Factors predicting perioperative outcomes in patients with myasthenia gravis or thymic neoplasms undergoing thymectomy by video-assisted thoracoscopic approach

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Abstract

Background: The purpose of this study was to identify the factors which predict the perioperative outcomes after video-assisted thoracicoscopic surgery (VATS) thymectomy in patients with myasthenia gravis (MG) or thymic neoplasms

Patients and Methods: Data of consecutive patients who had undergone VATS thymectomy in our institution from August 2016 to April 2018 were collected retrospectively from a prospectively maintained database followed by prospective recruitment of patients who underwent VATS thymectomy from April 2018 to February 2020.

Results: A total of 31 patients were included. Females were more common (51.6%), and 29 patients (93.5%) had MG. The most common indication for thymectomy was the presence of both MG and thymoma (51.6%). Most MG patients had moderate disease (55.2%) or severe (24.1%) disease preoperatively. Mean operative time and blood loss were 196.9 ± 63.5 min and 122.5 ± 115.3 ml, respectively. Mean hospital stay was 7.9 ± 6.7 days. The rate of major and minor complications was 16.18% and 35.4%, respectively. Multivariate linear regression analysis established that MG symptoms >12 months, prolonged invasive ventilation (intubation ≥24 h), and complications were associated significantly with a prolonged hospital stay. Adjusting for outliers, pre-operative disease severity (MG Foundation of America class), and intubation ≥24 h were the only factors that had a significant impact on perioperative outcomes.

Conclusion: Pre-operative disease severity and post-operative invasive ventilation are strong determinants of perioperative outcomes. Pre-operative optimisation and early extubation protocols can further reduce morbidity in patients undergoing thymectomy by the VATS approach.

Keywords: Minimally invasive thymectomy, myasthenia gravis, video-assisted thoracoscopic surgery thymectomy, video-assisted thymectomy, videoscopic thymectomy
INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder characterised by antibodies (AchR Abs) against the acetylcholine receptor. Thymic pathology has long been believed to be associated with the development of MG. Ever since Blalock et al. reported a case series showing improvement in MG symptoms after Thymectomy, many surgeons have utilised Thymectomy to treat MG. Conclusive evidence of the role of Thymectomy in MG management is now available. Thymectomy is universally indicated in all cases of Thymoma because of its local invasiveness and also for the additional benefit of improvement of MG. However, evidence shows that MG patients with Thymoma do not respond to thymectomy than those without thymoma.

Surgical approaches for thymectomy include both open and minimally invasive procedures. Regardless of the approach, thymectomy aims to achieve complete removal of all thymic and perithymic tissue, including the mediastinal fatty tissue, which may contain ectopic thymic tissue. Trans-sternal thymectomy has remained the gold standard approach for years. However, it is associated with significant cardiovascular and respiratory morbidity due to the sternal incision and the long-lasting post-operative pain. The Video-Assisted Thoracoscopic Surgery (VATS) approach has recently emerged as an alternative to the open technique with comparable neurological outcomes and better surgical outcomes. Various factors believed to influence outcomes after VATS Thymectomy, like old age, increased ventilatory support and post-operative myasthenic crisis (POMC), has been studied extensively. However, there is a paucity of data in the literature regarding the other factors which impact surgical outcomes. This study was undertaken to identify the factors which affect the perioperative outcomes of patients undergoing VATS Thymectomy for either MG or thymic neoplasms.

PATIENTS AND METHODS

Patient population
This ambispective study includes the retrospective collection of data from a prospectively maintained database of consecutive patients who underwent VATS thymectomy from August 2016 to March 2018, followed by prospective recruitment of patients from March 2018 to February 2020. Institutional Ethics Committee clearance was obtained for this study.

The diagnosis of MG was based on clinical, radiological and imaging characteristics. Equivocal results required single fibre electromyography for final confirmation. Pre-operative Disease severity was classified based on the MG Foundation of America (MGFA) clinical classification system. All patients were evaluated in the Department of Neurology for the severity of MG and started on immunosuppressant and acetylcholinesterase inhibitors as per requirement. Contrast-enhanced computed tomography of the chest was done to look for thymic mass in all patients. Patients were referred to surgery after a period of clinical stabilisation of myasthenic symptoms and when the oral corticosteroid (prednisolone) was tapered to a minimal dose of 10–15 mg/day before surgery. All thymic epithelial tumours were staged using the Modified Masoaka Koga system. Histological classification of thymic tumours was done based on the 2004 revision of the WHO classification system.

Criteria
Patients with Generalised MG between the ages of 18–70 years, with not more than 10 years of disease onset, were included in the study. Patients with thymic neoplasms deemed suitable for the VATS approach were also included. Exclusion criteria were patients unsuitable for Thymectomy by the VATS approach, those with the poor general condition and multiple uncontrolled co-morbidities, and pregnant or lactating mothers. Written informed consent was taken from all patients before recruitment.

Surgical technique
We performed a VATS Extended Thymectomy technique in all patients with Thymectomy irrespective of the presence or absence of MG. We usually preferred a right-sided approach for most patients with hyperplasia or central and right-sided thymic tumours due to constraints with the heart in a left-sided approach. In addition, the right-sided approach helps in more straightforward surgery because the superior vena cava-innominate vein junction can be easily identified, and the ergonomic advantage it offers for righthanded surgeons. Patients with large left-sided tumours underwent a bilateral approach. All patients were operated under General Anaesthesia with a double-lumen endotracheal tube with confirmation of position using Bronchoscopy. The patient is positioned in a partial left lateral decubitus position with the right chest elevated to 30 degrees using a sandbag. The right arm is kept abducted overhead and supported on armrest. Supine position with both arms abducted was used for bilateral approaches. We used triportal technique with one 10 mm camera port at the 5th intercostal space (ICS) in the midclavicular line and one 10 mm port at the 4th or 5th ICS in the midaxillary line and one 5 mm port in the 3rd ICS in the anterior axillary line, respectively.
Dissection was initiated at the right lower pole of the thymus after identifying the right phrenic nerve and incising the mediastinal pleural just anterior to it. After dissecting the right inferior pole along with fatty tissue, proceeds along the superior vena cava (SVC) using either hook electrocautery or bipolar energy device (Ligasure, Covidien). The next vital landmark to be identified is the SVC-innominate vein junction. The right upper cervical pole was identified anterior to the innominate vein and pulled gently down. The thyro-thymic ligament was divided using blunt dissection and bipolar cautery. Identification of thymic veins is crucial because they drain directly into innominate and can cause significant bleeding if uncontrolled. Gentle inferior traction would reveal thymic veins, which are either clipped or sealed using vessel sealer doubly. Once the right lobe of the thymus is freed completely, we next dissect the left inferior pole and proceed superiorly. Surgical boundaries include the bilateral phrenic nerves laterally, the brachiocephalic veins superiorly, and the dome of the diaphragm inferiorly. Any mediastinal lymph nodes detected incidentally were also biopsied. Specimen extraction was done using a wound protector by enlarging the 10 mm port or via a mini-thoracotomy incision for larger sized specimens to prevent crushing. Intercostal drainage tubes were placed ipsilaterally and contralaterally if the pleura was breached. Specimens were labelled according to ITMIG guidelines. All medications, including cholinesterase inhibitors and immunosuppressants, are continued post-operatively. Extubation was done as per the intensive care unit (ICU) protocol. Oral liquids were started after extubation and soft diet the next day. Patients were shifted after 24 h of observation in the ICU.

**Outcomes**
The primary endpoint of the study was the perioperative outcomes after VATS thymectomy. We decided upon the duration of hospital stay as the main indicator of perioperative outcomes. The hospital stay was calculated from the day of surgery to the date of discharge. A preset criterion for fitness for discharge, which included normal body temperature and cardio-respiratory parameters, no pain or minimal pain which was well controlled with oral analgesics, able to carry out normal daily activities, no intravenous infusions, taking normal diet orally was defined. Secondary endpoints include operative time, blood loss, and rate of complications. Complications were defined and graded based on Clavien Dindo grading of complications. POMC was defined as a total post-operative mechanical ventilation support time of more than 48 h with no post-operative cardiopulmonary complications or cholinergic crisis. Patients with respiratory failure from postop phrenic nerve palsy were excluded from post-operative crisis.

**Statistical analysis**
SPSS version 23 (SPSS Inc, Chicago, USA) was used for analysis. Categorical data were expressed as frequency and percentages, while continuous variables were expressed as means with standard deviations or as medians with interquartile range, where appropriate. Categorical variables were compared using the Chi-square or Fisher's exact tests. Continuous variables were compared using the Student's unpaired t-test or Mann–Whitney U-test. P < 0.05 were considered significant.

**RESULTS**

**Patient characteristics**
In this study involving 31 patients, the mean age was 40.7 years, and 51.6% were females. As described in Table 1, 38.7% had co-morbidities, with 9.6% having more than two comorbidities. Twenty-nine patients (93.5%) had MG, and the mean duration of MG symptoms was found to be 12.9 months. Early-onset Myasthenia (i.e., disease onset <45 years) was the most common type seen in 20 patients (64.5%). Most patients had moderate (55.2%) to severe (24.1%) disease defined as MGFA Class III or greater. Thymoma was detected in 18 (58%) of the participants, whereas the most common indication for a participant to undergo VATS thymectomy was found to be the presence of both MG and thymoma (51.6%). A comparative analysis of the perioperative outcomes in patients with and without thymoma revealed that there was no significant difference between the groups in terms of any of the variables, as mentioned in Table 2, except for the duration of intubation. A trend towards increased risk of complications was noted in the thymoma group (TG) but was statistically insignificant.

**Surgical outcomes**
All VATS surgeries were performed by the same surgical team. The majority of patients (86%) underwent a right-sided approach, while five patients (13.8%) underwent a bilateral approach for large left-sided lesions. Mean blood loss was 122.5 ml, and none of our patients required blood transfusions intraoperatively or post-operatively. No patient required conversion to thoracotomy or sternotomy. The mean duration of hospital stay was 7.9 days. Multivariate linear regression analysis established that MG symptoms >12 months, intubation ≥24 h, and complications were associated significantly with increased duration of hospital stay. However, adjusting for the outliers of hospital stay...
duration, it was found that the pre-operative disease severity (MGFA class) and intubation ≥4 h were the only factors that had a significant impact on hospital stay. Intubation ≥24 h was also associated with the presence of complications [Table 3]. PMAC was the most common (6.9%) major complication seen after VATS thymectomy. Subgroup analysis showed that complications following VATS Thymectomy were more commonly seen in the TG. Phrenic nerve palsy was seen in four patients in the TG group, for which one patient required diaphragmatic plication in the postop period. No patients had died in the perioperative period in both groups [Table 3].

Histopathological outcomes and follow-up
Histological diagnosis of Thymoma was made in 18 patients (58%), while nine patients had thymic hyperplasia (31%), and three patients had normal thymus (10.3%), and one patient (3.2%) had a thymic cyst. The most common histological subtype of thymoma in our cohort was B2 and B3 (25%). The mean tumour size was 5.6 cm (range 2.5–8 cm). All patients had Masaoka Stage I (62.5%) or Stage II (37.5%) tumours. Out of 6 patients with Stage II tumours, 2 (1.8%) had microscopic margin positivity (R1 resection) for which they received adjuvant radiation.

The median duration of follow-up was 14 months (2–32 months). Two patients in the TG group had died, one due to Myasthenic crisis 2 months after her surgery, and the other patient died of cardiac causes after 1 year. No mortality was seen in the Non thymoma group (NTG) group till now. One patient in NTG was lost to follow up. Response to MG was assessed by DeFilippi Classification. Table 4 highlights the response of MG to Thymectomy based on DeFilippi classification, and most of the study population were asymptomatic, on reduced medications (51.7%), while two patients (6.9%) had complete remission (CR). No significant difference between the thymoma and non-TG could be elicited (P = 0.39).

Table 1: Baseline characteristics

| Characteristic                                | n (%)               |
|----------------------------------------------|---------------------|
| Gender                                       |                     |
| Male                                         | 15 (48.4)           |
| Female                                       | 16 (51.6)           |
| Age (years), mean±SD                         | 40.7±14.9           |
| BMI (kg/m²), mean±SD                         | 23.4±4              |
| Comorbidities                                |                     |
| Yes                                          | 12 (38.7)           |
| No                                           | 19 (61.2)           |
| Indication for VATS thymectomy               |                     |
| Generalized MG                               | 13 (41.9)           |
| Thymoma                                      | 2 (6.4)             |
| MG + thymoma                                 | 16 (51.6)           |
| Patients with MG                             | 29/31 (93.5)        |
| Duration of MG symptoms (months), median (range) | 6 (1–48)         |
| Preoperative disease severity (MGFA class)   |                     |
| Mild (MG II)                                 | 6 (20.7)            |
| Moderate (MG III)                            | 16 (55.2)           |
| Severe (MG IV, V)                            | 7 (24.1)            |
| AchRAb positive MG                           | 27/29 (93.1)        |
| Hospital admissions due to MG related issues |                     |
| Yes                                          | 16 (55.2)           |
| No                                           | 13 (44.8)           |
| Previous history of myasthenic crisis        |                     |
| Yes                                          | 18 (58)             |
| No                                           | 13 (41.9)           |
| Median follow up and range (months)          | 14 (2–32)           |

SD: Standard deviation, BMI: Body mass index, VATS: Video-assisted thoracoscopic surgery, MG: Myasthenia gravis, MGFA: Myasthenia Gravis Foundation of America

Table 2: Perioperative outcomes in patients with and without thymoma

| Outcome                                      | Total (n=31) | With thymoma (n=18), n (%) | Without thymoma (n=13), n (%) | P† |
|----------------------------------------------|--------------|-----------------------------|-------------------------------|----|
| Operative duration (min)                     | 196.90±63.53 | 210.22±67.79                | 178.46±54.29                 | 0.17|
| Blood loss (ml)                              | 122.58±115.35| 138.89±141                  | 100.00±61.23                 | 0.36|
| ICU stay (h)                                 | 32.10±17.27  | 36.50±20.87                 | 26.00±7.74                   | 0.09|
| Duration of intubation (min)                 | 758.55±628.89| 990.00±639.71               | 438.08±466.25                | 0.01*|
| Hospital stay (days)                         | 7.97±6.92    | 9.78±8.52                   | 5.46±2.29                    | 0.08|
| Major complications‡                        | 5 (16.12)    | 5 (27.78)                   | 0                             | 0.058|
| Postoperative myasthenic crisis             | 2 (6.45)     | 2 (11.1)                    | 0                             | 0.058|
| Postoperative weakness causing reintubation  | 1 (3.22)     | 1 (5.55)                    | 0                             | 0.058|
| Phrenic nerve palsy requiring diaphragmatic  | 1 (3.22)     | 1 (5.55)                    | 0                             | 0.058|
| Pleural effusion requiring drainage          | 1 (3.22)     | 1 (5.55)                    | 0                             | 0.058|
| Minor complications‡                        | 11 (35.4)    | 6 (35.4)                    | 5 (38.46)                    | 0.76|
| Post-op weakness requiring noninvasive       | 3 (9.67)     | 2 (11.1)                    | 1 (7.69)                     | 0.76|
| Phrenic nerve palsy managed conservatively   | 3 (9.67)     | 3 (16.67)                   | 0                             | 0.12|
| Atrial fibrillation                          | 1 (3.22)     | 0                           | 1 (7.69)                     | 0.058|
| Port site infection                          | 2 (6.45)     | 0                           | 2 (15.38)                    | 0.058|
| Atelectasis                                  | 1 (3.22)     | 1 (5.55)                    | 0                             | 0.058|
| Others - postoperative depression            | 1 (3.22)     | 0                           | 1 (7.69)                     | 0.058|
| Phrenic nerve palsy                          | 4 (12.90)    | 4 (22.22)                   | 0                             | 0.058|
| 30-day mortality                             | 0            | 0                           | 0                             | 0.058|

*P<0.05, †Mann-Whitney U-test was used as the test of significance for continuous variables, and Fischer exact test was used for the categorical variables. ‡Major complications are defined as Clavien-Dindo Grade 3, 4 and 5 while Grade 1 and 2 are considered as minor complications.
DISCUSSION

Current evidence in the VATS approach shows better perioperative with equivalent neurological outcomes to the trans-sternal approach, even though data are mostly retrospective with a few prospective trials. We have presented our experience of VATS Thymectomy and compared our results to similar series published elsewhere (Table 5). Although Intraoperative and immediate post-operative outcomes are mostly comparable, there is a significant difference in the long-term neurological outcomes. Studies have shown that Thymectomy produced CR rates of 30%–60% depending on different follow-up periods and pre-operative severity of the disease. Our CR rates were low because our median follow-up was only 14 months. However, our clinical improvement rate was comparable to similar studies, indicating a longer duration of follow-up is an essential factor for achieving CR after Thymectomy. In this study, we have attempted to define the various factors which impact the perioperative outcomes to stratify patients better pre-operatively.

Our analysis (linear regression analysis accounting for outliers) identified that the older patient population had a significantly prolonged hospital stay. This is similar to previous studies, which have shown that increasing age is a risk factor for increased length of hospital and ICU stay. Older patients had lengthier ventilatory support than younger patients with MG. Old age >50 years is an independent prognostic factor for developing POMC, which significantly impacts the post-operative outcome. However, this should not preclude thymectomy’s role in this population as the long-term neurological outcomes and the benefits of decreased immunosuppression likely outweigh the short-term morbidity.

POMC is a severe complication with an incidence of 0%–24.7%. In our study, POMC incidence was 6.45%, and it was the most common major complication. Some authors argue that myasthenic crisis cannot be considered a surgical complication per se as it can also occur in patients managed conservatively. On the other hand, most authors include POMC as a part of surgical complications because it is a significant predictor of post-operative outcomes. We believe adequate pre-operative optimisation of disease status can decrease the incidence and severity of POMC and include it as a measure of pre-operative optimisation. Various predictive risk models for POMC have been developed, but none have been validated in a prospective study. Pre-operative disease severity, history of myasthenic crisis pre-operatively, presence of bulbar symptoms, disease duration of more than 2 years, increased body mass index, presence of Thymoma, and need for additional lung resection are some common factors which are included in most risk prediction models. Kanai et al. developed a POMC predictive score based on three

### Table 3: Factors associated with worse perioperative outcomes after video-assisted thoracoscopic surgery thymectomy

| Variable                                      | Hospital stay | Complications |
|----------------------------------------------|---------------|---------------|
| Age                                          | 0.84          | <0.05*        | 0.49          |
| Gender                                       | 0.17          | 0.32          | 0.23          |
| Comorbidity                                  | 0.54          | -             | 0.80          |
| MGFA class                                   | 0.37          | 0.07          | 0.04*         |
| MG symptoms >12 months                       | 0.10          | 0.02*         | 0.10          |
| Preoperative myasthenic crisis               | 0.15          | 0.78          | 0.82          |
| OT duration >3 h                             | 0.27          | 0.48          | 0.44*         |
| Blood loss >100 ml                           | 0.46          | -             | 0.78          |
| Intubation >24 h                             | 0.02*         | 0.04*         | 0.04*         |
| ICU stay >48 h                               | 0.54          | -             | 0.82          |
| Complications                               | 0.03*         | 0.03*         | 0.07          |
| Presence of thymoma                          | 0.08          | 0.34          | 0.02*         |

Mann-Whitney U-test was used as the test of significance for continuous variables, and Fischer exact test was used for the categorical variables.

### Table 4: Response of myasthenia gravis to thymectomy - DeFilippi classification

| DeFilippi classification                      | Total (n=29) | With thymoma (n=16) | Without thymoma (n=13) | P   |
|----------------------------------------------|--------------|---------------------|------------------------|-----|
| Remission, off medications                   | 2 (6.9)      | 2 (12.5)            | 0                      | 0.39|
| Asymptomatic, reduced medications           | 15 (51.7)    | 6 (37.5)            | 9 (69.23)              |     |
| Improved, on medications                     | 7 (24.1)     | 5 (31.25)           | 2 (15.38)              |     |
| No change                                   | 2 (6.9)      | 1 (6.25)            | 1 (7.69)               |     |
| Worse                                        | 1 (3.4)      | 1 (6.25)            | 0                      |     |
| Lost to follow up                            | 2 (6.9)      | 1 (6.25)            | 1 (7.69)               |     |

*Data of patient who had expired after 1 year included in TG group. TG: Thymoma group
Our analysis did not reveal any difference between thymoma and non-thymoma patients in perioperative outcomes. However, a trend towards increased complications was seen in thymoma patients. Phrenic nerve palsy was seen in four (12.9%) of all thymectomy patients, and all of them belonged to TG. All except one were left-sided lesions. Among this subgroup, the mean tumour size was 4.75 cm (2.5–8). The bilateral approach was used in two patients. Intraoperatively, the phrenic nerve was encased in two patients and two other patients, the mass was infiltrating the left pleura abutting the phrenic nerve. This suggests that critical tumour location rather than inadequate visualisation could be the cause of phrenic nerve injury. One patient required VATS re-exploration with diaphragmatic plication while the other three were managed conservatively.

As true for most surgeries, the surgeon factor is also one of the significant determinants of surgical outcomes. Toker et al.[26] had analysed their retrospective data of 90 patients undergoing VATS Thymectomy and concluded that at least 60 surgeries are to be performed before the results plateaued. The length of hospital stay was not dependent on the learning curve. Instead, it was dependent on the myasthenic condition of the patient. Subgroup analysis of our data into the first 15 patients and the next 16 patients showed no significant differences in the outcomes between the two groups.

Based on our study results, we believe that pre-operative MG optimisation is of utmost importance to improve surgical outcomes. The optimal timing of Thymectomy after Myasthenic crisis has not been established. Though we included patients for surgery only if they were well controlled on myasthenic medications, those with a history of crisis episodes <3 months ultimately developed POMC. Further research is required to identify the optimal duration between a crisis episode and surgery.

The strengths of our study include standardised surgical technique and post-operative care and the prospective collection of data. Limitations of the study include

| Variable | VATS approach, n (%) | Trans-sternal approach, n (%) |
|----------|----------------------|-------------------------------|
| Mean operative duration (min) | Our study (n=31) 196±90±63.53 | Rowse et al.[11] (n=45) 102±39 | Mineo and Ambrogi[12] (n=47) 150±35 | Xie et al.[13] (n=31) 80 |
| Mean blood loss (ml) | 122.5±88±115.35 | 65±41 | 180±39 | 120 |
| Mean hospital stay (days) | 7.97±9.2 | 3.8±1.2 | 9 (5-16) |
| Conversion to open | 0 | 0 | 4 (8.5) | 0 |
| Major complications | 5 (16.12) | 7 (16) | 1 (2.1) | 2 (6.5) |
| Complete remission | 2/29 (6.9) | 1/16 (6.3) | 19/47 (40) | 52.10 |
| Mean follow up (months) | 14** (2-32) | 18.4 | 149±45 | 42** (25-97) |

**Median follow-up. NA: Data not available

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[26] Toker et al.
the stringent inclusion criteria, which might affect the generalisability of the results. Small sample size and short duration of follow-up are other limitations. Other factors, like vital pre-operative capacity and drug dosages, have not been included in the analysis, which may affect our findings.

CONCLUSION

VATS approach for thymectomy offers excellent perioperative outcomes. Pre-operative Risk stratification can identify patient subgroups who require better optimisation. Standardisation of postoperative care, including early extubation, can further reduce perioperative morbidity and improve outcomes of the VATS approach.

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Conflicts of interest
There are no conflicts of interest.

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