Thymectomy in Ocular Myasthenia Gravis - Prognosis and Risk Factors Analysis

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Research Article

Keywords: ocular myasthenia gravis, thymoma, thymectomy, conversion, remission

Posted Date: March 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1426329/v1

Abstract

Background: Several retrospective studies have identified risk factors associated with ocular myasthenia gravis (OMG) generalization in non-operative patients. However, the outcome of OMG after thymectomy has not been properly investigated. This study aims to explore the clinical predictors for post-thymectomy OMG prognosis.

Methods: We performed a retrospective review of OMG patients at our institution who underwent thymectomy from January 2012 to December 2021. Kaplan-Meier and Cox proportional hazard regression analyses were used to evaluate associations between clinical features and prognosis. Outcome measures consisted of OMG conversion and complete stable remission (CSR).

Results: 58 patients were identified for conversion analysis. 13 developed generalized MG (GMG) at a median time of 12.7 (3-37.3) months from symptom onset. Repetitive nerve stimulation (RNS) positivity was associated with increased risk of conversion (p=0.002). Patients with histotype B2/B3 thymoma showed a higher risk of conversion (P =0.002) compared with patients with hyperplasia and AB/B1 thymoma. 52 patients fulfilled the criteria for CSR analysis. 16 achieved CSR at a median time of 28.7 (15-54) months after thymectomy. Patients achieved CSR showed a younger age of onset (p=0.022), lower percentage of acetylcholine receptor antibody (AchR Ab) seropositivity (p=0.029). Histologically, patients with thymic hyperplasia and stage I thymoma showed a higher chance of CSR (P =0.010) compared with patients with stage II/III thymoma. Multivariate analysis revealed that positive RNS (HR=6.007, p=0.021), histotype B2-3 thymoma (HR=4.611, p=0.048) were associated with OMG conversion. While, thymic hyperplasia and stage I thymoma (HR=0.300, p=0.026) were associated with OMG CSR after thymectomy.

Conclusion: For OMG patients after thymectomy, RNS positivity and histotype B2-3 thymoma are independent predictors of developing GMG. Whereas thymic hyperplasia and stage I thymoma independently predict CSR.

Background

Myasthenia gravis (MG) is an autoimmune disease caused by pathogenic autoantibodies to components of the postsynaptic muscle endplate. The typical manifestation is fluctuations in severity of muscle weakness(1). According to symptoms at disease onset, MG can be further divided into ocular MG (OMG, MGFA class I) and generalized MG (GMG, MGFA Class II-V). However, 50–65% of OMG patients will develop systemic neuromuscular weakness converting to secondary GMG (SGMG), typically in the first 2 years(2). Several retrospective studies have reported risk factors associated with SGMG(3) in non-operative patients. Such as sex, older age of onset, seropositivity(4), presence of other autoimmune diseases(5). However, there is limited evidence specifically regarding the factors associated with post-thymectomy outcome of OMG. Moreover, a significant correlation of the histologic subtype, Masaoka stage and MG pathogenesis has been described(6). The immunopathology of types B1-B3 thymomas

were reported favoring lack of self-tolerance and triggering of MG(6). Whether these differences would translate to differences in the post thymectomy outcome of OMG is intriguing. Furthermore, thymomas can vary in size and location in anterior mediastinum, whether these anatomical features could impact thymoma associated OMG prognosis is still unknown(7).

This study aims to address two issues pertinent to OMG patients after thymectomy: (1) calculate the rate and timing of OMG conversion and complete stable remission (CSR) after thymectomy. (2) report on factors affecting post-thymectomy OMG conversion and CSR.

Materials & Methods

1.1 Patient enrollment and definition

We conducted a retrospective study of eighty-two consecutive OMG patients who underwent thymectomy at Tianjin Medical University General Hospital from January 2012 to December 2021. The diagnosis of OMG was based on clinical evaluation (the presence of fluctuating diplopia, ptosis, or both) and at least 1 positive result of the following tests: (1) Anti-acetylcholine receptor antibody (Anti-AChR Ab), (2) repetitive nerve stimulation(RNS)or (3) clinical response to edrophonium chloride (Tensilon test) or pyridostigmine.

Inclusion criteria consisted of (1) onset age 18 years or older, (2) minimum 3 months isolated ocular disease. (3) R0 resection for thymoma (4) Follow-up duration: for OMG conversion analysis –2 years or more from onset of symptom or until GMG developed, for CSR analysis-2 years or more after thymectomy. We excluded thymic carcinomas or cyst because they have not been validated to be associated with MG pathogenesis(8). A patient with age < 15 years at the onset was also excluded.

Generalized myasthenia gravis (GMG) was defined as the development of symptoms or clinical findings in the limbs, bulbar, or respiratory muscles. CSR was defined as the absence of any symptoms or signs of MG for at least 1 year without any treatment for MG.

Extended thymectomy, defined as resection of the entire thymus and mediastinal fat tissue between the both phrenic nerves, was performed for all the patients. Indications for thymectomy included thymoma, a suspected thymic mass or hyperplasia on diagnostic imaging, inadequately respond to acetylcholinesterases, resistance to take immunosuppressive (IS) therapy or have contraindications to or refractory to IS agents. This study was approved by the ethics committee of Tianjin Medical University General Hospital (Ethical No. IRB2022-WZ-024) and conducted according to the principles of the Declaration of Helsinki. The need for patient consent was waived.

After inclusion and exclusion criteria screening, twenty-four patients were excluded from the study. Therefore, a total of 58 patients were finally identified for OMG conversion study, 52 patients were eligible for CSR analysis. The flowchart of recruitment and exclusion detail was shown in figure_1.

1.2 Clinical Predictors

The following variables were evaluated: age, gender, clinical symptoms at onset (diplopia, ptosis, or both), anti-AChR Ab, repetitive nerve stimulation (RNS), thymus histology, Masaoka-Koga Staging of thymoma, tumor location, tumor size, surgical approach, duration of symptoms before surgery, immunosuppressive treatment (corticosteroids, azathioprine or tacrolimus) after surgery.

The main outcome measures are: conversion or CSR status (development of GMG or CSR), time to GMG conversion (calculated from time of symptom onset) and CSR (calculated from thymectomy).

Thymus pathology. Thymoma histology were classified according to WHO criteria(9) by local surgical pathologists. To facilitate analysis, we assigned each thymoma to one of the WHO subtypes (A, AB, B1, B2, B3). However, six cases were combinations of type B1 and B2, five cases were combinations of type B2 and B3 thymomas. We classified these “B1 plus B2” to B2 thymomas and “B2 plus B3” to B3 thymomas, when there was any area in which the diagnostic histology of B2 or B3 could be recognized. The classification system of Masaoka-Koga(10) was adopted as the staging system. The stage was determined by review of the surgical records and pathologic reports.

Thymoma anatomical feature. The tumor location and size were determined from preoperative thoracic imaging examinations. Tumor boundary exceeds left/right sternal border was defined as left or right thymoma. Both maximum and mean tumor diameter (measured as average diameter of anteroposterior, vertical and transverse span length) were evaluated.

Serologic testing. Both AchR and muscle-specific receptor tyrosine kinase (MuSK) antibodies were tested for all patients. The presence of AChR Ab was considered positive for titer > 0.5 nmol/L and MuSK Ab for titer > 0.01 nmol/L, as assessed in radioimmune assays.

Electrodiagnostic testing. The RNS test was routinely conducted in bilateral orbicularis oculi muscle for OMG. A decrement of more than 10% was considered as a positive result with 3-Hz stimulation.

Post-thymectomy treatment. Pyridostigmine alone or in combination with prednisone were prescribed by neurologist according to OMG symptoms before surgery (Generally, prednisone was recommended for patients with diplopia). After symptom control was achieved, the dose was tapered over months to the minimum effective dose or withdrawal. When corticosteroids are ineffective, or when side effects limit their use, or when contraindications preclude their use entirely, additional immunosuppressive agents, such as tacrolimus, azathioprine, mycophenolate mofetil, or methotrexate would be considered.

1.3 Statistical Analysis

Categorical variables were analyzed using the chi-square and Fisher exact test. Continuous variables were analyzed with two-tailed t test. Cumulative incidence of OMG conversion and CSR were analyzed using the Kaplan–Meier method and the log-rank test. Univariate and Multivariate Cox proportional hazards regression was applied to determine the factors affecting OMG conversion and CSR during the

follow-up period. A P value less than 0.05 was considered significant. All data analyses were performed using SPSS Statistics for Mac version 25.0 (IBM Corp, Armonk, NY).

Results

2.1 Baseline Demographics And Clinical Features

2.1.1 Clinical features of converted OMG and pure OMG

The median follow-up duration after thymectomy was 59.3 (range 9-114.5) months. At last review, 13(22.4%) patients had developed GMG at a median conversion time of 9.2 (range 1.4–32.9) months after thymectomy, 12.7 (range 3-37.3) months from symptom onset; 11 of these 13 patients (84.6%) experienced GMG within 2 years of symptom onset. Of the 58 included, 24 (42.3%) were men and 34(57.7%) were women, with a median age at onset of symptoms of 54.7 years. The clinical characteristics of the 13 converted OMG patients and the 45 pure OMG patients are displayed in Table 1. No significant difference was observed in terms of gender, age, OMG symptoms at onset (ptosis/diplopia), disease duration before surgery, surgical approach, tumor location, tumor size, immunosuppressive treatment after surgery, post-operative follow-up duration. AchR Ab seropositivity showed a trend for increased risk of conversion to GMG (P = 0.085), although no statistical difference was reached. RNS positivity was associated with increased risk of conversion with 84.6% of those with a positive RNS converting to GMG compared with 35.6% of patients who had a negative RNS (p = 0.002). Patients with histologic subtype B2/B3 thymoma also showed a statistically increased risk of conversion (P = 0.002) compared with patients with hyperplasia and AB/B1 thymoma.

Table 1
Clinical characteristics of converted OMG and Pure OMG

	Overall(58)	Converted OMG (13)	Pure OMG (45)	*p* value
Gender				
male	24(41.4%)	7(53.8%)	17(37.8%)	0.300
female	34(58.6%)	6(46.2%)	29(62.2%)	
Age (y)	55.1 ± 13.2	56.3 ± 10.6	54.4 ± 14.1	0.646
Ptosis				
Left	19(32.8%)	4(30.8%)	15(33.3%)	0.448‡
Right	16(27.6%)	2(15.4%)	14(31.1%)	
Bilateral	23(39.7%)	7(53.8%)	17(35.6%)	
Diplopia (+)	25(43.1%)	7(53.8%)	18(40.0%)	0.375
Anti-AchR Ab (+)	40(69.0%)	12(92.3%)	28(62.2%)	0.085
RNS (+)	27(46.6%)	11(84.6%)	16(35.6%)	**0.002**
Disease duration before surgery (w)	19.3 ± 44.4	15.0 ± 27.1	20.5 ± 48.5	0.699
Surgical approach				
R/L-VATS	22(37.9%)	4(30.8%)	18(40.0%)	0.562‡
TS	8(13.8%)	3(23.1%)	5(11.1%)	
sub-xiphoid	28(48.3%)	6(46.2%)	22(48.9%)	
Tumor location				
left	23(52.3%)	7(58.3%)	16(50.0%)	0.624‡
right	19(43.2%)	4(33.3%)	15(46.9%)	
L + R†	2(4.5%)	1(8.3%)	1(3.1%)	
Maximum diameter(cm)	3.8 ± 1.6	3.5 ± 1.3	3.9 ± 1.7	0.441
Mean size (cm)	3.1 ± 1.2	2.8 ± 1.0	3.2 ± 1.3	0.351

Abbreviations: OMG, ocular myasthenia gravis; AChR-ab, anti-acetylcholine receptor antibody; RNS: repetitive nerve stimulation; R/L-VATS: right/left-video assisted thoracoscopic surgery; TS: trans-sternal

† Tumor boundary exceeds both sides of sternal border

‡ Fisher exact test

		Overall(58)	Converted OMG (13)	Pure OMG (45)	*p* value
Thymoma histotype + hyperplasia					
Thymoma	AB	10(17.2%)	1(7.7%)	9(20.0%)	0.137‡
	B1	4(6.9%)	0	4(8.9%)	
	B2	20(34.5%)	7(53.8%)	13(28.9%)	
	B3	10(17.2%)	4(30.8%)	6(13.3%)	
hyperplasia		14(24.1%)	1(7.7%)	13(28.9%)	
B2 + B3: AB + B1 + hyperplasia			11:2	19:26	**0.007**
Thymoma Stage + hyperplasia					
Thymoma	I	11(19.0%)	4(30.8%)	7(15.6%)	0.095‡
	IIA	12(20.7%)	1(7.7%)	11(24.4%)	
	IIB	13(22.4%)	3(23.1%)	10(22.2%)	
	III	8(13.8%)	4(30.8%)	4(8.9%)	
hyperplasia		14(24.1%)	1(7.7%)	13(28.9%)	
Post-operative prednisone(+)		20(34.5%)	4(30.8%)	16(35.6%)	1.000
Post-operative follow up duration(m)		59.3 ± 30.3	55.5 ± 36.3	60.5 ± 28.8	0.608

Abbreviations: OMG, ocular myasthenia gravis; AChR-ab, anti-acetylcholine receptor antibody; RNS: repetitive nerve stimulation; R/L-VATS: right/left-video assisted thoracoscopic surgery; TS: trans-sternal

† Tumor boundary exceeds both sides of sternal border

‡ Fisher exact test

2.1.2 Clinical Features Of Csr-omg And Non-csr Omg

Of the 52 patients included into analysis, 16 (30.8%) achieved CSR at a median time of 28.7 (range 15–54) months after thymectomy. No significant difference was observed in terms of gender, OMG symptoms at onset, disease duration before surgery, surgical approach, tumor location, tumor size, immunosuppressive treatment after surgery, However, patients achieving CSR showed a younger age of onset (48.3 ± 13.07 vs. 57.5 ± 12.6 years, p = 0.022). We then used the ROC curve to explore the best threshold for age (60.5y, AUC = 0.703, 95% CI: 0.561–0.846, sensitivity: 47.2%, specificity: 87.5%) (figure_2). The AchR Ab seropositivity was associated with a decreased probability of CSR (p = 0.029).

RNS positivity showed a trend for decreased probability of CSR (P = 0.063). Patients with thymic hyperplasia or stage I thymoma showed a statistically higher chance of achieving CSR (P = 0.010) compared with patients with stage II/III thymoma. Post-operative follow up duration was much longer in CSR group (78.3 ± 28.6 VS 58.3 ± 25.4 months, p = 0.015), indicating that with the extension of follow-up time, more patients would achieve CSR and 2 years may be not long enough to determine if CSR can be reached. We believe this follow-up duration difference also explained surgical approach outcome between these two groups, for unilateral VATS was routinely performed between 2012 to 2017 in our center, while sub-xiphoid method became mainstream in recent four years (Table 2).

Table 2
Clinical characteristics of CSR OMG and Non-CSR OMG

	Overall(52)	CSR OMG (16)	Non-CSR OMG (36)	*p* value
Gender				
male	22(42.3%)	5(31.3%)	17(47.2%)	0.282
female	30(57.7%)	11(68.8%)	19(52.8%)	
Age of onset (y)	54.7 ± 13.5	48.3 ± 13.7	57.5 ± 12.6	**0.022**
Age of onset (y)				
≤ 60	33(63.5%)	14(87.5%)	19(52.8%)	**0.016**
> 60	19(36.5%)	2(12.5%)	17(47.2%)	
Ptosis				
Left	18(34.6%)	6(37.5%)	12(33..3%)	0.765 §
Right	14(26.9%)	5(31.3%)	9(25.0%)	
Bilateral	20(38.5%)	5(31.3%)	15(41.7%)	
Diplopia (+)	21(40.4%)	9(56.3%)	12(33.3%)	0.120
Anti-AchR Ab (+)	34(65.4%)	7(43.8%)	27(75.0%)	**0.029**
RNS (+)	23(44.2%)	4(25.0%)	19(52.8%)	0.063
Disease duration before surgery (w)	19.4 ± 46.6	8.6 ± 9.9	24.1 ± 55.2	0.111
Surgical approach				
R/L-VATS	22(42.3%)	10(62.5%)	12(33.3%)	0.056 §
TS	8(15.4%)	3(18.8%)	5(13.9%)	
sub-xiphoid	22(42.3%)	3(18.8%)	19(52.8%)	
Tumor location				
left	19(48.7%)	4(40.0%)	15(51.7%)	0.448‡

Abbreviations: CSR, complete stable remission; OMG, ocular myasthenia gravis; AChR-ab, anti-acetylcholine receptor antibody; RNS: repetitive nerve stimulation; R/L-VATS: right/left-video assisted thoracic surgery; TS: trans-sternal

† Tumor boundary exceeds both sides of sternal border

‡ Fisher exact test

§ Likelihood Ratio test

		Overall(52)	CSR OMG (16)	Non-CSR OMG (36)	*p* value
right		18(46.2%)	5(50.0%)	13(44.8%)	
L + R[†]		2(5.1%)	1(10%)	1(3.4%)	
Maximum diameter(cm)		3.8 ± 1.6	3.6 ± 2.2	3.9 ± 1.4	0.592
Median size (cm)		3.1 ± 1.3	3.0 ± 1.7	3.1 ± 1.1	0.739
Thymoma histotype + hyperplasia					
Thymoma	AB	9(17.3%)	1(6.3%)	9(22.2%)	0.330[‡]
	B1	4(7.7%)	2(12.5%)	2(5.6%)	
	B2	18(34.6%)	4(25.0%)	15(38.9%)	
	B3	8(15.4%)	3(18.8%)	5(13.9%)	
hyperplasia		13(25.0%)	6(37.5%)	7(19.4%)	
Thymoma Stage + hyperplasia					
Thymoma	I	9(17.3%)	5(31.3%)	4(11.1%)	0.086[‡]
	IIA	12(23.1%)	1(6.3%)	11(30.6%)	
	IIB	13(23.1%)	2(12.5%)	10(27.8%)	
	III	6(11.5%)	2(12.5%)	4(11.1%)	
hyperplasia		13(25.0%)	6(37.5%)	7(19.4%)	
Hyperplasia + I : II + III		22:30	11:5	11:25	**0.010**
Post-operative prednisone(+)		18(34.6%)	5(31.3%)	13(36.1%)	0.734
Post-operative follow up duration(m)		60.5 ± 27.7	78.3 ± 28.6	58.3 ± 25.4	**0.015**

Abbreviations: CSR, complete stable remission; OMG, ocular myasthenia gravis; AChR-ab, anti-acetylcholine receptor antibody; RNS: repetitive nerve stimulation; R/L-VATS: right/left-video assisted thoracic surgery; TS: trans-sternal

[†] Tumor boundary exceeds both sides of sternal border

[‡] Fisher exact test

[§] Likelihood Ratio test

2.2 Cumulative Probability Of Omg Conversion And Csr

The cumulative probability of OMG conversion in the whole sample of 58 patients, according to RNS, AchR Ab, and thymus histology (B2/B3 versus hyperplasia + AB/B1), was calculated by the Kaplan-Meier method. Among these variables, RNS positivity (p = 0.002), histologic subtype of B2/B3 thymoma (p = 0.008), were associated with increased risk of OMG conversion compared with patients with negative RNS and histotype hyperplasia + AB/B1 thymoma (figure_3).

The cumulative probability of achieving CSR was also studied. The analysis showed that negative AchR Ab (p = 0.048) was associated with higher chance of achieving CSR. Patients with hyperplasia and stage I thymoma showed a higher chance of achieving CSR compared with stage II-III thymoma (p = 0.014) (figure_4).

2.3 Multivariate Analysis

Both univariate and multivariate analysis using a Cox proportional hazard model were performed to verify prognostic factors for OMG conversion and CSR. Among the variables considered, positive RNS (hazard ratio [HR] 6.007, CI 1.316–27.412, p = 0.021), histotype B2-3 thymomas (hazard ratio [HR] 4.611, CI 1.010–21.043, p = 0.048) were significantly associated with OMG conversion. While, thymic hyperplasia and Masaoka-Koga Stage I thymoma (hazard ratio [HR] 0.300, CI 0.104–0.864, p = 0.026) were independently associated with CSR in OMG patients after thymectomy. (Table 3)

Table 3
Univariate and multivariate Cox regression analysis for OMG conversion and CSR

	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Conversion				
RNS (+)	7.462 (1.651–33.718)	0.009	6.007 (1.316–27.412)	0.021
Anti-AchR Ab (+)	6.428 (0.832–49.681)	0.075		
B2/B3 thymoma	5.987 (1.325–27.044)	0.020	4.611 (1.010-21.043)	0.048
hyperplasia + AB/B1 thymoma	——		——	
CSR				
Age of onset ≤ 60	——	0.052		
Age of onset > 60	0.230 (0.052–1.011)			
RNS (+)	0.378 (0.122–1.175)	0.093		
Anti-AchR Ab (+)	0.396 (0.147–1.068)	0.067		
Hyperplasia + stage I thymoma	——	0.026	——	0.026
Stage II/III thymoma	0.300 (0.104–0.864)		0.300 (0.104–0.864)	

Abbreviations: CSR, complete stable remission; OMG, ocular myasthenia gravis; AChR-ab, anti-acetylcholine receptor antibody; RNS: repetitive nerve stimulation; HR: hazard ratio

3 Discussion

This is the first research simultaneously target on OMG conversion and CSR after thymectomy. Our retrospective study shows that RNS positivity and WHO subtype B2-B3 thymomas were significantly associated with post-thymectomy OMG conversion. While thymic hyperplasia and Masaoka-Koga Stage I thymoma was independently associated with post-thymectomy OMG CSR.

Thymectomy is required for patients with thymoma, has also been shown to result in better clinical outcomes in non-thymomatous AChR seropositive GMG(11). Efficacy of thymectomy in non-thymomatous OMG is debated because of limited convincing evidence(12). In our department, patients with OMG underwent thymectomy on condition of thymus abnormalities on diagnostic imaging. Fourteen patients with pathologically confirmed thymic hyperplasia were also included into our study. Correlation

between the degree of follicular hyperplasia and the level of anti-AChR antibodies suggest a causal relationship between thymic pathology and MG(13). Wong SH. et al(5) identified that thymic hyperplasia was a significant predictive factors for generalization in OMG patients without thymectomy. Patients with thymic hyperplasia showed a satisfying post thymectomy outcome (only 1 out of 14 patients converted to GMG, whereas 6 out of 13 achieved CSR) in our study cohort, which is in accord with some other previous studies(14, 15).Histologically, MG was reported associated mainly with type B thymomas and tended to be more frequent in type B2 or B3 thymomas(6). Our study further confirmed the correlation between thymus pathology and OMG prognosis.

Although no correlation was detected between OMG generalization and AChR antibodies, our study showed that patients with negative AChR antibodies were more likely to achieve CSR after thymectomy. With standard assays, AChR antibodies are detectable in approximately 50% of patients with OMG and nearly 90% of patients with GMG(16). Anti-MuSK Abs are rarely found in isolated OMG(17). Only one patient with negative AChR Ab was test positive for anti-MuSK Ab in our study, we did not incorporate this variable into analysis because of this small number. We must be aware that many of “seronegative” cases may harbor an autoantibody that is not detected by conventional means. The diagnostic yield of AChR Abs testing is significantly increased by cell-based assay(18), rather than the typical radioimmunoprecipitation technique. Moreover, other autoantibodies may also exist. Anti-LRP-4 Abs have been detected in about 20% of “double-negative” MG(19). Antibodies directed against cortactin (a postsynaptic protein required for clustering of AChRs) have been identified in 24% of double seronegative OMG patients(20). Whether the presence of these antibodies could have an effect on OMG prognosis requires further validation.

The presence of comorbidities at disease onset has been described as a risk factor for conversion to GMG(5). We did not incorporate this variable into analysis because of the small sample size (only 6 out of 58 patients were accompanied by another autoimmune disease). This link will need to be further validated externally for more robust confidence.

We take a minimum of three months of isolated ocular disease as an inclusion criterion. This 3-month duration is in keeping with the views of other researchers(5). Monsul et al.(21) suggested this time interval as the limit for purely ocular symptoms before classifying a patient as OMG. However, studies by Kupersmith(22) and Mee et al.(23) included patients who developed GMG within 3 months of symptom onset. This is an important question that should be clarified in future studies.

Our analyses did not show age as a risk factor for OMG conversion. The effect of age on OMG conversion is paradoxical among studies. Feng et al.(3) revealed that the onset age was correlated with the conversion rate of OMG, and the threshold of age was 43 years. Whereas Wong et al. did not show age as a risk factor both in univariable and multivariable analysis(5). However, we do find that younger patients showed a greater chance of achieving CSR in comparison with older cohort. ROC curve indicated the best threshold for age was 60.5 yeas (Fig. 6), which is older than the usual age limit to distinguish

early from late onset MG(24). Given the sparse data and dispute surrounding this issue, more cogent researches are needed.

Our study showed that positive RNS was strongly associated with OMG conversion in univariable analysis ($p = 0.002$), log-rank test ($p = 0.002$) and multi-variable COX regression ($p = 0.022$). Moreover, negative RNS hinted at a greater likelihood of CSR, although the difference was not statistically significant. The association between RNS and OMG conversion was reported by other studies(25). Kim. et al(26) revealed that an abnormal RNS test, especially in the limb muscles, is an independent predictor of the conversion from ocular to generalized MG. In addition, an abnormal RNS test related to a shortened time to generalization was reported(27). Since limb muscles were not routinely tested for OMG in our study, whether performing RNS testing in orbicularis oculi be sufficient for evaluating neurotransmission in extraocular muscles need further validation.

Previous studies have reported the effect of prednisone in delaying onset of GMG and its sustained benefit in reducing the incidence of GMG and controlling diplopia(21, 22). Generally, patients with diplopia were recommended for prednisone therapy. Safety concerns have been surrounding corticosteroids usage such as the development of hypertension, diabetes mellitus, osteoporosis, gastrointestinal disorders, or infectious illness, which are common with the chronic use of moderate to high dose. The administration of corticosteroids to eliminate extraocular muscle limitation and diplopia continues to be controversial.

Limited studies have discussed the importance of tumor size and location in determining clinicopathological features or its relationship to thymoma or MG prognosis. D. Tian et al. reported that thymomas located in the superior mediastinum were more likely to be associated with disease progression and tumor recurrence than those in the inferior mediastinum(28). M. Okumura et al(29) showed that tumor size determines both recurrence-free survival and disease-specific survival after surgical treatment for thymoma, with higher incidence of recurrence in patients with thymoma > 5.0 cm and of death in patients with thymoma > 8.0 cm. None of these studies ever mentioned the correlation of thymoma anatomic features with MG. Our study is the first demonstration of association between thymoma location/size with OMG prognosis, although no significant correlation was found.

The limitations of this study should be acknowledged. First, the current study was retrospective in design, which may have caused selection bias. Second, the number of patients with post-thymectomy OMG was small. The risk factors identified from this limited sample size may not be generalizable to all patients. Third, given the follow up duration difference between groups of CSR analysis, our inclusion criterion of a follow-up period of 2 years could have caused selection bias, which might have influenced the CSR rate and other associated risk factors. Forth, only AChR-Ab and MuSK-Ab was tested in our study. whether other autoantibodies, such as anti-LRP-4 Abs, anti-cortactin Abs would present as confounding factors was unknown.

In conclusion, this is the first report to demonstrate thymus pathology and thymoma anatomical features on prognosis of OMG after thymectomy. We found that RNS positivity and histotype B2-3 thymoma are

independent predictors of OMG conversion. Whereas thymic hyperplasia and stage I thymoma independently predict CSR after thymectomy. Patients with younger age of onset, negative anti-AchR Ab may also have a higher chance of achieving CSR. Further prospective studies with a larger number of patients are warranted to validate the present findings.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Tianjin Medical University General Hospital (Ethical No. IRB2022-WZ-024) and conducted according to the principles of the Declaration of Helsinki. The need for patient consent was waived.

Consent for publication

All authors have read and approved the content, and agree to submit for consideration for publication

Availability of data and material

All data were retrieved from the medical record database of Tianjin Medical University General Hospital. Please contact author for data requests.

Competing interests

The authors declare no competing financial interests.

Funding

None

Authors' contributions

Conceptualization and Methodology：Jinwei Zhang and Peng Zhang. Data Curation and investigation: Zeyang Zhang, Hui Zhang and Yuantao Cui. Formal Analysis: Jinwei Zhang, Zeyang Zhang, Yuan Chen and Peng Lv. Supervision and Visualization: Peng Zhang. Writing: Jinwei Zhang. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

Figure 1

Flowchart of recruitment and exclusion process of OMG patients after thymectomy. OMG, ocular myasthenia gravis. CSR, complete stable remission.

Figure 2

Estimated probability of CSR and ROC curve of onset age (60.5y, AUC = 0.703, 95% CI: 0.561–0.846, sensitivity: 47.2%, specificity: 87.5%). CSR, complete stable remission.

Figure 3

Kaplan-Meier curve of the cumulative probability of conversion to GMG after onset of symptoms in in different patient groups. (A) Patients with negative and positive RNS. (p=0.002). (B) patients with different thymic histology. (p=0.008). GMG, generalized myasthenia gravis. RNS, repetitive nerve stimulation.

Figure 4

Kaplan-Meier curve of the cumulative probability of CSR after thymectomy in different patient groups. (A) Patients with negative and positive anti-AchR Ab. (p=0.048). (B) Patients with different thymic stage. (p=0.014). CSR, complete stable remission. AchR Ab, acetylcholine receptor antibody.