Journal Club:

Effect of comorbidity on mortality in multiple sclerosis

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Multiple sclerosis (MS) is a chronic demyelinating disease of the CNS estimated to reduce life expectancy by 7–14 years compared to demographically similar groups in the general population.¹ While several disease complications pose a potential risk for mortality, results from large observational studies suggest that comorbidities substantially influence survival in MS.^{2,3}

In a recent *Neurology*[®] article, Marrie et al.⁴ applied an effective methodologic approach to assess the contribution of comorbidity to excess mortality in the MS population. Besides its considerable epidemiologic merit, the study has important implications for the management of patients with MS, particularly if closer surveillance and targeted interventions may reduce the burden of comorbidity among them and improve survival.

HYPOTHESIS AND DESIGN Does comorbidity affect survival in the MS population, and to what extent? Is the magnitude of association different from that in the general population? What are the underlying causes of death? To address these questions, Marrie et al. performed a retrospective matched cohort study using population-based administrative data. The authors stratified cohorts by birth year in order to study temporal changes in survival, hypothesizing that the latter improves in the MS population over time. They also hypothesized that comorbidity shortens the survival of persons with MS. Cox regression analysis employed for statistical analysis provides us with a thorough insight into the effect of multiple covariates on the time to death, whereas some other studies traditionally use logistic regression, which estimates the probability of binary survival response (died vs alive) over the period of observation. An alternative method with time-to-event outcome is the log-rank test, which does not allow adjustment for confounding factors.⁵

METHODS The authors combined data extracted from 2 data sources. The first was administrative (health) data from the province of Manitoba, Canada, covering 98% of the population. The second data

source was the Manitoba Vital Statistics Death Database, encompassing information on all deaths in Manitoba, including date and cause of death classified according to ICD-9 or ICD-10, depending on the time period. Using a validated administrative case definition, the authors identified all MS cases and up to 5 controls for each case, matched on sex, exact year of birth, and region of residence, from April 1, 1984, to March 31, 2012.

To analyze the survival in both populations, the authors used univariate Cox regression with age as the time scale. Unlike the standard approach of using time on study as the time scale in a Cox regression (which means estimating time from entry into the study until the event of interest, typically death), and adjusting the model for age, this alternative approach to use age as the time scale allows a straightforward adjustment for multiple effects of aging process, and is recommended for analyzing epidemiologic cohort data.⁶ On the other hand, the authors addressed a common source of bias in applications of survival analysis known as left truncation, which occurs when the individuals who have already passed the event of interest prior to study recruitment are not included in the study.⁵ They considered comorbidities to have time-varying nature, meaning that the value of the variable is not fixed over time, e.g., an individual develops comorbidity after the index date. The authors analyzed MS as a time-varying covariate as well, considering the age at onset, and thereby the duration of exposure. However, they did not separate the subtypes of MS. When estimating the association of comorbidity and mortality in the multivariable Cox proportional hazards model, the study controlled for important confounders such as sex, region of residence, and socioeconomic status.

RESULTS The study population consisted of 5,797 individuals with MS and 28,807 matched controls. The cohorts were well-matched on demographics, but were different with respect to comorbid conditions. Generally, the burden of comorbidities was higher in the MS population compared to the controls. Diabetes, hypertension, and ischemic heart

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disease were equally prevalent in both populations at the index date, and only ischemic heart disease remained so over the study period.

The median survival from birth was lower in the MS than in the matched population (75.9 vs 83.4 years, $p < 0.0001$). The age-specific mortality rates decreased in both populations over time, more markedly in the MS population and in younger ages. The adjusted hazard of death was increased in the MS population (hazard ratio 2.40; 95% confidence interval 2.25–2.57), and did not change when controlling the model for comorbidities. Taken separately, some particular comorbidities increased and some decreased the hazard of death. Diabetes, hypertension, ischemic heart disease, and chronic lung disease were more closely associated with mortality in the MS population than in the controls ($p < 0.0001$), whereas bipolar disorder was associated with increased and autoimmune thyroid disease decreased hazard of death, only in the matched population. The figure depicts the rate ratios of cause-specific mortalities in the MS and matched populations, derived from the provided supplementary tables.

INTERPRETATION The current study addresses the relevant question of increased mortality, and whether the comorbidity status contributes to poorer survival in the MS population compared to the general

population. The study design provides adequate power and allows generalizability of the results to the Canadian population. The combination of multiple data sources increases reliability of the results. The administrative health registry covers almost the entire population of the region and provides objective data avoiding bias related to patient recall. On the other hand, since the diagnosis codes serve as billing codes to justify medical services, the comorbidity events might be overreported.² Long follow-up time allows the proper assessment of mortality.

The main finding of the study was that mortality is increased in the MS over the general population, especially among younger adults, but is not attributable to the overall effect of comorbidities. In clinical practice, prior to tailoring an optimal disease management scheme, the information on predictive ability of individual comorbidities for the outcome is of particular relevance. Analyzing all comorbidities in a multi-variable model simultaneously, the study found some comorbidities to increase and some to decrease the hazard of death. In the supplementary material, there are also data demonstrating that the association of comorbidity count and mortality rates is not the same in both populations. Besides that, survival might be affected differently depending on comorbidity burden or severity of illness, as well as several comorbidities

Figure Forest plot of the odds ratios (logarithmic x-axis) and 95% confidence intervals (CIs) of cause-specific mortalities by ICD chapters in patients with multiple sclerosis (MS) vs the matched population

ICD = International Classification of Diseases. *Includes MS and other neurologic disorders.

that independently cause similar impairments and could additively or synergistically increase mortality.⁷ Therefore, detailed analysis of particular clinical states considering the kind and count of comorbidities, as well as their severity and potential fatality, would be of interest. It might also be suggested to create a variable corresponding to the comorbidity index, capturing their count, severity, and potential fatality. In addition, since some comorbidities, such as diabetes and hypertension, are believed to be mutually related, it would be also interesting to sort them, and estimate the summary effect of each group. An example of analysis to apply in this case could be the factorial analysis.

The authors properly accounted for common and relevant confounders. However, there are several factors the study was limited to address.

We noticed that although well-matched on several covariates, the MS population and the controls were not identical, particularly with regard to comorbidities, as shown in the study results, which makes the interpretation of their effect on mortality in comparison between 2 populations difficult. There were also differences in both populations concerning the dynamics of some comorbidities developed over the study period. For instance, the prevalence of hypertension was similar in both populations at the index date, but turned out to be significantly higher in the control population at the end of the study. This fact should not be dismissed given that hypertension is a major risk factor of death.⁸

In a multivariate model estimating hazards of death in 2 populations, the authors include MS as a time-varying covariate in order to account for disease duration. This approach allows more precise evaluation of the effect of MS on the risk of death. However, a review on mortality in MS found the survival of those having developed MS in later ages to be lower. Moreover, the same review reported faster time to death from disease onset in patients diagnosed with primary progressive MS and similar survival from birth regardless of disease course at the same time.¹ Therefore, the distinction between disease subtypes should be considered when analyzing MS as a time-varying covariate. It would be also reasonable to take into account the divergence between MS onset and MS diagnosis in time given that comorbidity delays the diagnosis of MS.⁹ If it would be feasible to determine the average delay to diagnosis for the MS population, a sensitivity analysis testing whether adding that variable into the equation would influence the results could be helpful.

Other important confounders that would be difficult to address within the scope of this study design are whether the patients received medications for comorbid conditions or disease-modifying therapy (DMT) and compliance. Since DMT is proven to increase life

expectancy in patients with MS,¹⁰ it is important to consider not only the claim of any treatment and its duration, but also whether it was started in early or late disease stages. Unhealthy lifestyle habits including smoking and alcohol abuse are of major importance as well, according to recent reports on their association with disease progression and survival.^{3,11}

Further studies should elucidate the particular influences of several comorbidities on the course and outcome of MS, which is important for better clinical care of the individual patient, as well as for developing health system optimization strategies.

AUTHOR CONTRIBUTIONS

Anush Karamyian: drafting/revising the manuscript, analysis or interpretation of data. Johann Sellner: revising the manuscript, analysis or interpretation of data, study supervision.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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SUMMARY OF COMPREHENSIVE SYSTEMATIC REVIEW: REHABILITATION IN MULTIPLE SCLEROSIS: REPORT OF THE GUIDELINE DEVELOPMENT, DISSEMINATION, AND IMPLEMENTATION SUBCOMMITTEE OF THE AMERICAN ACADEMY OF NEUROLOGY

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The systematic review by Haselkorn et al.¹ correctly identified that additional data from better-designed rehabilitation trials is desperately needed. The reference section was short, suggesting that a relatively small cohort of rehabilitation studies in multiple sclerosis (MS) was included. This may relate to the quality of the evidence, as the current review paradigm is geared more to evaluating pharmaceutical efficacy than rehabilitation studies. Class I evidence in rehabilitation is extremely difficult to obtain given challenges in designing double-blind placebo-controlled trials of sufficient power, especially with the levels of funding typically available for these studies. It is also possible that the paucity of included data relates to the lack of rehabilitation professionals (e.g., physical and occupational therapists) on the author panel. Regardless, evidence-based medicine does not suggest that the absence (or relative lack) of evidence proves a lack of effect and stresses the importance of clinical acumen, especially in the setting of insufficient data.^{2,3}

Instead of highlighting the need for better data, this review utilized a limited diversity of authors and included a limited cohort of data, potentially negatively impacting the care of people with MS by limiting their access to rehabilitative services.

Author Response: Melissa J. Armstrong, Gainesville, FL; Theodore R. Brown, Kirkland, WA; Jodie K. Haselkorn, George H. Kraft, Seattle; Pushpa Narayanaswami, Boston: We thank Jones et al. for the comments on our recent summary,¹ and agree that lack of evidence does not demonstrate lack of effect.

This work was a systematic review rather than a clinical practice guideline. Due to a lack of high-quality evidence, no practice recommendations were made. Our review assessed published data and identified the need for further research; systematically evaluating an important question is not at odds with good clinical care.

In addition to MS and evidence-based medicine specialists, the panel included 4 physicians who are board-certified in physical medicine and rehabilitation. The comprehensive literature search used MEDLINE, EMBASE, CINAHL, and Science Citation Index. The panel reviewed 5,464 abstracts and 491 full-text articles before rating 142 articles according to the American Academy of Neurology's rating scheme. The systematic review summary included only 71 references, but the full review (available as an e-appendix) included 106 references.

Although there are challenges to research design in rehabilitation medicine, the need for well-designed studies is clear. This systematic review is an important reference for the current state of the field that will further research efforts. Rather than suggesting limiting access to therapy, we support rehabilitation and strongly encourage funding and completion of studies to improve the evidence base for rehabilitative services.

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CORRECTION

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In the article "Journal Club: Effect of comorbidity on mortality in multiple sclerosis" by A. Karamyan and J. Sellner,¹ there is an error in the author byline and affiliations. Dr. Sellner does not hold a PhD, and the affiliation should read Paracelsus Medical University (without the word "Private" as originally published). The authors regret the error.

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1. Karamyan A, Sellner J. Journal Club: Effect of comorbidity on mortality in multiple sclerosis. *Neurology* 2016;86:e228–e230.

Author disclosures are available upon request (journal@neurology.org).