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Early use of high-efficacy disease-modifying therapies reduces the risk of progression independent of relapse and MRI activity in patients with relapsing-remitting multiple sclerosis

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Abstract

Background: Progression independent of relapse and MRI activity (PIRMA) is a major contributor to long-term disability in relapsing-remitting multiple sclerosis (RRMS). In Latin America, limited access to high-efficacy disease-modifying therapies (DMTs) may influence PIRMA risk, but real-world evidence is scarce. We aimed to estimate the causal effect of DMT efficacy on PIRMA in an Argentine cohort.

Methods: We conducted a retrospective observational study including 264 adults with RRMS meeting predefined disability follow-up criteria. Treatment exposure was modeled as a time-varying variable (low-efficacy vs moderate-/high-efficacy), applying a 60-day pharmacological lag after treatment switches. To address time-dependent confounding, we used a marginal structural model with overlap weighting and a weighted Cox proportional hazards model.

Results: Median age at treatment initiation was 31.5 years, 62.1% were female, and median baseline EDSS was 1.0. Over a median follow-up of 7 years, 26 PIRMA events occurred. Exposure to low- or moderate-efficacy DMTs was associated with a significantly higher risk of PIRMA compared with high-efficacy therapies (HR 7.05; 95% CI 1.15–43.35).

Conclusion: Exposure to low-/moderate-efficacy disease-modifying therapies was associated with a substantially higher risk of PIRMA compared with high-efficacy treatments, supporting the potential benefit of early access to high-efficacy therapies in RRMS

Keywords: PIRMA, PIRA, multiple sclerosis, progression, disease modifying therapies

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Data Availability Statement included at the end of the article

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease in which disability accumulation begins early and arises through two overlapping mechanisms: relapse-associated worsening and progression independent of relapse activity (PIRA). Contemporary large-scale cohort studies have demonstrated that PIRA emerges from the earliest stages of relapsing-remitting MS and represents a major determinant of long-term disability accumulation.[1,2] More recently, this concept has been further refined, by recognizing that true silent progression should also occur in the absence of radiological inflammatory activity. This stricter phenotype, progression independent of relapse and MRI activity (PIRMA), aims to capture disability worsening driven by smoldering or compartmentalized disease mechanisms rather than focal inflammatory events.[3–5]

Disease-modifying therapies (DMTs) reduce relapses and MRI activity, however, their impact on disability progression depends critically on both treatment efficacy and timing. Evidence from international registries and expert consensus consistently indicates that early initiation of high-efficacy therapies leads to superior long-term outcomes compared with delayed

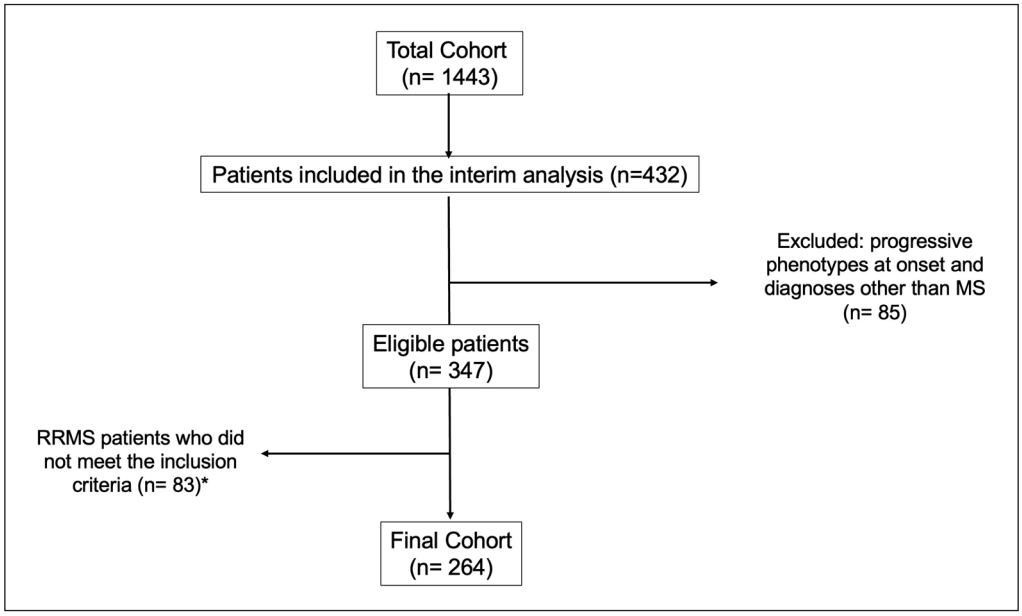

Figure 1. Flowchart.
MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.
[a]Patients were excluded because of missing relevant clinical data ($n = 34$), MRI studies not available for analysis ($n = 21$), or insufficient follow-up to assess study outcomes ($n = 28$).

use or escalation strategies, including reduced irreversible disability accumulation and delayed attainment of disability milestone.[6–8]

Despite this growing body of evidence, access to high-efficacy therapies remains uneven, particularly in low- and middle-income regions such as Latin America. In these settings, treatment selection is frequently influenced by structural and economical constraints rather than clinical needs, leading to extended exposure to low-/moderate-efficacy therapies.[6] However, few real-world studies have quantified the specific impact of treatment efficacy on PIRMA under such restricted therapeutic conditions.

In this study, we used longitudinal real-world data from Argentina to estimate the causal effect of treatment efficacy on the risk of developing PIRMA. Understanding how therapeutic efficacy shapes silent disability under constrained health-care conditions is essential to inform equitable treatment policies and optimize long-term outcomes for people living with MS.

Materials and methods

Study design and participants

This observational, longitudinal, retrospective cohort study collected clinical data from a tertiary MS center in Buenos Aires, Argentina. The analysis represents an interim evaluation of real-world data derived from an ongoing database comprising patients with MS who received one or more disease-modifying therapies (DMTs) between 2011 and 2025. Data extraction and curation were performed between 2024 and 2025. Only patients meeting prespecified criteria for longitudinal disability follow-up were included. The selection process is summarized in Figure 1.

Eligible participants were adults (⩾18 years) with at least three standardized clinical disability assessments per year and a minimum follow-up of 5 years. All included patients underwent at least one annual brain MRI; all examinations included at minimum T2/FLAIR and T1-weighted sequences, with most studies also incorporating volumetric FLAIR and post-contrast T1 acquisitions. All MRI scans were performed on 1.5T or 3T scanners. Patients with primary or secondary progressive MS at baseline were excluded. Collected demographic and clinical variables included age, sex, age at onset, disease duration, relapse history, EDSS scores and assessment dates, pyramidal functional system scores, and start and end dates of each DMT exposure, allowing full reconstruction of longitudinal treatment and disability trajectories.

Exposure. The exposure of interest was the efficacy category of the prescribed DMT, modeled as a binary

time-varying variable distinguishing low-/moderate- from high-efficacy treatments. Low-/moderate-efficacy agents included interferon preparations, glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. High-efficacy therapies comprised cladribine and monoclonal antibodies including alemtuzumab, natalizumab, ocrelizumab, ofatumumab, and rituximab. Disease-modifying therapies were categorized according to real-world effectiveness rather than trial-based relapse reduction alone; accordingly, fingolimod was classified as a moderate-efficacy agent based on comparative effectiveness data, and the grouping strategy was intended to reflect pragmatic treatment strata in routine care rather than biological homogeneity within each category. Because treatment switching was common in real-world practice, exposure status varied over time within individuals. Due to the limited number of PIRMA events, defining fixed mutually exclusive exposure groups was not considered appropriate, as this would have generated sparse subgroups and unstable estimates; therefore, treatment category was modeled as a time-varying variable. A 60-day lag was applied after each treatment switch to account for pharmacological onset. For treatment attribution, PIRMA events were dated according to the confirmation visit of disability worsening; therefore, the 60-day pharmacological lag after DMT initiation or switch was applied relative to the confirmation date, rather than the initial worsening assessment.

Outcome. The primary outcome was the occurrence of PIRMA events. Confirmed disability worsening (CDW) was defined as an increase in EDSS of $\geqslant$1.0-point for patients with baseline EDSS $<$ 5.5, or $\geqslant$0.5-points for those with baseline EDSS $\geqslant$ 5.5, sustained for at least 3 months. CDW events were classified as PIRMA if they were sustained across at least two consecutive visits separated by a minimum of 3 months, occurred in the absence of clinical relapse within 30 days before or after the worsening event, and were not associated with MRI activity in the preceding year (including on both brain and spinal cord).[7] In accordance with common observational definitions of PIRMA, MRI examinations performed within the preceding 12 months before confirmed disability worsening were used to adjudicate the absence of inflammatory activity. MRI disease activity was consistently defined throughout the study as the presence of new or enlarging T2/FLAIR lesions and gadolinium-enhancing lesions, despite changes in imaging protocols over time. EDSS assessments obtained during relapse periods were excluded from outcome adjudication. Patients who did not experience PIRMA were censored at the date of their last recorded clinical evaluation.

Covariates. Covariates included both baseline and time-varying factors: age at onset, sex, disease duration, MRI lesion load, relapse activity in the preceding 1 and 2 years, previous treatment class, number of prior treatment changes, and time since the most recent switch.

Statistical analysis. Because several time-varying covariates affected both treatment selection and the risk of the outcome, and were themselves affected by prior treatment decisions, the data set exhibited a treatment–confounder feedback structure. Under these conditions, conventional time-varying Cox may introduce bias by inappropriate adjustment for intermediate variables.[9] To appropriately address this issue, we used a marginal structural model with overlap weighting, as described elsewhere.[10] Kaplan–Meier curves were generated to provide a descriptive visualization of PIRMA-free survival across treatment categories. Because treatment exposure was modeled as time-varying and causal inference was derived from the marginal structural Cox model with overlap weighting, these Kaplan–Meier curves should be interpreted as descriptive summaries rather than causal estimates.

Longitudinal follow-up was structured using a counting-process framework to accommodate time-varying exposure and covariates. Overlap weights were estimated using logistic regression models predicting the probability of receiving a low-efficacy treatment at each interval, conditional on baseline and time-varying covariates (age at onset, disease duration, sex, MRI lesion load, relapses in the previous year and previous 2 years, number of prior treatment changes, previous treatment class, and time since the last switch). This approach balances covariates within the overlap population—patients with a non-negligible probability of receiving either treatment category.[11]

Weighted Cox proportional hazards models were then fitted, including treatment category and baseline covariates (age at onset, disease duration, sex, and baseline lesion load). Ninety-five percent confidence intervals for the treatment effect were obtained using a nonparametric cluster bootstrap with 500 patient-level resamples. The proportional hazards assumption was evaluated using weighted Schoenfeld residuals, and no relevant violations were detected.

To evaluate the robustness of this assumption, sensitivity analysis were repeated using extended pharmacological lag windows of 90 and 180 days following treatment initiation or switching. These analyses evaluated whether the estimated association between treatment category and PIRMA risk remained

Table 1. Baseline characteristics of the complete cohort ($n = 264$).[a]

Females, *n* (%)	164 (62)
Age at multiple sclerosis diagnosis, median (IQR)	31 (12)
Caucasian, *n*/*N* (%)	199/283 (70)
Smoking, *n*/*N* (%)	82/286 (29)
Cardiovascular risk factors, n/*N* (%)	19/287 (7)
Initial Clinical Manifestations	
Optic Neuritis, *n* (%)	68 (23)
Myelitis, *n* (%)	102 (35)
Brainstem/cerebellar, *n* (%)	59 (20)
Hemispheric, *n* (%)	45 (15)
Multifocal, *n* (%)	17 (6)
Other, *n* (%)	3 (1)
Positive OCB, n/*N* (%)	94/118 (80)
EDSS at first visit, median (IQR)	1.00 (2)
Gadolinium-Enhancing Lesions, n/*N* (%)	88/189 (47)
Spinal cord lesions, n/*N* (%)	104/125 (83)
T2 lesional load	
<10 lesions, *n* (%)	27 (10)
$>10<50$ lesions, *n* (%)	115 (43)
$>50<100$ lesions, *n* (%)	25 (10)
>100 lesions, *n* (%)	1 (1)
Inconclusive[b]	96 (36)
Disease modifying therapies at onset	
Low efficacy, *n* (%)	148 (56)
Moderate efficacy, *n* (%)	83 (31)
High efficacy, *n* (%)	33 (13)
Disease duration in years, median (IQR)	7.98 (4.2)
Switch to high-efficacy treatment during follow-up, *n* (%)	62 (24)

[a]Percentages are calculated based on available cases for each variable.
[b]In absence of volumetric sequences or MRI studies not available to review.

consistent under alternative lag specifications. All analyses were conducted using R statistical software.

Results

A total of 264 patients were included in final analysis, with a median follow-up of 7 years (IQR 6–10). The cohort was 62% female, with a median age at treatment initiation of 31 years (IQR 25–37). The most frequent initial clinical presentations were myelitis (34.5%), optic neuritis (23.0%), and brainstem or cerebellar syndromes (20.1%). Oligoclonal bands were detected in 79.7% of tested individuals, and spinal cord lesions were identified in 83.2% of the cohort. The median baseline EDSS was 1.0 (IQR 0–2). Baseline demographic and clinical characteristics of the cohort are summarized in Table 1. Baseline characteristics differed modestly according to initial treatment category (low-/moderate- vs high-efficacy DMTs), exposure, particularly with respect to MRI lesion load, reflecting real-world treatment allocation patterns (Table 2). These imbalances were adequately addressed using overlap weighting, resulting in adequate covariate balance in the weighted pseudo-population (Supplementary Table 1).

Patients frequently transitioned between low-/moderate-efficacy and high-efficacy therapies during follow-up, leading to heterogenous treatment exposure within individuals. Consequently, the analysis focused on estimating the causal effect of treatment efficacy category over time rather than comparing predefined patient groups based on initial therapy.

During the observation period, 26 PIRMA events were recorded. In the overall cohort, these events occurred over 1851.8 person-years of follow-up, corresponding to a crude incidence rate of 1.40 per 100

Table 2. Baseline characteristics by initial treatment type.[a]

	High efficacy ($n=33$)	Low/moderate efficacy ($n=261$)	p-value
Female, *n* (%)	17 (52)	147 (64)	0.2498
Age at disease onset	31.00 (14)	32.00 (11)	0.3533
Disease duration in years, median (IQR)	7.06 (3)	8.09 (4)	0.0036
Caucasian, *n*/*N* (%)	19/28 (68)	167/240 (70)	1.000
Smoking, *n*/*N* (%)	8/29 (28)	71/243 (29)	1.000
Cardiovascular risk factors,[b] *n*/*N* (%)	3/29 (10)	14/241 (6)	0.405
Initial clinical manifestations ($N=289$)			
Brainstem/cerebellum, *n*/*N* (%)	8/33 (27)	50/254 (20)	0.476
Hemispheric, *n*/*N* (%)	7/33 (23)	39/254 (15)	0.288
Multifocal, *n*/*N* (%)	2/33 (7)	14/254 (6)	0.676
Myelitis, *n*/*N* (%)	13/33 (43)	85/254 (33)	0.343
Optic Neuritis, *n*/*N* (%)	3/33 (10)	63/254 (25)	0.124
Other, *n*/*N* (%)	0/33 (0)	3/254 (1)	1.000
Positive OCB, n/*N* (%)	12/13 (92)	77/97 (79)	0.456
EDSS at first visit, median (IQR)	1.25 (1)	1.00 (2)	0.174
Gadolinium-enhancing lesions, *n*/*N* (%)	10/15 (67)	76/171 (44)	0.166
Spinal cord lesions, *n*/*N* (%)	8/10 (80)	94/113 (83)	0.679
T2 lesional load			
<10 lesions, *n* (%)	0 (0)	27 (10)	<0.001
$>10<50$ lesions, *n* (%)	8 (3)	107 (40)	<0.001
$>50<100$ lesions, *n* (%)	7 (3)	18 (7)	<0.001
>100 lesions, *n* (%)	1 (1)	0 (0)	<0.001
Inconclusive[c]	17 (6)	79 (30)	NA

[a]Percentages are calculated based on available cases for each variable.
[b]Cardiovascular risk factors included dyslipidemia, hypertension.
[c]In absence of volumetric sequences or MRI studies not available to review.

person-years (95% CI, 0.92–2.06). The relatively low number of PIRMA events likely reflects the stringent outcome definition used in this study. The cumulative event probability in the full population is shown in a Kaplan–Meier curve (Figure 2), and a descriptive summary of PIRMA events across DMT exposures is provided in Supplementary Table 2.

In the marginal structural model with overlap weighting, exposure to low-/moderate-efficacy therapy was associated with a significantly increased hazard of PIRMA compared with exposure to high-efficacy treatment (HR 7.05; 95% CI 1.15–43.35; $p=0.03$). In the overlap population, this finding suggests that exposure to high-efficacy therapies is associated with a substantially lower risk of PIRMA compared with exposure to low-/moderate-efficacy treatments. Age at onset, disease duration, sex, and baseline lesion load were included as adjustment covariates in the weighted model to control for potential confounding, rather than to estimate their independent effects on PIRMA risk Supplementary Table 3). The proportional hazards assumptions were met, as indicated by non-significant weighted Schoenfeld test, and post-weighting covariate balance was satisfactory, with standardized mean differences close to zero. Additional sensitivity analyses using longer pharmacological lag periods yielded similar results. The 90-day lag analysis produced results comparable to the primary model, whereas the 180-day lag analysis yielded extreme effect estimates and very wide confidence intervals, consistent with model instability due to the small number of attributable events (Supplementary Table 4). Weighted cumulative incidence curves for PIRMA further illustrate these results. Kaplan–Meier curves illustrate the cumulative incidence of PIRMA across treatment categories; however, these curves are presented for descriptive purposes only, as the primary treatment effect estimates were derived from the marginal structural Cox model accounting for time-varying exposure. Model-based cumulative incidence curves derived from the

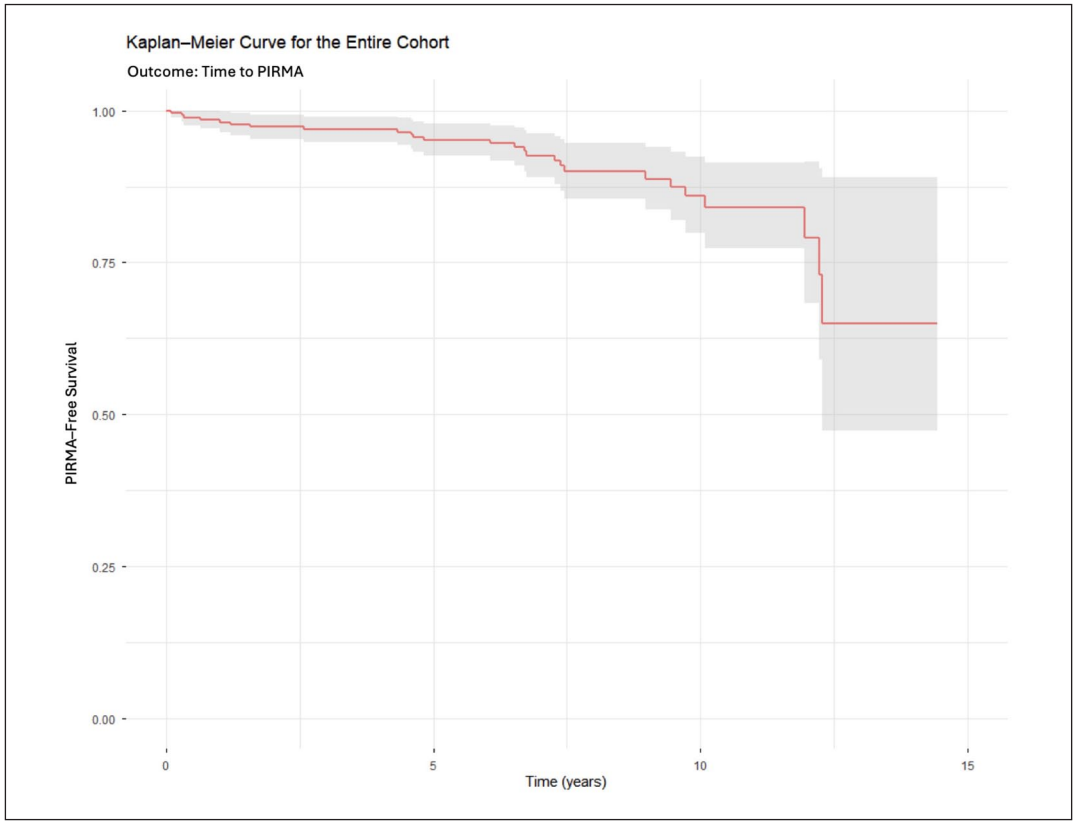

Figure 2. Kaplan–Meier curve for PIRMA-free survival in the overall cohort.
The curve shows the unadjusted probability of remaining free from PIRMA over follow-up in the population included in the weighted time-to-event analysis ($N=264$). Overall, 26 PIRMA events occurred during 1851.8 person-years of follow-up, corresponding to a crude incidence rate of 1.40 per 100 person-years (95% CI, 0.92–2.06). Shaded areas represent 95% confidence intervals. This figure is provided to contextualize the overall burden and timing of PIRMA events in the cohort, independent of treatment-specific time-varying exposure modeling.

weighted Cox model further illustrate these results (Figure 3). Periods of exposure to low-/moderate-efficacy treatment were associated with a visibly higher accumulated risk of PIRMA over time compared with periods of high-efficacy treatments, with divergence emerging during mid-to-late follow-up (Figure 3). The figure also depicts a hypothetical scenario in which patients switched from low-/moderate-efficacy to high-efficacy therapy at year five, demonstrating an intermediate risk trajectory. Together, these curves offer a visual representation of the increased susceptibility to silent disability progression associated with lower-efficacy treatment exposure and reinforce the protective effect observed with high-efficacy therapies throughout follow-up.

Sensitivity analyses restricting PIRMA events to those sustained for ⩾6 months, reclassifying fingolimod as a high-efficacy therapy, and excluding early follow-up years yielded directionally consistent results, supporting the robustness of the main findings.

Discussion

Accumulating evidence over the last decade has substantially reshaped the understanding of disability accumulation in MS, demonstrating that it begins from the earliest stages of the disease and represents a major driver of long-term outcome.[1,12] Large observational cohorts and pooled analyses from randomized clinical trials have consistently shown that a substantial proportion of confirmed disability worsening occurs in the absence of clinical relapses, challenging the traditional view that irreversible disability in MS is predominantly relapse-driven.[12,13] Collectively, these observations support a conceptual shift toward viewing MS as a biological continuum, characterized by the early coexistence of inflammatory and progression-related mechanisms rather than as a sequence of discrete clinical phenotypes.[4,14]

Within this evolving framework, increasing attention has focused on the role of DMTs in modulating not only relapse activity but also progression-related

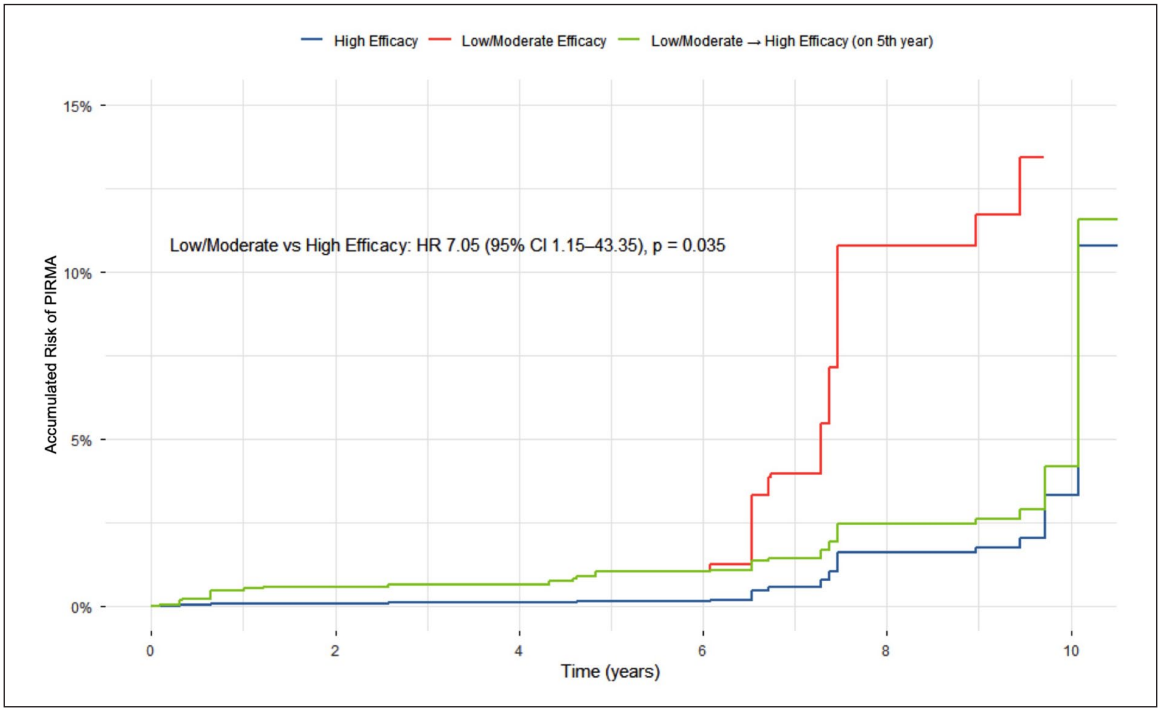

Figure 3. Estimated cumulative risk of PIRMA under representative treatment exposure scenarios from the weighted Cox model.

Curves illustrate model-based cumulative PIRMA risk under sustained high-efficacy treatment, sustained low-/moderate-efficacy treatment, and escalation from low-/moderate- to high-efficacy treatment at year 5. During follow-up, 62 patients (24% of the cohort) transitioned from low-/moderate-efficacy to high-efficacy therapies, resulting in heterogeneous treatment exposure within individuals. Because treatment exposure was modeled as a time-varying variable within a marginal structural framework, the curves represent counterfactual risk trajectories derived from the fitted model rather than observed patient cohorts. Covariates were set to weighted typical values in the overlap population, and risks are displayed over 10 years of follow-up. Kaplan–Meier–type curves are shown for descriptive visualization of PIRMA risk over time; however, the primary treatment effect estimates were derived from the marginal structural Cox model accounting for time-varying exposure.

outcomes. Evidence indicates that early initiation of high-efficacy therapies is associated with superior long-term disability outcomes compared with delayed treatment or escalation strategies, including reduced accumulation of irreversible disability and delayed transition to advanced disease stages.[6,15–17] Conversely, prolonged exposure to lower-efficacy therapies, particularly during the early inflammatory phase of the disease, has been associated with an increased risk of disability accrual that may not be reversible even after subsequent treatment intensification.[18]

However, much of the existing literature on PIRMA has relied on definitions that exclude clinical relapses but do not systematically account for subclinical inflammatory activity detectable on MRI, potentially conflating biologically distinct mechanisms of progression.[12] Recent studies have emphasized the importance of distinguishing between active PIRA, occurring in the presence of MRI activity, and non-active or "true" PIRA, which reflects disability accumulation independent of both relapses and radiological activity and is increasingly referred to as PIRMA.[3,7]

In parallel, growing evidence indicates that the timing of PIRA onset carries major prognostic significance. Large longitudinal cohorts have previously shown that a substantial proportion of patients develop PIRA within the first 5 years of disease onset, and that early PIRA is associated with more rapid disability accumulation and earlier attainment of irreversible disability milestones compared with late-onset PIRA.[19,20] These observations support the concept that early silent progression identifies a high-risk disease trajectory, likely reflecting an aggressive biological substrate rather than mere cumulative effect of inflammatory damage over time.[19,20]

This study builds directly on this conceptual framework by focusing on PIRMA in a real-world setting, outside the controlled environment of clinical trials. By requiring the absence of both clinical relapses and MRI activity in the adjudication of progression events, our analysis targets a more stringent and biologically homogeneous phenotype of silent disability progression, aligning with contemporary calls for harmonized and clinically meaningful definitions

applicable to observational data.[3,12] Although the number of PIRMA events observed during follow-up was limited, this likely reflects the rarity of rigorously defined PIRMA when strict criteria excluding both clinical relapses and MRI activity are applied. . The analytical strategy was therefore designed to prioritize unbiased estimation of the direction of association between treatment efficacy and silent disability progression rather than precise quantification of effect size. The use of a marginal structural model with overlap weighting mitigated time-dependent confounding inherent to real-world treatment allocation while restricting inference to the population with genuine treatment equipoise. Accordingly, the width of the confidence intervals should be interpreted as reflecting limited event frequency and residual uncertainty around magnitude, rather than instability of the observed association. Importantly, the consistency of the effect direction with prior large registry studies and biological models of early progression supports the robustness and clinical relevance of the observed relationship.

Using a causal inference framework with time-varying exposure and marginal structural modeling, we demonstrate that exposure to low-/moderate-efficacy therapies is associated with a substantially increased risk of PIRMA compared with high-efficacy treatments, supporting the hypothesis that a significant component of early silent progression remains sensitive to treatment efficacy. These findings suggest that early therapeutic decisions may influence not only relapse control but also the risk of clinically silent disability progression, reinforcing the potential long-term benefits of timely access to high-efficacy therapies. The biological plausibility of these findings is supported by converging neuropathological and imaging evidence indicating that smoldering inflammatory activity is present from the earliest disease stages and contributes to progressive neuroaxonal damage. Compartmentalized inflammation, chronic active lesions, meningeal immune aggregates, and microglial activation have all been implicated in the gradual accumulation of disability independent of overt relapses, providing a mechanistic substrate for PIRMA that may still be modulated by timely and effective suppression of inflammatory pathways.[21,22] In this context, our results are consistent with the observation that early progression is not a purely degenerative phenomenon but rather reflects a complex interplay between residual inflammatory activity and downstream neurodegenerative mechanisms.

An important strength of this study lies in its real-world Latin American setting, a region that remains underrepresented in MS research despite substantial heterogeneity in health-care access and treatment availability. Although monocentric, the cohort was derived from a tertiary referral center with standardized longitudinal follow-up and comprehensive treatment documentation, enabling robust reconstruction of treatment exposure and disability trajectories over a prolonged period. Notably, the observed treatment patterns, characterized by delayed access to high-efficacy therapies, frequent switching, and prolonged exposure to lower-efficacy agents, reflect common clinical realities in many low- and middle-income countries, thereby enhancing the external relevance of these findings beyond a single institution.

Despite the growing consensus supporting early use of high-efficacy therapies, access to these treatments remains uneven worldwide. Structural, regulatory, and economic barriers continue to delay optimal therapy even in high-income countries, while such limitations are often amplified in developing regions. Our findings highlight the tangible clinical consequences of these disparities, demonstrating that restricted access to high-efficacy therapies is associated with a markedly increased risk of silent disability progression. These data underscore the importance of incorporating progression-related outcomes, including PIRMA, into treatment algorithms and health policy decisions, particularly in resource-constrained settings.

Limitations of this study merit consideration. As an observational real-world study, residual confounding cannot be entirely excluded despite the use of advanced causal inference methods. Because the cohort spans multiple therapeutic eras (2011–2025), during which diagnostic timing, treatment intensity, and supportive care evolved, calendar-time effects independent of treatment efficacy cannot be fully excluded, as calendar year was not explicitly modeled as a stratification variable. The relatively small number of PIRMA events resulted in wide confidence intervals around effect estimates, even despite the mentioned long inclusion period. Temporal heterogeneity in MRI availability, acquisition protocols, and image quality represents an inherent limitation of this study. Although MRI disease activity was harmonized using standardized definitions, continuous improvements in scanner technology and protocol optimization over time may have affected the sensitivity to detect subtle inflammatory changes. Because MRI monitoring was performed at approximately annual intervals in routine clinical practice, transient inflammatory activity occurring between imaging studies may not have been detected, potentially leading to

conservative misclassification of some progression events such as PIRMA. In addition, the predefined exclusion windows for relapses and MRI activity may not have fully captured delayed or low-grade inflammatory activity surrounding disability worsening events. This could have led to misclassification of PIRMA status, particularly in earlier years, potentially resulting in conservative estimates of PIRMA frequency. In addition, advanced biomarkers of smoldering disease activity, such as paramagnetic rim lesions, quantitative brain or spinal cord atrophy, and serum neurofilament light chain, were not systematically available for inclusion in the analysis. Interpretation of progression-related outcomes must also consider the major changes in MS care that have occurred over recent decades. Also, potential confounders as subtle pre-progression signals, such as cognitive decline, fatigue, or mild pyramidal worsening, may influence treatment escalation but are not fully captured by relapse history or conventional MRI metrics. As a single-center tertiary referral study, these findings may not be fully generalizable to broader MS populations, particularly in settings with less intensive follow-up or different referral patterns. The expanding therapeutic armamentarium, increasing treatment efficacy, and progressive shortening of diagnostic delays represent an "era" or "epoch effect" that may substantially influence both the incidence and timing of PIRMA events. Population-based studies have shown a clear temporal improvement in multiple sclerosis prognosis across treatment eras, with slower disability accumulation, which may affect both the detection and clinical interpretation of PIRMA in contemporary cohorts.[4,23,24] Finally, although fingolimod has been considered a high-efficacy therapy by some authors, it was classified as a moderate-efficacy DMT in this study.[25] This choice was supported by a probable lower impact on disease activity compared with contemporary high-efficacy monoclonal antibody therapies.[26]

Future studies should aim to validate these findings in larger, multicenter cohorts across Latin America and other resource-constrained regions, allowing more precise estimation of treatment effects and a more granular analysis of early versus late PIRA and PIRMA phenotypes. Integration of advanced imaging and fluid biomarkers into longitudinal real-world frameworks will be essential to further disentangle inflammatory and smoldering mechanisms and to clarify how modern therapeutic strategies influence silent progression over time. Ultimately, such efforts may help refine risk stratification models and optimize early therapeutic decisions for patients at highest risk of irreversible disability accumulation.

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Declaration of Conflicting Interests

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Data Availability Statement

All data is available to interested investigators upon reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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