RESEARCH ARTICLE

Predictors of Disease Activity and Worsening in Relapsing-Remitting Multiple Sclerosis

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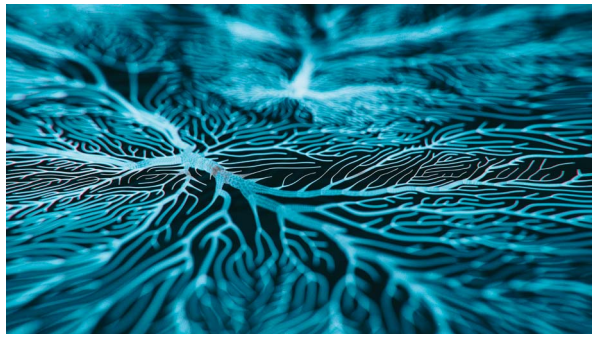
Abstract



Background and Objectives

Disease activity in multiple sclerosis (MS) is highly variable, and there are limited prospective studies on predictors of disease outcomes. The goal of this study is to identify and assess patient characteristics in MS that predict disease activity and worsening.

Methods

The study population consisted of a prospective cohort of 1,008 participants with relapsing-remitting onset MS enrolled in the CombiRx trial. Cox regression analysis was used to determine hazard ratio (HR) associations between baseline (BL) demographics, clinical history, MRI metrics, and treatment with outcomes of time to first new disease activity over up to 7 years of follow-up including relapse, MRI activity, and disease worsening.

Results

One thousand eight participants were randomized, with 959 eligible for assessment of disease activity and worsening on follow-up. In multivariable models, the risk of relapse was higher in participants younger than 38 years at BL than in those older (HR range 1.36–1.43), with the presence of gadolinium (Gd)+ lesions at BL (HR 1.38, [95% confidence interval, CI 1.14, 1.67]) and with BL EDSS ≥3.5 vs <3.5 (HR range 1.63–1.67). The risk of new MRI activity was higher in younger participants (HR range 1.58–1.84), with higher preexisting lesion counts greater than the median lesion count with ≥71 T2 hyperintense lesions vs <71 (HR 1.50, [95% CI 1.27, 1.77]), with the presence of BL Gd+ lesions (HR 1.75, [95% CI 1.49, 2.06]), and higher BL T2 lesion volume (HR 1.02 for every unit increase in baseline volume, [95% CI 1.01, 1.03]). The risk of new MRI activity was lower in those receiving combination therapy compared with those that in those receiving either glatiramer acetate (HR range 0.67–0.68) or interferon beta-1a (HR range 0.68–0.70). The risk of disease worsening was higher for those with higher T2 volume (HR for 1 unit increase in volume 1.01, 95% CI 1.004, 1.03) and BL EDSS <2 (HR range 2.79–2.96). There were no associations between sex, race, and disease duration on relapse, MRI activity, or disease worsening in the multivariable analysis.

Discussion

Prospective data from a large clinical trial cohort show that younger MS patients with high BL relapses and MRI lesion burden have the highest risk of subsequent disease activity.

Trial Registration Information

Clinical trial registration number NCT00211887. CombiRx was registered at ClinicalTrials.gov (NCT00211887) on September 21, 2005. Study enrollment began in January 2005.

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Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disorder CNS characterized by relapses and disability progression.[1] Disease course in MS is highly variable, and predicting disease activity would improve patient care through choosing appropriate disease-modifying therapies (DMTs) and knowing when to change therapy. Platform DMTs in MS including interferon beta-1a (IFN) and glatiramer acetate (GA) have been proven to be safe and have modest efficacy in reducing relapses and preventing new MRI lesions. In the pivotal trials of IFN and GA for relapsing-remitting MS (RRMS), the drugs reduced the annualized relapse rate by 32% and 30%, respectively, compared with that in placebo.[2,3] However, results from clinical trials represent the summary effect of the drugs and do not predict individual patient response to treatment. Because there are no established biomarkers to reliably foretell the disease course, clinicians rely heavily on patients' clinical and radiological features on presentation to optimize treatment strategies and identify patients at a high risk of disease activity or progression who may need high-efficacy therapy. Several observational studies have investigated associations between patient characteristics and disease outcomes with variable results largely due to lack of homogeneous data and differences in defining treatment response. Prospective studies are needed to overcome these limitations.

In this study, we performed an analysis of the CombiRx trial to identify and assess demographic and disease characteristics that could predict clinical and radiological disease activity and disease worsening in patients with RRMS treated with IFN, GA, or combination therapy.

Methods

Study Design

CombiRx was a phase 3, multicenter, double-blind, randomized clinical trial examining combination therapy of IFN and GA vs either single-agent therapy in 1,008 treatment-naïve RRMS participants enrolled between January 2005 and April 2009. Participants were randomized to receive intramuscular 30 μg of IFN weekly or 20 mg of subcutaneous GA daily or a combination of both therapies and were observed for a minimum of 3 years for the core study and up to 7 years for the extension phase. Clinical assessments were performed every 3 months, and MRIs were performed at baseline (BL), 6 months, 12 months, and annually thereafter. The protocol and all amendments received approval by the applicable central or institutional review boards. A full description of the methods of CombiRx is presented in the study conducted by the CombiRx investigators.[4,5]

Our analysis of CombiRx examined the relationship between participant BL characteristics and disease activity measurements during the clinical trial including relapses, MRI activity, and disease worsening. The CombiRx study used 3 definitions of MS relapses of different degrees of stringency: (1) suspected exacerbation (SE), defined as having new or worsening symptoms attributable to MS lasting over 24 hours in the absence of fever and preceded by 30 days of stability, (2) nonprotocol-defined exacerbations (NPDEs), defined as meeting criteria for SE and an increase in the EDSS score over the previous visit by ≥0.5 or a ≥2 increase in 1 functional system or a ≥1 increase in 2 functional systems except bladder or cognitive changes, and (3) protocol-defined exacerbations (PDEs), defined as meeting criteria for NPDEs and confirming EDSS change within 7 days of symptom onset. For the current analysis, relapses were defined as being either PDEs or NPDEs, and SEs were excluded because of lack of confirmed clinical changes. MRI activity was defined as any new combined unique active (CUA) lesion, which consists of any new or persisting gadolinium-enhancing (Gd+) T1-weighted lesions or new or enlarging T2-weighted lesions. Disease worsening refers to worsening neurologic examination related to relapse and is distinct from disease progression, which refers to gradual accumulation of disability independent of relapse. Owing to greater variations in EDSS at lower scores,[6] disease worsening in our study was defined as confirmed 6-month EDSS increase over BL by 1.5 points for BL EDSS 0, by 1 point for BL EDSS 1.0–5.5, or by 0.5 points for BL EDSS ≥6.0.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was exempt from the need for research and institutional review board approval.

Statistical Analysis

Participant characteristics were summarized using the median values and interquartile range or range (minimum, maximum) for continuous variables or n (%) for categorical variables. Three new onset disease activity outcomes were considered including time to: (1) first relapse, (2) new CUA, and (3) first 6-month confirmed disease worsening. Multivariable Cox regression analysis was used to determine hazard ratio (HR) and 95% confidence intervals (CIs) for associations between disease characteristics at BL and outcomes over a follow-up period up to 7 years using participant data from all treatment groups. Owing to multiple ways to characterize MRI predictors, 3 models were constructed for each outcome using different MRI predictors, defined as follows: 1) Gd+ lesions (present vs absent), 2) T2 lesion number (≥71 vs < 71), and 3) T2 volume. Other disease predictors considered included number of relapses in the previous 12 months (≤2 vs > 2) and BL EDSS (≥3.5 vs < 3.5 for predicting relapses and MRI activity and <2 vs ≥ 2 for predicting disease worsening). Covariates considered were age (37 years or younger vs older than 38 years), sex (male/female), race (White, Black/African American, or other), and treatment arm (IFN + GA vs GA or IFN + GA vs IFN). Cutoffs for dichotomous variables were based on the median values in the study except EDSS 3.5, which is a commonly used cutoff in studies assessing disease activity outcomes.

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Table 1 Participant Baseline Characteristics (N = 959)

Characteristic	All participants (n = 959)
Median age (IQR, range)	38 (31–45, 18–61)
Sex, n (%)	
Female	697 (72.7%)
Male	262 (27.3%)
Race, n (%)	
White	847 (88.3%)
African American	68 (7.1%)
Other	44 (4.6%)
Median years since diagnosis (IQR, range)	0 (0–1, 0–26)
Median years since symptom onset (IQR, range)	2 (1–6, 0–39)
Median relapses in the past year (IQR, range)	2 (1–2, 0–6)
Median BL EDSS (IQR, range)	2 (0–2.5, 0–6)
Median years of follow-up (IQR, range)	3.4 (2.7–5.0, 0.4–6.9)
Treatment, n (%)	
IFN + GA	472 (49.2%)
IFN	241 (25.1%)
GA	246 (25.7%)
Presence of Gd+ lesion, n (%)	378 (39.4%)
Median T2 lesion number (IQR, range)	71 (49–113, 6–379)

Abbreviations: BL = baseline; GA = glatiramer acetate; IFN = interferon beta-1a; IQR = interquartile range.

Full models were fit with BL participant characteristics (age, sex, race, and treatment), BL disease characteristics (years since diagnosis, relapse activity in the previous year, and BL EDSS), and one of the MRI predictors (the presence of Gd+ lesions, T2 lesion number, or T2 lesion volume). Non-statistically significant BL participant and disease characteristics were removed, and reduced models were fit with statistically significant covariates.

Owing to the secondary nature of this analysis, no adjustments were made for multiple testing. All BL covariates were required before study enrollments, and for Cox models, any participant without study outcome of interest was considered censored; therefore, no data imputation was performed for missing values. All analyses were performed with SAS v9.4 or JMP Pro 14–16 (Cary, NC). p values < 0.05 were considered meaningful.

Data Availability

Access to the CombiRx data set can be requested from the Coordinating Center or MS Center at the University of Alabama at Birmingham by completing a data use agreement that is reviewed by a committee overseeing the use of the data. Qualified researchers have or will obtain appropriate Institutional Review Board approval for the study request.

Results

There were 1,008 participants randomized in CombiRx, and 959 were included in this study based on availability of data for assessment of 6-month disease worsening and having at least 1 follow-up MRI (at 6 months or later). Participants were of median age 38 years (range 18–61) at BL; 72.7% female; 88.3% White and 7.1% African American; of median 0 (range 0–26) years since diagnosis; with median 2 (range 0–6) relapses in the previous 12 months; and with median EDSS 2 (range 0–6, Table 1). The median length of follow-up was 3.4 years (range 0.4–6.9).

Relapses

In all 3 multivariable models, the risk of relapse was increased in participants with younger age (HR range 1.36–1.43 in all 3 models, Table 2), higher EDSS at BL (HR range 1.63–1.67), and more relapses in the previous year (HR range 1.40–1.43, Figure). The risk of relapses was increased with the presence of Gd+ lesions at BL (HR 1.38 [95% CI 1.14, 1.67]; Table 3) and not associated with the number of T2 lesions at BL or (3) the volume of T2 lesions. There was no association with the other covariates, including treatment.

MRI Activity

In all 3 multivariable models, younger age at BL was associated with an increased risk of new MRI activity (HR range 1.58–1.84). The risk of new MRI activity was decreased for those treated with combination therapy compared with that for those treated with single-agent therapy with GA or IFN (HR range IFN + GA vs GA 0.67–0.68, HR range for IFN + GA vs IFN 0.68–0.70). The risk of new CUA lesion on MRI was associated with the presence of Gd+ lesions at BL (HR 1.75, [95% CI 1.49, 2.06]), greater number of T2 lesions at BL (HR 1.50, [95% CI 1.27, 1.77]), and volume of T2 lesions at BL (HR 1.02 for every unit increase in BL volume, [95% CI 1.01, 1.03]). There was no association with the other covariates.

Disease Worsening

In all 3 multivariable models, an EDSS <2 at BL was associated with an increased risk of worsening vs EDSS ≥2 at BL (HR range 2.79–2.96). The risk of disease worsening was not associated with the presence of Gd+ lesions at BL or T2 number but was associated with T2 volume (HR for 1 unit increase in volume 1.01, 95% CI 1.004, 1.03). There was no association with the other covariates, including treatment.

Discussion

DMTs for MS are effective at reducing relapse rate and new MRI lesions, but individual patient characteristics play an important role in predicting disease outcomes and help inform DMT selection or change. Previous studies using

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Table 2 Participant Characteristics and Predictors of Time to First Relapse, MRI Activity, or Disease Worsening (HR [95% CI])[a]

	Outcome								
	Relapse (PDE or NPDE)			MRI (new CUA)			Disease worsening (6 Month)		
Participant characteristic	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Age: 37 years or older vs older than 37 years	**1.36 (1.12, 1.64)**	**1.41 (1.16, 1.71)**	**1.43 (1.18, 1.73)**	**1.58 (1.34, 1.86)**	**1.84 (1.55, 2.17)**	**1.82 (1.54, 2.15)**	0.78 (0.60, 1.03)	0.80 (0.61, 1.05)	0.81 (0.61, 1.06)
Sex: male vs female	1.11 (0.90, 1.37)	1.11 (0.90, 1.37)	1.09 (0.89, 1.35)	1.13 (0.95, 1.35)	1.01 (0.90, 1.29)	1.01 (0.90, 1.29)	0.94 (0.70, 1.26)	0.92 (0.69, 1.24)	0.92 (0.68, 1.23)
Race: White vs African American	1.04 (0.72, 1.48)	1.00 (0.70, 1.43)	1.02 (0.71, 1.46)	0.99 (0.73, 1.34)	0.95 (0.70, 1.28)	1.02 (0.75, 1.38)	0.78 (0.48, 1.25)	0.77 (0.48, 1.24)	0.85 (0.52, 1.37)
White vs other	0.74 (0.49, 1.11)	0.77 (0.51, 1.16)	0.79 (0.52, 1.19)	0.89 (0.62, 1.29)	0.96 (0.66, 1.39)	1.03 (0.71, 1.49)	1.18 (0.58, 2.41)	1.19 (0.58, 2.43)	1.27 (0.62, 2.60)
African American vs other	0.71 (0.42, 1.20)	0.77 (0.46, 1.30)	0.77 (0.46, 1.30)	0.90 (0.57, 1.43)	1.01 (0.64, 1.61)	1.01 (0.64, 1.60)	1.52 (0.66, 3.49)	1.54 (0.67, 3.52)	1.50 (0.66, 3.44)
Treatment: IFN vs GA	1.32 (1.01, 1.71)	1.31 (1.01, 1.70)	1.32 (1.01, 1.71)	0.97 (0.78, 1.91)	0.97 (0.78, 1.20)	1.00 (0.80, 1.23)	0.88 (0.61, 1.27)	0.88 (0.61, 1.26)	0.90 (0.62, 1.29)
IFN + GA vs GA	1.05 (0.83, 1.33)	1.04 (0.82, 1.31)	1.04 (0.82, 1.31)	**0.67 (0.55, 0.82)**	**0.68 (0.56, 0.82)**	**0.68 (0.56, 0.82)**	0.88 (0.65, 1.20)	0.88 (0.64, 1.19)	0.87 (0.64, 1.19)
IFN + GA vs IFN	0.80 (0.64, 1.00)	0.79 (0.63, 0.99)	0.79 (0.63, 0.99)	**0.70 (0.57, 0.85)**	**0.70 (0.58, 0.85)**	**0.68 (0.56, 0.83)**	0.99 (0.71, 1.38)	1.00 (0.72, 1.39)	0.97 (0.70, 1.36)

Abbreviations: BL = baseline; CI = confidence interval; CUA = combined unique active; GA = glatiramer acetate; HR = hazard ratio; IFN = interferon beta-1a; NPDE = nonprotocol-defined exacerbation; PDE = protocol-defined exacerbation.
[a] All models included participant characteristics, BL disease characteristics, and for Model 1: Gd+ lesions (present/absent), Model 2: T2 lesions number (≥71 vs < 71), or Model 3: T2 lesion volume.

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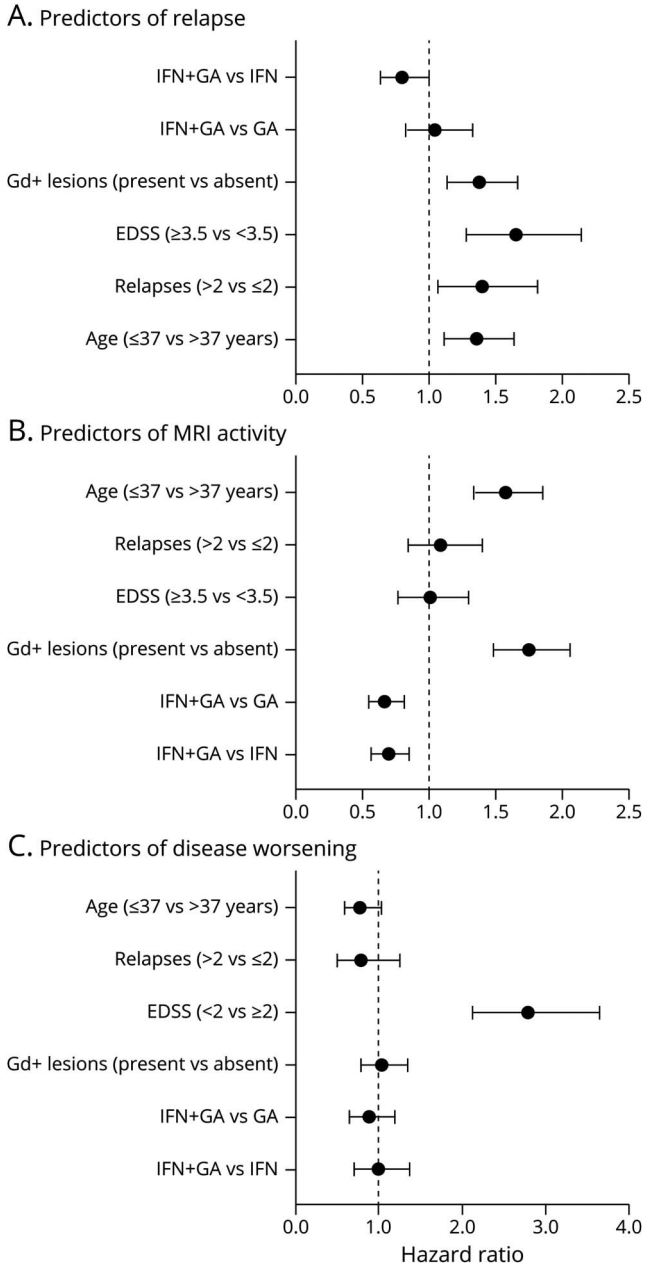
Figure Association of Participant Baseline Characteristics and (A) Risk of Relapse, (B) MRI Activity, and (C) Disease Worsening, Based on the Model Using Gd+ Lesions as the Baseline MRI Predictor



There were no associations between sex, race, and disease duration and risk of relapse, MRI activity, or disease worsening. EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; Gd+ = gadolinium-enhancing; IFN = interferon beta-1a.

retrospective data to define predictors of disease activity are limited by nonstandardized protocols, resulting in lack of homogeneous data. To overcome this limitation, we performed a reanalysis of the CombiRx trial to define predictors of MS disease outcomes in a large prospective cohort of RRMS patients treated with IFN, GA, or combination therapy using a multivariable approach accounting for demographic, clinical, and radiological covariates. Our results showed younger patients and those with the presence of Gd+ lesions were at a higher risk of both clinical and radiological disease activity. Higher EDSS at BL also increased the risk of relapse during the study period in the trial population of ambulatory RRMS participants with EDSS no greater than 6.0. Not surprisingly, greater BL relapses were associated with a higher risk of relapse on study. In addition, higher MRI T2 lesion burden at BL also predicted the risk of new MRI activity, and combination therapy reduced the risk of new MRI activity. BL EDSS level and higher T2 lesion volume were associated with disease worsening.

Our findings on the associations between patient characteristics and disease outcomes were not only similar but also distinct from the results of previous studies. Age has well-established associations with disease activity in MS with younger patients more likely to have higher relapse rates and more Gd+ lesions.[7,8] A retrospective cohort of 2,477 patients with RRMS showed that relapse rate decreased by 17% every 5 years.[7] Another study of 1,543 patients with CIS and MS found age to be the most important factor associated with Gd+ lesions, which decreases with age.[8] These observations reflect decreased focal inflammatory activity in MS with aging. Consistent with established findings, our study demonstrates in a prospective cohort that younger age predicts a higher risk of relapses and Gd+ lesions. The propensity for higher disease activity at younger age has encouraged treatment strategies favoring early use of high-efficacy DMTs, especially in younger patients.[9] Likewise, DMT discontinuation trials are underway in older patients who are less likely to have active disease.[10]

Gd+ lesions indicate areas of active focal inflammation and breakdown of the blood-brain barrier. An analysis of the BEYOND trial of 857 patients with MS treated with interferon beta-1b found that Gd+ lesions were associated with both relapses and MRI activity in univariable analysis, but the statistical significance was not maintained with covariate adjustment. In our study, Gd+ lesions were associated with a higher risk of both relapses and new MRI activity but not disease worsening in the multivariable analysis. This is consistent with the findings of previous reports that the number of Gd+ lesions does not predict EDSS changes at 1–2 years.[11] Despite having up to 7 years of follow-up, our study did not analyze the long-term implications of Gd+ lesions on conversion to secondary progressive MS (SPMS) due to the early nature of disease in most of the participants, resulting in insufficient sample size for those transitioning to SPMS. Other studies have shown that early Gd+ lesions are associated with the development of SPMS.[12] Similarly, their persistence on IFN therapy increased the risk of higher disability at a 15-year follow-up.[13]

Not surprisingly, in our study, more relapses at BL predicted the risk of additional relapses, and higher BL MRI T2 lesions predicted the risk of new MRI activity. On the contrary, increased T2 lesions did not predict the risk of relapse nor did more relapses predict the MRI activity. The disconnect between the

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Table 3 Disease Predictors of Time to First Relapse, MRI Activity, or Disease Worsening (HR [95% CI])[a]

	Outcome measure		
Disease characteristic	Relapse (PDE or NPDE)	MRI activity (new CUA)	Disease worsening (6 mo)
Model 1			
Gd+ lesions: Present vs absent	**1.38 (1.14, 1.67)**	**1.75 (1.49, 2.06)**	1.03 (0.79, 1.35)
Disease duration: per 1-y increase	1.01 (0.98, 1.04)	1.00 (0.97, 1.03)	1.00 (0.95, 1.00)
BL EDSS: ≥3.5 vs < 3.5	**1.66 (1.28, 2.15)**	1.01 (0.78, 1.30)	NA
<2 vs ≥ 2	NA	NA	**2.79 (2.13, 3.65)**
Relapses in previous year: >2 vs ≤ 2	**1.40 (1.07, 1.82)**	1.09 (0.85, 1.41)	0.79 (0.50, 1.25)
Model 2			
T2 lesion number: ≥71 vs < 71	0.99 (0.82, 1.20)	**1.50 (1.27, 1.77)**	1.20 (0.92, 1.56)
Disease duration: per 1-y increase	1.01 (0.98, 1.04)	0.69 (0.96, 1.02)	1.00 (0.95, 1.04)
BL EDSS: ≥3.5 vs < 3.5	**1.67 (1.28, 2.17)**	0.95 (0.73, 1.23)	NA
<2 vs ≥ 2	NA	NA	**2.85 (2.17, 3.73)**
Relapses in the previous year: >2 vs ≤ 2	**1.43 (1.09, 1.86)**	1.20 (0.93, 1.55)	0.82 (0.52, 1.28)
Model 3			
T2 lesion volume: per 1 unit increase	1.00 (1.00, 1.01)	**1.02 (1.01, 1.03)**	**1.01 (1.004, 1.03)**
Disease duration: per 1-y increase	1.01 (0.98, 1.04)	0.99 (0.96, 1.02)	1.00 (0.95, 1.05)
BL EDSS: ≥3.5 vs < 3.5	**1.63 (1.25, 2.13)**	0.90 (0.69, 1.17)	NA
<2 vs ≥ 2	NA	NA	**2.96 (2.25, 3.88)**
Relapses in the previous year: >2 vs ≤ 2	**1.42 (1.09, 1.85)**	1.15 (0.89, 1.48)	0.80 (0.51, 1.26)

Abbreviations: BL = baseline; CI = confidence interval; EDSS = expanded disability status scale; GA = glatiramer acetate; Gd+ = gadolinium-enhancing; HR = hazard ratio; IFN = interferon beta-1a; NA = not available; NPDE = nonprotocol-defined exacerbation; PDE = protocol-defined exacerbation.
Numbers represent HRs. HR greater than 1 indicates a positive association between predictor and outcome.
[a] All models included participant characteristics, baseline disease characteristics, and for Model 1: Gd+ lesions (present/absent), Model 2: T2 lesion number (≥71 vs < 71), or Model 3: T2 lesion volume.
Bold values represent statistically significant hazard ratios.

extent of MRI activity and clinical status has been referred to as the clinicoradiological paradox.[14] While most lesions are asymptomatic, lesions topographically located in clinically impactful sites such as the brainstem, cerebellum, and spinal cord are more likely to produce symptoms and changes in EDSS scores.[15,16] The lack of clinical impact of most MRI activity has led many clinicians to adopt a higher threshold for defining treatment failure in the setting of isolated radiological activity. In our study, there is a lower risk of new MRI activity for those taking combination therapy compared with those taking either single-agent alone. However, in the main CombiRx trial, using combination therapy did not result in improvement of clinical outcomes in RRMS. Our results further showed that higher BL disability predicted the risk of relapse. In patients with RRMS without BL progression, higher BL EDSS scores reflect incomplete recovery from previous attacks, which has been shown as a prognosticator of more aggressive disease.[17,18]

In our study, BL EDSS level was associated with disease worsening. Given higher variability for lower EDSS scores,[6] we adopted a definition of sustained progression that has been used in previous clinical trials to account for this variability.[19,20] Despite adjusting for EDSS variability, patients with lower EDSS were at higher risk of disease worsening in our study. This finding suggests that disease mechanisms distinct from inflammatory disease activity may be a driver of sustained changes in EDSS. While our definition of disease worsening captures sustained EDSS changes over 6 months, previous studies have shown that short-term sustained progression on EDSS used in clinical trials is often not maintained in a long-term follow up.[21] Previous epidemiologic studies have found that older age is associated with reaching disability milestones earlier.[17,22] In our study, age did not predict disease worsening, which may be due to the overall younger age of the clinical trial population because the average onset of disease progression occurs in the fifth and sixth decades.[23,24] Our study also did not show an association between clinical or radiological disease activity on disease worsening, which is consistent with previous findings that the absence of short term disease activity was not a predictor of long-term stability.[25] Therefore, even up to 7 years of follow-up in the CombiRx trial may not be sufficient to observe disease progression.

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TAKE-HOME POINTS

- Disease activity in MS is highly variable, but certain patient demographic and disease characteristics can help predict disease activity and worsening.
- Younger patients and those with the presence of Gd+ lesions are at a higher risk of both clinical and radiological disease activity.
- BL disability is predictive of disease worsening independent of relapse count or MRI lesion burden.

Some limitations were present in this study. The lack of a placebo control in CombiRx limits our analysis to only treated patients. However, all patients in the trial were treatment-naïve, thus eliminating potential confounders of previous treatment effects. In addition, as typical of many RRMS clinical trials, the CombiRx trial selected for younger patients with active disease, requiring 2 clinical relapses or 1 clinical relapse and new MRI activity in the 3 years before enrollment. This limits our analysis of older patients and those with stable disease. While the duration of follow-up in CombiRx was longer than that in most clinical trials, rates of disability worsening in treated MS patients are much lower compared with those observed in early natural history studies.[25] Therefore, an even longer follow-up would allow for more reliable associations to be made between BL disease characteristics and long-term outcomes such as conversion to SPMS.

In this prospective cohort of treatment-naïve RRMS patients using platform DMTs, younger age, increased BL relapses, and radiological activity predicted subsequent disease activity. Identifying factors predicting poor treatment outcome helps inform the need for more aggressive management. Younger patients with high BL relapses and MRI lesion burden should be especially considered for high-efficacy therapy to lower the risk of subsequent disease activity.

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Disclosure

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Name	Location	Contribution
Yinan Zhang, MD	Department of Neurology, The Ohio State University Wexner Medical Center, Columbus	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Stacey Cofield, PhD	Department of Biostatistics, University of Alabama at Birmingham	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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Appendix *(continued)*

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Gary Cutter, PhD	Department of Biostatistics, University of Alabama at Birmingham	Drafting/revision of the article for content, including medical writing for content
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Jerry S Wolinsky, MD	Department of Neurology, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston	Drafting/revision of the article for content, including medical writing for content
Fred Lublin, MD	Department of Neurology, Icahn School of Medicine at Mount Sinai, New York	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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