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Childhood-Onset Myasthenia Gravis Patients Benefited from Thymectomy in a Long-Term Follow-up Observation

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Abstract

Introduction The effect of thymectomy on the treatment of childhood-onset myasthenia gravis (CMG) remains debatable. The objective of this study was to evaluate the clinical outcome and relevant prognostic factors of thymectomy for CMG patients.

Materials and Methods A total of 32 CMG patients who underwent thymectomy before 18 years of age were included in this retrospective study. Clinical state following thymectomy was assessed by quantified myasthenia gravis (QMG) scores, myasthenia gravis–related activities of daily living (MG-ADL) scores, and Myasthenia Gravis Foundation of America postintervention status. Repeated-measures analysis of variance (ANOVA) examined the changes in postoperative scores during the 5-year follow-up. Univariate logistic regression was applied to identify factors associated with short-term (1-year postoperation) and long-term (5-year postoperation) clinical outcomes.

Results Repeated-measures ANOVA showed that QMG scores ($F = 6.737$, $p < 0.001$) and MG-ADL scores ($F = 7.923$, $p < 0.001$) decreased gradually with time. Preoperative duration (odds ratio [OR] = 0.85, 95% confidence interval [CI]: 0.73–1.00, $p = 0.043$), gender (OR = 0.19, 95% CI: 0.04–0.94, $p = 0.041$), and MG subgroup (OR = 13.33, 95% CI: 1.43–123.99, $p = 0.023$) were predictors for 1-year postoperative prognosis. Shorter disease duration (OR = 0.82, 95% CI: 0.70–0.97, $p = 0.018$) and generalized CMG (OR = 6.11, 95% CI: 1.06–35.35, $p = 0.043$) were found to have more favorable long-term results.

Conclusion Our results suggest that thymectomy is effective in treating CMG. Thymectomy could be recommended for CMG patients, especially for patients in the early course of GMG.

Keywords
- childhood-onset myasthenia gravis
- thymectomy
- prognosis

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Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by antibodies against postsynaptic membrane proteins at the neuromuscular junction.[1] Childhood-onset myasthenia gravis (CMG), with MG signs and symptoms before 14 years of age, accounts for more than 50% of all MG patients in Asians.[2] CMG cases present with higher frequency of ocular symptoms such as ptosis and ophthalmoplegia, and often show a benign course of disease.[3] The treatment modalities for CMG largely stem from adult regimens, but differences about the option for thymectomy exist between adult-onset myasthenia gravis (AMG) and CMG patients.[4]

Thymic abnormalities could be the initial step to trigger the production of circulating antibodies and the impairment of neuromuscular transmission in MG.[5] In CMG, thymomas can be detected in 10 to 15% of patients and thymic hyperplasia in 75 to 85% of patients.[3] Multiple studies have confirmed a beneficial response to thymectomy in AMG patients with high remission rates.[6,7] However, thymectomy during early childhood might increase future risk of autoimmunity or infection.[8]

Although data regarding the efficacy on children are limited, thymectomy is a choice of treatments for refractory CMG.[9] In the present study, we have retrospectively analyzed the short-term and long-term postoperative follow-up data to clarify the efficacy and predictors of thymectomy in CMG.

Materials and Methods

Study Subjects

This is an observational retrospective study. Among 267 consecutive CMG patients admitted to the Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology from July 2003 to March 2020, 32 patients who underwent thymectomy were included in this study. Ethical approval was permitted by Tongji Hospital Ethics Committee and all patients provided written informed consent before enrollment.

The inclusion criteria were (1) MG diagnosis (fluctuating muscle weakness with one or more of the following criteria: [a] positive AChR-ab assay; [b] the presence of a 10% or greater decrement following repetitive nerve stimulation; and [c] positive response to pyridostigmine treatment), (2) onset age younger than 14 years, (3) underwent thymectomy before 18 years of age, and (4) at least 5 years of follow-up after operation.

Patients with CMG have accepted thymectomy because medical therapy did not improve the systemic/bulbar/ocular symptoms or neoplasm of thymus detected by chest computed tomography/magnetic resonance imaging.

Classification Standards and Clinical Responses

Myasthenia Gravis Foundation of America (MGFA) clinical classification[10] was used to evaluate the severity of the disease: class I (ocular MG [OMG]); classes II to IV (generalized MG [GMG]). Quantified MG (QMG) scores[10] and MG-related activities of daily living (MG-ADL) scores[11] were collected annually. Relapse of MG was defined as recurrent or clinical signs and symptoms necessitating reintroduction of acetylcholinesterase inhibitors.[12]

The prognosis of the thymectomy for MG was defined according to MGFA Postintervention Status[13] as: complete stable remission, pharmacological remission, minor manifestation, improvement, unchanged, worse, exacerbation, and death. Good outcome was defined as improvement or better status as previously described.[14]

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range (25–75%); categorical variables were expressed as numbers and percentages (%). We reported outcome measures according to the length of follow up: short-term (1-year postoperation) and long-term (5-year postoperation). Binary logistic regression was applied to determine the independent predictors for improvement or better status. Repeated-measures data were statistically analyzed using repeated-measures analysis of variance (ANOVA). All statistical analyses were performed with IBM SPSS 24.0 and GraphPad Prism 8.01. The p-values less than 0.05 for two-sided tests were considered statistically significant.

Results

Clinical Data of All Cases

There were 17 females (53.13%) and 15 males (46.87%), with a mean age at operation of 13.77 $\pm$ 3.35 years included in this study. The median time of preoperative duration was 5.80 (1.88–12.13) years. Nine patients (28.13%) experienced relapse and their median time to the first relapse was 2.80 (1.33–3.50) years after the operation. The detailed information on each patient is listed in ►Table 1.

Efficacy of Thymectomy at Appointed Time Points

Proportions of improvement or better status after thymectomy were 65.63% in 1 year, 53.12% in 3 years, and 62.50% in 5 years (►Fig. 1A). Repeated-measures ANOVA showed that QMG scores ($F = 6.737$, $p < 0.001$) and MG-ADL scores ($F = 7.923$, $p < 0.001$) decreased gradually over time (►Fig. 1B).

At different time points, the short duration subgroup (< 6 years) showed more significant decreases in QMG scores ($F = 2.885$, $p = 0.033$; ►Fig. 2A) and MG-ADL scores ($F = 3.638$, $p = 0.013$; ►Fig. 2D) than the long duration subgroup (≥ 6 years).

Analyses of repeated measures also showed QMG scores ($F = 17.343$, $p < 0.001$; ►Fig. 2C) and MG-ADL scores ($F = 13.283$, $p < 0.001$; ►Fig. 2F) decreased significantly in the GMG subgroup compared with the OMG subgroup.

Short-Term and Long-Term Effects of Thymectomy in CMG

Effects of related variables on short-term and long-term outcomes are shown in ►Table 2. Univariate analysis showed that preoperative duration (odds ratio [OR] = 0.85, 95% confidence interval [CI]: 0.73–1.00, $p = 0.043$), sex (males vs. females, OR = 0.19, 95% CI: 0.04–0.94, $p = 0.041$), and MG

Table 1 Key clinical data from 32 patients with childhood-onset myasthenia gravis undergoing thymectomy

S. no.	Sex	Age at onset, y	Preoperative duration, y	Preoperative MGFA classification	AChR-Ab	Thymus histology	Surgical approach	Postoperative treatment	Time to relapse, y	Outcome	
										1-y postoperation	5-y postoperation
1	M	5.00	4.00	I	−	Hyperplasia	Open	Pyri + Pred	N	Unchanged	Unchanged
2	M	3.00	13.00	I	+	Hyperplasia	Open	Pyri + Pred + TAC	N	Unchanged	Unchanged
3	F	7.00	7.00	I	+	Thymolipoma	Open	Pyri + Pred + TAC	N	Unchanged	Improvement
4	F	2.00	5.00	IIa	+	Hyperplasia	VATS	Pyri + Pred	N	Improvement	Improvement
5	F	2.00	15.75	I	−	Hyperplasia	VATS	Pyri + Pred + TAC	N	Unchanged	Unchanged
6	M	8.42	1.00	IIb	+	Hyperplasia	Open	Pyri + Pred + TAC	0.50	Improvement	Unchanged
7	F	12.00	0.25	I	+	Hyperplasia	Open	Pyri	4.00	MM	MM
8	M	2.20	15.13	I	+	Normal	VATS	Pyri + Pred + TAC	N	Unchanged	Unchanged
9	M	11.00	6.80	I	−	Hyperplasia	Open	Pyri	N	MM	MM
10	F	14.00	3.84	I	−	Hyperplasia	VATS	Pyri + Pred	N	Unchanged	Unchanged
11	F	2.00	5.70	IIIb	+	Hyperplasia	VATS	Pyri + Pred + TAC	N	Improvement	MM
12	M	7.00	5.00	I	−	Hyperplasia	Open	Pyri	3.00	Unchanged	Unchanged
13	M	1.60	12.30	I	+	Hyperplasia	VATS	Pyri + Pred + TAC	N	Unchanged	Unchanged
14	F	2.50	8.90	IIa	+	Hyperplasia	Open	Pyri + Pred + TAC	2.70	Improvement	MM
15	F	13.00	0.17	IIa	−	B1 thymoma	Open	Pyri + Pred	N	MM	MM
16	F	2.70	11.00	IIIa	+	B2 thymoma	Open	Pyri + TAC	5.00	Improvement	Exacerbation
17	F	6.00	8.00	I	+	Hyperplasia	Open	Pyri + Pred	N	MM	CSR
18	F	6.00	11.60	I	+	Hyperplasia	VATS	Pred	2.80/5.00	CSR	Exacerbation
19	M	13.00	1.20	IIa	+	Thymolipoma	VATS	Pyri + Pred	N	MM	MM
20	F	2.18	14.00	I	+	Hyperplasia	VATS	Pyri + Pred + AZA	3.00	MM	MM
21	M	2.00	15.90	IIIb	−	Hyperplasia	VATS	Pyri + Pred + TAC	N	Unchanged	Improvement
22	M	11.00	0.25	I	+	Hyperplasia	Open	Pyri + Pred	N	MM	MM
23	F	6.00	11.50	I	+	B1 thymoma	Open	Pyri + Pred + TAC	N	MM	MM
24	F	10.50	3.00	IIa	+	Hyperplasia	VATS	Pyri + Pred + TAC	N	Improvement	MM
25	M	1.50	16.00	I	+	A thymoma	Open	Pyri + Pred	N	Unchanged	Unchanged
26	M	3.25	5.90	IIIa	+	Hyperplasia	Open	Pyri + Pred + TAC	N	Improvement	MM
27	F	13.50	0.75	IIb	+	Normal	Open	Pyri + Pred + TAC	1.75	MM	MM
28	M	11.15	1.50	IIb	−	Hyperplasia	Open	Pyri + Pred + MMF	N	MM	MM

(*Continued*)

Table 1 (*Continued*)

S. no.	Sex	Age at onset, y	Preoperative duration, y	Preoperative MGFA classification	AChR-Ab	Thymus histology	Surgical approach	Postoperative treatment	Time to relapse, y	Outcome	
										1-y postoperation	5-y postoperation
29	M	7.00	1.00	I	+	Hyperplasia	Open	Pyri	0.90	Unchanged	MM
30	F	3.00	14.00	I	+	Hyperplasia	VATS	Pyri + Pred + TAC	N	Improvement	Unchanged
31	F	12.33	4.07	I	+	Thymolipoma	Open	Pyri + Pred	N	Improvement	Improvement
32	M	8.00	5.30	IIIb	–	Hyperplasia	Open	Pyri + Pred	N	Improvement	MM

Abbreviations: AChR-Ab, acetylcholine receptor antibody; AZA, azathioprine; CSR, complete stable remission; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; MMF, mycophenolate mofetil; MTX, methotrexate; N, none; Pred, prednisone; Pyri, pyridostigmine; TAC, tacrolimus; VATS, video-assisted thoracoscopic surgery.

subgroup (GMG vs. OMG, OR = 13.33, 95% CI: 1.43–123.99, $p = 0.023$) were factors affecting the short-term results. Shorter disease duration (OR = 0.82, 95% CI: 0.70–0.97, $p = 0.018$) and GMG subgroup (OR = 6.11, 95% CI: 1.06–35.35, $p = 0.043$) were predictors associated with 5-year improvement or better status after thymectomy.

Discussion

Thymectomy has been generally accepted as an important option for treating AMG,[15,16] but the efficacy remains unclear in the sequence of treatments for CMG.[17] Here, our case series have suggested that thymectomy was effective for CMG patients and evaluated the factors affecting the short-term and long-term outcomes.

Thymectomy provided excellent clinical improvement for MG patients and this effect increased over time.[18] In our study, QMG scores and MG-ADL scores markedly decreased over time, indicating that various symptoms of CMG patients were relieved after the operation. The disease status in MG patients can remain unstable last from months to years after thymectomy.[19,20] Our results showed that about one-quarter of participants had a relapse within 5 years, which is consistent with the previous study.[21] Therefore, long-term follow-up is required as there is a likelihood of relapse.

Furthermore, there is insufficient evidence to determine the optimum timing for thymectomy in children.[22] Our data showed that a long preoperative duration in patients with CMG was related to the poor prognosis of thymectomy, so early surgical treatment is recommended. The association between the long duration and the poor prognosis is probably due to the prolonged and cumulative damage at the neuromuscular plate.[23,24] Some studies reported females with MG benefit more from the thymectomy,[25,26] whereas others found no significant sex difference.[27,28] This present study indicated the short-term benefits rather than the long-term benefits of thymectomy in the female gender. Further study on understanding the relationship between sex and the effect of thymectomy on CMG is required.

Thoracotomy is a traditionally surgical approach for MG patients as thoracoscopy has been widely performed.[29] Kim et al concluded that thoracoscopic thymectomy is an effective treatment choice for juvenile MG and can be safely applied to children as young as 20 months of age.[30] The minimally invasive approach is not superior to open thymectomy in disease control because thoracoscopy may be insufficient to remove all thymic tissue.[31] Based on the results of our research, both thoracoscopy and thoracotomy had similar short-term and long-term prognoses for CMG patients.

This study demonstrated that thymectomy had a positive effect on short-term and long-term neurologic outcomes in generalized CMG. It was found that thymectomy is an effective therapy for children with systemic symptoms.[32,33] Some experts suggested that thymectomy can improve the remission rate of ocular CMG, while others took the opposite attitude.[34] The results in our research showed that thymectomy is more effective in generalized CMG patients and it is still an option for ocular patients with the decreases in their

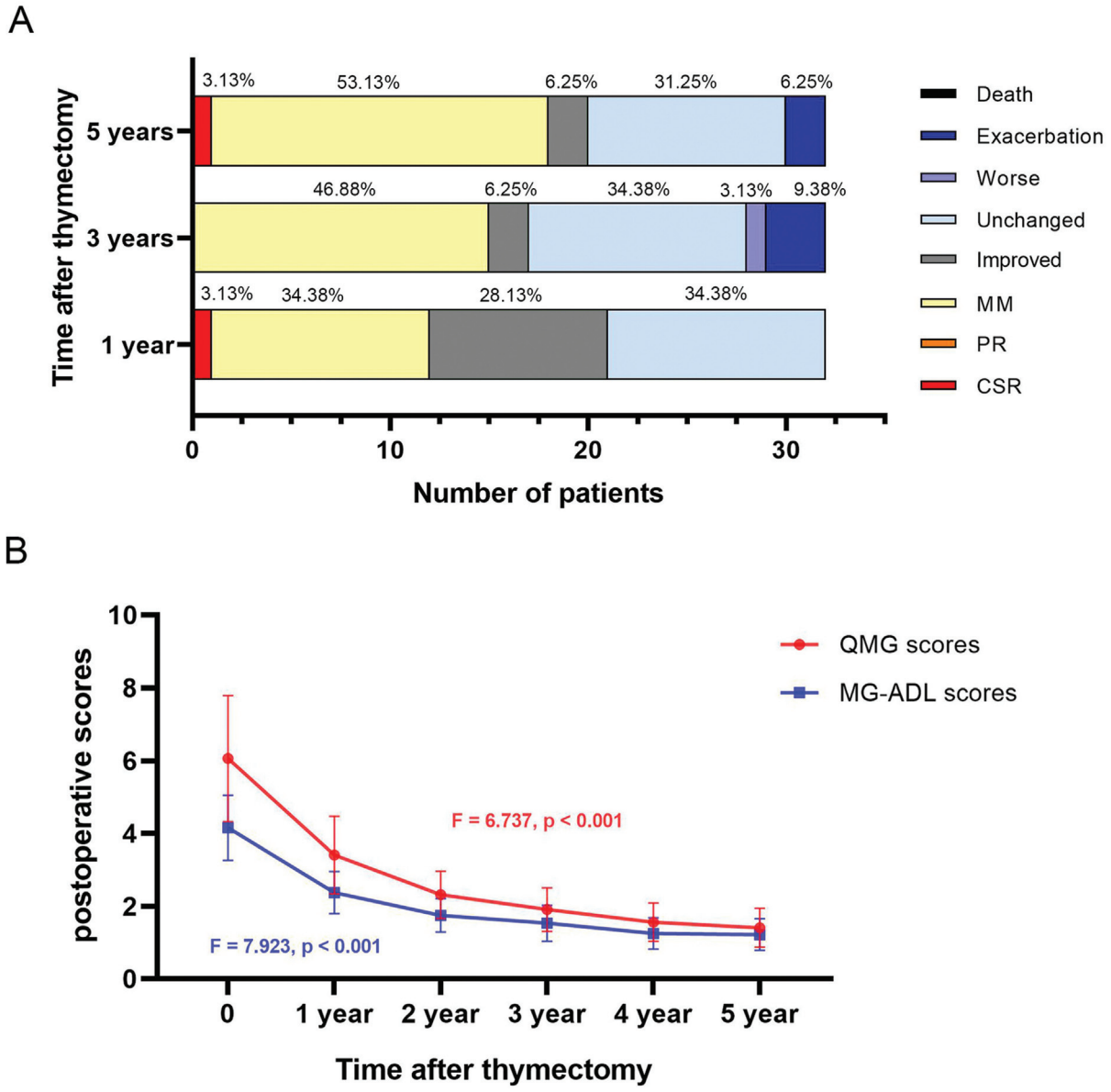

Fig. 1 Therapeutic effect at appointed times points after thymectomy. (**A**) Clinical status at 1 year, 3 years, and 5 years displayed as number of patients at each level of response. (**B**) Postoperative scores at appointed in patients underwent thymectomy. Error bars denote 95% confidence intervals for the measurement average. CSR, complete stable remission; MG-ADL, myasthenia gravis–related activities of daily living; MM, minimal manifestations; PR, pharmacologic remission; QMG, quantified myasthenia gravis.

QMG scores ($p < 0.05$; ►Fig. 2C) and MG-ADL scores ($p < 0.05$; ►Fig. 2F) over time.

Immunomodulators are often accepted by MG patients during the postthymectomy period, which can help stabilize the illness and improve the prognosis for patients.[35] A previous study by Liu et al demonstrated that tacrolimus can produce a favorable outcome in children with refractory MG.[36] In this study, 14 CMG patients were treated with prednisone in combination with tacrolimus postoperatively, but we did not find a predictive value of the combined immunotherapy for the prognosis. The different results were most likely due to the need to use tacrolimus to control symptoms in our patients with poor clinical conditions.

There are some limitations to this study. First, our analysis was based on a single-center retrospective study and lacked randomization. Second, the sample size was relatively small and, therefore, we did not conduct the multivariate regression analysis. Third, due to the large time span, therapeutic patterns and attitudes of physicians have changed with the accumulation of experience. Further studies comprising greater numbers of subjects from multicenter are required to evaluate the clinical heterogeneity in patients with CMG following thymectomy.

Conclusion

In summary, our case series have suggested that thymectomy is an effective treatment for CMG. QMG scores and MG-ADL

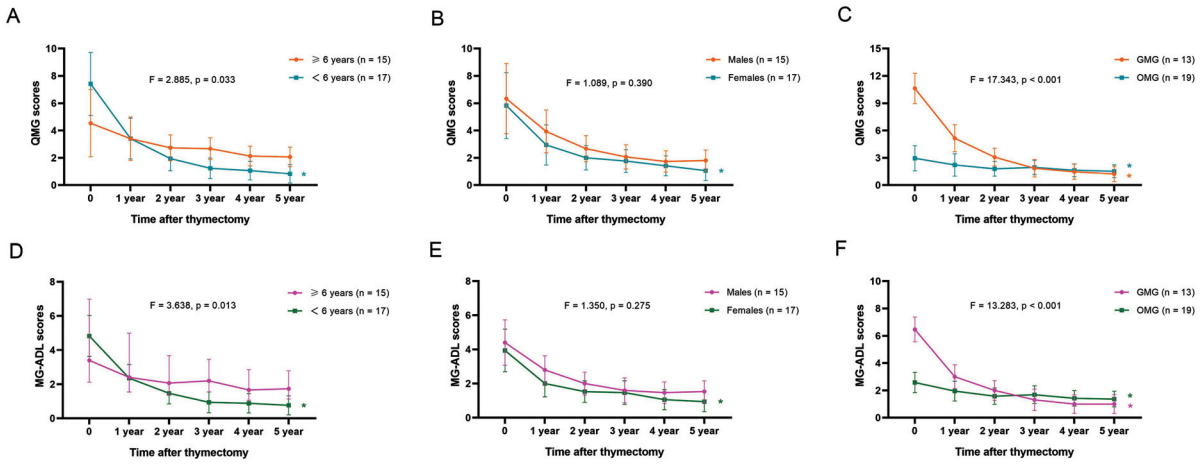

Fig. 2 Postoperative scores at appointed in patients underwent thymectomy: subgroup results. (**A–C**) Changes of QMG scores over time stratified by preoperative duration, sex, and MG subgroup. (**D, E**) Changes of MG-ADL scores over time stratified by preoperative duration, sex, and MG subgroup. Error bars denote 95% confidence intervals for the measurement average. GMG, generalized myasthenia gravis; MG-ADL, myasthenia gravis–related activities of daily living; OMG, ocular myasthenia gravis; QMG, quantified myasthenia gravis. *Significant difference within the subgroup between initial and final tests, $p < 0.05$.

Table 2 Effects of related variables on improvement or better status in univariate logistic regression analysis

Variable	Improvement or better status at 1-y postoperation			Improvement or better status at 5-y postoperation		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age at onset	1.20	0.98–1.46	0.083	1.21	0.99–1.48	0.058
Age at operation	0.88	0.69–1.12	0.285	0.83	0.65–1.06	0.142
Preoperative duration	0.85	0.73–1.00	**0.043**	0.82	0.70–0.97	**0.018**
Sex, males vs. females	0.19	0.04–0.94	**0.041**	0.48	0.11–2.04	0.318
MG subgroup, GMG vs. OMG	13.33	1.43–123.99	**0.023**	6.11	1.06–35.35	**0.043**
AChR-Ab, positivity vs. negativity	3.54	0.71–17.73	0.124	1.50	0.32–7.21	0.613
Thymus histology						
Thymoma vs. hyperplasia	1.71	0.15–19.36	0.663	0.571	0.07–4.88	0.609
Surgical approach						
VATS vs. open thoracotomy	0.60	0.14–2.67	0.503	0.42	0.10–1.89	0.262
Postoperative treatment						
Pyri + Pred vs. Pyri	0.57	0.06–5.78	0.635	1.13	0.09–15.51	0.930
Pyri + Pred + TAC vs. Pyri	1.60	0.17–15.27	0.683	0.39	0.04–4.80	0.461
Pyri + Pred + TAC vs. Pyri + Pred	0.91	0.17–4.81	0.916	0.44	0.08–2.44	0.345

Abbreviations: AChR-Ab, acetylcholine receptor antibody; CI, confidence interval; GMG, generalized myasthenia gravis; MG, myasthenia gravis; OMG, ocular myasthenia gravis; OR, odds ratio; Pred, prednisone; Pyri, pyridostigmine; TAC, tacrolimus; VATS, video-assisted thoracoscopic surgery.
Note: *p*-values less than 0.05 are marked in bold.

scores decreased gradually during the follow-up of 5 years. Patients with shorter course and generalized symptoms tended to have more favorable long-term outcomes. Therefore, thymectomy could be recommended for CMG patients, especially for patients in the early course of GMG.

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Conflict of Interest

None declared.

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