Intensive care unit admission in multiple sclerosis

Increased incidence and increased mortality

Ruth Ann Marrie, MD,
PhD
Charles N. Bernstein,
MD
Christine A. Peschken,
MD, MSc
Carol A. Hitchon, MD,
MSc
Hui Chen, MSc
Randy Fransoo, PhD
Allan Garland, MD, MA

Correspondence to
Dr. Marrie:
rmarrie@hsc.mb.ca

ABSTRACT

Objective: To compare the incidence of, and mortality after, intensive care unit (ICU) admission as well as the characteristics of critical illness in the multiple sclerosis (MS) population vs the general population.

Methods: We used population-based administrative data from the Canadian province of Manitoba for the period 1984 to 2010 and clinical data from 93% of admissions to provincial high-intensity adult ICUs. We identified 5,035 prevalent cases of MS and a cohort from the general population matched 5:1 on age, sex, and region of residence. We compared these populations using incidence rates and multivariable regression models adjusting for age, sex, comorbidity, and socioeconomic status.

Results: From January 2000 to October 2009, the age- and sex-standardized annual incidence of ICU admission among prevalent cohorts was 0.51% to 1.07% in the MS population and 0.34% to 0.51% in matched controls. The adjusted risk of ICU admission was higher for the MS population (hazard ratio 1.45; 95% confidence interval [CI] 1.19–1.75) than for matched controls. The MS population was more likely to be admitted for infection than the matched controls (odds ratio 1.82; 95% CI 1.10–1.32). Compared with the matched controls admitted to ICUs, 1-year mortality was higher in the MS population (relative risk 2.06; 95% CI 1.32–3.07) and was particularly elevated in patients with MS who were younger than 40 years (relative risk 3.77; 95% CI 1.45–8.11). Causes of death were MS (9.3%), infections (37.0%), and other causes (52.9%).

Conclusions: Compared with the general population, the risk of ICU admission is higher in MS, and 1-year mortality after admission is higher. Greater attention to preventing infection and managing comorbidity is needed in the MS population. *Neurology*® 2014;82:2112–2119

GLOSSARY

APACHE II = Acute Physiology and Chronic Health Evaluation II; **CCI** = Charlson Comorbidity Index; **CI** = confidence interval; **HR** = hazard ratio; **ICD-9-CM** = International Classification of Diseases, ninth revision, Clinical Modification; **ICD-10** = International Classification of Diseases, tenth revision; **ICU** = intensive care unit; **IRR** = incidence rate ratio; **MS** = multiple sclerosis; **OR** = odds ratio; **SES** = socioeconomic status.

Intensive care units (ICUs) are an important component of hospital care, consuming a disproportionate share of medical costs in industrialized countries.^{1–4} While chronic diseases are established risk factors for ICU admission and mortality,^{5,6} little is known about the influence of immune-mediated diseases such as multiple sclerosis (MS) on ICU admissions. MS is associated with increased risks of infection⁷ and ischemic heart disease,^{8,9} which could increase the risk of ICU admission. However, hospitalized elderly patients with MS have been reported to be less likely to use intensive or coronary care services than other patients.¹⁰ The risk of ICU admission in the nonelderly MS population has not been studied, and outcomes after ICU admission are largely unknown.¹¹ Knowledge of the characteristics and outcomes of critical illness is important to clinical decision-making.^{12–15} Treatment preferences depend heavily on expected outcomes^{12,13}; therefore, patients and health care providers need a realistic understanding of outcomes after critical illness.

Using a large population-based dataset, we compared the incidence of ICU admission, reasons for and severity of presentation at ICU admission, and mortality after ICU admission in the MS population and the general population. We hypothesized that persons with MS

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From the Departments of Internal Medicine (R.A.M., C.N.B., C.A.P., C.A.H., A.G.) and Community Health Sciences (R.A.M., C.A.P., R.F., A.G.), and IBD Clinical and Research Centre (C.N.B.), University of Manitoba, Winnipeg; and Manitoba Centre for Health Policy (H.C., R.F., A.G.), Winnipeg, Canada. Go to *Neurology.org* for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

experience elevated rates of ICU admission and of death after ICU admission, and that infections would be the most common reason for excess ICU admissions.

METHODS **Data sources.** We used 2 data sources, provincial administrative data and a clinical database, both housed at the Manitoba Centre for Health Policy. The administrative data were population-based, anonymized data, from April 1, 1984, to March 31, 2010, from the Canadian province of Manitoba. Manitoba's universal health insurance plan provides services to 98% of its 1.2 million citizens.¹⁶ All hospital, physician, and prescription claims are electronically captured at the time of service and include a

unique identifier indicating the person who received the service. A population registry captures when an individual moves into or out of Manitoba, or dies.

Since June 1999, the Winnipeg Regional Health Authority's clinical ICU database has captured all admissions to adult ICUs in Winnipeg,¹⁷ representing 93% of all high-intensity adult ICU admissions in Manitoba (individuals living outside Winnipeg who need high-intensity care are transferred as needed). The administrative data and clinical ICU database have been linked using the provincial identifier. The clinical database contains >50,000 records with prospectively collected clinical information on every admission, captured by trained abstractors using standardized data definitions and collection methods. Information captured includes the Acute Physiology and Chronic Health Evaluation II (APACHE II) acute physiology score,⁶ Glasgow Coma Scale score,¹⁸ use of life support measures within the initial 2 days of ICU admission (mechanical ventilation, IV vasoactive agents, renal dialysis), length of stay, and up to 6 reasons for ICU admission.

Study populations. Using administrative data, we identified Manitobans with MS based on the presence of ≥ 3 hospital, physician, or prescription claims for MS.¹⁹ All cases of MS so identified were included in our prevalent cohorts unless otherwise specified. The date of diagnosis (index date) was the date of the first health claim for demyelinating disease. To identify incident cases, we excluded individuals with demyelinating disease claims during a 5-year run-in period before the index date. Because administrative data began in 1984, the first year in which an incident case could be identified was 1989.

We identified a general population cohort, individually matched on sex, exact year of birth, and region of residence based on 6-digit postal code (if a full postal code match was not possible, we used the first 3 digits). We obtained up to 5 controls for each case, excluding individuals with any diagnostic codes for demyelinating disease. Individuals with inflammatory bowel disease or rheumatoid arthritis and related disorders were also excluded because we also explored critical illness in those populations (table e-1 on the *Neurology*[®] Web site at Neurology.org). General population controls were assigned the same index dates as their matched cases and had to be alive on the index date.

Incidence of critical illness. Hospital discharge abstracts contain coding for special care units, such as ICUs¹⁷; we identified ICU admissions separately in persons with incident and prevalent MS. We considered ICU care as that provided in any of the 12 high-intensity (levels 1 or 2) adult ICUs in Manitoba.²⁰ First, we determined the cumulative incidence of ICU admission among the incident MS cohort and their matched controls. Then, using Kaplan-Meier analysis and log-rank tests, we compared the time from the index date to the first ICU admission among the 2 cohorts. Persons not admitted to the ICU were censored as of death, migration out of Manitoba, or the end of the study period (March 31, 2010), whichever came first. To evaluate factors associated with ICU admission, we used a multivariable Cox proportional hazards model in which the outcome was the first ICU admission after the index date. Model covariates were age at diagnosis, sex, comorbidity, and socioeconomic status (SES). SES was divided into quintiles based on average household income in the postal code of residence by linkage to census data, separately for rural and urban residence. Comorbidity status was classified with a modified version of the Charlson Comorbidity Index (CCI) based on hospital discharge *ICD-9-CM/ICD-10* codes. The CCI is a weighted summary index of 17 chronic conditions, and predicts health outcomes and utilization in patients admitted to ICUs.²¹ The CCI includes hemiplegia and paraplegia. Because these items may be secondary to MS, we modified the CCI to exclude those diagnoses. We also collapsed the categories of diabetes with and without chronic complications, because this distinction was

Table 1 Characteristics of the incident MS cohort and general population controls at the index date

Characteristic	General population (n = 13,705)	MS (n = 2,547)	p Value
Female, n (%)	9,901 (72.2)	1,854 (72.8)	0.57
Age at MS diagnosis or index date for matched controls, y, mean (SD)	39.9 (12.5)	40.5 (12.7)	0.0265
Age group, y, n (%)			0.16
<40	7,131 (52.0)	1,277 (50.1)	
40-59	5,728 (41.8)	1,097 (43.1)	
≥ 60	846 (6.2)	173 (6.8)	
Duration of follow-up from the index date, ^a y, mean (SD)	9.85 (5.91)	10.2 (5.67)	0.0058
Region of residence, n (%)			0.78
Urban	9,036 (65.9)	1,672 (65.6)	
Rural	4,669 (34.1)	875 (34.4)	
Socioeconomic status, n (%)			0.48
Rural 1 (lowest rural)	715 (5.22)	141 (5.54)	
Rural 2	903 (6.59)	184 (7.22)	
Rural 3	959 (7.00)	157 (6.16)	
Rural 4	1,038 (7.57)	190 (7.46)	
Rural 5 (highest rural)	993 (7.24)	191 (7.50)	
Urban 1 (lowest urban)	1,543 (11.2)	275 (10.8)	
Urban 2	1,807 (13.2)	353 (13.8)	
Urban 3	1,942 (14.2)	338 (13.3)	
Urban 4	1,826 (13.3)	358 (14.0)	
Urban 5 (highest urban)	1,749 (12.8)	307 (12.0)	
Not calculated ^b	230 (1.67)	53 (2.08)	
Modified Charlson Index, n (%)			<0.0001
0	13,403 (97.8)	2,426 (95.5)	
1	86 (0.63)	40 (1.57)	
2-3	170 (1.24)	73 (2.87)	
4-5	13 (0.095)	0 (0)	
>5	33 (0.24)	0 (0)	

Abbreviation: MS = multiple sclerosis.

^aDuration of follow-up: follow-up from the index date to the end of the study period, death, or migration out of the province, whichever came first.

^bNot calculated: people living where the Canadian census does not calculate an average household income, most of whom reside in nursing homes or other chronic care facilities.

inaccurate in Manitoba before 2006,²² and the HIV/AIDS category was not included because of small numbers. We used a 5-year look-back period because this improves the prediction of health care utilization outcomes associated with comorbidity.²³ For the regression analysis, we used time-dependent covariates, updated at 5-year intervals, to account for possible temporal changes in SES and comorbidity.

Second, in the prevalent MS cases, we estimated the annual incidence of ICU admission in each year from fiscal years January 2000 to October 2009, because this is more relevant at the population level and for health services planning than the incidence of ICU admission among incident MS cases. Each year, a new matched cohort was extracted from the general population as described earlier. Also, we estimated the 10-year cumulative incidence of ICU admission for this period. To facilitate comparisons to other studies, we age- and sex-standardized the results to the 2007 Canadian population. We compared the incidence rates of ICU admission between the diseased and matched cohorts using incidence rate ratios (IRRs) and 95% confidence intervals (CIs).

Table 2 Adjusted hazard ratios and 95% CIs for the association among the incident MS cohort of time to first intensive care unit admission

Characteristic	Hazard ratio	95% CI
Population		
General population (reference)	1.0	
MS	1.46	1.20-1.77
Sex		
Male (reference)	1.0	
Female	0.49	0.46-0.54
Age group, y		
<40 (reference)	1.0	
40-59	4.71	4.07-5.45
≥60	13.4	11.6-15.5
Socioeconomic status		
Rural 1 (lowest rural)	1.26	1.01-1.56
Rural 2	0.87	0.70-1.09
Rural 3	0.76	0.61-0.95
Rural 4	1.24	1.01-1.56
Rural 5 (highest rural)	0.96	0.76-1.22
Urban 1 (lowest urban)	1.95	1.63-2.32
Urban 2	1.71	1.43-2.05
Urban 3	1.50	1.25-1.79
Urban 4	1.29	1.06-1.56
Urban 5 (highest urban; reference)	1.0	
Not calculated ^a	0.59	0.41-0.84
Modified Charlson Index		
0	1.0	
1	1.47	1.23-1.77
2-3	1.67	1.45-1.91
>3	1.20	0.92-1.56

Abbreviations: CI = confidence interval; MS = multiple sclerosis.

^aNot calculated: people living where the Canadian census does not calculate an average household income, most of whom reside in nursing homes or other chronic care facilities.

Characteristics of critical illness. We reviewed clinical data for initial ICU admissions in our MS cohort and matched controls from January 2000 through October 2009. Using admission diagnoses, 2 reviewers (R.A.M., A.G.) independently classified the primary reason for ICU admission as infection; exacerbation, or complications secondary to the underlying MS; and other acute serious illness unrelated to MS.²⁴ Complications included neuromuscular respiratory weakness, seizures, pressure ulcers, neurogenic bladder/urinary tract infection, and pneumonia. Disagreements were resolved by consensus.

We report frequency (percent) for categorical variables and mean (SD) or median (interquartile range) for continuous variables. We compared the characteristics of critical illness across cohorts using χ^2 tests for categorical variables and analysis of variance or Kruskal-Wallis tests for continuous variables. Using multivariable logistic regression analysis, we compared the risk of being admitted for infection in the MS and matched populations, adjusting for age at ICU admission, sex, SES, comorbidity, year of ICU admission, and disease duration as defined previously. Next, we included the use of drug therapies in the year before admission (yes vs no) in the model. Drug therapies considered were corticosteroids and immunomodulatory and immunosuppressive therapies (table e-2) as identified using Anatomical Therapeutic Classification System codes in prescription claims. We report odds ratios (ORs) and 95% CIs for the association between MS and infection. Assumptions of the logistic regression model were tested using standard methods.²⁵

Mortality. For the first ICU admissions among prevalent cohorts of MS and their controls, we estimated age- and sex-standardized mortality rates in the ICU, in the hospital, and at 30 days and 1 year after ICU admission. The Vital Statistics Death Database captures information from all provincial and territorial vital statistics registries on all deaths in Canada.²⁶ Using ICD coding, we categorized underlying causes of death as of December 31, 2009, as due to infection, MS, or other illness. We could not repeat these analyses for the incident MS cohort because of privacy regulations regarding small sample size.

Standard protocol approvals, registrations, and patient consents. The University of Manitoba Health Research Ethics Board and the Manitoba Health Information Privacy Committee approved the study. Statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS We identified 5,035 prevalent cases of MS, and one matched control for 6 cases, 2 controls for 30 cases, 3 controls for 212 cases, 4 controls for 938 cases, and 5 controls for the remaining cases, for a total of 23,699 controls. At the time of the first health claim for MS, the mean (SD) age was 42.1 (13.6) years and 70.8% were women. Of 5,035 prevalent cases of MS, we identified 2,547 incident cases. Characteristics of the cohorts at the index date are shown in table 1.

ICU admission in incident cohorts. Of the 2,547 incident cases of MS, 109 (4.3%) were admitted vs only 337 (2.4%) of matched controls. At their first ICU admission, persons with MS were younger on average than the general population (table e-3). Using Kaplan-Meier analysis, the ICU admission risk was increased in the MS population as compared with the general population ($p < 0.0001$). Male sex, older age, higher levels of

comorbidity, and lower SES were also associated with an increased risk of ICU admission (all $p < 0.0001$).

In the multivariable Cox model, the adjusted risk of ICU admission was elevated for the MS population vs controls (table 2). In an age-stratified analysis, the risk of ICU admission was highest among persons with MS younger than 40 years (hazard ratio [HR] 3.01; 95% CI 2.09–4.32), declining among those aged 40 to 50 years (HR 1.34; 95% CI 1.04–1.73), and lowest among persons 60 years or older (HR 0.58; 95% CI 0.32–1.06).

ICU admission in prevalent cohorts. The number of persons with MS living in Manitoba in each year from January 2000 to October 2009 varied from 3,068 to 3,524. The number of matched controls varied from 15,264 to 17,597. From January 2000 through October 2009, the age- and sex-standardized annual incidence of ICU admission ranged from 0.51% to 1.07% in the MS population vs 0.34% to 0.51% in the general population (figure e-1) and was consistently higher in the MS population. In 2009, for example, the IRR for MS was 1.91 (95% CI 1.01–3.39).

The crude 10-year average annual incidence of ICU admission was 0.79% (0.70%–0.89%) for the MS population and 0.41% (0.38%–0.44%) in controls. The average annual incidence of ICU admission increased with age in both cohorts; however, the incidence of ICU admission was higher in the MS population than in the controls at all ages, and was particularly high among those aged 18 to 39 years, consistent with the findings in the incident MS population (figure 1).

Based on 221 ICU admissions during 3,664 person-years of observation, the crude 10-year cumulative incidence of ICU admission was 6.03% (5.26%–6.80%)

in MS, while the age- and sex-standardized incidence was 6.95% (6.12%–7.77%). Based on 3,761 ICU admissions during 109,062 person-years of observation, the crude 10-year cumulative incidence of ICU admission in the matched cohort was 3.45% (3.34%–3.56%), while the age- and sex-standardized incidence was 4.52% (4.39%–4.64%). Thus, over 10 years, the risk of ICU admission was 1.5-fold higher in the MS population (IRR 1.54; 95% CI 1.30–1.77).

Reasons for ICU admission in incident cohorts. Clinical characteristics at first ICU admission differed between the MS population and controls (table 3). Note that the sample size is smaller here because the reasons for admission were available only in Winnipeg ICUs for the period January 2000 to October 2009. The MS population was younger, with higher APACHE II acute physiology scores, and was more likely to be mechanically ventilated. Findings were similar when all ICU admissions were considered (data not shown).

The distribution of reasons for admission differed between the populations (table e-4). After age- and sex-standardization, the most common reason for admission in MS was other acute illness unrelated to the underlying disease, followed by infection. The most common “other” reasons for admission were diseases of the circulatory system and of the respiratory system.

Compared with controls, the MS population was more likely to be admitted for an infection even after accounting for confounders (OR 1.82; 95% CI 1.10–3.02). The increased risk of admission for infection was only slightly attenuated when we included a single variable indicating treatment with any corticosteroids or immunosuppressive or immunomodulatory drugs in the model (OR 1.71; 95% CI 1.01–2.90). While immunosuppressive therapy was independently associated with admission for infection (OR 4.05; 95% CI 1.72–9.51), use of immunomodulatory therapy (OR 0.89; 95% CI 0.26–3.09) and corticosteroids (OR 0.96; 95% CI 0.58–1.59) was not.

Mortality. For the MS population, mortality during an ICU admission was 6.98%, while it was 26.0% 1 year after ICU admission (table e-5). When compared with controls, mortality was not elevated within the period of ICU admission or the ICU-containing hospitalization, but it was 2-fold higher 1 year after ICU admission in MS. This finding was largely driven by increased mortality in persons younger than 40 years (table 4). Overall, underlying causes of death included MS (29.4%, $n = 15$), circulatory (23.5%, $n = 12$), malignancy (13.7%, $n = 7$), infection (11.8%, $n = 6$), and other causes (21.6%, $n = 11$). Persons younger than 40 years had 75% lower odds of dying due to MS than persons older than 60 years (OR 0.25; 95% CI 0.12–0.53).

Figure 1 Average annual age-specific incidence rates: MS population and the general population controls

Text boxes show incidence rate ratios comparing incidence of ICU admission by age group in MS with the matched GP cohort. GP = general population; ICU = intensive care unit; MS = multiple sclerosis.

Table 3 Characteristics of incident MS and general population cohorts at the first intensive care unit admission in the Winnipeg Regional Health Authority in the interval January 2000 to October 2009^a

Characteristic	General population controls (n = 212)	MS (n = 78)	p Value
Female, n (%)	111 (52.4)	41 (52.5)	0.97
Age at admission, y, mean (SD)	60.5 (13.2)	51.7 (12.1)	<0.0001
Age group, y, n (%)			<0.0001
<40	14 (6.6)	13 (16.7)	
40-59	86 (40.6)	46 (59.0)	
≥60	112 (52.8)	19 (24.3)	
Disease duration, y, mean (SD)	9.13 (5.2)	9.09 (5.5)	
ICU length of stay, d, mean (SD)	4.78 (8.4)	6.36 (12.9)	0.12
Hospital length of stay, d, mean (SD)	19.6 (28.6)	48.3 (86.8)	0.05
APACHE II acute physiology score, mean (SD)	10.7 (6.7)	13.4 (9.22)	0.007
Glasgow Coma Scale score, median (IQR)	15 (15-15)	15 (11-15)	0.0008 ^b
Mechanical ventilation, n (%)	88 (41.5)	46 (59.0)	0.0082
Vasoactive agents, n (%)	83 (39.1)	28 (35.9)	0.61
Dialysis	c	c	1.0
Region of residence, n (%)			0.60
Urban	156 (73.6)	55 (70.5)	
Socioeconomic status, n (%)			0.75
Rural 1 (lowest rural)	10 (4.7)	c	
Rural 2	14 (6.6)	7 (9.0)	
Rural 3	c	c	
Rural 4	9 (4.2)	7 (9.0)	
Rural 5 (highest rural)	14 (6.6)	c	
Urban 1 (lowest urban)	31 (14.6)	11 (14.1)	
Urban 2	33 (15.6)	13 (16.7)	
Urban 3	37 (17.4)	9 (11.5)	
Urban 4	33 (15.6)	13 (16.7)	
Urban 5 (highest urban)	19 (8.9)	c	
Not calculated ^d	c	c	
Modified Charlson Index, n (%)			0.37
0	47 (22.2)	26 (33.3)	
1	59 (27.8)	13 (16.7)	
2-3	73 (34.4)	31 (39.7)	
>3	33 (15.6)	8 (10.2)	

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; ICU = intensive care unit; IQR = inter-quartile range; MS = multiple sclerosis.

^aNote that because of matching on the index date of diagnosis with MS, the cohorts are no longer matched by the time of first ICU admission, and numbers are smaller here than in table e-3 because reasons for admission were available in Winnipeg for only the period 2000 to 2010.

^bAlthough medians are the same, distributions differ significantly.

^cSuppressed because of small cell size to protect confidentiality.

^dNot calculated: people living where the Canadian census does not calculate an average household income, most of whom reside in nursing homes or other chronic care facilities.

DISCUSSION Using population-based cohorts, we evaluated the interplay between MS and critical illness. The 10-year cumulative incidence of ICU admission was 6%. The excess risk of ICU admission in the MS population was substantially

greater in younger persons than older persons, even after accounting for comorbidity. Mortality was 2-fold higher 1 year after ICU admission among the MS population, again particularly in young persons.

Table 4 Percent age-specific mortality 1 year after intensive care unit admission in multiple sclerosis as compared with the matched cohort from the general population

Age group, y	General population		Multiple sclerosis		
	No. at risk	Mortality (95% CI)	No. at risk	Mortality (95% CI)	Rate ratio (95% CI)
<40	98	13.3 (6.55–20.0)	14	50.0 (23.8–76.2)	3.77 (1.45–8.11)
40–59	881	12.8 (10.6–15.0)	110	17.3 (10.2–24.3)	1.34 (0.79–1.99)
≥60	1,381	21.9 (19.7–24.1)	91	33.0 (23.3–42.6)	1.50 (1.04–2.03)

Abbreviation: CI = confidence interval.

Prior work regarding the frequency of ICU admission is limited. In a questionnaire-based study in the United Kingdom, 16 of 1,942 persons (0.8%) reported having an ICU admission in the preceding 6 months.²⁷ In 1989, among elderly persons discharged from short-term general hospitals in the United States, those with MS were less likely to use ICU or coronary care unit (14.7%) services than those without MS (18.5%).¹⁰ However, that study was conducted 20 years earlier and was restricted to hospital survivors.

The excess risk of ICU admission in MS was greater in younger persons than older persons. In the general population, chronic illness affects a small proportion of young individuals, but it affects more than one-third of the population older than 40 years and nearly three-quarters of the population older than 60 years²⁸; thus, the disparity in the risk of ICU admission appears to diminish as the general population ages and acquires more chronic disease.

Cardiovascular disease was an important reason for admission in the MS population. We and others have shown a higher than expected incidence of cardiac disease in MS.^{8,9} As hypothesized, we found that infection was a more common reason for ICU admission in the MS population than in the general population. Immunosuppressive therapy was associated with admission for infection, but adjusting for immunosuppressive therapies did not eliminate the association with admission for infection. This suggests that the increased risk of infection requiring ICU admission in MS is likely also due to complications of MS such as neurogenic bladder, immobility, and respiratory dysfunction, which increase the risk of urinary tract infections, pressure ulcers, and pneumonia.⁷

Patients with MS admitted to the ICU were more acutely ill based on the APACHE II acute physiology score than other ICU patients, and were more likely to require mechanical ventilation. In a series of 18 patients with MS who required mechanical ventilation, the most common indications for ventilation were aspiration pneumonia, mucous plugging, mechanical respiratory failure, coma, and status epilepticus.¹¹ Of these individuals, 33% died within 6 months of being ventilated. We found that the risk of death was increased in

the year after ICU admission. The particularly high mortality rate among young persons raised the question of whether this was attributable to aggressive MS,²⁹ infection, or other causes. Although limited by small numbers, our findings did not suggest that aggressive MS had a differentially greater role at young ages. However, the high mortality rate suggests that patients discharged from the ICU may need more careful surveillance by primary care providers and specialists thereafter.

We lacked data regarding the clinical characteristics of the MS population including clinical course and disability status; therefore, we could not evaluate how those factors influenced the risk of ICU admission, but this warrants future evaluation. Administrative data may lack clinically precise coding, but we have established the validity of these data for identifying episodes of ICU care, and for identifying persons with MS.^{17,19} Some of our estimates had large CIs because of small sample sizes. While our analyses of ICU admission used all admissions in Manitoba, when we examined characteristics of critical illness, we restricted the admissions to those in Winnipeg (93% of provincial admissions). However, characteristics of these individuals were similar (tables 3 and e-3) to those in the provincial cohort, suggesting that selection bias is limited. Given the variation in health care delivery across health systems, findings may differ in other jurisdictions and should be evaluated. This study had several strengths. It was novel and population-based with comprehensive follow-up. We estimated the incidence of ICU admission among persons with incident and prevalent MS, carefully described their critical illness, and accounted for multiple confounders. Identifying the year post-ICU admission as requiring enhanced clinical attention considering the increased mortality rate was another important strength.

The risk of ICU admission and subsequent death is increased in MS, particularly among persons aged 18 to 39 years. Given the observed reasons for ICU admission, prevention of infection and management of comorbidities, including cardiovascular disease, may be important avenues for reducing ICU admissions in the MS population that should be pursued in future studies.

AUTHOR CONTRIBUTIONS

The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Ruth Ann Marrie, Charles Bernstein, Allan Garland, Carol Hitchon, and Christine Peschken designed the study and obtained funding. All authors contributed to the analysis and interpretation of the data. Ruth Ann Marrie drafted the manuscript. All authors revised the manuscript and approved of the final version to be published.

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REFERENCES

1. Jacobs P, Noseworthy TW. National estimates of intensive care utilization and costs: Canada and the United States. *Crit Care Med* 1990;18:1282–1286.
2. Sirio CA, Tajimi K, Taenaka N, Ujike Y, Okamoto K, Katsuya H. A cross-cultural comparison of critical care delivery: Japan and the United States. *Chest* 2002;121:539–548.
3. Wunsch H, Angus DC, Harrison DA, et al. Variation in critical care services across North America and Western Europe. *Crit Care Med* 2008;36:2787–2793.
4. Halpern NA, Bettles L, Greenstein R. Federal and nationwide intensive care units and healthcare costs: 1986–1992. *Crit Care Med* 1994;22:2001–2007.
5. Williams TA, Dobb GJ, Finn JC, et al. Determinants of long-term survival after intensive care. *Crit Care Med* 2008;36:1523–1530.
6. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. *Chest* 1991;100:1619–1636.
7. Redelings MD, McCoy L, Sorvillo F. Multiple sclerosis mortality and patterns of comorbidity in the United States from 1990 to 2001. *Neuroepidemiology* 2006;26:102–107.

8. Jadidi E, Mohammadi M, Moradi T. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. *Mult Scler J* 2013;19:1336–1340.
9. Marrie RA, Yu BN, Leung S, et al. Prevalence and incidence of ischemic heart disease in multiple sclerosis: a population-based validation study. *Mult Scler Relat Disord* 2013;2:355–361.
10. Fleming ST. Multiple sclerosis as a comorbidity: a study of resource utilization and outcomes of care. *Clin Perform Qual Health Care* 1995;3:23–30.
11. Pittock SJ, Weinshenker BG, Wijdicks EFM. Mechanical ventilation and tracheostomy in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2004;75:1331–1333.
12. Fried TR, Bradley EH. What matters to seriously ill older persons making end-of-life treatment decisions? A qualitative study. *J Palliat Med* 2003;6:237–244.
13. Fried TR, Bradley EH, Owle VT, Allore H. Understanding the treatment preferences of seriously ill patients. *N Engl J Med* 2002;346:1061–1066.
14. Stevenson LW, Hellkamp AS, Leier CV, et al. Changing preferences for survival after hospitalization with advanced heart failure. *J Am Coll Cardiol* 2008;52:1702–1708.
15. Murphy DJ, Burrows D, Santilli S, et al. The influence of the probability of survival on patients' preferences regarding cardiopulmonary resuscitation. *N Engl J Med* 1994;330:545–549.
16. Health Information Management Branch. Population Report. Winnipeg: Manitoba Health and Healthy Living; 2008.
17. Garland A, Yogendran M, Olafson K, Scales DC, McGowan KL, Fransoo R. The accuracy of administrative data for identifying the presence and timing of admission to intensive care units in a Canadian province. *Med Care* 2012;50:e1–e6.
18. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. *Lancet* 1974;2:81–84.
19. Marrie RA, Yu N, Blanchard JF, Leung S, Elliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. *Neurology* 2010;74:465–471.
20. Haupt MT, Bekes CE, Brilli RJ, et al. Guidelines on critical care services and personnel: recommendations based on a system of categorization of three levels of care. *Crit Care Med* 2003;31:2677–2683.
21. Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson Comorbidity Index using Canadian administrative databases: a perspective on risk adjustment in critical care research. *J Crit Care* 2005;20:12–19.
22. Garland A, Fransoo R, Olafson K, et al. The Epidemiology and Outcomes of Critical Illness in Manitoba. Winnipeg: Manitoba Centre for Health Policy; 2012.
23. Preen DB, Holman CDAJ, Spilsbury K, Semmens JB, Brameld KJ. Length of comorbidity lookback period affected regression model performance of administrative health data. *J Clin Epidemiol* 2006;59:940–946.
24. Camargo JF, Tobon GJ, Fonseca N, et al. Autoimmune rheumatic diseases in the intensive care unit: experience from a tertiary referral hospital and review of the literature. *Lupus* 2005;14:315–320.
25. Kleinbaum D, Klein M. Logistic Regression: A Self-Learning Text, 2nd ed. New York: Springer-Verlag; 2002.
26. Statistics Canada. Vital Statistics: Death Database [online]. Available at: <http://www.statcan.gc.ca/cgi-bin/imdb/p2SV.pl?Function=getSurvey&SDDS=3233&lang=en&db=imdb&adm=8&dis=2>. Accessed March 6, 2011.

27. McCrone P, Heslin M, Knapp M, Bull P, Thompson A. Multiple sclerosis in the UK: service use, costs, quality of life and disability. *Pharmacoeconomics* 2008;26:847–860.
28. Broemeling A, Watson DE, Prebtani F; Councillors of the Health Outcomes Steering Committee of the Health Council of Canada. Population patterns of chronic health conditions, co-morbidity and health care use in Canada: implications for policy and practice. *Health Q* 2008;11:70–76.
29. Menon S, Shirani A, Zhao Y, et al. Characterising aggressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2013;84:1192–1198.

This Week's *Neurology*[®] Podcast

Abnormal thalamic function in patients with vestibular migraine (See p. 2120)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the June 10, 2014, issue of *Neurology*. In the second segment, Dr. Joanna Jen talks with Dr. Gioacchino Tedeschi about his paper on abnormal thalamic function in patients with vestibular migraine. Dr. Adam Numis then reads the e-Pearl of the week about Gerstmann-Sträussler-Scheinker syndrome. In the next part of the podcast, Dr. Chenjie Xia focuses her interview with

Dr. Karen Roos on neurology and infectious diseases such as Lyme disease.

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