

Risk factors of myasthenia crisis after thymectomy among myasthenia gravis patients

A meta-analysis

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Abstract

Background: The purpose of the study was to determine the risk factors of post-surgery myasthenia crisis (PMC) among myasthenia gravis (MG) patients.

Methods: A meta-analysis to synthesize all eligible literatures was conducted to analyze PMC predictors among MG patients.

Results: A total of 15 trials with 2626 patients were included for the meta-analysis. As a result, patients with history of MC (RR = 3.36, 95%CI: 2.46–4.59, $P < .001$), generalized MG (RR = 0.39, 95%CI: 0.26–0.59, $P < .001$), bulbar symptom (RR=3.59,95% CI:2.53–5.09, $P < .001$), thymoma (RR = 2.10, 95%CI:1.37–3.21, $P = .001$), post-surgery morbidity presence (RR = 2.59, 95% CI:1.90–3.54, $P < .001$), high-dose pyridostigmine usage (SMD = 0.480,95%CI: 0.35–0.61 $P < .001$) tended to develop PMC. Large dose of steroid may reduce the incidence of PMC (RR = 0.41 95%CI: 0.18–0.94, $P = .036$). Regular steroid use ($P = .066$), immunosuppressive therapy ($P = .179$), gender ($P = .774$), and age at thymectomy ($P = .212$) had no impact upon PMC development.

Conclusion: History of PMC, thymoma, generalized MG, bulbar symptom, and concomitant complication are the risk factors of PMC.

Abbreviations: anti-AchR-Ab = anti-Acetylcholine-Receptor Antibody, MC = myasthenia crisis, MG = myasthenia gravis, PMC = post-operative myasthenia crisis, RR = relative risk, SMD = standardized mean difference, TS = trans-sternotomy, VATS = videoassisted thoracoscopic surgery.

Keywords: meta-analysis, myasthenia crisis, myasthenia gravis, risk factor, thymectomy

1. Introduction

Myasthenia gravis is an auto-immune disease, characterized by muscle weakness and the synthesis of anti-Acetylcholine-Receptor Antibody (anti-AchR-Ab).^[1] Most MG patients are pathologically associated with thymus abnormalities (including thymic malignancy and thymus hyperplasia), which are responsible for auto-antibodies in the circulation.^[2] Thymecto-

my, demanding an *en bloc* removal of thymic tissues, has been known as the standard option to treat MG and reduces the generation of anti-AchR Ab. It is reported that the remission rate after thymectomy reached 80%.^[3]

After thymectomy, a rapidly deteriorating function of neuromuscular junction may lead to postoperative myasthenia crisis (PMC), which is due to respiratory muscle paralysis and presented as prolonged mechanical ventilation or re-ventilation after extubation.^[4] So it is a life-threatening complication and a major problem after thymectomy. The incidence of PMC ranges from 6.2% to 30.3%.^[5,6]

Thymectomy was classified as 4 surgical ways, the most prevalent approaches of which are minimally invasive surgery (e.g., video-assisted thoracoscopic surgery, VATS) and trans-sternotomy (TS). Open surgery was considered increasing the risk of PMC compared with minimally invasive approach. Besides surgical ways, infections and other post-surgical complications, more severe MG status, and some other reasons may contribute to PMC.

However, predictive factors of PMC varied by studies and still no consensus on this problem has been reached. Thus, we made a meta-analysis to identify the clinical indicators predicting PMC occurrence.

2. Methods

2.1. Inclusive criteria and exclusive criteria

2.1.1. Inclusive criteria. Literatures were included in the meta-analysis if they met the following criteria:

1. Randomized controlled trial or cohort study.

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We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

None of the authors has any conflict of interest to disclose.

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- All subjects were about MG patients who received thymectomy.
- Outcome measure: Incidence of postoperative myasthenia crisis among MG patients after thymectomy.
- The clinical trial presented analysis of possible factors influencing the risk of PMC (age at surgery, gender, MC history, association of thymoma, MG stage, anti-AchR-Ab titer, etc) with detailed information.
- Literatures written either in English or Chinese.

2.1.2. Exclusive criteria. Literatures were excluded if any of the reasons as follows were matched

- Case report or review.
- Only description of general myasthenia crisis, but not MC after thymectomy.
- Experimental research or animal research.
- No available data was shown in the literature.

2.2. Literature retrieval

We searched databases of PubMed, EMBASE, and Cochrane to achieve related trials published before June 1, 2019. Sample search terms included “Myasthenia crisis” and “myasthenia gravis”

2.3. Filter of literature and data extraction

Two researchers screened all the literatures retrieved via reading abstracts and titles, papers cannot be removed by the criteria above were examined twice based on full texts. Articles conformed to the inclusive criteria were included in our trial. Information extracted from literatures included first author's name, publication year, mean ages of 2 groups (PMC and non-PMC), ratios of male to female of 2 groups (PMC and non-PMC), risk factors of developing PMC, and data presenting the influence of a factor upon the risk of PMC.

2.4. Statistical analysis

STATA11.0 (Stata-Corp LP, College Station, TX, USA) was applied to assess statistical significance. Between-study heterogeneity was assessed first with Q Test and inconsistency index (I^2).^[7] A P value $>.1$ combined with $I^2 < 50\%$ implied heterogeneity was insignificant and Fixed Effect Model (Mantel-Haenszel method)^[8] was available. Otherwise the heterogeneity was significant and we would look for clinical source of heterogeneity to try to reduce it. If the heterogeneity still existed, Random Effect Model (DerSimonian-Laird method)^[9] was applied. All P values less than .05 were considered statistically significant. For binary variables, relative risk (RR) was performed to assess the significance of the difference; as to numerable variables, Standardized Mean Difference (SMD) was applied to estimate the significance of the difference. If more than 10 articles were included in 1 meta-analysis, evaluation of publication bias was necessary.^[10] A P value less than .05 suggested publication bias was statistically significant.

2.5. Ethical statement

Because this study is a meta-analysis thus approval by ethic committee was not necessary according to local regulations

(Medical ethic committee of Sichuan University). In addition, informed consent from patients was also not necessary.

3. Results

3.1. Result of study selection

A total of 537 articles were retrieved in according with the search strategy, 130 duplicated articles were removed from the research first. Next the authors reviewed the abstracts of the remaining 407 articles according to the inclusive and exclusive criteria. Three hundred forty nine trials were further excluded during this process. Then full texts of the remaining 58 trials were examined. Finally, 15 trials were included for our research.^[4-6,11-22] The reasons of eliminating articles were summarized as follows and shown in Figure 1:

- The article focused on other topics without description of PMC ($n=294$).
- Duplicated articles from different databases ($n=130$).
- Review articles or case reports ($n=55$).
- Mere introduction of myasthenia crisis, but not crisis after surgery ($n=27$).
- No description of risk factors for PMC, or no available data presenting risk factors for PMC in the article ($n=11$).
- Article written in other languages ($n=5$).

3.2. Characteristics of all the studies

A total of 15 trials and 2626 MG patients were included in the meta-analysis (398 cases for PMC patients, 2228 cases for non-PMC). All articles were published between 2004 and 2017, and patients ranged from Asia to Europe. All included trials were cohort studies, and no randomized controlled trial on this issue has been published yet. Detailed information of each study was shown in Table 1.

3.3. Results of data synthesis

3.3.1. Patients' own characteristics. MG patients with history of myasthenia crisis had a higher risk of PMC than those without myasthenia crisis record. Heterogeneity was significant ($I^2 = 49.5\%$) and the source was not found, hence Random Effect Model was used. The outcome was, RR = 3.36 95%CI (2.46, 4.59) $P < .001$, shown in Figure 2a.

Generalized MG patients presented a higher incidence of PMC than ocular patients. Heterogeneity was low ($I^2 = 0.0\%$) and Fixed Effect Model was used. The outcome was, RR = 0.39 95%CI (0.26, 0.59), $P < .001$, Figure 2b. The incidence of PMC was higher in patients with bulbar symptom than in those without bulbar symptom, RR = 3.59 95%CI (2.53, 5.09) $P < .001$, Figure 2c.

Thymomatous MG patients showed a higher incidence of PMC than non-thymomatous MG patients. Heterogeneity was high and no clinical source was found. With Random Effect Model we achieved the outcome, RR = 2.10 95%CI (1.37, 3.21) $P = .001$, Figure 2d.

Female patients were similar with male cohorts in terms of the risk of PMC. The outcome was, RR = 1.03 95%CI (0.85, 1.24) $P = .774$, Figure 3a. With regard to the comparison of mean age between PMC patients and non-PMC patients, the difference reached no statistical significance (SMD = 0.11 95%CI: -0.06 to 0.29, $P = .212$, Fig. 3b).

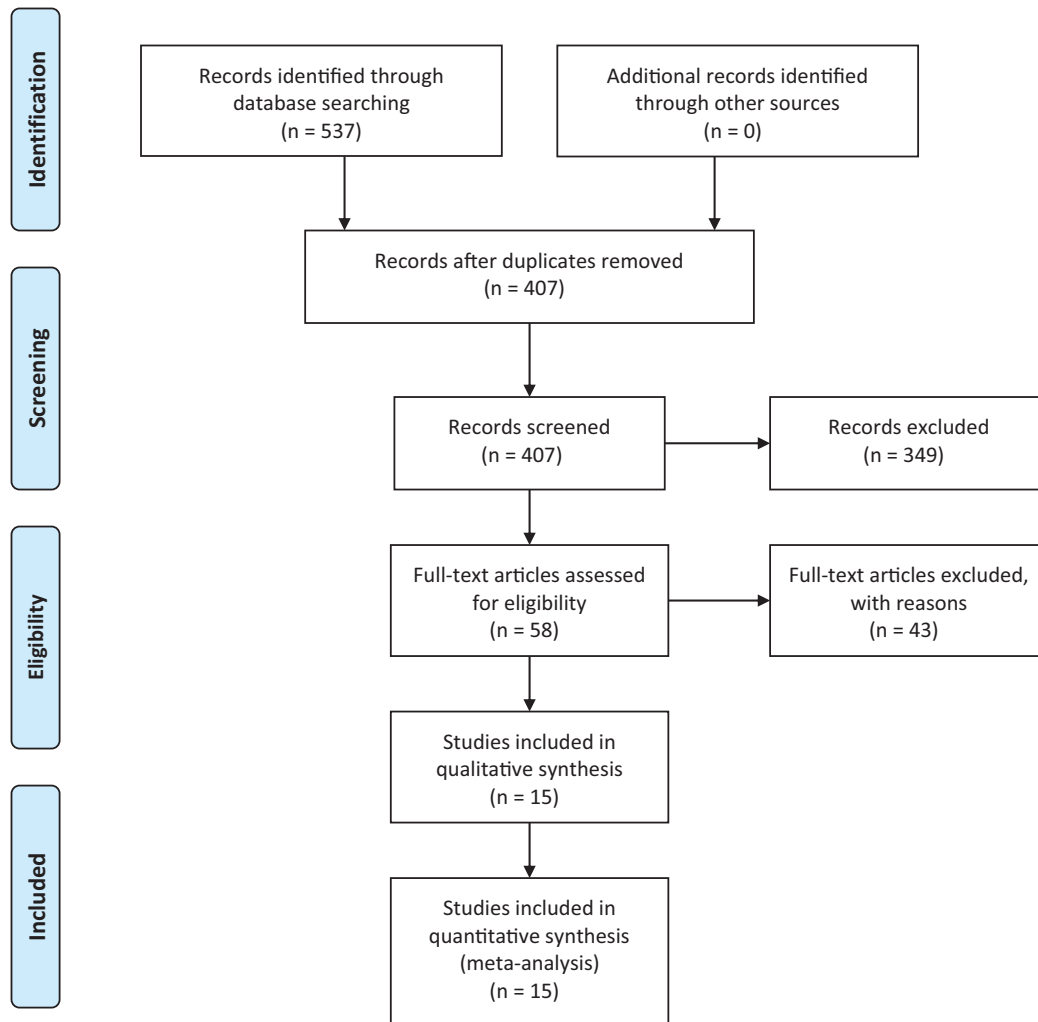


Figure 1. Process of selecting eligible articles for further research.

Table 1

Information of each study involved in the meta-analysis evaluating risk factors of PMC.

Trial	Year	Design	Number of patients		Mean age		Predictive factors of PMC
			PMC (M/F)	non-PMC (M/F)	PMC	non-PMC	
Watanabe ^[4]	2004	CS	14 (4/10)	108 (26/82)	47 ± 19	44 ± 16	Bulbar symptom, high level anti-AchR Ab titer, large amount of blood loss
Nam TS ^[5]	2011	CS	20 (7/13)	46 (16/30)	42.5	43.5	A history of MC
Ando T ^[11]	2014	CS	10 (3/7)	45 (22/23)	NS	NS	A history of MC, unstable MG
Zou J ^[12]	2016	CS	67 (30/37)	474 (226/228)	26.4 ± 11.7	27.0 ± 13.5	Pre-surgery anxiety
Luezzi G ^[13]	2014	CS	22 (10/12)	155 (60/95)	NS	NS	A history of MC, higher MG stages
Lee HS ^[14]	2014	CS	10 (1/9)	126 (25/101)	25	35	Weak pulmonary function
Choi KH ^[15]	2014	CS	12 (6/6)	36 (17/19)	48	47	Weak pulmonary function
Liu WB ^[16]	2006	CS	36 (17/19)	140 (57/83)	33 ± 14	31 ± 14	Bulbar symptom, history of MC, large dose of pyridostigmine
Chu XY ^[17]	2011	CS	44 (23/21)	199 (101/98)	NS	NS	Thymoma, higher MG stage, post-surgery complication
Wu Y ^[18]	2015	CS	11 (4/7)	66 (30/36)	52.2 ± 10.6	44.6 ± 11.2	A history of MC, large dose of pyridostigmine
Yu S ^[19]	2014	CS	44 (21/23)	134 (62/72)	40.7 ± 11.1	35.5 ± 14.2	Bulbar symptom, history of PMC, & longer surgery duration
Yamada ^[20]	2013	CS	10 (NS)	121 (NS)	NS	NS	Prednisolone pulse therapy
Soleimani ^[21]	2004	CS	25 (NS)	85 (NS)	NS	NS	NS
Li Y ^[22]	2017	CS	51 (27/24)	122 (63/59)	45.1 ± 12.0	46.1 ± 11.4	Bulbar symptom, partial resection
Kanai T (1) ^[6]	2017	CS	17 (8/9)	258 (98/160)	45.8 ± 16.1	49.2 ± 15.5	Weak pulmonary function, bulbar
Kanai T (2) ^[6]	2017	CS	5 (3/2)	113 (43/70)	44.0 ± 9.5	51.9 ± 14.7	symptom, duration from MG onset to thymectomy

AchR-Ab = Acetylcholine receptor antibody, CS = Cohort study, F = female, M = male, NS = not sure, PMC = Post-surgery myasthenia crisis. Kanai T (1) or (2): 2 clinical trials were included in the article.

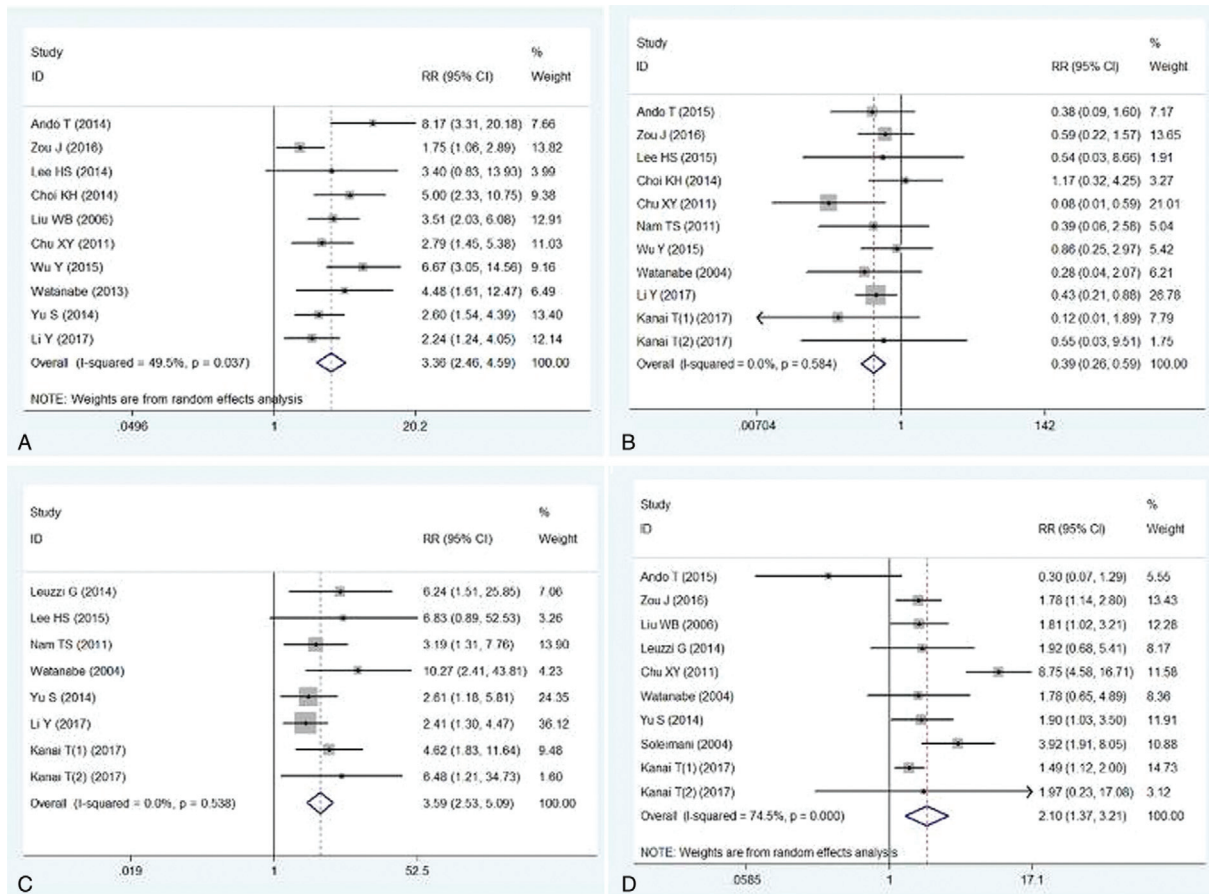


Figure 2. Meta-analysis evaluated the effect of MG status upon the risk of PMC. 2a: forest plot compared MG patients with history of MC and those without history of MC in terms of the risk of PMC. 2b: forest plot described generalized MG vs ocular MG with regard to the risk of PMC. 2c: forest plot evaluated the risk of PMC for MG patients with and without bulbar symptoms. 2d: Forest plot compared the incidence of PMC between thymomatous MG patients and non-thymomatous MG patients. MG: myasthenia gravis, PMC = post-operative myasthenia crisis.

3.3.2. Peri-operative treatment. When it came to the evaluation of steroid use, heterogeneity was significant ($I^2 = 46.1\%$). We found that regular steroid use was applied in 5 studies, while in another 3 studies MG patients were treated with steroid pulse therapy. Therefore sub-group analysis was applied in this indicator. No significant difference of PMC incidence was found between patients with regular steroid use and without steroid use (RR = 1.28 95%CI: 0.98–1.65 $P = .066$, Fig. 4a). However, MG patients with steroid pulse therapy or large dose steroid presented a lower PMC incidence than those without steroid therapy (RR = 0.41 95%CI: 0.18–0.94 $P = .036$, Fig. 4a).

Also no significant difference of PMC was found between immunosuppressive therapy group and non-immunosuppressive therapy group. The outcome was, RR = 1.29 95%CI (0.89, 1.88) $P = .179$, Figure 4b.

Patients underwent PMC took a larger mean dose of pyridostigmine than those without PMC. The outcome was, SMD = 0.48 95%CI: 0.35–0.61 $P < .001$, Figure 4c.

The risk of PMC was higher in MG patients with other post-operative complications than those without other complications. (RR = 2.59 95%CI: 1.90–3.54, $P < .001$, Fig. 5a).

Mean surgery time was longer in patients underwent PMC than those without PMC (SMD = 0.41 95%CI: 0.23–0.60,

$P < .001$, Fig. 5b). Patients underwent PMC suffered from more blood loss during thymectomy than non-PMC patients (SMD = 0.35 95%CI: 0.16–0.54 $P < .001$, Fig. 5c).

3.3.3. Publication bias. Publication bias was evaluated for the impact of thymoma ($P = .283$), history of MC ($P = .049$), MG stage ($P = .533$), and gender ($P = .827$) upon the incidence of PMC. The bias was only significant for history of MC ($P = .049$, detailed information was not shown).

4. Discussion

Myasthenia crisis occurs in 15% to 20% of MG patients.^[2,3] How to prevent PMC is of great importance to the treatment of post-surgery MG patients. But until now the predictors of PMC have not been confirmed yet.

Several clinical trials included in this study suggested history of myasthenia crisis is an independent risk factor of PMC (shown in Table 1). Our meta-analysis pooled a similar result and all literatures included in data synthesis suggested MG patients with a history of MC had a higher risk of PMC than those without any MC record (shown in Fig. 2). Hence the publication bias was of statistical significance because of the consistency of the results among the literatures. It was reported that MG patients with a record of MC may experience crisis recurrence, and the relapse

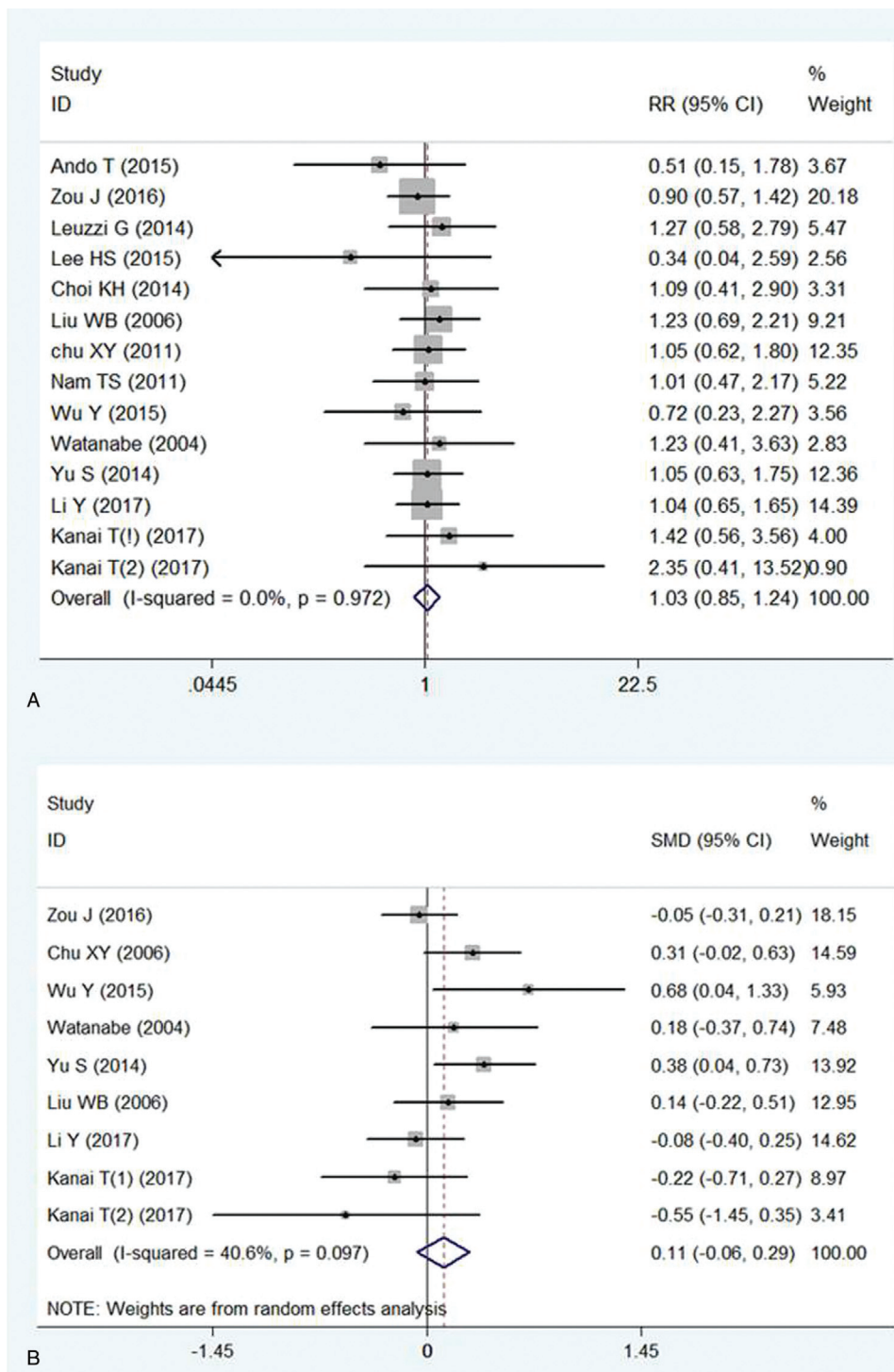


Figure 3. Meta-analysis evaluated the effect of basic characteristics upon the risk of PMC. Figure3a: forest plot compared the incidences of PMC between female MG patients and male MG patients. Figure3b: forest plot presented mean age for PMC patients versus non-PMC patients.

rate ranges from 30% to 50%.^[24,25] In addition, receiving thymectomy is another inducing factor of MC.^[25] Therefore, the presence of MC history should be valued before thymectomy for MG patients.

In this study we found thymoma is related to a higher risk of PMC, which may be explained by 2 possible reasons. First, about 10% to 20% of MG patients are associated with thymomas.^[26]

MG associated thymoma exports auto-reactive T cells to peripheral and then the auto-immunity is built in the circulation.^[3,27] During thymectomy, extrusion of thymoma is unavoidable so auto-reactive T cells may be released from thymoma, which leads to deterioration of MG status. Especially when invasive thymoma was not removed completely, auto-reactive T cells may be exported to peripheral continuously. Li

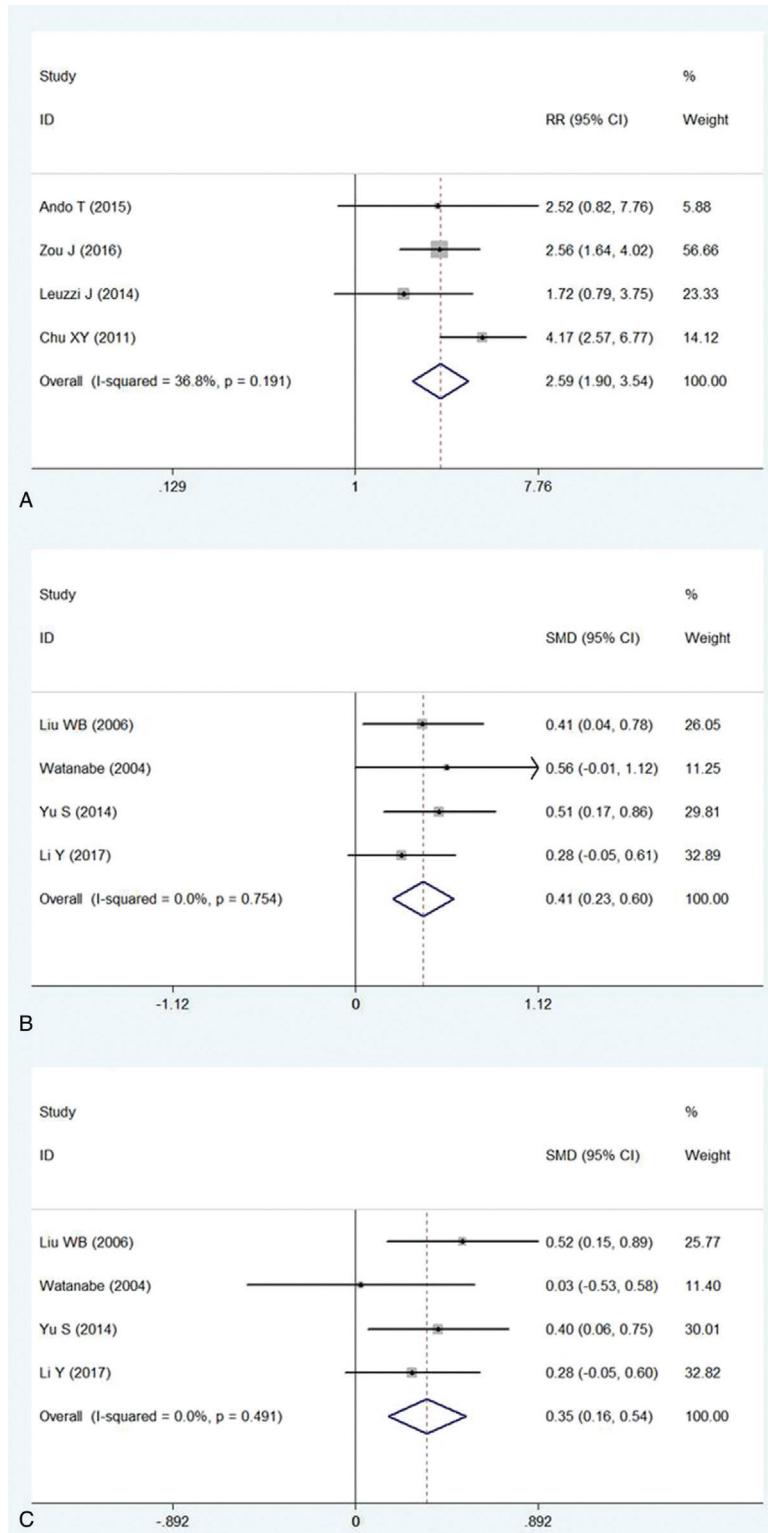


Figure 4. Meta-analysis evaluated the effect of peri-operative medications upon the risk of PMC. 4a: forest plot showed the difference of incidences of PMC between regular steroid use and no steroid use in peri-operative MG patients (sub-group 1), forest plot described the difference of the risk of PMC between high-dose steroid therapy and no steroid use in peri-operative MG patients (sub group 2). 4b: Forest plot presented the risk of PMC for patients treated with immunosuppressive therapy and those without such medication. 4c: forest plot compared mean dose of pyridostigmine between patients with PMC and patients without PMC.

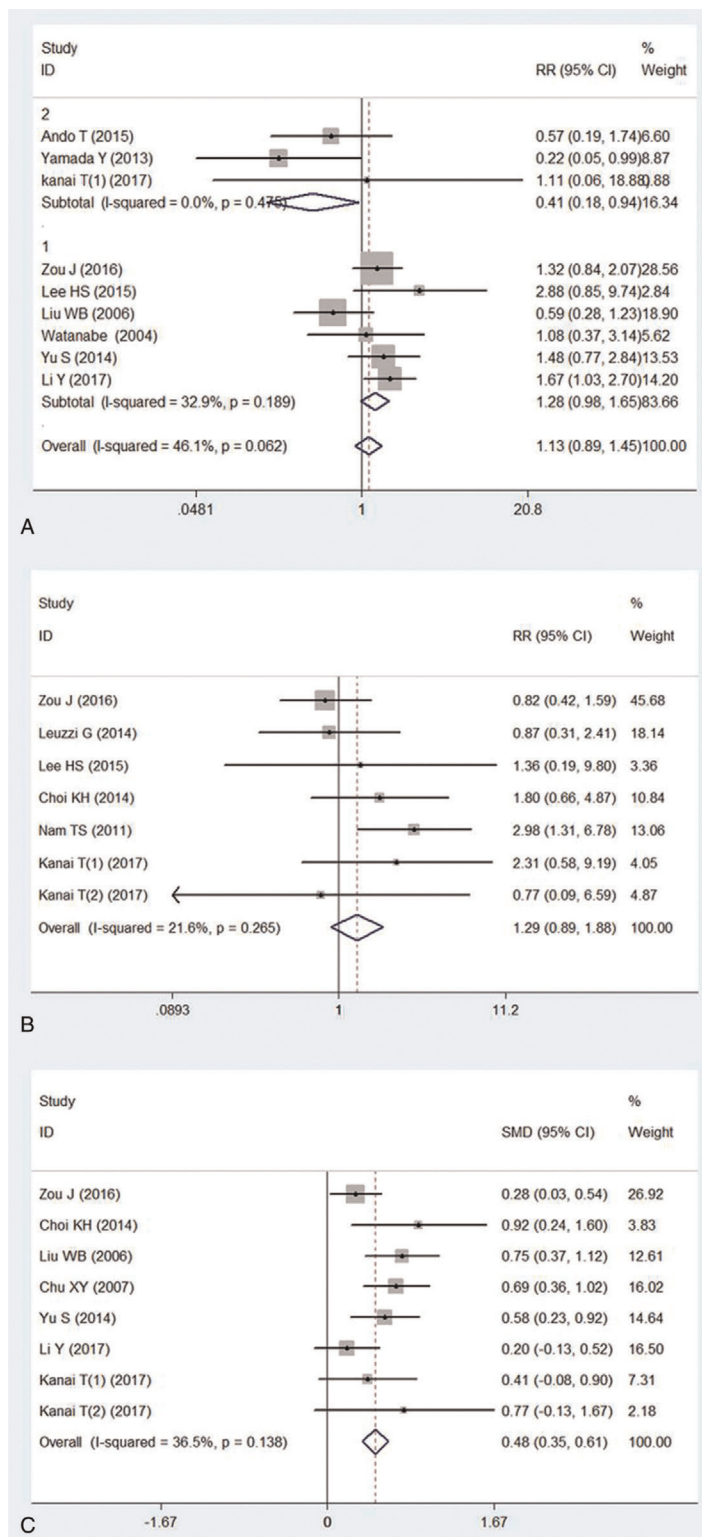


Figure 5. Meta-analysis evaluated the effect of surgical parameters upon the risk of PMC. 5a: forest plot compared possibilities of PMC for MG patients with post-operative complications and those without any complications. 5b: forest plot presented difference of mean surgery time between patients with PMC and patients without PMC. 5c: forest plot presented difference of mean blood loss between patients with and without PMC.

et al^[22] suggested that incomplete resection of thymoma is related to a higher PMC incidence. Second, if invasive thymoma involves surrounding structures (e.g., lung, pericardial and pleura), complete thymectomy requires extended resection. The

risk of PMC may be increased for MG patients underwent pleura resection and lung resection.^[13]

Whether complete resection of thymoma can be achieved is determined not only by extent of tumor invasion, but also by

surgical procedures and methods. To date, VATS has proved to be identical to TS in terms of complete resection of thymus malignancy.^[28] In addition, VATS, the minimally invasive approach most widely used, was once considered as the way of less injury to chest wall, less blood loss, and therefore less PMC occurrence than TS.^[29] But other studies also reported TS is similar with VATS regarding to the risk of PMC.^[30] According to the outcomes of another meta-analysis we found no difference of incidence of PMC between 2 surgical ways.^[31] Besides surgical methods, there are also some surgical factors affecting this complication. In this meta-analysis, the risk of myasthenia crisis increased with longer surgery time and more blood loss.

Severity of myasthenic symptoms also affects PMC occurrence. A more serious MG status may increase the risk of PMC. Depending on the present meta-outcome, generalized MG causes more PMC while ocular MG is safer. Moreover, accompanied by bulbar symptoms is another important predictor of PMC. These conclusions are consistent with findings in previous studies that MG symptoms worse than stage IIA (Osserman type) indicate a higher risk of PMC,^[13] and existence of bulbar symptom is the sign of PMC after thymectomy.^[32] Therefore, it should be cautious for thoracic surgeons to operate on severe generalized MG patients, especially upon those combined with bulbar symptoms.

It has been reported that post-surgery morbidities such as pulmonary infection may result in PMC.^[18] The outcome of present research confirmed this founding. Besides pneumonia, weak pulmonary function also has a strong correlation with PMC.^[14,15] In general, PMC was defined as the need of prolonged ventilation or re-ventilation after surgery for respiratory failure due to muscle weakness, which was brought by myasthenic exacerbation.^[4] Pulmonary weakness may contribute to this process so it is a potential predictor of PMC. Apart from pulmonary infection, other complications have not yet been proved to be related with PMC occurrence. For instance, neither phrenic nerve injury nor palsy was regarded as an inducing factor.^[4,14]

Peri-operative use of pyridostigmine is still controversial. The drug can be either applied for prevention of PMC^[33] or suspended due to prevention of cholinergic crisis.^[34] From this meta-analysis we suggest patients with PMC took a larger dose of pyridostigmine than non-PMC patients. In our opinion, the large-dose anti-cholinesterase medication was used in MG patients with worse MG situations and higher clinical stages, so large-dose pyridostigmine represents a higher risk of PMC. According to the outcome of this study, whether regular steroid and immunosuppressive therapy was applied makes no effect on the risk of PMC. Regular dose of steroid and immunosuppressive therapy are also widely used in MG patients with unstable status, thus no significant effect of preventing PMC was shown. Still no evidence suggests they are useful therapies against PMC. But steroid pulse medication or large-dose steroid use might be an effective way to prevent PMC. Besides steroid pulse therapy,^[21] plasma exchange and immunoglobulin^[35] are also possible options to avoid PMC.

We also found neither age of thymectomy nor gender influences PMC development. Still no evidence indicated age or sex as independent factors of PMC.

There are several limitations in this meta-analysis. Some clinical factors may affect the risk of PMC, such as anti-AchR Ab titer and concomitant disease were not involved in this research. Available articles were somehow few and no high-quality research was included in this meta-analysis.

In conclusion, myasthenia crisis history, post-surgery morbidities, generalized MG, thymoma, and bulbar symptoms are possible risk factors of PMC. Steroid pulse therapy may prevent PMC. Longer surgery duration and more blood loss may also contribute to PMC. Regular dose of steroid, application of immunosuppressive therapy, and male or female make no effect on PMC.

Author contributions

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Supervision: Yun Wang.

Validation: Yun Wang.

Writing—original draft: Yun Wang.

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