Developing and validating a nomogram to predict myasthenia gravis exacerbation in patients with postoperative thymoma recurrence

Biqi Cheng[1,2#], Yinping Xue[1,2#], Shanshan Gu[1,2], Hongxia Yang[1,2], Peng Liu[1,2], Guoyan Qi[1,2]

[1]Center of Treatment of Myasthenia Gravis, People's Hospital of Shijiazhuang, Hebei Medical University, Shijiazhuang, China; [2]Hebei Provincial Key Laboratory of Myasthenia Gravis, Shijiazhuang, China

Contributions: (I) Conception and design: B Cheng, Y Xue, G Qi; (II) Administrative support: P Liu, S Gu, H Yang; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: B Cheng, Y Xue, G Qi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Guoyan Qi. Chief Director, Center of Treatment of Myasthenia Gravis, People's Hospital of Shijiazhuang, Hebei Medical University, No. 365, Jianhuahan Street, Yuhua District, Shijiazhuang 050000, China. Email: zzjwlsys@163.com.

Background: Myasthenia gravis (MG) is one of the most common accessory syndromes for thymoma patients. To reduce MG exacerbation and guide clinical practice, we developed a nomogram for predicting MG exacerbation in patients with postoperative thymoma recurrence.

Methods: Retrospective study of 176 patients with recurrence following thymoma resection who were admitted to the People's Hospital of Shijiazhuang's Center of Treatment of Myasthenia Gravis between 2013 and 2021. Among them, 120 patients with recurrent thymoma from 2013 to 2020 were selected as the training cohort, and 56 patients in 2021 as the validation cohort. Univariate and multivariate logical regression was used to determine the risk factors and draw the nomogram, and the parameters in the nomogram were proportionally assigned from 0 to 100 points. Finally, the performance of the model is evaluated by internal inspection and external inspection.

Results: Multivariate analysis revealed that postoperative treatment plan and the pathologic classification of the thymoma were independent predictors of MG exacerbation in the training cohort (n=120), so they were used to create the nomogram, which had a well-fit calibration curve and good concordance index of 0.77 [95% confidence interval (CI): 0.69–0.86] for the training cohort and 0.74 (95% CI: 0.58–0.91) for the validation cohort, respectively. Calculations were made to determine the nomogram's sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). The training cohort were 75.7% (95% CI: 66.1–83.4%), 64.7% (95% CI: 38.6–84.7%), 92.9% (95% CI: 84.5–97.1%) and 30.6% (95% CI: 16.9–48.3%) respectively, while the corresponding validation cohort were 84.1% (95% CI: 69.3–92.8%), 66.7% (95% CI: 35.4–88.7%), 90.2% (95% CI: 75.9–96.8%) and 53.3% (95% CI: 27.4–77.7%) respectively.

Conclusions: We identified the risk factors for MG exacerbation in patients with postoperative recurrence of thymoma and drew a nomogram, which can be used to calculate the probability of MG exacerbation and guide clinicians to choose post-operative treatment.

Keywords: Exacerbation; myasthenia gravis (MG); prediction model; recurrence; thymoma

Introduction

Thymoma is a rare and potentially malignant tumor, and complete surgical resection is currently recognized globally as the first choice of treatment (1). Nevertheless, 10–30% of patients may have postoperative recurrence (2-4). Myasthenia gravis (MG) is an acquired neuromuscular junction (NMJ) transmission disorder caused by autoantibodies (5), and MG patients often have accompanying thymic abnormalities, including thymic hyperplasia, thymic atrophy, and thymoma. About 10–15% of MG patients have thymoma (6), and the prevalence increases with age. MG is also one of the most common accessory syndromes for thymoma patients. It is estimated that between 30% and 50% of patients with thymoma or thymic carcinoma will suffer from MG, according to the 2022 National Comprehensive Cancer Network (NCCN) guidelines for thymoma and thymic carcinomas.

Currently, both thymoma and MG have corresponding international diagnostic and treatment guidelines or expert consensus, but none for thymoma patients with MG. International studies of thymoma patients with MG (7-11) mainly focus on postoperative MG, MG aggravation, thymoma recurrence, and adjuvant therapy. Chinese scholars (7) believe that MG Osserman II–IV and WHO B2-B3 thymoma are independent risk factors for MG exacerbation, while German researchers believe thymoma is an independent predictor for a myasthenic crisis (MC) or MG (12). However, when thymoma recurs, not all patients will have MG exacerbation. MG hinders patients' performance of activities of daily living and other phenomena seriously affect their physical and mental health. Why MG worsens in some patients with recurrent thymomas but not in others, and whether it is related to the postoperative management of thymomas is unclear.

Therefore, considering the long-term prognosis of MG patients, we believed it was important to develop a predictive model for MG exacerbation in patients with postoperative recurrence of thymoma based on their clinical characteristics before the recurrence. This model can help us predict the possibility of MG exacerbation relatively accurately according to clinical factors, thus strengthening the management of high-risk groups and reducing the rate of MG exacerbation. At present, there is no relevant predictive model for reference in the available literature. Our research included both model development and validation. There are several types of predictive models, but nomograms can provide individualized, evidence-based, and accurate estimates of risk. At the same time, a nomogram is easy to use and can assist in decision making related to MG management. We present the following article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-549/rc).

Methods

Patients

Data for cases of thymoma in patients who were treated at the Center of Treatment of Myasthenia Gravis, People's Hospital of Shijiazhuang between January 1st, 2013, and December 31th, 2021, were retrospectively collected. According to statistics, a total of 176 patients met the criteria and were included in the study. We used the patients with recurrent thymoma from 2013 to 2020 as the training cohort (n=120), and the patients in 2021 as the validation cohort (n=56). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of the People's Hospital of Shijiazhuang (No. 2022045). Informed consent was obtained from all individual participants included in the study.

Basic data of patients were collected, including age, gender, MGFA classification, WHO histological classification, pathological stage, and postoperative treatment methods to determine the possible prediction factors. Inclusion criteria were: (I) clearly diagnosed recurrent thymoma after R0 resection of thymoma; (II) thymoma combined with MG before surgery (III) no preoperative thymoma metastasis; (IV) no preoperative treatment related to thymoma or MG; (V) achieved MM-2 or better in accordance with the American Myasthenia Gravis Foundation's Post-intervention Status (MGFA-PIS). MM-2 defined as no obvious MG symptoms, but electromyogram shows that some muscles still have weakness. At this stage, the patients can use immunosuppressants and pyridostigmine (<120 mg/day). Exclusion criteria were thymic carcinoma, concomitant with other autoimmune diseases (e.g., dermatomyositis, polymyositis, vitiligo, Sjogren syndrome, etc.), or incomplete clinical information/unknown pathology. The training cohort for creating the nomogram consisted of patients who satisfied the criteria between January 1st, 2013, and December 31st, 2020, and the validation cohort consisted of patients who fulfilled the inclusion standards between January 1st, 2021, and December 31st, 2021. All

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Table 1 Postoperative therapy

Treatment plan	Abbreviations
Radiotherapy + high-dose steroid pulse	RH
Radiotherapy + chemotherapy	RC
Radiotherapy + other	OR
High-dose steroid pulse	OH
Chemotherapy	OC
Other	OO

RH, radiotherapy combined with high-dose steroid pulse therapy; RC, synchronous chemoradiotherapy; OR, radiotherapy combined with other treatments; OH, high-dose steroid pulse therapy only; OC, chemotherapy only; OO, other treatments.

patients were followed up until March 2022. Data collation and analysis were conducted from January to April 2022, and article writing was conducted from June to July 2022.

Definition of recurrent thymoma and MG exacerbation

Preoperative diagnosis of thymoma was based on NCCN guidelines, and surgical resection included intact thymoma and surrounding tissue. The 2020 Chinese Guidelines for the diagnosis and treatment of myasthenia gravis served as the foundation for MG diagnosis. Thymoma recurrence was described as a new mass with an obvious pathologic diagnosis. Exacerbation of MG was evaluated by Xu's absolute and relative score (ARS-MG) (13). If the difference between the recurrent and postoperative ARS-MG scores was >5 points, then MG was aggravated.

Clinical variables

The pathologic classification of thymoma was based on the World Health Organization (WHO) (14) system, whereby types A, AB, and B1 are considered low-risk tumors, and types B2 and B3 are high-risk tumors. If the tumor was of mixed pathologic type, the highest pathological classification was the criterion; for example, type B2B3 belonged to type B3 thymoma. Clinical staging was based on the Masaoka-Koga staging proposed in 1994 (14), in which stage I is considered low invasion and stages II, III, and IV are high invasion. We evaluated the severity of MG in all patients in accordance with the MGFA classification.

Treatment after tumor resection included all treatments from the end of surgery to 3 months postoperative, which

included both thymoma and MG treatment, and all treatments were implemented according to the diagnostic and treatment guidelines. Special attention should be paid to the fact that high-dose steroid pulse therapy was first proposed in 2003 (15), and the MG symptoms of patients were significantly improved after its clinical application. Methylprednisolone is a commonly used drug for high-dose steroid pulse therapy; According to the scientific method, the intravenous infusion starts from 1 g/day and is reduced by half every three days until it reaches 60 mg/day. Then take methylprednisolone by mouth for 52 mg/day, and gradually reduce to discontinuation after discharge. To facilitate statistical analysis, we divided treatment plans into the 6 types shown in *Table 1*.

Other treatments included low-dose steroid pulse therapy and/or cholinesterase inhibitors and/or immunosuppressants, mainly taken orally. Immunosuppressants included azathioprine, cyclophosphamide, tacrolimus, and cyclosporine, etc. The RH plan combined radiotherapy and high-dose steroid pulse therapy; RC was synchronous chemoradiotherapy; OR was radiotherapy combined with other treatments; OH comprised high-dose steroid pulse therapy only; OC was chemotherapy only; OO was other treatments.

Statistical analysis

Continuous variables were converted into classified variables, and classified variables were analyzed in proportion. To identify risk factors significantly associated with MG exacerbation, univariate analysis was conducted using the χ^2 test or Fisher's exact test, and multivariate analysis was conducted using binary logistic regression to obtain independent risk factors of MG exacerbation. Based on the outcomes of the above, we created a nomogram, which was completed using R, version 4.1, and the rms installation package. In order to better utilize the nomogram in the clinic, we quantified and assigned the risk factors that were eventually included in the predictive model. The value was calculated by the regression coefficient of each risk factor in the outcomes of multivariate analysis, with a maximum of no more than 100 points and a minimum of no less than 0 points. Every variable's point was totaled and converted into a predicted probability. We used 1,000 bootstrap samples to calibrate the predictive model and assessed predictive efficiency with the concordance index (C-index).

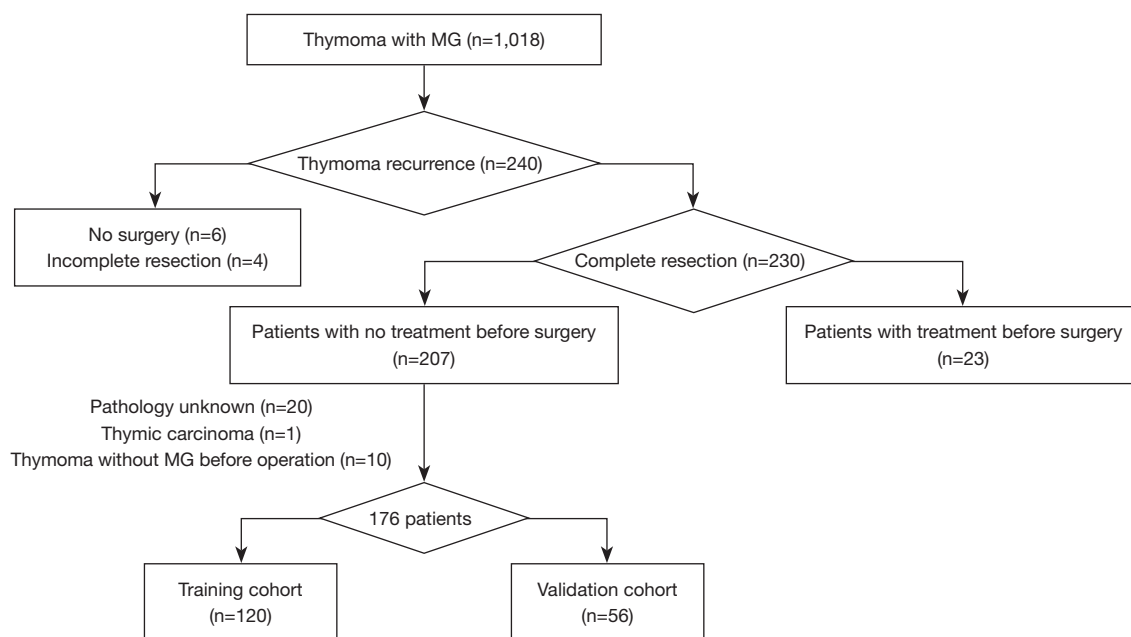We created a nomogram by using the data collected in

Figure 1 Flow chart of patient enrollment.

this study and calculated each patient's score accordingly. Receiver operating characteristic (ROC) curve analysis was used to calculate the best cut-off value according to the greatest Youden index (i.e., sensitivity + specificity − 1). The ideal cut-off value was chosen by five basic statistical indicators [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio]. In medical statistics, any diagnosis has two basic characteristics: sensitivity and specificity. Sensitivity refers to the probability of not missing a diagnosis of a disease, while specificity refers to the probability of correctly diagnosing the disease without misdiagnosis.

All P values were two-sided, and P<0.05 was used in the analysis as the test level to determine statistical significance. The analyses were conducted with SPSS26.0 and R, version 4.1 software packages.

Results

Clinical data

During the study period, 1,018 patients with thymoma accompanied by MG were treated, and 240 with postoperative recurrent thymoma were enrolled in the study. After application of the inclusion criteria, 176 patients comprised the study group: 120 patients in the training cohort and 56 patients in the validation cohort (*Figure 1*).

All the data required to establish the predictive model were available.

A summary of the baseline clinical characteristics of the two cohorts is given in *Table 2*. There was no statistical significance between them. MG exacerbation occurred in 84 (70.0%) and 41 (73.3%) patients in the two cohorts, respectively.

Development and validation of the nomogram

The pathogenic type of thymoma (P=0.006), Masaoka-Koga stage (P=0.008), as well as postoperative treatment strategy (P=0.001) were significantly connected with MG exacerbation following thymoma recurrence, according to the findings of the univariate analysis reported in *Table 3*. Types A, AB, and B1 thymomas were identified as independent risk variables for MG exacerbation by multivariate analysis (*Table 4*) [odds ratio (OR) =3.113; 95% confidence interval (CI): 1.175–8.246]. It was discovered that OO treatment was a distinct risk factor for MG exacerbation when compared with RC and OH treatment.

The thymoma pathology and postoperative treatment plan were included in the predictive model of MG exacerbation with postoperative thymoma recurrence (*Figure 2A*). One of the general techniques for assessing the discriminatory power of predictive models is the bootstrap

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Table 2 Baseline characteristics of patients with completely resected thymic epithelial tumors

Variable	Cohort, n (%)		P value
	Training (n=120)	Validation (n=56)	
Sex			0.368
Male	58 (48.3)	23 (41.1)	
Female	62 (51.7)	33 (58.9)	
Onset (age, years)			0.355
≤50	103 (85.8)	45 (80.4)	
>50	17 (14.2)	11 (19.6)	
MGFA			0.264
I	4 (3.3)	0	
IIa, IIb	25 (20.8)	10 (17.9)	
IIIa, IIIb	29 (24.2)	17 (30.4)	
IVa, IVb	41 (34.2)	14 (25.0)	
V	21 (17.5)	15 (26.7)	
Pathology			0.542
A	4 (3.3)	1 (1.8)	
AB	13 (10.8)	8 (14.3)	
B1	36 (30.0)	13 (23.2)	
B2	33 (27.5)	20 (35.7)	
B3	34 (28.3)	14 (25.0)	
Masaoka-Koga stage			0.975
I	41 (34.2)	19 (33.9)	
II	53 (44.2)	22 (39.3)	
III	12 (10.0)	10 (17.9)	
IV	14 (11.6)	5 (8.9)	
Treatment plan			0.082
RH	13 (10.8)	5 (8.9)	
RC	14 (11.7)	7 (12.5)	
OR	27 (22.5)	11 (19.7)	
OH	30 (25.0)	5 (8.9)	
OC	7 (5.8)	7 (12.5)	
OO	29 (24.2)	21 (37.5)	
MG exacerbation			0.662
Yes	84 (70.0)	41 (73.3)	
No	36 (30.0)	15 (26.7)	

MGFA, Myasthenia Gravis Foundation of America; RH, radiotherapy combined with high-dose steroid pulse therapy; RC, synchronous chemoradiotherapy; OR, radiotherapy combined with other treatments; OH, high-dose steroid pulse therapy only; OC, chemotherapy only; OO, other treatments; MG, myasthenia gravis.

Table 3 Univariate logistic regression analysis in the training cohort

Variable	Exacerbation (n=84)	No exacerbation (n=36)	χ^2	P value
Sex			3.076	0.079
Male	45 (53.6)	13 (36.1)		
Female	39 (46.4)	23 (63.9)		
Onset (age, years)			0.395	0.530
≤50	71 (84.5)	32 (88.9)		
>50	13 (15.5)	4 (11.1)		
MGFA			3.733	0.442
I	4 (4.8)	0 (0)		
IIa, IIb	16 (19.0)	9 (25.0)		
IIIa, IIIb	18 (21.4)	11 (30.6)		
IVa, IVb	29 (34.6)	12 (33.3)		
V	17 (20.2)	4 (11.1)		
Pathology			7.661	0.006
A, AB, B1	44 (52.4)	9 (25.0)		
B2, B3	40 (47.6)	27 (75.0)		
Massaoka-Koga stage			7.002	0.008
I	35 (41.7)	6 (16.7)		
II, III, IV	49 (58.3)	30 (83.3)		
Treatment plan			18.789	0.001
RH	8 (9.5)	5 (13.9)		
RC	6 (7.2)	8 (22.2)		
OR	19 (22.6)	8 (22.2)		
OH	18 (21.4)	12 (33.3)		
OC	5 (6.0)	2 (5.6)		
OO	28 (33.3)	1 (2.8)		

MGFA, Myasthenia Gravis Foundation of America; RH, radiotherapy combined with high-dose steroid pulse therapy; RC, synchronous chemoradiotherapy; OR, radiotherapy combined with other treatments; OH, high-dose steroid pulse therapy only; OC, chemotherapy only; OO, other treatments.

verification approach, which we used to demonstrate the model's correctness. The nomogram showed good accuracy in predicting the probability of MG exacerbation. The C index before adjustment was 0.77 (95% CI: 0.69–0.86), and 0.77 after internal validation. Moreover, the calibration curve was visually displayed, and the MG exacerbation risk

Table 4 Multivariate logistic regression analysis of the training cohort

Variable	β	SE	OR	95% CI	P value
Pathology (A/AB/B1 *vs.* B2/B3)	1.136	0.497	3.113	1.175–8.246	0.022
Masaoka-Koga stage (I *vs.* II/III/IV)	1.006	0.644	2.733	0.773–9.666	0.119
Treatment plan					0.070
RH *vs.* RC	−0.556	0.819	0.5736	0.115–2.856	0.497
RH *vs.* OR	0.599	0.744	1.820	0.423–7.827	0.421
RH *vs.* OH	−0.617	0.778	0.540	0.118–2.478	0.428
RH *vs.* OC	0.444	1.075	1.558	0.189–12.817	0.680
RH *vs.* OO	2.298	1.216	9.954	0.917–108.011	0.059
RC *vs.* OR	1.155	0.709	3.175	0.791–12.736	0.103
RC *vs.* OH	−0.61	0.761	0.941	0.212–4.186	0.937
RC *vs.* OC	1.000	1.054	2.718	0.344–21.448	0.343
RC *vs.* OO	2.854	1.203	17.362	1.643–183.515	0.018
OR *vs.* OH	−1.216	0.674	0.296	0.079–1.110	0.071
OR *vs.* OC	−0.155	0.985	0.856	0.124–5.900	0.875
OR *vs.* OO	1.699	1.148	5.469	0.577–51.863	0.139
OH *vs.* OC	1.060	0.970	2.888	0.431–19.325	0.274
OH *vs.* OO	2.915	1.106	18.445	2.111–161.184	0.008
OC *vs.* OO	1.854	1.348	6.388	0.455–89.678	0.169

RH, radiotherapy combined with high-dose steroid pulse therapy; RC, synchronous chemoradiotherapy; OR, radiotherapy combined with other treatments; OH, high-dose steroid pulse therapy only; OC, chemotherapy only; OO, other treatments; CI, confidence interval; OR, odds ratio; SE, standard error; β, regression coefficient.

estimated by the nomogram showed good consistency with the real-world incidence (*Figure 2B*).

Utilizing the validation cohort data to assess the MG exacerbation predictive model, the C index was 0.74 (95% CI: 0.58–0.91). Statistically speaking, there was no difference from the training cohort's C index. The calibration curve suitable for risk assessment is shown in *Figure 2C*.

Risk of MG exacerbation based on nomogram score

We regarded 60 points as the best cut-off value of the nomogram. Sensitivity, specificity, PPV and NPV were the four basic indicators to describe the predictive model and their values were 75.7% (95% CI: 66.1–83.4%), 64.7% (95% CI: 38.6–84.7%), 92.9% (95% CI: 84.5–97.1%), and 30.6% (95% CI: 16.9–48.3%) respectively in the training cohort and 84.1% (95% CI: 69.3–92.8%), 66.7% (95% CI:

35.4–88.7%), 90.2% (95% CI: 75.9–96.8%), and 53.3% (95% CI: 27.4–77.7%) in the validation cohort (*Table 5*).

Discussion

We reviewed 1,018 thymoma patients with MG in the same hospital over 9 years (from 2013 to 2021), collected and screened their clinical data, and constructed a predictive model of MG exacerbation using the data of patients with recurrent thymoma after R0 resection. The recurrence rate of thymoma in the whole database was 23.6%, which was consistent with previous reports (2-4). Multivariate analysis showed that the WHO type of thymoma and postoperative treatment plan were independent risk factors for MG exacerbation after thymoma recurrence. At present, the recurrence rate of thymoma in the cohort suggested formulating follow-up strategies more carefully and evaluating the treatment plans.
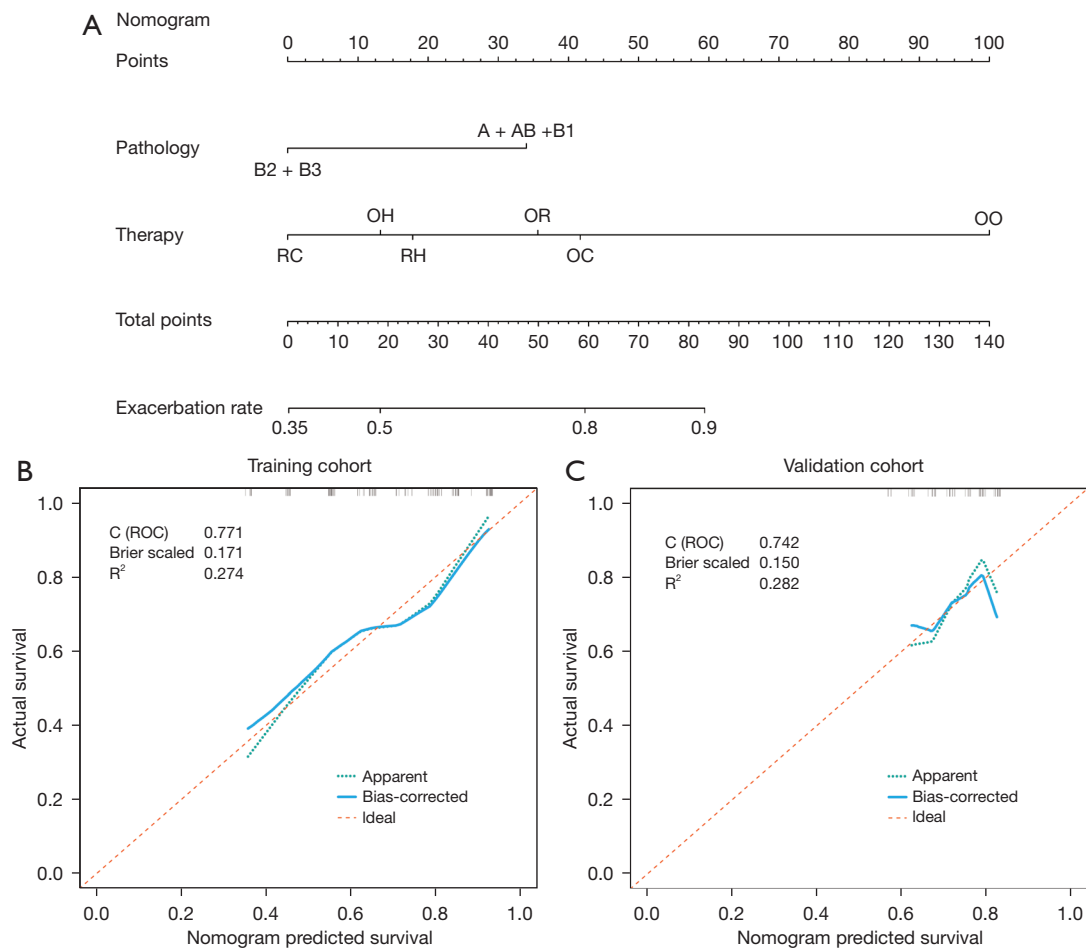
Figure 2 The probability of MG exacerbation was predicted by the nomogram based on pathology and therapy (A). The pathology and therapy values are found on the points axis, and the sum of the two values is found on the total points axis. The corresponding exacerbation rate of this value is used to predict the possibility of MG exacerbation. Calibration curve of (B) the Training Cohort and (C) the Validation Cohort. An x-axis represents the predictive potential for MG exacerbation and an y-axis represents the actual incidence of it. Perfect prediction based on an idealized model is represented by the diagonal dotted line. The ideal performance of the nomogram is represented by the solid line, and the closer the solid line fits the dotted line, the better the prediction will be. RC, synchronous chemoradiotherapy; OH, high-dose steroid pulse therapy only; RH, radiotherapy combined with high-dose steroid pulse therapy; OR, radiotherapy combined with other treatments; OC, chemotherapy only; OO, other treatments; ROC, receiver operating characteristic; MG, myasthenia gravis.

Previous studies (16-18) have shown that the pathologic classification may be related to the recurrence of thymoma, but the relationship between the pathologic classification and the prognosis of MG was unclear. Menon *et al.*'s (19) study showed that the thymoma pathologic classification did not correlate with the prognosis of MG. Xue *et al.* (7) suggested that type B2 and type B3 thymomas were independently associated with a postoperative MC, and Kim *et al.* (9) reported that type A and type AB thymoma were risk factors for postoperative MG. Some results are contradictory, and we believe that differences in sample

size and observation indicators may be the reason. It is worth noting that although there is no report on a MG exacerbation predictive model after thymoma recurrence, the results of Kim *et al.* were similar to ours. There was evidence that MG exacerbation was more likely to occur in individuals with recurrence of type A, AB, or B1 thymoma. The data revealed that 63.4% (64/101) of patients with type B2 and type B3 thymoma experienced MG exacerbation, compared with 81.3% (61/75) of those with type A, AB, and B1 thymoma. Among all the patients, type B2 thymoma accounted for the highest proportion (53/176, 30.1%),

Table 5 Accuracy of the predictive score of the nomogram for estimating the increased risk of MG after thymoma recurrence

Variable	Value (95% CI)	
	Training cohort	Validation cohort
AUC	0.771 (0.686–0.855)	0.742 (0.580–0.906)
Cut-off	60	60
Sensitivity	0.757 (0.661–0.834)	0.841 (0.693–0.928)
Specificity	0.647 (0.386–0.847)	0.667 (0.354–0.887)
Positive predictive value	0.929 (0.845–0.971)	0.902 (0.759–0.968)
Negative predictive value	0.306 (0.169–0.483)	0.533 (0.274–0.777)
Positive likelihood ratio	2.146 (1.117–4.122)	2.523 (1.122–5.673)
Negative likelihood ratio	0.375 (0.250–0.562)	0.239 (0.111–0.511)

MG, myasthenia gravis; CI, confidence interval; AUC, area under the curve.

which suggests that postoperative management of patients with this pathologic classification should be strengthened.

Liu *et al.* (18) created a predictive model for thymoma recurrence after statistically analyzing data from the Chinese Thymoma Research Alliance (ChART) database. Based on their nomogram, patients were classified into a high-risk or low-risk group. All B2 and B3 thymomas in stage T2 or T3, as well as thymic carcinoma and neuroendocrine tumors, were classified as high risk, and all other tumor types were classified as low risk. The low-risk group had a lower rate of thymoma recurrence. However, even with the large sample size of this study, the model neglected to account for the effect of postoperative adjuvant therapy on MG exacerbation. Additionally, the TNM stage (20) was less clinically practical than the Masaoka-Koga stage. We not only included preoperative clinicopathologic data, but also postoperative adjuvant therapy. The final study results were visualized with the nomogram (21) (*Figure 2A*), and the training cohort's C index was calculated to be 0.77 and 0.74 for the validation cohort. Good performance was also shown by the corresponding calibration curve.

The postoperative treatment plan was an independent predictor in our study, and OO was more likely to aggravate MG after thymoma recurrence than RC (P=0.018) or OH (P=0.008). Patients with advanced or inoperable thymoma are often treated with radiotherapy and chemotherapy, both of which are a type of immunotherapy that kills both tumor cells and lymphocytes, indirectly affecting MG symptoms. At present, several studies (10,11,22,23) have shown that postoperative radiotherapy can prolong disease-free survival (DFS) and overall survival (OS) in advanced thymoma

patients. Lu *et al.* (24) suggested that adjuvant radiotherapy within 1 month after surgery helps control postoperative MG in thymoma patients with MG. Compared with single radiotherapy, simultaneous chemotherapy can not only kill tumors but also increase radiotherapy sensitivity (25). Steroids are a common treatment for autoimmune diseases such as MG, and can induce apoptosis of lymphocytes as a lytic agent (26). At the same time, from the perspective of cell composition (14), thymomas of different pathologic types more or less contain lymphocytes, so we believe that steroid therapy is effective for thymomas, and patients with rich lymphocyte components have a more effective response than patients with fewer. Zouvelou *et al.* confirmed our hypothesis by reviewing cases and finding that preoperative prednisolone therapy can cause tumor shrinkage (26).

It is particularly noteworthy that the existing international expert consensus (5,27) does not detail specific doses or maintenance time of steroids in thymoma patients with MG. We not only evaluated the steroid treatment method and dose but also confirmed for the first time the long-term benefit of high-dose steroid pulse therapy on the prognosis of MG in patients with postoperative recurrence of thymoma. On the basis of these findings, we can design prospective clinical trials or randomized controlled trials for two major purposes: determining the applicable population for high-dose steroid pulse therapy and the difference between it and low-dose steroid pulse therapy.

Concerning the clinical application of the predictive model, we assessed the sensitivity, specificity, PPV, and NPV of MG exacerbation with a critical value of 60 (*Table 5*). Based on the sensitivity and specificity, we believe

that our nomogram has good accuracy. Patients with scores >60 points (38/176, 21.6%) were the high-risk subgroup of MG exacerbation (PPV, 91.5%). In light of this, the nomogram can be used as a tool to assess the risk of MG exacerbation after thymoma recurrence. In addition, it can also assist clinicians in postoperative adjuvant treatment selection and reduce the risk of MG exacerbation in patients.

Study limitations include single-center data, so it is important to confirm the results with data from several other institutions. Second, prospective studies are needed to further verify the nomogram's reliability. Third, despite having strong predictive accuracy, the nomogram had a false-positive rate of 35.3% and 33.3%, and a false negative rate of 24.3% and 15.9%, respectively, in the two cohorts. When predicting MG exacerbation in patients with postoperative recurrent thymoma, these statistics are still slightly high. Finally, the long postoperative OS of thymoma patients, the low probability of recurrence after R0 resection, and the long follow-up were all reasons for the loss of follow-up bias.

Conclusions

Combining the pathologic classification of thymoma and the postoperative treatment plan, we constructed a nomogram to assess the risk of MG exacerbation with postoperative recurrence of thymoma after R0 resection.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-549/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-549/dss

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-549/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of People's Hospital of Shijiazhuang (No. 2022045). Informed consent was obtained from all individual participants included in the study.

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