Systematic Review

Prevalence and risk factors of myasthenia gravis recurrence post-thymectomy

†*Fatmah Alqarni,* MBBS, MD, *Daifallah Almalki,* MBBS, MD, *Ziyad Aljohani,* MBBS, MD, *Abdulrahman Ali,* MBBS, MD, *Alanood AlSaleem,* MBBS, MD, *Noura Alotaibi,* RN, PhD, *Shahla Odeh,* MBBS, MD, *Sultan Al Dalbhi,* MBBS, MD.

ABSTRACT

الأهداف: تحديد مدى انتشار وعوامل الخطر لانتكاسة الوهن العضلي الوخيم بعد استئصال غدة التوتة.

المنهجية: أجرينا بحثًا منهجيًا في ستة قواعد بيانات إلكترونية قامت بنشر ابحاث عن انتكاسة الوهن العضلي الوخيم بعد عملية استئصال غدة التوتة وعوامل الخطر فيها من 1985 إلى 2018. تم الحصول على تقديرات مجمعة باستخدام نماذج الآثار العشوائية.

النتائج: حددنا 70 ورقة علمية احتوت على 7,287 مريضا يعانون من الوهن العضلي الوخيم الذين خضعوا لاستئصال غدة التوتة وتم متابعتهم بمتوسط 4.65 سنة. كان انتشار انتكاسة الوهن العضلي الوخيم بعد استئصال غدة التوتة 18.0%؛ وقد لوحظ عدم تجانس واضح. كان هناك ارتفاع معدل انتشار الانتكاسة في الذكور مقارنة بالإناث (31.3 مقابل 23.8%). كانت معدلات التكرار المجمعة لمرضى الوهن العضلي الوخيم الذين لديهم ورم في غدة التوتة (33.3%) أعلى من المعدل في المرضى بدون ورم في غدة التوتة (20.8%). كان معدل الفرق الاحصائي بين المجموعة ذو دلالة إحصائية معتدة. عوامل الخطورة للانتكاسة تشمل: كبر العمر، الذكور، وخامة المرض، الوهن العضلي الوخيم الذي يوجد به ورم في غدة التوتة، طول مدة المرض قبل استئصال غدة التوتة ووجود نسيج توتي منتبذ.

الخلاصة: خمس مرضي الوهن العضلي الوخيم يحدث لهم انتكاسة بعد استئصال غدة التوتة. يجب مراقبة المرضى المعرضين للخطر بشكل أوثق وهناك حاجة إلى مزيد من الدراسات لفهم التدخلات لمعالجة هذه المخاطر.

Objectives: To evaluate the prevalence and the factors associated with recurrence of myasthenia gravis following thymectomy.

Methods: Six electronic databases which reported on recurrence of myasthenia gravis following thymectomy and/or its risk factors from 1985 to 2018 were searched. Summary prevalence and risk values obtained based on the random effect models were reported.

Results: Seventy (70) papers containing 7,287 individuals with myasthenia gravis who received thymectomy as part of their management were retrieved. The patients had a mean follow-up of 4.65 years post-thymectomy. The prevalence of myasthenia gravis recurrence post-thymectomy was 18.0% (95% CI 14.7–22.0%; 1865/7287). Evident heterogeneity was observed (I^2=93.6%; p<0.001). Recurrence rate was insignificantly higher in male compared with female patients (31.3 vs. 23.8%; p=0.104). Pooled recurrence rates for thymomatous (33.3%) was higher than the rate among non-thymomatous (20.8%) myasthenia gravis patients (Q=4.19, p=0.041). Risk factors for recurrence include older age, male sex, disease severity, having thymomatous myasthenia gravis, longer duration of the myasthenia gravis before surgery, and having an ectopic thymic tissue.

Conclusion: A fifth of individuals with myasthenia gravis experience recurrence after thymectomy. Closer monitoring should be given to at-risk patients and further studies are needed to understand interventions to address these risks.

Neurosciences 2021; Vol. 26 (1): 4-14
doi: 10.17712/nsj.2021.1.20190041

From the Department of Medicine (Alqarni, AlSaleem, Odeh), Princess Nourah Bin Abdulrahman University, Department of Neurology (Ali), King Fahad Medical City, Riyadh, College of Nursing (Alotaibi), King Saud Bin Abdulaziz University for Health Sciences, Department of Nephrology (Al Dalbhi), Prince Sultan Military Medical City, Riyadh, Department of Internal Medicine (Almalki), Prince Sattam Bin Abdulaziz University, Al-Kharj, Department of Neurology (Aljohani), King Abdullah Medical City, Makkah, Kingdom of Saudi Arabia.

Received 31st January 2020. Accepted 30th August 2020.

Address correspondence and reprint request to: Dr. Sultan Al Dalbhi, Department of Nephrology, Prince Sultan Military Medical City Riyadh, Kingdom of Saudi Arabia. E-mail: saldalbhi_2014@hotmail.com
ORCID ID: https://orcid.org/0000-0002-0721-0057

Myasthenia gravis (MG) a rare clinical condition characterized by autoimmune abnormalities is also the commonest neuromuscular junction (NMJ) disorder.[1] Its pathophysiology involves the production of abnormal antibodies which binds to nicotinic acetylcholine receptors at the NMJ of skeletal muscles leading to alteration and damage of the NMJ.[1-2] The disease is common in young women, however, another peak in incidence may occur at the 6th or 7th decade of life mainly in men in some population; and it may exhibits no sex preference in others.[2] Clinically, patients with MG develop varying levels of skeletal muscle weakness affecting the ocular, bulbar, oculo-bulbar system, respiratory system, and the extremities.[1] The pattern and course of MG is complex, varying from early remission to acute exacerbation and even death.[3]

Previous research has revealed a strong relation between MG and disorders affecting the thymus. About 40 to 70% of individuals with MG have thymic follicular hyperplasia, and 10 to 21% of them have thymoma.[4-6] Also, 20-47% of individuals having a thymoma have already developed or will develop MG.[6-7] Findings from the literature indicate that 40 to 90% of individuals with MG attained remission following thymectomy compared with 10 to 20% among individuals with MG treated with medications without any surgery.[6,8] Also, a recent randomised controlled trial demonstrated that thymectomy for individuals with nonthymomatous MG demonstrated better treatment outcomes during a three-year period compared with pharmacological therapy alone.[9] Thus, guidelines now recommend thymectomy as a key treatment approach for MG.[10]

A number of systematic reviews and/or meta-analyses among individuals with MG have been carried out. Some of these reviews explored the differences in outcomes between thymectomy and conservative management of MG,[11,12] others compared surgical approaches of thymectomy,[13-15] or potential prognostic factors for remission among individuals with MG irrespective of histological type following thymectomy.[3,16] None assessed recurrence of MG following thymectomy or its risk factors. The identification of patient factors which are associated with recurrence of MG following thymectomy is crucial for the development of targeted interventions to address challenges associated with the care of individuals with MG. This systematic review and meta-analysis aimed to estimate the post-thymectomy recurrence rates and to investigate the factors associated with recurrence of MG following thymectomy in individuals with MG.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Methods. This systematic review was conducted according to PRISMA guidelines.[17] We performed an electronic search of: CINAHL, Clarivate Analytics Web of Science, Cochrane Library, SCOPUS, MEDLINE and DARE databases for relevant articles published between January 1985 and September 2018 which reported on recurrence of myasthenia gravis and its risk factors post-thymectomy. Keywords related to the study were used to evaluate the titles or abstracts of the papers identified during the literature search. Both terms retrieved from Medical Subject Heading (MESH) as well as Boolean operators were utilized during the search. We limited the literature search to publications in English. Search terms used included: [["Thymus"] OR ["Thymoma"] OR ["Thymectomy"] OR Thym. ti,ab.] AND [["Myasthenia gravis"[MeSH]] AND [["Myasthenia"[All Fields] AND "gravis"[All Fields]] AND [["recurrence"[MeSH] OR "recurrence"[All Fields] OR ["Worsening" OR "Remission"] OR ["risk factors" OR "determinants" OR "predictors"]. Furthermore, the references of published original studies and review papers were assessed for other potentially-relevant publications.

Inclusion and exclusion criteria. All publications on thymectomy in individuals with MG over the given period were included. The criteria for eligibility or inclusion is meeting the following conditions: (i) the population evaluated in the study consisted of mainly adults i.e., 18 years old or older; (ii) the publication reported on outcomes of thymectomy in individuals with MG, (iii) the outcome included recurrence defined based on the Myasthenia Gravis Foundation of America: as worsening, exacerbation or unchanged clinical status of the MG following thymectomy;[18] (iv) Individuals with MG who had thymectomy were monitored (followed-up) for at least six months or more after the surgical procedure; and (vi) regression analysis was performed to identify factors associated with the outcomes of the MG.

Publications with the following characteristics were excluded: (i) the age group of the population evaluated was not defined; (ii) publications that included individuals with MG who did not receive thymectomy as a management approach; (iii) studies that report post-thymectomy myasthenic crisis that occurred during or the immediate post-operative period, as well as

immediate post-operative outcomes of thymectomy in individuals with MG, (iv) Studies on post-thymectomy MG which developed in individuals with thymoma who had no preceding presentation of myasthenia gravis, (v) Studies with a sample size less than 10. Also, case reports, conference abstracts, editorials, commentaries, review articles and duplicate publications were deemed ineligible.

Data extraction. Two reviewers (FA and SA) independently reviewed the title and abstract of the identified studies. All disagreements between the reviewers were handled by discussion and reaching a consensus. The complete articles of papers identified for detailed review and data extraction were obtained. The 2 reviewers (FA and SA) performed the data extraction independently. Any conflicts between them was also reconciled by discussion and reaching a consensus. The information was retrieved from each of the selected studies include: author and year, country of study, date of data collection, number of patients, recurrence rates, and duration of monitoring or follow-up after the surgical procedure. The selected studies quality were extensively evaluated with the Joanna Briggs Institute's prevalence critical appraisal checklist for the evaluation of the quality of relevant publications.[11-19]

Statistical analysis. Summary prevalence values obtained based on the random effect models with their 95% confidence intervals (95% CIs) were reported.[20] The Q and I^2 statistics were used to assess for the occurrence of heterogeneity between the studies.[21] Publication bias was evaluated using an assessment of the funnel plot symmetry and the Egger's regression test. Also, the effect size measures used were extracted from the selected studies. The odds ratios (ORs) and their 95% CIs were extracted or where not available, were estimated (using the proportion of recurrence of MG post-thymectomy (ie, recurrence cases]) and non-recurrence of MG (ie, non-recurrence [controls]) groups) for each risk factor. All analyses were performed using thee Comprehensive Meta-Analysis software 2.2 (Biostat Inc, USA).[22] Sub-group meta-analysis was performed for the following groups: sex (male versus female), and type of myasthenia gravis (thymomatous versus non-thymomatous).

Results. ***Characteristics of the studies.*** The systematic search of the literature identified 8,797 potentially-relevant articles (**Figure 1**). Only 2,674 relevant articles remained after duplicate publications were identified and removed. Also, further analysis of the abstracts of the papers led to the removal of another 2,466 articles for lacking relevance to the study objectives. A total of 208 articles remained eligible for full text assessment. Overall, a total of 70 papers from 27 countries published between January 1985 and September 2018 met the inclusion requirements and were selected.[6,23-91] **Table 1** summarizes the characteristics of the studies included in the review. Majority of the selected publications 52 (74.2%) reported data on both thymomatous and non-thymomatous MG, 15 (21.4%) of the studies reported data only on non-thymomatous MG and 3 (4.3%) reported data only on thymomatous MG. Overall, 7,287 individuals with MG were analyzed in the review. The follow-up time of the individuals with MG following thymectomy ranges from 0.5 to 13.3 years, (mean: 4.65 years).

Quality assessment of included studies. The quality of the studies was evaluated according to 10 domains. The included papers had good quality in ≥5 of the domains assessed. Majority of the articles (n=36/70) met the requirements for high quality papers (a score of between 7 and 10 of the quality domains evaluated), and others (n=34/70) met the requirements for moderate quality papers (a score of between 5 and 6 in the quality domains evaluated). The commonest quality domains not met by the publications were: having small sample size, low-quality statistical analytical approach, lack of adjustment for confounders, and absence of sub-group analysis.

Prevalence of myasthenia gravis recurrence post-thymectomy. **Table 2** shows the summary analysis of the rate of recurrence of MG following thymectomy. The prevalence of MG recurrence post-thymectomy was 18.0% (95% CI 14.7–22.0%; 1865/7287). However, there was heterogeneity between the studies (I^2=93.6%; p<0.001). Also, the assessment of the funnel plot (**Figure 2**) indicate that there may be publication bias (p<0.001). We also explored sex differences in the recurrence rates of MG post-thymectomy. Overall, 13 studies reported data on the recurrence rates of MG post-thymectomy disaggregated according to sex of the patients. There was a high prevalence of recurrence of MG post-thymectomy in males compared with females (31.3 vs. 23.8%) respectively; but the differences between group was not significant (Q=2.60; p=0.107). In addition, studies that reported disaggregated data for thymomatous and non-thymomatous MG showed that pooled recurrence rates for thymomatous MG (33.3%) were higher than the rates among non-thymomatous MG (20.8%); and the difference was statistically significant (Q=4.19, p=0.041).

Risk factors for recurrence of myasthenia gravis post-thymectomy. **Table 3** summarises the meta-analysis of common risk factors of recurrence of MG

Table 1 - Characteristics of studies included in the systematic review.

s/no	Author, (year)	Countries	Study period	Type of MG	Total number of Patients	Recurrence	Mean/Median Follow-up period (years)
1	Palmisani, (1994)	Italy	1971-1991	Thymoma	111	20	>1
2	Mano, (1993)	Japan	N/A	Both	105	50	9.8
3	Ohmi, (1991)	Japan	1977 – 1989	Both	166	3	>1
4	Abo Elnasr, (2016)	Egypt	2013-2015	Non-thymoma	38	9	0.5
5	Budde, (2001)	USA	1974-1999	Both	92	23	4.3
6	Meyer, (2009)	USA	1992-2006	Both	81	3	6.0±4.0
7	Masaoka, (1996)	Japan	1973 – 1993	Both	321	47	1
8	Bachmann, (2009)	Germany	1980 – 2005	Non thymoma	84	23	9.8
9	Maggi, (2008)	Italy	1986 - 2006	Thymoma	197	62	7.69±6.0
10	Venuta, (1999)	Italy	1970 – 1997	Both	204	51	9.92
11	Kaufman, (2016)	USA	1941-2013	Both	1002	647	6
12	Poomthong, (2012)	Thailand	2010	Non thymoma	51	25	1
13	Glinjongol, (2004)	Thailand	1990-2004	Both	30	6	3.4
14	Ozdemir, (2003)	Turkey	1990-2000	Both	61	11	3.83
15	Takanami, (2009)	Japan	1991-2005	Both	54	18	6.0 ± 3.9
16	Soleimani, (2004)	Iran	1985 - 2002	Both	110	20	6.4 ± 4.3
17	[1]Nazarbaghi, (2015)	Iran	1999 - 2013	Both	25	0.5	7.3±4.2
18	Kumar, (2011)	India	1991 - 2007	Both	73	15	5.65
19	De Roxas, (2016)	Philippines	2009 – 2014	Both	69	27	1 year
20	Frist, (1994)	USA	1971 – 1992	Both	46	6	1
21	Gao, (2016)	China	2010 – 2014	Both	130	28	1.5
22	Hsu, (2006)	Taiwan	1986 - 2001	Both	154	62	1
23	Kim, (2018)	South Korea	1994 - 2016	Both	179	14	1
24	Muhammed, (2016)	Malaysia	2002 – 2012	Both	16	2	1 year
25	Mulder, (1989)	USA	1983 – 1987	Both	84	17	3.6
26	El-Medany, (2003)	Saudi Arabia	1986 – 2001	Both	100	18	7.6
27	Romi, (2003)	Norway	1973 - 2002	Both	48	33	8.7
28	Téllez-Zenteno, (2001)	Mexico	1987 – 1997	Both	132	41	3
29	Tsinzerling, (2007)	Sweden	1956 – 2006	Both	537	88	1.5
30	Werneck, (2000)	Brazil	1973 – 1995	Both	28	2	6.3
31	Yang, (2017)	China	2003 – 2013	Non-thymoma	123	19	4.42
32	Yu, (2015)	China	1984 – 2001	Both	297	56	8.6
33	Dube, (2017)	India	1993 – 2014	Thymoma	8	1	4.6
34	Zheng, (2017)	China	2013 – 2016	Both	73	16	2.2
35	Lin, (2010)	Taiwan	1995 – 2004	Non thymoma	60	9	3.7
36	Bachmann, (2008)	Germany	1980 - 2005	Both	98	17	8
37	Nieto, (1999)	Spain	1977 – 1994	Both	61	2	1
38	Jaretzki, (1988)	USA	1997 – 1985	Both	95	7	0.5
39	Calhoun, (1999)	USA	1989 – 1998	nonthymoma	78	12	5.0
40	Shrager, (2002)	USA	1992 – 1999	Both	78	8	4.6
41	Detterbeck, (1996)	USA	1977 – 1993	Both	100	22	5.4
42	de Perrot, (2001)	Switzerland	1979 – 1999	Both	35	26	8
43	Tansel, (2003)	Turkey	1980 – 2001	nonthymoma	204	20	7.2± 1.2
44	Siwachat, (2018)	Thailand`	2006 – 2013	Both	98	11	3.48
45	Seyfari, (2018)	Iran	2011 – 2015	Both	47	7	1
46	Waitande, (2007)	India	1994 – 2003	Both	57	17	2.4
47	Kattach, (2006)	United Kingdom	1987 - 1998	Both	85	3	4.5
48	Huang, (2005)	Taiwan	1986 - 2000	Both	154	18	8.2
49	Hase, (2006)	Japan	1987 – 2001	Both	17	4	0.5

50	Remes-Troche, (2002)	Mexico	1989 – 2000	Both	152	49	2
51	Pompeo, (2009)	Italy	1995 – 20003	Non thymoma	32	5	9.92
52	Liu, (2016)	China	2000 - 2010	Both	31	10	6.9
53	Yu, (2014)	China	1997 – 2012	Both	188	36	5.6
54	Busch, (1996)	Germany	1976 - 1993	Both	86	25	8.0
55	Bril, (1998)	Canada	1977 – 1986	Nonthymoma	52	5	8.4
56	Klein, (1999)	Germany	1984 – 1992	Both	51	7	3.9
57	Mineo, (2000)	Italy / Belgium	1993 – 1997	Both	31	1	3.3
58	Zielinski, (2004)	Poland	2000 – 2003	Nonthymoma	48	8	1
59	Yim, (2002)	Hong Kong	1985– 2000	Both	36	8	3.4
60	Manlulu, (2005)	China	1992 – 2004	Nonthymoma	36	3	5.8
61	Savcenko, (2002)	USA	1992 – 2002	Both	36	6	4.4
62	Uchiyama, (2001)	Japan	1998 – 2000	Both	23	2	1
63	Wright, (2002)	Australia	1997 – 2001	Nonthymoma	24	2	0.5
64	Nussbaum, (2002)	USA	1979 – 1991	Both	48	3	4.3
65	Cooper, (1988)	Canada	1977 – 1986	Both	65	3	3.5
66	Olanow, (1987)	Canada	1979 – 1986	Both	55	5	3.3
67	DeFilippi, (1994)	USA	1977 - 1991	Nonthymoma	21	4	4.3
68	Mack, (1996)	USA	1992 – 1995	Both	33	4	1.9
69	Ambrogi, (2012)	Italy	1980 – 2005	Nonthymoma	96	24	13.3
70	Mineo, (2013)	Italy	1980 - 2007	Nonthymoma	47	9	8.3

[1] = no recurrence during follow-up, 0.5 was assigned to allow for meta-analysis; N/A = not available

post-thymectomy. A meta-analysis of eight studies showed that older age (>35–60 years) was a risk factor of recurrence (OR 3.5; 95% C.I. 2.4–5.0). No heterogeneity was found between the studies (I^2=0), but evidence of publication bias existed (p=0.017). In a meta-analysis of five studies, male sex was also a risk factor for recurrence of MG following thymectomy (OR 2.8; 95% C.I. 1.5–5.4). There was minimal heterogeneity among the studies (I^2=34.8) as well as some publication bias (p-value <0.001). Also, a higher MG stage was a risk factor of recurrence following thymectomy in a meta-analysis of 10 studies (OR 4.8; 95% C.I. 3.1–7.7). There was minimal heterogeneity among the studies (I^2=39.6) and some publication bias (p=0.03).

Furthermore, a meta-analysis involving nine studies revealed that having a thymomatous MG was a risk factor for recurrence post-thymectomy (OR 2.1; 95% C.I. 1.6–2.7). There was minimal heterogeneity (I^2=24.3), but no publication bias was noted among the studies (p=0.118). A meta-analysis of six studies found that longer duration of the MG prior to the thymectomy was a risk factor for recurrence post-thymectomy (OR 2.3; 95% C.I. 1.04–4.9). A high level of heterogeneity was noted among the studies (I^2=79.2), but publication bias was not evident (p=0.433). In addition, having an ectopic thymic tissue was a risk factor of MG recurrence post-thymectomy according to a meta-analysis of three studies (OR 6.04; 95% C.I. 3.0–11.82). There was absent heterogeneity (I^2=0) and publication bias between the studies (p=0.687). A meta-analysis of four studies revealed that having a thymic hyperplasia was not a risk factor for recurrence of MG post-thymectomy (OR 1.1; 95% C.I. 0.2–757).

Thymic atrophy (OR 2.5; 95% C.I. 1.4–4.6), higher dosage of pyridostigmine (OR 2.8; 95% C.I. 1.4–5.3), and use of steroid before thymectomy (OR 2.6; 95% C.I. 1.5–4.5) were all found to be potential risk factors of MG recurrence post-thymectomy in a meta-analysis of two studies each (**Table 3**); however, the inadequate number of studies precluded any further analysis of these factors. Other less common risk factors for MG recurrence following thymectomy are summarised in **Table 4**. Overall, a duration of less than six years post-surgery (OR=1.37), having a previous thymectomy (OR=4.6), receiving plasampheresis post-surgery (OR=3.4), hyperthyroidism (HR=8.3), preoperative myasthenic crisis (OR=4.7), having bulbar symptoms (OR=3.3), long duration of thymectomy procedure (OR=1.03) and higher blood loss during surgery (OR=1.02) were all found to be potential risk factors.

Discussion. This systematic review of observational studies demonstrated that 18.0% of patients who had thymectomy as part of their management for MG experienced recurrence during follow-up. Also, post-

Table 2 - Pooled event rates of myasthenia Gravis recurrence Post-thymectomy.

Variables	Pooled event rate	n/N	No. of Studies	Heterogeneity I^2 (*P*-value)
MG Recurrence	% (95% CI)			
Total	18.0 (14.7 – 22.0)	1865/7287	70	93.6% (<0.001)
Stratified by Sex				
Male	31.3 (24.4 – 39.1)	148/432	13	53.3% (0.012)
Female	23.8 (18.7 – 29.8)	206/781	13	64.7% (0.001)
Stratified by Histology				
Thymomatous	33.3 (23.4 – 45.0)	175/682	17	82.2% (<0.001)
Non-thymomatous	20.8 (15.3 – 27.5)	2320/1782	17	85.1% (<0.001)

Table 3 - Summary of meta-analysis of risk factors of myasthenia gravis recurrence post-thymectomy.

Risk Factor	Number of primary studies	Effect size	Random-effects summary effect size (95% CI)	*P*-value (random)	I^2	Egger regression test (*P*–value)	Begg and Mazumdar correlation test (*P*–value)
Older age (>35 - 60) years	8	OR	3.45 (2.36 – 5.04)	<0.001	0	0.017	0.006
Male sex	5	OR	2.84 (1.51 – 5.35)	0.001	34.8	<0.001	0.027
Higher stage of the MG (>ii)	10	OR	4.80 (3.1 – 7.67)	<0.001	39.6	0.033	0.049
Thymomatous MG	9	OR	2.05 (1.56 – 2.68)	<0.001	24.3	0.118	0.25
Longer duration of MG before surgery	6	OR	2.27 (1.04 – 4.94)	0.039	79.2	0.433	0.260
Ectopic Thymic tissue	3	OR	6.04 (3.08 – 11.82)	<0.001	0	0.687	0.601
Thymic hyperplasia	4	OR	1.12 (0.17 - 757)	0.907	86.3	0.359	0.308
Thymic atrophy	2	OR	2.54 (1.41 – 4.58)	0.002			
Higher Pyridostigmine dosage (>240 mg)	2	OR	2.80 (1.48 – 5.28)	0.002			
Use of steroid before thymectomy	2	OR	2.58 (1.47 – 4.54)	0.001			

MG - myasthenia gravis

Table 4 - Less common risk factors of myasthenia gravis recurrence post-thymectomy.

Factors	Effect size type	Effect size (95% CI)
Less than six years post-surgery	OR	1.37 (0.61 – 3.07)
Previous thymectomy	OR	4.6 (0.31 – 132.7)
Receiving Plasmapheresis post-surgery	OR	3.4 (2.6 – 4.5)
Hyperthyroidism	HR	8.3 (2.1 – 33.3)
Preoperative myasthenia gravis crisis	OR	4.7 (1.6 – 13.4)
Having Bulbar symptom	OR	3.3 (1.3 – 8.4)
Longer operation time	OR	1.03 (1.003 – 1.039)
Higher blood loss during surgery	OR	1.02 (1.003 – 1.039)

HR - hazard ratio, OR - odds ratio

thymectomy MG recurrence rates were insignificantly higher in males compared with females and was significantly higher in individuals having thymomatous than non-thymomatous MG. In addition, we found that significant risk factors for MG recurrence post-thymectomy include: older age, male sex, MG severity, increased MG disease duration pre-surgery and ectopic thymic tissue. Other potential risk factors for MG recurrence post-thymectomy were also identified.

Previous meta-analyses were carried out either to evaluate the effectiveness of thymectomy relative to pharmacological therapy or to assess the effectiveness of thymectomy to achieve complete stable remission.[11,14-16] This is the first meta-analysis that assessed the recurrence rates of MG in patients who have had thymectomy. Our analyses showed that almost a fifth of the patients experienced MG recurrence after a mean follow-up duration of about 4.7 years post-thymectomy. This finding further lends credence to a recent report of a randomised controlled trial which demonstrated the additional benefit of surgical treatment (thymectomy) relative to pharmacological therapy alone for the

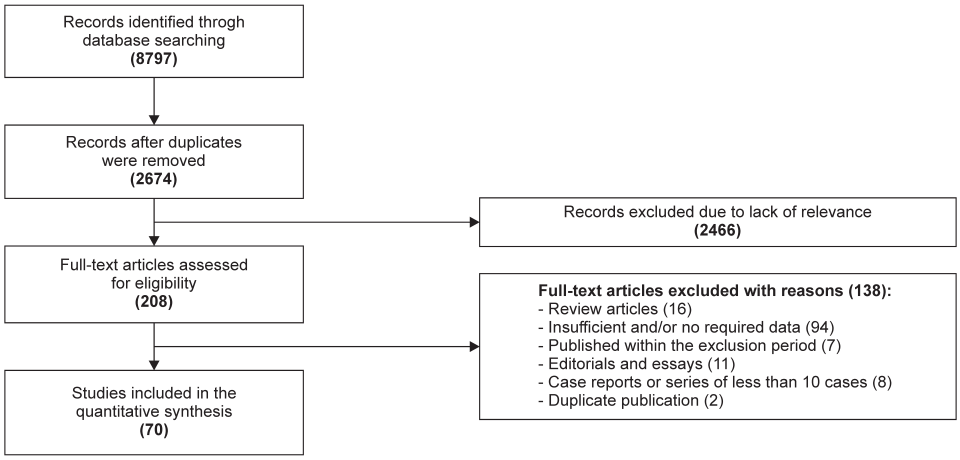

Figure 1 - Flow chart for article identification and exclusion process.

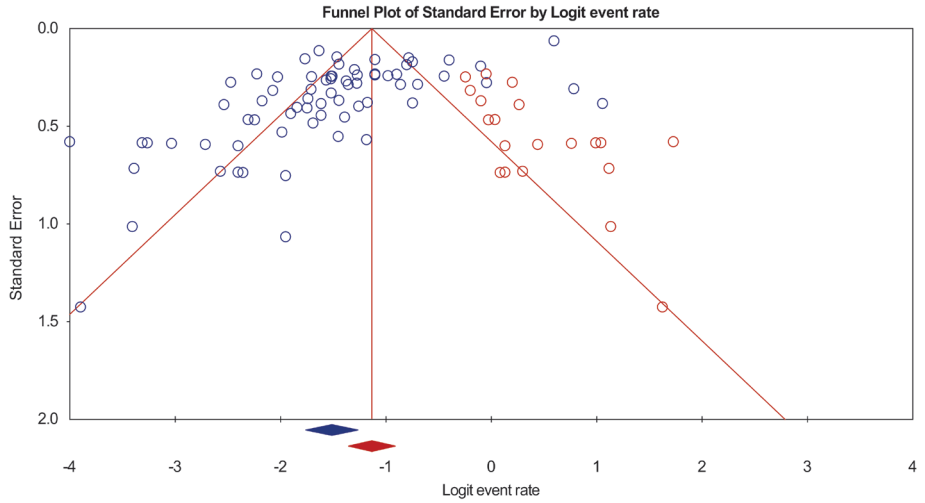

Figure 2 - Forest plot of the meta-analysis on prevalence of myasthenia gravis recurrence post-thymectomy. CI - confidence interval

management of individuals with MG.[9] This indicates that thymectomy is an important management strategy but additional care needs to be given in order to prevent recurrence among affected patients.

We found that older patients were over three times more likely to experience recurrence of their MG following thymectomy. Previous studies showed that younger age at onset of MG (<40 years) was a good prognostic factor for remission among thymectomized patients while others did not demonstrate this finding.[11,30,92] Our analysis demonstrates that older age is a risk factor for MG recurrence. The reason for the effect of age on recurrence rates among the patients is not clear. It may be that younger patients are more clinically-stable to tolerate thymectomy compared to older individuals. There is a need for properly-designed analytical studies to further evaluate the effect of age in individuals with MG who had had thymic excision. Also, sex is a biological factor showing variable associations in studies of individuals with MG. Some literature have reported improved outcomes in female subjects while others either reported improvements in males or no sex differences.[27,75] Our analysis indicates that men were almost thrice as likely to experience recurrence of MG following thymectomy than women. There is therefore a need for closer monitoring of men with MG during treatment.

Furthermore, higher stage of the MG (disease severity) was a risk factor of MG recurrence post-thymectomy. Previous studies have demonstrated that MG patients with mild disease had substantially increased survival and remission rates compared to

individuals having severe MG.[27,93] However, our finding may partly be because individuals with MG who underwent thymectomy were more likely to have had a more severe disease than those who did not.[94,95]

Also, we found that disease duration before surgery was a risk factor for recurrence. Previous studies have demonstrated that a longer duration of MG before the surgery is a prognostic factor for remission.[96,97] The reason why patients with longer duration of MG have higher rates of recurrence deserves further evaluation.

Thymic histology has been found to be a relatively consistent determinant of treatment response in individuals with MG. In many studies, hyperplasia has been found to be related with higher improvement rates.[27,77,98] Our meta-analysis demonstrates that hyperplasia was not a predictor of MG recurrence following thymectomy. However, patients having an ectopic thymic tissue were 6 times more likely to experience recurrence following MG. This indicates that patients with ectopic thymic tissue should be given closer monitoring and care following thymectomy.

A number of factors like thymic atrophy, higher pyridostigmine dosage (>240 mg) and use of steroid before thymectomy were all found to predict a higher risk of MG recurrence following thymectomy. A number of other potential risk factors found in single studies were: less than 6 years post-surgery, previous thymectomy, receiving plasmapheresis post-surgery, hyperthyroidism, preoperative myasthenia gravis crisis, having bulbar symptoms, longer operation time and higher blood loss during surgery. These factors need to be explored further in future studies.

There are a number of strengths and limitations of this analysis. A major strength is that we evaluated recurrence rates in 7,287 patients with MG following thymectomy. Second, although the studies included used varying classification systems and reporting of crude rates of remission and improvement, we were able to group the selected studies according to recurrence rates. Third, we identified major risk factors for MG recurrence following thymectomy. However, there are some limitations that require consideration. First, our meta-analysis mainly included descriptive and analytical studies; therefore, differences in the study design, patient characteristics and the type of care given before surgery may introduce some heterogeneity among the patients. Second, most of the studies included in the analyses have relatively small sample size and the risk factors obtained were not controlled for confounders. It may be likely that the pooled risk factor groups identified might overestimate the risk. Other sources of bias may be differences in the surgical skills of the surgeon who performed the thymectomy and the surgical approach used. Despite these limitations, the study provides valuable data necessary for clinical care and policy.

In conclusion, there is increasing interest on the effect of thymectomy in the management of MG and a better understanding of recurrence rates following thymectomy and its prognosis are crucial for clinical practice. We found that a fifth of the MG patients who had thymectomy developed recurrence and a number of demographic and clinical factors are predictors of MG recurrence post-thymectomy. Closer attention should be given to MG patients with the identified risk factors and there is a need for further well-designed studies to assess the effect of confounding on the risk factors identifies and a closer assessment of emerging risk factors.

Acknowledgment. *We would like to thank the professional editors at Editage, a division of Cactus Communications for English language editing.*

References

1. Kuks JBM. Clinical presentations of myasthenia gravis. In: Kaminski HJ, Kusner LL, editors. Myasthenia gravis and related disorders. Humana Press; 2018: 85-100.
2. Yildiz Celik S, Durmus H, Yilmaz V, Saruhan Direskeneli G, Gulsen Parman Y, Serdaroglu Oflazer P, et al. Late-onset generalized myasthenia gravis: clinical features, treatment, and outcome. ***Acta Neurol Belg*** 2020; 120: 133-140.
3. Na KJ, Hyun K, Kang CH, Park S, Lee HJ, Park IK, et al. Predictors of post-thymectomy long-term neurological remission in thymomatous myasthenia gravis: an analysis from a multi-institutional database. ***Eur J Cardiothorac Surg*** 2020; 57: 867-873.
4. Marx A, Ströbel, P, Weis C. Thymoma-associated myasthenia gravis. In: Kaminski HJ, Kusner LL, editors. Myasthenia gravis and related disorders. Humana Press; 2018: 85-100.
5. Banna GL, Sheel A, Sheel V, Bille A, Routledge T, Fernando S, et al. Treatment and prognostic factors of patients with thymic epithelial tumors at first recurrence or progression. ***Future Oncol*** 2017; 13: 2429-2439.
6. Siwachat S, Tantraworasin A, Lapisatepun W, Ruengorn C, Taioli E, Saeteng S. Comparative clinical outcomes after thymectomy for myasthenia gravis: Thoracoscopic versus trans-sternal approach. ***Asian J Surg*** 2018; 41: 77-85.
7. Shinohara S, Hanagiri T, So T, Yasuda M, Takenaka M, Nagata Y, et al. Results of surgical resection for patients with thymoma according to World Health Organization histology and Masaoka staging. ***Asian J Surg*** 2012; 35: 144-148.
8. Kaminski HJ. Treatment of myasthenia gravis. In: Marx A, Ströbel, P, Weis C. Thymoma-associated myasthenia gravis. In: Kaminski HJ, Kusner LL, editors. Myasthenia gravis and related disorders. Humana Press; 2018: 85-100.169-187
9. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Randomized trial of thymectomy in myasthenia gravis. ***N Engl J Med*** 2016; 375: 511-22.

10. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis: Executive summary. ***Neurology*** 2016; 87: 419-425.
11. Luo Y, Pan DJ, Chen FF, Zhu MH, Wang J, Zhang M. Effectiveness of thymectomy in non-thymomatous myasthenia gravis: a systematic review. ***J Huazhong Univ Sci Technolog Med Sci*** 2014; 34: 942-949.
12. Cataneo AJ, Felisberto Jr G, Cataneo DC. Thymectomy in nonthymomatous myasthenia gravis-systematic review and meta-analysis. ***Orphanet J Rare Dis*** 2018; 13: 99.
13. Xie A, Tjahjono R, Phan K, Yan TD. Video-assisted thoracoscopic surgery versus open thymectomy for thymoma: a systematic review. ***Ann Cardiothorac Surg*** 2015; 4: 495-508.
14. Tao S, Qiu T. A comparative meta-analysis on curative effects of thymectomy and sternotomy in treating the myasthenia gravis. ***Int J Clin Exp Med*** 2017; 10: 11703-11709.
15. Taioli E, Paschal PK, Liu B, Kaufman AJ, Flores RM. Comparison of conservative treatment and thymectomy on myasthenia gravis outcome. ***Ann Thorac Surg*** 2016; 102: 1805-1813.
16. Wang L, Zhang Y, He M. Clinical predictors for the prognosis of myasthenia gravis. ***BMC Neurol*** 2017; 17: 77.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. ***Ann Intern Med*** 2009; 151: 264-269.
18. Gronseth GS, Barohn R, Narayanaswami P. 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*** 2020; 94: 705-709.
19. Joanna Briggs Institute. Joanna Briggs Institute reviewers' manual: 2014 edition. Australia: The Joanna Briggs Institute. 2014.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. ***Contemp Clin Trials*** 2015; 45: 139-145.
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. ***Stat Med*** 2002; 21: 1539-1558.
22. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. ***Biometrics*** 2000; 56: 455-463.
23. Palmisani MT, Evoli A, Batocchi AP, Provenzano C, Tonali P. Myasthenia gravis associated with thymoma: clinical characteristics and long-term outcome. ***Eur Neurol*** 1994; 34: 78-82.
24. Mano K, Takegami T, Okamoto S, Takahashi A. Remission of myasthenia gravis: clinical, electrophysiological and immunological studies. ***Nagoya J Med Sci*** 1993; 55: 103-113.
25. Ohmi M, Ohuchi M. Recurrent thymoma in patients with myasthenia gravis. ***Ann Thorac Surg*** 1990; 50: 243-247.
26. Elnasr MM, El-Guindy DM, Al-Malt AM, Taha AH. Thymectomy in non thymomatous myasthenia gravis: Impact of pathology on outcome and role of surviving in pathogenesis. ***Eur J Cardiothorac Surg*** 2010; 37: 7-12.
27. Budde JM, Morris CD, Gal AA, Mansour KA, Miller Jr JI. Predictors of outcome in thymectomy for myasthenia gravis. ***Ann Thorac Surg*** 2001; 72: 197-202.
28. Meyer DM, Herbert MA, Sobhani NC, Tavakolian P, Duncan A, Bruns M, et al. Comparative clinical outcomes of thymectomy for myasthenia gravis performed by extended transsternal and minimally invasive approaches. ***Ann Thorac Surg*** 2009; 87: 385-391.
29. Masaoka A, Yamakawa Y, Niwa H, Fukai I, Kondo S, Kobayashi M, et al. Extended thymectomy for myasthenia gravis patients: a 20-year review. ***Ann Thorac Surg*** 1996; 62: 853-859.
30. Bachmann K, Burkhardt D, Schreiter I, Kaifi J, Schurr P, Busch C, et al. Thymectomy is more effective than conservative treatment for myasthenia gravis regarding outcome and clinical improvement. ***Surgery*** 2009; 145: 392-398.
31. Maggi L, Andreetta F, Antozzi C, Baggi F, Bernasconi P, Cavalcante P, et al. Thymoma-associated myasthenia gravis: outcome, clinical and pathological correlations in 197 patients on a 20-year experience. ***J Neuroimmunol*** 2008; 201: 237-244.
32. Venuta F, Rendina EA, De Giacomo T, Della Rocca G, Antonini G, Ciccone AM, et al. Thymectomy for myasthenia gravis: a 27-year experience. ***Eur J Cardiothorac Surg*** 1999; 15: 621-625.
33. Kaufman AJ, Palatt J, Sivak M, Raimondi P, Lee DS, Wolf A, et al. Thymectomy for myasthenia gravis: complete stable remission and associated prognostic factors in over 1000 cases. ***Semin Thorac Cardiovasc Surg*** 2016; 28: 561-568.
34. Poomthong P, Arayawichanont A. Response of thymectomy in myasthenia gravis patients: a one year retrospective study at Sappasithiprasong Hospital, Thailand. ***North-Eastern Thai Journal of Neuroscience*** 2009; 7: 71-78.
35. Glinjongol C, Paiboonpol S. Outcome after transsternal radical thymectomy for myasthenia gravis: 14-year review at Ratchaburi Hospital. ***J Med Assoc Thai*** 2004; 87: 1304-1310.
36. Özdemir N, Kara M, Dikmen E, Nadir A, Akal M, Yücemen N, et al. Predictors of clinical outcome following extended thymectomy in myasthenia gravis. ***Eur J Cardiothorac Surg*** 2003; 23: 233-237.
37. Takanami I, Abiko T, Koizumi S. Therapeutic outcomes in thymectomied patients with myasthenia gravis. ***Ann Thorac Cardiovasc Surg*** 2009; 15: 373-377.
38. Soleimani A, Moayyeri A, Akhondzadeh S, Sadatsafavi M, Shalmani HT, Soltanzadeh A. Frequency of myasthenic crisis in relation to thymectomy in generalized myasthenia gravis: a 17-year experience. ***BMC Neurol*** 2004; 4: 12.
39. Nazarbaghi S, Amiri-Nikpour MR, Mahmodlou R, Arjmand N, Rezaei Y. Clinical outcomes of myasthenia gravis with thymoma and thymic hyperplasia undergoing extended transsternal thymectomy: A single-center experience. ***N Am J Med Sci*** 2015; 7: 503-508.
40. Kumar N, Verma AK, Mishra A, Agrawal G, Agrawal A, Misra UK, et al. Factors predicting surgical outcome of thymectomy in myasthenia gravis: A 16-year experience. ***Ann Indian Acad Neurol*** 2011; 14: 267-271.
41. De Roxas RC, Bagnas MA, Baldonado JJ, Rivera JP, Roxas AA. Clinical profile and outcome of postthymectomy versus non-thymectomy myasthenia gravis patients in the Philippine general hospital: A 6-year retrospective study. ***Front Neurol*** 2016; 7: 96.
42. Frist WH, Thirumalai S, Doehring CB, Merrill WH, Stewart JR, Fenichel GM, et al. Thymectomy for the myasthenia gravis patient: factors influencing outcome. ***Ann Thorac Surg*** 1994; 57: 334-338.
43. Gao F, Zhao X, Zhang J, Cui X, Zhang Y, Li Q, et al. Clinical features of patients with Myasthenia gravis from the Henan province, China. ***Muscle Nerve*** 2016; 53: 711-716.
44. Hsu HS, Huang CS, Huang BS, Lee HC, Kao KP, Hsu WH, et al. Thymoma is associated with relapse of symptoms after transsternal thymectomy for myasthenia gravis. ***Interact Cardiovasc Thorac Surg*** 2006; 5: 42-46.

45. Kim H, Lim YM, Lee EJ, Oh YJ, Kim KK. Factors predicting remission in thymectomized patients with acetylcholine receptor antibody-positive myasthenia graviss. ***Muscle Nerve*** 2018; 58: 796-800.
46. Muhammed J, Chen CY, Hitam WH, Ghazali MZ. Thymectomy for Myasthenia Gravis: A 10-year Review of Cases at the Hospital Universiti Sains Malaysia. ***Malays J Med Sci*** 2016; 23: 71-78.
47. Mulder DG, Graves M, Herrmann C. Thymectomy for myasthenia gravis: recent observations and comparisons with past experience. ***Ann Thorac Surg*** 1989; 48: 551-555.
48. El-Medany Y, Hajjar W, Essa M, Al-Kattan K, Hariri Z, Ashour M. Predictors of outcome for myasthenia gravis after thymectomy. ***Asian Cardiovasc Thorac Ann*** 2003; 11: 323-327.
49. Romi F, Gilhus NE, Varhaug JE, Myking A, Aarli JA. Disease severity and outcome in thymoma myasthenia gravis: a long-term observation study. ***Eur J Neurol*** 2003; 10: 701-706
50. Téllez-Zenteno JF, Remes-Troche JM, García-Ramos G, Estañol B, Garduño-Espinoza J. Prognostic factors of thymectomy in patients with myasthenia gravis: a cohort of 132 patients. ***Eur Neurol*** 2001; 46: 171-177.
51. Tsinzerling N, Lefvert AK, Matell G, Pirskanen-Matell R. Myasthenia gravis: a long term follow-up study of Swedish patients with specific reference to thymic histology. ***J Neurol Neurosurg Psychiatry*** 2007; 78: 1109-1112.
52. Werneck LC, Cunha FM, Scola RH. Myasthenia gravis: a retrospective study comparing thymectomy to conservative treatment. ***Acta Neurol Scand*** 2000; 101: 41-46.
53. Yang J, Liu C, Li T, Li C. Prognosis of thymectomy in myasthenia gravis patients with thymus hyperplasia. ***Int J Neurosci*** 2017; 127: 785-789.
54. Yu S, Li F, Chen B, Lin J, Yang M, Fu X, et al. Eight-year follow-up of patients with myasthenia gravis after thymectomy. ***Acta Neurol Scand*** 2015; 131: 94-101.
55. Dube M, Sodani A, Chouksey D. Outcome of Myasthenia gravis treated with high-dose prednisolone and azathioprine: A single centre ambispective study from India. ***Acta Neurol Taiwan*** 2017; 26: 106-119
56. Zheng Y, Cai YZ, Shi ZY, Qiu Y, Zhang HL, Wang ZH, et al. Different neurologic outcomes of myasthenia gravis with thymic hyperplasia and thymoma after extended thymectomy: A single center experience. ***J Neurol Sci*** 2017; 383: 93-98.
57. Lin MW, Chang YL, Huang PM, Lee YC. Thymectomy for non-thymomatous myasthenia gravis: a comparison of surgical methods and analysis of prognostic factors. ***Eur J Cardiothorac Surg*** 2010; 37: 7-12.
58. Bachmann K, Burkhardt D, Schreiter I, Kaifi J, Busch C, Thayssen G, et al. Long-term outcome and quality of life after open and thoracoscopic thymectomy for myasthenia gravis: analysis of 131 patients. ***Surg Endosc*** 2008; 22: 2470-2477.
59. Nieto IP, Robledo JP, Pajuelo MC, Montes JA, Giron JG, Alonso JG, et al. Prognostic factors for myasthenia gravis treated by thymectomy: review of 61 cases. ***Ann Thorac Surg*** 1999; 67: 1568-1571.
60. Jaretzki 3rd A, Penn AS, Younger DS, Wolff M, Olarte MR, Lovelace RE, et al. "Maximal" thymectomy for myasthenia gravis. Results. ***J Thorac Cardiovasc Surg*** 1988; 95: 747-757.
61. Calhoun RF, Ritter JH, Guthrie TJ, Pestronk A, Meyers BF, Patterson GA, et al. Results of transcervical thymectomy for myasthenia gravis in 100 consecutive patients. ***Ann Thorac Surg*** 1999; 230: 555-559.
62. Shrager JB, Deeb ME, Mick R, Brinster CJ, Childers HE, Marshall MB, et al. Transcervical thymectomy for myasthenia gravis achieves results comparable to thymectomy by sternotomy. ***Ann Thorac Surg*** 2002; 74: 320-327.
63. Detterbeck FC, Scott WW, Howard Jr JF, Egan TM, Keagy BA, Starek PJ, et al. One hundred consecutive thymectomies for myasthenia gravis. ***Ann Thorac Surg*** 1996; 62: 242-245.
64. de Perrot M, Licker M, Spiliopoulos A. Factors influencing improvement and remission rates after thymectomy for myasthenia gravis. ***Respiration*** 2001; 68: 601-605.
65. Tansel T, Onursal E, Barlas S, Tireli E, Alpagut U. Results of surgical treatment for nonthymomatous myasthenia gravis. ***Surg Today*** 2003; 33: 666-670.
66. Seyfari B, Fatehi F, Shojaiefard A, Jafari M, Ghorbani-Abdehgah A, Nasiri S, et al. Clinical outcome of thymectomy in myasthenia gravis patients: A report from Iran. ***Iran J Neurol*** 2018; 17: 1-5.
67. Waitande SS, Thankachen R, Philip MA, Shukla V, Korula RJ. Surgical outcome of thymectomy for myasthenia gravis. ***Indian J Thorac Cardiovasc Surg*** 2007; 23: 171-175.
68. Kattach H, Anastasiadis K, Cleuziou J, Buckley C, Shine B, Pillai R, et al. Transsternal thymectomy for myasthenia gravis: surgical outcome. ***Ann Thorac Surg*** 2006; 81: 305-308.
69. Huang CS, Hsu HS, Huang BS, Lee HC, Kao KP, Hsu WH, et al. Factors influencing the outcome of transsternal thymectomy for myasthenia gravis. ***Acta Neurol Scand*** 2005; 112: 108-114.
70. Hase R, Sugiura H, Fukunaga A, Takahashi H, Simozawa E, Kondo S. Clinical outcomes following extended thymectomy for myasthenia gravis: report of 17 cases. ***Ann Thorac Cardiovasc Surg*** 2006; 12: 203-206.
71. Remes-Troche JM, Téllez-Zenteno JF, Estañol B, Garduño-Espinoza J, García-Ramos G. Thymectomy in myasthenia gravis: response, complications, and associated conditions. ***Arch Med Res*** 2002; 33: 545-551.
72. Pompeo E, Tacconi F, Massa R, Mineo D, Nahmias S, Mineo TC. Long-term outcome of thoracoscopic extended thymectomy for nonthymomatous myasthenia gravis. ***Eur J Cardiothorac Surg*** 2009; 36: 164-169.
73. Liu Z, Lai Y, Yao S, Feng H, Zou J, Liu W, et al. Clinical outcomes of thymectomy in myasthenia gravis patients with a history of crisis. ***World J Surg*** 2016; 40: 2681-2687.
74. Yu S, Lin J, Fu X, Li J, Li Y, Chen B, et al. Risk factors of myasthenic crisis after thymectomy in 178 generalized myasthenia gravis patients in a five-year follow-up study. ***Int J Neurosci*** 2014; 124: 792-798.
75. Busch C, Machens A, Pichlmeier U, Emskötter T, Izbicki JR. Long-term outcome and quality of life after thymectomy for myasthenia gravis. ***Ann Surg*** 1996; 224: 225-232.
76. Bril V, Kojic J, Ilse WK, Cooper JD. Long-term clinical outcome after transcervical thymectomy for myasthenia gravis. ***Ann Thorac Surg*** 1998; 65: 1520-1522.
77. Klein M, Granetzny A, Dauben HP, Schulte HD, Gams E. Early and late results after thymectomy in myasthenia gravis: a retrospective analysis. ***Thorac Cardiovasc Surg*** 1999; 47: 170-173.
78. Mineo TC, Pompeo E, Lerut TE, Bernardi G, Coosemans W, Nofroni I. Thoracoscopic thymectomy in autoimmune myasthenia: results of left-sided approach. ***Ann Thorac Surg*** 2000; 69: 1537-1541.
79. Zieliński M, Kużdżał J, Szlubowski A, Soja J. Transcervical-subxiphoid-videothoracoscopic "maximal" thymectomy—operative technique and early results. ***Ann Thorac Surg*** 2004; 78: 404-409.
80. Yim AP. Paradigm shift in surgical approaches to thymectomy. ***ANZ J Surg*** 2002; 72: 40-45.

81. Manlulu A, Lee TW, Wan I, Law CY, Chang C, Garzon JC, et al. Video-assisted thoracic surgery thymectomy for nonthymomatous myasthenia gravis. ***Chest*** 2005; 128: 3454-3460.
82. Savcenko M, Wendt GK, Prince SL, Mack MJ. Video-assisted thymectomy for myasthenia gravis: an update of a single institution experience. ***Eur J Cardiothorac Surg*** 2002; 22: 978-983.
83. Uchiyama A, Shimizu S, Murai H, Kuroki S, Okido M, Tanaka M. Infrasternal mediastinoscopic thymectomy in myasthenia gravis: surgical results in 23 patients. ***Ann Thorac Surg*** 2001; 72: 1902-1905.
84. Wright GM, Barnett S, Clarke CP. Video-assisted thoracoscopic thymectomy for myasthenia gravis. ***Intern Med J*** 2002; 32: 367-371.
85. Nussbaum MS, Rosenthal GJ, Samaha FJ, Grinvalsky HT, Quinlan JG, Schmerler M, et al. Management of myasthenia gravis by extended thymectomy with anterior mediastinal dissection. ***Surgery*** 1992; 112: 681-687.
86. Cooper JD, Al-Jilaihawa AN, Pearson FG, Humphrey JG, Humphrey HE. An improved technique to facilitate transcervical thymectomy for myasthenia gravis. ***Ann Thorac Surg*** 1988; 45: 242-247.
87. Olanow CW, Wechsler AS, Sirotkin-Roses M, Stajich J, Roses AD. Thymectomy as primary therapy in myasthenia gravis. ***Ann N Y Acad Sci*** 1987; 505: 595-606.
88. DeFilippi VJ, Richman DP, Ferguson MK. Transcervical thymectomy for myasthenia gravis. ***Ann Thorac Surg*** 1994; 57: 194-197.
89. Mack MJ, Landreneau RJ, Yim AP, Hazelrigg SR, Scruggsa GR. Results of video-assisted thymectomy in patients with myasthenia gravis. ***J Thorac Cardiovasc Surg*** 1996; 112: 1352-1360.
90. Ambrogi V, Mineo TC. Active ectopic thymus predicts poor outcome after thymectomy in class III myasthenia gravis. ***J Thorac Cardiovasc Surg*** 2012; 143: 601-606.
91. Mineo TC, Ambrogi V. Outcomes after thymectomy in class I myasthenia gravis. ***J Thorac Cardiovasc Surg*** 2013; 145: 1319-1324.
92. Donaldson DH, Ansher M, Horan S, Rutherford RB, Ringel SP. The relationship of age to outcome in myasthenia gravis. ***Neurology*** 1990; 40: 786-790.
93. Papatestas AE, Genkins GA, Kornfeld PE, Eisenkraft JB, Fagerstrom RP, Pozner JA, et al. Effects of thymectomy in myasthenia gravis. ***Ann Surg*** 1987; 206: 79-88.
94. Kawaguchi N, Kuwabara S, Nemoto Y, Fukutake T, Arimura K, Osame M, et al. Effects of thymectomy on late-onset myasthenia gravis without thymoma. ***Clin Neurol Neurosurg*** 2007; 109: 858-861.
95. Robertson NP, Deans J, Compston DA. Myasthenia gravis: a population based epidemiological study in Cambridgeshire, England. ***J Neurol Neurosurg Psychiatry*** 1998; 65: 492-496.
96. Beghi E, Antozzi C, Batocchi AP, Cornelio F, Cosi V, Evoli A, et al. Prognosis of myasthenia gravis: a multicenter follow-up study of 844 patients. ***J Neurol Sci*** 1991; 106: 213-220.
97. Cosi V, Romani A, Lombardi M, Raiola E, Bergamaschi R, Piccolo G, et al. Prognosis of myasthenia gravis: a retrospective study of 380 patients. ***J Neurol*** 1997; 244: 548-555.
98. Nicolaou S, Müller NL, Li DK, Oger JJ. Thymus in myasthenia gravis: comparison of CT and pathologic findings and clinical outcome after thymectomy. ***Radiology*** 1996; 201: 471-474.