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Preoperative risks of post-operative myasthenic crisis (POMC): A meta-analysis

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ABSTRACT

Introduction: Myasthenic crisis (MC) is a life-threatening condition in patients with myasthenia gravis (MG), for which thymectomy is known to be a predisposing factor. There are many preoperative factors that have been suggested to increase the occurrence of post-operative myasthenic crisis (POMC), but none have been unanimously concluded as definite risk factors.
Methods: We performed meta-analyses to assess preoperative risk factors for the occurrence of POMC in eligible case-control studies.
Results: A total of 10 articles were systematically reviewed and meta-analyses identified preoperative bulbar symptoms, a history of MC, and disease severity ($p < .0001$), as well as decreased vital capacity ($p = .002$), as risk factors for POMC. Among the identified risks, the presence of preoperative bulbar symptoms showed the least heterogeneity and was suggested to be the most reliable preoperative risks of POMC.
Conclusion: Presence of preoperative bulbar symptoms is an easily discernable risk factor for the occurrence of POMC. A history of preoperative MC will further increase the risk of POMC. Patients with these risks require extra caution and should be closely monitored for POMC upon thymectomy.

1. Introduction

Myasthenia gravis (MG) is caused by the failure of neuromuscular transmission mediated by autoantibodies (Ab) against acetylcholine receptor (AChR) [1] and other proteins such as muscle-specific receptor tyrosine kinase (MuSK) [2] and low-density lipoprotein (LDL) receptor-related protein 4 (Lrp4) [3] complex. Functional impairment of these proteins that are involved in synaptic transmission from nerves to muscles results in muscle weakness with easy fatigability. Myasthenic crisis (MC) is a critical and fatal aspect of MG accompanied by respiratory failure that requires artificial ventilation [4]. Furthermore, MC is associated with higher medical costs and prolonged hospitalization. Thus, managing risk and avoiding MC are highly important. Several factors might increase risk of MC and several retrospective case-control studies have evaluated preoperative risk factors for post-operative myasthenic crisis after thymectomy (POMC) [5–15]. These previous reports suggested that disease severity, decreased vital capacity, bulbar symptoms, short disease duration, thymoma, prolonged surgery, and excessive blood loss during surgery might be preoperative risks for POMC. We applied meta-analyses of the findings of 10 eligible previous studies to identify the most reliable and clinically useful risk factors to avoid MC.

2. Materials and methods

2.1. Search strategy for meta-analysis

We searched the MEDLINE, PubMed, Cochrane Library, Embase, and Google Scholar databases through December 2018 using MeSH and free-text terms. The terms applied to the initial searches were “post-operative myasthenic crisis”, “risk factors [MeSH]”, “myasthenic crisis”, and “thymectomy [MeSH]”. Reports that comprised only retrospective comparisons of clinical factors between post-operative patients with and without POMC were deemed eligible for meta-analysis.

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Table 1
List of the enrolled case-control studies for the meta-analyses.

Author (ref)	Country (Enrollment period)	POMC: non-POMC (n) [Male: Female]	Age at surgery (POMC ±)	Preoperative risks for POMC (POMC *vs* non-POMC)							Other suggested preoperative risks
				Respiratory dysfunction	Bulbar symptoms (Yes/No)	Severity (Osserman or MGFA ≥ III)	History of MC (Yes/No)	Anti-AChR-Ab titer [nmol/L]	Daily dose of PB [mg]	Thymoma	
Ando [5]	Japan 2000–13	10:45 [25:30]	[Age ≥ 60] p = .72	N.E.	N.E.	[MGFA ≥ II] (p = .28)	p = .0004	p = .009	N.E.	p = .092	Unstable preoperative MG symptom (p = .003)
Choi [6]	Korea 1996–09	12:36 [23:25]	[Onset age] p = .39	[%VC] p < .001	p = .19	N.E.	p = .0024	p = .38	p = .045	Thymoma only	
Kanai [7] [Deriv.]	Japan 2002–14	17:258 [106:169]	46 ± 16/49 ± 16: p = .38	[%VC] p < .0001	p = .0014	p = .0016	N.E.	p = .78	p = .10	p = .048	Preoperative disease duration ≤3 months (p = .0009)
Kanai [7] [Valid.]	Japan 2002–14	5:113 [46:72]	44 ± 10/52 ± 15: p = .24	[%VC] p = .0052	p = .068	p = .59	N.E.	N.E.	p = .049	p = 1.00	
Koinuma [8]	Japan 2003–09	6:57 [22:41]	62 ± 12/55 ± 16: p = .30	[%VC] p = .37	p = .025	p = 1.00	p = 1.00	p = .055	[Usage] p = 1.00	p = 1.00	Operation time (p = .027) Incomplete thymus resection (p = .043)
Lee [9]	Korea 2007–12	10:136 [36:110]	Median: 25/35: p = .16	[FVC] p < .001	p = .043	p = .0061	p = .14	p = .28	p = .29	p = 1.00	Decreased response of facial muscles on RNS (p < .001)
Leuzzi [10]	Italy 1995–11	22:155 [70:107]	[Age ≥ 60] p = .055	[%VC ≥ 80%] p = .025	p = .0020	p = .14	p = .071	p = .14	[Usage] p = .083	p = .23	Body mass index ≥28 (p = .0020)
Li [11]	China 2000–13	51:122 [90:83]	46 ± 12/47 ± 12: p = .63	N.E.	p = .0022	p = .126	p = .049	N.E.	p = .36	Thymoma only	Incomplete thymus resection (p = .025)
Nam [12]	Korea 1997–07	20:46 [23:43]	Median: 43/44: p = .55	[FEV1] p = .009 [FVC] p = .018	p = .0069	p = .015	p < .0001	p = .55	p = .16	p = .59	Use of immune-suppressants (p = .007)
Watanabe [13]	Japan 1985–02	14:108 [30:92]	47 ± 19/44 ± 16: p = .56	[%VC] p = .18	p = .0001	p = .010	p = .032	p = .0046	p = .97	p = .32	
Xue [14]	China 1997–07	13:114 [68:59]	[Age ≥ 50] p = .38	[FVC] p = .009	p = .040	p = .28	N.E.	N.E.	[Usage] p = .72	Thymoma only	WHO classification ≥ B2 (p = .03)

Abbreviations: AChR-Ab, acethylcholine receptor binding antibody; Deriv., derivation cohort; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MC, myasthenic crisis; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; N.E., not evaluated; MG, myasthenia gravis; PB, pyridostigmine bromide; POMC, post-operative myasthenic crisis; RNS, repetitive nerve stimulation; Valid., validation cohort; VC, vital capacity.

Table 2
Calculated heterogeneity and effect size of potential risk factors for POMC.

Risk factor	Datasets (n)	τ^2	I^2 [%]	[a]Odds ratio or [b]mean difference (95%CI)	p
Preoperative factors (Dichotomous variables)					
Bulbar symptoms	10	0.00	0	4.84 (3.22–7.28)[a]	< 0.00001
History of crisis	8	0.42	38	6.28 (2.98–13.24)[a]	< 0.00001
MGFA ≥ III/Osserman ≥ III	9	0.00	0	4.29 (2.61–7.05)[a]	< 0.00001
Immune suppressants	6	0.27	29	2.44 (1.11–5.35)[a]	0.03
Oral steroids	5	0.00	0	1.94 (1.11–3.40)[a]	0.02
Male propensity (Sex)	11	0.00	0	1.09 (0.78–1.54)[a]	0.61
Thymoma	8	0.02	3	1.54 (0.95–2.49)[a]	0.08
VATS	5	0.06	11	0.96 (0.49–1.89)[a]	0.91
Preoperative factors (Continuous variables)					
Low %VC	4	50.3	66	−14.38 (−23.28 - -5.48)[b]	0.002
Pyridostigmine dose (mg/day)	6	18.5	4	28.01 (10.98–45.04)[b]	0.001
Disease duration (months)	4	509	96	−17.20 (−40.11–5.70)[b]	0.14
Age at thymectomy	5	5.90	28	−1.07 (−5.05–2.92)[b]	0.60
BMI	4	2.05	57	−0.22 (−2.13–1.68)[b]	0.82
AChR-Ab titer (nmol/L)	6	1.10	26	0.36 (−1.40–2.11)[b]	0.69
Surgical duration (min)	3	0.00	0	15.53 (0.36–30.70)[b]	0.04
Blood loss (mL)	3	0.00	0	43.57 (−17.20–104.34)[b]	0.16

Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; FVC, forced vital capacity; VATS, video-assisted thoracoscopic surgery; VC, vital capacity.
[a] Odds ratio.
[b] Mean difference.

Among 18 initially-selected reports, three small case series and five reports that did not compare risks between those with and without POMC were excluded from meta-analysis. The remaining 10 retrospective case-control studies that compared clinical factors between post-operative patients with and without POMC were included [5–14]. One included study contained derivation and validation cohorts [7].

2.2. Meta-analysis

We used Review Manager v. 5.3 to evaluate the significance of each risk factor for POMC [16,17]. Explanatory variables before thymectomy comprising bulbar symptoms, history of crisis, Myasthenia Gravis Foundation of America (MGFA) clinical classification ≥ III or Osserman stage ≥ III severity, history of immune-suppressants and oral steroids, sex, existence of thymoma, surgery (video-assisted thoracoscopic surgery [VATS] or not), % vital capacity (%VC), pyridostigmine dosage, disease duration, age, body mass index (BMI), AChR-Ab titer, surgery duration, and blood loss during surgery were analyzed. A random effect model was applied. Heterogeneity of the studied variables among the included studies was assessed using the Higgins I^2 heterogeneity statistic and the τ^2 between-study heterogeneity variance, both of which are parameters of between-study dispersion. The PRISMA checklist was referenced in the process of meta-analysis [18]. Because multiple meta-analyses by using the included variables were simultaneously performed, a P-value lower than 0.01 was considered to indicate statistical significance in this study.

3. Results

3.1. Overview of the case-control studies

Data from the 10 case-control studies are summarized in Table 1. Preoperative presence of bulbar symptoms was evaluated as a possible risk for POMC in 9 of the 10 enrolled studies, of which it was suggested to significantly predispose individuals to POMC in 8 of them (88.9%). Preoperative disease severity (*i.e.* Osserman ≥ III or MGFA ≥ III) was evaluated in 8 of the 10 studies, and it was suggested to significantly predispose individuals to POMC in 4 of them (50.0%). Preoperative history of MC was evaluated in 8 of the 10 studies, and it was suggested to significantly predispose individuals to POMC in 5 of them (62.5%). Age at thymectomy was evaluated in 9 of the 10 studies, but was not suggested to be a risk factor for POMC. Sex was evaluated in all 10 studies, and was not suggested to be a risk factor for POMC.

Among the 10 enrolled studies, 7 studies included both thymomatous and non-thymomatous patients, but the other 3 studies enrolled thymomatous patients only. Among the 7 studies with both thymomatous and non-thymomatous patients, only one study (14.3%) weakly suggested thymoma as a possible risk factor for POMC.

3.2. Meta-analyses

Table 2 shows the results of the meta-analyses of all studied variables. Preoperative bulbar symptoms (odds ratio [OR], 4.84; 95% confidence interval [CI], 3.22–7.28), a prior history of myasthenic crisis (6.28; 2.98–13.24), disease severity with MGFA ≥ III or Osserman ≥ III (4.29, 2.61–7.05), and lower %VC (mean difference −14.38; −23.28 - 5.48) were significant risks for POMC. Among these four items, preoperative lower %VC had moderate to high statistical heterogeneity (I^2 = 66%). However, a higher preoperative %VC rather favored patients without POMC in all four studies that assessed this factor, suggesting that statistical heterogeneity in %VC was less significant, and that low %VC can be considered as a significant risk factor for POMC.

Preoperative treatment with immune suppressants or oral steroids did not reach statistical significance as a risk factor for POMC. Meanwhile, preoperative pyridostigmine dose [mg/day] was associated with the occurrence of POMC. Although the dose of pyridostigmine could have been affected by the preoperative disease severity, it was considered as another risk factor for POMC.

Thymoma, shorter disease duration, longer surgical duration, and larger volume of blood loss during surgery did not reach significance. Sex, age at thymectomy, BMI, and VATS were not selected as risk factors for POMC.

Fig. 1 shows forest plots of four preoperative variables with $p < .01$ for risk of POMC. Among them, heterogeneity was the smallest for preoperative bulbar symptoms, indicating that it might function as the most clinically reliable marker of risk for POMC. Predictive characteristics (*i.e.* sensitivity, specificity, likelihood ratios) of the suggested risk factors for POMC, together with thymoma, are summarized in Table 3. Preoperative bulbar symptoms showed much higher sensitivity for the following occurrence of POMC than disease severity or history of MC, suggesting that bulbar symptoms would be the best preoperative information to predict the following occurrence of POMC.

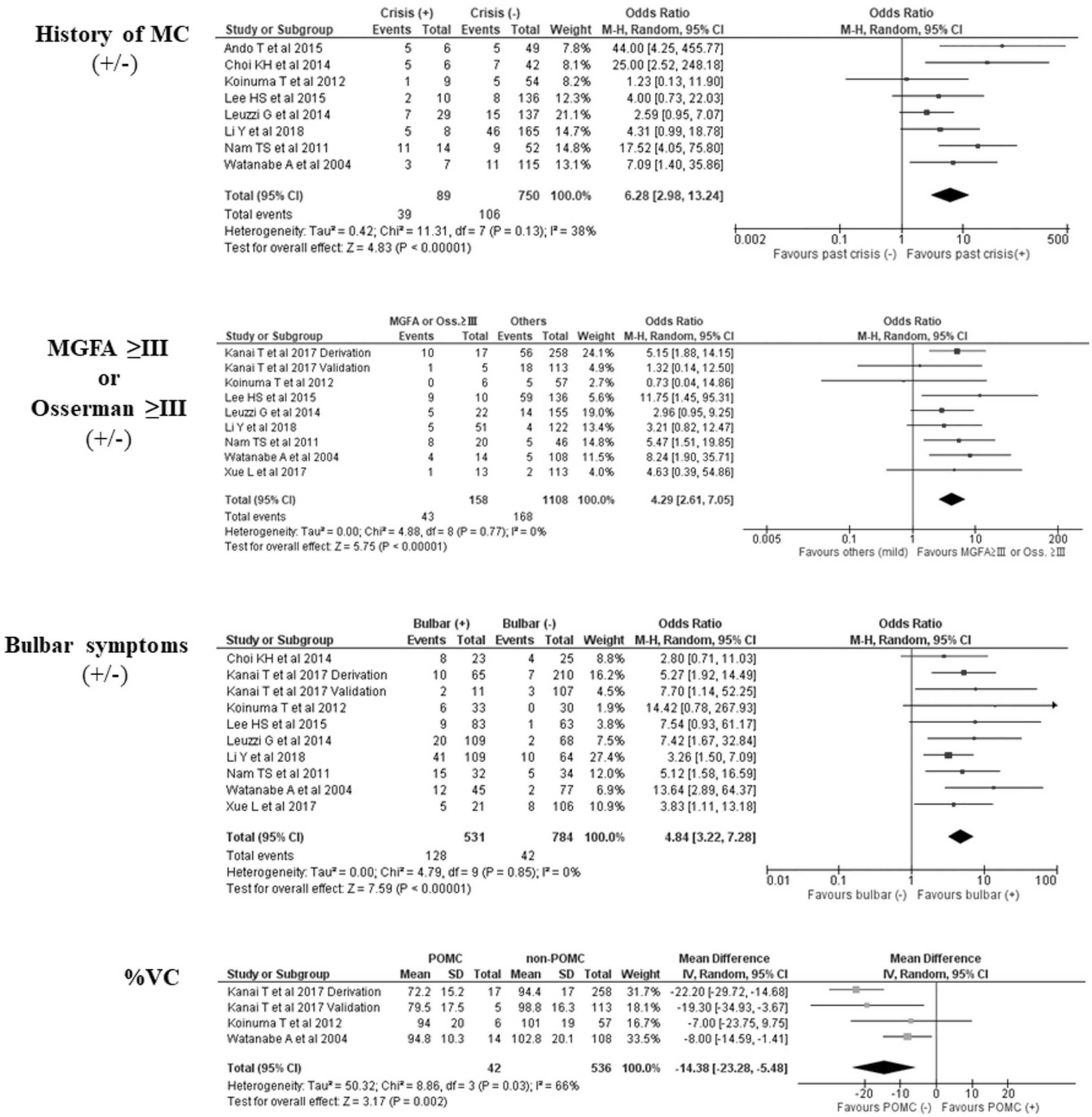

Fig. 1. Forest plots of preoperative risk factors for POMC.
The size of each square at the center of each error bar (horizontal bar) is proportional to the size of the sample in each included study; the larger the square, the greater the weight of the study. The error bars show estimated 95%CI of the OR, or mean differences in each study. The overall estimate and its CI in each meta-analysis are shown as a diamond at the bottom of each plot. If the diamond does not cross a value of 1.0, then the estimated OR is statistically significant at the level of 5%. Abbreviations: CI, confidence interval; MC, myasthenic crisis; MGFA, Myasthenia Gravis Foundation of America; OR, odds ratio; %VC, %vital capacity.

4. Discussion

The meta-analyses identified bulbar symptoms, history of myasthenic crisis, disease severity before surgery, and low %VC as definite risks for POMC. Bulbar symptoms had the least heterogeneity among the included studies. The presence of bulbar symptoms does not require a specific test, and thus, can comprise a simple and useful predictive marker of POMC. However, as shown in Table 3, more than half of the patients with preoperative bulbar symptoms will not develop POMC. To more efficiently pick up the patients with high risks of POMC, it will be useful to also obtain the preoperative history of MC. Because the presence of MC shows much higher predictive specificity for POMC than the presence of bulbar symptoms, this suggests that we need to take the utmost caution for individuals with preoperative MC history. Alternatively, those without preoperative bulbar symptoms show much lower risk for POMC, although approximately 25% of POMC cases occur in the absence of preoperative bulbar symptoms. As a limitation, the severity of bulbar symptoms was not evaluated in the enrolled studies and in this meta-analysis. Consequently, we do not know the difference in the risk of POMC between those with mild bulbar symptoms and those with severe bulbar symptoms (*e.g.* respiratory dysfunction, aspiration). Nevertheless, it is apparent from the results in Table 3 that those with the most severe preoperative bulbar symptoms that required intubation (*i.e.* myasthenic crisis) showed a much higher risk of POMC than those with milder bulbar symptoms.

The preoperative pyridostigmine dose was correlated with the occurrence of POMC, but the dosage could have been confounded by disease severity. Thus, preoperative pyridostigmine dosage should be considered as a variable to reflect the preoperative disease severity. However, the daily dosage itself seems to be another simple history to

Table 3
Diagnostic characteristics of the risk factors for post-operative myasthenic crisis.

Preoperative factors		Occurrence of POMC		p-Value	Diagnostic characteristics for predicting POMC			
		Yes (n)	No (n)		Sensitivity [%] (95%CI)	Specificity [%] (95%CI)	LR + (95%CI)	LR − (95%CI)
History of MC	Yes	39	50	< 0.0001	27.1 (19.8–34.3)	92.8 (90.8–94.7)	3.75 (2.57–5.47)	0.79 (0.71–0.87)
	No	105	642					
MGFA or Osserman ≥III	Yes	43	168	0.0002	27.7 (20.7–34.8)	84.4 (82.2–86.5)	1.77 (1.33–2.37)	0.86 (0.77–0.95)
	No	112	906					
Bulbar symptoms	Yes	128	403	< 0.0001	75.3 (68.8–81.8)	64.8 (62.0–67.6)	2.14 (1.90–2.40)	0.38 (0.29–0.50)
	No	42	742					
Thymoma	Yes	60	442	0.065	57.7 (48.2–67.2)	51.9 (48.6–55.1)	1.20 (1.00–1.43)	0.82 (0.65–1.03)
	No	44	476					

Based on the data from the enrolled 10 previous reports, diagnostic characteristics such as sensitivity, specificity, and likelihood ratios were calculated. Preoperative bulbar symptoms showed the highest sensitivity and the lowest negative likelihood ratio. Abbreviations: CI, confidence interval; LR +, positive likelihood ratio; LR −, negative likelihood ratio; MC, myasthenic crisis; MGFA, Myasthenia Gravis Foundation of America; POMC, post-operative myasthenic crisis.

predict the occurrence of POMC, no matter of the possible confounding effect from the preoperative disease severity.

Although surgery and general anesthesia are considerable risks for POMC *per se*, the type of surgery (VATS or trans-sternal thymectomy), surgical duration, and volume of blood loss during surgery were not identified as risk factors for POMC in the present meta-analysis. Clinicians must monitor for the occurrence of POMC, regardless of the process of thymectomy.

One study included in the present meta-analysis indicated that a short disease duration before thymectomy is a possible risk factor for POMC [7], although no other studies that evaluated disease duration did not [8,12,13]. The observed result that short disease duration before thymectomy could be a possible risk of POCM may suggest that insufficient controllability of disease activity without adequate therapeutic interventions before thymectomy may somewhat predispose the occurrence of POMC. In severe cases, trying to control disease states using only oral immune therapies can sometimes be time-consuming; combination of aggressive non-oral fast-acting immunotherapies such as plasmapheresis and intravenous immunoglobulin might be helpful to achieve better controllability before the surgery.

In conclusion, the presence of bulbar symptoms with or without preoperative history of MC is a simple risk factor for POMC. The occurrence rate of POMC is increased further if a patient has a history of MC in addition to bulbar symptoms. Preoperative patients with conspicuous bulbar symptoms or respiratory disturbance need to be managed with extra caution and additional therapeutic interventions to avoid the occurrence of POMC.

Contributors

All authors discussed the results, made substantial intellectual contributions to the work, critically reviewed the manuscript, and approved the final version of it. TA and MM originally conceived the study design, drafted the manuscript, independently reviewed the included reports for meta-analysis, and directly analyzed the data.

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