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Who Can Safely Discontinue Treatment in Myasthenia Gravis? Insights From a Long-Term Real-World Study

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ABSTRACT

Background: Optimal timing for treatment discontinuation in myasthenia gravis (MG) patients achieving minimal symptom expression (MSE) remains undefined.

Methods: This prospective cohort study enrolled 196 MG patients from the Huashan MG Registry who achieved MSE and subsequently discontinued all treatments. Cox regression was used to identify prognostic factors for relapse. Among these, 20 patients experienced two discontinuation events and were analyzed separately for their second discontinuation.

Results: Over a mean follow-up of 111.10 months, 108 patients (55.1%) experienced relapse. Multivariate analysis identified four independent prognostic factors: onset age ≥ 50 years as a risk factor (HR 1.68, 95% CI 1.04–2.70, $p = 0.032$), and rituximab administration (HR 0.43, 95% CI 0.17–0.89, $p = 0.015$), treatment duration ≥ 14.3 months (HR 0.54, 95% CI 0.34–0.85, $p = 0.008$), and time from MSE to discontinuation ≥ 6.1 months (HR 0.51, 95% CI 0.32–0.83, $p = 0.007$) as protective factors. Infection, fatigue, and psychological stress were common relapse triggers.

Conclusions: Complete treatment discontinuation after MSE in MG carries substantial relapse risk. Individualized discontinuation decisions incorporating younger onset age, prior rituximab use, adequate treatment and consolidation duration may optimize outcomes.

1 | Background

Myasthenia gravis (MG) is an acquired, chronic, heterogeneous autoimmune disease caused by pathogenic autoantibodies that impair neuromuscular junction function. The epidemiological landscape of MG has shifted substantially over recent decades. Systematic reviews report a global prevalence approaching 173 per million and incidence of 16 per million person-years, representing a near threefold increase from estimates in 2010 [1, 2]. In China, a national population-based study reported an age-standardized mortality rate of 1.86 per million in 2020, with an increasing temporal trend over the past decade [3]. This rising burden, combined with demographic shifts toward late-onset disease, has intensified the need for optimized, individualized treatment strategies.

The therapeutic spectrum for MG has expanded considerably, encompassing acetylcholinesterase inhibitors (AChEIs), steroids, nonsteroidal immunosuppressants (NSISTs), and targeted biologics including rituximab (RTX), complement

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inhibitors and neonatal Fc receptor antagonists [4]. A primary therapeutic goal in MG management is achieving minimal symptom expression (MSE), which represents optimal disease control and improved quality of life [5]. This endpoint is achievable in approximately 50% of patients within a median of 26 months and demonstrates robust sustainability, with over 85% of patients maintaining this status at 12-month follow-up [6, 7].

Despite advances in achieving disease control, a fundamental clinical question remains unanswered, namely the optimal timing and approach for treatment discontinuation in patients who reach this goal. The distinction between MSE and complete stable remission (CSR) is clinically important. CSR requires complete absence of symptoms and signs for at least 1 year without any MG therapy [8]. In a recent Chinese cohort of 256 MG patients treated with tacrolimus and prednisone, only 7.8% achieved CSR after a median follow-up of 2.9 years [9]. Although achieving CSR may imply that the immune system has re-established a certain equilibrium, whether this balance is fragile or robust remains unclear due to the lack of reliable biomarkers to assess immune tolerance stability [10]. In contrast, MSE represents a pragmatic threshold at which treatment modification becomes a consideration for many patients and clinicians. Critically, no major guidelines address treatment discontinuation protocols, leaving clinicians without evidence-based guidance for one of their most common clinical dilemmas.

While the potential benefits of discontinuation are evident, they must be carefully weighed against the risk of disease resurgence—a risk that is currently difficult to quantify due to scarce literature. Previous studies on MG treatment discontinuation are limited by retrospective designs, small sample sizes, heterogeneous populations, and focus on medication tapering rather than complete cessation [11, 12]. Reported relapse rates vary widely from 11% to 56%, reflecting differences in study design and heterogeneity in treatment regimens across cohorts [11–14]. Known risk factors for relapse during treatment tapering include rapid medication reduction, bulbar weakness at onset, and concomitant autoimmune disease, while isolated ocular involvement and early disease onset appear protective [9, 13]. However, these findings derive primarily from studies examining gradual dose reduction rather than complete treatment discontinuation.

To address this critical evidence gap regarding complete discontinuation, we conducted a prospective cohort study to systematically characterize relapse patterns and identify independent prognostic factors following complete treatment discontinuation in MG patients who had achieved MSE. Our findings provide the first, real-world estimates of relapse risk in this context and offer evidence-based insights to guide individualized discontinuation decisions in MG.

2 | Methods

2.1 | Study Population

This single-center, prospective and real-world cohort study utilized data from the Huashan MG Registry, a longitudinal database comprising 2719 MG patients registered between January 2015 and September 2025 (Figure 1). MG diagnosis required fluctuating weakness and fatigability plus at least one of: (1) positive neostigmine test; (2) abnormal low-frequency (2–3 Hz) repetitive nerve stimulation; or (3) positive serum Acetylcholine receptor antibody (AChR-Ab) or Muscle-specific kinase antibody (MuSK-Ab) [15].

We included patients who achieved minimal symptom expression (MSE) followed by complete treatment discontinuation. Exclusion criteria were incomplete medical records, failure to achieve MSE, or ongoing treatment at data censoring. Of the 2719 registered patients, 196 met all inclusion criteria with no exclusions and comprised the study cohort. Among these, 20 patients experienced two separate discontinuation events. Their first discontinuation was included in the primary analysis, and the second discontinuation event was analyzed separately.

2.2 | Definitions

MSE was defined as MG-ADL score 0–1 or Myasthenia Gravis Foundation of America (MGFA) class 0 (asymptomatic status) [16, 17]. Complete treatment discontinuation was defined as cessation of all MG-related therapies after achieving MSE, including AChEIs, steroid, NISITs, RTX, IVIg, and PE. Minimum washout periods were 1 year for RTX (to account for prolonged B-cell depletion) and 3 months for rapid-acting therapies (corresponding to 4–5 half-lives). MG relapse was defined as symptom recurrence with MG-ADL increase ≥ 2 points sustained for ≥ 24 h [18]. Disease trajectories were classified by comparing muscle group involvement between onset and last follow-up: improvement (reduction in affected groups), stable (unchanged distribution), or worsening (expansion to additional groups). Relapse triggers were identified through standardized patient assessment at the time of symptom recurrence. Fatigue as a relapse trigger referred to patient-reported physical or mental exhaustion preceding symptom worsening, such as prolonged overexertion or sustained sleep deprivation, which are recognized antecedent factors for MG exacerbation, and was distinguished from myasthenic fatigability as a core disease symptom [19].

2.3 | Clinical Assessments

Baseline demographic, clinical, and treatment characteristics were collected prospectively (Table 1). Follow-up assessments were conducted at 6-month intervals, with additional visits for symptom exacerbation. For relapsed patients, time to relapse, triggers, MGFA classification, and involved muscle groups were documented.

2.4 | Statistical Analysis

Statistical analyses were performed using RStudio (version 4.4.2) and GraphPad Prism (version 10.4.0). Continuous variables are reported as mean ± SD and compared using *t*-tests or ANOVA. Categorical variables are reported as percentages and compared using chi-square or Fisher's exact tests.

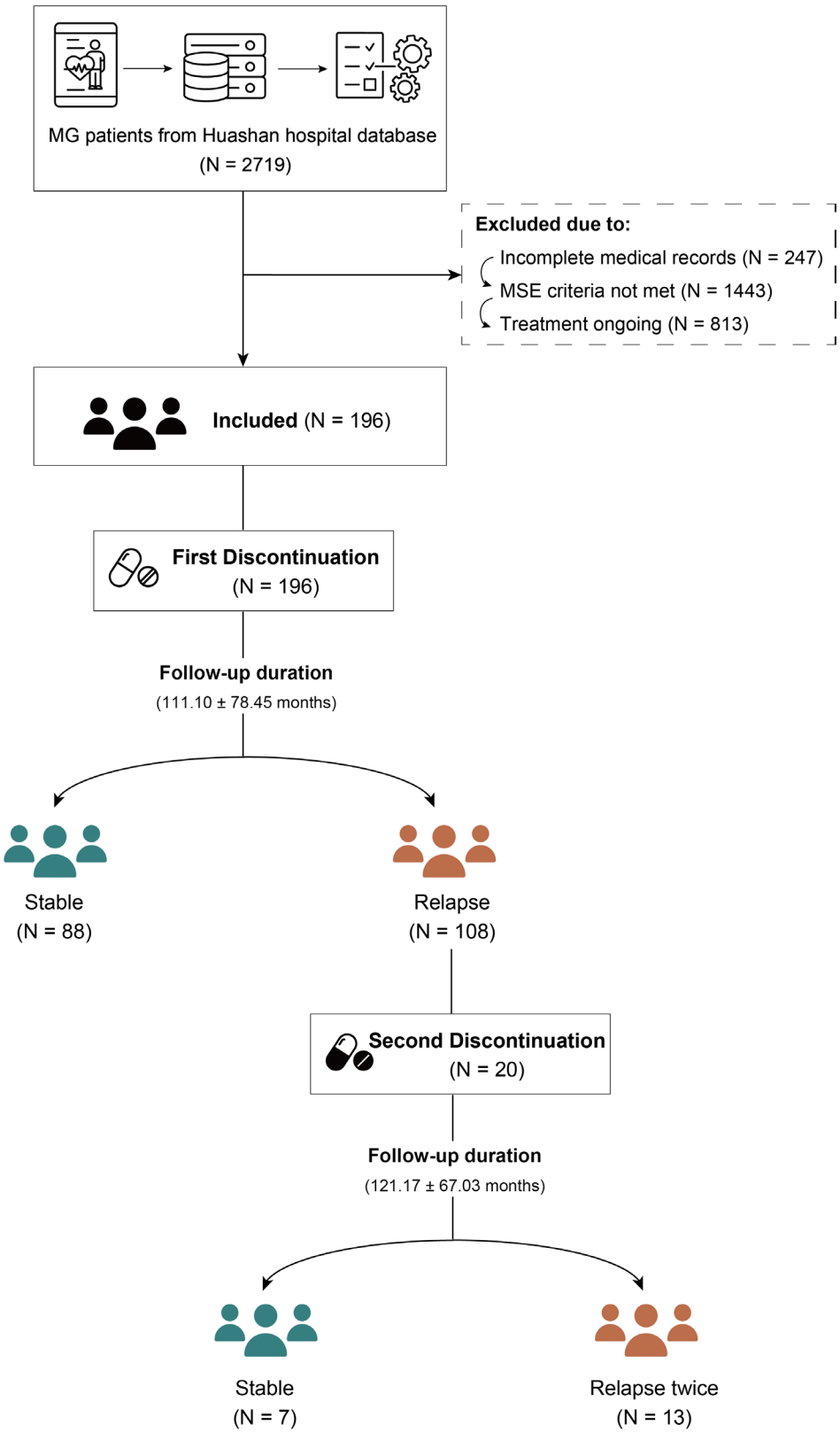

FIGURE 1 | Study flowchart. Flowchart illustrating patient selection from the Huashan MG Registry. Of 2719 patients enrolled between January 2015 and September 2025, 196 patients achieved MSE and subsequently discontinued all treatments. Among these, 20 patients experienced two discontinuation events; their second discontinuation was analyzed separately. MG, myasthenia gravis, MSE, minimal symptom expression.

TABLE 1 | Demographic features and clinical manifestations.

Variables	Total ($N=196$)	Stable ($N=88$)	Relapse ($N=108$)	p
Sex, *n* (%)				0.096
Female	99 (50.5)	53 (60.2)	46 (42.6)	
Male	97 (49.5)	35 (39.8)	62 (57.4)	
Age at onset (years), mean ± SD	38.17 ± 20.46	36.67 ± 16.91	41.88 ± 19.06	0.032
Follow-up duration (months), mean ± SD	111.10 ± 78.45	106.90 ± 69.39	111.20 ± 80.74	0.695
Antibody, *n* (%)				0.071
AChR antibody positive	136 (69.4)	55 (62.5)	81 (75.0)	
MuSK antibody positive	22 (11.2)	14 (15.9)	8 (7.4)	
MG subtype, *n* (%)				0.468
Ocular MG	64 (32.7)	22 (25.0)	42 (38.9)	
Generalized MG	132 (67.3)	66 (75.0)	66 (61.1)	
History of crisis, *n* (%)				0.380
Yes	12 (6.1)	7 (8.0)	5 (4.6)	
None	184 (93.9)	81 (92.0)	103 (95.4)	
Thymoma, *n* (%)				0.230
Yes	44 (22.4)	16 (18.2)	28 (25.9)	
None	152 (77.6)	72 (81.8)	80 (74.1)	
Thymectomy, *n* (%)				0.602
Yes	56 (28.6)	23 (26.1)	33 (30.6)	
None	140 (71.4)	65 (73.9)	75 (69.4)	
Comorbid AIDs, *n* (%)				0.884
Yes	23 (11.7)	10 (11.4)	13 (12.0)	
None	173 (88.3)	78 (88.6)	95 (88.0)	
Time from onset to MSE (months), mean ± SD	37.48 ± 54.50	44.57 ± 62.80	31.86 ± 46.44	0.111
Time from MSE to discontinuation (months), mean ± SD	16.16 ± 19.71	20.18 ± 18.45	12.88 ± 20.18	0.009
Time from therapy initiation to discontinuation (months), mean ± SD	41.98 ± 41.95	51.78 ± 50.65	34.38 ± 31.92	0.004
Time from AChEI initiation to discontinuation (months), mean ± SD	32.28 ± 32.22	35.31 ± 37.89	29.94 ± 27.04	0.273
Time from immunotherapy initiation to discontinuation (months), mean ± SD	43.00 ± 43.29	50.52 ± 51.21	36.07 ± 33.23	0.029
Reason for discontinuation, *n* (%)				0.213
Patient preference	34 (17.3)	11 (12.5)	23 (21.3)	
Physician recommendation	139 (70.9)	67 (76.1)	72 (66.7)	
Side effects	15 (10.8)	8 (9.1)	7 (6.5)	
Other reasons	8 (5.8)	2 (2.3)	6 (5.6)	
Previous regular treatment regimen, *n* (%)				< 0.001
AChEI only	13 (6.6)	1 (1.1)	12 (11.1)	

(Continues)

TABLE 1 | (Continued)

Variables	Total ($N=196$)	Stable ($N=88$)	Relapse ($N=108$)	p
Oral steroids ± AChEI	113 (57.7)	47 (53.4)	66 (61.1)	
NISITs ± Steroids ± AChEI	37 (18.9)	15 (17.0)	22 (20.4)	
RTX-based therapy	33 (16.8)	25 (28.4)	8 (7.4)	
Maximum steroid dose (mg/day), mean ± SD	33.46 ± 9.99	32.47 ± 9.26	42.31 ± 15.12	< 0.001
Types of NISITs, *n* (%)				0.640
AZA	26 (13.3)	14 (15.9)	12 (11.1)	
TAC	26 (13.3)	16 (18.2)	10 (9.3)	
MMF	5 (2.6)	2 (2.3)	3 (2.8)	

Abbreviations: AChEI, acetylcholinesterase inhibitor; AChR, acetylcholine receptor; AIDs, autoimmune diseases; AZA, azathioprine; MG, myasthenia gravis; MMF, mycophenolate mofetil; MSE, minimal symptom expression; MuSK, muscle-specific kinase; NSISTs, nonsteroidal immunosuppressants; RTX, rituximab; TAC, tacrolimus.

Changes in MGFA classification were analyzed using the Wilcoxon signed-rank test.

Relapse-free survival was estimated using Kaplan–Meier curves and compared by log-rank test. For continuous variables (treatment duration and time from MSE to discontinuation), optimal cut-off values were determined using the minimum p-value approach. Univariate Cox proportional hazards regression was performed to identify potential prognostic factors. Five variables with $p < 0.05$ in univariate analysis (age at onset, sex, RTX administration, treatment duration, and time from MSE to discontinuation) were entered into multivariate analysis. Given the correlation between treatment duration and time from MSE to discontinuation, variance inflation factors (VIF) were calculated to assess multicollinearity, and the VIF values below 5 were considered acceptable. Statistical significance was defined as two-sided $p < 0.05$.

2.5 | Ethics

This study was approved by the Ethics Committees of Huashan Hospital, Fudan University (2019-441, 2020-999 and 2022-913) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

3 | Results

3.1 | Demographic Features and Clinical Manifestations

A total of 196 MG patients were included in the primary analysis based on their first treatment discontinuation event (Table 1). Mean follow-up duration was 111.10 ± 78.45 months. During follow-up, 108 patients (55.1%) experienced relapse and 88 (44.9%) remained stable. Age at disease onset was higher in the relapse group than in the stable group (41.88 ± 19.06 vs. 36.67 ± 16.91 years, $p = 0.032$). Sex distribution, antibody status, MG subtype, history of myasthenic crisis, thymoma presence, thymectomy status, and comorbid autoimmune diseases did not differ significantly between groups (all $p > 0.05$).

Treatment-related parameters differed markedly between groups. Patients who remained stable had longer time from MSE to discontinuation (20.18 ± 18.45 vs. 12.88 ± 20.18 months, $p = 0.009$), longer total treatment duration (51.78 ± 50.65 vs. 34.38 ± 31.92 months, $p = 0.004$), and longer immunotherapy duration (50.52 ± 51.21 vs. 36.07 ± 33.23 months, $p = 0.029$) compared to those who relapsed. RTX-based therapy was more prevalent in the stable group (28.4% vs. 7.4%), whereas AChEI monotherapy was more common in the relapse group (11.1% vs. 1.1%; overall $p < 0.001$). Maximum steroid dose was higher in patients who subsequently relapsed (42.31 ± 15.12 vs. 32.47 ± 9.26 mg/d, $p < 0.001$). Reasons for discontinuation did not differ between groups ($p = 0.213$).

3.2 | Temporal Patterns of Treatment Discontinuation and Relapse

In the primary cohort with a single discontinuation event, the median time from treatment initiation to complete discontinuation was 30.4 months (IQR: 17.2–52.8 months; Figure 2A). Following discontinuation, median relapse-free survival was 49.7 months (IQR: 14.2–104.5 months; Figure 2B).

Twenty patients experienced two separate treatment discontinuation events and were analyzed separately (Figure 3). All 20 patients relapsed after the first discontinuation, with a mean time to first relapse of 19.71 ± 13.67 months. Following relapse, patients resumed treatment for a mean of 13.42 ± 14.05 months before attempting a second discontinuation. Of these, 13 (65%) experienced a second relapse, with a shortened mean interval of 13.13 ± 11.92 months. Patients who did not receive immunosuppressive therapy intensification after the first relapse were more likely to experience a second relapse. Among patients receiving RTX-based therapy during either treatment course, none experienced a second relapse (0/5), whereas 13 of 15 patients (86.7%) without RTX exposure relapsed twice, although this observation is limited by the small sample size. These findings suggest that repeated treatment discontinuation without therapeutic escalation may be associated with increased disease instability and accelerated relapse.

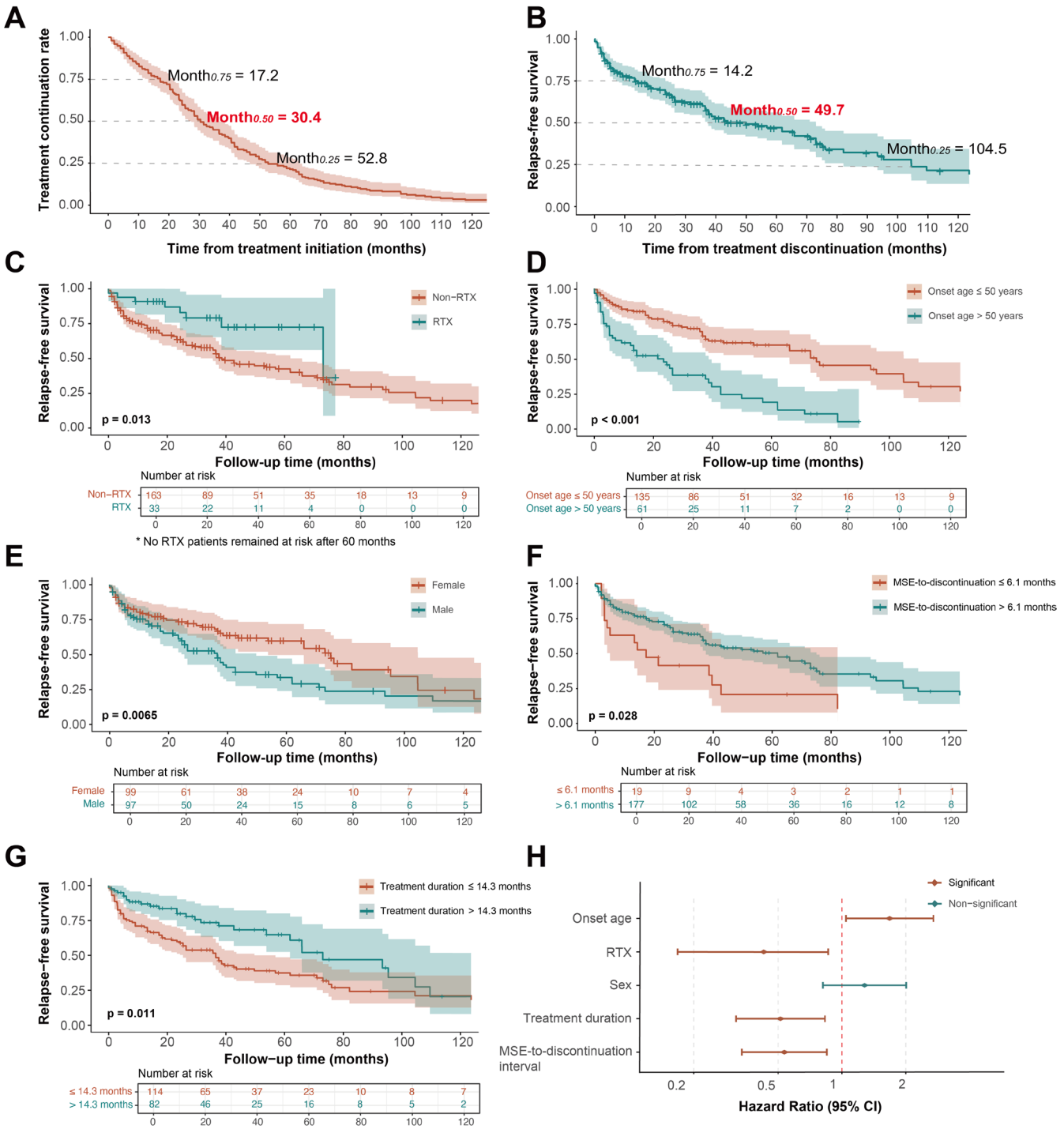

FIGURE 2 | Temporal patterns of treatment discontinuation and Kaplan–Meier survival analysis. (A) Time to discontinuation. (B) Overall relapse-free survival. Kaplan–Meier curves stratified by (C) RTX administration ($p = 0.013$), (D) MG onset age ($p < 0.001$), (E) sex ($p = 0.007$), (F) treatment duration ($p < 0.001$), (G) time from MSE to discontinuation ($p < 0.001$) (H) Forest plot summarizing multivariate Cox regression analysis. IQR, interquartile range, RTX, rituximab, MSE, minimal symptom expression, HR, hazard ratio, CI, confidence interval.

3.3 | Clinical Outcomes After Treatment Discontinuation

Cumulative muscle involvement patterns before discontinuation were associated with distinct outcomes (Figure 4A). Patients with isolated non-ocular involvement demonstrated excellent prognosis, with over 85% remaining stable. Patients with generalized involvement (ocular + limb + bulbar) showed favorable outcomes, with approximately half remaining asymptomatic. Isolated ocular involvement exhibited heterogeneous trajectories: one-third remained relapse-free, half relapsed with ocular symptoms only, and the remainder progressed to involve additional muscle groups.

MGFA classification improved significantly from onset to last follow-up (Wilcoxon signed-rank test: $Z = -6.63$, $p < 0.001$). At onset, patients were distributed across MGFA I (44.9%), II (45.4%), and III or higher (9.2%). At last follow-up, MGFA 0 became most prevalent

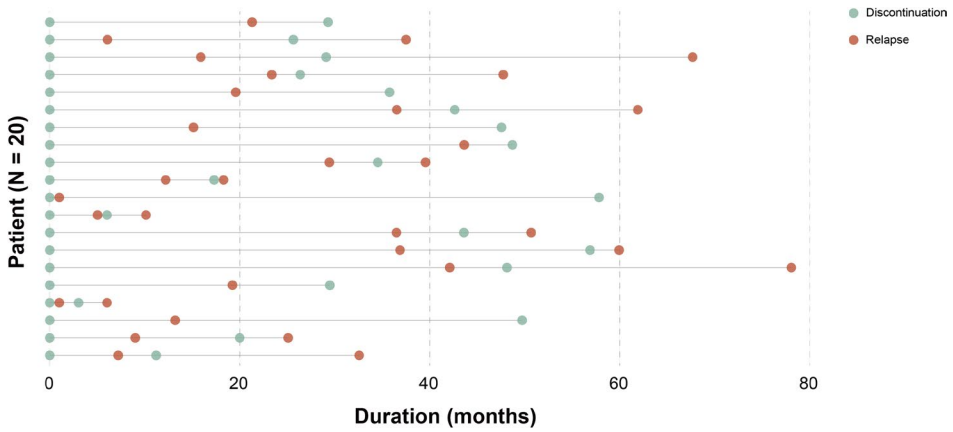

FIGURE 3 | Clinical course of patients with two treatment discontinuation events. Swimmer plot illustrating the treatment and relapse history of 20 patients who experienced two separate discontinuation events. Each horizontal bar represents one patient. RTX, rituximab, AChEI, acetylcholinesterase inhibitor, NSISTs, nonsteroidal immunosuppressants.

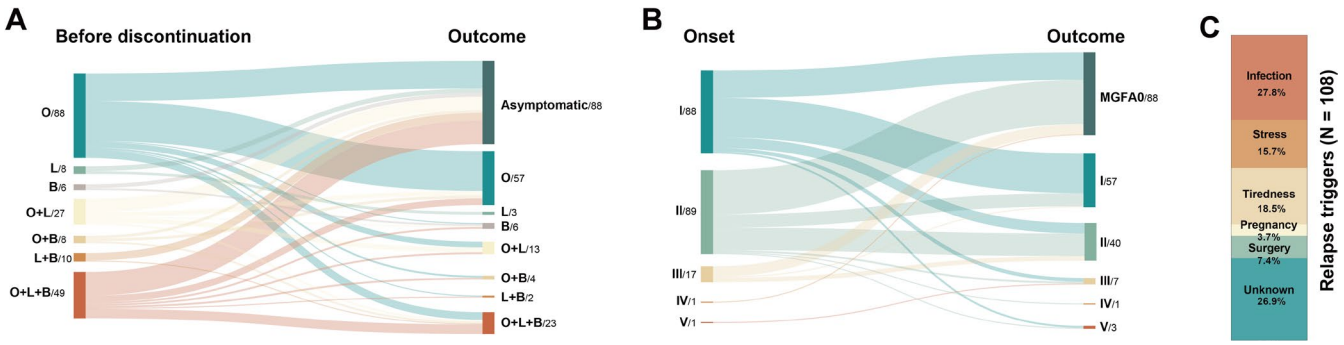

FIGURE 4 | Clinical outcomes after treatment discontinuation. (A) Sankey diagram showing the relationship between cumulative muscle involvement patterns before discontinuation and clinical outcomes. (B) Sankey diagram showing the change from onset to last follow-up based on MGFA classification. (C) Pie chart showing the distribution of relapse triggers among 108 patients who experienced relapse. MGFA, Myasthenia Gravis Foundation of America, O, ocular, L, limb, B, bulbar.

(44.9%), followed by I (29.1%), II (20.4%), and III or higher (5.6%). Individual trajectory analysis revealed improvement in 52.6%, stability in 35.7%, and worsening in 11.7% (Figure 4B).

Among 108 patients who relapsed, identifiable triggers were documented in 79 (73.1%): infection (27.8%), fatigue (18.5%), psychological stress (15.7%), surgery (7.4%), and pregnancy (3.7%). The remaining 29 patients (26.9%) experienced spontaneous relapse (Figure 4C).

3.4 | Prognostic Factors for Relapse

Kaplan–Meier analysis identified five factors associated with relapse-free survival (Table 2). Patients with onset age < 50 years had longer relapse-free survival than those ≥ 50 years (median 75.0 vs. 23.3 months, $p < 0.001$) (Figure 2D). Female patients had better outcomes than males (median 75.0 vs. 36.5 months, $p = 0.007$) (Figure 2E). RTX administration was associated with prolonged relapse-free survival (median 73.1 vs. 38.6 months, $p = 0.013$) (Figure 2C). Using optimized cut-offs, treatment duration ≥ 14.3 months (median 65.9 vs. 39.6 months, $p < 0.001$) and time from MSE to discontinuation ≥ 6.1 months (median 61.9 vs. 17.2 months, $p < 0.001$) were associated with favorable outcomes (Figure 2F,G). Disease subtype, antibody status, comorbid autoimmune diseases, thymoma, and maximum steroid dose were not significantly associated with relapse-free survival. Thymectomy status was not significantly associated with relapse-free survival, with 33 of 56 thymectomized patients experiencing relapse compared with 75 of 140 in the non-thymectomy group (58.9% vs. 53.6%, $p = 0.591$).

Univariate Cox regression confirmed these findings (Table 3). Risk factors included onset age ≥ 50 years (HR 2.49, 95% CI 1.59–3.90, $p < 0.001$) and male sex (HR 2.00, 95% CI 1.30–3.06, $p = 0.007$). Protective factors included RTX administration (HR 0.30, 95% CI 0.12–0.75, $p = 0.013$), treatment duration ≥ 14.3 months (HR 0.37, 95% CI 0.24–0.56, $p < 0.001$), and time from MSE to discontinuation ≥ 6.1 months (HR 0.33, 95% CI 0.22–0.51, $p < 0.001$).

Multivariate Cox regression identified four independent prognostic factors (Table 3). VIF values for treatment duration and time from MSE to discontinuation were 1.47 and 1.33, respectively, indicating acceptable multicollinearity. Three protective factors retained significance: RTX administration (HR 0.43, 95% CI 0.17–0.89, $p = 0.015$), treatment duration ≥ 14.3 months (HR 0.54, 95% CI 0.34–0.85, $p = 0.008$), and time from MSE

TABLE 2 | Kaplan–Meier survival analysis.

Variable	*N*	Events	Median survival (months)	95% CI	*p* (Log-rank)
Overall	196	108 (55.1)	42.67	35.53–65.90	
Sex, *n* (%)					0.007
Female	99	46 (46.5)	75.03	53.80–104.53	
Male	97	62 (63.9)	36.5	25.37–49.73	
Age at onset (years), *n* (%)					< 0.001
< 50 years	135	63 (46.7)	75	65.90–109.60	
≥ 50 years	61	45 (73.8)	23.3	12.20–38.60	
MG subtype, *n* (%)					0.279
Ocular MG	132	66 (50.0)	61.87	39.57–75.03	
Generalized MG	64	42 (65.6)	35.53	18.30–95.33	
Antibody, *n* (%)					0.249
AChR antibody positive	136	81 (59.6)	42.67	35.60–71.03	
MuSK antibody positive	22	8 (36.4)	148.13	38.50-NR	
Seronegative	38	19 (50.0)	65.9	29.43-NR	
Comorbid AIDs, *n* (%)					0.409
None	173	95	76.07	37.50–71.00	
Yes	23	13	93.4	24.40–NR	
Thymoma, *n* (%)					0.527
None	154	80 (51.9)	49.73	37.53–76.07	
Yes	42	28 (66.7)	42.67	17.20–95.33	
RTX administation, *n* (%)					0.013
None	163	100 (61.3)	38.57	35.53–65.90	
Yes	33	8 (24.2)	73.07	73.07–NR	
Time from MSE to discontinuation (months), *n* (%)					< 0.001
< 6.1 months	19	16 (84.2)	17.23	5.03–NR	
≥ 6.1 months	177	92 (52.0)	61.87	37.53–75.03	
Maximum steroid dose (mg/day), *n* (%)					0.413
> 30	47	32 (68.1)	37.53	26.40–75.03	
≤ 30	149	76 (51.0)	53.8	38.50–93.37	
Time from therapy initiation to discontinuation (months), *n* (%)					< 0.001
< 14.3 months	117	80 (68.4)	39.57	26.40–71.03	
≥ 14.3 months	79	28 (35.4)	65.93	37.53–104.53	

Abbreviations: AChR, acetylcholine receptor; AIDs, autoimmune diseases; CI, confidence interval; MG, myasthenia gravis; MSE, minimal symptom expression; MuSK, muscle-specific kinase; NR, not reached; RTX, rituximab.

to discontinuation ≥ 6.1 months (HR 0.51, 95% CI 0.32–0.83, $p = 0.007$). Onset age ≥ 50 years remained an independent risk factor (HR 1.68, 95% CI 1.04–2.70, $p = 0.032$) (Figure 2H). Male sex did not retain significance after adjustment (HR 1.28, 95% CI 0.81–2.01, $p = 0.291$).

4 | Discussion

Determining the optimal timing for treatment discontinuation in MG remains a clinical dilemma, with no established predictors to guide decision-making. In this study, we observed a

TABLE 3 | Cox regression analysis for relapse.

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age at onset (≥ 50 vs. < 50 years)	2.489 (1.589–3.902)	< 0.001	1.677 (1.044–2.695)	0.032
MG subtype (oMG vs. gMG)	1.117 (0.719–1.736)	0.623	—	—
Antibody type		0.400		
MuSK vs. AChR	0.587 (0.283–1.217)	0.159	—	—
Seronegative vs. AChR	0.902 (0.531–1.536)	0.705	—	—
Comorbid AIDs	0.954 (0.532–1.712)	0.875	—	—
Confirmed thymoma	0.791 (0.471–1.328)	0.375	—	—
RTX administration	0.304 (0.123–0.754)	0.013	0.428 (0.168–0.891)	0.015
Sex (Male vs. Female)	1.996 (1.304–3.057)	0.007	1.277 (0.812–2.008)	0.291
Time from MSE to discontinuation (≥ 6.1 vs. < 6.1 months)	0.331 (0.215–0.510)	< 0.001	0.513 (0.317–0.831)	0.007
Treatment duration (≥ 14.3 vs. < 14.3 months)	0.369 (0.243–0.558)	< 0.001	0.535 (0.337–0.849)	0.008
Maximum oral steroid dose (≤ 30 mg vs. > 30 mg)	1.330 (0.801–2.208)	0.271	—	—

Abbreviations: AChR, acetylcholine receptor; AIDs, autoimmune diseases; CI, confidence interval; MG, myasthenia gravis; MSE, minimal symptom expression; MuSK, muscle-specific kinase; NR, not reached; oMG, ocular myasthenia gravis; RTX, rituximab.

55.1% relapse rate following complete treatment discontinuation after achieving MSE and identified four independent prognostic factors: onset age ≥ 50 years as a risk factor (HR 1.68), and RTX administration (HR 0.43), treatment duration ≥ 14.3 months (HR 0.54), and time from MSE to discontinuation ≥ 6.1 months (HR 0.51) as protective factors. Multiple discontinuation attempts were associated with increased relapse risk and shortened relapse-free intervals. Common relapse triggers included infection, fatigue, and psychological stress, with most relapses presenting as mild disease predominantly affecting extraocular muscles.

Our study addresses a critical evidence gap in MG management. While previous studies have examined CSR achievement and relapse during medication tapering, prospective evaluation of outcomes following complete treatment discontinuation is lacking. Su et al. reported relapse rates of 29.6% during steroid tapering and 35.3% after steroid withdrawal in patients on steroid monotherapy [13]. Bi et al. observed that 48.6% of patients relapsed during tacrolimus dose reduction, with only 7.8% ultimately achieving CSR [9]. The only available estimate of post-CSR relapse comes from a retrospective azathioprine study, which reported a 33% relapse rate [20]. To our knowledge, the present study represents the first prospective cohort specifically designed to evaluate relapse following complete discontinuation of all MG-related treatments. The 55.1% relapse rate provides the first systematic estimate of this risk derived from a homogeneous population defined by standardized entry criteria, with the higher rate likely reflecting the more stringent endpoint of complete treatment discontinuation rather than dose reduction.

The identification of MG onset age ≥ 50 years as an independent risk factor aligns with the distinct immunopathology of late-onset MG (LOMG). Previous cross-sectional studies demonstrated that elderly MG patients had worse clinical outcomes, with higher disease-related mortality and greater emergency care requirements compared to early-onset MG [21–23]. Several mechanisms may underlie this vulnerability. Immunosenescence in older patients is characterized by accumulated inflammatory markers, declining naive T and B cell production, a shift toward memory immune populations, and impaired regulatory T cell function [24]. The absence of thymic hyperplasia in LOMG further suggests that autoantibodies may originate from alternative sites, such as bone marrow long-lived plasma cells or extrathymic germinal centers, which are more resistant to conventional immunosuppression and prone to reactivation after treatment discontinuation [25]. LOMG patients also exhibit increased CD11c + atypical B cells and altered memory B cell dynamics that may predispose to disease recurrence [26]. These findings carry direct clinical implications: discontinuation decisions in patients with onset age ≥ 50 years warrant particular caution, and longer consolidation periods or alternative treatment strategies may be necessary.

Notably, thymectomy did not significantly influence post-discontinuation relapse risk, consistent with the lack of association observed for thymoma status. As all thymectomies were performed well before treatment discontinuation, their therapeutic benefits had likely already been realized in facilitating MSE achievement rather than conferring additional protection after treatment cessation. Additionally, the autoimmune process in MG may become thymus-independent over time, with autoreactive B cells and long-lived plasma cells maintaining disease activity in peripheral niches, rendering thymectomy status less relevant for post-discontinuation outcomes [25].

RTX administration emerged as the strongest protective factor against post-discontinuation relapse (HR 0.43), extending prior observations that RTX may uniquely facilitate sustained treatment-free remission [27, 28]. The mechanistic basis relates to autoantibody class and production site. In MuSK-positive MG, pathogenic IgG4 antibodies are produced predominantly

by short-lived plasmablasts derived from CD20+ B cells, rendering them highly RTX-sensitive [29, 30]. In AChR-positive disease, RTX-mediated depletion of memory B cells may interrupt the replenishment of autoreactive plasma cell populations. The RINOMAX trial demonstrated that low-dose RTX was associated with greater probability of achieving minimal manifestations and reduced need for rescue medications compared with placebo, suggesting a potential disease-resetting effect [27]. In our cohort, RTX-treated patients demonstrated significantly longer relapse-free survival compared with those not receiving RTX (median 73.1 vs. 38.6 months, $p = 0.013$), and RTX-based therapy was more prevalent in the stable group than in the relapse group (28.4% vs. 7.4%). Although our cohort included predominantly AChR-positive patients (69.4%) and the number of MuSK-positive patients receiving RTX was limited, the protective effect remained significant in multivariate analysis adjusting for other prognostic factors. However, the durability of this protection warrants consideration. Fichtner et al. showed that pathogenic MuSK-specific B cell clones can survive B-cell depletion and reemerge months before clinical relapse, representing a reservoir that may eventually drive recurrence [31]. Our findings support the protective effect of prior RTX treatment but do not preclude eventual relapse, underscoring the need for continued surveillance even in patients with favorable prognostic profiles.

Both total treatment duration (≥14.3 months) and time from MSE achievement to discontinuation (≥6.1 months) independently predicted favorable outcomes. Interestingly, both variables retained significance in multivariate analysis despite their correlation (VIF 1.42 and 1.38, respectively), suggesting that they capture distinct aspects of treatment adequacy. Total treatment duration reflects cumulative immunosuppressive exposure from diagnosis, which may be necessary to exhaust long-lived plasma cells in bone marrow niches that persist for years and are resistant to conventional B-cell depletion [32]. The post-MSE consolidation period, by contrast, specifically measures the duration of continued treatment after achieving clinical remission. Extended treatment after achieving clinical remission may also restore regulatory T and B cell function, clear autoreactive memory B cell clones, and suppress germinal center activity that generates new autoantibodies through class switching and affinity maturation [33–35]. The independent prognostic value of post-MSE treatment duration supports the concept of a "consolidation window", a period following clinical remission during which continued treatment is essential for durable disease control. In our cohort, patients who remained stable had a mean post-MSE treatment duration of approximately 20 months, substantially longer than the 6.1 month minimum threshold identified in survival analysis. Experience from other autoimmune diseases corroborates this concept. In lupus nephritis, maintaining remission for 3–4 years before immunosuppressant discontinuation significantly reduced flare risk, and in rheumatoid arthritis, drug-free remission rates declined progressively from 94% at 12 months to 46% at 48 months [36–38]. Based on these findings, clinicians may consider maintaining treatment for at least 2 years after achieving MSE before attempting complete discontinuation, particularly in patients with additional risk factors such as late-onset disease. Premature discontinuation, even in patients meeting MSE criteria, may undermine long-term stability.

Analysis of patients with repeated discontinuation events ($n = 20$) revealed a concerning pattern of disease instability. All patients relapsed after the first discontinuation, and 65% experienced a second relapse with a markedly shortened interval (13.13 ± 11.92 vs. 19.71 ± 13.67 months). Patients who did not receive intensified immunosuppressive therapy after the first relapse were more likely to experience recurrence, whereas none receiving RTX-based therapy relapsed twice, although this observation is limited by the small sample size ($n = 5$). These findings suggest that repeated treatment discontinuation without therapeutic escalation may identify a subset of patients with heightened disease activity. The 2023 German MG guideline introduced the concept of highly active MG, defined as MGFA status ≥ IIb and/or at least two recurrent severe exacerbations requiring therapeutic intervention [39]. Although this subgroup was small, the pattern of progressively shorter relapse-free intervals aligns with this concept and supports caution against multiple discontinuation attempts in patients with recurrent disease activity.

Our findings support several clinical recommendations. Discontinuation decisions should be individualized based on identified prognostic factors, with particular caution in patients with onset age ≥ 50 years who face elevated relapse risk and may benefit from extended treatment duration or alternative strategies. As discussed above, an adequate consolidation window of at least 2 years following MSE achievement should be incorporated into treatment protocols, and brief treatment courses followed by early discontinuation are inadvisable. Prior RTX treatment confers independent protection, supporting its consideration in patients for whom treatment-free remission is a therapeutic goal. These recommendations align with emerging evidence that treatment duration and modality, not merely achieving clinical remission, influence long-term disease stability. Prospective validation of individualized prediction tools to guide discontinuation timing is warranted.

Several limitations warrant consideration: (1) The single-center design may limit generalizability to other populations and practice settings. (2) Immunological parameters, including longitudinal AChR and MuSK autoantibody titers, lymphocyte subsets, complement, and cytokine profiles, were not systematically monitored, precluding analysis of potential biomarkers for relapse prediction. Integrating serial autoantibody monitoring and comprehensive immunological monitoring represents an important future direction. (3) The optimal cut-off values for treatment duration (14.3 months) and post-MSE consolidation period (6.1 months) were derived from our cohort using the minimum p-value approach, which may be subject to overfitting. We identified prognostic factors but did not construct a validated prediction model with discrimination and calibration assessment, and the external validation in independent cohorts would be necessary before these specific thresholds can be recommended for clinical use. (4) The observational design cannot establish causality. The protective effect of RTX may reflect both direct immunological effects and selection bias toward patients with more favorable disease biology or those who responded well to initial treatment. (5) Detailed thymic pathology following thymectomy was not analyzed, which may influence outcomes independently of thymectomy status alone. (6) Different NSISTs may have distinct pharmacokinetic and immunological profiles affecting post-discontinuation dynamics. The sample size was insufficient for subgroup analyses comparing relapse patterns across specific NSISTs.

5 | Conclusions

In this prospective cohort, complete treatment discontinuation after achieving MSE in MG was associated with a 55.1% relapse rate over long-term follow-up. Onset age ≥ 50 years was associated with increased relapse risk, while prior RTX treatment, total treatment duration ≥ 14.3 months, and time from MSE to discontinuation ≥ 6.1 months appeared protective. These findings offer preliminary evidence to inform treatment discontinuation decisions in MG and suggest that individualized approaches incorporating age, treatment history, and adequate consolidation periods may optimize outcomes. Validation in multicenter prospective cohorts and integration of immunological biomarkers are warranted to refine risk stratification for treatment discontinuation in MG.

Author Contributions

Dingxian He: writing – original draft, formal analysis, investigation, and data curation. **Chong Yan:** writing – original draft, formal analysis, and investigation. **Baitong Wang, Yanlei Yang, Shengying Gu**, and **Jianying Xi:** writing – review and editing, methodology, and investigation. **Sushan Luo:** conceptualization, investigation, funding acquisition, and writing – review and editing. **Chongbo Zhao:** conceptualization, investigation, funding acquisition, supervision, resources, project administration, and writing – review and editing.

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Ethics Statement

All procedures with human participants involvement were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study protocol was approved by the Huashan Hospital Ethics Committee (2019-441, 2020-999 and 2022-913). All participants provided informed consent prior to their inclusion in the study.

Consent

Consent for publication was obtained from all participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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