Short-term and sustained clinical response following thymectomy in patients with myasthenia gravis

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Abstract

**Background and purpose:** This study was undertaken to investigate short- and long-term outcome following thymectomy in patients with acetylcholine receptor antibody (AChR-Ab)-positive myasthenia gravis (MG).

**Methods:** Rates of clinical response (defined as minimal manifestation, pharmacological remission, or complete stable remission) lasting for at least 1 year were retrospectively analyzed using Cox proportional hazard models. The occurrence of relapses was recorded during follow-up. Clinical factors associated with achieving an initial or a sustained response were analyzed.

**Results:** Ninety-four patients with a median age of 33 years (interquartile range \([IQR] = 22–51\)), 68% with nonthymomatous MG and 32% with thymoma-associated MG, were included. An initial clinical response was reached in 72% (68/94). Neither sex, age at onset, thymus histology, delay to surgery after disease onset, surgical approach, corticosteroid treatment, nor clinical severity before thymectomy was significantly associated with achieving this endpoint. During long-term follow-up (median \(= 89.5\) months, \(IQR = 46–189.5\)), only half of the patients with an initial response (34/68) had a sustained response without relapses. No clinical factors predicted whether the response would become sustained. In patients without immunosuppressive treatment before thymectomy \((n = 24)\), a high AChR-Ab reduction rate after thymectomy was associated with a higher likelihood of achieving an initial response \((p = 0.03)\).

**Conclusions:** Sustained long-term clinical response of MG patients after thymectomy is significantly lower than the initial response rates would suggest. The observation that none of the evaluated clinical factors was associated with a worse outcome supports the current clinical practice of patient selection for thymectomy. The relative decline of AChR-Abs after surgery appears to be a promising prognostic marker.

**Keywords**

antibody, myasthenia gravis, outcome, thymectomy
INTRODUCTION

Myasthenia gravis (MG) is an antibody-mediated autoimmune disorder of the neuromuscular junction, associated with a high morbidity due to fluctuating and often debilitating muscle weakness. The disease affects approximately one in 6,500 people, with up to 10% developing a treatment-refractory course, highlighting the need for more effective and individually tailored treatment strategies [1,2]. It is now recognized that there are several subtypes of the disease, with different underlying pathomechanisms, some of which also involve the thymus [3]. This is particularly the case for thymoma-associated MG (TAMG) and for nonthymomatous MG associated with antibodies against the nicotinic acetylcholine receptor (AChR-Abs), where the thymus often displays ectopic inflammation (lymphofollicular hyperplasia) [4]. Given these pathological changes, thymectomy has long been practiced, not only for thymomatous but also for nonthymomatous MG, although the effectiveness remained controversial for the latter. This controversy was finally settled in 2016 after publication of the seminal MGTX trial, which included patients with AChR-Ab-positive nonthymomatous MG younger than 65 years. Here, transsternal-extended thymectomy compared to medical therapy alone improved myasthenic symptoms and reduced the need for hospitalization and steroid treatment after 3 years of medical therapy alone improved myasthenic symptoms and reduced the need for hospitalization and steroid treatment after 3 years of follow-up [5]. Moreover, in a smaller subset of patients who completed the MGTX extension study, the effect was persistent after 5 years [6]. Although the beneficial effect was clearly proven for the whole group of patients as defined by the inclusion criteria, the study could not address whether this would extend equally to all subgroups within the inclusion criteria or would also apply beyond. In particular, it is being debated whether patients with an older age at onset (but within the age inclusion range) would benefit just as well as younger patients or whether a pretreatment with immunosuppressive drugs before thymectomy would matter. The question remains whether the time delay to surgery (up to 5 years after MG onset in the study), the type of thymectomy, the gender of the patient, or the histology of the thymus would influence the outcome. Although these questions are highly relevant in clinical routine, it is unlikely that they will ever be answered by randomized trials with strict inclusion criteria. It is therefore of particular interest to critically analyze real-world outcome data for any information on the relevance of patient variables affecting surgery outcome.

The aim of this retrospective study was to investigate the occurrence of a favorable outcome (i.e., achieving a clinical response defined as minimal manifestation, pharmacological remission, or complete stable remission lasting for 1 year) after thymectomy in a large real-world single center cohort in Austria over the past 30 years in dependence of several relevant clinical variables. As MG is a notoriously fluctuating disease, we additionally investigated whether any of these clinical variables would influence the durability of the achieved response or, in other words, the likelihood of a secondary deterioration after an initial response.

METHODS

Patients

We retrospectively evaluated clinical data of patients with MG who were being treated at the Department of Neurology of the Medical University of Vienna, Austria, between 1991 and 2019. Diagnostic criteria for MG were compatible myasthenic symptoms and the detection of AChR-Abs. We included only patients who underwent thymectomy at the Department of Thoracic Surgery of the Medical University of Vienna and had sufficient clinical data before thymectomy and follow-up data for at least 18 months after thymectomy to allow the assessment of a 1-year clinical response. The study was approved by the ethics committee of the Medical University of Vienna (Ec-Nr 2139/2019). The requirement to obtain patient consent was waived for this retrospective study.

Thymectomy and histology

We analyzed time from symptom onset to thymectomy and the rate of perioperative myasthenic worsening. Type of surgery was classified as described previously [7]. Histology was classified as (i) normal thymic tissue or atrophy, (ii) thymic lymphofollicular hyperplasia, and (iii) thymoma. Thymoma staging and histology were further classified according to the modified Masaoka staging system [8] and the classification system of the World Health Organization (WHO) [9].

Clinical outcome

We retrospectively extracted disease severity and treatment category at documented time points using the criteria of the Myasthenia Gravis Foundation of America (MGFA) class [3].

Primary outcome parameter

As the primary outcome parameter, we chose the occurrence of clinical response lasting for at least 12 months. Clinical response encompassed the MGFA postintervention status (MGFA-PIS) categories of complete stable remission, pharmacological remission, and minimal manifestation (1–3). Although not specifically mentioned in the MGFA classification, we also included asymptomatic patients on regular subcutaneous immunoglobulins (SCIg), intravenous immunoglobulins (IVIg), or immunoadsorption (IA) maintenance therapy, with or without additional immunosuppressive treatment but excluded those with documented worsening between cycles or the need to shorten treatment intervals. In effect, we only included situations where these treatment options were used as maintenance therapy but not as emergency therapy to treat an aggravation.
Secondary clinical outcome parameters

The following additional outcome variables were investigated:

(i) Rate of clinical relapse after reaching the primary endpoint (the absence of a relapse was defined as “sustained clinical response”);
(ii) MGFA and MGFA-PI score at last follow-up;
(iii) Worst MGFA following thymectomy defined as the highest MGFA class following thymectomy excluding the first month after surgery; and
(iv) Immunosuppressive treatment modification during the course of the disease after thymectomy (i.e., the start of a new treatment in previously treatment-naive patients, the change of treatment to another drug, or the addition of a new drug).

Antibody levels

Antibody levels measured by radioimmunoassay were retrospectively extracted. Change in antibody levels, that is, the AChR-Ab level reduction rate (RR-AChR-Ab) in %/day, which was proposed recently [10], was calculated in patients who had at least one measurement in the year before and after thymectomy using the following formula:

\[
RR(AchRAb) = \frac{(Ab_{preTx} - Ab_{postTx})}{Ab_{preTx} \times T(d)} \times 100
\]

where RR is the reduction rate of the AChR antibody titer (AchRAb) in % per day, \(Ab_{preTx}\) the antibody level closest before thymectomy, \(Ab_{postTx}\) the first measurement after thymectomy excluding the first 2 weeks after surgery, and \(T(d)\) the time in days between thymectomy and the measurement of antibody levels after thymectomy. Antibody measurements in patients on chronic immunoadsorption or within 14 weeks after acute plasmapheresis or immunoadsorption were excluded.

Statistical analysis

SPSS Statistics for Macintosh (v26.0, 2019, IBM), R (v4.0.2, 2020, R Foundation for Statistical Computing), and RStudio (v1.3.959, 2020, RStudio PBC) were used for statistical analysis. Univariate analyses were carried out with the chi-squared test, Student t-test, or Mann–Whitney U-test as applicable. Multivariate analysis of clinical response was carried out using Cox proportional hazards regression model, and Kaplan–Meier curves were calculated. Multivariate logistic regression was used to evaluate which patients relapsed after treatment. Receiver operating characteristic (ROC) curves were calculated for change in antibody titers in %/day (RR-AChR-Ab), and the cutoff value was defined by the value that represented the minimum Euclidian distance between the ROC curve and the upper left corner of the panel (i.e., where sensitivity and specificity are both 100%) as:

\[
ED = \sqrt{(1-Se)^2 + (1-Sp)^2}
\]

where ED is the Euclidian distance, Se the sensitivity, and Sp the specificity for each cutoff value investigated.

Multivariate logistic regression was performed to analyze clinical variables between patients above the cutoff and those at or below the cutoff of the ROC curve with the same covariates as above and all two-way interactions as above. \(p \leq 0.05\) was considered statistically significant. Bonferroni correction was applied to adjust \(p\)-values for multiple comparisons for univariate analyses.

RESULTS

Baseline characteristics

We retrospectively investigated 94 patients with MG after thymectomy (36 males, 58 females) with a median age at onset of 33 years (IQR = 22–51, range = 13–75). Sixty-four (68%) had nonthymomatous AChR-Ab MG (54% early onset MG [EOMG] and 14% late onset MG [LOMG]), and 30 (32%) had TAMG. Table 1 shows detailed baseline characteristics of all patients.

Median time from clinical onset to thymectomy was 8.5 months (IQR = 3–18, range = 0–85). The median age at thymectomy in the EOMG and LOMG groups was 29 years (IQR = 22–37, range = 14–50) and 57 years (IQR = 52–66, range = 50–76), respectively. Only seven patients were older than 60 years at the time of thymectomy. Thirty-nine (42%) patients underwent extended transsternal thymectomy, seven of whom were conversions from initial thoracoscoptic approaches. Videoscopic thymectomy was performed in 37 (39%) patients, of whom two had unilateral video-assisted thoracic surgery, 10 video-assisted thoracoscopic extended thymectomy with bilateral neck dissection, and 25 unilateral videoscopic thymectomy with robotic technology. Eighteen (19%) patients underwent transcervical thymectomy (13/18 with videoscopic technology).

All thymectomies were carried out as extended thymectomies with the removal of all thymic lobes en bloc with mediastinal fatty tissue between both phrenic nerves, the thyroid gland orally, and the diaphragm caudally.

In the 64 nonthymomatous patients, histology revealed normal thymic tissue in 28 (44%) and thymic lymphofollicular hyperplasia in 36 patients (56%). Of the TAMG patients, three (10%) had type A thymoma according to the WHO classification, four (13%) type B1, 14 (47%) type B2, six (20%) type B3, two (7%) type AB, and one (3%) type C (thymic carcinoma). Eighteen patients (60%) had Masaoka stage I, 10 (33%) stage II, and two (7%) stage III. Eight patients (27%) received adjuvant radiation therapy, one (3%) patient received chemotherapy, and two (7%) had a relapse after initial successful treatment.
Clinical outcome

The primary outcome of achieving a clinical response (defined as minimal manifestation, pharmacological remission, or complete stable remission according to the MGFA-PIS) lasting for 1 year was reached in 72% of patients (68/94). Kaplan–Meier plots for all patients and stratified according to histology are shown in Figure 1. Cox regression analysis showed that neither age (EOMG vs. LOMG), sex, histology (TAMG vs. normal vs. thymic lympho-follicular hyperplasia), time to thymectomy from clinical onset (within 1 year vs. after 1 year), nor pretreatment with steroids was associated with higher chance of clinical response. Figure 2 shows the adjusted hazard ratios for all variables. However, 34 of these 68 patients who achieved an initial response relapsed during

| Characteristic | All patients, n = 94 | Sustained clinical response, n = 34a | Relapse or no response, n = 60 | p^b |
|----------------|----------------------|-------------------------------------|-------------------------------|-----|
| Sex            | 36 (38%) males       | 18 (53%) males                     | 18 (30%)                      | 0.03^c |
|                | 58 (62%) females     | 16 (47%) females                   | 42 (70%)                      |     |
| Median age at onset, years (IQR) | 33 (22–51) | 40 (27–53) | 31 (22–49) | 0.30 |
| Median age at thymectomy, years (IQR) | 35 (25–51) | 42 (28–53) | 32 (24–50) | 0.30 |
| MG subtype, n (%) |                     |                                    |                               |     |
| AChR-Ab+ EOMG   | 51 (54%)             | 18 (53%)                           | 33 (55%)                      | 0.32 |
| AChR-Ab+ LOMG   | 13 (14%)             | 7 (21%)                            | 6 (10%)                       |     |
| AChR-Ab+ TAMG   | 30 (32%)             | 9 (26%)                            | 21 (35%)                      |     |
| Worst MGFA class within the year before thymectomy, n (%) | | | | |
| 1               | 11 (12%)             | 3 (9%)                             | 8 (13%)                       | 0.51 |
| 2               | 48 (51%)             | 21 (62%)                           | 27 (45%)                      |     |
| 3               | 25 (27%)             | 6 (17%)                            | 19 (32%)                      |     |
| 4               | 7 (7%)               | 3 (9%)                             | 4 (7%)                        |     |
| 5               | 3 (3%)               | 1 (3%)                             | 2 (3%)                        |     |
| Treatment before thymectomy | | | | |
| Corticosteroids, n (%) | 37 (39%) | 12 (35%) | 25 (42%) | 0.54 |
| Median time from start of corticosteroid treatment to thymectomy, weeks (IQR) | 8 (3–39) | 5 (2–10) | 13.5 (5–50) | 0.17 |
| Other immunosuppressants, n (%)d | 10 (11%) | 6 (18%) | 4 (7%) | 0.16 |
| Time from onset to thymectomy, months (IQR) | 8.5 (3–18.5) | 9 (2.75–18.5) | 8 (3–20.75) | 0.91 |
| Surgical approach, n (%) | | | | |
| Transsternal    | 39 (42%)             | 14 (41%)                           | 25 (42%)                      | 0.95 |
| Transcervical   | 18 (19%)             | 6 (18%)                            | 12 (20%)                      |     |
| Videoscopic or robotic | 37 (39%) | 14 (41%) | 23 (38%) |     |
| Clinical worsening after thymectomy, n (%) | | | | |
| MG worsening, excluding crisis | 6 (6%) | 2 (6%) | 4 (7%) | 0.16 |
| MG crisis [MGFA class 5] | 2 (2%) | 2 (6%) | 0 |     |
| Thymus histology, n (%) | | | | |
| Normal/atrophy  | 28 (30%)             | 10 (29%)                           | 18 (30%)                      | 0.62 |
| Hyperplasia     | 36 (38%)             | 15 (44%)                           | 21 (35%)                      |     |
| Thymoma         | 30 (32%)             | 9 (27%)                            | 21 (35%)                      |     |

Note: Baseline characteristics of all patients and univariate comparison of patients with any clinical response following thymectomy vs. no remission during the course of disease.
Abbreviations: AChR-Ab, acetylcholine receptor antibody; EOMG, early onset MG; IQR, interquartile range; LOMG, late onset MG; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; TAMG, thymoma-associated MG.
aThree patients had clinical response only at the last documented visit without further follow-up.
bProbability values were obtained with the Mann–Whitney U-test (for continuous variables) and the chi-squared test or Fisher exact test (for categorical variables) as appropriate.
cStatistically significant.
dNine patients received azathioprine and one patient methotrexate.
the observation period (median = 89.5 months, IQR = 46–189.5). Therefore, only 34 of 94 patients had a sustained clinical response. **Table 1** shows baseline characteristics of this patient group compared with patients who relapsed or never achieved a response. We found no difference in baseline characteristics except for male sex, which was more prevalent in the sustained clinical response group (univariate comparison: \( p = 0.03 \)). However, in the multivariate logistic regression, neither sex (odds ratio [OR] = 2.66, 95% confidence interval [CI] = 0.96–7.4, \( p = 0.06 \)), age at thymectomy (OR = 1.03, 95% CI = 0.99–1.07, \( p = 0.19 \)), histology (\( p = 0.14 \)), surgical approach (\( p = 0.86 \)), nor time from clinical onset to thymectomy (OR = 1, 95% CI = 0.97–1.02, \( p = 0.84 \)) was associated with a higher chance of sustained clinical response.

Patients with sustained clinical response had a shorter time from thymectomy to last follow-up (62.5 vs. 128 months, \( p = 0.05 \)) and lower rates of symptomatic treatment with acetylcholinesterase inhibitors (\( p = 0.001 \)) and immunosuppressive drugs (\( p = 0.006 \)) as well as lower rates of regular SCIg/IVIg cycles or regular plasma exchange therapy/IA (\( p = 0.05 \)) at last follow-up and lower corticosteroid exposure during the course of disease (\( p = 0.01 \)). However,

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**Figure 1** (a, b) Kaplan–Meier plots showing the probability of clinical response (defined as minimal manifestation, pharmacological remission, or complete stable remission according to the Myasthenia Gravis Foundation of America postintervention status) for at least 1 year after thymectomy for all patients (a) and according to histology (b) with univariate \( p \)-values in b for comparison. (c) Individual change of antibodies between the nearest measurement before thymectomy and the first after thymectomy (excluding the first 2 weeks after surgery) in patients who had antibody measurements in the year before and after thymectomy and did not receive an immunosuppressive treatment before thymectomy (\( n = 23/24 \); one patient is excluded from the graph who had very high (>300 nmol/L) antibody levels before and after thymectomy). (d) Rates of clinical response for at least 1 year and subsequent relapse as well as outcome at last follow-up for all patients following thymectomy. AChR-Ab, acetylcholine receptor antibody; IQR, interquartile range [Colour figure can be viewed at wileyonlinelibrary.com]
only the comparison for rates of symptomatic treatment with acetylcholinesterase inhibitors remained statistically significant after correction for multiple comparison (adjusted $\alpha = 0.004$). Moreover, an immunosuppressive treatment modification during the course of the disease was less often necessary in patients with sustained response as compared to patients without sustained response (44% vs. 77%, $p = 0.00!$). In the subgroup of 37 patients who received corticosteroid treatment before thymectomy (nine of whom were additionally treated with azathioprine), seven (19%) were able to suspend immunosuppressive treatment and 19 (51%) were able to stop therapy with corticosteroids. Table 2 shows the results of the secondary outcome measures.

### AChR-Ab levels and clinical response

Fifty-two patients had AChR-Ab levels measured in the year before and after thymectomy (25 females, 27 males; 28 EOMG, nine LOMG, 15 TAMG; median age at thymectomy = 34.5 years, IQR = 26.5–51.75). The median time interval between the first antibody level measurement and thymectomy was 53 days (IQR = 26.75–87.25), and the median time between thymectomy and the second measurement thereafter was 53.5 days (IQR = 28.75–123.25). The median RR-AChR-Ab in %/day was 0.22 (IQR = −0.14 to 1.07). The area under the ROC curve (AUC) of RR-AChR-Ab for achieving any clinical response was 0.57 (95% CI = 0.37–0.78), indicating that RR-AChR-Ab was not a suitable variable for predicting clinical response in this patient group. The same was found for achieving a sustained clinical response (AUC = 0.53, 95% CI = 0.36–0.69).

Because any effect of thymectomy on the RR-AChR-Ab could have been masked by the start of an immunosuppressive treatment before thymectomy, we further analyzed patients who were treatment-naïve regarding immunosuppressive drugs before thymectomy ($n = 24$, 13 males, 11 females; median age at thymectomy = 32 years, IQR = 23.5–52.5; 13 EOMG, five LOMG, six TAMG). The median time from the first antibody measurement to thymectomy was 47 days (IQR = 29.75–80.5), and the median time between thymectomy and the second measurement was 43.5 days.
| TABLE 2 | Results of secondary outcome measures |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | All patients, n = 94 | Sustained response, n = 34 | Relapse or never had response, n = 60 | p<sup>a</sup> |
| Median time from thymectomy to last follow-up, months (IQR) | 89.5 (46–189.5) | 62.5 (40–169) | 128 (58–193) | 0.05 |
| MGFA at last FU, n (%) | | | | |
| Asymptomatic | 52 (55%) | 34 (100%) | 18 (30%) | NA |
| 1 | 10 (11%) | 0 | 10 (17%) | |
| 2 | 26 (28%) | 0 | 26 (43%) | |
| 3 | 6 (6%) | 0 | 6 (10%) | |
| 4 | 0 | 0 | 0 | |
| 5 | 0 | 0 | 0 | |
| MGFA-PIS at last FU, n (%) | | | | |
| CSR | 12 (13%) | 9 (27%) | 3 (5%) | NA |
| PR | 9 (10%) | 6 (18%) | 3 (5%) | |
| MM-0 | 0 | 0 | 0 | |
| MM-1 | 1 (1%) | 0 | 1 (2%) | |
| MM-2 | 4 (4%) | 3 (9%) | 1 (2%) | |
| MM-3<sup>b</sup> | 26 (28%) | 16 (47%) | 10 (17%) | |
| Not asymptomatic | 42 (45%) | 0 | 42 (70%) | |
| Patients with ≥1 myasthenic crisis after thymectomy, n (%) | 8 (9%) | 3 (9%) | 5 (8%) | 1.00 |
| Patients with ≥1 rescue treatments after thymectomy, n (%) | 19 (20%) | 4 (12%) | 15 (25%) | 0.13 |
| Standard ISTs, median n (range) | 2 (1–2) | 2 (1–2) | 2 (0–2) | 0.07 |
| Immunosuppressive treatments during the disease course, n (%) | | | | |
| Corticosteroids | 76 (81%) | 23 (68%) | 53 (88%) | 0.01 |
| Azathioprine | 53 (56%) | 16 (47%) | 37 (62%) | 0.17 |
| Mycophenolate-mofetil | 12 (13%) | 3 (9%) | 9 (15%) | 0.53 |
| Methotrexate | 1 (1%) | 1 (3%) | 0 | 0.36 |
| Escalation IST<sup>c</sup> | 8 (9%) | 1 (3%) | 7 (12%) | 0.42 |
| Treatment modification, n (%)<sup>d</sup> | 61 (65%) | 15 (44%) | 46 (77%) | 0.001<sup>e</sup> |
| Treatment at last FU, n (%) | | | | |
| Pyridostigmine | 66 (70%) | 17 (50%) | 49 (82%) | 0.001<sup>e</sup> |
| Immunosuppressive treatment | 66 (70%) | 18 (53%) | 48 (80%) | 0.006 |
| Regular SClg/IVlg/PLEX/IA | 12 (13%) | 1 (3%) | 11 (18%) | 0.05 |
| No treatment | 12 (13%) | 9 (27%) | 3 (5%) | 0.03 |

Note: Results of secondary outcome measures. Patients with sustained clinical response include all patients who fulfilled the definition of clinical response and remained clinically asymptomatic at last follow-up. Note that a subgroup of patients with relapse after clinical response still became asymptomatic at last follow-up. Three patients with sustained clinical response had no further follow-up. Significance level after correction for multiple comparisons (Bonferroni correction) is p ≤ 0.004.

Abbreviations: CSR, complete stable remission; FU, follow-up; IA, immunoadsorption; IQR, interquartile range; IST, immunosuppressive treatment; IVlg, intravenous immunoglobulins; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestation; NA, not applicable; PIS, postintervention status; PLEX, plasma exchange therapy; PR, pharmacologic remission; SClg, subcutaneous immunoglobulins.

<sup>a</sup>Probability values were obtained with the Mann–Whitney U-test or Student t-test (for continuous variables) and the chi-squared test (for categorical variables) as appropriate.

<sup>b</sup>MM-3 also included asymptomatic patients with regular SClg or IVlg or IA maintenance therapy with or without IST without documented worsening between cycles or need for change of intervals.

<sup>c</sup>Escalation IST was defined as treatment with rituximab (n = 6), cyclophosphamide (n = 1), or eculizumab (n = 1). The single patient in the sustained response group received rituximab.

<sup>d</sup>Immunosuppressive treatment modification after thymectomy was defined as either the start of a new treatment in previously treatment-naïve patients, the change of treatment to another drug, or the addition of a new drug.

<sup>e</sup>Statistically significant.
(IQR = 26–123) in these patients. Disease severity defined by the highest MGFA class within the year before thymectomy did not differ between treatment-naïve patients and patients who received immunosuppressive treatment (p = 0.54). In 10 patients, corticosteroid treatment before the measurement of the second antibody level was started after a median of 32.5 days (IQR = 2–64), and two of these patients received additional treatment with azathioprine. The median RR-AChR-Ab in %/day was 0.23 (IQR = −0.12 to 0.62). The AUC of the RR-AChR-Ab for achieving any clinical response after thymectomy was 0.79 (95% CI = 0.61–0.98), thus nearly at the commonly used threshold of 0.8 for a meaningful AUC of a test variable. The optimal cutoff value for RR-AChR-Ab was 0.19%/day. Patients in the high RR-AchR-Ab group above the cutoff value had a significantly higher chance of achieving an initial clinical response than patients in the low RR-AchR-Ab group (13/13 [100%] vs. 7/11 [64%], p = 0.03).

In the multivariate logistic regression analysis, neither age, sex, histology, nor surgical method differed between patients above and those at or below the cutoff. There was no significant difference in the AUC between the 10 patients who received additional corticosteroid treatment after thymectomy and the 14 patients who did not (AUC = 0.75 vs. 0.83, p = 0.68). The individual changes per patient are shown in Figure 1c.

**DISCUSSION**

In this retrospective single center cohort study, we investigated whether the real-world clinical postoperative outcome of patients with AChR-Ab-positive MG after thymectomy varied in dependence on a number of clinical variables and demographic characteristics. These variables partly define the suitability of patients for surgery (such as age at onset or delay since disease onset), and it is still unclear whether all patients within the wide range of inclusion criteria of the MGTX trial would benefit equally from thymectomy.

The first finding of this study was that the main clinical characteristics, that is, the disease subtype (thymoma-related vs. non-thymoma-related MG), age at onset (early vs. late onset), type of surgery, immunosuppressive treatment before thymectomy, delay to thymectomy, and evidence of thymic lymphofollicular hyperplasia in the histology, were all not significantly associated with clinical outcome after thymectomy.

Compared to the previous literature, our rate of clinical response (72%)—defined as having achieved an MGFA-PIS of minimal manifestation or better—was at the upper end of the reported range of between 38% and 72% [11] which probably also reflects the recent improvements in MG therapies. In contrast to our results, some previous studies reported a better outcome in various subgroups of patients, namely, in those with lymphofollicular hyperplasia of the thymus, younger age, a shorter time from symptom onset to thymectomy [11,12], TAMG, or a lower MGFA class before thymectomy [13–15]. Although the power of a single center study is inevitably limited, we can at least exclude large effects of the investigated parameters in our cohort, whereas smaller effects might have been missed due to the comparably small sample size. In our interpretation, the conflicting literature regarding almost all of those clinical variables would suggest that no single clinical factor is currently suitable for the prediction of the outcome following thymectomy in patients with AChR-Ab-positive MG.

The only surgical technique employed in the MGTX trial was the transsternal-extended approach [5], and less invasive techniques might have a higher risk for leaving residual thymic tissue or for less extensive removal of surrounding fatty tissue [16]. Nevertheless, previous nonrandomized studies reported reassuring results with minimal invasive approaches, especially robotic thymectomy [17–21], a finding that is underscored by our results, which showed no significant differences between surgical approaches. Regarding age at thymectomy, the MGTX trial inclusion criteria specified an age of 18–65 years. We found no difference in the outcome between EOMG and LOMG subgroups in our study, but the median age in the LOMG group at thymectomy was 57 years, and therefore most patients in our study were younger than the 65-year cutoff, which would support the inclusion criteria of the MGTX trial.

In this study, we were also interested in the durability of the achieved clinical response, which has rarely been investigated in the context of thymectomy before. We report here that the rate of sustained clinical response is considerably lower than the initial clinical response, as approximately half of all patients who had a clinical response for at least 1 year relapsed (usually transiently) during the long-term follow-up irrespective of age, histology, or surgical approach. This contrasts with some previous data. In the extension study of the randomized MGTX study [6], only two of the 35 patients in the thymectomy group (and 2/33 in the prednisone control group) had a ≥2-point increase in the Quantitative Myasthenia Gravis Score between Months 36 and 60, indicative of clinical worsening. Another observational study reported no relapses at all, although the comparison is limited, as they used the stricter criterion of complete stable remission following thymectomy [22]. Although differences in patient populations or follow-up periods could in part explain the conflicting results, we believe that our data show that relapses in routine clinical settings and long follow-up times can occur and seem to be much more frequent than previously reported. Our detected relapse rates are comparable to those in the general MG population [3]. That patients after thymectomy can suffer from relapses is perhaps not surprising, given the fluctuating nature of the disease, and also cautions against the use of the initial clinical response as the sole evaluation parameter after thymectomy. A possible pathophysiological explanation for clinical relapses after thymectomy in MG might be a peripheral spread of the autoimmune process from the thymus to peripheral lymphatic tissue. In this scenario, functionally defective regulatory T cells and AChR/immune complexes—which are capable of activating antigen-presenting cells, ultimately leading to autoantibody-producing B cells—might contribute to continuous disease activity [4,23]. This would suggest that in patients with ongoing disease activity or clinical relapse after thymectomy some form of immunosuppressive treatment is likely to be necessary; however, thymectomy might allow a dose reduction, as was shown
in the MGTX trial, where patients in the thymectomy group had an overall lower prednisone dose and fewer patients were treated with azathioprine [6].

A third potentially interesting result of this study concerns the role of AChR-Ab titers as a marker for clinical outcome. This analysis was inspired by the results of a recent study showing that the normalized decline per day (RR-AChR-Ab) between before and after the start of immunosuppressive treatment might be associated with a better outcome [10]. Our results showed that the RR-AChR-Ab in all our patients who had antibody measurements within the year before and after thymectomy was not a suitable marker for prediction of a clinical response. However, in the subgroup of patients without immunosuppressive treatment before thymectomy, patients in the high RR-AChR-Ab group (>0.19%/day) had a significantly higher rate of initial clinical response. This is interesting because this subgroup offers a better chance of studying the immunological effects of thymectomy in relative isolation, although some of these patients received immunosuppressive drugs shortly before the second AChR-Ab measurement after thymectomy. The association of the degree of the relative decline of antibodies with a more favorable outcome could then be taken as an indication of the effectiveness of thymectomy, at least on an immunological level. If this association of relative antibody decline with the outcome could be confirmed (ideally in a prospective study), this parameter might serve as an early biomarker for the success of thymectomy with respect to the initial clinical response.

The strength of our study lies in the large amount of detailed clinical information during long-term follow-up, with a median of 7 years and up to nearly 28 years after thymectomy, which allowed us to analyze not only rates of an initial clinical response but subsequent relapse rates and rates of sustained clinical response, respectively. Moreover, our center has longstanding surgical experience not only in transsternal and transcervical approaches but also in robotic thymectomy, thus ensuring extended removal of thymic tissue and surrounding fatty tissue in nonthymomatous MG and of thymoma [24].

This study has some limitations. First, the definition of clinical response for MG in general requires absence of symptoms for at least 1 year. Therefore, a selection bias excluding patients with rapid improvement during the first year after thymectomy and subsequent loss of follow-up cannot be ruled out. However, we believe that at our specialized neuromuscular tertiary care center, most patients remained in treatment and observation for a sufficient amount of time. Second, the time to follow-up varied, and it is likely that the rate of relapse will increase with a longer disease course. Nonetheless, this would only strengthen our point that the initial clinical response must be differentiated from the long-term disease course in the outcome assessment. Third, one must be aware that our analysis focused on a limited number of predictive factors but that many other variables such as dosing, timing, and type of treatments may play a role. However, modeling all these factors was beyond the scope of this retrospective study.

In conclusion, our data argue that the current clinical practice of patient selection for thymectomy does not result in significantly worse outcomes for any of the investigated subgroups. We also emphasize that the long-term disease course must be evaluated separately from the initial clinical response. The rate of antibody level decline (RR-AChR-Ab) after thymectomy should be further evaluated as a prognostic marker for treatment response. Future studies should also evaluate whether new laboratory or genetic biomarkers such as complement levels, specific micro-RNAs, or presurgical imaging features (e.g., the differentiation of hyperplasia from atrophic tissue by magnetic resonance imaging) might predict outcome after thymectomy and allow a more targeted management approach in different subtypes of MG.

CONFLICT OF INTEREST
There are no relevant conflicts of interest to disclose related to the article.

AUTHOR CONTRIBUTIONS
Jakob Rath: Conceptualization (equal), data curation (equal), formal analysis (lead), methodology (lead), project administration (equal), visualization (lead), writing–original draft (lead), writing–review & editing (equal). Manuela Taborsky: Conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), writing–review & editing (equal). Bernhard Moser: Data curation (equal), writing–review & editing (equal). Gudrun Zulehner: Data curation (equal), formal analysis (equal), writing–review & editing (equal). Martin Krenn: Data curation (equal), writing–review & editing (equal). Hakan Cetin: Data curation (equal), writing–review & editing (equal). José Ramon R. Matilla: Data curation (equal), writing–review & editing (equal). Fritz Zimprich: Conceptualization (equal), data curation (equal), project administration (equal), supervision (lead), writing–original draft (equal), writing–review & editing (equal).

DATA AVAILABILITY STATEMENT
Data will be made available from the corresponding author (friedrich.zimprich@meduniwien.ac.at) upon reasonable request.

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