Identifying Adult Patients with Nonrelapsing Secondary Progressive Multiple Sclerosis Using Algorithms in US-based Healthcare Databases

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BACKGROUND

- Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS). It is categorized into phenotypes depending on whether the disease is relapsing (relapsing-remitting MS [RRMS]) or progressive (primary progressive MS [PPMS] or secondary progressive MS [SPMS]).^{1,2}
- People with SPMS who still experience relapses are defined as having active SPMS (aSPMS).² In the US, disease modifying therapies (DMTs) approved for the treatment of RRMS can be used to treat aSPMS.
- However, many patients with SPMS no longer experience relapses, which can be termed nonrelapsing SPMS (nrSPMS) and may not be benefiting from currently approved DMTs.
- Given this unmet need and disease burden on these patients, an in-depth understanding of nrSPMS is important, particularly in the context of real-world evidence.
- While there is one ICD-10 code for MS, there are no codes for specific MS phenotypes, including none for SPMS overall or the nrSPMS subtype.

OBJECTIVE

This study aimed to develop a validated algorithm capable of identifying adult patients with nrSPMS in US-based electronic health records (EHR) or claims databases.

METHODS

• We developed algorithms capable of identifying patients with nrSPMS and tested them in two data sources – patient medical records (including billing records) and a large commercial database (Figure 1)

| Cognitive interviews with neurologists | Three neurologist were interviewed to provide clinical input to develop potentia |
|---|---|
| Development of potential algorithms | Based on clinical input from neurologists, candidate algorithms were developed |
| Study protocol & obtaining IRB approval | Study protocol and data collection tool were developed to collect the data from The aim was to collect data on 200 adult patients with MS across 3 patient coho 100 patients with nrSPMS (as true positives) 100 patients with either aSPMS or RRMS (as controls to serve as the compari Central IRB approval was obtained |
| Study population, data collection from medical charts, and billing records | Study population eligibility criteria included: MS diagnosed patient ≥18 years Patients last seen at the clinic no more than 2 years before the end of the study 3 years of available medical records, with at least 1 visit per calendar year Physician diagnosis of nrSPMS (no clinical relapses in 2 years before index), at index) or RRMS at baseline De-identified patient data were collected from patient medical records and clint All data were collected retrospectively (prior to the study end date of 12/30/2027) |
| Performance testing of algorithm candidates | Tested the performance (sensitivity, specificity, positive predictive value [PPV], a hundreds of versions of the algorithms in both medical records & clinical billing |
| Face validity of the leading algorithms in US-based claims databases | Tested the face validity of the 2 best performing nrSPMS algorithms in a large US-best observing whether the demographic, clinical, and utilization characteristics we would with nrSPMS A retrospective cross-sectional analysis was conducted using IQVIA Pharmetric Descriptive statistics was conducted for the considered measures The measured characteristics were compared among patients with nrSPMS with from published clinical studies, other sources, and patient medical records colleged |
| aSPMS, active secondary progressive multiple sclerosis; DMT, disease mod RRMS, relapsing-remitting multiple sclerosis. | difying therapy; eCRF, electronic case report form; IRB, institutional review boards; NPV, negative predictive value; nrSPMS, nonrelapsing seco |

Disclosures

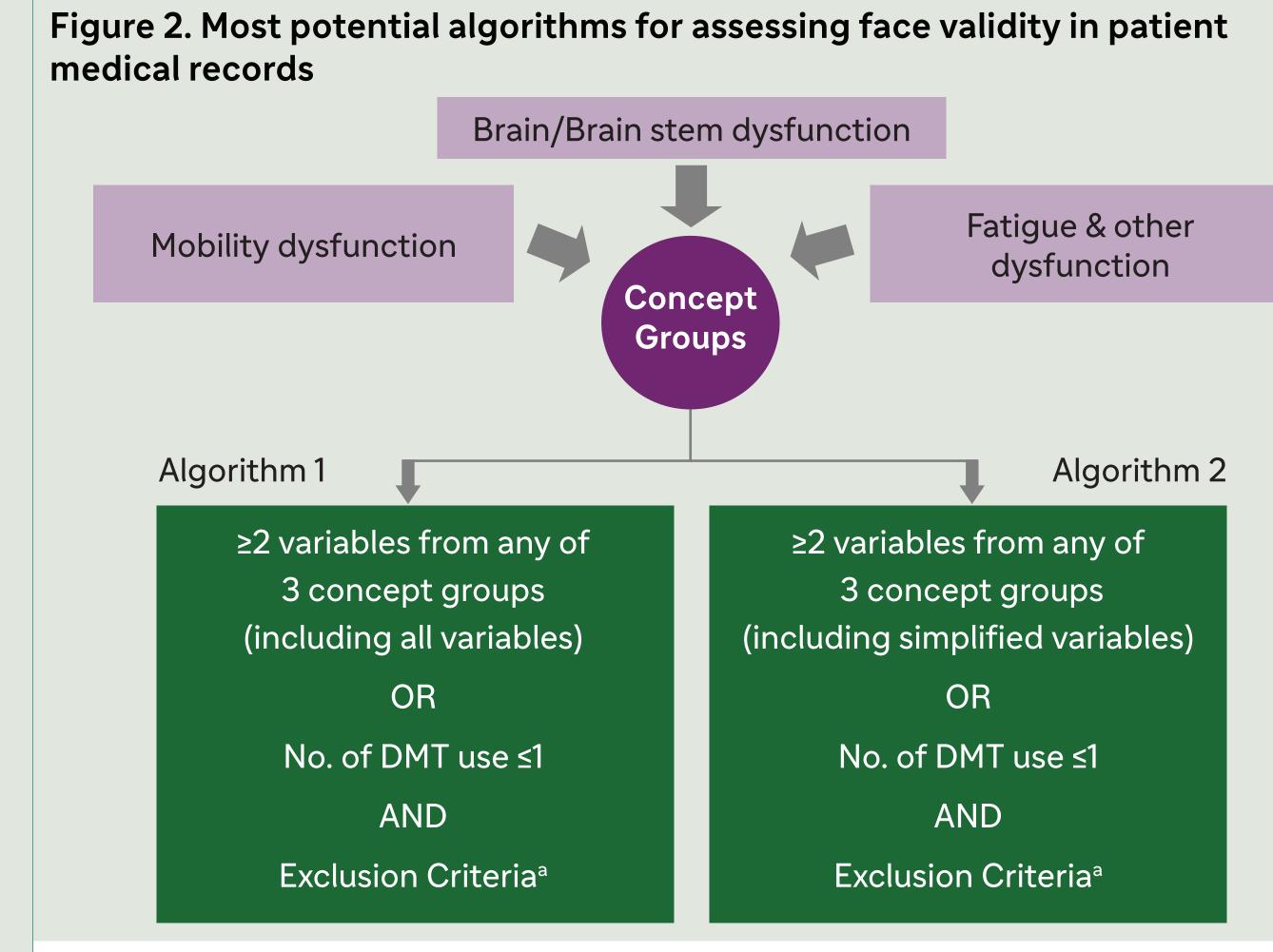
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RESULTS

- Candidate algorithms (8 clinically recommended algorithms and hundreds of variations based on exploratory analysis) made up of variables with existing ICD codes were developed to identify patients with nrSPMS in US-based healthcare claims datasets. Based on their performance in medical and billing records of 195 patients with MS across the US, 2 best-performing algorithms were identified to be further tested in IQVIA Pharmetrics Plus[®] claims database (2016-2020) **(Figure 2)**.
- In both medical/billing records, algorithm 1 resulted in 93%/92% sensitivity, 86%/90% PPV, 74%/84% specificity, and 87%/86% NPV, while algorithm 2 showed 93%/92% sensitivity, 76%/84% specificity, 86%/90% PPV, and 87%/86% NPV **(Table 1)**.



Algorithm 1: ≥2 variables from any of 3 concept groups (mobility dysfunction, brain/brain stem dysfunction, other) OR (no. of DMT use and no exclusions) Spinal cord dysfunction: Gait dysfunction AND use of dalfampridine (Ampyra); spasticity AND use of spasticit lication; use of ambulatory devices (e.g., cane, walker, wheelchair); physical therapy for ≥6 weeks in any 1-year period; occupation therapy for ≥6 weeks in any 1-year period; documented falls; ataxia, 2) Brain dysfunction: Neuropathic pain AND use of pain medication trigeminal neuralgia AND use of pain medication; swallowing dysfunction (dysphagia); speech dysfunction (dysarthria); pseudobulbar affect AND use of Nuedexta (dextromethorphan/quinidine); optic neuritis; impaired cognition, and 3) Fatigue & Other dysfunction: Neurogenic bladder; neurogenic bowel; use of urinary catheter (e.g., self-catheterization, suprapubic catheter); bowel or bladder incontinence; in females - hospitalization for urinary tract infections (including acute cystitis, urosepsis, or kidney infection); hospitalization for respiratory infections; fatigue; insomnia; sleep apnea; sleep studies; circadian rhythm sleep disorder AND use of Provigi (modafinil) or Nuvigil (armodafinil).

Algorithm 2: Same as algorithm 1, but a shorter list of variables from the 3 concept groups. where, Mobility dysfunction: Use of spasticity medication, Use of ambulatory devices (e.g., cane, walker, wheelchair), Ataxia; Brain/brain stem dysfunction: Neuropathic pain AND use of pain medication, Trigeminal neuralgia, Speech dysfunction (dysarthria), Pseudobulbar affect, Optic neuritis, Impaired cognition; Fatigue & Other dysfunction: Neurogenic bladder, Use of urinary catheter (e.g., self-catheterization, suprapubic catheter), Bowel or bladder incontinence; Fatigue, Insomnia

^aExclusion criteria : Age >70 years, OR Primary diagnosis of other neurological disorder (Alzheimer's, Parkinson's Disease, Myasthenia gravis, or stroke), OR \geq 1 inpatient visit with a discharge diagnosis of multiple sclerosis (MS), OR \geq 1 outpatient visit with a diagnosis of MS AND use of dexamethasone, methylprednisolone, prednisolone, prednisone, or adrenocorticotropin hormone on day of or within 7 days following the visit. DMT, disease modifying therapy.

Table 1. Selected algorithm performance in EHR

| Data source | Algorithm | Sensitivity | PPV | Specificity | NPV |
|--|-------------|-------------|-----|-------------|-----|
| Medical records | Algorithm 1 | 93% | 86% | 74% | 87% |
| Medical records | Algorithm 2 | 93% | 86% | 76% | 87% |
| Billing records (assuming all | Algorithm 1 | 92% | 90% | 84% | 86% |
| inpatient visits and medications matched the data in the medical records) | Algorithm 2 | 92% | 90% | 84% | 86% |

EHR, electronic health record; NPV, negative predictive value; PPV, positive predictive value.

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tial candidate algorithms

m patient medical records and clinic billing data

arison group)

tudy (i.e., IRB approval date 12/30/2021)

, aSPMS (≥1 relapse in the past 2 years before

linic billing records from various neurology sites

and negative predictive value [NPV]) of data of 195 patients

-based commercial claims database by vould expect are found among patients identified

ics Plus[®] database

ith known (i.e., expected) information derived llected in this study

econdary progressive multiple sclerosis; PPV, positive predictive value;

| | Patients with a medical claim for MS between 1/1/2016 and 12/31/2018 (N = 197,097) | | |
|---|--|---|-----------|
| | | | |
| | Patients (≥ 18 years) continuously enrolled with a health plan after 2 years since start date (n = 53,773) | | |
| | claims with a p of MS ≥30 | * nt claim, or ≥2 outpatient rimary diagnosis days apart 33,244) | |
| Algorithm 1 | (11 00,211) | | Algorithm |
| Patient with ≥2 out of 3 concept groups ^a OR used ≤1 DMT (n = 30,627) Patients (≤70 years) with no primary diagnosis of other neurological disorders ^b (n = 28,667) No inpatient hospitalization with a discharge diagnosis of MS (n = 27,652) | | Patient with ≥2 out of 3 concept group OR used ≤1 DMT (n = 30,947) | |
| | | Patients (≤70 years) with no primary diagnosis of other neurological disorders ^b (n = 28,983) No inpatient hospitalization with a discharge diagnosis of MS (n = 27,960) | |
| | | | |
| No outpatient visit with MS diagnosis AND use of medication ^c or adrenocorticotropin hormone on day of or within 7 days of visit (n = 19,661) | | No outpatient visit with MS diagnosis AND use of medication [°] or adrenocorticotropin hormone on day o [°] or within 7 days of visit (n = 19,783) | |

• A total of 33,244 MS patients were identified in the IQVIA database between

- After applying additional algorithm-specific criteria, the total nrSPMS

for algorithm identification.

19,783 patients **(Figure 3)**.

1/1/2016 and 12/31/2018. A random MS claim during this period was selected as

patients identified by algorithm 1 were 19,661 patients and algorithm 2 were

the start date, and 2 years observation period since the start date were used

^aconcept groups: Spinal cord dysfunction, brain dysfunction, other (neurogenic bladder, neurogenic bowel, fatigue, insomnia, etc); ^bAlzheimer's, Parkinson's Disease, Myasthenia gravis, or stroke;^cdexamethasone, methylprednisolone, prednisolone, prednisone. N, number of patients; DMT, disease modifying therapy; MS, multiple sclerosis.

 Demographic, clinical, and utilization characteristics of these patients were reported in **Table 2**.

 Table 2. Demographics and clinical characteristics of patients with nrSPMS

| | Algorithm 1 (N = 19,661) | Algorithm 2 (N = 19,783) |
|----------------------|-----------------------------|-----------------------------|
| Age, year, Mean (SD) | 48.6 (10.5) | 48.5 (10.5) |
| Female | 14,903 (75.8) | 14,998 (75.8) |
| Geographic region | | |
| Midwest | 5,814 (29.6) | 5,840 (29.5) |
| Northeast | 4,381 (22.3) | 4,419 (22.3) |
| South | 6,484 (33.0) | 6,527 (33.0) |
| West | 2,982 (15.2) | 2,997 (15.1) |
| Insurance status | | |
| Commercial | 11,958 (60.8) | 12,024 (60.8) |
| Medicaid | 198 (1.0) | 198 (1.0) |
| Medicare | 1,326 (6.7) | 1,334 (6.7) |
| Other/Unknown | 6,179 (31.4) | 6,227 (31.5) |
| | | |

Table 2. (Cont'd)

Clinical Characteristics Gait dysfunction Fatigue Spasticity Bowel or bladder incontinent Optic neuritis Insomnia Use of ambulatory devices walker, wheelchair) DMT

Glatiramer acetate

Dimethyl fumarate

Beta interferon

Fingolimod

Other Medications Use

Pain medication

Spasticity medication

Comorbidity Conditions of In Multiple sclerosis comorbidit

Burning/numbness/tingling

Healthcare utilization

LOS (days) per patient amon

Inpatient hospitalizations

Receiving ICU care

Any ED visits

No. of outpatient hospital v (SD)

All data are presented as n (%) unless otherwise menti N, number of patients; DMT, disease modifying therapy secondary progressive multiple sclerosis; SD, standard deviation

- validit
- database compared to algorithm 1.

References

1. Lublin FD, et al. *Neurology.* 2014;83:278-86. 2. Klineova S, Lublin FD. *Cold Spring Harb Perspect Med.* 2018;8.

| | Algorithm 1 (N = 19,661) | Algorithm 2 |
|--------------|-----------------------------|---------------|
| | | |
| | | (N = 19,783) |
| | | |
| | 3,527 (17.9) | 3,534 (17.9) |
| | 6,437 (32.7) | 6,505 (32.9) |
| | 2,240 (11.4) | 2,228 (11.3) |
| ice | 3,265 (16.6) | 3,304 (16.7) |
| | 1,815 (9.2) | 1,825 (9.2) |
| | 1,715 (8.7) | 1,742 (8.8) |
| e.g., cane, | 1,087 (5.5) | 1,083 (5.5) |
| | 14,433 (73.4) | 14,555 (73.6) |
| | 3,529 (17.9) | 3,573 (18.1) |
| | 3,074 (15.6) | 3,117 (15.8) |
| | 2,613 (13.3) | 2,645 (13.4) |
| | 1,873 (9.5) | 1,898 (9.6) |
| | | |
| | 4,947 (25.2) | 5,004 (25.3) |
| | 5,930 (30.2) | 6,101 (30.8) |
| nterest | | |
| ty | 15,370 (78.2) | 15,489 (78.3) |
| | 3,766 (19.2) | 3,781 (19.1) |
| | | |
| ıg utilizers | 1,853 (7.57) | 1,864 (7.52) |
| | 1,853 (9.4) | 1,864 (9.4) |
| | 278 (1.4) | 280 (1.4) |
| | 3,877(19.7) | 3,904 (19.7) |
| sits, mean | 7.5 (10.8) | 7.5 (10.8) |

• To assess the face validity of the above 2 algorithms, characteristics of the patients identified using these algorithms were compared to published clinical studies and with patient medical records collected in this study. The characteristics were consistent, indicating that both algorithms 1 & 2 had face

• While both algorithms 1 and 2 were specific (patients identified with either are likely to have nrSPMS), algorithm 2 missed fewer patients with nrSPMS in IQVIA

LIMITATIONS

- Algorithm performance may be influenced by the quality of the data source used. For example in some data sources, characteristics may be recorded inconsistently or incompletely, causing some potential misclassification of patients.
- While some items included may increase the sensitivity of the algorithm, they may also decrease the specificity.
- Cost was not included in the algorithms as it was not identified as a significant criteria in identifying nrSPMS patients and future studies using our algorithms will likely explore healthcare cost.

CONCLUSIONS

- The proposed algorithms showed high performance when tested in patient medical record data.
- Additionally, the algorithms identified a cohort of patients in claims data that appeared consistent with clinically identified patients with nrSPMS (based on inclusion/exclusion criteria).
- These algorithms can be applied in other US EHR or claims-based datasets to facilitate further research to better identify and describe the nrSPMS population.



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