



# Effect of thymectomy in elderly patients with non-thymomatous generalized myasthenia gravis

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## Abstract

Whether thymectomy is beneficial in elderly patients with myasthenia gravis (MG) is unclear. Thus, we assessed whether conducting thymectomy in MG patients aged  $\geq 50$  years is beneficial. This retrospective cohort study included patients with MG between 1990 and 2018. Thymectomy and control cohorts were selected from among the population of MG patients with an age at onset of  $\geq 45$  years and elevated concentrations of acetylcholine-receptor antibodies. Patients with evidence of thymic malignancy were excluded. Of these patients, those who underwent thymectomy at the age of  $\geq 50$  years were designated as the thymectomy group and those who received only medical treatment were designated as the medical treatment group. We compared the Myasthenia Gravis Foundation of America post-intervention status between the thymectomy and medical treatment groups. Landmark analysis was conducted with the landmark set at 24 months. A total of 34 and 105 patients were classified into the thymectomy and medical treatment groups, respectively. Before landmark analysis, the thymectomy group had a higher cumulative incidence of pharmacologic remission ( $p=0.009$ ) and complete stable remission ( $p=0.022$ ) than the medical treatment group. After landmark analysis, the thymectomy group had a 2.22-fold (95% confidence interval 1.01–4.80) increased chance of achieving pharmacologic remission compared to the medical treatment group after adjustment for age, sex, and disease severity. No significant difference was observed in the rate of relapse after pharmacological remission between the thymectomy (16.7%) and medical treatment groups (21.4%). In conclusion, thymectomy may have a beneficial effect in elderly patients with non-thymomatous generalized MG.

**Keywords** Myasthenia gravis · Thymectomy · Remission · Prognosis

## Introduction

Myasthenia gravis (MG) is an autoimmune disorder caused by auto-antibody-mediated response to acetylcholine receptors (AChR) or related molecules located in the neuromuscular junction [1]. Thymectomy has been conducted in patients with non-thymomatous generalized MG because the thymus is known to induce antibody production in these

patients [2]. Some studies have demonstrated a beneficial effect of thymectomy in terms of a lower rate of myasthenic crisis or a higher rate of clinical remission compared to non-thymectomized patients [3, 4]. Recently, a randomized control study was conducted to assess the effect of thymectomy in patients with generalized non-thymomatous MG, and the results showed that the patients who underwent thymectomy had lower disease severity, immunosuppressant requirement, and disease exacerbation [5].

Thymectomy in non-thymomatous MG patients has been mostly conducted in patients with early onset MG. The theoretical background is that patients with early onset MG are likely to have thymic hyperplasia and removal of the hyperplastic thymus may contribute to the decrease in antibody production. By contrast, debate surrounds the effect of thymectomy in patients with late-onset MG. Because patients with late-onset MG typically have thymic atrophy [2, 6], removing the thymus may have no major effect on the disease course. Previous studies have shown contradictory

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results: some reports have revealed no substantial benefit of thymectomy in patients with late-onset MG [7, 8], whereas others have suggested a potential benefit [3, 9]. In addition, only a few studies have directly compared the prognosis of MG patients who have undergone thymectomy and those who have not.

In the present study, we assessed the effect of thymectomy in elderly patients with MG. We compared the Myasthenia Gravis Foundation of America post-intervention status (MGFA-PIS) in patients with AChR antibody-positive generalized MG who underwent thymectomy at  $\geq 50$  years of age and those who received only medical treatment.

## Materials and methods

### Patient enrollment

This retrospective cohort study included patients with a diagnosis of MG who visited the Department of Neurology, Severance Hospital, South Korea between January 1990 and December 2017 and the medical records of these patients were retrospectively reviewed. The diagnosis of MG was based on clinical features, decrement responses on repetitive nerve stimulation, improvement of symptom after the injection of neostigmine, and serum levels of AChR and/or muscle-specific kinase antibodies. The cohort of elderly patients with MG was retrospectively constructed using the following inclusion criteria: (1) diagnosis of generalized MG, (2) positive AChR antibodies, (3) onset of MG at  $\geq 45$  years, and (4) no evidence of thymic malignancy in either chest computed tomography (CT) or histopathologic evaluation. Among this cohort, patients who underwent thymectomy at the age of  $\geq 50$  years with or without concurrent medical treatment were designated as the thymectomy group and those who received only medical treatment were designated as the medical treatment group. Patients with insufficient follow-up duration were excluded based on the following criteria: (1) duration of follow-up after the diagnosis of MG of  $< 12$  months, and (2) duration of follow-up after thymectomy of  $< 12$  months. Of the 164 patients who satisfied the inclusion criteria, 34 patients underwent thymectomy at  $\geq 50$  years of age and 129 patients received only medical treatment. After 24 patients with a follow-up duration of  $< 12$  months were excluded, 34 patients were finally classified into the thymectomy group and 105 patients were classified into the medical treatment group (supplementary Fig. 1).

### Data collection and definition

Basic demographic and clinical data of the patients were recorded by reviewing medical records. Myasthenia Gravis Foundation of America (MGFA) clinical classification,

which ranges from class I (ocular muscle weakness only) to class V (state of intubation), was also recorded [10]. The following clinical and pathological characteristics associated with thymectomy were recorded: age at time of thymectomy, duration of intensive care unit stay, duration of hospital stay after thymectomy, presence of complications associated with thymectomy, and histologic diagnosis of the thymus. Patients were defined as having thymic hyperplasia if the number of lymphoid follicles was increased in a standard hematoxylin and eosin (H&E)-stained section, regardless of enlargement of the thymus. The prognosis of each patient was graded at the last follow-up visit using MGFA-PIS [10]. The prognosis was regarded as favorable if the MGFA-PIS was complete stable remission (CSR) or pharmacologic remission (PR). CSR was defined as the absence of any symptoms or signs of MG for at least 1 year without any treatment for MG. PR was defined similarly to CSR, but allowing for therapy for MG other than cholinesterase inhibitors [10].

### Landmark analysis

In the present cohort, group designation was determined not at the point of initial diagnosis, but during the follow-up period; all of the included patients were initially assigned to the medical treatment group at the point of diagnosis and were switched to the thymectomy group at the point of thymectomy. Thus, the patients who achieved PR or CSR during the early course of the disease were less likely to undergo thymectomy. To avoid this bias, which is known as guarantee-time bias or immortal time bias [11], we used landmark analysis by splitting the follow-up period at a common time point and considering only the outcome events that occurred after the landmark. The median duration from diagnosis of MG to thymectomy was 22.5 months and the landmark was set at 24 months after diagnosis.

### Statistical analysis

The data are expressed as numbers (percentages) for categorical variables and means  $\pm$  standard deviation or medians (Q1–Q3) for continuous variables depending on the assumption of normality. Fisher's exact tests and Chi-square tests were used to compare categorical variables and the Mann–Whitney test or *t* test was used to compare continuous variables between the two groups. Kaplan–Meier analysis was performed to analyze the cumulative incidence curve of PR and CSR between the patients who underwent thymectomy and those who received only medical treatment. Kaplan–Meier plots between the two groups were compared using the log-rank test. The Cox proportional hazards regression model was used to estimate the effect of thymectomy on achieving PR after adjustment for age, sex, and disease severity. For

statistical analysis, the patients with MGFA class II or III were classified as having mild disease and those with MGFA classification IV or V were classified as having severe disease. All *p* values were two-sided and a *p* value of < 0.05 was considered statistically significant. SAS 9.4 software (SAS Institute, Cary, NC, USA) was used for the statistical analysis. R software (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria) was used to draw the cumulative incidence curves.

## Results

### Baseline demographics and clinical features

The clinical characteristic of the 34 patients who underwent thymectomy and the 105 patients who received only medical treatment are displayed in Table 1. All patients in the thymectomy group also received medical treatment for MG after thymectomy. No significant difference was observed in terms of sex, symptoms at initial onset or comorbidities including hypertension, diabetes mellitus, coronary artery

**Table 1** Basic clinical features of the elderly patients with acetylcholine receptor antibody-positive generalized myasthenia gravis who underwent thymectomy and those who received only medical treatment

	Thymectomy ( <i>n</i> = 34)	Medical treatment ( <i>n</i> = 105)	<i>p</i> value
Sex, female	26 (76.5)	70 (66.7)	0.298
Age at onset, years	50.5 (47.8–54.3)	55.0 (50.0–66.0)	0.053
Age at diagnosis, years	52.0 (49.0–55.0)	57.0 (51.0–67.0)	0.002
Duration of follow-up after diagnosis, months	75.5 (55.3–132.3)	62.0 (30.0–113.0)	0.053
Symptom at onset			
Ocular	26 (76.5)	86 (81.9)	0.618
Bulbar	8 (23.5)	21 (20.0)	0.808
Limb	7 (20.6)	25 (23.8)	0.817
Neck	1 (2.9)	6 (5.7)	1
Respiratory	1 (2.9)	4 (3.8)	1
MGFA clinical classification, total			0.634
Class II	15 (44.1)	42 (40.0)	
Class III	14 (41.2)	38 (36.2)	
Class IV	2 (5.9)	6 (5.7)	
Class V	3 (8.8)	19 (18.1)	
MGFA II + III:IV + V	29:5	80:25	0.341
MGFA B classification	18 (52.9)	41 (39.0)	0.168
MG crisis	3 (8.8)	19 (18.1)	0.282
Abnormal RNS response, initial			
Abductor digiti minimi	15 (44.1)	39 (37.1)	0.545
Flexor carpi ulnaris	17 (50.0)	51 (48.6)	1
Orbicularis oculi	15 (44.1)	52 (49.5)	0.694
Nasalis	20 (58.8)	64 (61.0)	0.842
Trapezius	15 (44.1)	55 (52.4)	0.435
Any muscle	25 (73.5)	81 (77.1)	0.817
Acetylcholine receptor antibody, nmol/L	9.7 ± 3.8	8.7 ± 5.3	0.223
Treatment			
Cholinesterase inhibitor	34 (100)	105 (100)	–
Corticosteroid	23 (67.6)	84 (80.0)	0.161
Azathioprine	12 (35.3)	37 (35.2)	1
Cyclosporine	6 (17.6)	11 (10.5)	0.365
Mycophenolate mofetil	2 (5.9)	3 (2.9)	0.596
Tacrolimus	6 (17.6)	17 (16.2)	1

Data are expressed as counts (percentages), median (Q1–Q3) or means ± standard deviation

MG myasthenia gravis, MGFA Myasthenia Gravis Foundation of America, RNS repetitive nerve stimulation

disease, cerebrovascular accident, chronic kidney disease, and extra-thymic malignancy. However, the mean ages at the diagnosis of MG were significantly younger in the thymectomy group [median (Q1–Q3), 52.0 (49.0–55.0)] than in the medical treatment group [57.0 (51.0–67.0),  $p = 0.002$ ]. No significant difference was observed in terms of the overall MGFA classification, proportion of patients showing abnormal response at initial repetitive nerve stimulation, or serum level of AChR antibodies between the two groups. In addition, no significant difference was observed in the proportion of patients receiving cholinesterase inhibitors, corticosteroids, or immunosuppressive drugs between the two groups.

The histological results and clinical features associated with surgery among the 34 patients in the thymectomy group are presented in Table 2. Eighteen (52.9%) patients had thymic hyperplasia and 16 (47.1%) had involuted thymus or thymic atrophy. The median age at the time of thymectomy was 53.0 (Q1–Q3, 51.8–57.3) years and the duration from the diagnosis of MG to thymectomy was 22.5 (2.0–44.5) months. The median duration of intensive care unit stay after thymectomy was 0 (0–3.0) days. No life-threatening adverse events were observed after thymectomy. Other adverse events included urinary tract infection ( $n = 1$ ) and upper respiratory tract infection ( $n = 1$ ), which subsided within a few days. Aggravation of MG symptoms was reported in three patients. In one patient, transient worsening of dyspnea was observed, which gradually improved without the application of mechanical ventilation or other treatments. In the remaining two patients, high-dose steroid treatment was applied immediately after thymectomy and clinical worsening was observed a few days after the initiation of the steroid treatment. The worsening improved spontaneously in one of these patients, whereas it improved after treatment with intravenous immunoglobulin in the other patient.

## Clinical remission in the thymectomy and medical treatment groups

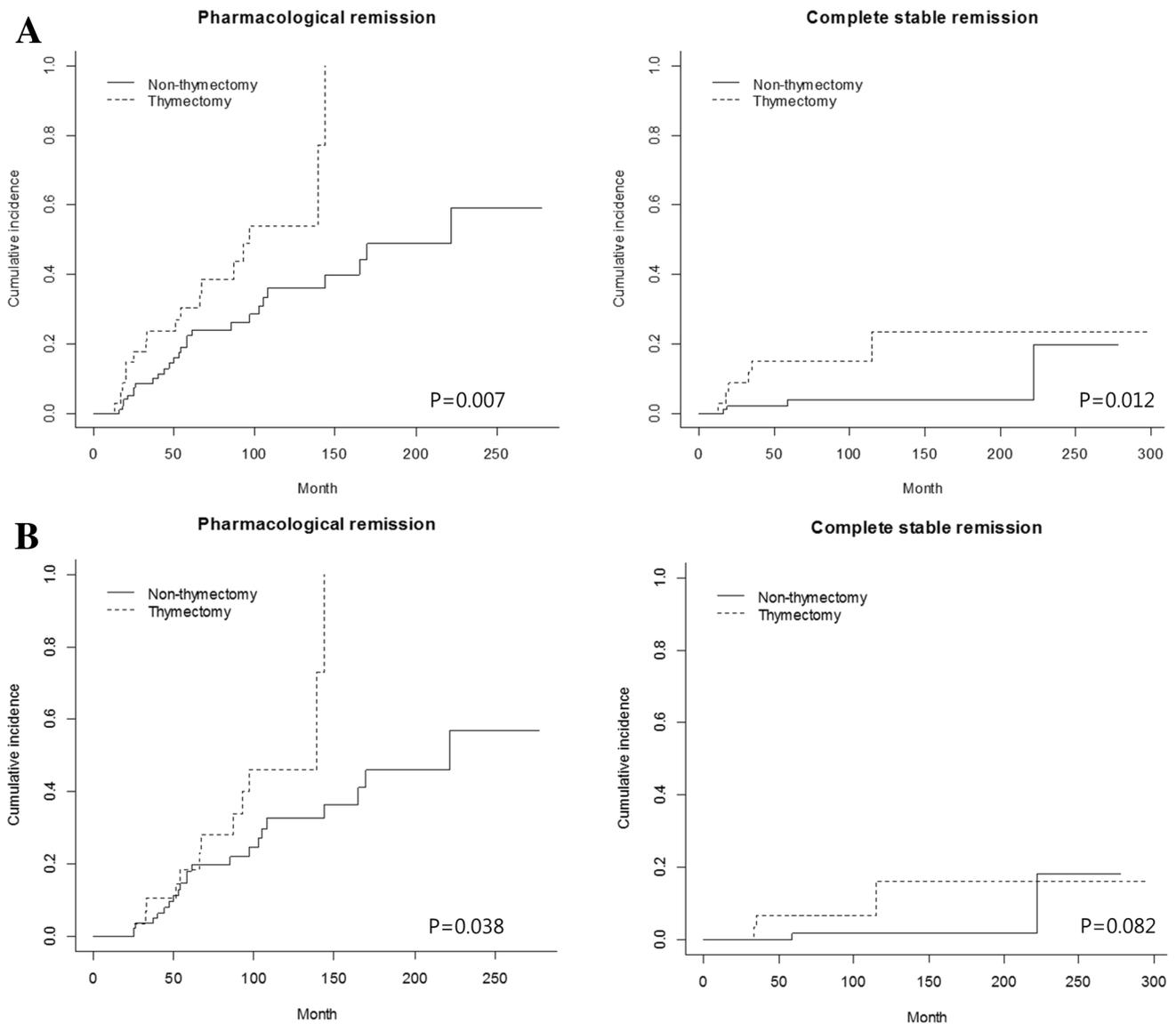
The cumulative probability of achieving PR or CSR in the thymectomy and medical treatment groups is shown in Fig. 1a. The cumulative incidence of PR and CSR was significantly higher among the thymectomy group than among the medical treatment group ( $p = 0.007$  and  $p = 0.012$ , respectively). In the raw model before the landmark analysis, the thymectomy group had a 2.29-fold [hazard ratio (HR) = 2.29, 95% confidence interval (CI) 1.24–4.26] higher chance of achieving PR and a 4.45-fold (HR = 4.45, 95% CI 1.24–15.93) higher chance of achieving CSR compared to the medical treatment group (Table 3). The independent effect of thymectomy on achieving PR was further evaluated using the Cox proportional hazards regression model to adjust for the confounding effects of other variables. The thymectomy group still had a 2.53-fold (HR = 2.53, 95% CI 1.29–4.96) increased probability of achieving PR than the medical treatment group after adjustment for age, sex, and disease severity. Age at onset was not significantly associated with PR in either univariate analysis ( $p = 0.322$ ) or multivariate analysis ( $p = 0.300$ ). Figure 2 presents the number of patients who underwent thymectomy and who achieved PR depending on the age at onset.

We also conducted landmark analysis by splitting the follow-up period at 24 months after the diagnosis (Fig. 1b). The thymectomy group had a 2.10-fold (HR = 2.10, 95% CI 1.02–4.29) higher chance of achieving PR than the medical treatment group. In the multiple Cox regression model, the thymectomy group still had a 2.22-fold (HR = 2.22, 95% CI 1.01–4.80) increased chance of achieving PR than the medical treatment group after adjustment for age, sex, and disease

**Table 2** Clinical and histological features of the patients with acetylcholine receptor antibody-positive generalized myasthenia gravis who underwent thymectomy

	Thymectomy ( $n = 34$ )
Age at thymectomy, years	53.0 (51.8–57.3)
Duration from onset of MG to thymectomy, months	33.0 (12.5–60.0)
Duration from diagnosis of MG to thymectomy, months	22.5 (2.0–44.5)
Duration of follow-up after thymectomy, months	62.0 (22.8–87.0)
Admission for thymectomy	
Duration of intensive care unit stay, days	0 (0–3.0)
Duration of total hospital stay, days	11.0 (7.0–19.0)
Duration of hospital stay after thymectomy, days	7.5 (5.0–15.0)
Worsening of MG symptoms after thymectomy	3 (8.8)
Infection after thymectomy	2 (5.9)
Histopathology	
Thymic hyperplasia	18 (52.9)
Thymic involution or atrophy	16 (47.1)

Data are expressed as counts (percentages) or median (Q1–Q3)  
MG myasthenia gravis



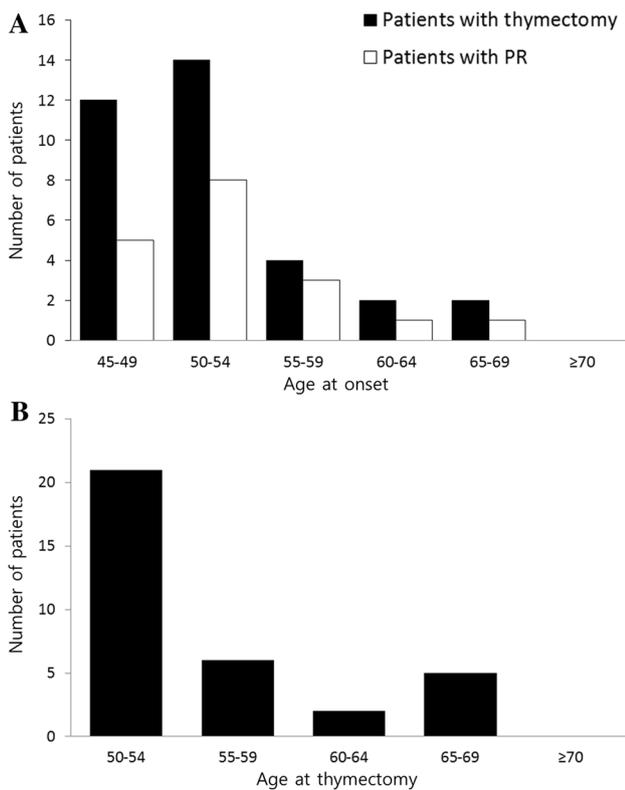
**Fig. 1** Cumulative incidence curves for pharmacological remission and complete stable remission in the patients with myasthenia gravis who underwent thymectomy and those who did not, based on analyses of (a) the raw model and (b) a landmark set at 24 months

**Table 3** Hazard ratios for achieving pharmacologic remission or complete stable remission in patients with myasthenia gravis who underwent thymectomy compared to those who received only medical treatment, based on analyses of the raw model and a landmark set at 24 months

	Univariate		Multivariate <sup>a</sup>	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Pharmacologic remission				
Raw model	2.29 (1.24–4.26)	0.009	2.53 (1.29–4.96)	0.007
Landmark set at 24 months	2.10 (1.02–4.29)	0.043	2.22 (1.01–4.80)	0.046
Complete stable remission				
Raw model	4.45 (1.24–15.93)	0.022		
Landmark set at 24 months	4.42 (0.72–27.25)	0.110		

HR hazard ratio, CI confidence interval

<sup>a</sup>Adjusted for onset age, sex, and disease severity



**Fig. 2** **a** Number of patients with myasthenia gravis who underwent thymectomy and who achieved pharmacologic remission based on the age at onset, and **b** the distribution of patients' age at thymectomy

severity. However, the increased probability of achieving CSR was no more significant in the landmark analysis at 24 months.

### Relapse after pharmacological remission

We compared the rate of relapse in the patients who achieved PR between the two groups to evaluate whether the patients were in a stable state at the point of PR. Three of the 18 patients (16.7%) who achieved PR in the thymectomy group and 6 of the 28 patients (21.4%) who achieved PR in medical treatment group experienced relapse, and no significant difference was observed in the rate of relapse after PR. We further compared treatment-related factors in the patients who achieved PR between the thymectomy and medical treatment groups to assess the factors that may affect the rate of relapse after achieving PR. No difference was observed in the duration of follow-up after achieving PR, daily dose of prednisolone after achieving PR, or proportion of patients who used immunosuppressants between the thymectomy group [median 37 months, Q1–Q3 (8.8–49.5), 3.9 mg (1.1–5.1), and 33.3%, respectively] and the medical treatment group [14 months (5.5–23.8), 4.5 mg (0–5.0), and 25.0%;  $p=0.060$ ,  $p=0.963$ , and  $p=0.540$ , respectively]. In addition, no significant difference was observed in the type of treatment at the time of relapse between the two groups.

### Comparison of clinical features depending on thymic pathology

We analyzed the clinical features of the 34 patients who underwent thymectomy depending on histopathologic results (Table 4). Of the 18 patients with thymic hyperplasia at histology, the results of pre-operative chest CT were normal thymus in 13 patients (72.2%), hyperplasia in 3 patients (16.7%), and thymoma in 2 patients (11.1%). Of the 16 patients with a normal/involuted thymus, pre-operative chest CT was normal in 11 patients and suspicious of thymoma

**Table 4** Comparison of clinical features of the elderly patients with acetylcholine receptor antibody-positive generalized myasthenia gravis who underwent thymectomy depending on thymic pathology

	Hyperplasia (n=18)	Involution (n=16)	p value
Sex, female	14 (77.8)	12 (75.0)	1
Age at onset, years	50.0 (47.0–52.3)	51.5 (48.5–58.5)	0.151
Age at thymectomy, years	53.0 (50.8–54.5)	55.0 (52.0–65.5)	0.211
Duration of follow-up after thymectomy, months	43.5 (19.8–85.3)	68.5 (28.0–99.8)	0.208
Acetylcholine receptor antibody, nmol/L	9.9 ± 3.6	9.4 ± 4.2	0.679
MGFA clinical classification, before thymectomy			0.835
Class II	9 (50.0)	6 (37.5)	
Class III	7 (38.9)	7 (43.8)	
Class IV	1 (5.6)	1 (6.2)	
Class V	1 (5.6)	2 (12.5)	
Achievement of remission			
Pharmacologic remission	10 (55.6)	8 (50.0)	1
Complete stable remission	3 (16.7)	3 (18.8)	1

Data are expressed as counts (percentages), median (Q1–Q3) or means ± standard deviation  
 MGFA Myasthenia Gravis Foundation of America

in one patient. Chest CT results were unobtainable in the remaining four patients. No significant differences were observed in terms of sex, age at onset, age at thymectomy, duration of follow-up after thymectomy, and MGFA classification before thymectomy between the two groups. No significant difference was observed in the rate of achieving remission between the patients with thymic hyperplasia (55.6%) and those with a normal/involved thymus (50%,  $p = 0.746$ ).

## Discussion

The present study demonstrated the beneficial effect of thymectomy at  $\geq 50$  years of age in patients with non-thymomatous generalized MG compared to medical treatment alone. The thymectomy group had a 2.22-fold increased probability of achieving PR after adjustment for age, sex, and disease severity. Most of the patients tolerated thymectomy well and no life-threatening adverse events occurred thereafter. The proportion of relapse after achieving PR was no higher than in the medical treatment group. Thus, thymectomy could be considered as a treatment option in elderly patients with generalized MG. However, this finding should be interpreted with caution because no significant benefit was found in the probability of achieving CSR and because the effects of thymectomy in the patients aged  $\geq 70$  years could not be determined based on the present results.

Before the recent randomized trial of thymectomy in patients with MG [5], numerous cohort studies analyzed the effect of thymectomy on prognosis [12, 13]. However, the effects of thymectomy in elderly patients could not be determined because some studies failed to demonstrate the beneficial effect of thymectomy itself [14], and thymectomy was mostly performed in patients with early onset MG [15, 16]. Even in the studies that demonstrated the beneficial effect of thymectomy, old age was frequently associated with worse outcomes [4, 16, 17], and no benefit was observed in those aged  $\geq 50$  years in a previous study [17]. Thus, whether thymectomy is beneficial in elderly patients with MG has been under debate and thymectomy has generally been excluded from the treatment options for elderly patients unless a thymoma is present [18].

Recently, a randomized trial of thymectomy was conducted with patients ranging in age from 18 to 65 years [5]. The results revealed that thymectomy improved clinical outcome in terms of a lower average quantitative MG score and a lower average prednisolone dose compared to the medical treatment group. The benefit of thymectomy was still observed in a subgroup analysis of the patients with an age at disease onset of  $\geq 40$  years. In addition to the aforementioned randomized trial, a few studies have also suggested the favorable effect of thymectomy in patients with

late-onset generalized MG. Kawaguchi et al. analyzed the clinical outcomes of patients with generalized late-onset MG and found that the proportion of patients with MGFA class II–V at the end of follow-up was significantly lower in patients who underwent thymectomy than in those who did not [3]. Uzawa et al. analyzed the clinical outcomes of patients with non-thymomatous late-onset MG after thymectomy and found that the patients with thymic hyperplasia had a higher proportion of remission than those with thymic involution [3]. These findings add increasing support for the suggestion that thymectomy should be considered in patients with late-onset generalized MG with an age at onset ranging from 50 to 65 years [1, 19].

However, previous studies have had certain limitations that led to uncertainty regarding thymectomy in patients with late-onset MG. First, only a few studies have directly compared outcomes between thymectomy and control groups with a randomized control or retrospective cohort design [12]. Second, even among the studies that resembled retrospective cohort studies, some did not focus on elderly patients [4], used non-conventional definitions of clinical outcomes [3, 4], or demonstrated the effect only in a subgroup of patients [3]. Third, although the recent randomized controlled trial demonstrated the beneficial effect of thymectomy, no significant difference in primary outcome was observed between thymectomy and prednisolone-only groups in a subgroup of patients with an age of  $\geq 50$  years at enrollment [5]. This may have resulted from the small number of patients (nine patients with thymectomy) with an age of  $\geq 50$  years at enrollment. Thus, we investigated the beneficial effect of thymectomy in elderly patients with MG using a retrospective cohort study that directly compared the outcomes between thymectomy and medical treatment groups and used PR and CSR definitions provided by the MGFA as the primary outcomes [10]. In addition, we used landmark analysis to overcome guarantee-time bias, a selection bias in longitudinal observational studies that occurs when an event that took place during the follow-up period is falsely assumed to have been recognized at baseline.

More than half of the patients who underwent thymectomy had thymic hyperplasia in the current study. The association between the high proportion of patients with thymic hyperplasia and good clinical outcomes is uncertain. Thymic hyperplasia has been suggested to be associated with favorable clinical outcomes in some previous studies [20–23], and Uzawa et al. suggested that thymic hyperplasia is associated with better clinical outcomes in patients with late-onset MG [9]. Thus, favorable clinical outcomes in the thymectomy group in the present study may have resulted from the high proportion of patients with thymic hyperplasia. However, other reports have shown that the clinical outcomes of patients with thymic atrophy are similar to or rather slightly better than those with thymic hyperplasia [24,

25]. To confirm this finding, Chen et al. demonstrated that B-cell activation, represented by thymic CD19, CD 21, and B-cell activating factor receptor expression, was not reduced in patients with thymic atrophy compared with those with thymic hyperplasia [25]. In the present study, no significant difference was observed in the proportion of patients who achieved PR between the patients with thymic hyperplasia and thymic involution. Further study is required to elucidate the association between thymic pathology and clinical outcomes in elderly patients.

Predicting thymic hyperplasia based on chest CT findings in elderly patients with MG is difficult. In the present study, the sensitivity and specificity of chest CT in predicting thymic hyperplasia were 16.7% and 100%, respectively. The low sensitivity and high specificity of chest CT in predicting thymic hyperplasia was also suggested in a previous report; Pirroni et al. reported sensitivity and specificity of chest CT in predicting thymic hyperplasia as 36% and 95%, respectively [26]. In contrast to thymoma, which can be detected by CT with sufficient sensitivity and specificity, thymic hyperplasia exhibits various morphologies and the degree of CT attenuation is similar to that of the normal thymus, making the two difficult to distinguish [27, 28]. Moreover, the thymus in elderly patients is typically entirely replaced by fat tissue and the morphologic features of hyperplasia can be difficult to recognize. Some studies have suggested considering thymectomy in patients with late-onset MG if an enlarged thymus is observed on imaging [19], and in fact most of patients who show an enlarged thymus on chest CT are likely to have thymic hyperplasia. However, a substantial number of patients with a normal-looking thymus on CT may also have thymic hyperplasia, and these patients may also benefit from thymectomy.

The present study had several limitations. First, the current study was retrospective in design, which may have caused selection bias. Most crucially, the age of the patients at diagnosis was significantly younger in the thymectomy group than that in the medical treatment group. The neurologists and thoracic surgeons may have been reluctant to perform thymectomy in elderly patients and this may have caused significant bias. In addition, although not statistically significant, the proportion of patients that experienced MG crisis and the proportion of patients who were treated with corticosteroids, cyclosporine, or mycophenolate differed between the two groups, and the net effect of these differences may have influenced the outcome. Second, the current study was based on a small study population from a single center. Because of the small number of included patients and primary outcomes, we were unable to conduct landmark analysis for landmarks other than 24 months. In addition, surgical outcomes or post-operative complications may differ among centers. Third, the age of the patients at the point of thymectomy ranged from 50 to 69 years, and

the effects of thymectomy in the patients outside of this range cannot be adequately assessed based on the current data. Fourth, the high frequency of thymic hyperplasia in the current study contrasts with previous reports that have suggested that thymic hyperplasia is rare in patients with late-onset MG [6, 29]. This may have been because of the small study population or because the definitions of thymic hyperplasia differed among the reports. Thymic hyperplasia in the present study was defined as an increased number of lymphoid follicles in a standard H&E-stained section. However, a recent report that graded thymic follicular hyperplasia from grade I to grade IV mentioned that grade I hyperplasia can be observed in normal thymic tissue [30]. Thus, the proportion of thymic hyperplasia may have been overestimated in the current study. Further study is required to reveal the frequency of thymic hyperplasia in late-onset MG.

In conclusion, the probability of achieving PR was significantly higher in patients who underwent thymectomy at  $\geq 50$  years of age compared to the patients with MG who received only medical treatment. The beneficial effect of thymectomy may be limited because the probability of achieving CSR was not significantly greater in the thymectomy group than in the medical treatment group. Despite the limitation, thymectomy could be considered as a treatment option in elderly patients with MG whose ages range from 50 to 69 years. A prospective, randomized study focusing on patients  $> 50$  years of age is necessary to clarify the effect of thymectomy compared to that of medical treatment in elderly patients with MG.

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## Compliance with ethical standards

**Conflicts of interest** None of the authors has any conflicts of interest to disclose.

**Ethics approval** The study including human participants has been approved by the Severance Hospital Institutional Review Board (Approval No. 4-2018-0869) and has, therefore, been performed in accordance with the Declaration of Helsinki.

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