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ORIGINAL ARTICLE

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THORACIC

Thymectomy in severe (Myasthenia Gravis Foundation of America classes IV–V) generalized myasthenia gravis: is the game really worth the candle?

A retrospective analysis from a multi-institutional database

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Key question

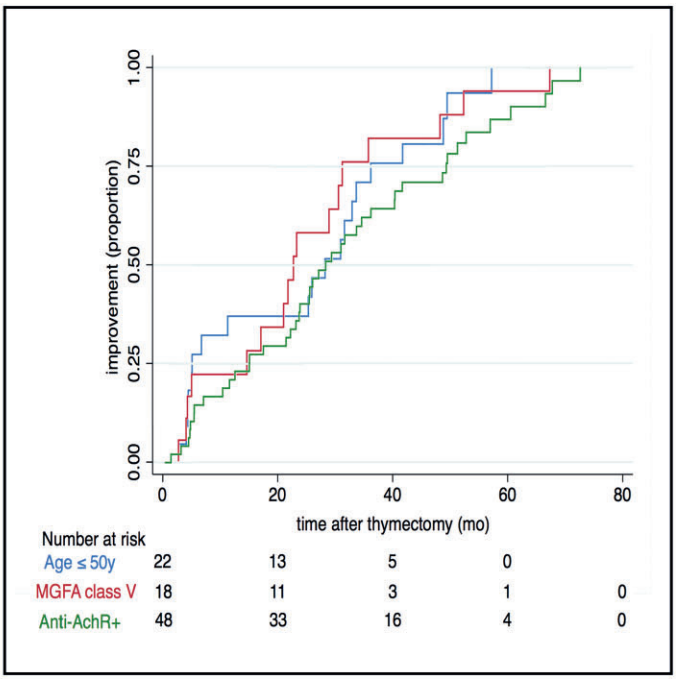
Does thymectomy in patients with severe myasthenia gravis provide any neurological advantage?

Key finding(s)

5-years MG improvement rate was 84%. Younger age, class V MG and anti-AchR positivity provided better improvement rates.

Take-home message

Thymectomy in patients with severe MG yields good perioperative outcomes and satisfactory long-term neurological improvement.



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Abstract

OBJECTIVES: Total thymectomy in addition to medical treatment is an accepted standard therapy for myasthenia gravis (MG). Patients with severe generalized MG present life-threatening events, poor prognosis and higher risk of postoperative myasthenic crisis. The aim of our study is to investigate neurological and surgical results in patients with Myasthenia Gravis Foundation of America (MGFA) class IV and V MG following thymectomy.

METHODS: Data on 76 MG patients with preoperative MGFA classes IV and V who underwent thymectomy were retrospectively collected. Primary end points included short-term surgical outcomes and long-term neurological results including the achievement of complete stable remission and any improvement as defined by MGFA Post-Intervention Status criteria.

RESULTS: There were 27 (35.5%) males and 49 (64.5%) females; 53 (69.7%) were classified as MGFA class IV and 23 (30.3%) as class V. Thymectomy was performed through sternotomy in 25 (32.9%) patients, Video-assisted thoracic surgery (VATS) in 5 (6.6%) and Robot-assisted thoracic surgery (RATS) in 46 (60.5%). The median operative time was 120 (interquartile range: 95; 148) min. In-hospital mortality was observed in 1 (1.3%) patient and postoperative complications in 14 (18.4%) patients. The median postoperative hospital stay was 4 (interquartile range: 3; 6) days. Pathological examination revealed 31 (40.8%) thymic hyperplasia/other benign and 45 (59.2%) thymomas. Cumulative complete stable remission and improvement probabilities were 20.6% and 83.7% at 5 years and 66.9% and 97.6% at 10 years, respectively. A significant improvement rate was found in patients with age at the time of thymectomy of ≤50 years ($P = 0.0236$), MGFA class V ($P = 0.0154$) and acetylcholine receptor antibodies positivity ($P = 0.0152$).

CONCLUSIONS: Thymectomy in patients with severe MG yields good perioperative outcomes and satisfactory long-term neurological improvement, especially for patients younger than 50 years, with MGFA class V and anti-AChR+ MG.

Keywords: Thymectomy • Myasthenia gravis • Myasthenia Gravis Foundation of America • Thymoma

ABBREVIATIONS

AchR	Acetylcholine receptors
CI	Confidence interval
CSR	Complete stable remission
HRs	Hazard ratios
ICU	Intensive care unit
IQR	Interquartile range
MG	Myasthenia gravis
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post-Intervention Status
PR	Pharmacological remission

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease caused by an antibody-mediated autoimmune attack directed against acetylcholine receptors (AchR) at neuromuscular junctions, causing varying levels of skeletal weakness affecting the ocular, bulbar, respiratory muscles and extremities. About 40–70% of patients with MG have follicular benign thymic hyperplasia, while 10–21% have thymoma. Extended thymectomy as defined by the International Thymic Malignancy Interest Group guidelines [1] has been widely accepted as an effective treatment option for long-term remission of MG in both thymomatous and non-thymomatous patients [2, 3]. In published series, a wide range of complete stable remission (CSR) and improvement rates of myasthenic symptoms have been reported, progressively increasing from 27–37.4% to 37–58.2% and 46–75% at 3, 10 and 15 years of follow-up [2–5]. This variability depends on: (i) different follow-up time, (ii) heterogeneity of patient characteristics including the presence of thymoma, MG severity and variable length of preoperative symptoms, (iii) subjective clinical evaluations still relying on different clinical classifications and (iv) different therapeutic approaches among neurologists and centres.

Patients with severe generalized MG present life-threatening events, poor prognosis and higher risk of postoperative myasthenic crisis. In this setting, surgical treatment could help in the weaning off or at least reducing the dose of acetylcholinesterase inhibitors and immunomodulating therapies which are associated with side effects such as nausea, vomiting, increased risk of infection, weight gain or liver damage [6]. Moreover, the problems related to the immunosuppression make the perioperative management of these patients extremely challenging, thus explaining the absence of clinical studies focusing on this issue.

In this particular subset of patients, the use of mini-invasive approaches may play a leading role, being them associated with reductions in postoperative pain, hospital length of stay and fewer complications, including myasthenic crisis [7]. However, no study analyses the real impact of surgical approach in patients with severe MG and available studies suggest that surgical approach does not influence on the neurological outcomes [8, 9].

The purpose of this study is to focus on the neurological and surgical outcomes of both thymomatous and non-thymomatous patients with severe MG undergoing thymectomy, following the Myasthenia Gravis Foundation of America (MGFA) recommendations for MG clinical research standards [10].

MATERIALS AND METHODS

Ethical statement

This study has been approved by the Ethics Committee of the University Hospital of Bari on the 12 October 2022, with ID number 934556. General written informed consent for the storage and sharing of data was collected during the hospitalization; specific informed consent for the study was waived.

Patient population

This study was conducted and reported in concordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting checklist.

This is a retrospective multicentre observational analysis on thymomatous and non-thymomatous patients with MG with preoperative MGFA classes IV and V undergoing thymectomy through either an open or a mini-invasive approach in 4 high-volume centres in Italy (Thoracic Surgery Units of Pisa, Padua, Rome and Bari), between 2000 and 2021. The detailed protocol and criteria had been clearly defined prior to study initiation and approved by the Ethical Review Board.

The exclusion criteria were: (i) children aged under 12 years old; (ii) poor cardiopulmonary function excluding surgery; and (iii) MG MGFA class other than IV and V.

The MGFA recommendations for clinical research standards classification were followed for the clinical classification, preoperative and postintervention clinical status evaluation [10].

All data were retrospectively collected from the medical records of the patients, including the demographic, clinical and serological characteristics of patients, WHO pathological subtype of thymoma according to the Masaoka–Koga classification, presence or absence of thymic follicular hyperplasia and MGFA Post-Intervention Status (MGFA-PIS) [10].

Preoperative evaluation included neurological assessment for MG diagnosis, contrast-enhanced computed tomography to assess the evidence or not of a thymoma and to exclude any other chest pathology, electrocardiogram and spirometry. The diagnosis of MG was based on clinical criteria, electromyography, edrophonium chloride test results (Tensilon; ICN Pharmaceuticals, Inc, Costa Mesa, CA), circulating anti-AchR and anti-MuSK antibodies' levels. The MG status as defined according to the MGFA classification referred to the immediate preoperative period. All patients were optimally stabilized before surgery, when possible. A detailed therapeutic scheme for each patient is provided in Supplementary Material, Table S1. Plasma exchange therapy or intravenous immunoglobulin treatments were preoperatively administered to patients at risk for postoperative respiratory failure on the basis of the clinical judgement of a neurologist.

Follow-up

Patients were followed up by the thoracic surgeons and neurologists at intervals of 3–6 months for the first 2 years postoperatively and then annually for the adjustment of MG medications or whenever it was required by the deterioration of symptoms. Follow-up data were collected from the medical records of the neurology clinic treating the patient and by serial telephone interviews for those who stopped visiting the clinic.

Myasthenia gravis postoperative assessment

Postoperative symptom control was classified based on the MGFA-PIS at last outpatient visit. Patients were classified as having achieved CSR, pharmacological remission (PR), minimal manifestations, had unchanged severity (U), had worse severity (W) or had died (D) from MG. For the purpose of this study, we further classified patients into 3 groups: (i) CSR including patients without symptoms or signs of MG for at least 1 year and no therapy; (ii) 'improved' including patients whose postoperative myasthenic symptoms improved and amount of medication decreased (patients with CSR, PR, minimal manifestations and I MGFA-PIS) and (iii) 'unchanged and/or worsened' including patients with MGFA-PIS unchanged, worse, exacerbation and died of MG. CSR and PR were calculated at the end of a minimal 12-month follow-up period.

Objectives

Objectives of the study were: (i) to evaluate perioperative results in patients with MGFA class IV and V MG submitted to thymectomy [median operative time, postoperative complications, median postoperative stay, postoperative intensive care unit (ICU) stay, postoperative ventilator support time and 30-day mortality] on the basis of the surgical approach and (ii) to investigate long-term neurological results (CSR and improvement) trying to identify prognostic factors for better neurological outcomes.

Statistical analysis

Shapiro–Wilk test and Skewness and Kurtosis test were used to assess whether variables were normally distributed. Normally distributed continuous variables were described as mean ± standard deviation and compared by the two-tailed Student's *t*-test. Non-normally distributed data were presented as median [interquartile range (IQR)] and compared by the Mann–Whitney *U*-test. Categorical variables are reported as counts and percentages and analysed by using either Pearson's chi-squared test or Fisher's exact test, as appropriate.

Kaplan–Meier analyses were performed to estimate cumulative probability of achieving CSR and improvement. Differences were compared by log-rank test. Univariable and multivariable Cox regression models were employed to identify factors associated with CSR and improvement at follow-up. Results were presented as hazard ratios (HRs), 95% confidence interval (CI), and *P*-value. Factors with a *P*-value of smaller than 0.1 were included for final multivariable analysis.

To account for competing risks, Fine–Gray regression [11] was employed. Subdistribution hazard ratios obtained from the Fine–Gray model were reported, together with 95% CI, and *P*-values.

The selection of variables potentially influencing improvement and/or CSR was guided by clinical knowledge and literature [12]. Included variables from literature were: 'antibodies anti-AchR titer'; 'histology (thymic hyperplasia vs thymoma)'; and 'age (≤50 vs >50 years) at the time of thymectomy', 'gender (female vs male)' and 'MGFA class (IV vs V)'. Other potential explanatory variables included in the models were: 'surgical approach (open vs VATS/RATS)'.

Proportionality assumption for the Cox model was checked using the Schoenfeld residuals. No attempt to replace missing values was made. A *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed on STATA 14.0 statistical software (StataCorp.2015. 'Stata Statistical Software: Release 14'. College Station, TX: StataCorp LP).

RESULTS

A total of 76 (27 males, 49 females) patients with a mean age of 47.6 years were enrolled. Twenty-five (32.9%) patients underwent

transsternal thymectomy, whereas 51 (67.1%) patients underwent thymectomy through a mini-invasive approach, including both unilateral VATS (6.6%) and RATS (60.5%).

Table 1 summarizes the preoperative characteristics of the included patients.

Patients who underwent the mini-invasive thymectomy were most female, had a lower percentage of comorbidities and had mostly a benign histology. Comorbidities included hypertension, cardiopathy, diabetes, thyreopathy and previous neoplastic malignancies. No differences were found as to preoperative MGFA class, AChR antibody status, history of myasthenic crisis, Masaoka–Koga stage and presurgery therapy.

Table 2 summarizes the perioperative and postoperative outcomes after thymectomy. Among these patients, 8 (10.5%) experienced postoperative myasthenic crisis/acute respiratory failure requiring intubation and mechanical ventilation for 24–48 h; 15 (19.7%) patients required postoperative ICU stay with a median ICU length of stay 0 days (IQR: 0; 1). In 9 (11.8%) and 3 (3.9%) cases, intravenous immunoglobulins or plasmapheresis respectively were administered to stabilize patients before surgery. Postoperative myasthenic crisis required plasmapheresis in 1 case and the administration of intravenous immunoglobulins in 3 cases in the immediate postoperative period. Overall mortality was 6.6% (5 patients). There was 1 death in the perioperative period due to septicaemia, while the other 4 patients died 4, 2 (2 patients) and 1 year after thymectomy because of exacerbation of MG symptoms, pulmonary embolism and heart attack; in 1 case, the cause of death was unknown. The median operative time was 120 min (IQR: 95; 148) and the median postoperative in-hospital stay was 4 days (IQR: 3; 6).

The overall rate of postoperative complication was 18.4%. Although no statistical difference was found in the overall rate of postoperative complications between the 2 groups, the transsternal group experienced a higher rate of infections (including a case of mediastinitis and 1 of empyema) than the thoracoscopic one (8.0 vs 0.0%, $P = 0.041$) and had a statistically significant longer median postoperative stay (6 vs 3.5 days, $P = 0.000$).

The median follow-up time was 4.7 (IQR: 0–19.5) years. At the last follow-up, the postintervention therapy status assessment (Table 3) showed a suspension/reduction in the median dose of cholinesterase inhibitor and prednisone in 63.3 and 81.2% of patients; 9 patients (11.8%) stopped taking any medications.

The estimated cumulative probability of CSR and improvement were 20.6% (95% CI: 9.9–39.7%) and 66.9% (95% CI: 25.9–98.3%) at 5 and 10 years and 83.7% (95% CI: 72.3–92.3%) and 97.6% (95% CI: 89.5–99.8%) at 5 and 10 years, respectively (Fig. 1).

Kaplan–Meier analysis demonstrated significant differences in the cumulative probabilities of improvement between subgroups (Fig. 2) stratified by age at time of intervention, preoperative MGFA class and anti-AchR status.

Cox proportional hazards regression model analysis (Table 4) of the variables associated with CSR proved the presence of thymoma to be a potential predictor of remission (HR: 0.11, 95% CI: 0.01–0.85, $P = 0.034$). Cox proportional hazards regression model analysis (Table 5) showed younger age (<50 years), MGFA

Table 1: Baseline characteristics of the study population by surgical approach

	Total (76)	Transsternal group (25)	Thoracoscopic group (51)	*P*-Value
Age (years), mean ± SD	47.59 ± 16.25	48.08 ± 13.9	47.35 ± 17.38	0.855
Sex, *n* (%)				**0.013**
Male	27 (35.5)	14 (56.0)	13 (25.5)	
Female	49 (64.5)	11 (44.0)	38 (74.5)	
Preoperative MGFA, *n* (%)				0.196
Class IV	53 (69.7)	15 (60.0)	38 (74.5)	
Class V	23 (30.3)	10 (40.0)	13 (25.5)	
AchR antibodies, *n* (%)				0.122
Positive	62 (81.6)	23 (92.0)	38 (74.5)	
Negative	13 (17.1)	2 (8.0)	11 (21.6)	
History of myasthenic crisis, *n* (%)	22 (28.9)	10 (40.0)	12 (23.5)	0.724
Comorbidities, *n* (%)	41 (53.9)	18 (72.0)	23 (45.1)	**<0.001**
Histology, *n* (%)				**<0.001**
Thymus without thymoma	31 (40.8)	3 (12.0)	28 (54.9)	
Thymoma	45 (59.2)	22 (88.0)	23 (45.1)	
Thymoma A	13 (17.1)	5 (20.0)	8 (15.7)	0.666
Thymoma AB	5 (6.6)	2 (8.0)	3 (5.9)	0.726
Thymoma B1	4 (5.2)	1 (4.0)	3 (5.9)	0.730
Thymoma B2	18 (23.7)	10 (40.0)	8 (15.7)	**0.019**
Thymoma B3	5 (6.6)	4 (16.0)	1 (1.9)	**0.020**
Masaoka–Koga stage, *n* (%)				
I	9 (20.0)	3 (12.0)	6 (11.8)	0.177
IIa	11 (24.4)	4 (16.0)	7 (13.7)	0.191
IIb	9 (20.0)	6 (24.0)	3 (5.9)	0.335
III	4 (8.9)	3 (12.0)	1 (1.9)	0.245
IVa	3 (6.7)	3 (12.0)	0 (0)	0.087
N/A	9 (20.0)			
Pre-surgery therapy, *n* (%)				
Intravenous Immunoglobulins	9 (11.8)	4 (16.0)	5 (9.8)	0.804
Plasmapheresis	3 (3.9)	0 (0)	3 (5.9)	0.139

Significant *P*-values are in bold.

AchR: acetylcholine receptor; MGFA: Myasthenia Gravis Foundation of America; N/A: not available; SD: standard deviation.

Table 2: Perioperative and postoperative surgical results

Variable	Total (76)	Transsternal group (25)	Thoracoscopic group (51)	*P*-Value
Operative time (min), median (IQR)	120 (95; 148)	115 (95; 150)	120 (100; 144.5)	0.740
Postoperative complications, *n* (%)	14 (18.4)	6 (24.0)	8 (15.7)	0.350
Myasthenic crisis	7 (9.2)	2 (8.0)	5 (9.8)	0.280
Acute respiratory failure	1 (1.3)	–	1 (2.0)	0.481
Infections	2 (2.6)	2 (8.0)	–	**0.041**
AF	1 (1.3)	1 (4.0)	–	0.150
Haemothorax	1 (1.3)	–	1 (2.0)	0.481
Postoperative stay (days), median (IQR)	4 (3; 6)	6 (5; 10)	3.5 (3; 4)	**0.000**
Postoperative ICU stay, *n* (%)	15 (19.7)	5 (20.0)	10 (19.6)	0.476
Median postoperative ICU stay (days), median (IQR)	0 (0; 1)	0 (0; 2)	0 (0; 1)	0.162
30-Day mortality, *n* (%)	1 (1.3)	1 (4.0)	–	0.150

AF: atrial fibrillation; ICU: intensive care unit; IQR: interquartile range.
Bold values denote statistical significance at the $p < 0.05$ level.

Table 3: Numbers of patients on medications preoperatively and postoperatively

	Preoperative medication, *n* (%)	Postoperative medication at latest follow-up, *n* (%)						
		Increased	No changes	Total	Reduced	Interrupted	Total	N/A
Cholinesterase inhibitors	68 (89.5)	8 (11.8)	12 (17.6)	**20 (29.4)**	25 (36.8)	18 (26.5)	**43 (63.3)**	5 (7.3)
Steroids	64 (84.2)	1 (1.6)	6 (9.4)	**7 (11.0)**	45 (70.3)	7 (10.9)	**52 (81.2)**	5 (7.8)
Azathioprine	18 (23.7)	–	4 (22.2)	**4 (22.2)**	2 (11.1)	10 (55.6)	**12 (66.7)**	2 (11.1)
Cyclosporine	4 (5.3)	–	2 (50.0)	**2 (50.0)**	–	2 (50.0)	**2 (50.0)**	–
None	0 (0)	9 (11.8)						

N/A: not available.
Bold values denote statistical significance at the $p < 0.05$ level.

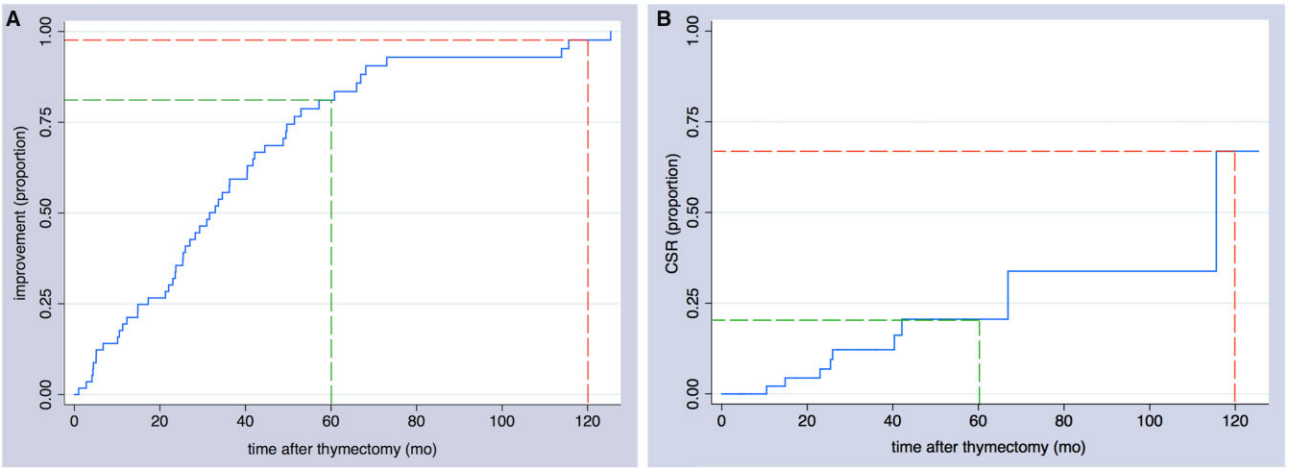

Figure 1: Kaplan–Meier curves for the cumulative probability of improvement (**A**) and CSR (**B**). CSR: complete stable remission.

class V and anti-AchR positivity to be potential predictors of improvement at univariable analysis. At the final multivariable analysis, only age at thymectomy ≤50 years (HR: 0.51, 95% CI: 0.27–0.97, $P = 0.040$) was identified as an independent predictor of improvement after thymectomy. Furthermore, subgroup analyses were performed in both thymomatous and non-thymomatous group patients (Table 6).

The Fine and Gray's standard deviation regression analysis was employed account for competing risks. The subdistribution hazard ratios for improvement and CSR generated by the models are shown in Supplementary Material, Table S2.

DISCUSSION

Extended thymectomy as defined by the International Thymic Malignancy Interest Group guidelines [1] has been accepted as a treatment option for long-term remission of MG, since Blalock reported its efficacy in the 40s [2, 3]. The presence of a thymoma implies the surgical treatment for oncological reasons and performing an extended thymectomy in this case may play a role in the neurological remission of the myasthenia, too. Otherwise, the benefit of surgical approach in non-thymomatous MG is still uncertain, thus being supported by scarce evidence [3]. The

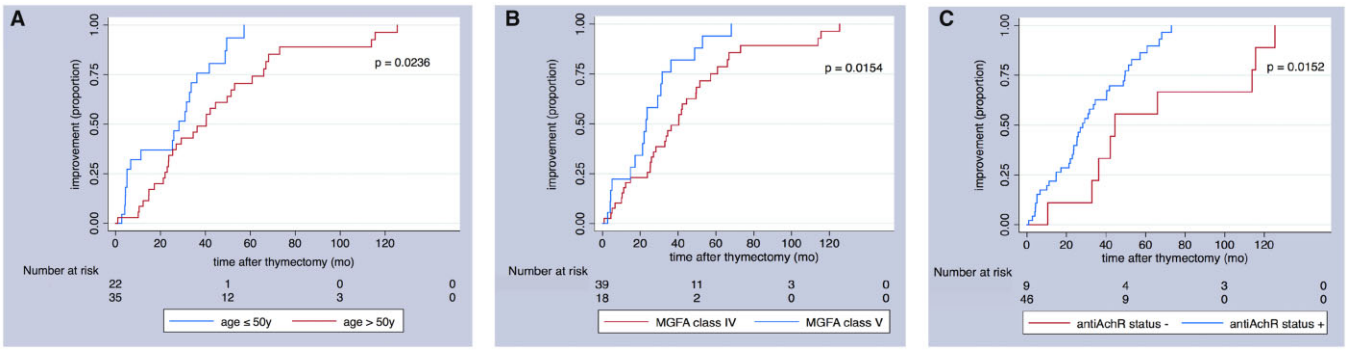

Figure 2: Kaplan–Meier curves for the cumulative probability of improvement for the whole cohort stratified by age at time of surgery (**A**), by Myasthenia Gravis Foundation of America class (**B**) and by AbAchR status (**C**).

Table 4: Cox proportional hazards regression model analysis of clinical characteristics associated with complete stable remission after thymectomy

	HR	95% CI	*P*-Value
MGFA class V	0.54	0.07–4.47	0.571
Mini-invasive approach	2.24	0.45–11.19	0.324
Thymoma	0.11	0.01–0.85	**0.034**
AbAchR+	1.12	0.22–5.76	0.892
Female	1.99	0.41–9.74	0.396
Age <50 years	2.53	0.30–21.24	0.390

AchR: acetylcholine receptor; CI: confidence interval; HR: hazard ratio; MGFA: Myasthenia Gravis Foundation of America.
Bold values denote statistical significance at the $p < 0.05$ level.

Table 5: Cox proportional hazards regression model analysis of clinical characteristics associated with improvement after thymectomy

	Univariable model			Multivariable model		
	HR	95% CI	*P*-Value	HR	95% CI	*P*-Value
MGFA class V	2.07	1.13–3.77	**0.018**	1.76	0.93–3.33	0.080
Mini-invasive approach	1.27	0.71–2.28	0.423	–	–	–
Thymoma	0.94	0.54–1.64	0.843	–	–	–
AbAchR+	2.87	1.19–6.96	**0.019**	2.06	0.80–5.28	0.133
Female	0.96	0.54–1.71	0.883	–	–	–
Age <50 years	0.46	0.25–0.84	**0.012**	0.51	0.27–0.97	**0.040**

AchR: acetylcholine receptor; CI: confidence interval; HR: hazard ratio; MGFA: Myasthenia Gravis Foundation of America.
Bold values denote statistical significance at the $p < 0.05$ level.

'International consensus guidance for management of myasthenia gravis' [13] supports thymectomy in non-thymomatous MG as an option to potentially avoid or minimize the dose or duration of immunotherapy or if patients fail to respond to immunotherapy or have intolerable side effects. Due to the rarity of the incidence of MG and to the highly heterogenous characteristics of patients which can impact on the prognosis, published series have described a wide range of CSR and improvement rates of myasthenic symptoms after thymectomy [2–5]. Moreover, this heterogeneity has also been affected by the lack of common and standardized preoperative and postoperative classifications, thus making the published studies poorly comparable. In 2000, the MGFA published the recommendations for MG clinical research standards [10], which have been applied only in the last years.

Most studies have shown decreased rates of CSR in patients with more severe symptoms [14–16]; lately, a recent meta-analysis by Alqarni *et al.* [17] found decreased rates of CSR in patients with more severe symptoms, thus identifying a higher MG stage as a risk factor of recurrence following thymectomy. In contrast, a review conducted by the American Academy of Neurology reported clinical improvement after thymectomy in cases with more severe MG [18]. These results raise the question of the utility of surgical treatment in patients affected by severe generalized MG.

Perioperative results in our series proved thymectomy, achieved through either an open or a mini-invasive approach, to be safe and feasible, being affected by low mortality and complication rates. RATS was the preferred approach in our series, accounting for >60% of patients.

Currently, there is no definitive evidence in the literature that supports the use of 1 minimally invasive approach over the others but many reports refer to RATS as the best alternative for mediastinal dissection. The high-resolution three-dimensional view of the operating field and attenuation of hand tremor and articulation of the robotic arms may increase the quality of the dissection in difficult-to-reach areas such as the contralateral mediastinum and supra innominate vein region [19, 20]. The completeness of removal of all thymic tissue, including the thymic foci which are spread in the anterior mediastinal fat in up to 98% of patients, is the single most important surgery-dependent variable that influences postoperative neurological outcomes.

Having chosen a selected high-risk subgroup of patients, neurological optimization including preoperative administration of intravenous immunoglobulin or plasmapheresis, has been fundamental to ensure an early and safe recovery in the postoperative course and to minimize the risks of postoperative myasthenic complications. These neurological needs, in the case of thymoma, have been balanced in our study cohort with the oncological needs [21]. In accordance with previous studies [4], when comparing the perioperative results by surgical approach, we found the transsternal approach to be linked to a longer hospital length of stay and a higher percentage of infections. The reason might be that the transsternal approach has larger incisions, having it been chosen electively for patients with

Table 6: Cox proportional hazards regression model analysis of clinical characteristics associated with improvement after thymectomy in *thymomatous* and *non-thymomatous* patients

	Univariable model			Multivariable model		
	HR	95% CI	*P*-Value	HR	95% CI	*P*-Value
Thymomatous patients						
MGFA class V	2.14	0.97–4.69	0.058	1.66	0.69–3.93	0.254
Mini-invasive approach	1.40	0.64–3.04	0.398	–	–	–
AbAchR+	3.90	0.51–30.1	0.191	–	–	–
Female	0.48	0.22–1.05	0.066	0.32	0.12–0.81	**0.017**
Age <50 years	0.38	0.17–0.87	**0.023**	0.27	0.09–0.58	**0.002**
Non-thymomatous patients						
MGFA class V	2.06	0.75–5.64	0.159	–	–	–
Mini-invasive approach	1.37	0.40–4.67	0.615	–	–	–
AbAchR+	2.88	1.04–8.05	**0.042**	2.14	0.76–6.08	0.151
Female	4.69	1.06–20.74	**0.042**	3.53	0.78–16.06	0.102
Age <50 years	0.68	0.24–1.89	0.455	–	–	–

AchR: acetylcholine receptor; CI: confidence interval; HR: hazard ratio; MGFA: Myasthenia Gravis Foundation of America.
Bold values denote statistical significance at the $p < 0.05$ level.

thymoma, especially larger and advanced ones, requiring a more aggressive dissection.

In literature, CSR is described in 10–20% of thymomatous cases after 5 years, compared with 30–60% in case of non-thymomatous MG [21]. Our results, although regarding severe myasthenia gravis in both thymomatous and non-thymomatous patients, showed CSR and improvement rates of 20.6% and 83.7% at 5 years, respectively. This result is highly encouraging and interesting from a clinical point of view, since suggests good neurological outcomes even in patients with severe MG after surgery.

When analysing the possible prognostic factors connected with MG remission and/or improvement, the presence of a 'thymoma' was the only 1 influencing CSR, although it seemed not to impact on improvement. The role of histology on prognosis is still not clear; historically, the absence of coexisting thymoma has been related to postoperative remission [4, 19] while the presence of thymoma has been regarded as poor prognostic factor because of the lesser response to treatment and greater severity of symptoms [15, 22]. However, recent studies demonstrated favourable prognosis after thymectomy in patients with thymomatous MG, probably due to the improvements in the medical therapy of MG and to a more accurate preoperative assessment of MG patients, allowing an earlier diagnosis of thymomas at earlier stages [21, 23, 24]. Moreover, in literature, the relationship between the preoperative disease duration before thymectomy and the incidence of postoperative myasthenic crisis has already been investigated and a longer duration of MG was reported to contribute to the risk of postoperative myasthenic crisis and to poorer neurological response to treatment, probably due to the accumulation of damage at the neuromuscular junction [25]. We may speculate that, in our series, thymomatous patients experienced better neurological outcomes as that they came earlier for surgery instead of the non-thymomatous ones because of the oncological needs, shortening the time of symptom duration before surgery.

The effect of MGFA class on achieving improvement in our study was significant; patients with MGFA class V, in fact, showed better neurological outcomes. Although previous studies proved lower scores on the MGFA severity score (I–II) or Osserman classification (1/2A) to be associated with remission after thymectomy [21, 26, 27], till now, no study has electively compared MGFA stages IV and V nor has focused on this subset of patients. Interestingly, De Rosa *et al.* [28] found that patients with a more severe MG (III–V MGFA classes) experienced less MG exacerbations than others, probably due to the beneficial effect of higher doses of steroids administered in preparation for surgery.

The effect of the anti-AchR status on improvement in our study was significant. Also, in this case, published studies differ in their results. Some analyses evaluated the prognostic value of AChR-Ab in MG and reported significant improvement rate in patients with positive AbAchR status [5]; others proved that the level of preoperative AbAChR did not affect the MG remission rate after thymectomy [26, 29].

Since 2000s, age at the time of thymectomy has been identified as a predictor of better neurological outcomes, thus discouraging surgical treatment in the elderly. In accordance with previous reports [30], we found age at surgery younger than 50 years to positively impact on MG symptoms.

Limitations

This study has some limitations. First, the retrospective data collection is a potential source of bias; for this reason, not all data on medications and doses and on the preoperative duration of symptoms were available. Second, since we aimed to the long-term effect of thymectomy, we used the MGFA-PIS classification that requires at least 1 year without symptoms to classify as remission; this classification has been scarcely adopted till now; therefore, our results may be hardly comparable with previous studies.

Moreover, the multicentric nature of this study could be regarded as a source of bias, thus involving different clinical practices and approaches regarding pre-, intra- and postoperative managements.

CONCLUSIONS

In conclusion, thymectomy in patients with severe generalized MG yields good perioperative and long-term neurological outcomes.

Surgical approach used for thymectomy does not significantly affect either neurological or surgical perioperative outcomes. Neurological improvement was significantly better in patients younger than 50 years, with MGFA class V and with anti-AchR-positive status.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Debora Brascia: Conceptualization; Data curation; Formal analysis; Investigation; Writing—original draft. **Marco Lucchi:** Conceptualization; Writing—review & editing. **Vittorio Aprile:** Data curation; Investigation; Validation; Writing—review & editing. **Melania Guida:** Investigation; Methodology; Writing—review & editing. **Roberta Ricciardi:** Investigation; Methodology; Writing—review & editing. **Federico Rea:** Conceptualization; Writing—review & editing. **Giovanni Maria Comacchio:** Data curation; Validation; Writing—review & editing. **Marco Schiavon:** Investigation; Validation. **Maria Carlotta Marino:** Data curation; Writing—review & editing. **Stefano Margaritora:** Conceptualization; Writing—review & editing. **Elisa Meacci:** Data curation; Validation; Writing—review & editing. **Gregorio Spagni:** Data curation; Methodology; Writing—review & editing. **Amelia Evoli:** Data curation; Writing—review & editing. **Giulia Lorenzoni:** Formal analysis; Methodology; Writing—review & editing. **Giulia De Iaco:** Data curation; Writing—review & editing. **Angela De Palma:** Data curation; Writing—review & editing. **Giuseppe Marulli:** Conceptualization; Supervision; Writing—review & editing.

Reviewer information

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