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Can Non-Thymomatous Late-Onset Myasthenia Gravis Benefit From Thymectomy? A Systematic Review and Meta-Analysis

Jiaxin Chen[1,2] | Chunhua Su[3] | Huiyu Feng[2] | Henry J. Kaminski[1]

[1]Department of Neurology & Rehabilitation Medicine, The George Washington University, Washington, DC, USA | [2]Department of Neurology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China | [3]Department of Thoracic Surgery, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China

Correspondence: Henry J. Kaminski (hkaminski@mfa.gwu.edu)

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Keywords: effective | late-onset | myasthenia gravis | older or elderly population | response | thymectomy

ABSTRACT

Background: Thymectomy is beneficial for treating early-onset acetylcholine receptor antibody-positive myasthenia gravis (MG); however, its effects on late-onset MG (LOMG) remain less well understood. Given the increasing incidence of MG among the population 50 years old and above, addressing the question of whether thymectomy is effective for this age group is critically important. This study aimed to assess the present evidence for the efficacy of thymectomy in LOMG and identify potential characteristics that may predict the treatment response.

Methods: Four electronic databases were searched from their inception to September 10, 2024. Six studies with both thymectomy and medical therapies in LOMG patients, along with another 14 studies with only a surgical group, were enrolled in the meta-analysis. The primary outcome was the response (remission and minimal manifestations status) to thymectomy in LOMG.

Results: In LOMG, response in the surgical group was greater than in the medical therapies alone group (OR = 1.42 [0.86–2.35], $p = 0.169$), but not significantly. However, subgroup analysis showed that when the age of MG onset was ≥ 45 years old or the age at thymectomy was ≥ 50 years old, thymectomy appeared better than medical therapies alone (OR = 1.92 [1.06–3.48], $p = 0.031$). Across all 20 studies, 34% (24%–44%) of LOMG patients improved with thymectomy. A higher response was observed in patients with a preoperative duration of less than 3 years from diagnosis [39% (16%–65%), $p < 0.001$, $q < 0.001$].

Conclusion: Thymectomy may be a potentially effective treatment for LOMG, particularly in patients who undergo the procedure soon after diagnosis. A randomized controlled study for LOMG patients is needed.

1 | Introduction

Myasthenia gravis (MG) is a heterogeneous rare autoimmune disease mediated by specific antibodies compromising conduction of the neuromuscular junction [1]. The annual incidence is estimated roughly at 10 to 29 per million, while the prevalence estimates range from 100 to 350 cases per million, with both incidence and prevalence increasing over the past two decades [2]. Further analysis across age groups indicates that this increasing trend is more prominent among the elderly population. In Poland, the incidence of MG is 23.6 per million, with a mean age of 61.37 years. For those older than 50, it reaches 49.8 cases per

million [3]. In China, the incidence of hospitalized MG increases steadily with age and peaks in the age group of 70 to 74 years (18.9 per million) [4]. Similar phenomena have been observed in several other countries and regions, showing an increase with age and a late peak appearing in the fifth decade or after [5–8].

Based on the age of onset, MG is typically classified as early-onset MG (EOMG) and late-onset MG (LOMG), with a cutoff ranging from 40 to 50 years old across studies [9]. Fundamental differences in clinical features, genetic predisposition, and thymic pathology are evident between these two subgroups. Moreover, based on the thymic pathology, LOMG patients can be further divided into thymoma-associated (TAMG) and non-thymomatous groups. Complete removal of all thymic tissue is necessary for the best disease control in MG patients with thymoma and thymic hyperplasia. Given the increasing access to minimally invasive thymectomy and enhanced pre- and post-operative care, the risk of complications, even in the LOMG group, is much less than in past decades. However, whether thymectomy provides clinical benefit in non-thymomatous LOMG patients has been questioned for many years, with varying conclusions across different studies [1, 10–14]. The previous review primarily emphasized comparing surgical outcomes between LOMG and EOMG while briefly analyzing the effects of thymectomy versus medical therapies alone in a limited number of LOMG patients, which did not adequately address the issue [10]. Here, through larger sample sizes, rigorous methodologies, and detailed subgroup analyses, we focus on LOMG and aim to estimate their response rate to thymectomy and identify potential characteristics of a response group, providing valuable insights for clinical practice and future studies.

2 | Materials and Methods

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were followed. The review was registered with PROSPERO (CRD42024510953) and reported according to PRISMA guidelines. The protocol of this study is available online.

2.1 | Search Strategy

A systematic search of the PubMed, Medline, Cochrane Library, and Chinese National Knowledge Infrastructure databases was performed from the inception to September 10, 2024. A search strategy was developed for each database using a combination of medical subject headings and the terms “myasthenia gravis” and “thymectomy.” No language restrictions were placed on the searches or search results.

2.2 | Study Selection Criteria

Two of the authors first screened the abstract and then further screened the full text for eligibility. Each publication was independently reviewed by the reviewers, and disagreements were resolved through discussion or by the judgment of a third reviewer, a senior neurologist. The inclusion criteria were as follows: cut-off age: 40 years or older, definition of outcomes (the response to thymectomy): based on the Myasthenia Gravis Foundation of America (MGFA) post-intervention status [15] or other similar clear criteria described in studies, such as DeFilippi postoperative classification [16] and Oosterhuis classification [17], and follow-up time (mean) of more than 1 year after thymectomy. The exclusion criteria were as follows: type of publications: reviews, systematic reviews, meta-analyses, editorials, case reports, news articles, conference proceedings, and protocols; (2) population: TAMG or MG without the complete data about age or pathological report; and (3) study design: clinical trials of specific novel medicines. In the case of multiple reports from the same data set, the most recent or comprehensive report was selected.

2.3 | Data Extraction

For each study included, study data and patient characteristics were extracted independently and in duplicate using a standardized data extraction sheet; afterward, the results were cross-checked. Discrepancies were resolved by consensus or with the judgment of a third reviewer. The extracted study and patient characteristics included the publication year, age cut-off (definition of late-onset), sample size, participants' age, gender, age of MG onset, MG duration, autoantibody status, age at thymectomy, thymus pathology, follow-up time, and outcome. Based on the criteria of MGFA post-intervention status, “Response” was defined as remission (including complete stable remission and pharmacological remission) or minimal manifestation (MM) status. The primary outcome of this study was the response to thymectomy in LOMG.

2.4 | Quality Assessment

The study quality assessment was performed according to the validated scale recommended by Cochrane [18]. Two authors independently extracted data from eligible studies and summarized them using a data extraction form. The Newcastle–Ottawa Scale (NOS) was used to assess the studies, with scores of 7 or more considered to indicate high methodological quality. For each study, two reviewers independently assigned scores to each of the following domains: selection, comparability, and outcome. Discrepancies in the quality assessments were resolved by consensus or by a third reviewer.

2.5 | Statistical Analysis

The response to thymectomy in LOMG was calculated from raw proportions and 95% confidence intervals (CI). In the meta-analysis, the response rates for each included study were pooled, stratified across the studies, and analyzed using random-effects or fixed-effect models with inverse variance weighting. A fixed-effect model was used when the I^2 statistics was $< 50\%$ or $p > 0.05$. A random-effects model was used when the I^2 was $\geq 50\%$ or $p < 0.05$. For sensitivity analysis, a funnel plot and Egger's test were used to evaluate potential publication bias. Some studies provided detailed case information, which was extracted for subgroup analysis. Subgroups with a sample size of less than 50 in the thymectomy group were excluded from analysis to prevent data bias. The two-proportion Z-test was used to compare the outcomes in subgroups. p-values were adjusted to minimize

the false discovery rate based on the Benjamini and Hochberg method and are shown as *q*-values. In cases where multiple post-intervention statuses from different follow-up time points were available in the same study, the time point closest to the surgery was selected to assess for early prediction of treatment response.

The statistical analyses were performed using STATA (version 11.2, StataCorp, College Station, TX 77845, USA) and SPSSAU (version 24.0, Online Application Software, https://www.spssau.com).

3 | Results

Twenty studies were selected for inclusion (Figure 1). Only the MGTX study [14] was a randomized controlled trial, and the remaining 19 were case–control, cross-sectional, or cohort studies that were included in the systematic review. The NOS scores for all studies were above 7, indicating high methodological quality (Table S1). The response to thymectomy compared with medical therapies alone in LOMG was reported in six studies and was included in the meta-analysis. The remaining 14 studies only had a surgical group and were also enrolled in the meta-analysis of proportions.

3.1 | Compared With Medical Therapies Alone, LOMG Patients Benefit From Thymectomy

The six enrolled two-arm studies examined 323 LOMG patients, with cutoffs at 40, 45, and 50 years old across studies. The thymectomy group consisted of 114 patients, while the medical therapies group included 209 subjects. Detailed information on sample size, gender, age of MG onset, preoperative MG duration, age at surgery, AChR-Ab status, follow-up time, and outcomes was extracted from the studies, and data are summarized in Table 1.

Meta-analysis demonstrated that in LOMG, the frequency of response in the thymectomy group was greater than in the medical

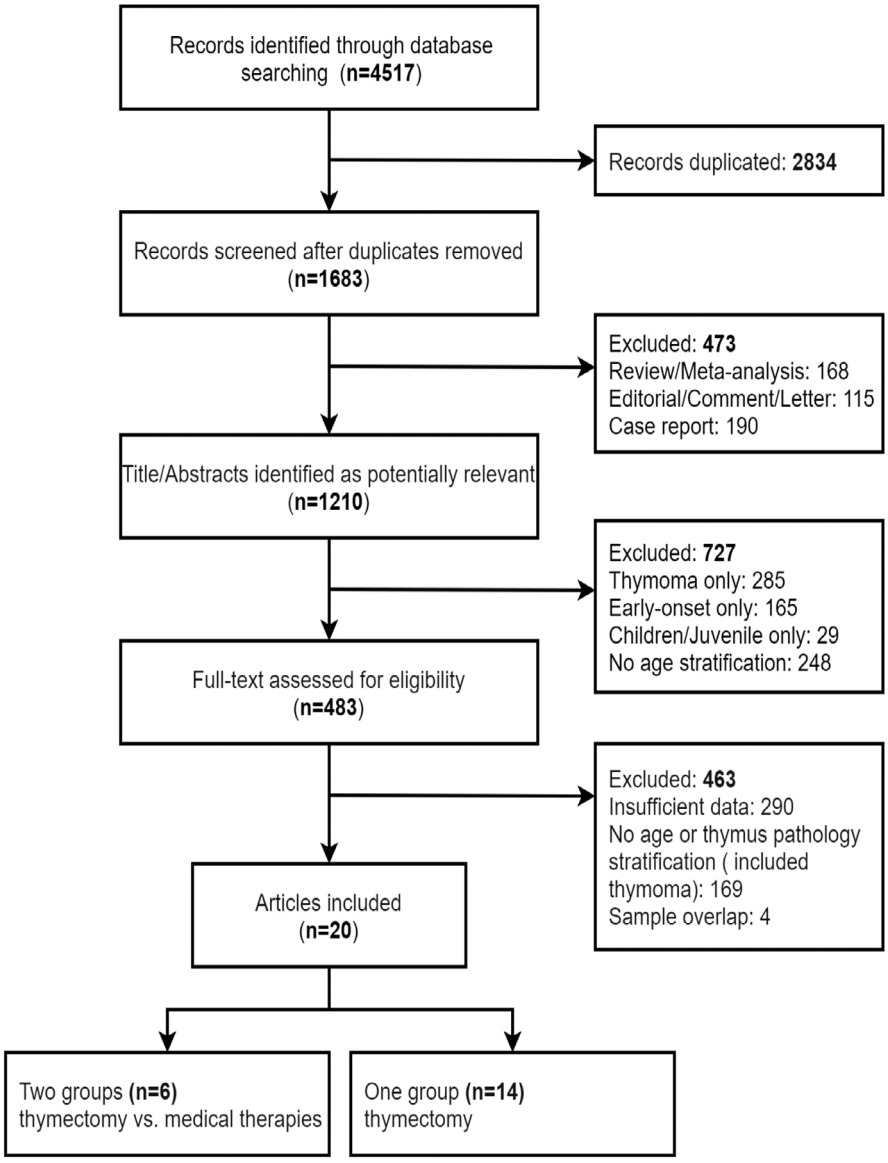

FIGURE 1 | Flowchart of study selection.

TABLE 1 | Summary of the included two-arm studies.

Study	Kim [11]		Sakai [19]		Kawaguchi [20]		Romi [12]		Valli [13]		Wolfe [14]	
Cutoff	45 years old		50 years old		50 years old		50 years old		40 years old		40 years old	
Groups	Thy	Med	Thy	Med	Thy	Med	Thy	Med	Thy	Med	Thy	Med
Sample size	34	105	10	36	20	14	21	22	15	15	18	18
Gender	8 M/26 F	35 M/70 F	4 M/6 F	18 M/18 F	10 M/10 F	3 M/11 F	11 M/10 F	12 M/10 F	NA	NA	5 M/13 F	7 M/11 F
Age of onset	50.5 (47.8, 54.3)	55.0 (50.0, 66.0)	> 50	> 50	61 (50–77)	67 (55–78)	63 ± 8	69 ± 7	> 40	> 40	50.22 (40–63)	48.94 (40–61)
Disease duration (year(s))	2.75 (1.04, 5)	NA	0.65 ± 0.52 (0.05–1.83)	0.52 ± 0.71 (0.02–3)	NA	NA	All ≤ 3 year 12 ≤ 1 year	NA	NA	NA	0.97 (0.08–2.92)	1.37 (0.33–2.58)
AChR-Ab positive	34 (100%)	105 (100%)	9 (90%)	30 (88.2%)	18 (90%)	11 (78.6%)	21 (100%)	22 (100%)	NA	NA	18 (100%)	18 (100%)
MG severity	MGFA:15 II/14 III/ 5 IV + V	MGFA:42 II/38 III/ 25 IV + V	6/10 (60%) OMG	25/36 (69.4%) OMG	MGFA:10 II/10 III & upper	MGFA: 12 II/ 2 III & upper	Modified Osserman: mean 2.9	Modified Osserman: mean 2.6	NA	NA	MGFA:11 II/7 III&upper	MGFA:14 II/4 III
Age of Thy	53.0 (51.8, 57.3)	/	57.2 ± 7.0 (50–74)	/	> 50	/	64 ± 8	/	> 40	/	50.83 (41–63)	/
Thymus pathology	18 hyperplasia, 16 involution/ atrophy	/	3 hyperplasia, 3 thymic cyst	/	NA	/	21 atrophy	/	NA	/	NA	/
Prednisone before Thy	23 (67.6%)	/	7 (70%)	/	17 (85%)	/	No treatment	/	NA	/	18 (100%)	/
Follow-up (year(s))	5.17 (1.9, 7.25)	5.17 (2.5, 9.4)	3	3	Mean 9.2	Mean 7.6	2–5	2–5	≥ 2	≥ 2	3	3
Outcome	24 (70.6%) R	48 (45.7%) R	8 (80%) MM	27 (75%) MM	6/16 (37.5%) R	3/13 (23.1%) R	6 (28.6%) R	7 (31.8%) R	9 (60.0%) R	12 (80.0%) R	10 (55.6%) MM	11 (61.1%) MM

Note: Data are expressed as counts (percentages), median (Q1, Q3) or means ± standard deviation or mean(range).
Abbreviations: AChR-Ab, acetylcholine receptor antibodies; F, female; M, male; Med, medical therapies alone; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestation; NA, not available; R, remission (complete stable remission and/or pharmacological remission); Thy, thymectomy; y, year(s).

therapies alone (OR = 1.42 [0.86, 2.35], $p = 0.169$, $I^2 = 25.7\%$), but the difference was not statistically significant (Figure 2). For sensitivity analysis, funnel plot and Egger's test for publication bias are presented in Figure S1.

Subgroup analysis was conducted to further investigate differences in responses between surgical and medical treatments in LOMG (Figure 3). Following guideline definitions, MG patients aged ≥ 50 years were classified as LOMG to compare the effects of thymectomy versus medical therapies alone. However, the small sample size (only 47 in the surgical group) highly increased the risks of data and selection bias. To mitigate this limitation, patients who developed MG after age 45 but underwent surgery after age 50 years were included. Outcome following thymectomy was better compared to medical therapies alone (OR = 1.92 [1.06, 3.48], $p = 0.031$, $I^2 = 0$). The study by Kim (2019) [11] provided more details about the age of onset. In the thymectomy group, patients with an onset age ≥ 55 years were more likely to achieve pharmacological remission compared to those with an onset age ≥ 45 and < 55 years old (5/8 vs. 13/26, 62.5% vs. 50.0%). The presence of AChR-Ab (OR = 1.66 [0.91, 3.04], $p = 0.097$, $I^2 = 47.2\%$) and the demanding response level (which means only remission not including MM status) (OR = 1.60 [0.90, 2.84], $p = 0.110$, $I^2 = 48.6\%$) showed a better trend in the thymectomy group but were not significant.

3.2 | LOMG Patients With a Preoperative Duration of Less Than 3 Years Exhibit a Better Response to Thymectomy

We used 20 studies of patients with thymectomy and pooled the data to evaluate the frequency of response to thymectomy in LOMG. A total of 488 thymectomy patients were identified, but only 464 cases with follow-up data were included in the study. Detailed information from these additional 14 studies (not listed in Table 1) is shown in Table 2.

Meta-analysis of proportions showed that the response rate to thymectomy in LOMG was 34% (95% CI: 24%–44%) (Figure 4). Age of MG onset, age at thymectomy, presence of AChR-Ab, preoperative MG duration, thymic pathology, and follow-up time were used in subgroup analysis (Table 3 and Figures S2–S7). A higher response rate was observed in patients with a preoperative duration of less than 3 years (39% [16%–65%], $p < 0.001$, $q < 0.001$). Besides, AChR-Ab [40% (21%–61%), $p = 0.02$, $q = 0.06$] and thymic involution/atrophy [46% (23%–69%), $p = 0.294$, $q = 0.588$] also showed higher response rates, though the difference was not significant.

4 | Discussion

International guidelines recommend that for EOMG, thymectomy should be considered early in the disease to improve clinical outcomes and minimize the need for immunotherapy [33–36]. Given the limited research on thymectomy in MG patients over 50, these guidelines do not support thymectomy in older patients. However, some guidelines recommend surgery up to the age of 65 years, highlighting a debate and contradiction [37–39]. Here, the meta-analysis showed that thymectomy may be more effective than medical therapies alone in a subgroup of LOMG. The meta-analysis of proportion showed that 34% (24%–44%) of LOMG can reach remission or MM status after thymectomy. Additionally, patients with a shorter disease duration showed significantly better response to thymectomy.

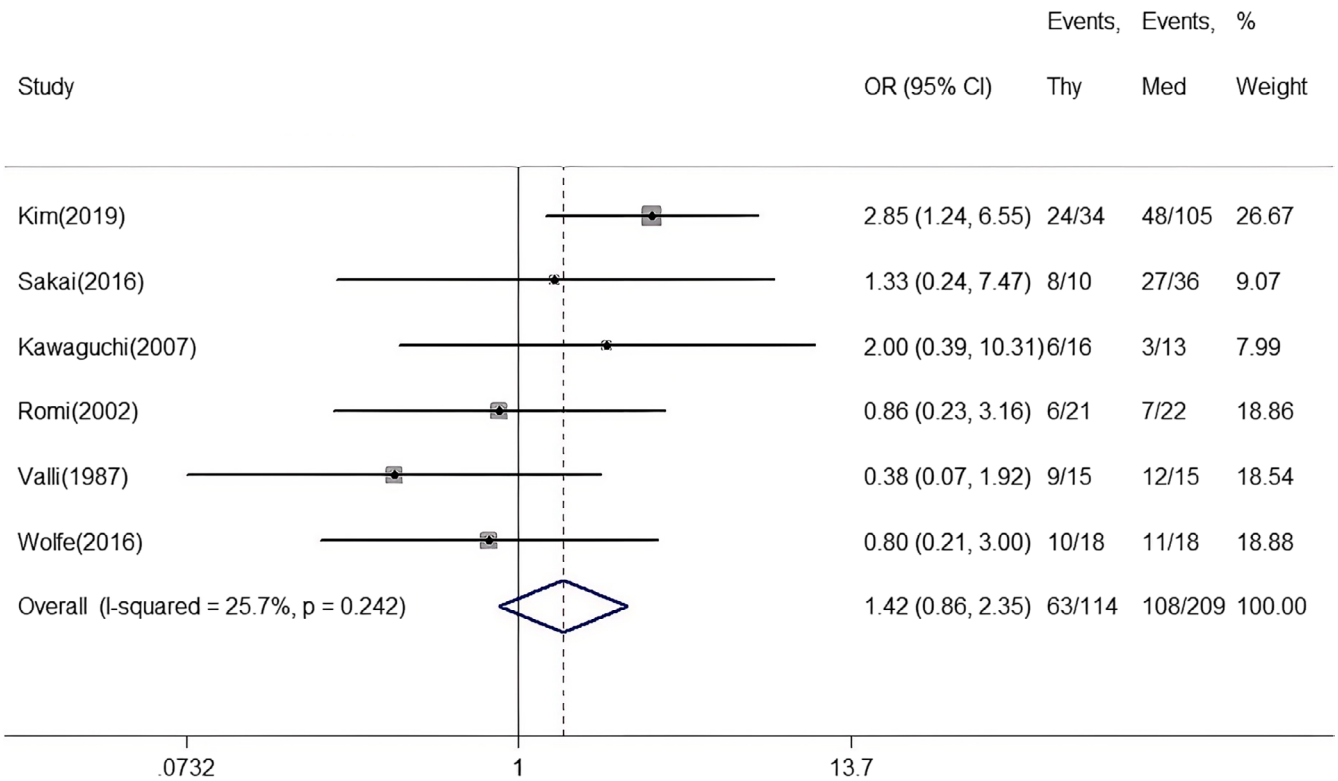

FIGURE 2 | Forest plot for the response to thymectomy and medical therapies alone.

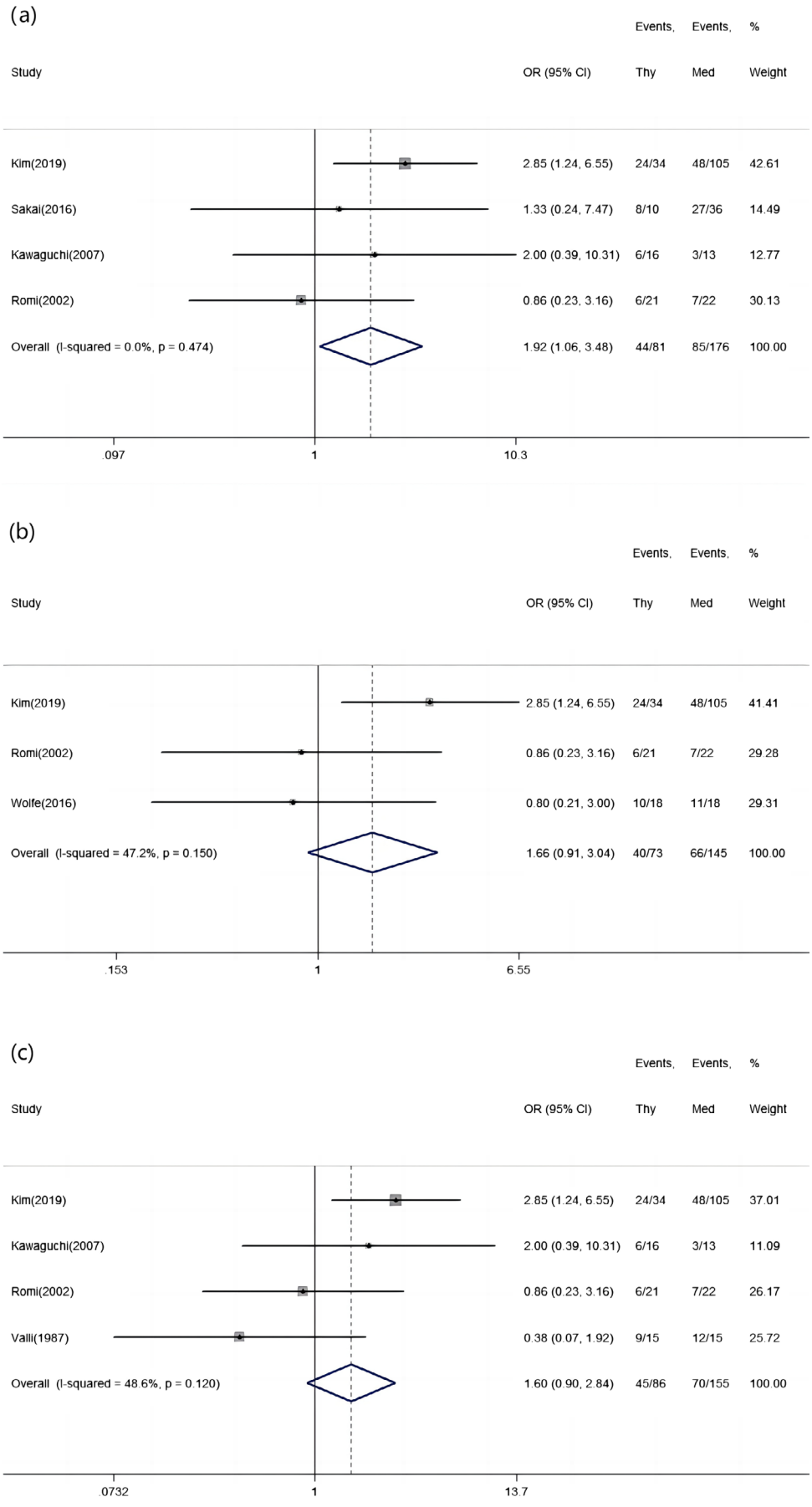

FIGURE 3 | Forest plot for the response to thymectomy and medical therapies alone in subgroup analysis. (a) age of MG onset ≥ 45 years old or age at thymectomy ≥ 50 years old, (b) the presence of AChR-Ab, (c) a demanding response.

TABLE 2 | Summary of the additional 14 thymectomized studies.

Study	Age of cutoff	Sample size	Gender (M/F)	Age of onset	Disease duration (y)	AChR-Ab positive	MG severity	Age of Thy (y)	Thymus pathology	Prednisone before Thy	Follow-up (after Thy)	Outcome
Sarkkinen [21]	50	14	10/4	62.8 ± 8.9	NA	10/13 (76.9%)	2 OMG, 12 GMG	64 ± 8.4	12 normal, 2 hyperplasia	NA	2 y; 10 ± 4.7 year(s)	2/13 (15.4%) PR; 4/13 (30.8%) MM (last follow-up)
Li [22]	60	43	32/11	67 (61–82)	1.08 (0. 17–14)	40 (93%)	6 OMG, 37 GMG	> 60	6 hyperplasia, 37 involution	31 (72. 1%)	5 (1–21.75) year(s)	6/32 (18.8%) remission+MM
Uzawa [23]	50	39	20/19	61.7 (50–74)	1.45 (0. 1–11.7)	39 (100%)	MGFA: 31 II, 7 III, 1 IV	62.7 (51–76)	5 hyperplasia, 34 atrophy	30 (76.9%)	2 year	12 (30.8%) remission
Liu [24]	40*	46	NA	NA	NA	NA	NA	> 40	NA	NA	5.2 (3.1–7.2) year(s)	21 (45.7%) CSR
Lin [25]	40	18	NA	NA(40–78)	NA	NA	NA	> 40	NA	NA	4.5 (1–10.9) year(s)	4 (22.2%) CSR
Zielinski [26]	40*	18	NA	NA	NA	NA	NA	NA (40–70)	NA	NA	At least 3.5 year	4 (22.2%) CSR
Mantegazza [27]	40	21	NA	> 40	NA	NA	NA	> 40	NA	NA	2 and 6 year(s)	2 (9.5%) remission, same at 6 year
Tsuchida [28]	70	6	2/4	71.2 (69–75)	0.83 (0.17–2.83)	6 (100%)	Osserman 6 IIA	71.8 (70–75)	1 hyperplasia, 3 atrophy, 2 normal	3 (50%)	Mean 4.4 year	No remission; 4 (66.6%) improved
Mack [16]	40	5	4/1	61.85 (47–83.5)	1.75 (0.5–4)	NA	Osserman: 5 II	63.6 (48–84)	2 hyperplasia, 2 atrophy, 1 normal	2 (40%)	2.02 (0.58–3.08) year(s)	No remission; 3 (60%) improved
First [17]	40	9	5/4	50.29 (42–61)	2.04 (0. 1–7)	6/8 (75%)	Oosterhuis: 2 I, 2 II, 2 III, 3 IV	52.33 (43–67)	NA	NA	6.25 (0.83–21) year(s)	2 (22.2%) remission
Maggi [29]	40	121	NA	> 40	NA	NA	NA	> 40	NA	NA	NA	31/117 (26.4%) remission
Olanow [30]	40	19	11/8	NA	1.5 (0.08–12)	14 (73.7%)	Modified Osserman:13 II, 5 III, 1 IV	57.4 (40–82)	1 hyperplasia, 17 atrophy, 1 cyst	10 (52.6%)	3.8 (1.5–5.8) year(s)	13 (68.4%) remission
Moden [31]	50	8	3/5	50–59	NA	NA	Modified Osserman: 1 I, 7 II	> 50	NA	NA	3 and 5 year(s)	2/4 (50%) remission; same at 5 year
Rubin [32]	40*	3	0/3	NA	NA	NA	1/1 (100%)	> 40	2 hyperplasia, 1 NA	NA	3.5 (0.5–7) year(s)	1/3 (33.3%) CSR

Note: Data were expressed as counts (percentages), median (Q1, Q3), mean ± SD, or mean (range). *The cut-off age of Liu [24], Zielinski [26] and Rubin [32] was the age at surgery.
Abbreviations: AChR-Ab, acetylcholine receptor antibodies; F, female; M, male; MG, myasthenia gravis; OMG, ocular MG; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestation; NA, not available; R, remission (complete stable remission and/or pharmacologic remission); Thy, thymectomy.

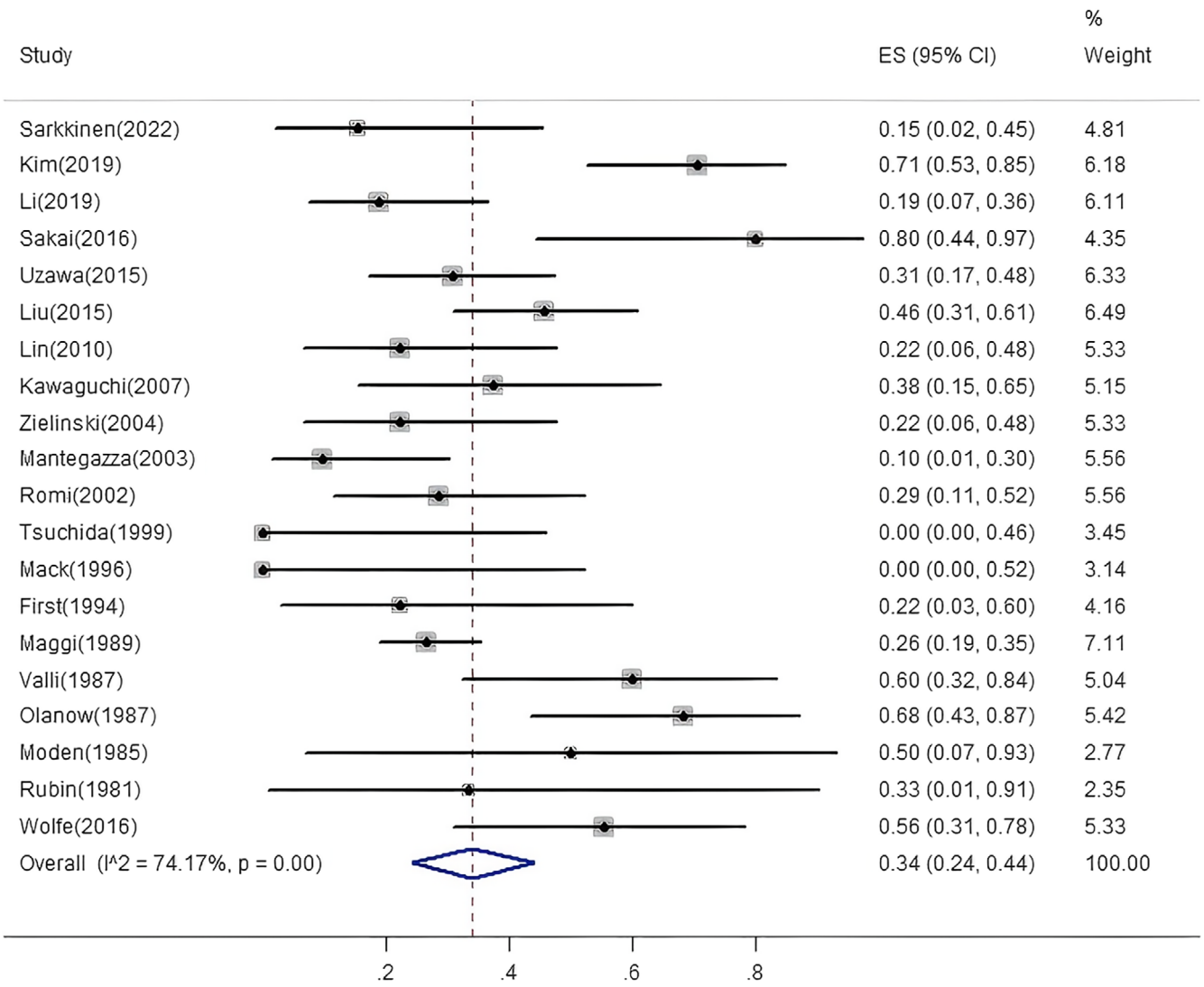

FIGURE 4 | Response to thymectomy in all enrolled studies.

TABLE 3 | Subgroup analysis of thymectomized studies.

Total	Subgroups	Studies	Sample size	Meta of proportion (95% CI)	*Z*-test
20 studies, 464 subjects, 34% (24%–44%)	Age at MG onset (≥ 50 years old)	12	161	31% (17%–46%)	$z = -0.795$, $p = 0.426$, $q = 0.639$
	Age at thymectomy (≥ 50 years old)	13	198	35% (19%–51%)	$z = 0.055$, $p = 0.956$, $q = 0.956$
	AChR-Ab positive	8	139	40% (21%–61%)	$z = 2.330$, $p = 0.020$, $q = 0.060$
	MG duration ≤ 3 years	8	87	39% (16%–65%)	$z = 4.917$, $p < 0.001$, $q < 0.001$
	Thymic involution/ atrophy	6	93	46% (23%–69%)	$z = 1.050$, $p = 0.294$, $q = 0.588$
	Postoperative follow-up time ≤ 3 years	9	114	34% (15%–56%)	$z = -0184$, $p = 0.854$, $q = 0.956$

Note: The *q*-values represent the adjusted *p*-values that minimize the false discovery rate using the Benjamini–Hochberg method.

Our findings support additional assessment of thymectomy for older patients.

MG is divided into EOMG and LOMG, but there is no consensus on a boundary for these groups, and studies included population from 40 to 50 years of age [9]. Emerging evidence does support that EOMG and LOMG have distinct biological characteristics, which presumably translate to potential differences in treatment response. The MGTX study found thymectomy to be beneficial for adult patients up to 65 years old, although subgroup analysis of individuals aged 50 to 65 years was inconclusive [14]. A critical gap in knowledge is defining the degree to which the thymus in patients at more advanced age is driving pathology. Many investigations indicated that the thymus becomes increasingly atrophic during normal aging [40]. Sarkkinen (2022) [21] found a steep decline of germinal centers after the age of 40 years, and the number of germinal centers was negligible after the age of 45 years. A comprehensive assessment of thymus pathology of MGTX thymus found no relationship in follicle number or thymic fat with age or outcome [41]. We do not believe that there should be an assumption that the thymus is immunologically inactive in patients with LOMG. This point is supported by the observation that the thymus from older individuals bears similarities to MG thymus, with alterations in perivascular space volumes and thymic epithelial space [42, 43]. Since the patient with MG has a dysregulated immune system regardless of age, such common alterations support the potential of active signaling to promote the autoimmune response in LOMG. Our subgroup analysis supports this conclusion. We found that for LOMG patients with an onset age ≥ 45 or a surgical age ≥ 50 years old, thymectomy was superior to medical therapies alone. The response rate of LOMG patients with thymic involution and atrophy was not inferior to those of the overall surgical group. These findings suggest that decisions regarding thymectomy should not be based solely on the onset age or a particular age cutoff. Other clinical characteristics should be considered when making the surgical decision for LOMG patients.

The thymus, which expresses subunits of AChR as tissue-specific antigens and displays functional receptors, serves as a pathological effector organ and a source of autoantibodies in MG patients [44]. The thymic pathology is also linked to titin-Ab and RyR-Ab, commonly found in thymoma-associated MG and severe late-onset cases [45, 46]. AChR-Ab, as the primary pathogenic antibody, is a positive biomarker for thymectomy [1, 9]. In the present study, a better trend appeared in AChR-Ab-positive patients both in comparison with medical therapies and the response subgroup analysis, though it did not meet significance. Few studies on thymectomy in LOMG have focused on titin and RyR antibodies. Only Romi [12] found that the presence of these two antibodies lowered the response to treatment. When both titin and RyR antibodies were negative, full clinical remission appeared in 4/21 (19.0%) thymectomy patients and 2/22 (9.1%) medical therapy patients. However, when both titin and RyR antibodies were positive, there were no remissions in either group. Additionally, apart from remission or MM, Sakai [19] indicated that the proportion of crises in LOMG patients who underwent thymectomy (0/10, 0%) was significantly lower than in those who received only medical therapies (4/36, 11.1%). This may be because these two antibodies (titin and RyR) are associated with more severe conditions and are less likely to achieve remission or MM [45, 46]. Nonetheless, as observed in EOMG patients with titin or RyR antibodies, thymectomy may stabilize or improve their disease condition [47]. Firm conclusions cannot be made because of the low numbers of subjects in these studies.

The meta-analysis of proportion indicates that preoperative duration of less than 3 years is associated with a better response to thymectomy in LOMG. Disease duration plays a key role in treatment response, and preoperative duration has been suggested to impact the effectiveness of thymectomy [48–51]. Another study, focusing on both thymomatous and non-thymomatous MG patients, also reported that a shorter duration before surgery (<12 months) correlated with better outcomes ($p=0.016$) [48]. Early diagnosis and timely thymectomy lead to more favorable improvements [49]. In a single-center, cross-sectional study, patients without thymoma were classified into early and late thymectomy groups based on whether the onset of MG occurred more than 2 years before the surgery [50]. There were 65 (46.8%) patients in the early surgical group and 74 (53.2%) in the late group. The early thymectomy group had a higher remission rate compared to the late group (67.7% vs. 50.0%, $p=0.035$). Further, compared with medical therapies alone, late thymectomy still showed better outcomes (50.0% vs. 25.2%, $p<0.001$). These findings suggested that implementing an adequate and active treatment regimen early may prevent permanent damage to the neuromuscular junction and reduce the generation and migration of long-lived plasma cells from the thymus to the periphery, thereby improving long-term outcomes. Postoperative follow-up time is an important metric to consider. The response to thymectomy may improve over time. Maggi [29] found that the best remission rate was observed with a follow-up period of 5–10 years. In the study by Sarkkinen [21], the response rate was 15.4% (2/13) at 2 years after surgery and increased to 30.8% (4/13) at an average of 10 ± 4.7 years. However, this trend was absent in two other studies. Mantegazza [27] followed up their patients for 2 and 6 years, both showing a response rate of 9.5%. Moden [31] followed up for 3 and 5 years, also reporting the same result of 50.0% at both time points.

We acknowledge limitations in our study. First, the age-defining criteria of LOMG was not consistent across studies [33]. The studies included in our review do not fully meet these criteria and may include patients with cases of EOMG, ocular MG, and seronegative MG. Therefore, a subgroup analysis was performed in the study to minimize bias. Those published researches span from 1984 to 2022, a period marked by rapid advancements in MG treatment, including both surgical management and targeted medical therapies. There is significant heterogeneity across most estimates, likely due to variations in populations, measurement conditions, and study designs. Some pooled evaluations may under- or overestimate the response to thymectomy. Additionally, other factors, such as the surgical approach and the preoperative and postoperative treatments, were either not documented or lacked sufficient detail; therefore, they could not be extracted. These factors may also influence the response to thymectomy. Despite these limitations, the systematic review and meta-analysis suggest the need to assess the potential benefit of thymectomy for LOMG.

With the rising number of elderly MG patients and the notable peak in late-onset cases, addressing the appropriate age

for thymectomy has become an urgent clinical need. However, given the likely greater potential morbidity in older patients with multiple comorbidities, surgical intervention must be tailored to the individual and preoperative care of the patient [52].

5 | Conclusion

Thymectomy may be a potentially effective treatment for LOMG, particularly in patients who underwent the procedure early in the course of the disease following diagnosis. Our results support the development of a randomized trial for patients with LOMG.

Author Contributions

Jiaxin Chen: conceptualization, methodology, writing – original draft, data curation, formal analysis, software. **Chunhua Su:** data curation, writing – review and editing, formal analysis, methodology. **Huiyu Feng:** conceptualization, writing – review and editing, supervision, methodology, data curation. **Henry J. Kaminski:** conceptualization, writing – review and editing, supervision, formal analysis, methodology, validation.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and analyzed for the current study are included in this review and its Supporting Information and can be found on the registered website (PROSPERO: CRD42024510953).

References

1. H. J. Kaminski, P. Sikorski, S. I. Coronel, and L. L. Kusner, "Myasthenia Gravis: The Future Is Here," *Journal of Clinical Investigation* 134, no. 12 (2024): e179742, https://doi.org/10.1172/JCI179742.

2. A. R. Punga, P. Maddison, J. M. Heckmann, J. T. Guptill, and A. Evoli, "Epidemiology, Diagnostics, and Biomarkers of Autoimmune Neuromuscular Junction Disorders," *Lancet Neurology* 21, no. 2 (2022): 176–188, https://doi.org/10.1016/S1474-4422(21)00297-0.

3. E. Sobieszczuk, L. Napiorkowski, P. Szczudlik, and A. Kostera-Pruszczyk, "Myasthenia Gravis in Poland: National Healthcare Database Epidemiological Study," *Neuroepidemiology* 55 (2021): 62–69, https://doi.org/10.1159/000512973.

4. J. Chen, D. C. Tian, C. Zhang, et al., "Incidence, Mortality, and Economic Burden of Myasthenia Gravis in China: A Nationwide Population-Based Study," *Lancet Regional Health—Western Pacific* 5 (2020): 100063, https://doi.org/10.1016/j.lanwpc.2020.100063.

5. J. S. Park, K. Y. Eah, and J. M. Park, "Epidemiological Profile of Myasthenia Gravis in South Korea Using the National Health Insurance Database," *Acta Neurologica Scandinavica* 145, no. 5 (2022): 633–640, https://doi.org/10.1111/ane.13596.

6. H. Yoshikawa, Y. Adachi, Y. Nakamura, et al., "Two-Step Nationwide Epidemiological Survey of Myasthenia Gravis in Japan 2018," *PLoS One* 17, no. 9 (2022): e0274161, https://doi.org/10.1371/journal.pone.0274161.

7. D. A. Garcia Estevez, L. M. Lopez Diaz, M. Pardo Parrado, et al., "Epidemiology of Myasthenia Gravis in the Province of Ourense (Galicia, Spain)," *Neurología* 38, no. 2 (2023): 75–81, https://doi.org/10.1016/j.nrleng.2020.06.013.

8. E. Salort-Campana, P. Laforet, G. de Pouvourville, et al., "Epidemiology of Myasthenia Gravis in France: A Retrospective Claims Database Study (STAMINA)," *Revue Neurologique* 180, no. 3 (2024): 202–210, https://doi.org/10.1016/j.neurol.2023.09.004.

9. N. E. Gilhus and J. J. Verschuuren, "Myasthenia Gravis: Subgroup Classification and Therapeutic Strategies," *Lancet Neurology* 14, no. 10 (2015): 1023–1036, https://doi.org/10.1016/S1474-4422(15)00145-3.

10. J. Zhang, Y. Chen, H. Zhang, Z. Yang, and P. Zhang, "Effects of Thymectomy on Late-Onset Non-Thymomatous Myasthenia Gravis: Systematic Review and Meta-Analysis," *Orphanet Journal of Rare Diseases* 16, no. 1 (2021): 232, https://doi.org/10.1186/s13023-021-01860-y.

11. S. W. Kim, Y. C. Choi, S. M. Kim, H. S. Shim, and H. Y. Shin, "Effect of Thymectomy in Elderly Patients With Non-Thymomatous Generalized Myasthenia Gravis," *Journal of Neurology* 266, no. 4 (2019): 960–968, https://doi.org/10.1007/s00415-019-09222-2.

12. F. Romi, N. E. Gilhus, J. E. Varhaug, A. Myking, G. O. Skeie, and J. A. Aarli, "Thymectomy and Anti-Muscle Autoantibodies in Late-Onset Myasthenia Gravis," *European Journal of Neurology* 9, no. 1 (2002): 55–61, https://doi.org/10.1046/j.1468-1331.2002.00352.x.

13. G. Valli, S. Jann, S. Premoselli, and G. Scarlato, "Myasthenia Gravis Treatment: Twelve Years Experience on 110 Patients," *Italian Journal of Neurological Sciences* 8, no. 6 (1987): 593–601, https://doi.org/10.1007/BF02333667.

14. G. I. Wolfe, H. J. Kaminski, I. B. Aban, et al., "Randomized Trial of Thymectomy in Myasthenia Gravis," *New England Journal of Medicine* 375, no. 6 (2016): 511–522, https://doi.org/10.1056/NEJMoa1602489.

15. A. Jaretzki, 3rd, R. J. Barohn, R. M. Ernstoff, et al., "Myasthenia Gravis: Recommendations for Clinical Research Standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America," *Neurology* 55, no. 1 (2000): 16–23, https://doi.org/10.1212/wnl.55.1.16.

16. M. J. Mack, R. J. Landreneau, A. P. Yim, S. R. Hazelrigg, and G. R. Scruggs, "Results of Video-Assisted Thymectomy in Patients With Myasthenia Gravis," *Journal of Thoracic and Cardiovascular Surgery* 112, no. 5 (1996): 1352–1360, https://doi.org/10.1016/s0022-5223(96)70151-4.

17. W. H. Frist, S. Thirumalai, C. B. Doehring, et al., "Thymectomy for the Myasthenia Gravis Patient: Factors Influencing Outcome," *Annals of Thoracic Surgery* 57, no. 2 (1994): 334–338, https://doi.org/10.1016/0003-4975(94)90993-8.

18. M. Cumpston, T. Li, M. J. Page, et al., "Updated Guidance for Trusted Systematic Reviews: A New Edition of the Cochrane Handbook for Systematic Reviews of Interventions," *Cochrane Database of Systematic Reviews* 10, no. 10 (2019): ED000142, https://doi.org/10.1002/14651858.ED000142.

19. W. Sakai, N. Matsui, M. Ishida, et al., "Late-Onset Myasthenia Gravis Is Predisposed to Become Generalized in the Elderly," *eNeurologicalSci* 2 (2016): 17–20, https://doi.org/10.1016/j.ensci.2016.02.004.

20. N. Kawaguchi, S. Kuwabara, Y. Nemoto, et al., "Effects of Thymectomy on Late-Onset Myasthenia Gravis Without Thymoma," *Clinical Neurology and Neurosurgery* 109, no. 10 (2007): 858–861, https://doi.org/10.1016/j.clineuro.2007.08.006.

21. J. Sarkkinen, J. Dunkel, A. Tuulasvaara, et al., "Ectopic Germinal Centers in the Thymus Accurately Predict Prognosis of Myasthenia Gravis After Thymectomy," *Modern Pathology* 35, no. 9 (2022): 1168–1174, https://doi.org/10.1038/s41379-022-01070-2.

22. F. Li, R. Takahashi, G. Bauer, et al., "Results of Robotic Thymectomy Performed in Myasthenia Gravis Patients Older Than 60 Years at Onset," *Annals of Thoracic Surgery* 108, no. 3 (2019): 912–919, https://doi.org/10.1016/j.athoracsur.2019.02.016.

23. A. Uzawa, N. Kawaguchi, T. Kanai, et al., "Two-Year Outcome of Thymectomy in Non-Thymomatous Late-Onset Myasthenia Gravis," *Journal of Neurology* 262, no. 4 (2015): 1019–1023, https://doi.org/10.1007/s00415-015-7673-z.

24. Z. Liu, J. Yang, L. Lin, J. Huang, and G. Jiang, "Unilateral Video-Assisted Thoracoscopic Extended Thymectomy Offers Long-Term Outcomes Equivalent to That of the Bilateral Approach in the Treatment of Non-Thymomatous Myasthenia Gravis," *Interactive Cardiovascular and Thoracic Surgery* 21, no. 5 (2015): 610–615, https://doi.org/10.1093/icvts/ivv176.

25. M. W. Lin, Y. L. Chang, P. M. Huang, and Y. C. Lee, "Thymectomy for Non-Thymomatous Myasthenia Gravis: A Comparison of Surgical Methods and Analysis of Prognostic Factors," *European Journal of Cardio-Thoracic Surgery* 37, no. 1 (2010): 7–12, https://doi.org/10.1016/j.ejcts.2009.05.027.

26. M. Zielinski, J. Kuzdzal, A. Szlubowski, and J. Soja, "Comparison of Late Results of Basic Transsternal and Extended Transsternal Thymectomies in the Treatment of Myasthenia Gravis," *Annals of Thoracic Surgery* 78, no. 1 (2004): 253–258, https://doi.org/10.1016/j.athoracsur.2003.11.040.

27. R. Mantegazza, F. Baggi, P. Bernasconi, et al., "Video-Assisted Thoracoscopic Extended Thymectomy and Extended Transsternal Thymectomy (T-3b) in Non-Thymomatous Myasthenia Gravis Patients: Remission After 6 Years of Follow-Up," *Journal of the Neurological Sciences* 212, no. 1–2 (2003): 31–36, https://doi.org/10.1016/s0022-510x(03)00087-x.

28. M. Tsuchida, Y. Yamato, T. Souma, et al., "Efficacy and Safety of Extended Thymectomy for Elderly Patients With Myasthenia Gravis," *Annals of Thoracic Surgery* 67, no. 6 (1999): 1563–1567, https://doi.org/10.1016/s0003-4975(99)00167-8.

29. G. Maggi, C. Casadio, A. Cavallo, R. Cianci, M. Molinatti, and E. Ruffini, "Thymectomy in Myasthenia Gravis. Results of 662 Cases Operated Upon in 15 Years," *European Journal of Cardio-Thoracic Surgery* 3, no. 6 (1989): 504–511, https://doi.org/10.1016/1010-7940(89)90109-7.

30. C. W. Olanow, A. S. Wechsler, M. Sirotkin-Roses, J. Stajich, and A. D. Roses, "Thymectomy as Primary Therapy in Myasthenia Gravis," *Annals of the New York Academy of Sciences* 505 (1987): 595–606, https://doi.org/10.1111/j.1749-6632.1987.tb51328.x.

31. Y. Monden, K. Nakahara, Y. Fujii, et al., "Myasthenia Gravis in Elderly Patients," *Annals of Thoracic Surgery* 39, no. 5 (1985): 433–436, https://doi.org/10.1016/s0003-4975(10)61951-0.

32. J. W. Rubin, R. G. Ellison, H. V. Moore, and G. P. Pai, "Factors Affecting Response to Thymectomy for Myasthenia Gravis," *Journal of Thoracic and Cardiovascular Surgery* 82, no. 5 (1981): 720–728.

33. P. Narayanaswami, D. B. Sanders, G. Wolfe, et al., "International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update," *Neurology* 96, no. 3 (2021): 114–122, https://doi.org/10.1212/WNL.0000000000011124.

34. Neuroimmunology Branch of Chinese Immunology Society, "Chinese Guidelines for Diagnosis and Treatment of Myasthenia Gravis (2020)," *Chinese Journal of Neuroimmunology and Neurology* 28, no. 1 (2021): 1–12, https://doi.org/10.3969/j.ISSN.1006-2963.2021.01.001.

35. A. Evoli, G. Antonini, C. Antozzi, et al., "Italian Recommendations for the Diagnosis and Treatment of Myasthenia Gravis," *Neurological Sciences* 40, no. 6 (2019): 1111–1124, https://doi.org/10.1007/s10072-019-03746-1.

36. H. Murai, K. Utsugisawa, M. Motomura, T. Imai, A. Uzawa, and S. Suzuki, "The Japanese Clinical Guidelines 2022 for Myasthenia Gravis and Lambert–Eaton Myasthenic Syndrome," *Clinical and Experimental Neuroimmunology* 14, no. 1 (2023): 19–27, https://doi.org/10.1111/cen3.12739.

37. H. Wiendl, A. Abicht, A. Chan, et al., "Guideline for the Management of Myasthenic Syndromes," *Therapeutic Advances in Neurological Disorders* 17 (2024): 17562864241246400, https://doi.org/10.1177/17562864241246400.

38. S. Nafissi, A. A. Okhovat, F. Sinaei, et al., "Iranian Consensus Recommendations for Treatment of Myasthenia Gravis," *Archives of Iranian Medicine* 25, no. 1 (2022): 37–49, https://doi.org/10.34172/aim.2022.07.

39. G. S. Gronseth, R. Barohn, and P. Narayanaswami, "Practice Advisory: Thymectomy for Myasthenia Gravis (Practice Parameter Update): Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology," *Neurology* 94, no. 16 (2020): 705–709, https://doi.org/10.1212/WNL.0000000000009294.

40. F. Truffault, V. de Montpreville, B. Eymard, T. Sharshar, R. Le Panse, and S. Berrih-Aknin, "Thymic Germinal Centers and Corticosteroids in Myasthenia Gravis: An Immunopathological Study in 1035 Cases and a Critical Review," *Clinical Reviews in Allergy and Immunology* 52, no. 1 (2017): 108–124, https://doi.org/10.1007/s12016-016-8558-3.

41. C. A. Weis, I. B. Aban, G. Cutter, et al., "Histopathology of Thymectomy Specimens From the MGTX-Trial: Entropy Analysis as Strategy to Quantify Spatial Heterogeneity of Lymphoid Follicle and Fat Distribution," *PLoS One* 13, no. 6 (2018): e0197435, https://doi.org/10.1371/journal.pone.0197435.

42. K. G. Flores, J. Li, G. D. Sempowski, B. F. Haynes, and L. P. Hale, "Analysis of the Human Thymic Perivascular Space During Aging," *Journal of Clinical Investigation* 104, no. 8 (1999): 1031–1039, https://doi.org/10.1172/JCI7558.

43. A. I. Kousa, L. Jahn, K. Zhao, et al., "Age-Related Epithelial Defects Limit Thymic Function and Regeneration," *Nature Immunology* 25, no. 9 (2024): 1593–1606, https://doi.org/10.1038/s41590-024-01915-9.

44. Y. Li, Y. Peng, and H. Yang, "Serological Diagnosis of Myasthenia Gravis and Its Clinical Significance," *Annals of Translational Medicine* 11, no. 7 (2023): 290, https://doi.org/10.21037/atm-19-363.

45. F. Romi, G. O. Skeie, J. A. Aarli, and N. E. Gilhus, "The Severity of Myasthenia Gravis Correlates With the Serum Concentration of Titin and Ryanodine Receptor Antibodies," *Archives of Neurology* 57, no. 11 (2000): 1596–1600, https://doi.org/10.1001/archneur.57.11.1596.

46. A. Meisel, F. Baggi, A. Behin, et al., "Role of Autoantibody Levels as Biomarkers in the Management of Patients With Myasthenia Gravis: A Systematic Review and Expert Appraisal," *European Journal of Neurology* 30, no. 1 (2023): 266–282, https://doi.org/10.1111/ene.15565.

47. Y. Chen, X. Tao, Y. Wang, et al., "Clinical Characteristics and Prognosis of Anti-AChR Positive Myasthenia Gravis Combined With Anti-LRP4 or Anti-Titin Antibody," *Frontiers in Neurology* 13 (2022): 873599, https://doi.org/10.3389/fneur.2022.873599.

48. S. Cunha, P. Faustino, A. Jorge, et al., "The Impact of Thymectomy in Thymomatous and Nonthymomatous Myasthenia Gravis—the Experience of a Tertiary Center," *Portuguese Journal of Cardiac Thoracic and Vascular Surgery* 30, no. 4 (2024): 31–38, https://doi.org/10.48729/pjctvs.328.

49. V. Bak, P. Spalek, M. Rajcok, L. Danihel, and M. Schnorrer, "Importance of Thymectomy and Prognostic Factors in the Complex Treatment of Myasthenia Gravis," *Bratislavské Lekárske Listy* 117, no. 4 (2016): 195–200, https://doi.org/10.4149/bll_2016_037.

50. H. Y. Chung, S. W. Kim, J. G. Lee, H. S. Shim, and H. Y. Shin, "Thymectomy and Disease Duration in Non-Thymomatous Acetylcholine Receptor Antibody-Positive Myasthenia Gravis: A Single-Centre, Cross-Sectional Study," *Journal of Neurology, Neurosurgery, and Psychiatry* 94, no. 4 (2023): 328–330, https://doi.org/10.1136/jnnp-2022-329834.

51. M. Tomschik, E. Hilger, J. Rath, et al., "Subgroup Stratification and Outcome in Recently Diagnosed Generalized Myasthenia Gravis,"

Neurology 95, no. 10 (2020): e1426–e1436, https://doi.org/10.1212/WNL.0000000000010209.

52. H. J. Kaminski, L. L. Kusner, G. R. Cutter, et al., "Does Surgical Removal of the Thymus Have Deleterious Consequences?," *Neurology* 102, no. 12 (2024): e209482, https://doi.org/10.1212/WNL.0000000000209482.

Supporting Information

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