Glucocorticoid-associated blood glucose response and MS relapse recovery

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ABSTRACT

Objective: To determine the relationship between MS relapse recovery and blood glucose (BG) response to IV methylprednisolone (IVMP) treatment.

Methods: We retrospectively identified 36 patients with MS admitted for IVMP treatment of acute relapse who had adequate data to characterize BG response, relapse severity, and recovery. The relationship between glucocorticoid-associated nonfasting BG (NFBG) and relapse recovery was assessed.

Results: Highest recorded nonfasting BG (maximum NFBG [maxNFBG]) values were significantly higher in patients with MS without relapse recovery compared with those with recovery (271 ± 68 vs 209 ± 48 mg/dL, respectively; $p = 0.0045$). After adjusting for relapse severity, MS patients with maxNFBG below the group median were 6 times (OR = 6.01; 95% CI, 1.08–33.40; $p = 0.040$) more likely to experience relapse recovery than those with maxNFBG above the group median. In a multiple regression model adjusting for age, sex, and relapse severity, a 1-mg/dL increase in the maxNFBG was associated with 4.5% decrease in the probability of recovery (OR = 0.955; 95% CI, 0.928–0.983; $p = 0.002$).

Conclusions: These findings suggest that higher glucocorticoid-associated NFBG values in acutely relapsing patients with MS are associated with diminished probability of recovery. This relationship could reflect steroid-associated hyperglycemia and/or insulin resistance, defects in non–steroid-associated (e.g., prerelapse) glucose metabolism, or both. This study included only those admitted for an MS relapse, and it is this subset of patients for whom these findings may be most relevant. A prospective study to evaluate glucose regulation and MS relapse recovery in a broader outpatient MS population is under way. ***Neurol Neuroimmunol Neuroinflamm* 2017;4:e378; doi: 10.1212/NXI.0000000000000378**

GLOSSARY

BG = blood glucose; **EDSS** = Expanded Disability Status Scale; **EMR** = electronic medical record; **FSS** = Functional System Score; ***ICD-9*** = *International Classification of Diseases-9*; **IVMP** = IV methylprednisolone; **maxNFBG** = maximum NFBG; **NFBG** = nonfasting BG.

Comorbid medical conditions can substantially affect neurologic disease outcomes. In most studies addressing the relationship between glucose regulation and patient outcomes in neurologic disorders (e.g., stroke), higher blood glucose (BG) concentration at presentation is associated with poorer outcomes.[1–8] Although this has not been specifically addressed in MS, diabetes and cardiovascular comorbidities are associated with accelerated MS disease progression and development of disability.[9–11]

The standard treatment for MS relapse is IV methylprednisolone (IVMP), 1,000 mg/d for 3–5 days. Hyperglycemia is a common consequence of glucocorticoid administration, largely attributed to reductions in insulin sensitivity.[12] Individuals with pretreatment insulin resistance

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are more likely to exhibit a hyperglycemic response, and risk factors for insulin resistance (e.g., reduced mobility, sedentary lifestyle, and repeated glucocorticoid exposure) are common in MS. Despite the potential risk of hyperglycemia, IVMP is commonly administered in the outpatient setting without glucose monitoring.[13] To our knowledge, no published studies have addressed the relationship between (1) glucose regulation in the setting of glucocorticoid treatment of acute MS relapse and (2) MS relapse recovery outcomes.

Despite standardized treatment, the degree of recovery from any single MS relapse is both variable and unpredictable, but the likelihood of residual deficits after an MS relapse ranges from 40% to 57%.[13–16] Although relapse severity appears to predict recovery, data are inconsistent regarding the impact of other factors, such as sex, age, and site of relapse.[13,15,17] We hypothesized that high glucocorticoid-associated BG responses would be associated with reduced degree of relapse recovery.

METHODS Standard protocol approvals, registrations, and patient consents. This retrospective chart review study was approved by the Institutional Review Board at the University of Virginia, and the study was executed in accordance with the Health Insurance Portability and Accountability Act of 1996.

We performed an administrative database search (2008–2015) to identify patients admitted to the inpatient service with a diagnostic code for MS between 2008 and June 2015 (MS *International Classification of Diseases–9* [*ICD-9*] codes: *340, 341, 341.1, 341.2, 341.21, and 341.22*). Patient and disease characteristics were abstracted from our electronic medical records (EMRs) using the following eligibility criteria: age 18–55 years (inclusive), confirmed diagnosis of MS, administration of IVMP 1,000 mg/d diluted in 0.9% normal saline (minimum 1 day exposure), serum BG values drawn prior to glucocorticoid treatment from a basic or comprehensive metabolic panel, availability of at least 1 nonfasting BG (NFBG) level (i.e., drawn between 09:00 and 24:00 hours) obtained within 18 hours after recorded glucocorticoid administration, no known diagnosis of diabetes, absence of glucose-regulating medications (e.g., metformin), and availability of demographic data in the EMR (e.g., age and sex).

Data collected from the EMR included age, sex, height, weight, glucocorticoid dose and number of days treated, time of glucocorticoid administration, and if sliding scale insulin was administered during hospitalization. Postglucocorticoid BG was defined as any BG drawn within 18 hours of glucocorticoid administration. (The half-life of MP has an estimated range of 18–24 hours.) Glucocorticoid-associated hyperglycemia is most prominent in the postprandial state, with relatively mild changes in fasting BG; thus, to provide a more sensitive assessment of glucocorticoid-associated BG changes, we classified BG values as either fasting or nonfasting. Since inpatient breakfast is routinely served at 8:00 AM, any BG measured between 9:00 AM and 24:00 AM was considered to be an NFBG. Because of our inability to get reliable information on the frequency and dosing of sliding scale insulin administration, we chose to focus on the highest measured NFBG during glucocorticoid treatment (maximum NFBG [maxNFBG]). Given the very high doses and long duration of action of MP, we suspect that time since administration did not play a major role in differential glucose responses, at least within the 18-hour time frame of our study.

An Expanded Disability Status Scale (EDSS)-certified neurologist (MDG), who was masked to BG values, classified patients with MS as recovered (full, partial, or none) retrospectively using outpatient and inpatient medical records and examinations of visits occurring before, during, and after the acute relapse. Prerelapse and postrelapse examinations were taken from available records obtained within 6 months of relapse assessment. The recovery classification was based on the compendium of available event-related data collected from clinical notes before, during, and after relapse, including patient reports and treating physician impressions, neurologic examinations, and motor strength testing in available physical therapy records focused on the relapse-affected area (e.g., documented return to full power in an affected limb). When the available data indicated a return to prerelapse function, the patient was classified as recovered. When the data indicated persistent neurologic deficits, examinations were compared with prerelapse records to determine whether there was no or partial recovery. To provide further granularity, relapse-relevant EDSS Functional System Scores (FSS) before, during, and after the acute relapse were extracted from chart-based neurologic examinations and documented on the standard neurostatus scoring form (neurostatus.net/scoring/index.php). When needed (e.g., in cases of optic neuritis), additional ophthalmology notes for visual acuity were used for the visual FSS. Relapse severity was then calculated for prerelapse, intrarelapse, and postrelapse FSS domains (e.g., vision, brainstem, pyramidal, sensory, or cerebellar) based on the standard neurostatus scoring. Severity was calculated by subtracting the prerelapse FSS from the intrarelapse FSS for relapse-relevant domains; similarly, FSS-based recovery was calculated by subtracting the postrelapse FSS from the prerelapse FSS for relapse-relevant domains. For patients with more than one relapse-relevant FSS, an average was calculated for both severity and recovery of the FSS-based scores. Using these FSS obtained from through neurologic examinations available in the medical records, the EDSS scores were calculated based on these 8 FSS in the standard fashion.

We compared patient characteristics using 1-way analysis of variance, t tests, or χ^2 tests as appropriate. Logistic regression analysis was used to examine the association between the maxNFBG and relapse recovery. We estimated 1 unadjusted model to predict recovery using the highest NFBG alone and 2 other models that adjusted for relapse severity (mild, intermediate, and severe) and demographic variables such as age and sex. We additionally grouped patients into high and low maxNFBG using the median maxNFBG, thereafter using logistic regression to compare the probability of recovery between low and high maxNFBG. For all logistic regression models, we computed the area under the receiver operating characteristic curves as well as the Hosmer-Lemeshow goodness of fit statistic. We used SAS 9.2.6 (SAS Institute, Cary, NC) and Stata SE 14 (Statacorp, College Station, TX) for statistical analysis and graphing.

RESULTS Our administrative database search identified 413 patients with one of the 6 searched *ICD-9* codes. Among those, we identified 68 nondiabetic MS patients who were admitted for MS relapse

Table 1 Demographic characteristics and nonfasting blood glucose levels for the study sample (n = 36)

	Full recovery, n = 17	Partial recovery, n = 10	No recovery, n = 9	*p* Value
Age, y, mean ± SD	33.7 ± 9.3	35.3 ± 10.9	41.3 ± 12.4	0.23
Sex, female:male (% female)	14:3 (82.1)	9:1 (90)	4:5 (44.4)	0.05
Body mass index, kg/m^2, mean ± SD	29.8 ± 5.6	29.6 ± 8.5[a]	28.2 ± 7.8[b]	0.86
Days treated, mean ± SD	3.6 ± 1.0	3.6 ± 1.0	3.9 ± 1.2	0.76
MS disease duration, mean ± SD	5.2 ± 6.0	4.6 ± 6.9	6.4 ± 6.8	0.82
Time from event to recovery assessment, mo, mean ± SD	2.7 ± 1.4	3.3 ± 2.5	2.8 ± 3.1	0.78
Relapse-related EDSS				
Mean ± SD	5.1 ± 2.2	6.3 ± 1.3	6.1 ± 2.3	0.31
Median (25th, 75th quartile)	6.0 (3.0, 6.5)	6.5 (6.0, 7.5)	6.5 (6.5, 7.5)	
Relapse severity				
Mild, n (%)	6 (35.3)	0 (0.0)	1 (11.1)	0.21
Moderate, n (%)	6 (35.3)	4 (44.4)	5 (55.6)	
Severe, n (%)	5 (29.4)	5 (55.6)	3 (33.3)	
Relapse-related FSS				
Vision, n (%); median FSS	2 (11.8); 4.0	2 (20.0); 3.5	1 (11.1); 1.0	0.07
Brainstem, n (%); median FSS	10 (58.8); 2.0	7 (70.0); 2.0	6 (66.7); 2.0	0.69
Pyramidal, n (%); median FSS	16 (94.1); 3.0	10 (100); 3.0	9 (100); 3.0	0.11
Cerebellar, n (%); median FSS	8 (47.1); 2.0	8 (80.0); 3.0	4 (44.4); 3.0	0.60
Sensory, n (%); median FSS	13 (76.5); 2.0	7 (70.0); 3.0	6 (66.7); 3.0	0.04

Abbreviations: EDSS = Expanded Disability Status Scale; FSS = Functional System Score.
All percentages are of column totals, unless otherwise noted.
[a] n = 9.
[b] n = 8.

between January 2008 and June 2015. Subsequent detailed chart review resulted in exclusion of 32 patients for the following reasons: dosing of IVMP 500 mg/daily (n = 1), no recovery data available (n = 5), no blood draws within 18 hours of steroid administration (n = 6), no available NFBG values (n = 19), and body mass index >40 kg/m^2 (n = 1). This resulted in a total of 36 patient admissions meeting all study eligibility criteria (table 1). The most common cause of exclusion was the absence of required NFBG records. Among the 36 patients used for analysis, only 2 (5.6%) had received 2 days of steroids; all other patients received ≥3 days of IVMP. maxNFBG values were measured on day 1 or 2 in 29 patients (72%). There was no difference in the timing of maxNFBG measurement between recovery groups (table 2).

Patients with MS were categorized according to recovery status (full, partial, or no recovery) based on relapse-related FSS and available medical records. Table 1 provides details about the demographic characteristics, relapse severity, and relapse-related FSS by MS recovery subgroups. Those patients with no recovery from their MS relapse were older and more likely to be men. Among those with a full recovery, we found an overall lower EDSS and a larger proportion with mild relapse severity. However, median relapse EDSS scores were similar (6.0–6.5) for all 3 recovery groups, and the proportion with moderate and severe relapse was well distributed across all 3 recovery groups (table 1).

Table 2 shows glucocorticoid-associated BG levels for each of the 3 recovery groups. Because of the small sample sizes, we dichotomized recovery groups by either (1) combining the 2 groups with any recovery (i.e., some recovery [full or partial] vs no recovery) or (2) combining the 2 groups without complete recovery (i.e., full recovery vs partial or no recovery) and computed their BG levels. The maxNFBG was significantly different among the 3 recovery groups (p = 0.018). Dichotomized Group comparison finds a significant difference between any vs no recovery (p = 0.005) and a positive trend between complete vs incomplete recovery (p = 0.076), with lower maxNFBG than the no-recovery group (table 2).We note that correctional ("sliding scale") insulin is part of the routine order set for such patients in our institution, and 21 patients (~58%) received at least 1

Table 2 Glucocorticoid-associated BG levels

	Full recovery, N = 17	Partial recovery, N = 10	No recovery, N = 9	*p* Value
Preglucocorticoid fasting BG, mg/dL				
Mean ± SD	93.8 ± 10[a]	96.7 ± 10	91.9 ± 14.2[b]	0.31
Median (25th, 75th quartile)	80 (84.5, 101.5)	100 (89, 102)	85.5 (74, 97)	
Time from steroid administration to maxNFBG measurement, hrs				
Mean ± SD	8.2 ± 5.5	10.8 ± 4.2	9.3 ± 3.3	0.38
Lowest NFBG, mg/dL				0.82
Mean ± SD	127.8 ± 30.8	135.6 ± 34.4	129.3 ± 28.4	
Median (25th, 75th quartile)	120 (109.5, 145)	131 (110, 148)	128 (111, 149)	
Lowest NFBG recovery subgroups, mg/dL	Any recovery (n = 27)		No recovery (n = 9)	0.91
Mean ± SD	130.7 ± 31.8		129.3 ± 28.4	
	Complete (n = 17)	Incomplete (n = 19)		0.64
	127.8 ± 30.8	132.6 ± 31.0		
Average NFBG, mg/dL				0.30
Mean ± SD	167.6 ± 38.4	166.1 ± 30.3	188.1 ± 30.7	
Median (25th, 75th quartile)	154.5 (133.2, 193.0)	158.5 (144.0, 180.0)	182.3 (168.9, 208.9)	
Average NFBG recovery subgroups, mg/dL	Any recovery (n = 27)		No recovery (n = 9)	0.12
Mean ± SD	167.1 ± 35.0		188.1 ± 30.7	
	Complete (n = 17)	Incomplete (n = 19)		0.45
	167.6 ± 38.4	176.5 ± 31.7		
maxNFBG, mg/dL				0.018
Mean ± SD	205.9 ± 56.3	213.2 ± 30.8	271.1 ± 68.0	
Median (25th, 75th quartile)	204.0 (171, 248)	206 (186, 235)	248 (222, 308)	
maxNFBG recovery subgroups, mg/dL	Any recovery (n = 27)		No recovery (n = 9)	0.005
Mean ± SD	208.6 ± 47.9		271.1 ± 68.0	
	Complete (n = 17)	Incomplete (n = 19)		0.079
	205.8 ± 56.4	240.6 ± 58.4		

Abbreviations: BG = blood glucose; maxNFBG = maximum NFBG; NFBG = nonfasting blood glucose.
[a] n = 16.
[b] n = 6.

dose of insulin during their inpatient stay. This was one of the main reasons we focused our analysis on maxNFBG. Six of 9 (67%) in the no-recovery group and 15 of 27 (56%) in the recovery group received insulin; this apparent difference is in keeping with higher maxNFBG values in the no-recovery group.

Table 3 shows 3 logistic regression models that predicted any degree of recovery based on the high vs low maxNFBG groups divided by the median maxNFBG. After adjusting for relapse severity (model 2), patients with lower maxNFBG were 6 times (OR = 6.01; 95% CI, 1.08–33.40; $p = 0.040$) more likely to achieve some degree of relapse recovery compared with those with higher maxNFBG. In a multiple regression model that additionally adjusted for age and sex (model 3), the maxNFBG still showed a strong and significant association with the probability of recovery (OR = 13.69; 95% CI, 1.40–134.12; $p = 0.025$).

An additional logistic regression model using maxNFBG as a continuous variable suggested that a 1-unit increase in maxNFBG (i.e., 1 mg/dL) was associated with a 4.5% lower likelihood (OR = 0.955; 95% CI, 0.928–0.983; $p = 0.002$) of any recovery (model 3 in table 4) after adjusting for relapse severity, age, and sex. The estimated probability of any recovery from this model is plotted against the maxNFBG in figure, which shows a very strong relationship between maxNFBG and recovery. The figure additionally reveals that all patients with maxNFBG <200 mg/dL achieved some recovery, but no patient with maxNFBG >300 mg/dL experienced recovery.

DISCUSSION Patients with MS exhibit remarkable variability with respect to MS relapse frequency and severity. While prior relapse severity

Table 3 Odds ratios and 95% CIs for recovery from acute MS relapse (any vs no recovery) as predicted by high vs low NFBG groups

	Model 1 (N = 36)		Model 2 (N = 35)		Model 3 (N = 35)	
Variables	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Highest NFBG[a] (vs low)						
High	5.091 (0.864-30.001)	0.072	6.012 (1.082-33.403)	0.040	13.686 (1.396-134.123)	0.025
Severity (vs mild [>−1])						
Intermediate (−1.5 to −1)			0.308 (0.027-3.515)	0.343	0.132 (0.004-4.118)	0.248
Severe (−3 to −1.75)			0.634 (0.053-7.543)	0.718	0.274 (0.008-8.856)	0.465
Age, y						
Male					0.866 (0.779-0.963)	0.008
Female					0.933 (0.837-1.039)	0.205
Hosmer-Lemeshow χ^2	[b]		1.79 ($p = 0.618$)		2.92 ($p = 0.939$)	
C-statistic	0.685		0.748		0.872	

Abbreviations: BG = blood glucose; NFBG = nonfasting BG.
[a] Highest NFBG with high and low groups was defined using the median.
[b] There are only 2 distinct quantiles because of ties and the χ^2 statistic could not be computed.

is often associated with future relapse severity,[17] risk factors for relapse severity are not fully understood. Similarly, the degree of recovery from any single MS relapse is both variable and unpredictable. It is important that the likelihood of residual deficits after an MS relapse ranges from 40% to 57%.[13–16] Poor recovery with residual neurologic deficits from any single MS relapse contributes to cumulative disability and portends a poorer long-term prognosis.[14,15,18–20] Thus, understanding the determinants of MS relapse recovery is of critical importance: the identification of modifiable risk factors may lead to improved MS relapse recovery and reduced disability accumulation.

To the best of our knowledge, this study is the first to examine the relationship between glucocorticoid-associated BG values and MS relapse recovery. While this study used a small retrospective sample, the relationship between BG and relapse recovery is clear and significant. Higher glucocorticoid-associated BG levels were associated with a substantially lower probability of recovery. Indeed, every patient with a peak NFBG <200 mg/dL recovered, while none with >300 mg/dL did.

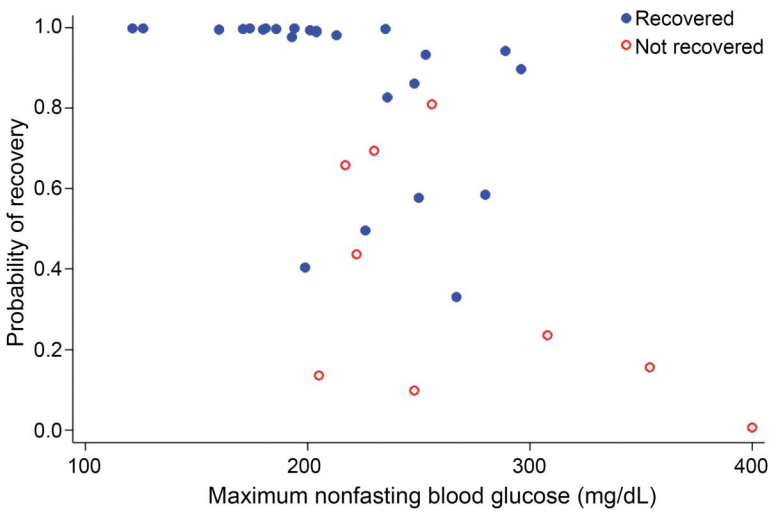
There is increased recognition that comorbidities are significant factors in the MS disease course and associated with worsened outcomes.[9–11] In addition, accumulating data suggest that patients with MS may have underlying glucose intolerance,[2–4,20,21] implying that these patients are more insulin resistant and at higher risk for glucocorticoid-induced hyperglycemia. Our data provide important insights into 1 possible mechanism that impaired glucose tolerance may be contributing to increased progression among patients

Table 4 Odds ratios and 95% CIs for recovery from acute MS relapse (any vs no recovery) as predicted by maxNFBG (as a continuous variable)

	Model 1 (N = 36)		Model 2 (N = 35)		Model 3 (N = 35)	
Variables	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Highest NFBG, mg/dL	0.979 (0.967-0.991)	0.001	0.976 (0.962-0.989)	0.001	0.955 (0.928-0.983)	0.002
Severity (vs mild [>−1])						
Intermediate (−1.5 to −1)			0.590 (0.046-7.603)	0.685	0.466 (0.013-17.301)	0.679
Severe (−3 to −1.75)			2.449 (0.127-47.182)	0.553	5.558 (0.134-231.266)	0.367
Age, y						
Male					0.843 (0.740-0.961)	0.011
Female					0.924 (0.814-1.049)	0.223
Hosmer-Lemeshow χ^2	4.50 ($p = 0.810$)		4.05 ($p = 0.852$)		11.32 ($p = 0.184$)	
C-statistic	0.780		0.821		0.927	

Abbreviations: FSS = Functional System Score; NFBG = nonfasting blood glucose; Severity = mean prerelapse FSS − mean relapse FSS.

Figure Scatter plot of predicted probability of recovery from an acute MS relapse and maximum nonfasting blood glucose level (n = 36)



Probability of recovery was estimated from model 3, shown in table 3.

with MS, even those without a confirmed diagnosis of diabetes. Although our study strongly suggests a meaningful relationship between glucose regulation and relapse outcomes, our retrospective data do not allow us to assess the relative roles of hyperglycemia vs underlying insulin resistance in relapse recovery, nor do they allow us to assess the relative roles of pretreatment abnormalities vs glucocorticoid-related (on-treatment) abnormalities. Prospective studies are needed to further characterize relative contributions of these risk factors to MS relapse recovery and, subsequently, the potential benefit of BG regulation during acute MS treatment. Based on the findings described herein, this appears to be a worthy area of research. Indeed, we suggest that this work represents the first look into a potentially modifiable factor, treatment of which could improve recovery from an individual relapse, which might ultimately mitigate the accumulation of relapse-related disability. Our findings also raise concerns about the current clinical practice under which increasingly more patients are being treated with IVMP in outpatient or home-based settings without BG monitoring. In particular, as the practice of home treatment, routinely without BG or other monitoring, has been encouraged by an expanding number of articles that emphasize the substantial cost savings.[21–24]

The limitations of our study reflect its retrospective nature. We did not have a reliable source of data for race, a potentially important clinical factor. In addition, restricting data collection to inpatients with clinical laboratory test results potentially introduces a selection bias in our population: those in whom BG was measured may have been most likely to experience hyperglycemia. However, relapse severity did not appear to drive the observed association between maxNFBG and recovery. In addition, given the very high dose of MP used and its very rapid effects of glucose tolerance, we do not anticipate that the length of time on MP (or cumulative dose) affected the BG values.

The retrospective nature of our study also limited the number of patients with MS available for inclusion, primarily because of 2 issues: (1) most patients with MS in our practice receive glucocorticoids in the outpatient setting and (2) our routine inpatient practice is to draw laboratory test results in the early morning, limiting the numbers of patients who had postprandial BG values available. These limitations resulted in a more severe MS relapsing cohort, and it is this subset of the MS relapsing population for whom these findings may be most relevant. Future work will need to confirm and validate these findings in patients with MS receiving outpatient MS relapse management. Finally, FSS and EDSS assessments were performed retrospectively based on chart reviews and may lack accuracy a prospective assessment can provide, but the assessor was masked to the patient BG levels to mitigate against potential bias. In addition, these measures are based on and calculated from the completion of a thorough neurologic examination. Therefore, we believe it to be a reasonable strategy to retrospectively calculate FSS and EDSS using thorough examinations that were performed and available in the medical records.

This study represents the first to demonstrate a significant association between glucocorticoid-associated BG responses and the likelihood of relapse recovery in patients with MS. Future prospective studies are under way to confirm and extend these findings.

AUTHOR CONTRIBUTIONS

M.D. Goldman: study concept development and design, statistical analysis and interpretation, and manuscript drafting and revising. S. Koenig: data collection and manuscript preparation and revision. C. Engle: data collection and manuscript preparation and revision. C.R. McCartney: study results interpretation and critical revision of manuscript. M.-W. Sohn: data analysis and interpretation and critical revision of manuscript.

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DISCLOSURE

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