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Validation of an algorithm to detect severe MS relapses in administrative health databases

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ABSTRACT

Background: Severe relapses that required treatment were important outcomes in the sentinel trials of disease-modifying therapy (DMT). Identifying such relapses in administrative data would allow comparative-effectiveness studies of DMTs to be conducted in real-world clinical settings.

Methods: All relapsing-remitting (RRMS) and secondary-progressive (SPMS) patients living in Manitoba between 1999 and 2015 were identified using a validated case definition and linkage to the Manitoba MS Clinic database. All healthcare interactions potentially due to relapses were extracted from population-based administrative (hospital, physician claims and prescription) databases. These "relapse markers" included varying thresholds of outpatient prednisone scripts, day hospital or emergency room (ER) codes for intravenous (IV) methylprednisolone therapy, family physician, neurologist or ER physician billing codes and hospital admissions due to MS. Algorithms using combinations of these markers were compared with a reference standard of neurologist-defined relapses. The most useful algorithms were also examined on a biannual basis over the study period to assess for trends in the sensitivity of relapse detection.

Results: 1131 participants with RRMS or SPMS were linked to administrative databases. Analysis of potential relapse markers over the whole 1999–2015 time period was limited by inconsistent coding of same day or ER admissions for IV methylprednisolone administration.

Widespread adoption of high-dose oral outpatient prednisone for relapses since 2009 resulted in a progressive improvement in relapse marker sensitivity. The best algorithm consisted of oral prednisone prescriptions > 50 mg/day for 3–60 days and same day hospital or ER assessment codes with MS as the most responsible diagnosis (sensitivity 70%, specificity 100%, PPV 100%, NPV 96%, kappa 0.8 in 2013–2015).

Conclusions: Severe relapses can be identified from administrative datasets with reasonable accuracy. The trend since 2009 toward outpatient relapse treatment will improve the sensitivity of relapse detection with longitudinal follow-up of this cohort and will allow comparison of severe relapse rates between different DMTs, supporting future comparative effectiveness studies.

1. Introduction

In recent years, the number of disease-modifying therapies (DMTs) available for relapsing-remitting MS (RRMS) has increased dramatically (Comi et al., 2017). However, regulatory approval of these agents is based on clinical trials that are only two to three years long. Whether this short-term efficacy translates into effective improvements in long-term clinical outcomes at the individual level and consequently decreased health-care resource utilization (HCRU) at the population level is not known. Even less is known about the relative effectiveness of second generation DMTs in comparison to the first generation DMTs, including interferon-β formulations and glatiramer acetate. Clinical trials of some of the newer second generation agents suggest greater efficacy in reducing relapse rates, however, few head-to-head comparison clinical trials have been conducted (Cohen et al., 2010, 2012; Fox et al., 2012). Developing a framework to support long-term comparative-effectiveness studies is of great importance to policy makers, clinicians and persons with MS (pwMS).

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Population-based administrative (health claims) datasets offer a potentially efficient, cost-effective and generalizable approach to such studies. While the primary outcome of most DMT trials is overall relapse rate reduction, severe MS relapses are of specific importance as these are linked to both greater residual disability (incomplete remission) and increased health-care costs (Lublin et al., 2003; O'Brien et al., 2003). Identifying such severe MS relapses, here defined as those requiring treatment, in administrative health-care databases is critical for performing comparative-effectiveness studies of DMTs in a real-world setting. Other investigators have used commercial health claims databases to estimate relapse rates, (Bergvall et al., 2013; Chastek et al., 2010; Ivanova et al., 2012; Steinberg et al., 2010; Tan et al., 2011), however only one group (Chastek et al., 2010) formally validated their case definition. Furthermore, case definitions developed in the United States may not perform adequately in Canada given the differences in health care delivery between these countries. Therefore, we developed and validated an algorithm to detect severe MS relapses, defined as those requiring medical therapy and/or hospitalization, using administrative data.

2. Methods

2.1. Data sources

This study was conducted in Manitoba, Canada. The administrative databases held at the Manitoba Centre for Health Policy (MCHP) include comprehensive health claims covering 98% of the provincial population (Health Information Branch, 2008). For this study we used four databases. The Population Registry captures date of birth, sex, dates of health care coverage, and region of residence (postal code). The Discharge Abstracts Database captures hospital admission and discharge dates, and up to 25 discharge diagnoses listed using 4-digit International Classification of Disease (ICD) − 10-CA codes. Before 2004, discharge diagnoses were recorded using five-digit ICD-9-CM codes. The first discharge diagnosis is considered the most responsible reason for a hospitalization. Canadian Classification of Health Intervention (CCI) codes are also available since 2004 to capture inpatient procedures, such as plasmapheresis. The Medical Services database captures physician claims, including service date, and 3-digit ICD-9-CM code for the physician-assigned diagnosis. These services include physician visits for MS relapses and hematologists overseeing plasmapheresis for relapses. The Drug Program Information Network (DPIN) database includes all outpatient prescription drug dispensations including date, drug name and drug identification number (DIN). All prescriptions, regardless of funding source (e.g. self-pay, insurance), are included. These databases can be linked using an anonymized (scrambled) version of each resident's unique personal health identification number (PHIN).

The Manitoba MS Clinic is the sole specialized provider of MS care in Manitoba. All persons who receive DMT must be evaluated in the MS Clinic annually. Eighty-nine percent of pwMS attending the clinic have agreed to participate in the MS Clinic registry (MSCR), which began in 2011. The registry captures patient identifiers, PHIN, and clinical course classified as relapsing-remitting MS (RRMS), secondary progressive (SPMS), primary progressive (PPMS), progressive relapsing MS (PRMS) and unknown (Lublin et al., 1996). The clinical course is updated at each clinic visit.

2.2. Study population

All pwMS living in the province between fiscal years (FY) 1999/2000 and 2014/2015 (the first full fiscal year when DMTs were available on the provincial formulary to most recent year of available data) were identified using a validated case definition developed in Manitoba (Marrie et al., 2010). The year of MS onset was defined as the year with the first International Classification of Disease (ICD) − 9/10 administrative claim code for any demyelinating disease (e.g. optic neuritis, MS). Given the focus on relapses and DMTs, the population was then restricted to persons with relapsing-onset MS (RRMS, SPMS), the group who meet provincial criteria to access DMTs. As administrative records do not contain information on specific MS subtypes, this was done by linkage with the MSCR for consenting participants.

2.3. Relapse case definitions (administrative data)

All health care encounters potentially associated with relapse requiring treatment (relapse markers [RM]) in the relapsing-onset cohort were identified. These included: (1) outpatient prednisone prescriptions with varying thresholds for daily dose and treatment duration issued by any prescriber; (2) outpatient prednisone prescriptions prescribed by a MS Clinic-based neurologist; (3) emergency-room (ER) or hospital-based outpatient intravenous (IV) methylprednisolone therapy; (4) ER visits or hospital admissions with MS listed as the most responsible diagnosis in the discharge abstracts database; and (5) inpatient therapeutic plasmapheresis identified through either hematologist billing codes (2605, 2606 and 2607, available 1999–2015) or hospitalization abstract procedure codes (Canadian Classification of Health Intervention codes 1. LZ.20.^^, available from 2004 to 2015). All individual RMs considered are listed in tables e1 and e2. The RMs were designed to explore a range of potential indicators of either inpatient or outpatient relapse care. Each RM could consist of a single item (an outpatient prednisone script or inpatient admission) or multiple items in combination (a prednisone script and a concurrent clinic appointment or a hospital admission and plasmapharesis). All RMs occurring within a 30-day period were considered to represent the same relapse. Of all the potential RMs assessed, the ones that captured either outpatient or inpatient relapse-management most accurately were combined to create candidate relapse case definitions. While we also captured outpatient physician visits with a MS diagnosis code, because these could include routine follow-up visits as well as urgent relapse assessments, these were only used in combination candidate RMs (ie: an outpatient MS visit and concurrent outpatient prednisone script).

2.4. Reference standard

Concurrently, a trained research nurse reviewed MS Clinic records to create a list of MS neurologist-confirmed relapses that served as the reference standard. Relapses could be confirmed through assessments in clinic, on receipt of appropriate documentation from evaluations conducted by other providers (such as ophthalmologists), or in documentation of conversations between the pwMS and clinic staff. In all cases, symptoms had to last at least 24 h, and in the absence of fever or intercurrent infection. Events treated by non-MS neurologists as relapses were not classified as such if the MS neurologist had not documented that they concurred with this diagnosis. Abstracted data included the date of relapse, whether and how it was treated (IV or oral steroids, plasmapheresis, observation), and if hospital admission was required. The type of treating physician (neurologist, family physician), and the way in which the relapse was determined was not recorded. Severity of relapses (mild, moderate, severe) was graded based on the degree of EDSS change where documented. We estimated that we would need to identify ~660 relapses with known treatment status from randomly selected charts to detect a kappa of 0.60 (substantial agreement) between the candidate case definitions and the reference standard if alpha = 0.05, beta = 0.80, and the null hypothesis was 0.40 (moderate agreement).

2.5. Analysis

The reference standard was the presence of a neurologist-confirmed, treated relapse with clearly documented month and year of relapse-onset. Each proposed administrative relapse case definition was applied