A clinical predictive score for postoperative myasthenic crisis
(重症筋無力症術後クリーゼ予測スコアの確立)

千葉大学大学院医学薬学府
先端医学薬学専攻
神経内科学
(主任：桑原聡教授)
金井　哲也

ABSTRACT

Objective: Myasthenia gravis (MG) is an autoimmune disease mostly caused by autoantibodies against acetylcholine receptor (AChR) associated with thymus abnormalities. Thymectomy has been proven to be an efficacious treatment for patients with MG, but postoperative myasthenic crisis often occurs and is a major complication. We aimed to develop and validate a simple scoring system based on clinical characteristics in the preoperative status to predict the risk of postoperative myasthenic crisis.

Methods: We studied 393 patients with MG who underwent thymectomy at six tertiary centers in Japan (275 patients for derivation and 118 for validation). Clinical characteristics, such as gender, age at onset and operation, body mass index, disease duration, MG subtype, severity, symptoms, preoperative therapy, operative data, and laboratory data, were reviewed retrospectively. A multivariate logistic regression with LASSO penalties was used to determine the factors associated with postoperative myasthenic crisis and score was assigned. Finally, the predictive score was evaluated using bootstrapping technique in the derivation and validation group.

Results: Multivariate logistic regression identified three clinical factors for predicting postoperative myasthenic crisis risk: (1) vital capacity < 80%, (2) disease duration < 3 months, and (3) bulbar symptoms immediately before thymectomy. The postoperative myasthenic crisis predictive score, ranging from 0 to 6 points, had areas under the curve of 0.84 (0.66 – 0.96) in the derivation group and 0.80 (0.62 – 0.95) in the validation group.

Interpretation: A simple scoring system based on three preoperative clinical characteristics can predict the possibility of postoperative myasthenic crisis.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune-mediated disease, and most patients with MG have autoantibodies against the acetylcholine receptor (AChR).[1] Anti-AChR antibody production is considered to be strongly associated with thymus abnormalities, such as thymoma and hyperplasia; therefore, thymectomy is considered the standard treatment for patients with MG.[2] Recently, it has been reported that thymectomy improved clinical outcomes over a 3-year period in patients with non-thymomatous MG.[3] Postoperative myasthenic crisis, a severe condition associated with respiratory muscle paralysis, is a major problem related to thymectomy. Patients need mechanical ventilation, and they can experience serious cardiopulmonary complications.[4] The incidence of postoperative myasthenic crisis ranges from 11.5 to 18.2%.[5,6] Patients with myasthenic crisis have high mortality rates;[7] thus, identifying triggers for myasthenia crisis is important for reducing the emergency. Several groups have reported scoring systems[8,9] or risk factors for postoperative myasthenic crisis,[10–13] such as severe MG symptoms, bulbar symptoms, high anti-AChR antibody titer, and high body mass index (BMI). However, these previous studies were conducted in single centers and had no validation group.

In this study, we aimed to develop and validate a simple clinical prediction score for postoperative myasthenic crisis risk based on data from patients with MG who underwent thymectomy at multiple centers in Japan.

PATIENTS AND METHODS

Study design and subjects

A total of 275 patients with MG and anti-AChR antibodies who underwent thymectomy at Chiba University Hospital or Keio University Hospital from January 2002 to December 2014 were enrolled as the derivation cohort of the clinical scoring system for postoperative myasthenic crisis. Then, the score was validated using 118 patients with MG who had anti-AChR antibodies and who underwent thymectomy from January 2002 to December 2014 at four centers (Tokyo Medical and Dental University Hospital, Juntendo University Hospital, Saitama Medical University Hospital, and Kitasato University Hospital). MG was diagnosed on the basis of the characteristic clinical features of MG and anti-AChR antibody positivity,

edrophonium test data, or electrophysiological test findings (repetitive nerve stimulation test and/or single-fiber electromyography). Patients who had a history of previous thymectomy (n = 1 in the derivation group), those with undiagnosed MG before thymectomy (n = 3 in the derivation group), and those with insufficient data at the prethymectomy phase (n = 2 in the validation group) were excluded from the study. This study was approved by the ethics committee of each hospital (IRB No. 2266, in Chiba University Hospital, the primary investigating institute). Patients were enrolled via an opt-out methodology.

Evaluation parameters in the derivation and validation cohorts

In the derivation cohort (n = 275), we reviewed clinical data regarding gender, age at onset and thymectomy, BMI, duration between disease onset and thymectomy, MG subgroups, Myasthenia Gravis Foundation of America (MGFA) classification,[14] myasthenic symptoms (presence of bulbar palsy [detected subjectively and/or objectively] and neck weakness [manual muscle test, MMT $\leq$ 4] within a week before thymectomy), preoperative therapy within 4 weeks before operation (pyridostigmine, oral prednisolone, immunosuppressants, intravenous high dose of methylprednisolone treatment, plasmapheresis, and intravenous immunoglobulin), operative data (procedure and concurrently resected parts [pleura, pericardium, lungs, and phrenic nerve]), anti-AChR antibody titer, and forced vital capacity (FVC) or vital capacity (VC) within a week before thymectomy. Patients with MG were classified into three subgroups: early-onset MG (EOMG) with an age at onset of less than 49 years without thymoma, late-onset MG with an age at onset of more than 50 years without thymoma, and thymoma-associated MG (TAMG). Thymus histology was classified into three types: thymoma, hyperplasic thymus, and involuted thymus. Surgeons decided the operation procedure, namely trans-sternal extended thymectomy or video-assisted thoracoscopic thymectomy. Resection of the pleura, pericardium, lungs, and phrenic nerve was performed whenever appropriate. In this study, postoperative myasthenic crisis was defined as an event requiring prolonged postoperative intubation (more than 24 hours) or re-intubation within a week after thymectomy.[5] In the validation group, the reviewers acquired the patients' data with the predictive score blinded.

Statistical analysis

All data were analyzed according to the intention-to-treat principle. Regarding patient characteristics, summary statistics were constructed using frequencies and proportions for categorical data and means and standard deviations for continuous variables. Patient characteristics were compared using Fisher's exact test for categorical outcomes, and the Wilcoxon rank sum test was used for continuous variables, as appropriate.

Development of the risk score model

To identify baseline and clinical variables associated with postoperative myasthenic crisis, all variables were considered through univariate logistic regression analysis for numerical outcomes and Fisher's exact test for categorical outcomes in the derivation dataset. Then, we used multivariate logistic regression analyses with LASSO penalties to select the potential predictors to be further used by shrinking the coefficients toward zero through setting a constraint on the sum of the absolute standardized coefficients. In the model fitting, the shrinkage estimates with LASSO provided an important way for adjusting model's overfitting and preventing extreme predictions.[15,16] We then assessed the effect potential predictors using a multivariate logistic regression analysis with using Firth's bias reduction method on the basis of a linear combination of these predictors weighted by their coefficients, using a formula as following: $Score = \sum_{i=1}^{n} x_i$, where Score is risk score, x_i is predictors, n is the number of predictors. Then we round the parameter estimate to the nearest integer as points. The optimal cutpoints used to categorize patients into a high and low risk group were defined to be the ones maximizing the Youden-Index = Sensitivity + Specificity – 1.

Validation of the risk score model

The bootstrap resampling was used to evaluate the risk score model's internal validity, which allows for computation of an unbiased estimate of predictive accuracy with showing the area under the ROC curve (AUC). The risk score model performance was evaluated by AUC with bootstrap technique using 2000 bootstrap replicate. As the external validation, using the validation dataset for the risk score model, we

calculated sensitivity, specificity, and bootstrapping AUC. The difference of AUCs in each dataset was tested by a bootstrap approach.[17]

All comparisons were planned, and the tests were two-sided. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria), SAS ver. 9.4 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA), JMP Pro 12.1.0 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA) and SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient profiles

The characteristics of the 393 patients with MG (275 in the deviation group and 118 in the validation group) are summarized in Table 1. The frequency of postoperative myasthenic crisis was similar for the derivation (6.2%) and validation groups (4.2%), whereas there were some differences between the groups regarding the frequencies of EOMG and TAMG and preoperative MGFA classification. We never experienced patients with cholinergic crisis, probably because pyridostigmine was discontinued in the perioperative period.

Predictive score for postoperative myasthenic crisis risk in the derivation cohort

The clinical characteristics of patients with and without postoperative myasthenic crisis in the derivation group are summarized in Table 2. Factors significantly associated with the occurrence of postoperative crisis were the time between MG onset and thymectomy (particularly less than 3 months), MG severity using the MGFA classification, TAMG, bulbar symptoms, neck weakness, and FVC (%FVC) or VC (%VC). These potential predictors and non-significant variables were refined by LASSO selection, which were generated by multivariate logistic regression model. Eventually, 3 risk factors (%VC or %FVC less than 80%, disease duration before thymectomy of less than 3 months, and bulbar symptoms immediately before thymectomy) were included in the final LASSO model for postoperative myasthenic crisis risk

(Table 3). We assigned a referent risk using the parameter estimate with a base risk of 0 points, yielding a total score ranging from 0 to 6 points (Table 4). These three factors were incorporated into the postoperative myasthenic crisis predictive score. The bootstrap resampling of derivation set showed an AUC (95% confidence interval [CI]) of 0.84 (0.66 – 0.96). The sensitivity and specificity at each point of this model were shown in Figure 1; postoperative myasthenic crisis score of 3 was optimal cut-point with a sensitivity of 88.2 (66.9–96.7)%, a specificity of 83.3 (81.9–83.9)%, a positive predictive value of 25.9 (19.6–28.3)%, a negative predictive value of 99.1 (97.4–99.7)%, a positive likelihood ratio of 5.3 (3.7–6.0), and a negative likelihood ratio of 0.14 (0.04–0.4) (Table 5; $p < 0.0001$). The fraction of postoperative crisis was 0.9% and 25.9% in low (less than 3 points) and high (3 or more points) score group, respectively. The observed fraction of postoperative myasthenic crisis at each point was shown in Figure 2.

Validation cohort

The characteristics of patients with and without postoperative myasthenic crisis in the validation group are summarized in Table 6. There were no significant differences between the crisis and non-crisis group in disease duration ($p = 0.16$), thymoma ($p = 0.66$), involuted thymus ($p = 1.00$), and bulbar symptom ($p = 0.067$), except for %VC or %FVC ($p = 0.0052$). BMI and pyridostigmine dose were significantly higher in the crisis group ($p = 0.047$ and 0.049, respectively). For the validation cohort, the postoperative myasthenic crisis predictive score had a bootstrapping AUC (95% CI) of 0.80 (0.62 - 0.95). The bootstrapping AUCs were not different between the derivation and validation group ($p = 0.39$). This model also indicated a cut-off of 3 points with a sensitivity of 80.0% and a specificity of 87.8% ($p = 0.0005$). The low (less than 3 points) and high (3 or more points) score group experienced 1.0% and 22.2% of postoperative myasthenic crisis, respectively. The observed and predicted fraction for postoperative myasthenic crisis based on the predictive score in validation group patients with MG are shown in Figures 2 and 3.

DISCUSSION

This large multicenter study established a clinical scoring system predicting the risk of postoperative myasthenic crisis. Notably, the clinical score, which includes %VC < 80%, a disease duration of less than 3

months, and bulbar palsy immediately before thymectomy, displayed extremely good discriminative ability for postoperative myasthenic crisis in both the derivation and validation cohorts.

A recent randomized trial proved that thymectomy improved clinical outcomes even in patients with non-thymomatous MG;[3] therefore, thymectomy will be performed much more frequently in patients with MG. To reduce treatment-related mortality, the prediction of postoperative myasthenic crisis is important. In this regard, this scoring system could be a good practical tool for identifying groups at high risk for myasthenic crisis.

In previous studies, bulbar symptoms, low VC, disease severity (Osserman classification), operative factors (operation time and blood loss), and disease duration were identified as strong predictors of the risk of postoperative myasthenic crisis.[5,6,8–13] Bulbar symptoms, which contribute to the risk of postoperative myasthenic crisis,[5,10–12] are derived from weakness of the pharyngeal muscles, and they cause airway collapse or larynx obstruction due to weakness of the vocal cord abductor muscles. Myasthenic crisis is an event of respiratory failure requiring intubation or mechanical ventilation; hence, pulmonary function, including VC, was another critical risk factor for postoperative myasthenic crisis.[8–10,13] The severity of MG could be a major risk factor for myasthenic crisis. Indeed, the Osserman classification has been the risk factor and is judged on the basis of the severity and progress of the disease, but instead of this classification, the MGFA classification, which is more frequently used, displayed significant changes in univariate logistic regression in our study. Surgical variables were also identified as risk factors for postoperative myasthenic crisis;[5,12] however, we tried to predict the postoperative myasthenic crisis risk using preoperative clinical features and could not collect full surgical data in some centers, leading to the exclusion of surgical data from this study. A longer duration of MG was reported to contribute to the risk of postoperative myasthenic crisis.[8.9] A long disease duration is generally related to a poor treatment response,[18] probably due to the accumulation of damage at the neuromuscular junction. On the contrary, some reports, in accordance with our study, revealed a tendency for a short disease duration to be related to the risk of postoperative myasthenic crisis.[5,12] A short disease duration can reflect rapid progression of MG or an insufficient treatment response to suppress disease activity. Further analysis of the relationship between myasthenic crisis and disease duration is needed.

Other factors related to the risk of postoperative myasthenic crisis were high BMI[9] and anti-AChR antibodies titers.[5,6] There was no association between these factors and postoperative myasthenic crisis risk in our study. This discrepancy may be derived from differences in body constitution between Caucasians and Asians. The mean BMI of our patients was 22.9, whereas that of patients in Leuzzi's study was 25.9.[9] Concerning anti-AChR antibody, it has been reported that serum anti-AChR antibody levels did not correlate with the risk of myasthenic crisis[19, 20] or the severity of MG.[21]

Leuzzi's and Leventhal's studies indicated that long disease duration, high BMI, high pyridostigmine dosage, severe MG symptoms, and low VC were risk factors for myasthenic crisis.[8,9] Unfortunately, their scores did not predict the postoperative myasthenia crisis in our cohort (p = 0.69 and 0.68, respectively, analyzed by logistic regression and Fisher's exact test). The discrepancy may be derived from the difference in patients' profiles. A major difference between our study and those reported previously was disease duration at thymectomy: the proportion of short duration MG patients (less than 1 year) was 66.1 % in our study, whereas in previous studies it was 29%.

We aimed to predict the risk of postoperative myasthenic crisis using preoperative clinical features. Our scoring model exhibited superior predictive power, with a sensitivity of 88.2% and a specificity of 83.3%, compared with Leuzzi's score, with a sensitivity of 36.8% and a specificity of 93.8%. Our predictive score had a high negative predictive value, meaning that it can rule out the risk of postoperative myasthenic crisis when the score is low (less than 3 points). Although positive predictive value of our score was relatively low, the expected risk of postoperative myasthenic crisis increased as the score elevated (Figure 3). If patients have the high postoperative myasthenic crisis score (3 or more points), we are able to inform the patients of the observed possibility of postoperative myasthenic crisis as approximately 25%, which is much higher than low score group (approximately 1%) and propose whether further additional treatment (e.g., intravenous immunoglobulin or plasmapheresis) before thymectomy should be done or not. Although most patients with high score group may not need further treatment for preventing crisis, considering additional treatment in these patients is reasonable because postoperative myasthenic crisis is very severe and fatal condition. In fact, some reports showed that preoperative intravenous immunoglobulin or plasmapheresis reduced the postoperative myasthenic crisis.[22-24] However, it is unclear that the further

additional treatment can reduce the risk of postoperative myasthenic crisis in high score group. To clarify this, a prospective interventional study is needed.

Some limitations in this study need to be addressed. (1) Our predictive score for postoperative myasthenic crisis was based on retrospective research, which might restrict its general applicability. (2) Patients who did not have sufficient clinical data were excluded, which may have resulted in selection bias. (3) The number of patients with myasthenic crisis in the validation set was small, which led that the observed fraction of postoperative myasthenic crisis was not linear and the CIs of the predicted postoperative MG crisis fraction at high scores were wide in the validation set. (4) The model was based only on Japanese patients with MG. The crisis risk of patients with MG from other areas might depend on other factors including treatment methods and surgical procedure. (5) The lack of standardized medical treatment for patients enrolled in the study might be a confounding factor. Prospective and large-scale analysis is required to establish a more evident model for postoperative MG crisis risk, and research concerning adequate treatment for patients with a high risk of postoperative MG crisis is also needed.

In conclusion, our myasthenic crisis clinical predictive score including three factors, namely %FVC or %VC of less than 80%, a duration of MG before thymectomy of less than 3 months, and bulbar symptoms immediately before thymectomy, displayed accuracy in both the derivation and validation groups, indicating that the score can be used as a comprehensive and reliable tool for MG patients with thymectomy to predict the risk of postoperative myasthenic crisis in clinical practice.

ACKNOWLEDGEMENT

KY and NH receive donations for endowed research departments from Nihon Pharmaceutical Co., Ltd, Asahi Kasei Medical Co., Ltd, and Japan Blood Products Organization.

AUTHOR CONTRIBUTIONS

TK, AU, SS, NK, and SaK contributed to the study concept, design, and writing of the manuscript. YS performed statistical analysis and drafted the manuscript. TK, AU, SS, NK, KH, FO, YO, JN, NS, YT, SaI,

TY, TO, KY, NH, ShI, SO, KyN, JK, KaN, and IY contributed to acquisition of data and analysis. All authors approved the final version.

POTENTIAL CONFLICTS OF INTERESTS

Nothing to report.

REFERENCES

1. Vincent A, Palace J, Hilton-Jones D. Myasthenia gravis. Lancet 2001; 357: 2122–28.
2. Gilhus NE, Verschuuren JJ. Myashenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 2015; 10: 1023–36.
3. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med 2016; 375: 511–22.
4. Gritti *P*, Sgarzi M, Carrara B, et al. A standardized protocol for the perioperative management of myasthenia gravis patients. Experience with 110 patients. Acta Anaesthesiol Scand 2012; 56: 66–75.
5. Watanabe A, Watanabe T, Obama T, et al. Prognostic factors for myasthenic crisis after transsternal thymectomy in patients with myasthenia gravis. J Thorac Cardiovasc Surg 2004; 127: 868–76.
6. Ando T, Omasa M, Kondo T, et al. Predictive factors of myasthenic crisis after extended thymectomy for patients with myasthenia gravis. Eur J Cardiothorac Surg 2015; 48: 705–9.
7. Joel VC. Myasthenia gravis: management of myasthenic crisis and perioperative care. Semin Neurol 2004; 24: 75–81.
8. Leventhal SR, Orkin FK, Hirsh RA. Prediction of the need for postoperative mechanical ventilation in myasthenia gravis. Anesthesiology 1980; 53: 26–30.
9. Leuzzi G, Meacci E, Cusumano G, et al. Thymectomy in myasthenia gravis: proposal for a predictive score of postoperative myasthenic crisis. Eur J Cardiothorac Surg 2014; 45: e76–88.
10. Loach AB, Young AC, Spalding JM, Smith AC. Postoperative management after thymectomy. Br Med J 1975; 1: 309–12.
11. Gracey DR, Divertie MB, Howard FM Jr, Payne WS. Postoperative respiratory care after transsternal thymectomy in myasthenia gravis. A 3-year experience in 53 patients. Chest 1984; 86: 67–71.
12. Yu S, Lin J, Fu X, et al. Risk factors of myasthenic crisis after thymectomy in 178 generalized myasthenia gravis patients in a five-year follow-up study. Int J Neurosci. 2014; 4: 792–98.

13. Lee HS, Lee HS, Lee HE, et al. Predictive factors for myasthenic crisis after videoscopic thymectomy in patients with myasthenia gravis. Muscle Nerve 2015; 52: 216–20.
14. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards, Task Force of Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology 2000; 55: 16–23.
15. Steyerberg E. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. 1st ed. New York: Springer-Verlag New York; 2009.
16. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med. 2004; 66: 411-21.
17. Pepe M, Longton G, Janes H. Estimation and Comparison of Receiver Operating Characteristic Curves. Stata J. 2009; 9: 1.
18. Tellez-Zenteno JF, Remes-Troche JM, Garcia-Ramos G, et al. Prognostic factors of thymectomy in patients with myasthenia gravis: a cohort of 132 patients. Eur Neurol 2001; 46: 171–7.
19. O'Riordan JI, Miller DH, Mottershead JP, et al. The management and outcome of patients with myasthenia gravis treated acutely in a neurological intensive care unit. Eur J Neurol 1998; 5: 137–42.
20. Younger DS, Raksadawan N. Medical therapies in myasthenia gravis. Chest Surg Clin N Am 2001; 11: 329–36.
21. Qureshi AI, Suri MF. Plasma exchange for treatment of myasthenia gravis: pathophysiologic basis and clinical experience. Ther Apher 2000; 4: 280–6.
22. Huang CS, Hsu HS, Kao KP, et al. Intravenous immunoglobulin in the preparation of thymectomy for myasthenia gravis. Acta Neurol Scand 2003; 108:136-8.
23. Sarkar BK, Sengupta P, Sarkar UN. Surgical outcome in thymic tumors with myasthenia gravis after plasmapheresis- a comparative study. Interact Cardiovasc Thorac Surg 2008; 7: 1007-10.
24. Yeh JH, Chen WH, Huang KM, et al. Prethymectomy plasmapheresis in myasthenia gravis Journal of Clinical Apheresis 2005; 20: 217-21.

Table 1. Demographic data of all patients with MG

	Derivation cohort (*n* = 275)	**Validation cohort (*n* = 118)**	***p***
Age at onset, years ± SD	47.2 ± 16.1	50.1 ± 14.8	0.093
Age at thymectomy, years ± SD	49.0 ± 15.5	51.6 ± 14.6	0.12
Sex, M:F	106: 169	46:72	1.00
Body mass index, mean ± SD	22.9 ± 4.3	23.2 ± 3.7	0.96
Time between MG onset and thymectomy, months (range)	6.3 (4.0–19.0)	6.5 (3.2–14.0)	0.18
Early-onset MG, *n* (%)	81 (29.5%)	21 (17.8%)	0.013
Late-onset MG, *n* (%)	49 (17.8%)	19 (16.1%)	0.67
Thymoma-associated MG, *n* (%)	145 (52.7%)	78 (66.1%)	0.013
Preoperative MGFA, *n* (%)			0.038
I	54 (19.6%)	16 (13.6%)	
II	155 (56.4%)	83 (70.3%)	
III	46 (16.7%)	15 (12.6%)	
IV	6 (2.2%)	0 (0.0%)	
V	14 (5.1%)	4 (3.4%)	
Surgical approach; trans-sternal: VATS, *n*	193:82	80:38	0.63
Postoperative myasthenic crisis, *n* (%)	17 (6.2%)	5 (4.2%)	0.43

MG: myasthenia gravis, MGFA: Myasthenia Gravis Foundation of America classification, SD: standard deviation, VATS: video-assisted thoracic surgery

Table 2. Comparison of patients with and without postoperative myasthenic crisis in the derivation group

	Crisis (*n* = 17)	Non-crisis (*n* = 258)	Odds ratio (95% CI)	*p*
Age at onset ± SD	45.4 ± 16.4	47.3 ± 16.1	1.00 (0.97–1.03)	0.62
Age at thymectomy ± SD	45.8 ± 16.1	49.2 ± 15.5	1.01 (0.98–1.04)	0.38
Sex, M:F	8:9	98:160	0.6 (0.2–1.8)	0.46
Body mass index, mean ± SD	22.6 ± 3.7	22.9 ± 4.3	1.01 (0.91–1.15)	0.80
Time between MG onset and thymectomy, months (range)	4.1 (3.0–8.3)	10.4 (4.5–31.9)	1.05 (1.00–1.14)	0.020
0–3 months, *n* (%)	6 (35.3%)	16 (6.2%)	8.2 (2.7–25.1)	0.0009
0–6 months, *n* (%)	12(70.6%)	114 (44.2%)	3.0 (1.0–8.8)	0.033
0–12 months, *n* (%)	15 (88.2%)	91 (35.2%)	4.0 (0.9–18.2)	0.062
Early-onset MG, *n* (%)	3 (17.7%)	78 (30.2%)	0.4 (0.1–1.7)	0.24
Late-onset MG, *n* (%)	1 (5.9%)	48 (18.6%)	0.2 (0.03–2.1)	0.13
Thymoma-associated MG, *n* (%)	13 (76.4%)	132 (51.2%)	3.1 (0.9–9.7)	0.037
MGFA, *n* (%)				0.0010
I	0(0.0%)	54(20.9%)	0	0.029
II	7(41.2%)	148(57.4%)	0.5 (0.1–1.4)	0.19
III	7(41.2%)	39(15.1%)	3.8 (1.3–10.6)	0.015
IV	2(11.8%)	4(1.6%)	8.4 (1.4–49.9)	0.040
V	1(5.9%)	13(5.0%)	1.2 (0.1–10.9)	0.82
Bulbar symptoms, *n* (%)	10 (58.8%)	55(21.3%)	5.2 (1.9–14.4)	0.0013
Neck weakness, *n* (%)	8 (47.1%)	55(21.3%)	3.2 (1.2–8.8)	0.023
Pyridostigmine, mean ± SD	112.9 ± 89.7	81.0 ± 77.6	0.99 (0.98–1.00)	0.10
Prednisolone, mean ± SD	15.8 ± 21.2	21.3 ± 21.8	1.01 (0.98–1.03)	0.31
Preoperative plasmapheresis, *n* (%)	5 (29.4%)	52 (20.2%)	1.6 (0.5–4.8)	0.38
Immunoglobulin, *n* (%)	1 (5.9%)	8 (3.1%)	1.9 (0.2–16.5)	0.44
High-dose methylprednisolone, *n* (%)	0 (0.0%)	6 (2.3%)	0	1.00
Immunosuppressive agents, *n* (%)	2 (11.8%)	13 (5.0%)	2.5 (0.3–10.2)	0.23
Thymus histology				0.089
Thymoma, *n* (%)	13 (76.5%)	132 (51.2%)	3.1 (0.9–9.7)	0.037
Hyperplasic thymus, *n* (%)	2 (11.8%)	30 (11.6%)	1.0 (0.2–4.6)	0.98
Involuted thymus, *n* (%)	2 (11.8%)	96 (37.2%)	0.2 (0.05–1.0)	0.021
Surgical approach				
Trans-sternal, *n* (%)	13 (76.5%)	180 (69.8%)	1.4 (0.4- 4.4)	0.54
VATS, *n* (%)	4 (23.5%)	78 (30.2%)	0.7 (0.2- 2.2)	0.54
Pleura resection, *n* (%)	2 (11.8%)	18 (7.0%)	1.7 (0.3–8.3)	0.49
Pericardium resection, *n* (%)	3 (17.7%)	16 (6.2%)	3.2 (0.8–12.4)	0.12
Phrenic nerve resection, *n* (%)	2 (11.8%)	6 (2.3%)	5.6 (1.0–30.1)	0.080
Pulmonary resection, *n* (%)	3 (17.7%)	20 (7.8%)	2.5 (0.6–9.6)	0.15
%VC or %FVC, % ± SD	72.2 ± 15.2	94.4 ± 17.0	1.07 (1.04–1.11)	< 0.0001
%VC or %FVC < 80%, *n* (%)	14 (82.4%)	43 (16.7%)	23.3 (6.4–84.6)	< 0.0001
Anti-AChR antibody, nmol/L ± SD	86.6 ± 117.8	75.8 ± 160.1	0.99 (0.99–1.00)	0.78

CI: confidence interval, FVC: forced vital capacity, MG: myasthenia gravis, VATS: video-assisted thoracic surgery, VC; vital capacity

Table 3. Estimates of the parameters of the multivariable model

Risk factor	Parameter estimate	Standard error	Adjusted OR	95% CI	*p*
Intercept	-4.4757	0.5774			
Preoperative %FVC or %VC < 80%	2.5276	0.6408	12.5	3.57 - 43.9	<0.0001
Disease duration < 3 months	1.6449	0.66	5.18	1.42 - 18.8	0.012
Preoperative bulbar symptom	0.9426	0.5757	2.57	0.83 - 7.93	0.10

AUC: area under the curve, CI: confidence interval, FVC; forced vital capacity, MG; myasthenia gravis, VC; vital capacity
Preoperative = within a week before thymectomy

Table 4. Postoperative myasthenic crisis predictive score

	Category	Score
Preoperative bulbar symptom	Yes	1
	No	0
Preoperative %FVC or %VC	<80%	3
	≥80	0
Duration of MG	<3 months	2
	≥3 months	0

FVC; forced vital capacity, MG; myasthenia gravis, VC; vital capacity
Preoperative = within a week before thymectomy

Table 5. Numbers of patients according to postoperative myasthenic crisis and predictive score in derivation group

Predictive score	Postoperative myasthenic crisis		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
	Yes	No				
≥3 points	15	43	88.2 % (66.9–96.7)	83.3% (81.9–83.9)	25.9% (19.6–28.3)	99.1% (97.4–99.7)
≤2 points	2	215				

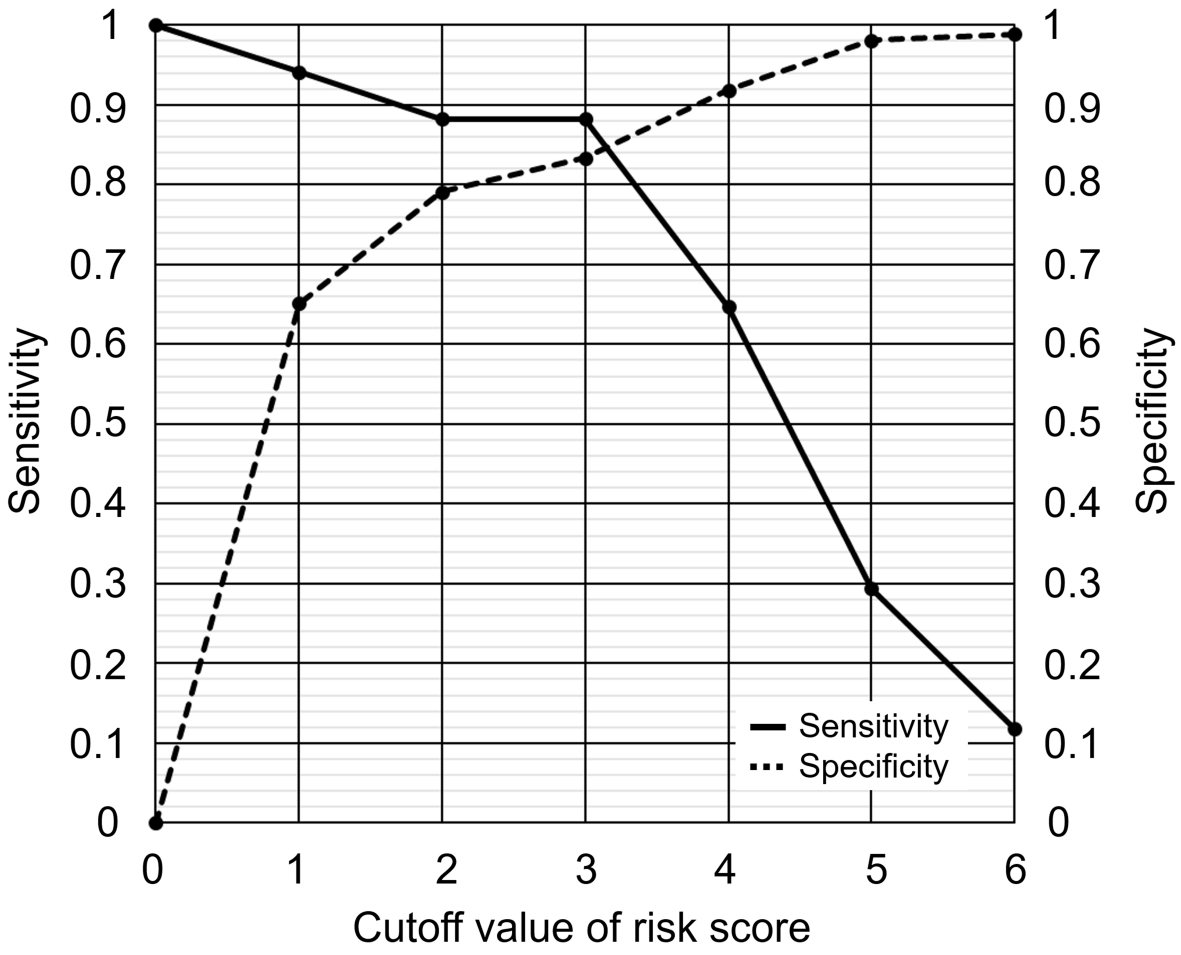
CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

Table 6. Comparison of patients with and without postoperative myasthenic crisis in the validation group

	Crisis (*n* = 5)	**Non-crisis (*n* = 113)**	**Odds ratio (95% CI)**	***p***
Age at onset ± SD	43.5 ± 9.3	50.4 ± 1.4	1.00 (0.97–1.03)	0.31
Age at thymectomy ± SD	44.0 ± 9.5	51.9 ± 14.7	1.01 (0.98–1.04)	0.24
Sex; M:F, *n*	3:2	43:70	0.6 (0.2–1.8)	0.37
Body mass index, mean ± SD	26.7 ± 4.2	23.0 ± 3.6	1.01 (0.91–1.15)	0.047
Time between MG onset and thymectomy, months (range)	5.6 (2.7–9.3)	23.4 (3.3–14.5)	1.05 (1.00–1.14)	0.16
0-3 months, *n* (%)	1 (20.0%)	16 (14.2%)	1.5 (0.2–14.4)	0.72
0-6 months, *n* (%)	3(60.0%)	49 (43.4%)	1.9 (0.3–12.2)	0.46
0-12 months, *n* (%)	4 (80.0%)	79 (69.9%)	1.7 (0.2–15.9)	0.61
Early-onset MG, *n* (%)	1 (20.0%)	20 (17.7%)	1.2 (0.1–10.9)	1.00
Late-onset MG, *n* (%)	0 (0.0%)	19 (16.8%)	0	1.00
Thymoma-associated MG, *n* (%)	4 (80.0%)	74 (65.5%)	2.1 (0.22–19.5)	0.66
MGFA, *n* (%)				0.29
I	0(0.0%)	16(14.2%)	0	1.00
II	4(80.0%)	79(69.9%)	1.7 (0.2–15.9)	1.00
III	1(20.0%)	14(12.3%)	1.7 (0.2–16.9)	0.49
IV	0(0.0%)	0(0.0%)	0	*N.A.*
V	0(0.0%)	4(3.5%)	0	1.00
Bulbar symptoms, *n* (%)	2 (40.0%)	9(7.9%)	7.7 (1.1–52.2)	0.067
Pyridostigmine, mean ± SD	192.0 ± 50.2	134.4 ± 75.5	1.00 (0.96–1.08)	0.049
Prednisolone, mean ± SD	10.0 ± 22.4	13.2 ± 17.6	0.98 (0.95–0.99)	0.68
Immunosuppressive agents, *n* (%)	1 (20.0%)	28 (24.3%)	0.64 (0.06–6.00)	1.00
Thymus histology				0.61
Thymoma, *n* (%)	4 (80.0%)	75 (66.3%)	2.1 (0.22–19.5)	0.66
Hyperplasic thymus, *n* (%)	0 (0.0%)	9 (8.0%)	0	1.00
Involuted thymus, *n* (%)	1 (20.0%)	29 (25.7%)	0.7 (0.07–6.7)	1.00
Surgical approach				
Trans-sternal, *n* (%)	3 (60.0%)	77(68.1%)	0.7 (0.1–4.4)	0.65
VATS, *n* (%)	2 (40.0%)	36 (31.8%)	1.4 (0.2–8.9)	0.65
%VC or %FVC, % ± SD	79.5 ± 17.5	98.8 ± 16.3	1.1 (1.02–1.21)	0.0052
%VC or %FVC < 80%, *n* (%)	4 (80.0%)	13 (11.5%)	30.7 (3.1–296.7)	0.0014

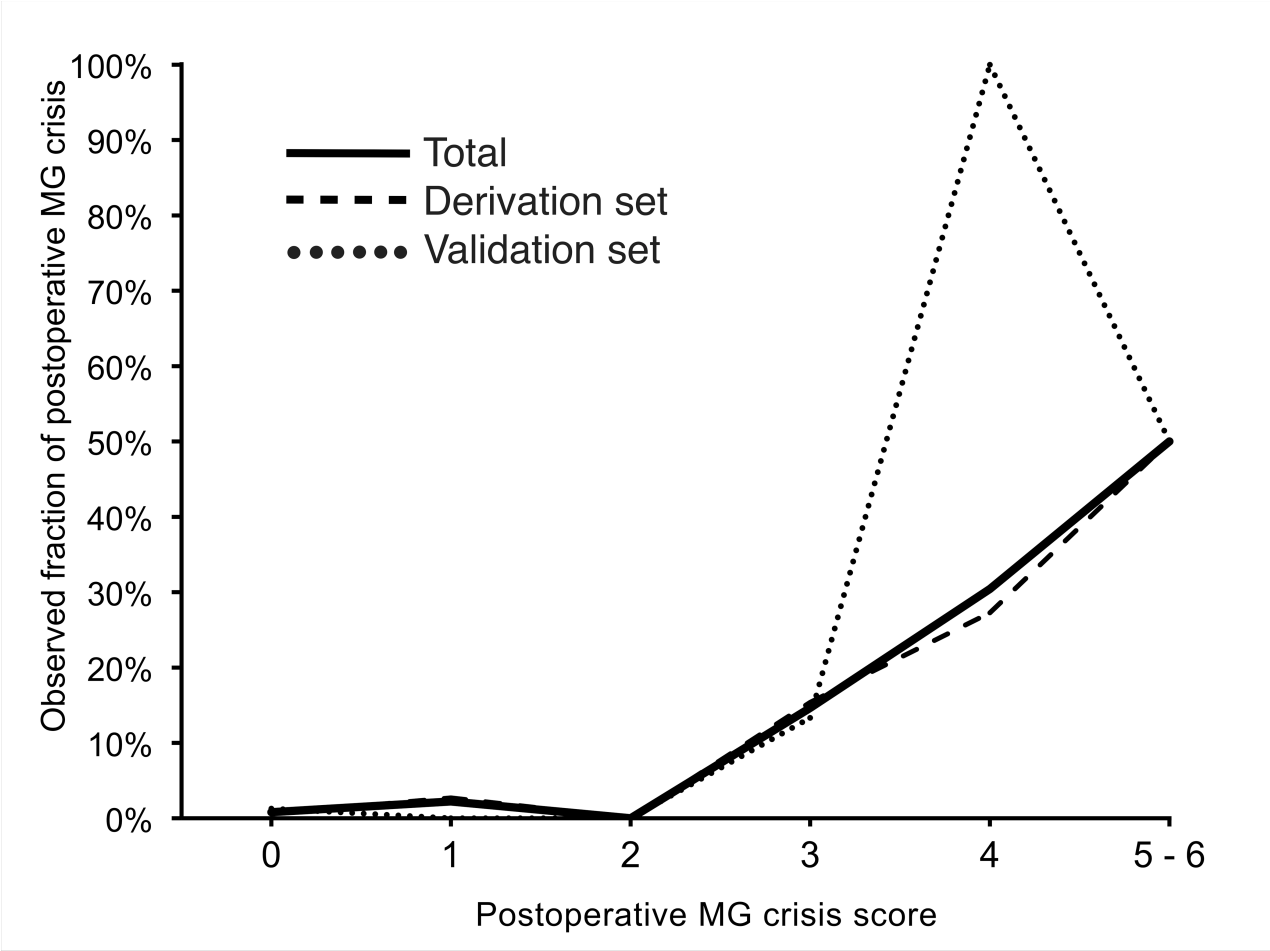
CI: confidence interval, SD: standard deviation, FVC: forced vital capacity, *N.A.*: not available, MG: myasthenia gravis, VATS: video-assisted thoracic surgery, VC; vital capacity

Figure 1. The sensitivity and specificity at each point of the postoperative myasthenic crisis predictive score in the derivation group



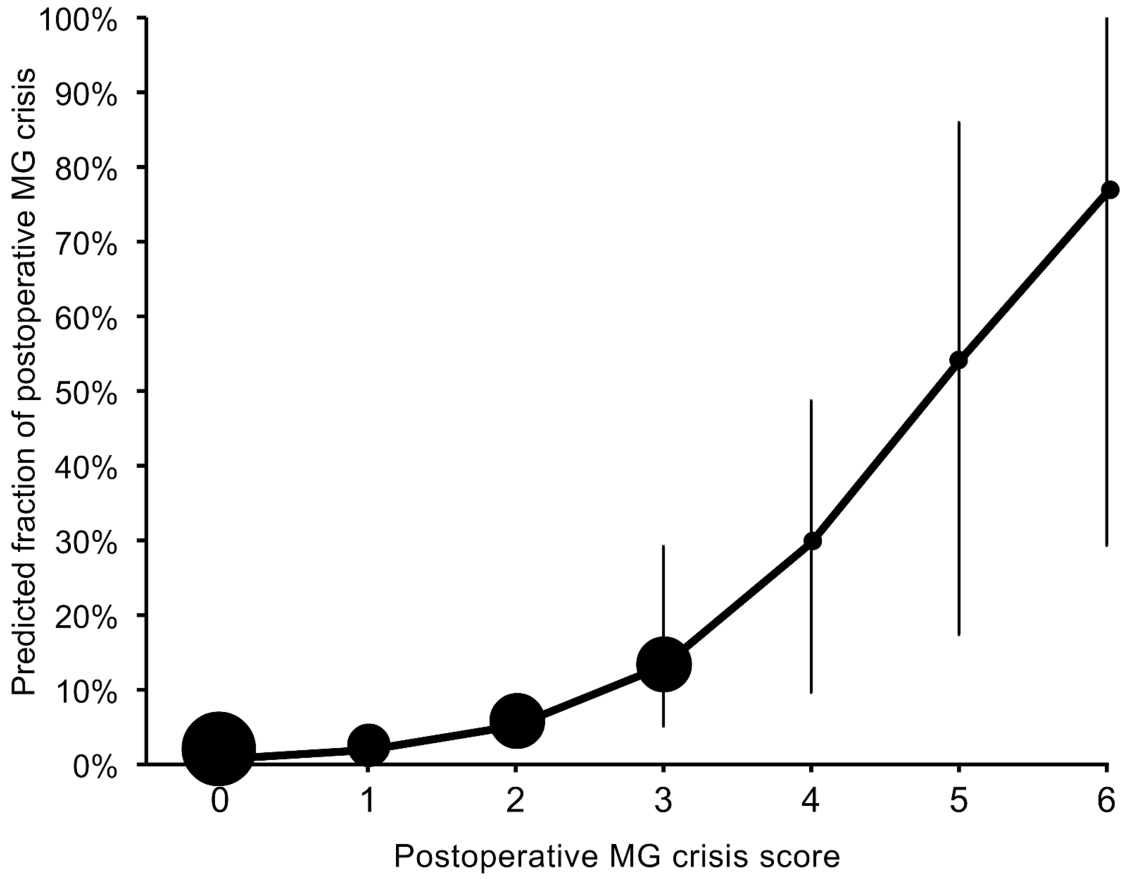
The cut-off point of 3 showed the strongest discrimination power with sensitivity (88.2%) and specificity (83.3%).

Figure 2. Observed ratio of postoperative myasthenic crisis.



The observed fractions of postoperative myasthenic crisis in total set, derivation set, and validation set are shown.

Figure 3. Predicted risk of postoperative myasthenic crisis



The probability of developing postoperative myasthenic crisis in the validation group (n = 118) was calculated using the predictive score. Point sizes are proportional to the number of patients with a specific score. Vertical bars indicate the 95% confidence interval.

Annals of Neurology vol.82 No.5
平成 29 年 11 月 10 日公表済