Analysis of Diagnoses Associated with Multiple Sclerosis–Related In-Hospital Mortality Using the Premier Hospital Database

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Background: *We sought to compare mortality rates and related diagnoses in hospitalized patients with multiple sclerosis (MS), those with diabetes mellitus (DM), and the general hospitalized population (GHP).*

Methods: *Patients who died between 2007 and 2011 were identified in the US hospital–based Premier Healthcare Database. Demographic information was collected, mortality rates calculated, and principal diagnoses categorized.*

Results: *Of 55,152 unique patients with MS identified, 1518 died. Mean age at death was 10 years younger for the MS group (63.4 years) than for the DM (73.3 years) and GHP (73.1 years) groups. Age-adjusted mortality rates, based on the 2000 US Standard Million Population, were 1077, 1248, and 1133 per 100,000, respectively. Infection was the most common principal diagnosis at the hospital stay during which the patient died in the MS cohort (43.1% vs. 26.3% and 24.0% in the DM and GHP groups, respectively). Other common principal diagnoses in the MS group included pulmonary (17.5%) and cardiovascular (12.1%) disease. Septicemia/sepsis/septic shock was a secondary diagnosis for 50.7% of patients with MS versus 36.0% and 31.0% of patients in the DM and GHP cohorts, respectively.*

Conclusions: *Patients with MS had a shorter life span than patients with DM or the GHP and were more likely to have a principal diagnosis of infection at their final hospital stay. However, the database was limited to codes recorded in the hospital; diagnoses received outside the hospital were not captured.* ***Int J MS Care*****. 2016;18:154–161.**

Multiple sclerosis (MS) is a chronic neurodegenerative disorder with a clinical course that evolves over decades.[1,2] Multiple prospective, retrospective cohort, and registry studies of varying durations have shown relatively high mortality rates in patients with MS compared with the general population.[3-7] Standardized mortality rates for patients with MS have been shown to increase 2 years after diagnosis and to continue to rise for 10 years.[8] Indeed, patients with MS have been shown to have a 2.9-fold increased risk of death and an approximate life span reduction of 10 years compared with age-matched controls.[9]

Although evidence is accumulating that patients with MS have a reduced life expectancy relative to non-MS populations,[3-6,10-16] debate continues to surround the primary causes of death in patients with this disease. Previ-

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ous research has shown high rates of death in this population, attributed to cardiovascular disease, infection, respiratory disease, and MS itself.[3-6,12,15,16] Interpretation of these findings is complicated by the different—and subjective—determinants of causes of death (eg, death certificates and registry data) used across studies or the length of time for the analysis, as many longitudinal studies have spanned decades, with medical advances over time confounding interpretation.[3,12,13,15,16] Studies examining large numbers of patients over a relatively short period using objective measures of mortality are, therefore, needed.

Clearly, identifying causes of death in this population is challenging. If the clinical presentation is benign, MS is unlikely to be recorded as a cause of death despite its potential contribution to mortality, although many studies have attributed more than 50% of deaths in this population to MS.[3-6,12,15,16] Patients also often have multiple comorbid conditions that may overshadow the effects of MS on survival outcomes.[5] In addition, only a few studies have focused on US-based cohorts,[7,13,17,18] and none have reported in-hospital mortality using objective disease classification codes.

Aside from analyzing death certificates, examining the diagnoses recorded during the hospitalization in which the patient died could provide some understanding of the drivers behind the excess mortality in patients with MS. To this end, a retrospective analysis of records from patients hospitalized in the United States was conducted. The aim of the present study was to compare in-hospital mortality rates and related diagnoses in patients with MS with those with another well-documented chronic condition observed in hospitalized patients, diabetes mellitus (DM), and patients in the general hospitalized population (GHP).

Patients and Methods

Patient Population

Data were derived from the Premier Healthcare Database, a large US hospital–based database developed for quality and utilization benchmarking (Premier Healthcare Solutions, Inc, Charlotte, NC; available at https://www.premierinc.com). The Premier database contains information from more than 700 geographically diverse, nonprofit, nongovernment, community, teaching, and nonteaching hospitals, corresponding to approximately 20% of all annual acute-care hospitalizations in the United States. Information on more than 75 million discharged patients between 2000 and the present is included, with a mean of 6 million discharges per year. Data are submitted quarterly or monthly and undergo several quality checks by the hospital-based users.

Patient diagnoses and procedures were categorized according to the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* coding system. As recorded in the patient's hospital discharge record, the principal diagnosis code reflected the diagnosis that was responsible for the patient's hospitalization, and secondary diagnosis codes indicated all other (nonprincipal) diagnoses. The *ICD-9-CM* codes provided by the hospital were assumed to be correct and complete, as with all similarly derived administrative databases. Death certificates were not analyzed for this study. The database is compliant with the provisions of the Health Insurance Portability and Accountability Act of 1996. Patient data are de-identified to protect the patients whose data are represented. Consequently, this study did not require institutional review board waiver or approval.

In this retrospective database analysis, three mutually exclusive populations of patients 18 years or older were assembled according to the primary and secondary *ICD-9-CM* codes listed in the database: patients with MS, patients with DM, and the GHP. Patients with MS listed as a primary or secondary diagnosis were included in this analysis if the code for MS (*ICD-9-CM* code 340) was recorded for the hospitalization in which they died. Patients with DM listed as a primary or secondary diagnosis were included if they had at least one code for DM (*ICD-9-CM* code 250.00–250.93) for the hospitalization in which they died and if they did not have any codes for MS. The GHP included patients with any *ICD-9-CM* code other than 340 or 250.00 to 250.93 for the hospitalization in which they died. For all three patient groups, inclusion depended on their being discharged as an inpatient between January 1, 2007, and December 31, 2011.

Statistical Analysis

Descriptive statistics were used to describe hospital characteristics (eg, number of beds and geographic location), patient demographics, diagnosis category frequency, and age at death. Mortality outcomes were compared using unadjusted mortality rates. These outcomes were measured from birth (not from diagnosis because the database did not record information on age at disease onset) and were adjusted according to the 2000 US Standard Million Population.[19] A t test at the $P < .05$ threshold of significance was used to analyze each con-

tinuous variable (ie, mean age at death) in the cohorts. A χ^2 test was used to compare the distributions of categorical variables (sex, race/ethnicity, All Patient Refined Diagnosis Related Group [APR-DRG; 3M, St. Paul, MN] severity of illness, and hospital characteristics).[20]

To gain a better understanding of the types of diagnoses associated with hospitalization, diagnosis codes were grouped into categories. These categories were derived by an expert panel consisting of a physician with MS expertise, an epidemiologist, and a pharmacoeconomist. Principal diagnosis codes were grouped into six categories: infection (including pulmonary infection), pulmonary disease (excluding infection), cardiovascular disease, cancer, MS, and all other diagnoses. Secondary diagnosis codes were grouped into three categories for analysis because the following relevant categories are frequently not coded as principal diagnoses (except for septicemia): septicemia/sepsis/septic shock, accidental death, and suicide. Multiple secondary (nonprincipal) diagnoses were available for most patients, but the patient was counted only once if there were multiple codes indicating the same condition (eg, 038.xx and 995.92 are two diagnoses related to sepsis). Because a patient could have both a principal and a secondary diagnosis recorded in the database, these analyses were conducted separately to avoid counting a patient more than once.

Results

Patient Disposition

A total of 55,152 unique inpatients with MS were identified from the Premier database, 1518 of whom died in the hospital or after discharge to hospice care (Table 1). Of the patients with MS who died, 70.2% were female, 73.0% were white, and 71.1% had extreme illness according to the APR-DRG classification. Significant differences in sex, ethnicity, and illness severity were noted between deceased patients in the MS cohort and those who died in the DM group (n = 140,283) and the GHP (n = 305,339). The mean (SD) lengths of stay in the MS, DM, and GHP cohorts were somewhat similar: 9.5 (39.5) days, 9.6 (33.6) days, and 8.9 (41.4) days, respectively ($P < .05$ for DM vs. GHP only). Median lengths of stay were similar at 4, 5, and 4 days, respectively.

Mortality

Age-adjusted mortality rates, based on the 2000 US Standard Million Population, were 1077 per 100,000 for MS, 1248 per 100,000 for DM, and 1133 per 100,000 for GHP despite the generally younger age at death in the MS population (Table 2). In patients who died in the hospital, the mean age at death was approximately 10 years younger for patients with MS (63.4 years) than for patients with DM (73.3 years) and those in the GHP (73.1 years) (Figure 1). Median age at death was 63 years in the MS cohort, compared with 75 and 77 years in the DM and GHP cohorts, respectively. The differences in age at death between patients with MS and those in the DM and GHP cohorts were significant ($P < .0001$ for both comparisons). In an age group analysis, the MS cohort showed a peak mortality rate between 60 and 64 years of age (Figure 2). This contrasts with the DM and GHP cohorts, which showed a continual rise in the death rate as age increased. Because of the differences in distribution of deaths by age group among the different cohorts, proportional mortality rates were not calculated.

Infection (including pulmonary infection) was the most common principal diagnosis in deceased patients with MS, accounting for 43.1% of deaths (compared with 26.3% for the DM cohort and 24.0% for the GHP cohort) (Figure 3). Other common principal diagnosis categories associated with death in the MS cohort included pulmonary disease (excluding infection, 17.5%) and cardiovascular disease (12.1%). In the non-MS comparator cohorts, cardiovascular disease and infection were the most common principal diagnosis categories associated with death. Principal diagnoses of cancer were less common in patients with MS (5.2%) than in patients with DM (7.2%) or the GHP (11.7%).

The secondary diagnosis of septicemia/sepsis/septic shock was recorded in 773 patients (50.9%) in the MS cohort (Figure 4). In the DM and GHP cohorts, this secondary diagnosis was recorded less frequently (36.0% and 31.0%, respectively). Relatively little difference between cohorts was seen in rates of accidents or suicide, which were limited to those who presented to the hospital and were subsequently admitted.

Discussion

Patients with MS in this study had an approximately 10-year lower mean age at death than those with DM or in the GHP, with most deaths occurring in individuals 55 to 69 years of age. In contrast, in the DM and GHP cohorts, most deaths occurred in those 70 years and older. The peak in mortality between 60 and 64 years of age in the MS population seems to suggest that mortality decreased with age, but this is likely not

Table 1. Patient and hospital characteristics

Characteristic	Cohort			*P* values[a]		
	MS (n = 1518)	DM (n = 140,283)	GHP (n = 305,339)	MS vs. DM	MS vs. GHP	DM vs. GHP
Patient characteristics						
Female sex, No. (%)	1066 (70.2)	68,612 (48.9)	171,210 (56.1)	<.0001	<.0001	<.0001
Race/ethnicity, No. (%)				<.0001	.0011	<.0001
White	1108 (73.0)	89,221 (63.6)	235,305 (77.1)			
Black	133 (8.8)	19,893 (14.2)	34,300 (11.2)			
Hispanic	27 (1.8)	6522 (4.6)	10,941 (3.6)			
Other	250 (16.5)	24,647 (17.6)	58,830 (19.3)			
3M APR-DRG severity of illness, No. (%)				.1309	<.0001	<.0001
Mild	8 (0.5)	865 (0.7)	10,204 (3.3)			
Moderate	80 (5.3)	7685 (5.5)	31,530 (10.3)			
Severe	350 (23.1)	35,825 (25.5)	98,489 (32.3)			
Extreme	1080 (71.1)	95,908 (68.4)	199,743 (65.4)			
Unknown	0	0	1 (<1)			
Length of stay, mean (SD), d (median)	9.5 (39.5) (4)	9.6 (33.6) (5)	8.9 (41.4) (4)	.8810	.5485	<.0001
Hospital characteristics						
Region, No. (%)				<.0001	<.0001	<.0001
Midwest	316 (20.8)	23,870 (17.0)	50,104 (16.4)			
Northeast	359 (23.6)	26,662 (19.0)	62,382 (20.4)			
South	507 (33.4)	63,436 (45.2)	130,353 (42.7)			
West	327 (21.5)	26,315 (18.8)	61,536 (20.2)			
Unknown	9 (0.6)	0	964 (0.3)			
Beds, No. (%)				.0842	.0512	<.0001
<100	49 (3.2)	3850 (2.7)	9174 (3.0)			
100–199	158 (10.4)	12,957 (9.2)	29,311 (9.6)			
200–299	293 (19.3)	24,853 (17.7)	51,869 (17.0)			
300–399	309 (20.4)	29,170 (20.8)	61,814 (20.2)			
400–499	262 (17.3)	24,488 (17.5)	53,351 (17.5)			
≥500	447 (29.4)	44,965 (32.1)	99,820 (32.7)			
Urban, No. (%)	1355 (89.3)	125,117 (89.2)	271,400 (88.9)	.9378	.6533	.0005
Teaching, No. (%)	626 (41.2)	56,290 (40.1)	123,902 (40.6)	.3654	.6125	<.0001

Abbreviations: APR-DRG, All Patient Refined Diagnosis Related Group classification; DM, diabetes mellitus; GHP, general hospitalized population; MS, multiple sclerosis.
[a]χ^2 test, $\alpha = .05$, except 2-sided *t* test used for mean length of stay.

Table 2. Age-adjusted mortality rates for patients in the MS, DM, and GHP cohorts who died[a]

Cohort	MS	DM	GHP
No. of unique patients identified	55,152	2,856,862	10,950,874
No. of patients who died	1518	140,283	305,339
Age-adjusted mortality rate (per 100,000 people)[b]	1077	1248	1133

Abbreviations: DM, diabetes mellitus; GHP, general hospitalized population; MS, multiple sclerosis.
[a]All patients younger than 18 years were excluded.
[b]Age-adjusted mortality rate per 100,000 people = (total expected deaths)/[(total standard population)(100,000)]. Total standard population = 741,999 (based on Surveillance Epidemiology and End Results US Standard Million Population in 2000).[16]

the case. Rather, it is more likely that deaths in the older patients were not captured in the database. This could have occurred if the patients died outside of the hospital or if they had switched to a different hospital that did not participate in the database. However, the proportion of deaths outside the hospital does not seem to be systematically different for patients with MS relative to those with DM or in the GHP; no data are known that suggest that more patients die at home with MS than with other disease states. The reduced life span in the MS population in this study is consistent with that in previous studies.[4-6,9-11,14]

The most common principal diagnosis (ie, the most common diagnosis responsible for the patient's hospi-

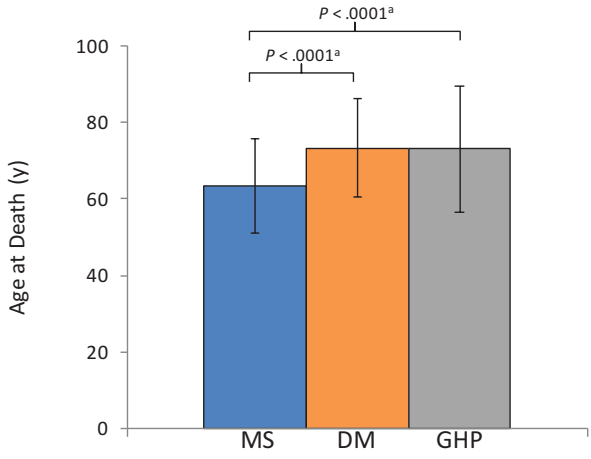
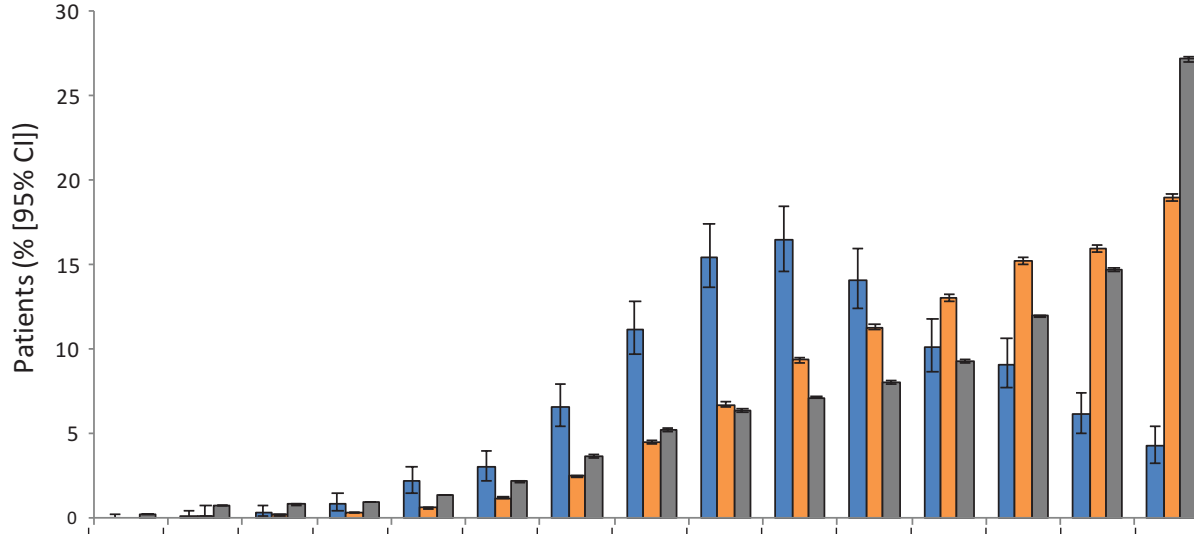


***Figure 1.* Mean (SD) age at death in the multiple sclerosis (MS), diabetes mellitus (DM), and general hospitalized population (GHP) cohorts**

Patients in the MS cohort had a younger age at death than those in the DM and GHP cohorts. [a]*T* test, 2-sided, $\alpha = .05$.

talization) in deceased patients with MS was infection, with septicemia/sepsis/septic shock commonly recorded as a secondary diagnosis. This finding is in agreement with several other studies in which infections/sepsis were commonly cited as the cause of death in patients with MS.[4,5,12,13,15,17] Comparisons of causes of death across studies may, however, be confounded by methodological differences. For example, two studies that examined government records to determine causes of death differed in whether infections were considered independent of or related to MS.[4,8] In a Finnish study, deceased patients were stratified into two categories: death from MS or MS-related causes (including infections related to underlying MS) and death due to any cause.[16] In contrast, MS and infectious diseases were categorized as separate causes of death in a Norwegian study, regardless of the underlying cause of infection.[4] Consequently, the proportion of deaths attributed to MS in the two studies differed: 70.3% in the Finnish study versus 56.5% in the Norwegian study. Such disparities may also exist among the hospitals supplying data to the Premier database.

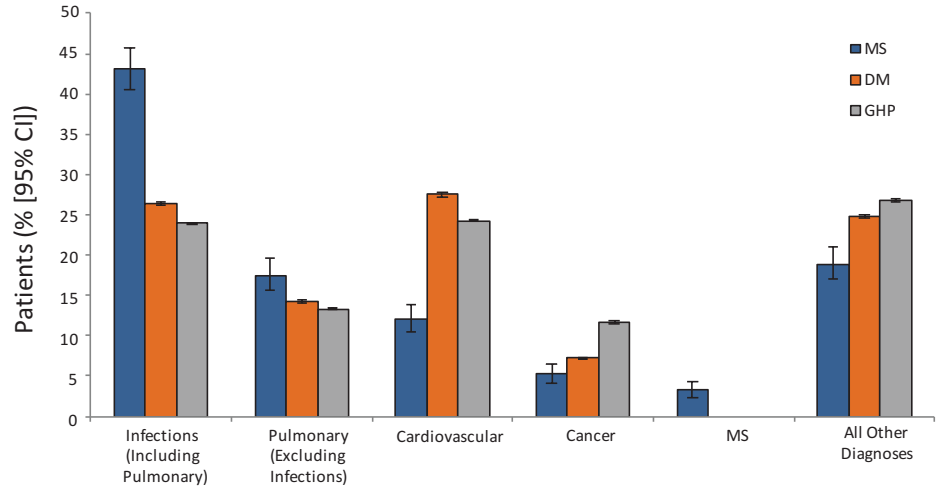
Generally, the *ICD-9-CM* codes reported in the Premier database are considered to be associated with, rather than official causes of, death because of these potential reporting differences and because the information provided to the database could not be checked against official cause of death data sources, such as the National



	18-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
MS	0.07	0.30	0.45	1.20	2.47	3.89	5.69	11.98	15.34	16.54	14.45	9.43	8.31	5.69	4.19
DM	0.02	0.10	0.20	0.36	0.71	1.28	2.66	4.68	6.83	9.47	11.40	12.99	15.32	15.70	18.27
GHP	0.25	0.74	0.84	0.93	1.41	2.25	3.73	5.26	6.22	6.99	7.91	9.27	12.08	14.99	27.14

***Figure 2.* Percentage of deaths stratified by age**

The highest proportion of deaths in the multiple sclerosis (MS) cohort occurred in the 60- to 64-year-old range. CI, confidence interval; DM, diabetes mellitus; GHP, general hospitalized population.



Diagnosis	MS, No. (%)	DM, No. (%)	GHP, No. (%)
Infections (including pulmonary infections)	654 (43.1)	36,958 (26.3)	73,132 (24.0)
Pulmonary disease (excluding infections)	266 (17.5)	19,867 (14.2)	40,576 (13.3)
Cardiovascular disease	183 (12.1)	38,592 (27.5)	74,114 (24.3)
Cancer	79 (5.2)	10,152 (7.2)	35,587 (11.7)
MS	49 (3.2)	–	–
All other diagnoses	287 (18.9)	34,714 (24.7)	81,930 (26.8)

***Figure 3.* Proportion of patients with each principal diagnosis category at their final hospitalization**

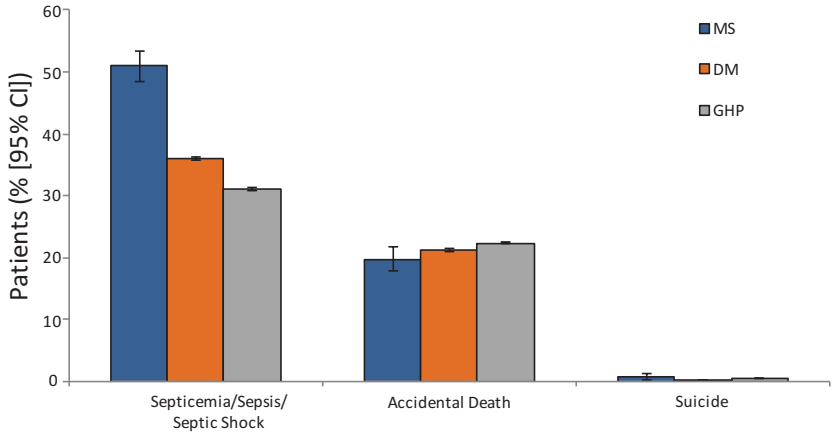
The most common principal diagnoses associated with death in the multiple sclerosis (MS) population were infections, pulmonary disease, and cardiovascular disease. CI, confidence interval; DM, diabetes mellitus; GHP, general hospitalized population.

Death Index.[21] The data in this article provide a fairly indirect measure of the cause of death as it may appear on a death certificate, as emphasized by the low rate at which MS was identified as the principal diagnosis.

The selection of a principal diagnosis may have been influenced by the coding system used on the death certificate. In January 1999, the United States began to use the *ICD-10* coding system to classify mortality data from death certificates; however, hospitals in the United States have not yet adopted *ICD-10* for their recordkeeping and reporting activities. Therefore, the Premier hospital database relies on the use of *ICD-9-CM* codes. Consequently, only one principal diagnosis code for each hospital stay is recorded, and it tends to capture the most prominent focus of treatment during the hospital stay as opposed to the underlying treated condition resulting in the outcome of the stay. Some patients with MS may also have had DM or other chronic diseases that were not analyzed; the comparator group of patients with DM included those having DM and possibly other chronic diseases but not MS. As such, the presence of DM as a comorbidity may increase the risk of infection in patients with MS, and possibly the risk of death.

Other potential limitations of this study must be noted. First, hospital-based data reflect care provided in the hospital setting only. Therefore, other factors outside of the patient's hospital stay that may have influenced survival outcomes (eg, medication adherence and over-the-counter drug use) were not captured. These missing data would be particularly important for the MS population because early initiation of disease-modifying therapy has been shown to prolong survival.[22] Furthermore, the restriction to the hospital setting is likely to have excluded many cases of accident/suicide, and, hence, the interpretation of the findings for these causes of death is unclear. Another limitation is that different forms of MS were not distinguishable using *ICD-9* coding, and patients with primary progressive MS are known to have a significantly shorter life span than those with relapsing-remitting MS,[4] although a more recent publication found no difference.[23]

Additionally, as a comparison group, DM is common and chronic but is not primarily a neurologic condition and is often diagnosed at a later age than MS; thus, age at death might be expected to be greater for patients with DM than for patients with MS. However, this limitation does not diminish the relevance of the finding that age at death in patients with MS was found to be similar to findings in other studies.[4-6,9-11,14] Moreover, DM is known to increase the risk of infection and possibly mortality, and the infection diagnosis findings in patients with MS may be related to the comorbid diabetes or another infection-prone status that was not identified.



Diagnosis	MS, No. (%)	DM, No. (%)	GHP, No. (%)
Septicemia/sepsis/septic shock	773 (50.9)	50,551 (36.0)	94,744 (31.0)
Accidental death	299 (19.7)	29,729 (21.2)	68,229 (22.3)
Suicide	9 (0.6)	206 (0.1)	1599 (0.5)

***Figure 4.* Proportion of patients with septicemia/sepsis/septic shock, accidents, or suicide listed as secondary diagnoses during their last hospital admission**

A higher proportion of patients with multiple sclerosis (MS) had septicemia/sepsis/septic shock listed as a secondary diagnosis than those in the diabetes mellitus (DM) or general hospitalized population (GHP) cohorts. CI, confidence interval.

One reason for earlier death in patients with MS, as found in this study, may be frailty secondary to severe neurologic disability; however, measures of the severity of MS disability were not available in the data. It has been recognized that physical or cognitive disability can predispose patients with MS to other illnesses, such as pneumonia, sepsis, and thrombosis, which can be fatal in and of themselves.[24] Congruent with the findings of this study, a recent study using commercial insurance claims data also identified infections, aspiration pneumonias, and ischemic or embolic cardiovascular events, which are all often associated with immobility, as significant causes of death in patients with MS.[25]

Insofar as underrecognized deaths may have been a study limitation, it is possible that some patients in each of the comparison groups were discharged to hospice facilities (Table 1) that were not recorded by the hospital according to Centers for Medicare and Medicaid Services reporting standards. If such guidelines were not followed, it could have increased the sample size of one or more of the cohorts in this study and might have altered the distribution of other patient characteristics in one or more groups. However, it is unknown to what extent, and in what direction, any of the study results might have changed as a result of different discharge information. For example, older patients with MS may more often reside and die in nursing homes, without exposure to hospital settings, from which the study data originated.

This study has the advantage of capturing data from a large sample of patients collected over a short time frame (January 1, 2007–December 31, 2011). In contrast, previous studies reached large patient numbers only over decades-long observation periods,[4,9,16] which presents the risk of introducing substantial time effects due to changes in the natural history,[26] diagnostic criteria,[27,28] and treatment of MS.[29] Protracted time frames can, therefore, result in study populations that are not sufficiently homogeneous to draw meaningful conclusions.

In conclusion, use of the Premier database has permitted the identification of a large number of patients with MS who died in the hospital, indicating that this population has a 10-year lower mean age at death—but a lower age-adjusted mortality rate—than patients with DM and those in the GHP. Based on the analysis of

PracticePoints

- Patients with MS have, on average, a shorter life span compared with non-MS populations, but the causes of in-hospital mortality in this population are not well understood.
- In a retrospective analysis of a hospital discharge database, the most common principal diagnoses in the terminal hospitalization for patients with MS included infection (43.1%), pulmonary disease (17.5%), and cardiovascular disease (12.1%).
- The most common secondary diagnoses were septicemia/sepsis/septic shock.
- Better knowledge of the diagnoses associated with death during a hospitalization in patients with MS can improve the care of these patients.

objective *ICD-9-CM* codes, infection was the most common principal diagnosis in deceased patients with MS. Greater awareness of the pertinent diagnoses associated with the death of patients with MS during a hospitalization might help improve care for this population. Future research into differences between deaths in the hospital compared with other locations may be warranted, as may analyses of the linkages between clinically relevant issues, such as infection and other comorbid medical conditions, neurologic disability, or deaths occurring in hospitals compared with skilled nursing facilities or other locations. □

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