Original Research Paper

Identifying people with multiple sclerosis in the Canadian Primary Care Sentinel Surveillance Network

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Abstract

Background: We validated a case definition for multiple sclerosis using a clinical cohort linked with the Manitoba Primary Care Research Network of the Canadian Primary Care Sentinel Surveillance Network, and applied this definition to describe multiple sclerosis epidemiology using the Canadian Primary Care Sentinel Surveillance Network repository.

Methods: We developed candidate case definitions for multiple sclerosis in the Manitoba Primary Care Research Network using diagnoses and medications. We compared these case definitions to multiple sclerosis diagnoses identified by applying a validated definition to population-based administrative data (reference standard 1) and multiple sclerosis diagnoses recorded by the provincial Multiple Sclerosis Clinic (reference standard 2) using sensitivity, specificity, positive predictive value and negative predictive value. We applied the preferred case definition to the national Canadian Primary Care Sentinel Surveillance Network dataset.

Results: The Manitoba Primary Care Research Network included 160,904 patients. The preferred case definition required ≥ 2 billing records for multiple sclerosis within 2 years or multiple sclerosis listed as a health condition or ≥ 1 multiple sclerosis-specific prescription. This definition had a low sensitivity versus administrative (44.25%) and clinic datasets (53.41%) but high specificity versus administrative data (99.95%). Specificity was lower versus clinic data (71.43%), but the positive predictive value was high.

Conclusion: We developed a case definition for multiple sclerosis that can be applied to the Canadian Primary Care Sentinel Surveillance Network dataset for studies examining primary care of persons with multiple sclerosis.

Introduction

Comorbidities are common in multiple sclerosis (MS) and they are associated with multiple adverse outcomes.[1–4] Although MS-specific care is typically managed by a neurologist-led team, care for comorbidities is usually led by primary care providers. Therefore, efforts aimed at understanding management of comorbidities must focus on primary care.

A necessary first step is accurately identifying persons with MS within primary care datasets.

The Canadian Primary Care Sentinel Surveillance Network (CPCSSN) is a multi-system database that collects de-identified information derived from electronic medical records (EMR) of participating primary care practices across Canada. Case definitions have been validated for identifying other chronic

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diseases in CPCSSN.[5] Ontario-based investigators used the EMR Administrative Data Linked Database (EMRALD) to develop and test several EMR-based definitions of MS.[6] However, the performance of these definitions may differ between EMRALD and CPCCSN because of inherent differences between the data sources and processing within the networks, leading to differences in data quality and availability.

Therefore, we aimed to validate an EMR-based definition of MS within CPCSSN and apply this definition to describe the epidemiology of MS within the national CPCSSN repository.

Methods

We conducted a retrospective cohort study in Manitoba, Canada to develop our case definition, followed by a national retrospective cohort study using the CPCSSN repository. Manitoba has a population of approximately 1.3 million people and provides universal, publicly funded healthcare. The University of Manitoba Health Research Ethics Board, Manitoba's Health Information Privacy Committee and CPCSSN Standing Research and Surveillance Committee approved the study.

Data sources

We linked clinical data from the Manitoba MS Clinic, administrative (health claims) data from Manitoba and the Manitoba Primary Care Research Network (MaPCReN), the Manitoba network of CPCSSN, using an encrypted unique personal health identification number.

Clinical reference cohort

The Winnipeg MS Clinic maintains a clinic registry that captures current diagnoses for persons attending the MS Clinic. Over 89% of those approached agreed to participate in the registry and to linking their clinical and administrative data.

Manitoba administrative (health claims) data

Manitoba Health maintains electronic databases related to delivery of publicly funded health services. We accessed the population registry, hospital Discharge Abstract Database (DAD), medical services database, and Drug Program Information Network (DPIN) database housed at the Population Health Data Repository at the Manitoba Centre for Health Policy, covering the period 1 April 1984 to 31 March 2016 (except for DPIN, which is available from 1995/96 onwards). The population registry provided information regarding dates of birth and death,

sex, region of residence (postal code) and dates of health insurance coverage. The DAD captures discharge diagnoses, coded using the International Classification of Disease 9th edition, clinical modification (ICD-9-CM) or ICD, 10th edition, Canadian modification (ICD-10-CA) system depending on the year, and admission and discharge dates. The medical services database captures physician claims for inpatient and outpatient visits and diagnostic tests. Each claim includes the ICD-9-CM code for one physician-assigned diagnosis, service type and date. The DPIN database captures all community-dispensed prescriptions including the drug identification number (DIN) and dispensation date. The DIN is linked to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System.[7] These databases were linked to create the 'administrative dataset'.

The MaPCReN

The MaPCReN is one of 11 primary care practice-based research networks that form the CPCSSN. Presently, the MaPCReN contains information extracted from over 45 primary care offices, representing over 266 providers and more than 288,000 Manitobans. For this study, we accessed data held in the MaPCReN repository for the period 1 April 1998 to 31 March 2016. Data used included age, sex, postal code, comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease (COPD) and depression), diagnoses recorded in the billing diagnosis and problem lists, and prescription medications. Prescription medications are identified using ATC codes.

The CPCSSN

The CPCSSN, a pan-Canadian network,[9] captures longitudinal EMR data to support research, chronic disease surveillance and primary healthcare practice quality improvement. Presently, CPCSSN extracts de-identified patient data from >1,800,000 Canadians using the EMRs of >1200 primary care practitioners in eight provinces and one territory. All patients with consenting providers at participating clinics are included unless they opt out. De-identified data extracted for this analysis included demographic information (sex, birth month and year, postal code), health conditions for which validated case definitions exist (hypertension, diabetes, COPD, depression) and medications prescribed. Data from each provincial network are standardized, then merged into the national database held at Queen's University. We accessed data in the CPCCSN repository as of 31 March 2016.

Study populations

First, we identified all patients aged ≥18 years with ≥1 record in the MaPCReN data between 1 April 1998 and 31 March 2016 (MaPCReN dataset). Second, we applied a validated case definition for MS to the Manitoba administrative dataset to identify all persons with MS (MS administrative dataset). Consistent with our prior work, the case definition required ≥3 hospital, physician or prescription claims for MS in any combination, and has a sensitivity of 99.5% and specificity of 99%.[10] Hospital and physician claims for MS were identified using ICD-9-CM/10-CA codes 340/G35. Prescription claims included those for MS-specific disease-modifying therapies (DMT) from 1996 onwards.

Third, we identified all persons in the MS Clinic database who had consented to linking their clinical data to administrative data (MS clinical dataset), regardless of their final diagnosis. The Winnipeg MS Clinic is the main source of subspecialty MS care in Manitoba; all persons who receive provincially funded DMT must attend the clinic annually. However, some individuals with MS receive care from community neurologists. The MS Clinic maintains a clinic registry and database, which captures demographic characteristics and current diagnoses for all persons attending visits there. Over 89% of those approached agree to participate and to linking their clinical and administrative data. Current diagnoses are based on neurologist diagnoses as applied using prevailing diagnostic criteria at diagnosis.[11–14] Diagnostic categories include MS, clinically isolated syndrome, neuromyelitis optica and not MS. For this analysis, MS was classified as MS, and all other diagnoses were classified as not MS. Finally, we linked these three data sources.

Electronic medical record case definitions of MS

Previously, investigators in Ontario used the Electronic Medical Record Administrative Data Linked Database (EMRALD) to develop EMR-based definitions of MS.[6] We adapted this approach to the MaPCReN dataset to develop four candidate case definitions, which incorporated a combination of diagnoses from billing claims, the health conditions table and prescription medications (Table 1); these were labelled as MS1 through MS4. The health condition table in CPCSSN contains conditions diagnosed and entered in a problem list and is analogous to the term cumulative patient profile used by EMRALD. Diagnoses contained in the health condition and billing tables are coded using the

Table 1. Candidate case definitions for identifying multiple sclerosis (MS) in the Manitoba Primary Care Research Network (MaPCReN) electronic medical records.

MS1	MS2	MS3	MS4
One billing record for MS (ICD-9-CM 340) OR One health condition for MS (ICD-9-CM 340)	≥2 billing records for MS (ICD-9-CM 340) within 2 years OR One health condition for MS (ICD-9-CM 340)	≥2 billing record for MS (ICD-9-CM 340) within 2 years OR One health condition for MS (ICD-9-CM 340) OR ≥1 prescription for ATC codes: L03AB07, L03AB08, L03AB13, LO3AX13, L04AA23, L04AA27, N07XX09, L04AA31, L04AC01, L04AA34[a]	≥1 billing record for demyelinating disease[b] (ICD-9-CM 340, 377.3, 341.2 323.82, 323.x, 341.9) OR One health condition for demyelinating disease (ICD-9-CM 340, 377.3, 341.2 323.82, 323.x, 341.9) OR ≥1 prescription for ATC codes: L03AB07, L03AB08, L03AB13, LO3AX13, L04AA23, L04AA27, N07XX09, L04AA31, L04AC01, L04AA34[a]

ICD-9-CM: International Classification of Disease, 9th edition, clinical modification; ATC: Anatomical Therapeutic Chemical Classification System.
[a]Excludes patients with leukemia ICD-9-CM 204, 205, 206, 207, 208, 209 as this medication may also be used to treat leukemia.
[b]ICD-9-CM codes: 340 (multiple sclerosis), 377.3 (optic neuritis), 341.2 (transverse myelitis), 323.82 (other causes of myelitis, traverse myelitis NOS), 323.x (acute disseminated encephalomyelitis), 341.9 (demyelinating disease of the central nervous system, unspecified).

ICD-9-CM classification. The billing table represents encounter diagnoses entered into the EMR for remuneration. Prescription medications are coded using the ATC system. All approved DMT for MS are specific to MS, except alemtuzumab. Alemtuzumab used for MS can be distinguished from alemtuzumab used for leukemia using DINs, but not using ATC codes; therefore, for anyone identified solely on the basis of an alemtuzumab prescription we required there also be no diagnosis of leukemia. We sought to include definitions that would range from being highly specific but potentially less sensitive, and from being highly sensitive but potentially less specific. For the latter situation we incorporated diagnoses for any demyelinating disorder (e.g. optic neuritis, acute disseminated encephalomyelitis), rather than limiting diagnoses exclusively to MS. We applied these definitions to the MaPCReN dataset to identify all cases of MS (MS-MaPCReN = yes). Participants in the MaPCReN dataset who did not meet the definition were classified as MS-MaPCReN = no.

Analysis
We characterized the MaPCReN cohort using descriptive statistics. Then, we compared the MS-MaPCReN case definition to the two reference sources: MS-administrative and MS-clinical, using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Because all Manitobans are captured in the MS-administrative dataset we expected the use of this dataset would capture all individuals in the MaPCReN dataset, maximize the detection of MS cases with a prevalence similar to what would be expected in the MaPCReN and provide a population of non-MS cases; it constituted the primary reference source. We included the MS clinical dataset as a secondary reference source to confirm our chosen case definition by comparison to clinical records, recognizing that the number of non-MS cases included would be small. We also compared agreement between data sources using a kappa (κ) statistic, and interpreted κ as follows: slight (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) and almost perfect agreement (0.81–1.0).[15] We also report a prevalence and bias-adjusted kappa.[16]

Finally, after we identified a preferred case definition for MS (definition with the highest sensitivity, specificity and PPV in both reference cohorts) we applied this to the national CPCSSN dataset. We then summarized the characteristics of the

Table 2. Characteristics of the Manitoba Primary Care Research Network cohort between 1 April 1998 and 31 March 2016 (n = 160,904).

Characteristic	
Age (years), mean (SD)	52.5 (20.1)
Female sex, n (%)	89,410 (55.6)
Urban, n (%)	93,382 (58.0)
Annual primary care visits, mean (SD)	9.5 (9.5)
Hypertension, n (%)	39,158 (24.3)
Diabetes, n (%)	17,527 (10.9)
Chronic obstructive pulmonary disease, n (%)	4199 (2.6)
Depression, n (%)	19,609 (12.2)

MS population using descriptive statistics for the purpose of establishing the face validity of the case definition.

Statistical analyses were conducted using SAS V9.4 (SAS Institute Inc., Cary, NC).

Results
Between 1998 and 2016, 160,904 patients aged ≥18 years had ≥1 encounter with a primary care provider participating in MaPCReN (Table 2). Over half of patients were women and lived in urban areas. Of these, 337 were identified as having MS in the MS-clinical dataset and 818 were identified as having MS in the MS-administrative dataset (Table 3).

Case definition
Of the 160,904 patients in the MaPCReN dataset, 433 (0.269%) met case definition MS1, whereas 432 (0.268%) met definition MS2, 437 (0.271%) met definition MS3 and 474 (0.294%) met definition MS4, the most liberal definition. As compared to the MS-administrative dataset (n = 160,904), which captured all patients in the MaPCReN dataset, the performance of all four of the MaPCReN case definitions was similar (Table 4). All case definitions had low sensitivities, ranging from 43.89% to 44.25%, but had high specificities exceeding 99.95%, and high PPV and NPV.

Compared to the MS-clinical dataset, which captured only 386 patients in the MaPCReN dataset, the case definitions still had modest sensitivities although they were higher than observed in the MS administrative dataset. Specificities and NPV were

Table 3. Demographic characteristics of the members of the Manitoba Primary Care Research Network identified as having multiple sclerosis in each dataset.

Characteristic	MaPCReN[a]	Administrative[b]	Clinical[c]
N	437	818	337
Age (years), mean (SD)	55.5 (13.4)	58.6 (13.6)	53.7 (12.2)
Female sex, n (%)	299 (73.3)	611 (74.7)	263 (78.3)
Urban residence, n (%)	241 (55.2)	548 (67.0)	229 (68.0)

[a]Based on the application of case definition MS3: ≥ 2 billing records for MS (ICD-9-CM 340) within 2 years OR one health condition for MS OR ≥ 1 prescription for an MS-specific disease-modifying therapy.
[b]Participants in the MaCPReN meeting the administrative case definition of MS.
[c]Participants in the MaCPReN with MS in the MS Clinic database.
MaCPReN: Manitoba Primary Care Research Network; MS: multiple sclerosis; ICD-9-CM: International Classification of Disease, 9th edition, clinical modification.

Table 4. Performance of candidate electronic medical record case definitions as compared to two reference standards, administrative and clinical.

Case definition	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	Kappa (95% CI)	PABAK
Administrative[a]						
1	43.89 (40.45, 47.37)	99.95 (99.94, 99.96)	82.91 (79.03, 86.34)	99.71 (99.69, 99.74)	0.57 (0.54, 0.61)	0.99
2	43.77 (40.33, 47.24)	99.95 (99.94, 99.96)	82.87 (78.98, 86.30)	99.71 (99.69, 99.74)	0.57 (0.54, 0.60)	0.99
3	44.25 (40.82, 47.73)	99.95 (99.94, 99.96)	82.84 (78.97, 86.25)	99.72 (99.69, 99.74)	0.57 (0.54, 0.61)	0.99
4	44.25 (40.82, 47.73)	99.93 (99.92, 99.94)	76.37 (72.28, 80.13)	99.72 (99.69, 99.74)	0.56 (0.53, 0.59)	0.99
Clinical[b]						
1	52.82 (47.34, 58.25)	71.43 (56.74, 83.42)	92.71 (88.98, 95.24)	18.04 (15.14, 21.36)	0.11 (0.04, 0.17)	0.10
2	52.82 (47.34, 58.25)	71.43 (56.74, 83.42)	92.71 (88.98, 95.24)	18.04 (15.14, 21.36)	0.11 (0.04, 0.17)	0.098
3	53.41 (47.93, 58.84)	71.43 (56.74, 83.42)	92.78 (89.09, 95.29)	18.23 (15.29, 21.58)	0.11 (0.04, 0.18)	0.11
4	53.12 (47.63, 58.54)	65.31 (50.36, 78.33)	91.33 (87.62, 94.00)	16.84 (13.82, 20.37)	0.08 (0.02, 0.15)	0.10

Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value: PABAK: prevalence and bias-adjusted kappa; MS: multiple sclerosis; CI: confidence interval.
Grey shading indicates preferred case definition.
[a]Administrative case definition of MS as reference standard.
[b]MS Clinic Database diagnosis as reference standard.

lower than observed in the MS-administrative dataset, but PPV were higher.

The preferred case definition (MS3), based on performance compared to both reference standards, required either two billing records for MS within 2 years or MS listed as health condition or a single MS-specific prescription. After we applied definition MS3 to the MaPCReN dataset, we identified 437 patients with MS. Table 4 shows their characteristics compared to the 818 patients in the MaPCReN dataset who were also identified in the MS-administrative dataset and the 337 patients who were also identified in the MS-clinical dataset.

Table 5. Characteristics of participants with multiple sclerosis in the Canadian Primary Care Sentinel Surveillance Network.

Characteristic	Multiple sclerosis
N	2926
Age (years), mean (SD)	52.8 (13.5)
Female sex, *n* (%)	2166 (74.0)
Urban residence, *n* (%)	2461 (84.1)
Province, *n* (%)	
British Columbia	141 (4.8)
Alberta	594 (20.3)
Manitoba	328 (11.2)
Ontario	1452 (49.6)
Quebec	28 (0.96)
Nova Scotia	228 (7.8)
Newfoundland	118 (4.0)
NWT	37 (1.3)
Comorbidity, *n* (%)	
Diabetes	298 (10.2)
Hypertension	666 (22.8)
Depression	913 (31.2)
Chronic obstructive pulmonary disease	142 (4.8)
Current smoker, *n* (%)	873 (29.8)

NWT: Northwest Territories.

CPCSSN MS population

When we applied our preferred case definition (MS3) to the national CPCSSN dataset, we identified 2926 individuals with MS, representing a crude prevalence of 0.30% or 301 per 100,000 people (Table 5). The crude prevalence of MS varied across provinces, with the lowest prevalence observed in Quebec (28/10,873, 0.26%), the Northwest Territories (37/13,673, 0.27%) and Ontario (1452/51,270, 0.28%). The highest prevalence estimates were observed in Newfoundland (118/31,538, 0.37%), Nova Scotia (228/59,987, 0.38%) and British Columbia (141/34,676, 0.40%). Three-quarters of the CPCCSN MS population were female, over 80% lived in urban areas and one-third had comorbid depression.

Discussion

We validated a case definition to identify MS in the CPCSSN repository by comparing candidate case definitions to MS identified using two reference standards. Compared to the population-based administrative dataset, the PPV and NPV of the case definition were acceptably high despite low sensitivity, and agreement between the MaCPReN and the administrative datasets was moderate. As anticipated, the sensitivity was higher but the specificity was lower when we used the confirmatory clinical reference standard rather than the administrative reference standard. The low NPV reflects the high prevalence of MS as the MS Clinic database largely captures individuals with MS, or highly suspected to have MS, and very few individuals without MS. A case definition is likely to be better at distinguishing individuals who clearly do and do not have MS than distinguishing between individuals who do have MS or might have MS but do not meet diagnostic criteria yet. Primary care providers may also struggle with this distinction. Regardless of the reference standard used, the PPV for the preferred case definition was acceptably high. Thus, although we would fail to identify some cases of MS, we can be very confident the cases classified as having MS are actually affected. Given the total number of MS cases in the CPCSSN repository was low, consistent with the prevalence in the general Canadian population,[17] any missed cases are unlikely to substantially influence the characteristics of the CPCSSN population classified as 'not MS'.

An American study developed electronic health record-based algorithms to identify persons with relapsing–remitting MS using data from unstructured clinical notes for 5 million persons in Utah and Idaho.[18] Similar to our findings the PPV was high (99.1%), however, sensitivity, specificity and NPV were not reported. The performance of our case definition was lower than the optimal case definition developed using the EMRALD Primary Care EMR. That case definition had a sensitivity of 91.5%, specificity of 100%, PPV of 98.7% and NPV of 100%.[6] In the EMRALD database, the use of two billing codes in 2 years had a sensitivity of 49.8%, which is similar to our findings for two billing codes even after we added cases identified using the patient problem list. In contrast, the use of the cumulative patient profile alone had a sensitivity of 94.7% in EMRALD, suggesting non-billed diagnoses are captured less effectively in CPCSSN than EMRALD. This could reflect provider and system factors, such as the variation in EMRs used in CPCSSN, whereas EMRALD uses a single EMR. Some primary care providers may not record diagnoses for conditions that are primarily managed by specialists. Similarly, CPCSSN does not capture specialist consultation letters; their inclusion should be considered as the network expands. The use of prescription medications was not particularly useful in CPCSSN or EMRALD, likely reflecting that

primary care providers do not enter medications that are primarily prescribed by specialist providers. In most Canadian provinces, provincial funding programmes limit which types of physicians are permitted to prescribe DMT. Additionally, narrative free text records were not included in this study; so, it is possible some diagnoses were present in a patient's chart but not in a field with a coded diagnosis (i.e. billing/problem list). Future studies should explore this possibility. For some studies, linking administrative data to the MaPCReN may be an effective means of overcoming the low sensitivity of our case definition, although such strategies are unlikely to be feasible for studies seeking to examine MS using the entire CPCSSN dataset given the need for province-specific data-linkage approaches.

Several other case definitions have been validated for identifying chronic diseases in CPCSSN, including diabetes, hypertension, COPD, depression, dementia, osteoarthritis, parkinsonism, epilepsy and hyperlipidemia.[5,19] Performance of these case definitions varies with respect to sensitivity and PPV. Sensitivity is lowest for osteoarthritis (77.8%) and highest for dyslipidemia (98.8%). PPV ranges from 72.1% for COPD to 100% for dyslipidemia. In contrast, specificity is uniformly high, exceeding 93.5% for all definitions. The PPV for the case definitions for neurologic conditions (dementia: 72.8%; parkinsonism: 82.0%; epilepsy: 85.6%) were similar to those we observed for our MS case definition when compared to the administrative data reference standard.

Application of the MS case definition to the national CPCSSN dataset provided support for the face validity of the definition. The crude prevalence of MS in the CPCSSN dataset of 0.30% (0.29–0.31%) is similar to the prevalence of 0.29% (0.26–0.32%) based on the Canadian Community Health Survey in 2011,[17] and only slightly higher than the crude prevalence of 0.27% (95% confidence interval: 0.26–0.27%) reported across Canada by the Canadian Chronic Disease Surveillance System in 2015.[20] A slightly higher prevalence of MS in the primary care population than in the general population would be consistent with prior findings that persons with MS are more likely to visit primary care providers than persons without MS,[21,22] and are 15% more likely to have a regular source of care.[23] The validity of the case definition is further supported by the characteristics of the CPCSSN MS population. As expected, the female: male ratio was 2.85:1, consistent with findings using population-based data sources.[10] The prevalence of depression, diabetes and hypertension generally fell within the bounds of prior estimates of the prevalence of these conditions in a systematic review.[24]

We validated our case definition by comparing it to two existing reference standards to minimize costs and maximize efficiency compared to chart review. Also, by applying an administrative case definition with a PPV of 99.5% and NPV of 97.5%[10] to the entire Manitoba population as a primary reference standard, we could conduct an analysis using the entire MaCPReN dataset. We only validated the case definition in one CPCSSN participating network (MaPCReN) and performance of the case definition could vary across provinces, given variation in provider billing practices, documentation and EMRs.[25] However, prior work suggests performance of case definitions in MaPCReN with respect to PPV is largely similar to performance reported for CPCSSN algorithms developed in other provinces.[25] Moreover, the characteristics of the MS population identified by applying our case definition are consistent with the epidemiology of MS. Other limitations should be considered. We could not examine the reasons for discordance between the case definition and the reference standards; identifying these issues could offer a means of improving the sensitivity of the definition while maintaining specificity. The MaPCReN may not be fully representative of the Manitoba population, which will need to be considered by future studies using this dataset.

We developed a case definition for MS for use in CPCSSN that is simple to apply, has face validity and a sufficiently high PPV to support its use in research examining the health and care of individuals with MS in primary care settings.

Conflict of Interests

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