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Hospitalization is associated with subsequent disability in multiple sclerosis

Allan Garland[a,b,c], Luanne M. Metz[d,e], Charles N. Bernstein[a,f], Christine A. Peschken[a,b], Carol A. Hitchon[a], Ruth Ann Marrie[a,b,*]

[a] Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Canada
[b] Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Canada
[c] Manitoba Centre for Health Policy, Winnipeg, Canada
[d] Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada
[e] Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada
[f] IBD Clinical and Research Centre, University of Manitoba, Winnipeg, Canada

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ABSTRACT

Background: Although an increasing amount of research has evaluated interactions between MS and comorbid chronic disease, few data exist regarding the interactions between MS and acute illness. As compared to age and sex-matched persons without MS, persons with MS experience higher rates of hospitalization and critical illness, and higher mortality rates and health care utilization following critical illness. We aimed to determine whether acute illness requiring hospitalization is associated with progression of multiple sclerosis (MS).

Methods: We conducted this population-based, retrospective cohort study by linking data from the regional MS Clinic in Calgary, Canada with the Canadian Discharge Abstract Database to identify non-obstetric hospitalizations. We included individuals with a confirmed diagnosis of MS, at least one recorded Expanded Disability Status Scale (EDSS) measurement, and known age of symptom onset of age 10 years or older. Using data from 2009 to 2014, we used generalized linear models with generalized estimating equations to establish the association within individuals between hospitalization and the time course of MS-related disability (as measured by the EDSS), adjusting for sex, age, disease course at onset, and use of disease-modifying therapies.

Results: We included 2104 individuals with MS in the analysis, who had a median of 4 EDSS measurements each. Of these 491 (23.3%) had at least one hospitalization. Most subjects were female, with a relapsing disease course at onset, and a mean (SD) age at symptom onset of 33.0 (10.0) years. The underlying rate of disability progression averaged 0.9 EDSS points per decade. Following hospitalization, there was a step increase in EDSS, averaging 0.23 points, equivalent to 2.5 years of time-related disease progression. Hospitalization did not alter the subsequent temporal rate of disability progression. The findings did not differ in those hospitalized for MS versus other reasons.

Conclusions: Acute illness requiring hospitalization is associated with a worsening of MS-related disability.

1. Introduction

Many people with a given chronic illness have comorbid chronic conditions (van den Akker et al., 1998; Broemeling et al., 2008). In multiple sclerosis (MS), comorbidities are now recognized to influence the length of the delay between MS onset and diagnosis, disability progression, use of disease-modifying therapy, health care utilization and mortality (Marrie et al., 2016; Zhang et al., 2016). Although an increasing amount of research has evaluated interactions between MS and comorbid chronic disease few data exist regarding the interactions between MS and acute illness. As compared to age and sex-matched persons without MS, persons with MS experience higher rates of hospitalization and critical illness, and higher mortality rates and health care utilization following critical illness (Marrie et al., 2014a, 2014b, 2015a, 2015b; Karamyan et al., 2016).

However, the interactions between chronic and acute illness are likely to be bidirectional. For example, in older adults cognitive impairment increases the risk of pneumonia, and pneumonia accelerates the progression to dementia (Shah et al., 2013). The effects of intercurrent acute illness on MS are poorly understood. Therefore, we aimed to evaluate the association between acute illnesses requiring hospitalization and the subsequent progression of MS-related disability. We hypothesized that such acute illnesses would result in both acquisition of disability following hospitalization, and that the subse-

* Correspondence to: Health Sciences Centre, GF 543- 820 Sherbrook Street, Winnipeg, MB, Canada R3A 1R9.
E-mail address: rmarrie@hsc.mb.ca (R.A. Marrie).

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quent progression of disability would be greater than before hospitalization.

2. Materials and methods

This was a retrospective cohort study conducted using two population-based data sources from the Calgary Health Region of the Canadian province of Alberta, population 1.54 million. We linked two existing databases, both obtained from the Canadian Institute for Health Information (CIHI), the Calgary MS Clinic Database (CMSD) and the Canadian Discharge Abstract Database (DAD). The University of Manitoba Health Research Ethics Board approved the study.

2.1. Calgary MS clinic database

The Calgary MS Clinic provides care to 98% of persons with MS in the surrounding region. Diagnoses of MS are confirmed by the treating neurologist based on the prevailing diagnostic criteria at the time of diagnosis (Poser et al., 1983; McDonald et al., 2001; Polman et al., 200, 2011). The Calgary MS Clinic Database (CMSD) captures standardized demographic and clinical information regarding all persons with MS seen in the clinic including a unique patient identifier, date of birth, sex, date of MS symptom onset, and disease course at onset (relapsing, progressive or unknown). The date of each clinic visit is recorded as well as disability status as measured using the Expanded Disability Status Scale (EDSS), and the use of disease-modifying therapies. The EDSS is a physician-scored measure used as the gold standard for disability progression in MS clinical trials. It is scored from 0 (no disability) to 10 (death due to MS). A score of 6 indicates the need for unilateral assistance (e.g. cane), while a score of 6.5 indicates the need for bilateral assistance (e.g. crutches), and a score of 7.0 indicates wheelchair use (Kurtzke, 1983). The EDSS scores are recorded by experienced MS physicians and trainees using a standardized scoring form. The MS physicians are formally trained to do the EDSS and certified. If a trainee is involved in assessing the individual with MS, this is verified by the attending neurologist. Data were available for clinic visits from September 21, 2009 to March 31, 2014.

2.2. Discharge abstract database

The DAD contains information about every hospitalization in Canada, excluding those in Quebec (Canadian Institute for Health Information, 2014a; Canadian Institute for Health Information, 2014b). Data are collected by rigorously trained personnel in each hospital, using uniform definitions and collection methods, regardless of the site of care or reason for admission. Further validation and data cleaning are performed by the provincial health departments, and subsequently by CIHI. We obtained DAD records of all discharges from acute care hospitals for the period April 1, 2005, to March 31, 2015, for all the individuals in the CMSD. This allowed us to identify hospitalizations among participants in the CMSD even if they occurred outside Alberta. Variables include a unique patient identifier, sex, date of birth, postal code, dates of admission and discharge, whether the admission was elective vs. emergent/urgent, up to 25 hospital diagnoses in International Classification of Disease (ICD)-10-CA format, whether the hospitalization included any time in an intensive care unit (ICU), and post-hospital disposition. The DAD includes separate records when an individual is directly transferred between hospitals, therefore we combined such records into episodes of hospital care as described elsewhere, allowing a maximum difference in admission dates of 24 h (Fransoo et al., 2012).

2.3. Study population and period

We merged the two datasets deterministically using the scrambled unique identifier provided by CIHI for this project. Inclusion criteria included: (i) a confirmed diagnosis of MS, and (ii) at least one recorded EDSS measurement (n = 3532). Subjects were excluded if their date of symptom onset was missing because this was used to calculate disease duration, or if age at symptom onset was < 10 years (Fig. e-1). Exclusion criteria for individual EDSS measurements were: values predating the listed date of symptom onset, or within 120 days of the end of the DAD data because hospitalization records were dated by discharge dates, and the 99th percentile of hospital length of stay in this dataset was 120 days. Finally, to minimize confounding due to effects of prior hospitalizations, we required that the first EDSS measurement used was not predated by a hospitalization within five prior years, which also excluded all measurements before April 1, 2010.

2.4. Variables

The primary outcome was the EDSS, while the primary exposure of interest was an inpatient, non-obstetric, hospitalization. Obstetric admissions were removed from the DAD dataset by CIHI using obstetric-related diagnosis and procedure codes (Table e-1). Covariates included in this analysis were age at symptom onset (continuous), sex (male as reference group), whether the reason for admission was for MS or not based on whether MS was listed as the most responsible hospital diagnosis (ICD-10-CA diagnosis code G35), clinical course at onset (relapsing [reference group], progressive, unknown/not recorded), whether a disease-modifying therapy was being used at the time of each EDSS assessment, and socioeconomic status (SES, continuous). We linked the first three digits of the postal code to the 2011 Canadian census to derive area-level median household income as a measure of SES.

2.5. Statistical analysis

Clinical and demographic characteristics were summarized using frequency (percent), mean (standard deviation) or median (interquartile range [IQR]) as appropriate. We conducted the multivariable analysis using a generalized linear model with generalized estimating equations (GEE) to account for clustering of the repeated EDSS measures within individuals (Hardin and Hilbe, 2003). The model was parameterized to estimate three key aspects of the trajectory of EDSS over time, starting from MS symptom onset. First was a slope representing the rate of change of EDSS during the whole study interval for those who had no hospitalizations; this same slope also applied to the time from MS onset until right before the first hospitalization for those who had any hospitalizations during the study interval. Second, for those who had any hospitalizations during the study interval, we allowed for a possible step change in EDSS from before to after the hospitalization. Finally, for those who had any hospitalizations during the study interval, we estimated a slope representing the change in EDSS over time after the hospitalization, which was allowed to differ from that before hospitalization. The core of the analysis was to assess whether the pre-hospital to post-hospital EDSS step change and slope change were statistically and clinically significant.

We utilized an identity link and an exchangeable correlation matrix based on observed pairwise correlations of EDSS values that all ranged from 0.71 to 0.89. GEE models generate effect estimates that are population averages of within-subject and between-subject effects over time (Neuhaus and Kalbfleisch, 1998). Since we were interested in assessing the change in EDSS related to hospitalization *within* individuals, we created separate “within-patient” and “between-patient” components of: (a) time from symptom onset (TIME), and (b) an indicator variable identifying whether the EDSS was measured pre- or post-hospitalization (PREPOST) (Neuhaus and Kalbfleisch, 1998; Begg and Parides, 2003). We also created interaction terms between these components of TIME and PREPOST. For this study, the coefficients of main interest are the within-patient versions, which have the following meanings: (a) $TIME_{within}$ is the slope of the temporal change in EDSS for

patients before the first (index) hospitalization, or for the entire interval if the person had no hospitalizations; (b) $PREPOST_{within}$ is the step-change in EDSS from before the first hospitalization to after it; and (c) the interaction between $PREPOST_{within}$ and $TIME_{within}$ is the difference between the pre-hospitalization and post-hospitalization slopes of temporal change in EDSS.

The baseline model considered EDSS values as being before or after the index hospitalization, and included the variables $TIME_{within}$, $TIME_{between}$, $PREPOST_{within}$ and $PREPOST_{between}$, the interaction terms, as well as age at symptom onset, sex, course at onset, and use of disease-modifying therapy. Sensitivity analyses included: (i) exclusion of individuals with only one recorded EDSS (n = 267); (ii) inclusion of SES in the model [omitted for the baseline model due to some missing values]; (iii) categorization of hospitalizations as elective vs. urgent or emergent; (iv) categorization of hospitalizations as including an ICU admission or not; (v) categorization of hospitalizations as due to MS or not; (vi) categorization of hospitalizations as short stay (≤10 days) or longer stay (> 10 days); and (vii) accounted for the presence of a second hospitalization if it occurred after the first hospitalization by creating additional $TIME_{within}$, $TIME_{between}$, $PREPOST_{within}$ and $PREPOST_{between}$ terms. As extensions of the baseline model, analyses (iii)–(vi) were effected by creating two sets of within-patient and between-patient TIME, PREPOST and interaction variables.

We used Stata 14.1 (StataCorp, College Station, Texas) for analysis; *P*-values < 0.05 were considered statistically significant.

3. Results

The analysis included 2104 individuals with MS, with 9076 EDSS measurements; each individual had a median of 4 EDSS measurements (Table 1). Most subjects were female, with a relapsing disease course at onset, and a mean (SD) age at symptom onset of 33.0 (10.0) years. About half used disease-modifying agents at some point in the study interval. Approximately one-fifth had at least one hospitalization, of which 29% were elective admissions, 12% were for a primary diagnosis of MS. Reasons for admission are summarized by ICD-10-CA chapter in Table e-2. Five percent of admissions included time in an ICU. One hundred and fifty-six (7%) members of this cohort had at least two hospitalizations. The frequency of second hospitalizations following MS-related admission was higher (44.2%) than following non-MS related admissions (30%, p = 0.028). The median length of hospitalization was 3 days, and 80% of those hospitalized had a length of stay of 10 days or less. The median (IQR) number of EDSS measurements was the same before (2 [1–4]) and after (2 [1–3]) hospitalization.

The baseline model showed that the rate of disability progression, as assessed by a rise in the EDSS, averaged almost 1 EDSS point per decade (Table 2). Hospitalization altered disability progression; on average, the EDSS increased by 0.23 points, equivalent to approximately 2.5 years of time-related disease progression. However, the interaction term ($TIME_{within\text{-}patient} \times PREPOST_{within\text{-}patient}$) was not statistically significant, indicating that other than the step increase in disability, hospitalization did not change the subsequent rate (slope) of disability progression. On average, disability was lower among women, subjects with an earlier age at symptom onset, and those with a relapsing (vs. progressive) course at onset. After we excluded subjects with only one EDSS measurement, the findings were similar (Table 3). The addition of SES to the model did not change the main findings, but we found that for each additional $1000 of income, the EDSS was statistically significantly, but only slightly lower (0.006 points; 95%CI: −0.002, −0.009).

The remaining sensitivity analyses suggested heterogeneity in the effects of hospitalization on disability, with this heterogeneity only affecting the step change in EDSS following hospitalization (final four data columns of Table 4). The step change worsening in the EDSS was greater for urgent/emergent vs. elective hospitalizations (0.26 vs. 0.16, p = 0.32), for hospitalizations that required ICU care vs. those that did not (0.65 vs. 0.21, p = 0.10), when the main admission diagnosis was not MS vs. MS (0.32 vs. 0.22, p = 0.56), and for longer rather than shorter lengths of stay (0.35 vs. 0.20, p = 0.22) although these differences were not statistically significant. Finally, assessing the step changes in EDSS with up to two successive hospitalizations showed similar average effects for the first and second hospitalization (both 0.19, p = 0.98 for the difference between them, Fig. 1). Just as in the baseline model, hospitalization did not significantly change the trajectory (slope) of EDSS over time in any of the sensitivity analyses.

Table 1
Demographic and clinical characteristics of study cohort (n = 2104).

Variable	Value
Age (years) at symptom onset, mean (SD)	33.2 (10.0)
Females, N (%)	1538 (73.1)
Area-level median household income at first EDSS value, mean (SD)[a]	67,231 (15,207)
Disease course at onset, N (%)	
progressive	224 (10.7)
relapsing	1844 (87.6)
not documented	36 (1.7)
Using disease-modifying therapies, N (%)	
at time of first EDSS	611 (29.0)
at any point	1024 (48.7)
EDSS measurements, N	9076
EDSS measurements/person, median (IQR)	4 (2, 5)
EDSS measurements/person, range	1–21
Years from symptom onset to first EDSS used in analysis, median (IQR)	10.8 (5.3, 17.1)
Years from first to last EDSS used in analysis, median (IQR)	2.9 (1.1, 3.8)
EDSS values, median (IQR)	
first EDSS measurement	2.0 (1.5, 4.0)
all measurements	2.5 (1.5, 5.0)
Hospitalized, N (%)	491 (23.3)
Elective admissions	142
Most Responsible Hospital Diagnosis of MS	61
Including time in an Intensive Care Unit	24
Years from first EDSS used to index hospitalization, median (IQR) (n = 491)	1.4 (0.3, 2.6)
Hospitalization characteristics	
Modified Charlson Comorbidity Score[b], median (IQR)	0 (0, 0)
Modified Charlson Comorbidity Score[b], mean (SD)	0.26 (0.77)
Length of stay, days	3 (2, 7)
Died in hospital, N	5
Hospitalized and any EDSS measurements afterwards, N (%)[c]	315 (18.3)
Years (median, (IQR)) from index hospitalization to:	
immediately prior EDSS (n = 404)	0.41 (0.19, 0.75)
immediately subsequent EDSS (n = 382)	0.47 (0.19, 1.19)
last EDSS used (n = 491)	1.1 (0.1, 2.8)
Individuals with at least 2 hospital admissions, N (%)	156 (7.4)
Years from 1st to 2nd hospital admissions, mean (SD) (n = 156)	0.65 (0.17, 1.55)

EDSS = Expanded Disability Status Scale; IQR = interquartile range, MS = multiple sclerosis.

[a] Unavailable for 114 subjects.

[b] Modified by omitting points due to hemiplegia/paraplegia to avoid misclassifying these symptoms of MS as comorbidity (Marrie et al., 2014a, 2014b).

[c] 81 additional subjects had hospitalization without any EDSS measurements afterwards.

4. Discussion

We used population-based clinical and administrative datasets to show that following acute hospitalization for any cause, people with MS experienced a step worsening of disability, as measured by the EDSS, equivalent to 2.5 years of time-related disease progression. Hospitalization did not alter the subsequent temporal rate of disability progression. The effect of a second hospitalization was similar and additive. While none of our sensitivity analyses showed statistically significant heterogeneity in the change in disability with hospitalization, the point estimates showed a greater than 3-fold higher rise for hospitalizations that included time in an ICU; since only 24 subjects had

Table 2
Baseline regression model of disability progression.

Variable	Coefficient[a]	95% CI	*P*-value
Sex			
male	Reference	Reference	Reference
female	−0.27	−0.10, −0.40	0.002
Age at symptom onset (per 10 years)	0.45	0.37, 0.53	< 0.0001
On disease-modifying drug(s)	−0.36	−0.20, −0.42	< 0.0001
Disease course at onset			
relapsing	Reference	Reference	Reference
progressive	1.44	1.18, 1.69	< 0.0001
not recorded	−0.31	−0.91, 0.28	0.31
$TIME_{within\text{-}patient}$ (per year)	0.091	0.074, 0.107	< 0.0001
$PREPOST_{within\text{-}patient}$	0.23	0.14, 0.33	< 0.0001
$TIME_{within\text{-}patient} \times PREPOST_{within\text{-}patient}$	−0.02	−0.10, 0.064	0.64
$TIME_{between\text{-}patients}$	0.097	0.088, 0.105	< 0.0001
$PREPOST_{between\text{-}patients}$	0.95	0.48, 1.42	< 0.0001
$TIME_{between\text{-}patients} \times PREPOST_{between\text{-}patients}$	−0.01	−0.037, 0.17	0.47

[a] Change in disability as measured by the Expanded Disability Status Scale.

ICU-containing hospitalizations, it seems plausible that this effect is real but lacks statistical significance due to the small size of that subgroup. Previously we showed that among hospitalized persons with MS, in the year following admission those who were admitted to the ICU had statistically significantly greater mean numbers of hospital days (15.6 vs. 7.8), and physician visits (27.0 vs. 19.9) (Marrie et al., 2015a, 2015b). These findings would be consistent with increased health care needs due to increased disability post-hospitalization. Collectively these findings and our prior work demonstrate that there are bidirectional effects between acute illness and MS.

Little is known about the effect of acute intercurrent illness on the progression of chronic disease including MS. In community-dwelling persons aged 70 years or older without disability, illness or injuries leading to hospitalization are associated with an increased risk of developing disability (Gill et al., 2010). In chronic obstructive lung disease (COPD), lung function tests provide a measure of disease progression, and two studies have explored how acute COPD exacerbations influence the trajectory of forced expiratory volume in one second (FEV1), which normally falls with age but declines faster in COPD (Kanner et al., 2001; Donaldson et al., 2002). Both studies showed that the rate of FEV1 decline became more rapid after hospitalization for a COPD exacerbation, but they did not evaluate a possible step-change effect.

Factors that influence disease progression in MS remain poorly understood and therapies to slow progression are only modestly effective therefore it is important to understand potentially modifiable events. Our finding that acute illness precedes a worsening of the chronic disease is consistent with evidence showing that hospitalization with or without critical illness results in long-lasting functional decline (Cuthbertson et al., 2010; Feemster et al., 2015). Given the high frequency of hospitalizations in MS (Evans et al., 2012), our finding that acute illness requiring hospitalization affects disability in MS progression offers a potential avenue for mitigating some disease progression. Individuals with MS are at increased risk of hospitalizations due to influenza, urinary tract infections and pressure ulcers (Marrie et al., 2014a, 2014b), all of which can potentially be prevented. Comorbid illnesses are associated with increased risks of hospitalization, (Marrie et al., 2015a, 2015b) therefore better management of comorbidities is also important. The increased frequency of second hospitalizations following MS-related admissions suggests that individuals hospitalized for MS may warrant closer follow-up after discharge. Our findings cannot be solely attributed to an intrinsic effect of MS (e.g. relapses), as we found that the effects of hospitalization were similar for MS-related and non-MS related admissions.

This study had several strengths, including the use of a linked population-based clinical and administrative dataset, and an analytic approach aimed at understanding the effects of exposure to hospitalization on disability progression at the individual level. We considered several potential confounders, and conducted several sensitivity analyses. The effects of sex and SES were consistent with findings in other cohorts (Shirani et al., 2012), and the average increase in the EDSS of 0.9 over 10 years is similar to the average increase of 1 point over 10 years reported elsewhere (Pittock et al., 2004), suggesting that findings from our cohort are generalizable.

Some study limitations should also be noted. First, the number of people who were hospitalized was relatively small. Second, due to the relatively small number of EDSS measurements per individual, we were constrained to assess linear rates of EDSS change with time, rather than allowing for a nonlinear relationship. Although it is possible that if our dataset encompassed more years and allowed for assessing a nonlinear relationship, we might have observed a return of hospital-associated worsening in disability towards the pre-hospital value, this seems unlikely given that MS relapses generally have completed their recovery within weeks to a few months (Vollmer, 2007), while our median interval from hospitalization to the final EDSS measurement was 1.1 years. Third, the EDSS has known limitations and would be relatively insensitive to cognitive changes, potentially underestimating the impact of hospitalization on MS. Fourth, we did not have Functional System Scores, therefore we could not determine what specific changes were driving the observed changes in the EDSS. Fifth, we used an area-level measure of SES as a proxy for individual-level SES, but a study comparing the associations between area-level and individual-level measures of SES and health outcomes produced similar findings (Mustard et al., 1999). Finally, we did not account for the effects of comorbid disease as this information was not available in the clinical database, and could only be derived from the DAD for those hospitalized. As comorbidity is associated with the risk of hospitalization in MS and with disability progression (Marrie et al., 2010, 2015a, 2015b), future studies should consider this factor.

Acute illness requiring hospitalization is associated with greater disability in MS, regardless of the reason for hospitalization. This suggests that acute illness may be a modifiable risk factor for disability in MS.

Table 3
Key coefficients from sensitivity analyses that are simple base case modifications.

Model	No. subjects	$TIME_{within\text{-}patient}$ (per year)		$PREPOST_{within\text{-}patient}$	
		Coefficient[a]	95% C.I.	Coefficient	95% C.I.
Base case	2104	0.091	0.074, 0.11	0.23	0.14, 0.33
Exclude subjects with only 1 EDSS value	1837	0.091	0.075, 0.11	0.23	0.13, 0.33
Include median household income	2022	0.087	0.070, 0.10	0.25	0.15, 0.35

[a] Change in disability as measured by the Expanded Disability Status Scale.

Table 4
Key coefficients from sensitivity analyses adding a variable to the base case (n = 2104).

Model	$TIME_{within\text{-}patient}$ (per year)		$PREPOST_{within\text{-}patient}$			
	Coefficient[a]	95% CI	Coefficient[a]	95% CI	Coefficient[a]	95% CI
Base case	0.091	0.074, 0.107	0.23	0.14, 0.33	–	–
First hospitalization being elective vs. urgent/emergent	0.091	0.074, 0.11	Elective admission		Urgent/emergent admission	
			0.16	0.001, 0.33	0.26	0.15, 0.37
First hospitalization with vs. without time in an ICU	0.091	0.074, 0.11	Without ICU care		With ICU care	
			0.21	0.12, 0.31	0.65	0.13, 1.18
Main hospital diagnosis was vs. was not MS	0.091	0.074, 0.11	Hospitalized for MS		Hospitalized for non-MS reason	
			0.22	0.12, 0.32	0.32	0.012, 0.62
First and second hospitalizations	0.089	0.073, 0.11	First hospitalization		Second hospitalization	
			0.19	0.088, 0.29	0.19	−0.006, 0.38
Short stay vs. long stay hospitalizations	0.091	0.074, 0.11	Length of stay ≤ 10 days		Length of stay > 10 days	
			0.20	0.099, 0.31	0.35	0.14, 0.57

[a] Change in disability as measured by the Expanded Disability Status Scale.

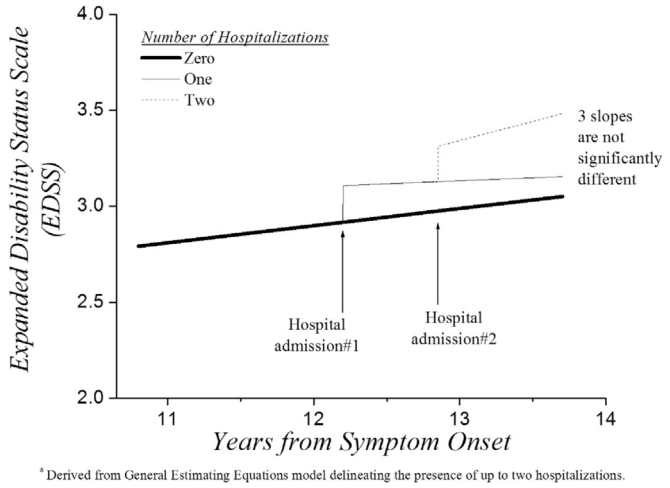

Fig. 1. Average trajectory of Expanded Disability Status Scale Score according to number of hospitalization.

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Appendix A. Supporting information

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