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Analysis of influencing factors of postoperative myasthenic crisis in 564 patients with myasthenia gravis in a single center

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Abstract

Objective: To study the influencing factors of myasthenic crisis in patients with myasthenia gravis during perioperative period.

Methods: A total of 564 myasthenia gravis (MG) patients who underwent standard expanded resection of thymoma/thymoma in the Department of Thoracic Surgery of Beijing Hospital from January 2011 to March 2022 were retrospectively included in the study. Clinical indicators such as gender, age, thymoma, American Society of Anesthesiologists (ASA) score, operation time, intraoperative blood loss, and some others were recorded.

Results: Osserman-stages IIB + III + IV (odds ratio [OR] 16.091, 95% confidence interval [CI] 5.170–50.076, p value < 0.001), the dosage of pyridostigmine bromide more than 240 mg (OR 6.462, 95% CI 3.110–13.427, p value < 0.001), ASA score 2 and 3 (OR 3.203, 95% CI 1.461–7.020, p value = 0.004), low diffusion lung capacity for carbon monoxide (DLCO%) (OR 0.981, 95% CI 0.963–1.000 p value = 0.049), and blood loss greater than 1000 ml (OR 16.590, 95% CI 1.911–144.011, p value = 0.011) were independent risk factors for myasthenic crisis.

Conclusions: Patients with poor Osserman stages, higher preoperative dosage of pyridostigmine bromide, higher ASA score, poor pulmonary function (low DLCO%), and more intraoperative bleeding should be highly vigilant for the occurrence of postoperative myasthenic crisis.

KEYWORDS
ASA score, myasthenia gravis, myasthenic crisis, thymectomy, thymoma

INTRODUCTION

Myasthenia gravis (MG) is a rare autoimmune disorder of the neuromuscular junction (NMJ) characterized by fluctuating weakness and fatigability of skeletal muscles due to autoantibodies directed against the acetylcholine receptor (AChR) or associated proteins that interfere with the function of the NMJ.[1,2] Since the first thymectomy of MG was reported by Saubruch in Germany in 1912, in which the symptoms of MG were significantly improved after the removal of hyperplastic thymus tissue, the surgical treatment of MG has experienced a long process of development. With the deepening understanding of the role of thymus in the pathogenesis of MG, thymectomy has been paid more and more attention as one of the treatment methods for MG. Ten years after thymectomy, the remission rate of MG symptoms can reach 69.1%.[3] In 2016, a multicenter prospective study published by Wolfe et al.[4] greatly strengthened the level of evidence on the improvement effect of surgery on MG. Surgery and anesthesia can cause great trauma to MG patients, who are prone to postoperative myasthenic crisis (POMC), which is the most serious complication and one of the main causes of death in MG patients after surgery. Once POMC occurs, it will certainly

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affect the recovery of patients and increase the length of hospital stay and cost of patients. It is therefore particularly important to reduce the occurrence of POMC or to make early warning of POMC in advance.

METHODS

A total of 564 MG patients who underwent standard extended thymic/thymoma resection at the Department of Thoracic Surgery, Beijing Hospital from January 2011 to March 2022 were included. The Institutional Review Board approval number is 2020BJYYEC-010-01.

The surgical methods included median sternotomy, bilateral thoracoscopy, right or left thoracoscopy, and subxiphoid thoracoscopy. The surgical resection range was as follows: the upper margin of the surgical range was the lower margin of the thyroid gland, the lower margin to the surface of the diaphragm, about 1 cm in front of the phrenic nerve on both sides, the front was behind the sternum, the upper part of the deep layer was the perivascular fat of the brachiocephalic trunk and innominate vein, the lower part was the pericardial surface and the bilateral diaphragmatic angle fat. In the majority of patients with thymoma, the thymic tissue including the tumor was completely resected, and in some patients the lung tissue, pericardium, and phrenic nerve invaded by the tumor were resected at the same time, and even the tumor was completely resected by superior vena cava replacement.

Patients with POMC were defined as those who need endotracheal intubation or noninvasive ventilator-assisted breathing for more than 24 h from the end of surgery to 1 month after surgery, or those who need endotracheal intubation again due to inability to breathe or the discharge of too much secretion after removal of the endotracheal intubation. The American Society of Anesthesiologists (ASA) scores were determined after excluding MG. Some patients with Osserman type IIb or above and unsatisfactory MG symptom control were treated with gamma-globulin before operation.

All patient information, including gender, age, thymoma, other autoimmune diseases, history of myasthenic crisis, preoperative MG course, Osserman classification, preoperative pyridostigmine bromide dosage, immunosuppressants, glucocorticoid, comorbidities, preoperative ASA score, preoperative pulmonary function, operation time, intraoperative blood loss, drainage volume over the first 3 days after operation, postoperative hospital stay, myasthenic crisis, and other complications (including pneumonia, unexpected secondary surgery, atrial arrhythmias requiring treatment, myocardial infarction, deep venous thrombosis requiring treatment, other gastrointestinal complications, chylothorax, etc.), was collected in detail.

Statistical analysis

SPSS 26.0 statistical software was used for statistical analysis. For continuous variables, the normality test shall be carried out. If it conforms to the normal distribution, it shall be expressed as the mean ± standard deviation, and t-test shall be carried out; If it does not conform to the normal distribution, the Mann Whitney U test is used to describe it in the form of median combined with numerical range. Specific values of categorical variables are recorded in the statistical table, and the χ^2 test or Fisher's exact test were performed. Univariate and multivariate logistic regression models were used to analyze the risk factors of postoperative myasthenic crisis. All statistical tests were two-way, and p values less than 0.05 were considered statistically significant.

RESULTS

A total of 564 patients with MG (292 men, 272 women) were included in this study. The mean age was 47.1 years (15–86 years). One hundred and seventy-seven MG patients were associated with thymoma. POMC occurred in 80 (14.2%) patients. The data for the patients are shown in Table 1.

Gender, age, thymoma, other autoimmune disorders, preoperative history of myasthenic crisis, preoperative course, Osserman stages, preoperative daily dose of pyridostigmine bromide, immunosuppressants and glucocorticoid, ASA score, forced expiratory volume in 1 s (FEV1), FEV1/forced vital capacity (FVC), FEV1%, maximal voluntary ventilation (MVV%), diffusion lung capacity for carbon monoxide (DLCO%), operation time, surgical procedure, intraoperative blood loss, drainage volume over the first 3 days and ectopic thymus were included as variables in the logistic regression analysis (Table 2).

Univariate analysis showed age >65 years ($p = 0.036$), thymoma ($p = 0.011$), preoperative history of myasthenic crisis ($p < 0.001$), preoperative course of >12 months ($p = 0.012$), Osserman-stages IIB + III + IV ($p < 0.001$), preoperative daily dose of pyridostigmine bromide ≥240 mg ($p < 0.001$), ASA grades 2 and 3 ($p < 0.001$), low FEV1 ($p < 0.001$), low FEV1% ($p < 0.001$), low MVV% ($p < 0.001$), low DLCO% ($p = 0.002$), open thoracotomy ($p = 0.087$), and intraoperative blood loss >1000 ml ($p = 0.025$) were risk factors for POMC.

Variables that showed p value <0.1 in univariate logistic regression analysis were entered into a multivariate logistic regression analysis. The result showed that Osserman stages IIB + III + IV ($p < 0.001$), preoperative daily dose of pyridostigmine bromide ≥240 mg ($p < 0.001$), ASA grades 2 and 3 ($p = 0.004$), low DLCO% ($p = 0.049$), and intraoperative blood loss >1000 ml ($p = 0.011$) were independent risk factors for POMC.

DISCUSSION

Due to the low incidence of MG, with an annual incidence of 4.4–6.1 per million,[5] few single-center large sample studies have been reported. Previous studies were either small

TABLE 1 Basic data

Variables	Data of all patients	Data of POMC patients
n	564	80
Gender (male/female)	292/272	44/36
Age (years old)	47.1 ± 15.6	49.6 ± 16.2
With/without thymoma	177/387	35/45
Other autoimmune disorders (no/yes)	506/58	73/7
Preoperative history of myasthenic crisis (no/yes)	545/19	66/14
Preoperative course (<12 months/ ≥12 months)	367/197	42/38
Osserman stage		
I	124 (22.0%)	0
IIA	174 (30.9%)	4 (5.0%)
IIB	209 (37.1%)	38 (47.5%)
III	28 (5.0%)	19 (23.8%)
IV	29 (5.1%)	19 (23.8%)
Preoperative daily dose of pyridostigmine bromide (<240 mg/≥240 mg)	450/114	34/46
Immunosuppressants (no/yes)	494/70	69/11
Steroid (no/yes)	512/52	69/11
ASA score		
1	285 (50.5%)	23 (28.8%)
2	223 (339.5%)	44 (55.0%)
3	56 (9.9%)	13 (16.2%)
FEV1	2.5 ± 0.8	2.0 ± 0.7
FEV1/FVC	81.0 ± 9.5	80.0 ± 10.5
FEV1%	81.8 ± 19.0	67.9 ± 20.6
MVV%	76.7 ± 22.3	65.2 ± 27.5
DLCO%	88.2 ± 19.2	81.0 ± 18.5
Operation time (min)	129.0 ± 43.0	131.7 ± 48.9
Surgical procedure (*n* [%])		
OT	90 (16.0%)	18 (22.5%)
VAST	474 (84.0%)	62 (77.5%)
Intraoperative blood loss (0–1000 ml/>1000 ml)	553/11	77/3
Drainage volume over the first 3 days (0–800/>800ml)	399/165	54/26
Ectopic thymus (no/yes)	534/30	76/4
Preoperative application of gamma globulin (no/yes)	517/47	60/20
The rate of POMC in patients with ivIG	15.71% (11/70)	

Abbreviations: ASA, American Society of Anesthesiologists; DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MVV, maximal voluntary ventilation; OT, open thoracotomy; POMC, postoperative myasthenic crisis; VATS, video-assisted thoracic *surgery*.

studies or meta-analyses that aggregated many different small studies. The included studies are not completely consistent with the definition of POMC. Other standards were more difficult to achieve consistency. Many individual studies lacked detailed data and, consequently, further subgroup analyses were not able to be conducted to explore the sources of heterogeneity. The consistency of definitions, procedures, perioperative management, and other criteria is also a problem in multicenter studies. Our study is retrospective, so problems such as selection bias are inevitable. In our study, owing to an MG center existing in our hospital, the sample size was larger, the data were more comprehensive, and the standards were more consistent. We conducted this retrospective study to make some hints about the risk factors of POMC. In clinical work, POMC should be avoided as much as possible, or early warning and preparation should be made in advance to avoid serious complications caused by POMC.

The incidence of POMC is very different, about 10–35%.[6–8] The huge difference is mostly caused by the reasons discussed above. It was 14.18% in our study, slightly less than the 17.48% reported by Liu et al.[9]

Osserman stages were generally recognized as a risk factor for POMC,[9–13] and we also concluded that Osserman stages IIb + III + IV was an independent risk factor for POMC ($p = 0.000$). Patients with Osserman stages IIb-IV present with bulbar symptoms, which cause the muscles involved in swallowing, chewing, articulation, breathing and others weak. Most researchers believe that type IIb or above involves respiratory muscles and are prone to dyspnea. Our clinical observations suggest that most of the dyspnea is caused by intraoperative tracheal intubation stimulation and the presence of bromipyridamole, which lead to excessive airway secretions and insufficient strength to cough up. In addition, saliva in the mouth (1000–1500 ml of saliva is secreted normally each day) is hard to swallow or spit out due to insufficient strength, which can cause aspiration. We therefore observed that POMC and cholinergic crisis were often mixed, with both respiratory muscle weakness and a high level of secretions that cannot be discharged.

Preoperative history of MG crisis has always been considered as a risk factor for POMC[9] and it was also an independent risk factor in our study. It indicates that the patients' MG symptoms have been very severe in the past. Even if symptoms are properly managed and controlled preoperatively, MG crisis may occur again after anesthesia and surgery.

In many previous studies,[14,15] a longer preoperative course was an independent influence factor on POMC and was also associated with a poorer response to treatment.[16] This may be due to cumulative damage at the neuromuscular junction or it may be that more long-memory antibodies are produced in the thymus and released into the blood, even removal of the thymus gland does not significantly improve symptoms. In our study, univariate analysis showed that duration of MG symptoms >12 months was an influential factor for POMC, but it was not an independent risk factor. On the contrary, some reports[17,18] showed that a short preoperative course was associated with the risk of POMC. Kanai et al.[19] found disease duration <3 months as a risk

TABLE 2 Logistic regression analysis

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Gender						
Female	Reference					
Male	0.860	0.535–1.383	0.533			
Age (years)						
<65	Reference			Reference		
≥65	1.871	1.041–3.363	0.036	1.020	0.394–2.441	0.966
With/without thymoma	1.873	1.156–3.037	0.011	0.811	0.356–1.845	0.617
Other autoimmune disorders	0.814	0.356–1.863	0.626			
Preoperative history of myasthenic crisis	20.321	7.090–58.248	0.000	2.938	0.659–13.099	0.158
Preoperative course						
<12 months	Reference			Reference		
≥12 months	1.849	1.147–2.983	0.012	1.741	0.831–3.649	0.142
Osserman classification						
I + IIA	Reference			Reference		
IIB + III + IV	29.4	10.582–81.684	0.000	16.091	5.170–50.076	0.000
Preoperative daily dose of pyridostigmine bromide						
≤240 mg	Reference			Reference		
>240 mg	8.277	4.960–13.812	0.000	6.462	3.110–13.427	0.000
Preoperative immunosuppressants	1.148	0.575–2.294	0.695			
Preoperative steroid	1.723	0.845–3.511	0.135			
ASA score						
1	Reference			Reference		
2 + 3	2.925	1.746–4.907	0.000	3.203	1.461–7.020	0.004
FEV1	0.299	0.193–0.464	0.000	0.666	0.266–1.668	0.386
FEV1/FVC	0.988	0.961–1.015	0.373			
FEV1%	0.959	0.945–0.973	0.000	0.987	0.959–1.016	0.391
MVV%	0.97	0.956–0.983	0.000	1.004	0.985–1.023	0.695
DLCO%	0.977	0.962–0.991	0.002	0.981	0.963–1.000	0.049
Operation time (min)	1.002	0.996–1.007	0.553			
Surgical procedure						
OT	Reference			Reference		
VAST	0.602	0.337–1.077	0.087	1.399	0.550–3.560	0.481
Blood loss						
0–1000 ml	Reference			Reference		
>1000 ml	6.329	1.254–31.932	0.025	16.590	1.911–144.011	0.011
Drainage volume over the first 3 days						
0–800 ml	Reference					
>800 ml	1.195	0.719–1.985	0.491			
Ectopic thymus	0.939	0.319–2.768	0.910			

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MVV, maximal voluntary ventilation; OR, odds ratio; OT, open thoracotomy; VATS, video-assisted thoracic surgery.

factor for POMC. Patients in Osserman stage III mostly have a short disease duration and this stage is more prone to POMC. Moreover, the disease progresses rapidly and preoperative control of MG symptoms is inadequate. Treatment can hardly be individualized and precise because the course of the disease is so short, and everyone responds differently to treatment. The specific mechanism and course of MG requires further analysis.

MG is an autoimmune disease and is frequently combined with other autoimmune diseases. Approximately 10% of patients with MG have coexistent autoimmune thyroid diseases,[20,21] but few reports have analyzed the effect of

other autoimmune diseases on POMC. Chen et al.[22] previously reported that combined immune disease (hyperthyroidism) was a significant predictor of POMC, but this was not found in our study. We found that 10.28% of MG patients were suffered with other autoimmune diseases. Patients with MG are rare, and even fewer patients have other autoimmune diseases, so far, all of these studies have included a small number of cases. Further studies are needed to validate whether other autoimmune diseases are risk factors for POMC.

Thymectomy in patients with MG is divided into traditional sternotomy and thoracoscopic surgery. Liu et al.[9] concluded that sternotomy was an independent risk factor for POMC by meta-analysis. They considered that this factor may be related to the traumatic bleeding of traditional incision operations, which predisposes to postoperative pulmonary infection. In our study, univariate analysis showed sternotomy was a risk factor. All of our sternotomies were performed with a median sternum incision, and this incision caused more intraoperative bleeding than video-assisted thoracoscopic surgery (VATS), which disrupts the integrity and stability of the thorax, has a greater impact on pulmonary function, and increases the risk of POMC. However, multivariate analysis showed that thoracotomy was not an independent risk factor. Watanabe[17] reported that intraoperative blood loss >1000 ml was a prognostic factor for POMC, and the risk was 18.52 times higher in the patients with blood loss >1000 ml than in the patients with blood loss ≤Unidentified 1000 ml. We came to a similar conclusion, but a convincing explanation for the mechanism by which blood loss >1000 ml affects POMC is not available.

Our results showed that a preoperative daily dose of pyridostigmine bromide ≥240 mg was an independent risk factor for POMC, which is similar to the conclusions of many other studies.[9] It was suggested that acetylcholinesterase inhibitors (AChEI) improve muscle contraction, strength, and function by blocking acetylcholinesterase at the neuromuscular junction. High-dose cholinesterase inhibitors can activate muscarinic receptors, accelerate the destruction of postsynaptic AChRs at the neuromuscular junction, reduce the ability of postoperative expectoration, cause excessive respiratory secretions, increase the risk of respiratory infection, and increase the risk of crisis. On the other hand, a higher dosage of pyridostigmine bromide also indicates that the symptoms of MG are more severe.

It is generally believed that preoperative pulmonary function tests play an important role in predicting POMC,[22–24] especially ventilate function, which represents the function and compliance of respiratory muscles. In univariate analysis, we found that the p values of FEV1, FEV1%, and MVV% were all 0.000, and DLCO% was also an influencing factor for postoperative POMC ($p = 0.002$), but in multivariate analysis only DLCO% was an independent risk factor. MG patients are prone to respiratory muscle weakness and when the diffusion function is also problematic, POMC is more likely to occur. This risk factor has not been suggested in other studies.

The relationship between POMC and thymoma is controversial.[25,26] In our study, univariate analysis showed that thymoma was a risk factor, but not an independent risk factor in multivariate analysis. Some thymomas are invasive and often lead to surgical difficulties. Sometimes, to achieve R0 resection, it is necessary to resect the adjacent tissues invaded by the thymomas at the same time, such as part of the pericardium, lung tissue, the phrenic nerve (phrenic nerve injury seriously affects respiratory function), and even superior vena cava molding or replacement, etc., so the surgical trauma is greater and may be more likely to lead to POMC.

Some studies[18,27] have reported a significant association between operation time and POMC. Longer operation time often means more severe surgical trauma, and a longer anesthesia time may lead to a larger amount of anesthetic drugs, especially muscle relaxers, which may lead to a higher incidence of POMC. However, no effect of operation time on POMC was found in our study. It may be that a single dose of muscle relaxants was usually given before tracheal intubation in MG patients, and that muscle relaxants were rarely applied during the operation, therefore, even if the operation time was prolonged, the risk of POMC was not increased.

Besides MG, other comorbidities and the underlying health status of patients may also affect POMC. We therefore applied the ASA system to grade patients before surgery. Many studies[28,29] have analyzed the correlation between ASA score and the incidence of postoperative complications and mortality, and found it to be significant. After ruling out the effect of MG, we evaluted the ASA score for each patient, and found that in the univariate analysis, the higher ASA scores might be the influence factors of POMC, after multivariable statistical, the higher ASA scores became independent factor, which indicated that patients with more complications and poorer general health condition achieved POMC more likely.

Patients with preoperative application of gamma globulin were all Osserman type IIb or above, and symptom control was not ideal. To further control the symptoms of MG and try to make the patients achieve better preoperative status, gamma-globulin were used. In this study, 47 patients were treated with gamma-globulin before surgery and 20 patients still had POMC, with an incidence rate of 42.55%. With high risk, it make sense that they had a higher incidence of POMC. Many surgeons believe that gamma-globulin can reduce the risk of POMC, but Gamez conducted a prospective randomized controlled study in 2019 that concluded that the application of gamma-globulin did not reduce the risk of POMC in patients with well-controlled preoperative MG symptoms. The effect of gamma-globulin on POMC therefore requires further study.

There were a number of limitations to this study. First, it was a retrospective study, which inevitably had some selection bias. Second, some patients with high risk of POMC

were treated with gamma-globulin before operation and some of them still developed POMC, which inevitably led to statistical errors. In addition, there are many missing preoperative pulmonary function indicators, especially for patients who were unable to cooperate with this examination, which may lead to inaccurate results. There were no routine MG-related antibody tests in the early years of the study analysis, especially in the patients with thymoma, so the antibodies were not included in the statistical analysis.

CONCLUSIONS

Among the numerous risk factors for POMC, we concluded that the independent risk factors were Osserman stages, preoperative dose of pyridium bromide, low DLCO% value, ASA classification, and large intraoperative blood loss. Patients with these conditions should be on high alert for postoperative MG crisis.

AUTHOR CONTRIBUTIONS

H.T.: project administration and supervision. P.J.: conceptualization, methodology, data curation, and writing original draft. F.W.: methodology, data curation, writing original draft, and editing. Y.L.: data curation, writing original draft, and editing. Y.S., W.T., H.Y., C.H., D.L., Q.W., and C.M.: data curation, writing review, and editing. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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