Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Development of a Risk Stratification Nomogram for Predicting Generalization in Adult Ocular Myasthenia Gravis: A Multicenter Study

Jingting Fu
Henan Medical University
Mingming Ma
Zhengzhou University
Xianzhao Zheng
Henan Medical University
Hongjuan Zhang
Henan Medical University
Xiaoli Ma
Henan Medical University
Qianqian Qu
Henan Medical University
Wenhao Cui
Henan Medical University
Jiaxuan Wang
Henan Medical University
Haidong Lyu
hnlhd666@163.com

Henan Medical University

Research Article

Keywords:

Posted Date: November 13th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11558682/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Development of a Risk Stratification Nomogram for Predicting Generalization in Adult Ocular Myasthenia Gravis: A Multicenter Study

Jingting Fu[1], Mingming Ma[2], Xianzhao Zheng[1], Hongjuan Zhang[3], Xiaoli Ma[1], Qianqian Qu[1], Wenhao Cui[1], Jiaxuan Wang[1], Haidong Lyu[1*]

[1*]Department of Neurology, Jiaozuo People's Hospital Affiliated to Henan Medical University, Shanyang District, Jiaozuo, 454002, Henan Province, China.

[2*]Department of Neurology, Henan Provincial People's Hospital Affiliated to Zhengzhou University, Jinshui District, Zhengzhou, 450000, Henan Province, China.

[3]Department of Neurology, Jiaozuo Central Coal Group Hospital, Jiefang District, Jiaozuo, 454001, Henan Province, China.

*Corresponding author(s). E-mail(s): hnlhd666@163.com;
Contributing authors: 2272358433@qq.com; Macklon12@163.com ; rmyyzxz@163.com; zhanghong_juan@163.com; maxiaoli1590@163.com; 3301535@qq.com; cwhmxd@126.com; wangjiaxuanyo@163.com;

Abstract

Purpose: The aim of this study is to investigate factors influencing the progression of ocular myasthenia gravis (OMG) to generalized myasthenia gravis (GMG) in adults and to construct a multidimensional risk stratification nomogram to identify individuals at high risk.

Methods: A retrospective analysis was conducted on clinical data from 322 adults diagnosed with OMG. Feature selection utilized the Boruta algorithm and Lasso regression. Independent predictors of generalization were identified through Cox

regression, and a nomogram was developed. Model performance was internally validated using the Bootstrap method. Population stratification was performed with the X-tile program, based on scores derived from the nomogram.

Results: Multivariate Cox regression analysis identified sex, age at onset, body mass index (BMI), antibody type, Repetitive Nerve Stimulation (RNS), thymic status, thymectomy, concomitant autoimmune diseases, the Charlson Comorbidity Index (CCI), and treatment status as significant independent predictors of generalization in adult OMG. The nomogram developed from these ten factors demonstrated lower Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values compared to any individual factor. The bootstrap-corrected concordance index (C-index) for the nomogram was 0.802 (95% CI 0.771, 0.833). The calibration curve showed a strong correlation between predicted and observed values, supporting the model's accuracy. Decision curve analysis confirmed its potential clinical utility. Kaplan-Meier curve analysis demonstrated that the nomogram effectively distinguishes among low-, medium-, and high-risk groups for generalization in adult OMG ($P < 0.0001$), validating its efficacy in predicting clinical outcomes.

keywords: adult, ocular myasthenia gravis (OMG), generalization, predictive model, nomogram

Key Summary Points

Why carry out this study?

Adults with OMG are at substantial risk of generalization, particularly during the early months after disease onset. Given the heterogeneity in the timing of progression and the potential adverse effects associated with long-term immunosuppressive therapy, reliable tools for individualized risk prediction are needed. In this study, X-tile software was used to determine the optimal cut-point of the risk score for stratification, enabling classification of patients into low-, medium-, and high-risk groups. This approach may assist clinicians in estimating the likelihood of progression to GMG and in tailoring the intensity of follow-up and early interventions.

What additional value does this study provide beyond prior studies?

This study was conducted in a real-world clinical setting with the objective of developing a risk prediction model for generalization in adults with OMG. In addition to predictors identified in previous studies, several potentially relevant variables were included, such as T2DM, history of statin use, IVMP therapy, thyroid dysfunction, and non-thymomatous thymic abnormalities. The CCI was also incorporated to quantitatively assess the overall burden of multisystem comorbidities, thereby broadening the range of candidate predictors associated with generalization.

RCS were applied to continuous variables to explore potential non-linear associations. Model selection was guided by the AIC and BIC to achieve an optimal balance between goodness-of-fit and model complexity.

Introduction

Myasthenia gravis (MG) is an acquired autoimmune disorder characterized by autoantibodies that target proteins in the postsynaptic membrane of the neuromuscular junction. This immune response disrupts acetylcholine-mediated neuromuscular transmission and results in fluctuating muscle weakness. MG primarily affects extraocular, bulbar, limb, respiratory, and trunk muscles. In particular, the structural and molecular characteristics of extraocular muscles (EOMs), including hypoplastic postsynaptic membrane folding, reduced acetylcholine receptor density, and low expression of the complement regulator, as the decay-accelerating factor (DAF) [1–4], contribute to the frequent involvement of EOMs as the initial manifestation of MG. Notably, more than half of patients present with diplopia or ptosis at diagnosis [4]. Furthermore, 50% to 80% of individuals with OMG may develop to GMG within two years of symptom onset [5–7]. In contrast to adults, a significantly lower proportion of juvenile myasthenia gravis (JMG) patients develop generalized symptoms [8]. A review of the literature indicates that only 21.9% of JMG patients progress to GMG [9]. This underscores the

necessity of accurately predicting the risk of generalization in adults with OMG, in order to facilitate the development of personalized treatment strategies.

Numerous studies have identified risk factors associated with the transition from OMG to GMG [10–16]. However, most research remains focused on traditional clinical factors and may overlook additional clinical correlation variables. We conducted a systematic review of the literature and found that patients with MG frequently exhibit metabolic abnormalities. Regarding blood lipids, a meta-analysis reported a combined hyperlipidemia rate of 23.64% (95% CI: 17.01% to 30.98%) in the MG population [17]. Simultaneously, several studies have demonstrated that statins can induce MG or exacerbate symptoms in diagnosed patients [18, 19], potentially due to the combined effects of myogenic injury and antibody-mediated postsynaptic dysfunction [20]. With respect to blood glucose, case-control studies have shown that a significant proportion of MG patients were diagnosed with type 2 diabetes mellitus (T2DM) prior to disease onset, suggesting that T2DM may be a risk factor for developing MG [21]. The related mechanism may involve the enhanced differentiation of Tfh cells to amplify the abnormal humoral immune response [22]. Furthermore, the incidence of hyperthyroidism among patients with MG ranges from 3% to 8.8%, and thyroid hormone-mediated hyperthyroidism may exacerbate the symptoms of MG [23].

Beyond metabolic abnormalities, therapeutic regimens and thymic function also play a crucial role in the progression of OMG. The thymus, a central lymphoid organ, is critical for T cell maturation and the establishment of autoimmune tolerance [24]. In this study, we evaluate the common thymic abnormalities observed in MG patients. Additionally, the Charlson Comorbidity Index (CCI) is used to assess the baseline health status of patients [25].

Building on this background, our study integrates multi-dimensional clinical data, such as demographic characteristics, metabolic abnormalities, thymic status, comorbidities and treatment regimens, to construct and validate a nomogram for predicting generalization in adult OMG. Risk stratification based on nomogram scores aims to facilitate individualized clinical decision-making.

Methods

Study Subjects

This study was a multi-center, retrospective observational investigation that analyzed clinical data from patients diagnosed with OMG at Jiaozuo People's Hospital, Henan Provincial People's Hospital, and Jiaozuo Central Coal Group Hospital between January 2019 and June 2023. Ethical approval was obtained from the Ethics Committee of Jiaozuo People's Hospital (approval No. 2026-003-K03), which served as the leading committee for this multicenter study. This study strictly adhered to the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. Strict inclusion and exclusion criteria, based on the Chinese guidelines for the diagnosis and treatment of myasthenia gravis, were applied to ensure data reliability [26].

The inclusion criteria were as follows: (1) patients aged ≥18 years; (2) initial clinical symptoms consistent with fluctuating extraocular muscle weakness; (3) completion of serological examination, neostigmine test, and repetitive nerve stimulation for MG, with at least one positive result; (4) disease initially presenting solely as isolated extraocular muscle involvement, with symptom duration of at least three months; (5) all patients underwent routine chest imaging, such as chest CT or MRI, to assess thymic status, with thymic biopsy performed when indicated; (6) completion of baseline examinations at diagnosis, including thyroid function, thyroid autoimmune antibodies, and rheumatic immune-related screening; (7) patients demonstrated good treatment compliance and were able to participate in outpatient follow-up for a minimum of two years after diagnosis. The Global Autoimmune Institute (GAI) made a list of recognized autoimmune diseases available, and we regarded it as an inclusion criterion for autoimmune diseases.

Exclusion criteria were: (1) patients with missing or abnormal data; (2) patients with intellectual disability or mental illness who were unable to cooperate with treatment. The screening flow chart is presented in Figure 1.

Generalized outcome measure

The generalization of OMG was evaluated according to the Oosterhuis diagnostic criteria[27, 28]. Patients who were reclassified as having generalization if they developed fluctuating weakness in additional muscle groups, such as limb, pharyngeal, trunk, or respiratory muscles, after ocular symptoms persisted for at least three months. The interval from baseline to the onset of generalized symptoms was recorded. If generalization did not occur by the end of follow-up, the duration from baseline to the end of follow-up was documented in months.

Candidate Predictors

Candidate predictors based on prior research and clinical practices, this study incorporated 16 risk factors, categorized into three distinct dimensions. All data were obtained from patients during the phase of isolated extraocular muscle involvement.

Demographic and health status indicators included age at onset, sex, BMI, CCI, Comorbidities (T2DM, other autoimmune diseases, hyperthyroidism), and statin use history.

The core clinical variables included repetitive nerve electrical stimulation, neostigmine test, antibody type, thymic status (normal, thymoma, thymic hyperplasia, benign thymic abnormal changes), and initial symptoms (diplopia, unilateral ptosis, bilateral ptosis, diplopia with ptosis).

Treatment and intervention characteristics included treatment regimen (no or symptomatic management, glucocorticoid therapy, non-steroidal immunosuppressive therapy, glucocorticoids combined with non-steroidal immunosuppressive agents), IVMP (yes or no), and thymectomy (yes or no).

Statistical Methods

All statistical analyses were performed using R software version 4.3.1. Descriptive statistics were first applied to the dataset. Continuous variables with a normal distribution were expressed as mean ± standard deviation, while non-normally distributed variables were reported as median (interquartile range). For between-group comparisons, independent-samples t tests were used for normally distributed continuous variables, whereas the Wilcoxon rank-sum test was applied for non-normally distributed variables. Categorical variables were presented as frequencies (percentages), and differences between groups were analyzed using the Pearson chi-square test. Fisher's exact test was used when the expected cell counts were less than five. Restricted cubic splines (RCS) were applied to examine nonlinear associations between continuous variables and generalization. Variables showing significant nonlinearity were categorized according to the identified inflection points and incorporated into subsequent analyses. Variable selection utilized the least absolute shrinkage and selection operator (LASSO) regression in combination with the Boruta algorithm, and clinically relevant variables identified in previous studies were included to construct Cox proportional hazards models. Nomograms were subsequently developed to predict 1-year and 2-year generalization.

The goodness of fit for the nomogram was evaluated using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Discriminative ability was measured with the concordance index (C-index). Internal validation was conducted using the bootstrap method with 500 resamples. Calibration curves were generated to assess calibration performance, and decision curve analysis was applied to evaluate clinical utility. X-tile version 3.6.1 was used to identify the optimal cutoff value of the score for risk stratification. The Kaplan–Meier method and the log-rank test were applied to estimate and compare the cumulative incidence of generalization between groups.

Results

Demographics and clinical features

The study sample comprised 322 adult patients with OMG who met the study's inclusion criteria. The median age at onset (interquartile range [IQR]) was 57 (49, 67) years, with 47% being female. During the follow-up period, 185 (57.45%) patients developed generalized symptoms, and the median follow-up duration was 20 (IQR: 4, 53) months. A comparison of the baseline characteristics between the groups revealed statistically significant differences ($P < 0.05$) in several variables, including sex, the CCI, concomitant autoimmune diseases, the initial clinical manifestations, results of repetitive nerve stimulation, antibody type, thymic status, the treatment regimens, and the follow-up duration. A detailed presentation of the data is provided in Table 1.

Association of continuous variables with generalization

Restricted cubic splines (RCS) were utilized to assess the nonlinear association between continuous variables and the incidence of generalization in OMG (Figure 2). There

was no significant overall or nonlinear association identified between age at onset and generalization (P-overall = 0.117, P-nonlinear = 0.287). Nevertheless, the increasing incidence of late-onset myasthenia gravis represents a global trend [29, 30], and epidemiological studies in China have identified a peak onset age of 70-74 years [31]. Accordingly, age at onset was stratified into three subgroups: early-onset myasthenia gravis (EOMG, age $\leq$ 50 years, n=100), late-onset myasthenia gravis (LOMG, 50 $<$ age $<$ 65 years, n=120), and very late-onset myasthenia gravis (VLOMG, age $\geq$ 65 years, n=102).

RCS analysis demonstrated a significant association between the CCI and the incidence of generalization, characterized by an approximately linear positive correlation (P-overall = 0.001, P-nonlinear = 0.408). BMI was also significantly associated with generalization (P-overall = 0.024) and displayed a nonlinear trend (P-nonlinear = 0.011), following a J-shaped curve with an inflection point near 21.5 (Figure 2D).

Predictor Selection

Clinical features were transformed into dummy variables and analyzed using LASSO regression. The coefficient paths illustrated how feature coefficients deviated from zero as the regularization parameter λ decreased, with several variables maintaining non-zero coefficients across a wide range of λ values, indicating a stable association with the outcome (Figure 3A). Cross-validation was used to identify the optimal λ corresponding to the minimum prediction error, at which 18 dummy variables were retained (Figure 3B).

Subsequent feature selection was conducted using the Boruta algorithm, which identified seven key features, including comorbid autoimmune diseases, RNS, thymoma, antibody type, and immunosuppressive therapy regimens (Figure 3C). Comparison of the results from LASSO regression and Boruta revealed a shared subset of important predictors (Figure 3D). These predictors, together with factors previously identified as clinically significant, were selected as the final variables for model construction.

Establishment of a nomogram

The final model incorporated ten predictive variables: sex, age at onset, BMI, comorbid autoimmune diseases, the CCI, RNS, thymic status, history of thymectomy, antibody type, and treatment regimens. A multivariate Cox proportional hazards regression model was employed to develop a prediction model for generalization in adults with OMG, evaluating independent effects of each variable on generalization.

Multivariate analysis revealed that male (HR=0.71, 95% CI: 0.52–0.97, P=0.030), late-onset age (HR=0.56, 95% CI: 0.36–0.88, P=0.012), very late-onset age (HR=0.51, 95% CI: 0.30–0.85, P=0.010), BMI>21.5 (HR = 0.63, 95% CI: 0.42–0.94, P = 0.022), and thymectomy (HR = 0.56, 95% CI: 0.33–0.95, P = 0.030) as independent protective factors. In contrast, comorbid autoimmune disease (HR=1.49, 95% CI: 1.03–2.16, P=0.033), the CCI (HR=1.20, 95% CI: 1.10–1.31, $P < 0.001$), RNS positivity (HR=1.89, 95% CI: 1.38–2.60, $P < 0.001$), thymoma (HR=1.51, 95% CI: 1.02–2.24, P=0.040), and positive anti-acetylcholine receptor antibody (HR=2.83, 95%

CI: 1.14–7.07, P=0.025) were independent risk factors. Treatment with glucocorticoids (HR=0.23, 95% CI: 0.15–0.36, $P < 0.001$), non-steroidal immunosuppressants (HR=0.35, 95% CI: 0.18–0.68, P=0.002), and combination therapy (HR=0.09, 95% CI: 0.03–0.29, $P < 0.001$) significantly reduced the risk of generalization (Figure 4).

A nomogram model was developed using these ten independent variables to predict the 1-year and 2-year incidence of generalization in adult patients with OMG (Figure 5).

The discrimination and goodness-of-fit of the nomogram

We assessed the model's discrimination and goodness of fit using the C-index, AIC, and BIC. The original C-index of the nomogram was 0.783 (95% CI: 0.760-0.819), significantly higher than the C-index of individual predictors ($P < 0.001$). After 500 iterations of bootstrap resampling, the overall C-index of the nomogram was 0.802 (95% CI: 0.771-0.833). Regarding goodness of fit, the nomogram's AIC and BIC were lower than those of all individual predictors, indicating better model fit (Table 2). Additionally, time-dependent C-index analysis, both before and after bootstrap correction, showed that the nomogram model exhibited superior clinical prediction accuracy for generalization compared to individual predictors (Figure 6).

Predictive capacity and net benefit of the nomogram

Calibration curves and decision curve analysis (DCA) were employed to evaluate the predictive performance and net benefit of the nomogram. The bootstrap-corrected calibration curve demonstrated strong agreement between the predicted values of the nomogram and the actual observed outcomes (Figure 7). The clinical applicability of the predictive model was further evaluated using decision curve analysis with multiple fitted models (Figure 8). At both the 1-year and 2-year follow-up time points, the DCA curve for the nomogram exceeded those of Model 1 (excluding the CCI comorbidity index) and Model 2 (excluding high AIC/BIC variables and the CCI), and substantially outperformed the baseline strategies of 'full intervention' and 'no intervention'. Finally, an online dynamic survival rate calculation tool was developed based on the nomogram to assist clinicians in predicting patients' long-term generalization-free survival (GFS)(https://jingting-fu.shinyapps.io/dynnomapp/).

Risk stratification based on the nomogram

We calculated the total score for each patient using the nomogram and classified them into three risk groups using the X-Tile: low-risk group (n = 156, total score $\leq$ 203.5), moderate-risk group (n = 104, 203.5 $<$ total score $\leq$ 239.2), and high-risk group (n = 62, total score $>$ 239.2). Kaplan-Meier survival analysis demonstrated excellent discriminative ability of this risk stratification for the 2-year generalized conversion rate in adults with OMG ($P < 0.0001$, Figure 9). Compared to the low-risk group, the intermediate-risk group (HR = 4.41, 95% CI: 3.05-6.38, $P < 0.001$) and the high-risk group (HR = 11.93, 95% CI: 7.93-17.96, $P < 0.001$) had significantly higher hazards of conversion to GMG (Figure 10).

Discussion

At present, predictive models for generalization in adult OMG can generally be classified into two categories. The first category is closely aligned with clinical practice and incorporates core variables such as sex, age at onset, concomitant autoimmune diseases, RNS, antibody type, thymic status, and treatment regimens[32] . The second category comprises generalized risk prediction models based on the natural history of the disease, which are constructed using factors including sex, age at onset, RNS, antibody type, and thymic status [33]. To address the complexity of real-world clinical scenarios and to comprehensively identify potential risk factors, the present study selected 10 independent predictors from 16 candidate variables to develop a predictive risk stratification model for secondary generalized myasthenia gravis (SGMG) in adults. The model stratifies patients into low-, moderate-, and high-risk groups for generalization. Following internal validation using 500 bootstrap resamples, the nomogram demonstrated good discriminative ability, with the C-index of 0.802 (95% CI, 0.771–0.833). Calibration curves showed strong agreement between the predicted and observed probabilities of generalization at 1 and 2 years. Overall, the model exhibits robust predictive performance and effectively distinguishes patients across different risk categories, providing a practical decision-support tool for personalized intervention strategies in clinical practice.

Our study found that adult OMG patients who are female, AChR-Ab seropositivity, have concomitant autoimmune diseases, and exhibit positive RNS test results are more likely to progress to GMG. This finding is consistent with previous research reports. A meta-analyse indicate that the average incidence of progression to SGMG in female patients ranges from approximately 28% to 72% [34], and multiple studies suggest that female sex may be an independent risk factor for generalization [10, 12]. This phenomenon may be related to the joint regulation of immune function by sex hormone levels and genetic susceptibility. Studies have confirmed that estrogen promotes $CD4^+$ Th2 cell and B cell-mediated immune responses, thereby inducing B cell-mediated autoimmune diseases. This mechanism may also explain the gender susceptibility differences commonly observed in autoimmune diseases such as Sjögren's syndrome and systemic lupus erythematosus [35, 36].

Multiple studies have identified positive anti-acetylcholine receptor antibodies as a robust predictor of OMG progression to GMG [10–14, 32–34, 37]. Shima et al. conducted immunohistochemical staining and semi-quantitative analysis of the biceps brachii motor endplates in 13 OMG adults, revealing that seropositivity for AChR-Ab group exhibited significantly fewer AChRs at the motor endplates compared to the seronegative group, with a trend toward reduced AChR density. Given the established relationship between reduced AChR quantity and decreased muscle strength, these findings suggest a potential histological mechanism underlying the increased risk of progression in AChR-OMG patients. Nevertheless, the study has limitations due to its small sample size and the absence of multivariate regression analysis to control for confounding factors [38].

Furthermore, several studies have confirmed a significant association between abnormal RNS findings and generalization [11, 13–16]. Some research has further delineated the predictive value of RNS abnormalities across different muscle groups. Kim

KH et al. reported that initial abnormal RNS findings, particularly in limb muscles, serve as an independent predictor of SGMG [15]. In contrast, a study conducted in northwest China among OMG patients receiving immunosuppressive therapy identified positive RNS in facial muscles as a predictive factor for generalization [16]. These results indicate that abnormal RNS is closely associated with the risk of OMG generalization, and its predictive value may be influenced by the distribution of affected muscle groups and the therapeutic context.

Our study suggests that patients with EOMG exhibit a significantly higher rate of progression to GMG. However, the role of age at onset as a risk factor for generalized progression in adults remains controversial across studies. Some studies indicate that LOMG is associated with a higher probability of generalization[12, 32, 33], whereas others identify EOMG as a risk factor [39, 40]. Hoffmann's review emphasizes that age at onset is a major driver of heterogeneity in clinical phenotype, immunopathology, and treatment response in MG. It further concludes that EOMG has a significantly higher risk of progression to GMG compared to LOMG and VLOMG [41], which is consistent with the findings of our study.

Regarding immunosuppressive therapy, Deepak Menon et al. utilized rigorous statistical approaches, such as propensity score matching, inverse probability of treatment weighting, and time-dependent exposure modeling, to control for confounding variables in their analysis. Their results demonstrated that both corticosteroid and non-steroidal immunosuppressive treatments for OMG significantly reduce the risk of generalization. While the risk ratio for non-steroidal immunosuppressants was lower than that for glucocorticoids in that study, potential additive effects from combination therapy limit definitive comparisons of the efficacy of individual immunosuppressive agents [42]. Notably, a multicenter retrospective cohort study by Ruan Z et al. in China, using inverse probability weighting, demonstrated that combination therapy with corticosteroid and non-steroidal immunosuppressants was associated with a further reducted incidence of SGMG compared with corticosteroid monotherapy, supporting the findings of the present study [43].

Thymic abnormalities in MG demonstrate considerable heterogeneity, including thymoma, thymic hyperplasia, thymic atrophy or involution, and thymolipoma [44, 45]. Several case reports have indicated that some patients with MG presented with thymic cyst, and clinical symptoms in these individuals often improved significantly following thymectomy [46, 47]. Additionally, clinical observations in our cohort identified incomplete thymic involution in a few patients. Meanwhile, studies of other autoimmune diseases have shown that systemic sclerosis and rheumatoid arthritis are also associated with incomplete thymic involution [48], suggesting that it may represent a shared feature among multiple autoimmune disorders. Therefore, these relatively rare thymic abnormalities were classified as benign thymic abnormalities for further analysis (Table 3). Cox regression analysis identified thymoma as an independent risk factor for SGMG (HR=1.51, 95% CI 1.02–2.24, P=0.040), which is consistent with previous findings [11, 13, 14]. In contrast, the associations between thymic hyperplasia or benign thymic abnormalities and generalization did not reach statistical significance (P=0.186 and 0.609, respectively), which may be partially attributable to limited sample sizes in these subgroups. Consequently, the impact of thymic hyperplasia and

benign thymic abnormalities on the risk of generalized disease in adults with OMG requires further validation in larger-scale studies.

The optimal timing of thymectomy for patients with isolated ocular muscle involvement remains a subject of ongoing debate. Recent multicenter retrospective studies suggest that early thymectomy, particularly in adults with OMG, may provide benefits by preventing progression to generalized disease. This strategy appears especially pertinent for patients with non-thymoma MG and those with imaging evidence of thymic hyperplasia. Early surgical intervention has been associated with an increased likelihood of achieving long-term complete stable remission (CSR) and a lower risk of perioperative neurological deterioration [49]. Additionally, another multicenter retrospective cohort study demonstrated that thymectomy performed within two years of ocular symptom onset, regardless of thymoma status, significantly reduces the risk of progression to GMG. Notably, patients who underwent surgery showed a markedly lower five-year cumulative incidence of generalization compared with those who did not receive surgical intervention [50].

Taking into account patients' baseline health status, the CCI was incorporated into the analysis of generalized factors associated with adult OMG. The findings indicate that the CCI serves as an independent risk factor for SGMG (HR=1.20, 95% CI 1.10-1.31, P<0.001), demonstrating that a higher burden of comorbidity significantly increases the likelihood of progression to GMG. To assess the incremental predictive value of the CCI, DCA was employed to compare three predictive models. The results show that the comprehensive model including the CCI provides a higher clinical net benefit than the simplified models, thereby improving the clinical utility of risk assessment for SGMG.

Previous studies have suggested an association between higher BMI and greater disease severity in patients with MG [51]. In a multicenter prospective cohort study, Chen et al. reported that a higher baseline BMI was associated with an increased risk of SGMG [52]. Building on these findings, our study identified an approximately J-shaped nonlinear association between BMI and the risk of generalization. An inflection point was observed at approximately 21.5 kg/m^2, below which BMI was inversely associated with risk, and above which BMI was positively associated with risk. Although a higher BMI appeared to confer a protective effect in the dichotomized Cox model, this association was attenuated and no longer statistically significant when BMI was modeled continuously in sensitivity analyses (Figure 11). This discrepancy suggests that the observed effect may result from model simplification and instability of risk estimates, likely due to the limited sample size within the low-BMI subgroup. Further studies with larger sample sizes are warranted.

This study has several limitations. As a retrospective analysis, it is subject to selection bias and potential confounding factors. Additionally, no training or validation set splitting was performed. Instead, modeling was conducted on the full dataset using Bootstrap internal validation. This approach was adopted because some multiclass variables contained sparse subgroups, and dataset partitioning could have reduced the effective number of events, leading to less stable parameter estimates. The absence of external independent validation means that the model's generalizability remains

unconfirmed. Furthermore, although thymic status was treated as a multiclass variable, only thymoma showed statistical significance in Cox regression. While thymic hyperplasia and benign thymic abnormalities were included in the nomogram, their small sample sizes require further validation in larger studies to accurately determine their risk effects. Addressing these limitations through larger-scale, multicenter studies would improve the model's stability and generalizability.

In summary, this study systematically investigated generalization risk factors for adult OMG and developed a predictive model for risk stratification for generalized conversion. The resulting model offers a quantitative tool for early clinical identification of adults at high risk of generalization. With further external validation and optimization, this model may serve as a simple, reliable, and precise prognostic assessment tool in clinical practice, thereby informing the development of personalized intervention strategies.

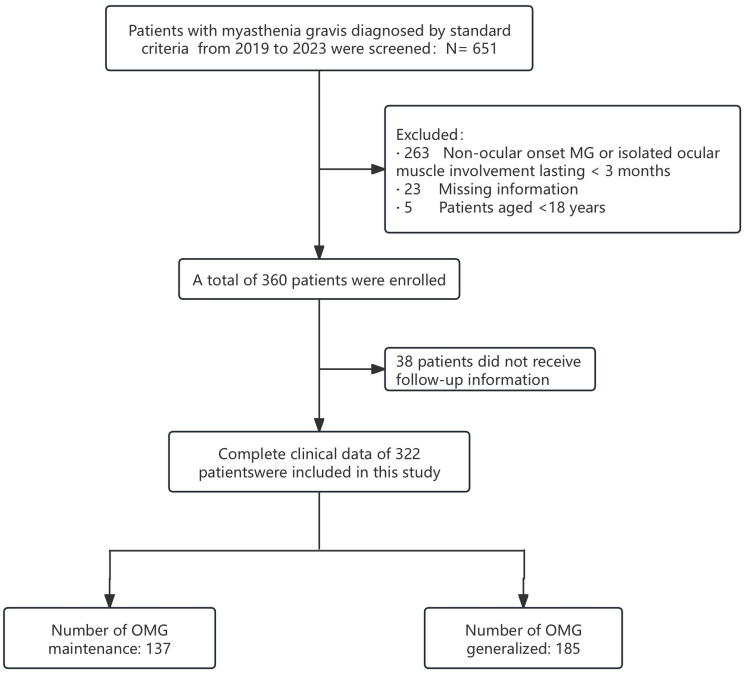


Fig. 1: Flowchart of patients included in the study.

Table 1: Baseline demographic and clinical characteristics.

Characteristic	Total $N = 322$[1]	OMG $N = 137$[1]	SGMG $N = 185$[1]	p-value[2]
Age at onset	57 (49, 67)	55 (47, 65)	59 (49, 68)	0.078
Sex				0.021
female	151 (47%)	54 (39%)	97 (52%)	
male	171 (53%)	83 (61%)	88 (48%)	
CCI	3 (2, 4)	2 (1, 4)	3 (2, 5)	0.003
BMI	25.1 (23.1, 27.2)	24.8 (22.8, 26.7)	25.5 (23.4, 27.5)	0.12
Comorbid autoimmune disease	54 (17%)	13 (9.5%)	41 (22%)	0.003
Diabetes mellitus	62 (19%)	30 (22%)	32 (17%)	0.3
Statin	66 (20%)	23 (17%)	43 (23%)	0.2
Hyperthyroidism	24 (7.5%)	13 (9.5%)	11 (5.9%)	0.2
Initial symptom				0.024
diplopia	59 (18%)	34 (25%)	25 (14%)	
unilateral ptosis	138 (43%)	59 (43%)	79 (43%)	
bilateral ptosis	54 (17%)	16 (12%)	38 (21%)	
diplopia+ptosis	71 (22%)	28 (20%)	43 (23%)	
Neostigmine test	302 (94%)	127 (93%)	175 (95%)	0.5
Repetitive nerve stimulation	155 (48%)	43 (31%)	112 (61%)	<0.001
Antibody type				<0.001
seronegative	25 (7.8%)	20 (15%)	5 (2.7%)	
AChR-Ab seropositivity	297 (92%)	117 (85%)	180 (97%)	
Thymus status				<0.001
normal	241 (75%)	115 (84%)	126 (68%)	
thymoma	61 (19%)	13 (9.5%)	48 (26%)	
thymichyperplasia	7 (2.2%)	2 (1.5%)	5 (2.7%)	
benign thymic abnormalities	13 (4.0%)	7 (5.1%)	6 (3.2%)	
Thymectomy	40 (12%)	19 (14%)	21 (11%)	0.5
Treatment				<0.001
symptomatictreatment	185 (57%)	40 (29%)	145 (78%)	
glucocorticoid	84 (26%)	57 (42%)	27 (15%)	
NS-IST	27 (8.4%)	17 (12%)	10 (5.4%)	
combined therapy	26 (8.1%)	23 (17%)	3 (1.6%)	
IVMP	9 (2.8%)	6 (4.4%)	3 (1.6%)	0.2
Follow-up time	20 (4, 53)	58 (40, 77)	5 (3, 12)	<0.001

[1] n (%); Median (Q1, Q3)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Benign thymic lesions (including thymic cyst, incomplete thymic involution, thymic atrophy/involution and thymolipoma)

Comorbid autoimmune diseases [included Vitiligo, Hashimoto's Thyroiditis (HT), Connective Tissue Disease (CTD), Dermatomyositis(DM), Sjögren's Syndrome(SS), Asthma, Polymyositis(PM), Psoriasis and Rheumatoid Arthritis (RA)]

CCI: The Charlson Comorbidity Index

NS-IST: Non-Steroidal Immunosuppressive Therapy

IVMP: Intravenous infusion of methylprednisolone

combined therapy: glucocorticoids combined with NS-IST therapy

Table 2: The AIC, BIC, and C-index of prognostic factors and the nomogram for predicting generalization.

	C-index(95%CI)	*p*-value	AIC	BIC
Sex	0.556(0.515-0.595)		1996.576	1999.796
BMI	0.530(0.496-0.557)		2001.171	2004.391
Age at onset	0.526(0.505-0.570)		2003.773	2010.214
Comorbid autoimmune disease	0.533(0.506-0.561)		1996.341	1999.561
CCI	0.557(0.514-0.602)		1992.235	1995.456
RNS	0.618(0.585-0.654)		1970.12	1973.34
Thymus	0.569(0.545-0.607)		1988.872	1998.533
Thymectomy	0.506(0.499-0.532)		2003.265	2006.485
Antibody	0.540(0.520-0.560)		1987.18	1990.4
Treatment	0.691(0.660-0.723)		1912.525	1922.186
Nomogram	0.783(0.760-0.819)		1860.902	1909.207
Nomogram versus Sex		<0.001		
Nomogram versus BMI		<0.001		
Nomogram versus Age at onset		<0.001		
Nomogram versus Comorbid autoimmune disease		<0.001		
Nomogram versus CCI		<0.001		
Nomogram versus RNS		<0.001		
Nomogram versus Thymus		<0.001		
Nomogram versus Thymectomy		<0.001		
Nomogram versus Antibody		<0.001		
Nomogram versus Treatment		<0.001		

C-index, concordance index; 95% CI, 95% confdence interval;
AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Table 3: Distribution of thymic abnormalities in our cohort.

Thymic abnormalities	
Thymoma	61 (19%)
Thymic hyperplasia	7 (2.2%)
Benign thymic abnormal changes	
Thymic cyst	3 (0.9%)
Thymic atrophy/involution	2 (0.6%)
Thymolipoma	1 (0.3%)
Incomplete thymic involution	7 (2.2%)

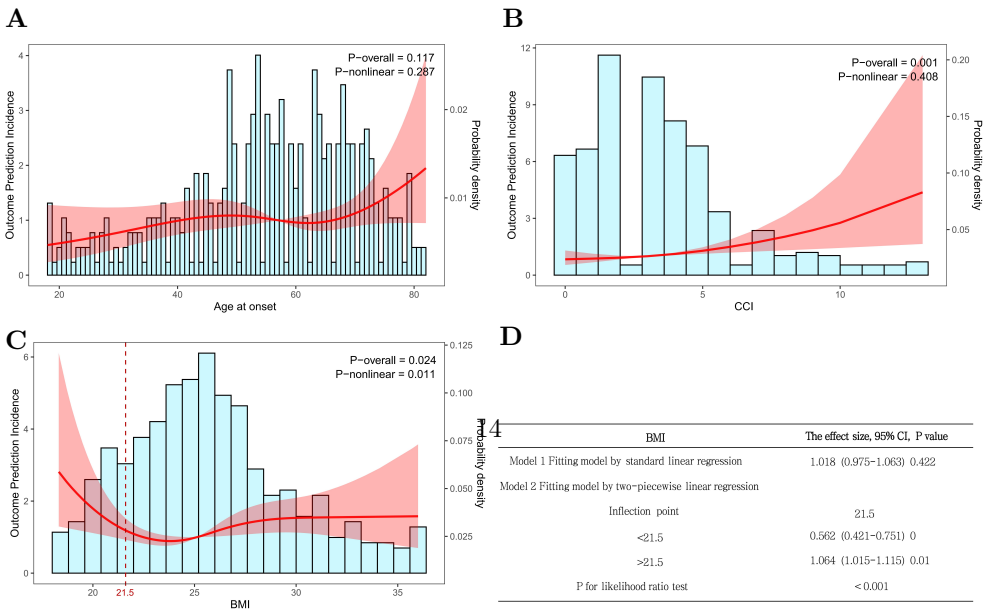


Fig. 2: Restricted cubic spline curves for continuous predictors. (A) Relationship between age at onset and the risk of SGMG. (B) Relationship between CCI and the risk of SGMG. (C) Relationship between BMI and the risk of SGMG. (D) Results of the two-piecewise linear regression model for BMI. For BMI values below 21.5 kg/m^2, BMI was negatively associated with the risk of generalization, whereas for BMI values above 21.5 kg/m^2, BMI was positively associated with the risk of generalization. The likelihood ratio test demonstrated that the piecewise linear model fitted the data significantly better than the single linear model (P<0.001).

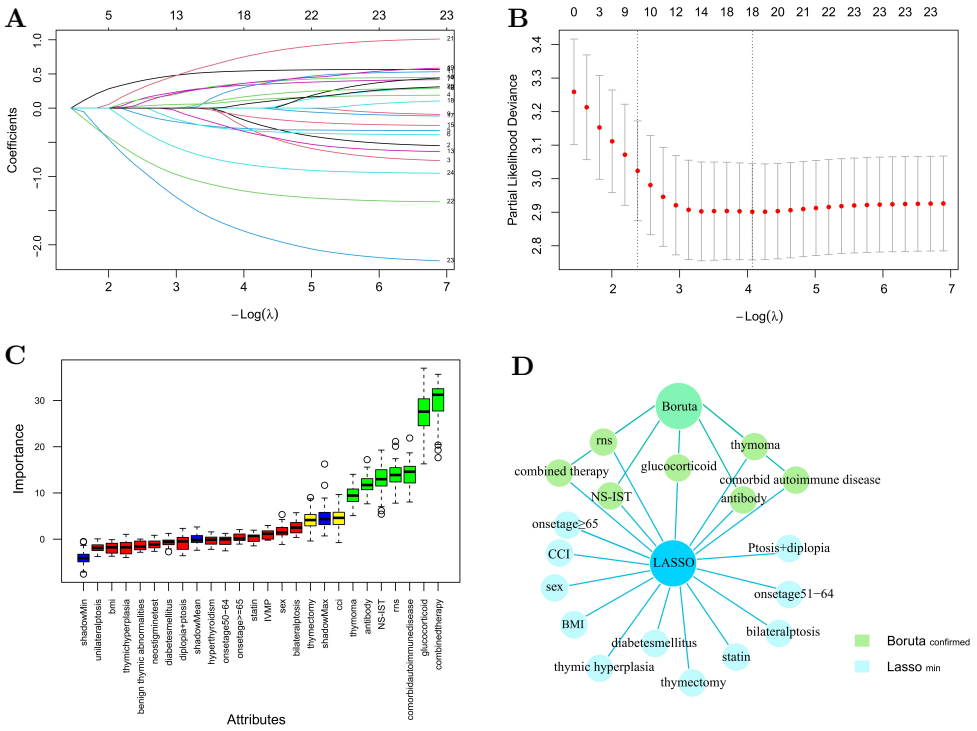


Fig. 3: Predictor screening results. (A) LASSO regression model screening variable trajectories; (B) Factor screening based on the LASSO regression model, with the left dashed line indicating the best lambda value for the evaluation metrics (lambda. min) and the right dashed line indicating the lambda value for the model where the evaluation metrics are in the range of the best value by one standard error (lambda.1se); (C) Boruta; (D) common predictors between Boruta and LASSO.

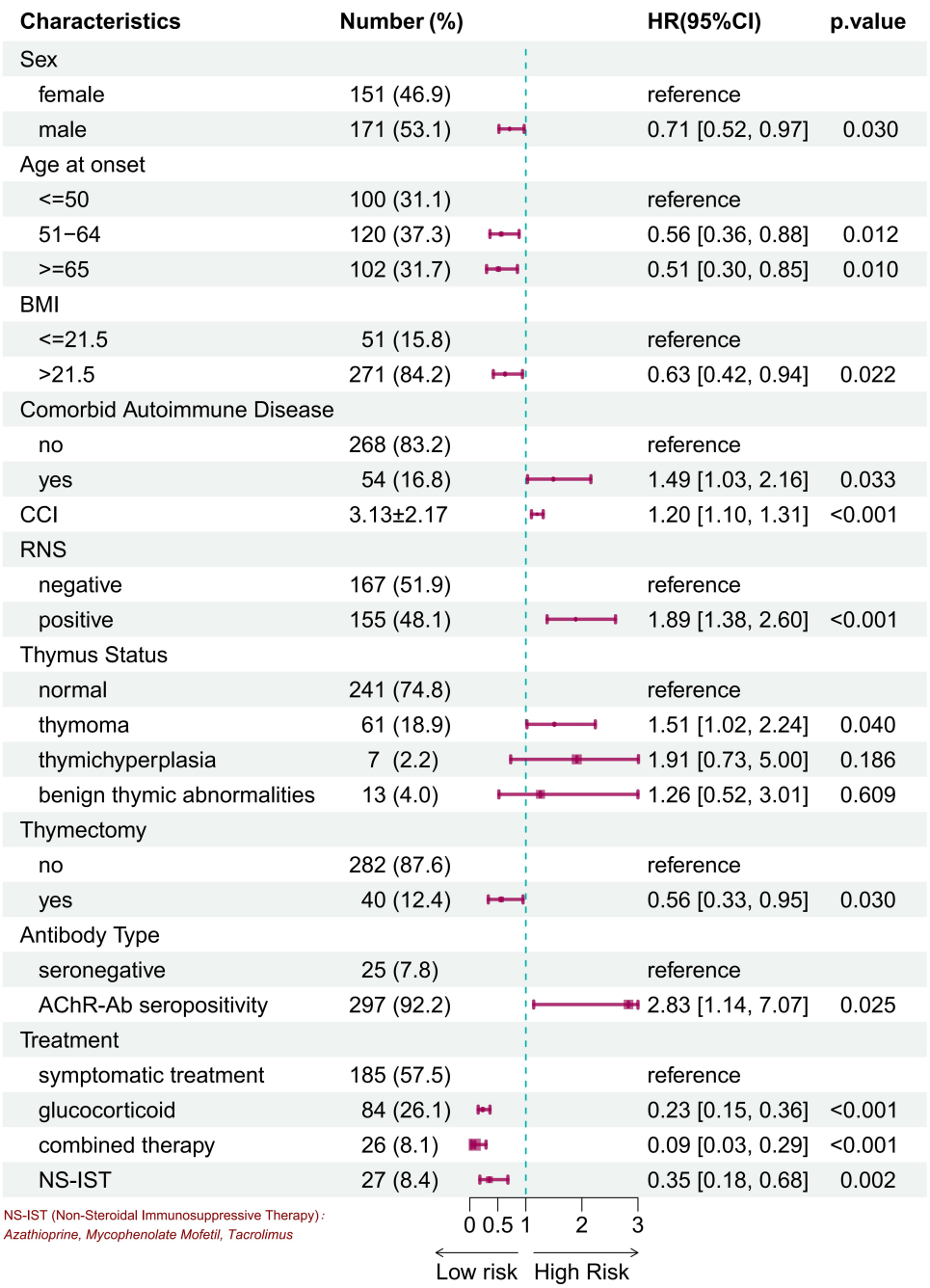


Fig. 4: Forest Plot of Multivariable Cox Regression Analysis for generalization.

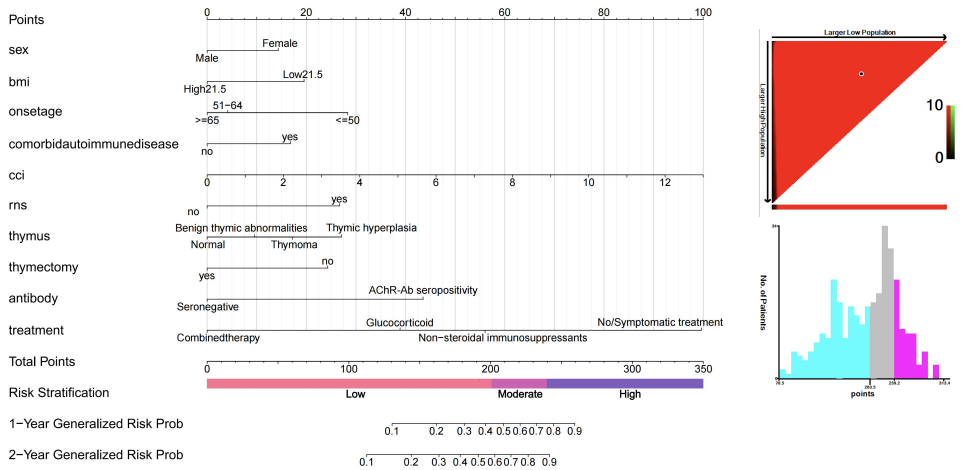


Fig. 5: A risk-stratified nomogram for predicting 2-year generalization in adult patients with OMG.

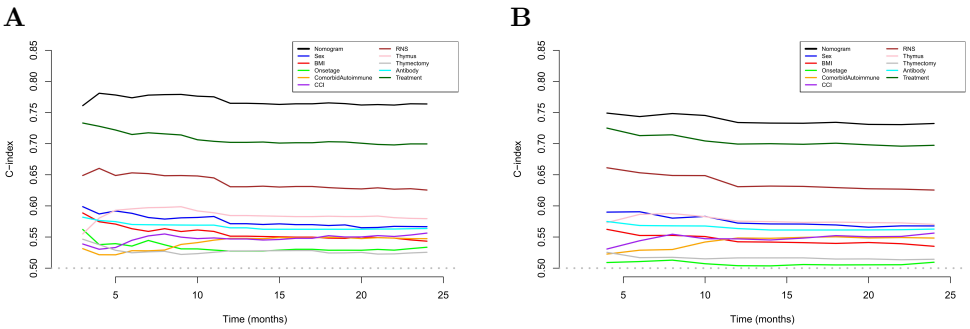


Fig. 6: Time-dependent concordance index curves for the prediction of generalization in adult patients with OMG. (A) Time-dependent C-index of the nomogram compared with individual prognostic factors in the original cohort. (B) Internally validated time-dependent C-index using a bootstrap resampling method.

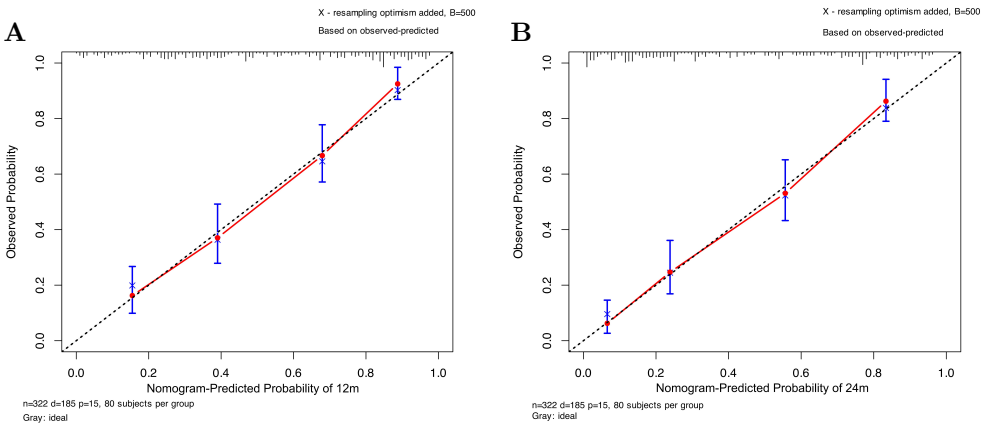


Fig. 7: Calibration curves for 1-year generalization (A), 2-year generalization (B) of nomogram predictions.

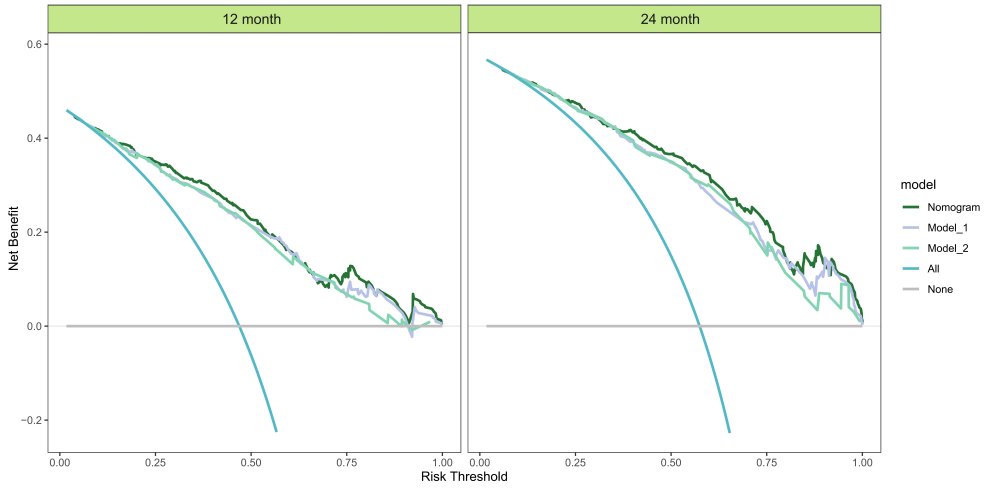


Fig. 8: Decision curve analysis (DCA) of the nomogram and alternative prediction models at 12-month and 24-month follow-up. The net benefit of the nomogram, the model excluding CCI (Model 1), the model excluding variables with high AIC/BIC together with CCI (Model 2), as well as the "treat-all" and "treat-none" strategies, is plotted against a range of threshold probabilities. The threshold probability reflects the clinically acceptable risk of false-positive intervention. A higher net benefit indicates greater clinical usefulness in guiding decision-making.
$Model_1 : sex + bmi + ageatonset + comorbidautoimmunedisease + rns + thymus + thymectomy + antibody + treatment$
$Model_2 : sex + comorbidautoimmunedisease + rns + thymus + antibody + treatment$

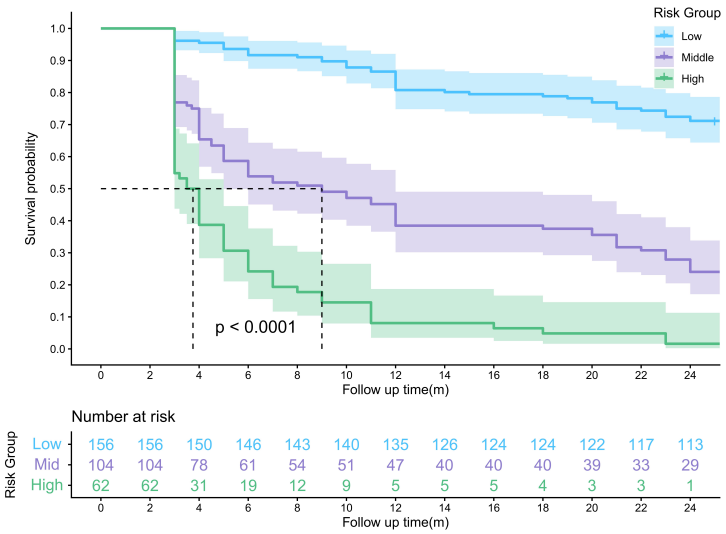


Fig. 9: Kaplan–Meier curves for generalization in adult patients with ocular myasthenia gravis stratified into low-, intermediate-, and high-risk groups based on the total nomogram score. The curves represent the cumulative generalization-free survival probability for each risk group over time (follow-up time in months). The number of patients at risk at each time point is shown below the plot. The log-rank test indicated a statistically significant difference in the risk of generalization among the three groups ($P < 0.0001$).

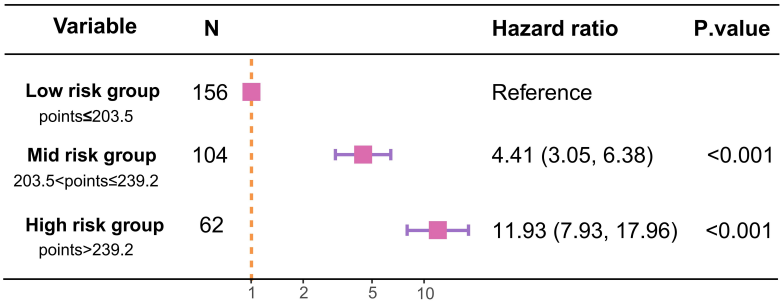


Fig. 10: Forest plot of the risk of generalization based on nomogram-derived risk stratification. The figure presents the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the risk of generalization among patients stratified into low-, intermediate-, and high-risk groups according to the nomogram.

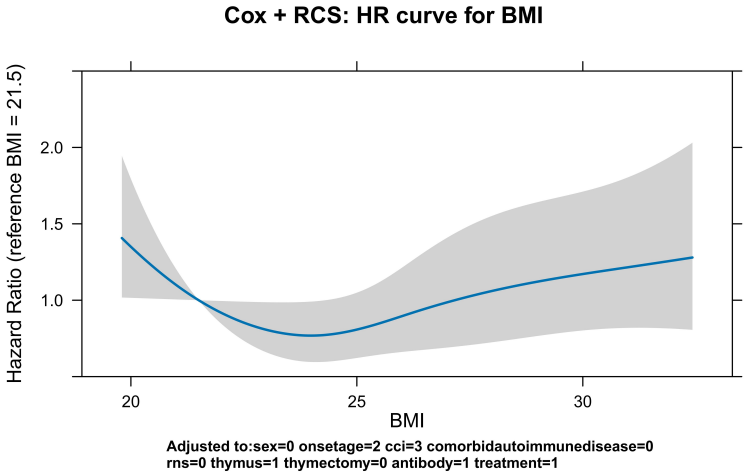


Fig. 11: BMI and generalization risk in adult OMG: restricted cubic spline Cox regression analysis. Multivariable-adjusted hazard ratio (HR) curve for generalization across BMI levels (reference = 21.5 kg/m^2). Adjustments included sex, age at onset, CCI, comorbid autoimmune disease, RNS, thymic status, thymectomy, autoantibody type, and treatment. The shaded area indicates the 95% CI. The relationship between BMI and risk showed a J-shaped pattern, with the lowest risk around BMI 23–24 kg/m^2.

Supplementary information. All statistical analyses were conducted using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). The following R packages were utilized to implement the described statistical methods, with version numbers corresponding to the stable releases used in the study:

- `base` (v4.3.1): Basic descriptive statistics (included in core R, no separate installation required)
- `gtsummary`(v1.7.2): For generating standardized descriptive statistics tables and summarizing regression model results.
- `dplyr` (v1.1.4): Data manipulation and preprocessing
- `ggplot2` (v3.5.1): Data visualization (including calibration curves)
- `stats` (v4.3.1): Core statistical tests (independent-samples t-tests, Wilcoxon rank-sum test, Pearson chi-square test, Fisher's exact test, log-rank test; included in core R)
- `rms` (v6.7-0): Restricted cubic splines (RCS) analysis for nonlinear associations
- `glmnet` (v4.1-8): Least absolute shrinkage and selection operator (LASSO) regression for variable selection
- `Boruta` (v7.0.0): Boruta algorithm for variable selection
- `survival` (v3.5-7): Cox proportional hazards models and Kaplan–Meier survival analysis
- `rms` (v6.7-0): Nomogram construction and concordance index (C-index) calculation
- `boot` (v1.3-28): Bootstrap resampling for internal validation

- `DecisionCurve` (v1.0): Decision curve analysis (DCA) to evaluate clinical utility

Acknowledgements. I sincerely thank Professor Mingming Ma and Professor Hongjuan Zhang for their substantial support and invaluable contributions to this study. I am also deeply grateful to Professor Haidong Lyv for his expert guidance and insightful comments on the manuscript. Additionally, I extend my heartfelt thanks to the staff of the Department of Neurology at Jiaozuo People's Hospital for their dedicated efforts and professional assistance throughout this research.

Declarations

- Funding
  This study was supported by the 2024 Henan Provincial Medical Science and Technology Research Plan (Joint Construction Project) with the project number: LHGJ20240705.
- Conflict of interest/Competing interests
  The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
- Ethics approval and consent to participate
  This research adhered to the ethical guidelines set forth in the Declaration of Helsinki and was approved by the Ethics Committee at Jiaozuo People's Hospital Affiliated of Henan Medical University (approval No.2026-003-K03). Due to the retrospective nature of the study, the requirement for written informed consent for the utilization of clinical data was waived.
- Consent for publication
  All authors have approved the final version of the manuscript and consent to its publication. Given the retrospective nature of this study, the data used were de-identified (e.g., no names, medical record numbers, or other directly identifiable information were included), and only aggregated or anonymized information (such as gender, age ranges, and disease duration) was presented. Therefore, specific informed consent for publication is not required, as the risk of identifying individual participants is negligible. This approach is consistent with the ethical approval from the Ethics Committee at Jiaozuo People's Hospital Affiliated of Xinxiang Medical University.
- Data availability The data that support the findings of this study are available from the corresponding author on reasonable request.
- Author contribution
  Jingting Fu: Conceiving and designing the experiment, conducting the research, drafting the article, and performing statistical analysis. Mingming Ma: Critically reviewing the intellectual content, providing data support, and offering guidance. Xianzhao Zheng: Critically reviewing the intellectual content, providing administrative/technical/material support, and offering guidance. Hongjuan Zhang: Data collection, patient follow-up, and providing data support. Xiaoli MA : Critically reviewing the intellectual content and providing guidance. Qianqian QU : Collecting data and patient follow-up. Wenhao Cui: Collecting data and patient follow-up.

Jiaxuan Wang: Collecting data and patient follow-up. Haidong Lyv *: Critically reviewing the intellectual content, obtaining research funds, and providing guidance.

References

[1] Khanna, S., Richmonds, C.R., Kaminski, H.J., Porter, J.D.: Molecular organization of the extraocular muscle neuromuscular junction: Partial conservation of and divergence from the skeletal muscle prototype. Investigative Ophthalmology & Visual Science **44**(5), 1918–1926 (2003) https://doi.org/10.1167/iovs.02-0890

[2] Liu, R., Xu, H., Wang, G., Li, J., Gou, L., Zhang, L., Miao, J., Li, Z.: Extraocular muscle characteristics related to myasthenia gravis susceptibility. PLOS ONE **8**(2), 1–14 (2013) https://doi.org/10.1371/journal.pone.0055611

[3] Kaminski, H.J., Li, Z., Richmonds, C., Lin, F., Medof, M.E.: Complement regulators in extraocular muscle and experimental autoimmune myasthenia gravis. Experimental Neurology **189**(2), 333–342 (2004) https://doi.org/10.1016/j.expneurol.2004.06.005

[4] Jacob, S.: Treating myasthenia gravis beyond the eye clinic. (2024) https://doi.org/10.1038/s41433-024-03133-x

[5] Grob, D., Brunner, N., Namba, T., Pagala, M.: Lifetime course of myasthenia gravis. Muscle & Nerve **37**(2), 141–149 (2008) https://doi.org/10.1002/mus.20950

[6] Oosterhuis, H.J.: The natural course of myasthenia gravis: a long term follow up study. Journal of Neurology, Neurosurgery & Psychiatry **52**(10), 1121–1127 (1989) https://doi.org/10.1136/jnnp.52.10.1121

[7] Kupersmith, M.J., Latkany, R., Homel, P.: Development of generalized disease at 2 years in patients with ocular myasthenia gravis. Archives of Neurology **60**(2), 243–248 (2003) https://doi.org/10.1001/archneur.60.2.243

[8] Vanikieti, K., Lowwongngam, K., Padungkiatsagul, T., Visudtibhan, A., Poonyathalang, A.: Juvenile ocular myasthenia gravis: Presentation and outcome of a large cohort. Pediatric Neurology **87**, 36–41 (2018) https://doi.org/10.1016/j.pediatrneurol.2018.06.007

[9] Lin, Y., Kuang, Q., Li, H., Liang, B., Lu, J., Jiang, Q., Yang, X.: Outcome and clinical features in juvenile myasthenia gravis: A systematic review and meta-analysis. Frontiers in Neurology **Volume 14 - 2023** (2023) https://doi.org/10.3389/fneur.2023.1119294

[10] Díaz-Maroto, I., García-García, J., Sánchez-Ayaso, P.A., Alcahut-Rodríguez, C., González-Villar, E., Pardal-Fernández, J.M., Segura, T.: Ocular myasthenia gravis and risk factors for developing a secondary generalisation: description

of a spanish series. Neurología (English Edition) **38**(4), 229–235 (2023) https://doi.org/10.1016/j.nrleng.2020.09.004

[11] Gengadharan, P.N., Ong, W.T., Tan, J.Y., Shahrizaila, N., Goh, K.J., Tan, C.Y.: Ocular myasthenia gravis: determining the predictive factors of secondary generalisation. Acta Neurologica Belgica **125**(2), 351–358 (2025) https://doi.org/10.1007/s13760-024-02693-9

[12] Mazzoli, M., Ariatti, A., Valzania, F., Kaleci, S., Tondelli, M., Nichelli, P.F., Galassi, G.: Factors affecting outcome in ocular myasthenia gravis. International Journal of Neuroscience **128**(1), 15–24 (2018) https://doi.org/10.1080/00207454.2017.1344237 . PMID: 28625092

[13] Kısabay, A., Özdemir, H.N., Gökçay, F., Çelebisoy, N.: Risk for generalization in ocular onset myasthenia gravis: experience from a neuro-ophthalmology clinic. Acta Neurologica Belgica **122**(2), 337–344 (2022) https://doi.org/10.1007/s13760-020-01582-1

[14] Guo, R.-J., Gao, T., Ruan, Z., Zhou, H.-Y., Gao, F., Xu, Q., Yu, L.-P., Wu, S.-D., Lei, T., Li, H.-H., Sun, C., Zhang, M., Gao, Y.-W., Lu, X.-D., Tang, Y.-L., Tang, B.-L., Huo, F.-Y., Zhu, Y., Li, Z.-Y., Chang, T.: Risk factors for generalization in patients with ocular myasthenia gravis: A multicenter retrospective cohort study. Neurology and Therapy **11**(1), 73–86 (2022) https://doi.org/10.1007/s40120-021-00292-x

[15] Kim KH, S.H. Kim SW: Initial repetitive nerve stimulation test predicts conversion of ocular myasthenia gravis to generalized myasthenia gravis. Journal of Clinical Neurology (Seoul, Korea) **17**(2), 265–272 (2021) https://doi.org/10.3988/jcn.2021.17.2.265

[16] Ding, J., Zhao, S., Ren, K., Dang, D., Li, H., Wu, F., Zhang, M., Li, Z., Guo, J.: Prediction of generalization of ocular myasthenia gravis under immunosuppressive therapy in northwest china. BMC Neurology **20**(1), 238 (2020) https://doi.org/10.1186/s12883-020-01805-1

[17] Giannopapas, V., Smyrni, V., Papagiannopoulou, G., Salakou, S., Kitsos, D.K., Bethani, I., Zompola, C., Tzartos, J.S., Tsivgoulis, G., Giannopoulos, S., Kosmidou, M.: Dyslipidemia in myasthenia gravis: A systematic review and meta-analysis. Medicina (Kaunas, Lithuania) **61**(6), 1067 (2025) https://doi.org/10.3390/medicina61061067

[18] Keogh, M.J., Findlay, J.M., Leach, S., Bowen, J.: Statin-associated weakness in myasthenia gravis: a case report. Journal of Medical Case Reports **4**(1), 61 (2010) https://doi.org/10.1186/1752-1947-4-61

[19] Sheikh, S., Alvi, U., Soliven, B., Rezania, K.: Drugs that induce or cause deterioration of myasthenia gravis: An update. Journal of Clinical Medicine **10**(7)

(2021) https://doi.org/10.3390/jcm10071537

[20] Yan, L., Huang, D., Shen, J., Yang, M., Wang, S.: Statin-associated myasthenia gravis: a real-world retrospective and pharmacovigilance study. Expert Opinion on Drug Safety **0**(0), 1–8 (2025) https://doi.org/10.1080/14740338.2025.2467183 . PMID: 39939175

[21] Liu, Y.-D., Tang, F., Li, X.-L., Liu, Y.-F., Zhang, P., Yang, C.-L., Du, T., Li, H., Wang, C.-C., Liu, Y., Yang, B., Duan, R.-S.: Type 2 diabetes mellitus as a possible risk factor for myasthenia gravis: a case–control study. Frontiers in Neurology **Volume 14 - 2023** (2023) https://doi.org/10.3389/fneur.2023.1125842

[22] Li, T., Yang, C.-L., Du, T., Zhang, P., Zhou, Y., Li, X.-L., Wang, C.-C., Liu, Y., Li, H., Zhang, M., Duan, R.-S.: Diabetes mellitus aggravates humoral immune response in myasthenia gravis by promoting differentiation and activation of circulating tfh cells. Clinical Immunology **245**, 109141 (2022) https://doi.org/10.1016/j.clim.2022.109141

[23] ENGEL, A.G.: Thyroid function and myasthenia gravis. Archives of Neurology **4**(6), 663–674 (1961) https://doi.org/10.1001/archneur.1961.00450120077009

[24] Myasthenia gravis with antibodies against the achr, current knowledge on pathophysiology and an update on treatment strategies with special focus on targeting plasma cells. Autoimmunity Reviews **24**(10), 103875 (2025) https://doi.org/10.1016/j.autrev.2025.103875

[25] Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R.: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases **40**(5), 373–383 (1987) https://doi.org/10.1016/0021-9681(87)90171-8

[26] Neuroimmunology, C.S.: Chinese guideline for diagnosis and treatment of myasthenia gravis (2025 edition). Chinese Journal of Neurology (07) (2025) https://doi.org/10.3760/cma.j.cn113694-20250120-00041

[27] Oosterhuis, H.: The natural course of myasthenia gravis: a long term follow up study. Journal of Neurology, Neurosurgery & Psychiatry **52**(10), 1121–1127 (1989)

[28] Sommer, N., Sigg, B., Melms, A., Weller, M., Schepelmann, K., Herzau, V., Dichgans, J.: Ocular myasthenia gravis: response to long-term immunosuppressive treatment. Journal of Neurology, Neurosurgery & Psychiatry **62**(2), 156–162 (1997)

[29] Matsui, N., Nakane, S., Nakagawa, Y., Kondo, K., Mitsui, T., Matsumoto, T., Arisawa, K., Kaji, R.: Increasing incidence of elderly onset patients with myasthenia gravis in a local area of japan. Journal of Neurology, Neurosurgery & Psychiatry

80(10), 1168–1171 (2009) https://doi.org/10.1136/jnnp.2008.152637

[30] Hellmann, M.A., Mosberg-Galili, R., Steiner, I.: Myasthenia gravis in the elderly. Journal of the Neurological Sciences **325**(1), 1–5 (2013) https://doi.org/10.1016/j.jns.2012.10.028

[31] Chen, J., Tian, D.-C., Zhang, C., Li, Z., Zhai, Y., Xiu, Y., Gu, H., Li, H., Wang, Y., Shi, F.-D.: Incidence, mortality, and economic burden of myasthenia gravis in china: a nationwide population-based study. The Lancet Regional Health–Western Pacific **5** (2020) https://doi.org/10.1016/j.lanwpc.2020.100063

[32] Bi, Z., Cao, Y., Gui, M., Lin, J., Zhang, Q., Li, Y., Ji, S., Bu, B.: Dynamic nomogram for predicting generalized conversion in adult-onset ocular myasthenia gravis. Neurological Sciences **44**(4), 1383–1391 (2023) https://doi.org/10.1007/s10072-022-06519-5

[33] Ruan, Z., Sun, C., Lang, Y., Gao, F., Guo, R., Xu, Q., Yu, L., Wu, S., Lei, T., Liu, Y., Zhang, M., Li, H., Tang, Y., Gao, T., Gao, Y., Lu, X., Li, Z., Chang, T.: Development and validation of a nomogram for predicting generalization in patients with ocular myasthenia gravis. Frontiers in Immunology **Volume 13 - 2022** (2022) https://doi.org/10.3389/fimmu.2022.895007

[34] Fang, C.E.H., Bokre, D., Wong, S.H.: Clinical characteristics associated with secondary generalization in patients with ocular myasthenia gravis: A systematic review and meta-analysis. Neurology **101**(16), 1594–1605 (2023) https://doi.org/10.1212/WNL.0000000000207642

[35] Delpy, L., Douin-Echinard, V., Garidou, L., Bruand, C., Saoudi, A., Guéry, J.-C.: Estrogen enhances susceptibility to experimental autoimmune myasthenia gravis by promoting type 1-polarized immune responses. The Journal of Immunology **175**(8), 5050–5057 (2005)

[36] Whitacre, C.C.: Sex differences in autoimmune disease. Nature immunology **2**(9), 777–780 (2001) https://doi.org/10.1038/ni0901-777

[37] Peeler, C.E., De Lott, L.B., Nagia, L., Lemos, J., Eggenberger, E.R., Cornblath, W.T.: Clinical utility of acetylcholine receptor antibody testing in ocular myasthenia gravis. JAMA Neurology **72**(10), 1170–1174 (2015) https://doi.org/10.1001/jamaneurol.2015.1444

[38] Shima, T., Nagaoka, A., Yoshimura, S., Tsujino, A.: Association between acetylcholine receptor characteristics in biceps motor endplates and the epidemiological predictors for conversion from ocular to generalized myasthenia gravis. Acta medica Nagasakiensia **66**(1), 21–27 (2022) https://doi.org/10.11343/amn.66.21

[39] Kamarajah, S.K., Sadalage, G., Palmer, J., Carley, H., Maddison, P., Sivaguru, A.: Ocular presentation of myasthenia gravis: a natural history cohort. Muscle &

Nerve **57**(4), 622–627 (2018) https://doi.org/10.1002/mus.25971

[40] Feng, X., Huan, X., Yan, C., Song, J., Lu, J., Zhou, L., Wu, H., Qiao, K., Lu, J., Xi, J., *et al.*: Adult ocular myasthenia gravis conversion: a single-center retrospective analysis in china. European Neurology **83**(2), 182–188 (2020) https://doi.org/10.1159/000507853

[41] Hoffmann, S.: Chapter nine - special populations in myasthenia gravis: Early, late, and very late-onset mg **182**, 197–204 (2025) https://doi.org/10.1016/bs.irn.2025.04.032

[42] Menon, D., Alharbi, M., Katzberg, H.D., Bril, V., Mendoza, M.G., Barnett-Tapia, C.: Effect of immunosuppression in risk of developing generalized symptoms in ocular myasthenia gravis. Neurology **103**(4), 209722 (2024) https://doi.org/10.1212/WNL.0000000000209722

[43] Ruan, Z., Guo, R., Zhou, H., Gao, F., Lin, Y., Xu, Q., Yu, L., Wu, S., Lei, T., Zhang, M., Gao, Y., Lu, X., Li, H., Sun, C., Tang, B., Li, Z., Chang, T.: Association of immunosuppression treatment with generalization among patients with ocular myasthenia gravis: A propensity score analysis. European Journal of Neurology **29**(6), 1805–1814 (2022) https://doi.org/10.1111/ene.15292

[44] Marx, A., Ströbel, P., Weis, C.-A.: The pathology of the thymus in myasthenia gravis. Mediastinum **2**(0) (2018)

[45] Mané-Damas, M., Schöttler, A.K., Marcuse, F., Molenaar, P.C., Mohile, T., Hoeijmakers, J.G.J., Hochstenbag, M., Damoiseaux, J., Maessen, J.G., Abdul-Hamid, M., Hausen, A., Baets, M.H., Losen, M., Martinez-Martinez, P.: Myasthenia gravis with antibodies against the achr, current knowledge on pathophysiology and an update on treatment strategies with special focus on targeting plasma cells. Autoimmunity Reviews **24**(10), 103875 (2025) https://doi.org/10.1016/j.autrev.2025.103875

[46] Latini, E., Guida, M., Zirafa, C.C., Rizzo, S., Cepele, A., Romano, G., Aprile, V., Lucchi, M., Siciliano, G., Ricciardi, R., Maestri Tassoni, M.: Long-term effectiveness of thymectomy in late-onset myasthenia gravis. Journal of Neurology **272**, 714 (2025) https://doi.org/10.1007/s00415-025-13424-2

[47] Wang, X., Chen, K., Li, X., Li, Y., Yang, F., Li, J., Jiang, G., Liu, J., Wang, J.: Clinical features, diagnosis and thoracoscopic surgical treatment of thymic cysts. Journal of Thoracic Disease **9**(12), 5203–5211 (2017) https://doi.org/10.21037/jtd.2017.10.148

[48] Meunier, M., Bazeli, R., Feydy, A., Drape, J.-L., Kahan, A., Allanore, Y.: Incomplete thymic involution in systemic sclerosis and rheumatoid arthritis. Joint Bone Spine **80**(1), 48–51 (2013) https://doi.org/10.1016/j.jbspin.2012.01.016

[49] Nachira, D., Congedo, M.T., Kuzmych, K., Evoli, A., Iorio, R., Vita, M.L., Petracca-Ciavarella, L., Nocera, A., Sassorossi, C., Evangelista, J., Lyberis, P., Comacchio, G.M., Brandolini, J., Aprile, V., Zifara, C.C., Mastromarino, M.G., Patirelis, A., Asteggiano, E., Anile, M., Venuta, F., Imperatori, A., Ambrogi, V., Solli, P., Dell'Amore, A., Lucchi, M., Melfi, F., Ibrahim, M., Ruffini, E., Rea, F., Margaritora, S., Meacci, E.: Thymectomy in ocular myasthenia gravis: Results before and after generalization and prognostic predictors of outcomes. Journal of Clinical Medicine **14**(21) (2025) https://doi.org/10.3390/jcm14217840

[50] Li, H., Ruan, Z., Gao, F., Zhou, H., Guo, R., Sun, C., Xu, Q., Lu, Q., Zhou, Y., Zhao, Z., Yu, L., Wu, S., Lei, T., Gao, T., Tang, Y., Li, C., Huo, F., Zhu, Y., Sun, J., Tang, B., Zhang, M., Gao, Y., Lu, X., Li, Z., Chang, T.: Thymectomy and risk of generalization in patients with ocular myasthenia gravis: A multicenter retrospective cohort study. Neurotherapeutics **18**(4), 2449–2457 (2021) https://doi.org/10.1007/s13311-021-01129-z

[51] Wilcke, H., Glaubitz, S., Kück, F., Anten, C., Liebetanz, D., Schmidt, J., Zschüntzsch, J.: Female sex and overweight are associated with a lower quality of life in patients with myasthenia gravis: a single center cohort study. BMC Neurology **23**(1), 366 (2023) https://doi.org/10.1186/s12883-023-03406-0

[52] Chen, H.-x., Wang, Z.-y., Zhang, N.-n., Lin, X., Shi, Z.-y., Wang, X.-f., Zhang, Y., Du, Q., Kong, L.-y., Sun, D.-r., Wang, R., Zhang, Y.-y., Li, S.-j., Da, Y.-w., Feng, H.-y., Zhou, H.-y.: Impact of body mass index on clinical presentation and prognosis in myasthenia gravis. Orphanet Journal of Rare Diseases **20**(1), 361 (2025) https://doi.org/10.1186/s13023-025-03902-1