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Survival in commercially insured multiple sclerosis patients and comparator subjects in the U.S.

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Abstract
Objective: Compare survival in patients with multiple sclerosis (MS) from a U.S. commercial health insurance database with a matched cohort of non-MS subjects.
Methods: 30,402 MS patients and 89,818 non-MS subjects (comparators) in the OptumInsight Research (OIR) database from 1996 to 2009 were included. An MS diagnosis required at least 3 consecutive months of database reporting, with two or more ICD-9 codes of 340 at least 30 days apart, or the combination of 1 ICD-9-340 code and at least 1 MS disease-modifying treatment (DMT) code. Comparators required the absence of ICD-9-340 and DMT codes throughout database reporting. Up to three comparators were matched to each patient for: age in the year of the first relevant code (index year – at least 3 months of reporting in that year were required); sex; region of residence in the index year. Deaths were ascertained from the National Death Index and the Social Security Administration Death Master File. Subjects not identified as deceased were assumed to be alive through the end of 2009.
Results: Annual mortality rates were 899/100,000 among MS patients and 446/100,000 among comparators. Standardized mortality ratios compared to the U.S. population were 1.70 and 0.80, respectively. Kaplan–Meier analysis yielded a median survival from birth that was 6 years lower among MS patients than among comparators.

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Conclusions: The results show, for the first time in a U.S. population, a survival disadvantage for contemporary MS patients compared to non-MS subjects from the same healthcare system. The 6-year decrement in lifespan parallels a recent report from British Columbia.

1. Introduction

Multiple sclerosis (MS) is a chronic, demyelinating disease of the central nervous system which progresses into a relentlessly degenerative phase in the majority of affected patients (Noseworthy et al., 2000). There are 250,000–350,000 patients with multiple sclerosis in the United States (Anderson et al., 1992), an overall prevalence of roughly 1/1000, with peak prevalence occurring in midlife (Confavreux, 2008). While immediate mortality due to acute or subacute MS attacks or lesions is relatively rare, data suggest that compared to the general population, patients experience a decrease in life expectancy of 5–10 years (Bronnum-Hansen et al., 2004; Compston and Coles, 2008; Grytten Torkildsen et al., 2008; Kingwell et al., 2012; Ragonese et al., 2010; Sadovnick et al., 1992). Survival in most populations has been improving over time, with the 10-year excess mortality reduced by as much as 50% since the mid-20th century (Bronnum-Hansen et al., 1994, 2004; Riise et al., 1988). Most information on survival patterns in MS has come from Europe, where populations, risk factors, medical practice, and supportive care may be different than in the U.S. Given the large number of MS patients in the U.S., the lack of data from this country represents a significant knowledge gap that should be addressed. Further, in patients who do not exhibit relapses but only experience progression, there are no approved therapies and it appears that they begin their relentless declines sooner and faster than the majority relapsing-remitting patients (Confavreux et al., 2000). Thus, the disability effects of the disease which define the condition lead ultimately towards mortality, where information is lacking.

US health plan and claims databases capture large patient cohorts and mortality is an objective endpoint that is well recorded in the US through the Social Security Administration Death Master File (SSA DMF)(Social Security Administration, 2013) and the National Death Index (NDI) (Centers for Disease Control and Prevention, 2013). We conducted a retrospective cohort study comparing survival and mortality patterns in patients with MS and a matched cohort of non-MS subjects drawn from the OptumInsight Research (OIR) database, which contains claims data from a national U.S. commercial health insurance plan. Mortality data covering 1996 through 2009 were analyzed.

2. Material and methods

2.1. Selection of subjects and determination of mortality

The OIR database contains billing claims information for over 39 million individuals insured through United HealthCare; there are approximately 15 million covered lives per year, and 7.5 million patients with laboratory data (OptumInsight, 2013). Pharmacy claims data can be tracked for medication refill patterns and changes in medications. The database is geographically diverse and representative of the U.S. commercially insured population. Compared with the general U.S. population the OIR population has a similar sex ratio, but contains fewer individuals aged 65 or older, fewer minorities, and is of higher socioeconomic status.

MS patients were initially selected for inclusion in the present study if they met the following criteria:

- Inclusion in the database for ≥ 3 consecutive months during 1996–2009.
- At least two ICD-9 diagnosis codes of 340 (multiple sclerosis) ≥ 30 days apart *or* the combination of one ICD-9-340 code and at least one billing code for a MS disease modifying treatment (DMT), defined as any of the following drugs: interferon β-1a, interferon β-1b, glatiramer acetate, natalizumab.
- Age ≥ 18 years at the time of the first code.

The date of the first relevant code was used as the index date.

The presence of a diagnostic code together with a DMT prescription was considered to be sufficient evidence that the subject actually had MS, with no further validation required. To determine the accuracy of diagnoses when no DMT codes were present (36% of all MS patients), a chart review was conducted for 85 patients randomly selected from that group. The diagnosis was inconclusive for six patients, and 17 were judged not to have MS; 62 patients (73%) were judged to have definite MS – 32 on the basis of their physicians' notes, three because the use of DMTs or azathioprine was documented despite the absence of a claim for this in the database, 26 on both factors, and one who was judged by the neurologist reviewer to have MS based on other factors. Consequently, the *maximum* expected false-positive diagnostic rate is only 10% (0.36*0.27) in these circumstances. We concluded, therefore, that the "two-code" definition was sufficiently accurate for purposes of the present study.

Up to three non-MS subjects (*comparators*) were selected and matched to the MS patients according to the following criteria:

- Inclusion in the database for ≥ 3 months during the year of the matched patient's index date.
- No ICD-9-340 codes *and* no DMT codes at any time during enrollment in the database.
- The same age at index year, sex, and residence region (U.S. Census categories Northeast, Midwest, South, West) at index year as the matched patient.

Deaths among the selected subjects were identified by linkage with the NDI(Centers for Disease Control and Prevention, 2013) and the SSA DMF (Social Security