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Mortality and comorbidities in patients with multiple sclerosis compared with a population without multiple sclerosis: An observational study using the US Department of Defense administrative claims database

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ABSTRACT

Background: Data are limited for mortality and comorbidities in patients with multiple sclerosis (MS).
Objectives: Compare mortality rates and event rates for comorbidities in MS (n=15,684) and non-MS (n=78,420) cohorts from the US Department of Defense (DoD) database.
Methods: Comorbidities and all-cause mortality were assessed using the database. Causes of death (CoDs) were assessed through linkage with the National Death Index. Cohorts were compared using mortality (MRR) and event (ERR) rate ratios.
Results: All-cause mortality was 2.9-fold higher in the MS versus non-MS cohort (MRR, 95% confidence interval [CI]: 2.9, 2.7–3.2). Frequent CoDs in the MS versus non-MS cohort were infectious diseases (6.2, 4.2–9.4), diseases of the nervous (5.8, 3.7–9.0), respiratory (5.0, 3.9–6.4) and circulatory (2.1, 1.7–2.7) systems and suicide (2.6, 1.3–5.2). Comorbidities including sepsis (ERR, 95% CI: 5.7, 5.1–6.3), ischemic stroke (3.8, 3.5–4.2), attempted suicide (2.4, 1.3–4.5) and ulcerative colitis (2.0, 1.7–2.3), were higher in the MS versus non-MS cohort. The rate of cancers was also higher in the MS versus the non-MS cohort, including lymphoproliferative disorders (2.2, 1.9–2.6) and melanoma (1.7, 1.4–2.0).
Conclusions: Rates of mortality and several comorbidities are higher in the MS versus non-MS cohort. Early recognition and management of comorbidities may reduce premature mortality and improve quality of life in patients with MS.

1. Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory disease affecting approximately 400,000 people in the USA and 2.3 million people worldwide (Multiple Sclerosis International Federation, 2013). Relative to the general population, patients with MS have an increased risk of premature mortality (Kaufman et al., 2014; Kingwell et al., 2012b; Lalmohamed et al., 2012; Sumelahti et al., 2010) and comorbidities such as infection-related hospital admissions (Montgomery et al., 2013), cardiovascular disease

Abbreviations: CI, confidence interval; CLD, cause most directly leading to death; CM, clinical modification; CNS, central nervous system; CoDs, causes of death; CVD, cardiovascular disease; DMTs, disease-modifying therapies; DoD, Department of Defense; EMR, electronic medical record; ER, event rate; ERR, event rate ratio; ICD, International Classification of Disease; ICD-9, International Classification of Diseases 9th revision; ICD-10, International Classification of Diseases 10th revision; MR, mortality rates; MRR, mortality rate ratio; MS, multiple sclerosis; NA, not applicable; NDI, National Death Index; SD, standard deviation; UTI, urinary tract infection.

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(CVD) (Christiansen et al., 2010; Jadidi et al., 2013) and other autoimmune conditions (Berkovich et al., 2011; Christiansen, 2012; Marrosu et al., 2002), while studies assessing the risk of cancer in patients with MS have been inconclusive (Bloomgren et al., 2012; Handel and Ramagopalan, 2010; Kingwell et al., 2012a). The autoimmune pathogenesis of MS may contribute to the predisposition to certain comorbidities, including type 1 diabetes and inflammatory bowel diseases (Berkovich et al., 2011). However, socioeconomic status, reduced levels of physical activity and immunomodulatory treatment may also affect the risk of premature mortality and comorbidities (Eyre et al., 2004).

Differences in mortality rates (MRs), causes of death (CoDs) and comorbidity event rates (ERs) in individuals with MS and those without MS have not been fully investigated. Such data may have important implications for the management of patients with MS, particularly if the risk of comorbidities can be reduced by focused surveillance, which may permit early detection or diagnosis, and targeted intervention. Furthermore, establishing baseline expectations of mortality and comorbidity rates in patients with MS can provide a reference against which the relative safety profiles of disease-modifying therapies (DMTs) can be assessed. Therefore, this study is an administrative claims database analysis comparing MRs, CoDs and ERs for comorbidities in a cohort of patients with MS versus a matched cohort of individuals without MS, using the US Department of Defense (DoD) Military Health System database.

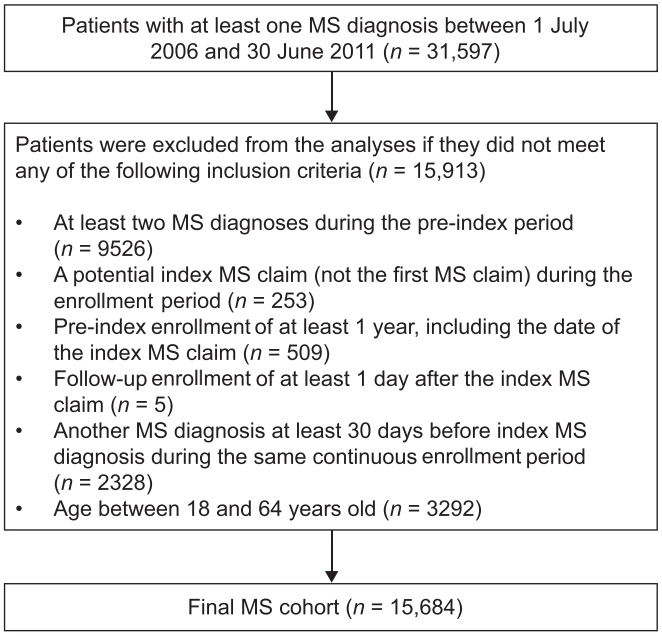

Fig. 1. Attrition of the MS cohort. MS, multiple sclerosis.

2. Materials and methods

The DoD database contains information on over 10 million active US military personnel, their dependents, and retirees, and includes information on patient demographics, enrollment, healthcare providers, diagnoses, procedures and prescriptions (Dorrance et al., 2013). The DoD database also contains mortality data, and through linkage with the US National Death Index (NDI), CoDs can be identified. Demographics of the DoD database population relative to the US general population are summarized in Supplementary Fig. 1 and Supplementary Table 1. Characteristics of the DoD database are further described by Dorrance et al. (2013).

Individuals aged 18–64 years were selected from the DoD database between 1 July 2006 and 30 June 2011. An algorithm (Chastek et al., 2010), appropriate for use in administrative claims databases (Song et al., 2013), was applied to the DoD database to identify patients with MS, for whom diagnosis codes for MS (International Classification of Diseases [ICD] 9 Clinical Modification [CM] 340.xx) appeared on two or more occasions at least 30 days apart (Chastek et al., 2010). Patients were excluded from the MS cohort if they did not meet the inclusion criteria (Fig. 1). The index date for patients in the MS cohort was the date of the second entry of the MS diagnosis code in their healthcare records (Suissa, 2008). To enable assessment of medical history, only individuals with at least 1 year of pre-index enrollment were included. The MS cohort comprised treated and untreated patients with incident (newly diagnosed after entry into the DoD healthcare system) and prevalent (diagnosed before entry into the DoD healthcare system) MS. From the same time period, five individuals with no MS claims in their healthcare records and at least 1 year of pre-index enrollment, were matched to each patient with MS by age (within 5 years), gender and index date to create the non-MS cohort. Individuals aged ≥ 65 years on the index date, who may also have concurrent access to Medicare coverage, were excluded from the study due to the risk of incomplete follow-up information if treatments were reimbursed via Medicare (Social Security Administration, 2014).

To include all medical encounters during the study period, individuals in both cohorts were followed from their index date until the date that they ceased receiving DoD healthcare benefits, their death or the end of the study period; patients were not censored if they turned 65 years of age during the follow-up period.

Individuals with the occurrence of a clinical event in the follow-up period were subsequently censored for reoccurrences of that event but continued to be assessed for the occurrence of other comorbidities. Death of an individual was identified through the registration date of their death in the NDI. To determine CoD, ICD-10-CM codes on the death certificate were ordered, listing the immediate CoD (final disease or condition resulting in death), any secondary CoDs and the primary underlying CoD (the disease or injury that initiated the events leading to death) (Goodin et al., 2014). The cause most directly leading to death (CLD) was considered as the main CoD analysis in this study because it may be more meaningful in patients with MS than immediate and primary underlying CoDs, and allows for designation of suicide (Goodwin et al., 2014). We used a definition similar to that of Goodwin et al. (2014) assess CLD, which was the ICD-10-CM code closest to the time of death, with the following exceptions: suicide was the CLD if it appeared anywhere on the death certificate; MS was the CLD only if no cause other than cardiac or respiratory arrest was given or MS was the only code mentioned; cardiac or respiratory arrest were designated as the CLD only if those causes and no others were provided on the death certificate. Over 200 comorbidities were assessed using ICD-9-CM codes. Comorbidities among a subgroup of patients in the MS cohort who had one or more claims for DMTs (fingolimod, natalizumab, glatiramer acetate, interferon beta-1a, interferon beta-1b or mitoxantrone), at any time during the study (treated MS cohort) were also compared with those in a matched non-MS cohort. In this study, the prevalence of comorbidities in the post-index period was assessed and ERs referred to both acute and chronic conditions. The distributions of mortality and event rate ratios (MRRs and ERRs) were also assessed according to gender and age.

Differences between the MS and non-MS cohorts in terms of pre-index characteristics were assessed using a *t*-test for continuous variables and a Wilcoxon rank-sum test, a χ^2 test or a Fisher's exact test for categorical variables. MRs and ERs for comorbidities were calculated for each cohort and used to derive MRRs and ERRs with 95% confidence intervals (CIs; Table 1). Rate