E visits‖, n (%)	1059 (34.0)	699 (31.6)	742 (32.7)	221 (26.4)
DMT‖, n (%)	684 (22.0)	509 (23.0)	552 (24.3)	214 (25.6)
Corticosteroids (high dose) or ACTH‖,¶, n (%)	356 (11.4)	249 (11.3)	260 (11.5)	99 (11.8)
Brain or spinal MRI‖, n (%)	1508 (48.5)	1068 (48.3)	1082 (47.6)	484 (57.8)
MS-related symptoms‖, n (%)	1688 (54.3)	1128 (51.0)	1187 (52.3)	417 (49.8)
MS-related symptom therapy‖,**, n (%)	1237 (39.8)	815 (36.8)	857 (37.7)	335 (40.0)
Medications used for progressive disease‖,††, n (%)	31 (1.0)	3 (0.1)	3 (0.1)	6 (0.7)
KFSS†, mean/median (range)				
Pyramidal functions	0.36/0 (0–6)	0.27/0 (0–6)	0.28/0 (0–6)	0.31/0 (0–5)
Cerebellar functions	0.08/0 (0–4)	0.07/0 (0–4)	0.07/0 (0–4)	0.04/0 (0–3)
Brainstem functions	0.26/0 (0–5)	0.2/0 (0–5)	0.21/0 (0–5)	0.22/0 (0–5)
Sensory functions	0.81/0 (0–5)	0.77/0 (0–5)	0.77/0 (0–5)	0.77/0 (0–5)
Bowel and bladder function	0.13/0 (0–6)	0.09/0 (0–6)	0.1/0 (0–6)	0.09/0 (0–6)
Visual function	0.07/0 (0–6)	0.06/0 (0–6)	0.06/0 (0–6)	0.06/0 (0–6)
Cerebral (or mental) functions	0.18/0 (0–5)	0.13/0 (0–5)	0.14/0 (0–5)	0.16/0 (0–5)
EDSS‖, mean/median (range)	1.58/0 (0–7.5)	1.36/0 (0–7.5)	1.38/0 (0–7.5)	1.45/0 (0–7)
Disease duration until index date (y), mean	3.95	3.73	3.85	4.50
MS supportive therapy‖, n (%)				
Nursing home	8 (0.3)	5 (0.2)	4 (0.2)	1 (0.1)
Home health	26 (0.8)	6 (0.3)	10 (0.4)	2 (0.2)
Selected rehabilitation/DME	360 (11.6)	214 (9.7)	222 (9.8)	81 (9.7)

A&E, accident and emergency; ACTH, adrenocorticotropic hormone; DME, durable medical equipment; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; EHR, electronic health record; KFSS, Kurtzke Functional System Score; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

* Inclusion criteria for cohorts of patients with RRMS (RRMS subtype by EHR-based algorithm; MS by claims-based algorithm) to be evaluated using algorithm 2 to exclude progressive MS.

† Based on algorithm 1 positive and not positive for any algorithm 2 (progressive MS).

‡ Patients may be found by more than one algorithm.

§ Included in the "Other" group for the cohort of patients with MS were African American (0.6%), Hispanic (0.1%), Asian (0.4%), Pacific Islander (0.2%), and Native American (0.3%) patients. Proportions of patients with these ethnicities were similar in the cohort of patients with RRMS.

‖ In the 12 mo before the index date.

¶ Methylprednisolone and prednisone. No patients were receiving ACTH, dexamethasone, or prednisolone.

Symptoms included fatigue, spasticity, impaired ambulation, optic neuritis, paresthesia, bladder and sexual dysfunction, facial weakness, muscle weakness, trigeminal neuralgia, diplopia, neuropathic pain, paraplegia, hemiplegia, depression, ataxia, tremor, or gait disturbance.

** Therapy for fatigue, spasticity, impaired ambulation, bladder and sexual dysfunction, neuropathic pain, depression, or gait disturbance.

†† Medications were mitoxantrone, cyclophosphamide, and methotrexate.

Table 2 – RRMS attrition for algorithm 2 (exclusion criteria) applied to the results of algorithm 1 (inclusion criteria).

Criteria	Claims-based algorithms (n)*	EHR-based algorithms (n)*	Combined (claims-based or EHR-based) algorithms (n)
Patients positive for algorithm 1†	2960	990	3111
Patients positive for algorithm 1 and any algorithm 2‡	689	153	898§
Patients positive for algorithm 1 and negative for algorithm 2a	2899	NA	2783‖
Patients positive for algorithm 1 and negative for algorithm 2b	2352	NA	2287‖
Patients positive for algorithm 1 and negative for algorithm 2c	2915	NA	2796‖
Patients positive for algorithm 1 and negative for applicable algorithm 2—final RRMS cohorts	2271¶	837	2213

EHR, electronic health record; MS, multiple sclerosis; NA, not applicable; RRMS, relapsing-remitting multiple sclerosis.
* Patients may be found by more than one algorithm.
† Inclusion criteria for cohorts of patients with RRMS (RRMS subtype by EHR-based algorithm; MS by claims-based algorithm) to be evaluated using algorithm 2 to exclude progressive MS. Among 3111 patients, there were 839 patients overlapped between both EHR- and claims-based algorithms 1.
‡ Cohorts of patients with progressive MS.
§ Includes patients positive for claims- and/or EHR-based algorithm 1 and positive for any claims- and/or EHR-based algorithm 2. Among 898 patients, there were 689 patients positive for claims-based, 153 patients positive for EHR-based, and 56 patients positive for any algorithm 2.
‖ Includes patients positive for claims- and/or EHR-based algorithm 1 and not positive for the respective claims- and/or EHR-based algorithm 2.
¶ Includes patients positive for claims-based algorithm 1 and not positive for any claims-based algorithm 2.
Includes patients positive for claims- and/or EHR-based algorithm 1 and not positive for any algorithm 2.

Of the 137 sample patients identified from the claims-based algorithms, 122 were positive, 7 were likely, 1 was possible, 0 were unknown, and 7 were negative for RRMS. The claims-based algorithms had high accuracy (94.6% [95% CI 89.1%–97.8%] to 94.9% [95% CI 89.8%–97.9%]) identifying patients with RRMS for all methods of calculating PPV (Table 4). PPV was similar whether using algorithm 2a, 2b, or 2c (results not shown), although use of algorithm 2b to exclude patients with progressive disease had a slightly higher PPV than those of the other options, but this was not statistically significant because of overlapping CIs.

Discussion

EHR databases contain a wealth of clinical information that can be used to identify conditions and diagnoses relevant for research and surveillance. Extraction of this information is reliant on algorithms to accurately select appropriate study cohorts. This study evaluated the ability of EHR- and claims-based algorithms (see Appendix Tables 2 and 4 in Supplemental Materials) to identify patients with RRMS without evidence of progressive MS.

The approaches for this study involved multiple criteria and options to assess the contributions of each factor toward positively distinguishing patients with RRMS from those with SPMS, PPMS, or relapsing progressive MS. Although no clear threshold has been defined for PPV, PPVs of 70% or more, between 50% and 70%, and less than 50% are usually considered high, moderate, and poor test performance, respectively [19]. Validation of the algorithms showed that the EHR-based algorithms had high performance with a PPV of 99.1% under most scenarios. The claims-based algorithms also performed well, with PPVs of 94.6% to 94.9%. For completeness, PPVs were calculated including unknown cases as negative. As expected using this criterion, PPV was lower for the EHR-based algorithms (96.4%). Nevertheless, we assert that the inclusion of the unknown cases as negative for validation purposes is not appropriate, and the alternative analyses used are more suitable.

There were some limitations of our validation study, including the potential for excluding patients with RRMS via claims-based

Table 3 – PPVs for EHR-based algorithms (positive for algorithm 1 and negative for algorithm 2) to identify RRMS without progressive MS.

EHR-based algorithm results		Positive from NLP chart review, n	Negative from NLP chart review, n	PPV, % (95% CI)
Positive cases	Negative cases			
Yes/certain, likely, possible*	No†	107	1	99.1 (94.2–100)
Yes/certain, likely, possible*	No, unknown	107	4	96.4 (90.5–98.8)
Yes/certain, likely, possible, unknown*	No	110	1	99.1 (94.4–100)

CI, confidence interval; EHR, electronic health record; MS, multiple sclerosis; NLP, natural language processing; PPV, positive predictive value; RRMS, relapsing-remitting multiple sclerosis.
* Zero cases were likely or possible.
† Three "unknown" cases were excluded from analyses.

Table 4 – PPVs for claims-based algorithms (positive for algorithm 1 and negative for algorithm 2) to identify RRMS without progressive MS.

Claims-based algorithm results		Positive from medical chart review, n	Negative from medical chart review, n	PPV, % (95% CI)
Positive cases	Negative cases			
Yes/certain, likely, possible	No*	130	7	94.9 (89.8–97.9)
Yes/certain, likely	No*	129	7	94.9 (89.7–97.9)
Yes/certain	No*	122	7	94.6 (89.1–97.8)

CI, confidence interval; MS, multiple sclerosis; PPV, positive predictive value; RRMS, relapsing-remitting multiple sclerosis.
* Zero "unknown" cases resulted from this validation.

algorithm 2 criteria. Mitoxantrone, cyclophosphamide, or methotrexate may have been prescribed for active RRMS and not progressive MS. This criterion identified only 61 patients for exclusion and thus had minimal impact. Most of the progressive MS cases excluded were identified by the change in EDSS score during the most recent year of coverage; for some cases, however, the increase in the EDSS score may have been due to a relapse episode or partial remission. Because relapse events and MRI results were not measured, it was not possible to definitively determine reasons for increases in EDSS scores.

The EHR-based algorithms excluded patients explicitly documented with progressive subtypes during the study period. One EHR study reported that 36% of the records had multiple MS subtypes documented, possibly reflecting disease progression or challenges in assessing subtype [10]. The claims-based algorithms excluded most of the progressive MS cases by change in the EDSS score during the most recent year of coverage. This approach was used to maximize the likelihood that all progressive MS cases were excluded. Assessing the most recent year of coverage was less restrictive than assessing the entire study period, as with EHR-based algorithms. We do not know the level of agreement between disability progression during that year of coverage and clinical documentation of progressive MS subtype over the study period.

Both the EHR- and claims-based algorithms had high PPV. Because PPV is a function of RRMS prevalence, increasing the previous probability of RRMS in the base cohort by requiring one MS diagnosis code and at least one mention of MS in a clinical note for the EHR-based algorithms inflated the PPV compared with application of the algorithms to the entire database. Because the claims-based algorithm 1 required at least one MS diagnosis code, application of the claims-based algorithms to the base cohort or the population provided the same PPV. The EHR-based algorithms had nonstatistically higher PPVs, but identified fewer patients with RRMS than did the claims-based algorithms.

Because PPV was the only validation measure calculated, physicians who reviewed medical charts for validation were not blinded to the algorithm results. This could have inadvertently introduced bias, resulting in higher PPV. Sensitivity, specificity, and negative predictive value were not calculated. This study prioritized PPV as the validation measure because the main goal was to ensure the cohort identified included patients who truly had RRMS [20]. Other case ascertainment algorithm studies similarly calculated only PPV [21–23]. Without measurement of other validation measures, it is difficult to assess generalizability of the cohort or measure the extent of false negatives.

In common with the findings of this study, EHR-based algorithms in appropriate populations have generally had high PPVs in other reports. A study of EHR data from the Department of Veterans Affairs used *ICD-9-CM* codes to identify patients with MS, and NLP keywords and phrases for determining MS subtype. The methodology was reported to have a PPV of 96.4% and a specificity of 93.8% for identification of MS subtypes [10]. Another study using EHR from a university medical center database used four previously published algorithms based on *ICD-9-CM* codes, MS treatment prescriptions, and keywords to identify MS subtype. Precision of 88% for identifying MS subtypes was reported [11].

The validation procedure used in this study for the EHR-based algorithms required explicit documentation by a clinician of the subtype. In common with other algorithm studies [10,11], data were, at times, incomplete. Two MS algorithm studies found that medical records searched did not routinely record MS subtype in either database [10,11]. Similarly, in the present study, one-third of patients randomly selected for validation of claims-based algorithms were assigned as "unknown" during a manual validation of clinical notes only, with MS subtype not recorded and insufficient evidence of MS subtype documented. Symptoms and course of care were often well documented, but no clear indication of subtype was found. At times, this occurred when precise MS subtype had not been clinically determined or when more time was required for the patient's pattern of MS symptoms to present. Another scenario encountered was when patients were relatively stable clinically, and so MS subtype may not have seemed relevant to the patient's care and was not documented. This scenario may help explain why the algorithm using only clinical notes identified a much smaller number of patients with RRMS compared with the claims-based algorithm, which did not explicitly require clinical documentation of RRMS subtype.

Medical chart reviews of clinical notes only for the claims-based algorithms yielded limited results in this study because of the low proportion of MS subtype recorded in the clinical notes. The manual chart review of comprehensive patient profiles proved effective for validation of the claims-based algorithm, resulting in zero unknown cases. Use of medical chart review of clinical notes instead of traditional medical chart review was efficient and cost-effective, and showed high performance for validating the NLP-driven EHR-based algorithms. Nevertheless, assessment of the EHR-based algorithms in other integrated delivery networks is recommended before applying these algorithms to other data sources.

Conclusions

EHR and claims databases can be used to provide a variety of information relating to MS. The algorithms evaluated in this study identified a real-world cohort of patients with RRMS that can be studied in clinical research with confidence.

Supplementary material

Supplemental material accompanying this article can be found in the online version as a hyperlink at https://doi.org/10.1016/j.jval.

2018.06.014 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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