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Myasthenia is a poor prognostic factor for perioperative outcomes after robotic thymectomy for thymoma

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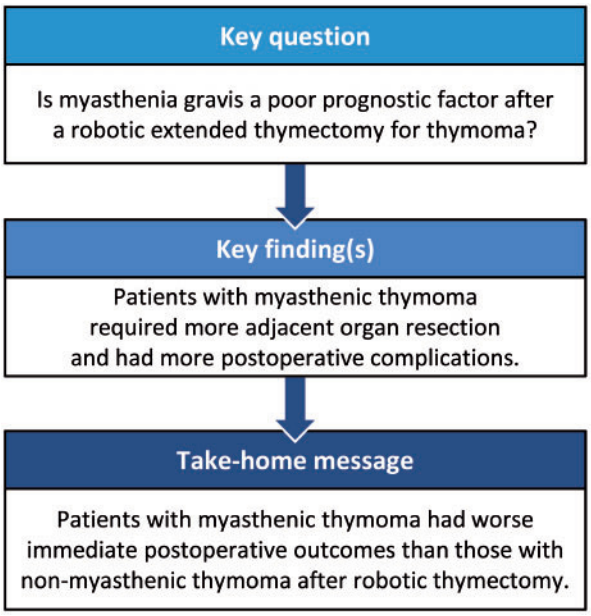

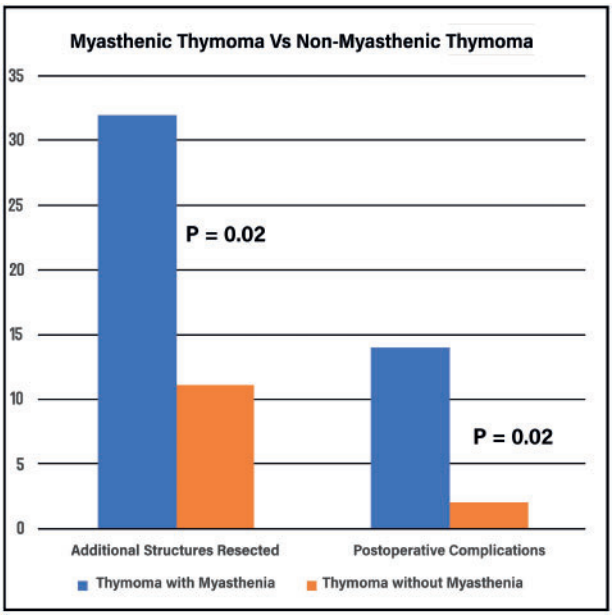

Abstract

OBJECTIVES: The goal of this study was to compare the early and intermediate surgical outcomes, including the survival of those with and without myasthenic thymoma, following robotic thymectomy.

METHODS: This is a retrospective analysis of prospectively maintained data of 111 patients who underwent robotic thymectomy for thymoma over 7 years in a thoracic surgery centre in India. We performed a comparative analysis of demographics, intraoperative variables and postoperative outcomes including survival of those with and without myasthenic thymoma.

RESULTS: Of 111 patients, 68 patients were myasthenic and 43 were non-myasthenic. The need to resect surrounding structures and conversions was greater in the myasthenic group ($P = 0.02$, $P = 0.04$). Postoperative complications were significantly higher in the myasthenic group ($P = 0.02$). No differences were observed in intensive care unit stay, the need for postoperative ventilation and the hospital stay. On correlation, a higher Masaoka stage [odds ratio 1.96, 95% confidence interval (CI) 1.22–3.15] and an aggressive World Health Organization

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histological diagnosis (odds ratio 1.58, 95% CI 1.10–2.26) were more likely in patients with myasthenia gravis. A total of 7 deaths (6.3%) occurred during the median follow-up of 4.2 years, 5 among those with myasthenic thymoma and 2 among patients with non-myasthenic thymoma. Due to the small number of deaths, there is insufficient evidence to draw any conclusion about the effect of myasthenia gravis on survival after surgery (hazard ratio 0.51, 95% CI 0.09–2.71; $P = 0.43$).

CONCLUSIONS: The presence of myasthenia with thymoma is associated with more adjacent structure resection, higher postoperative complications and more conversions. The use of robotic surgery for thymoma resection in patients with myasthenia could not overcome the early postoperative problems related to myasthenia gravis.

Keywords: Thymoma • Robotic thymectomy • Myasthenia gravis • Prognostic factors

ABBREVIATIONS

CI	Confidence interval
CT	Computed tomography
MG	Myasthenia gravis
VATS	Video-assisted thoracic surgery
WHO	World Health Organization

INTRODUCTION

Thymoma is the most common anterior mediastinal tumour in adults [1]. Although thymomas are known for their indolent behaviour, it is not uncommon to find them invading surrounding structures and even disseminating to pleura and distant organs. Complete surgical resection with negative margins is the most significant factor that determines the prognosis [2]. The rarity of these tumours has made development of standards for staging, histological diagnosis and treatment difficult. Commonly used staging systems include the modified Masaoka–Koga clinical staging system [3], the modified World Health Organization (WHO) Histological classification system [4] and The Myasthenia Gravis Foundation of America classification for myasthenia gravis (MG) status [5].

Extended thymectomy via a median sternotomy has been largely accepted as the gold standard for thymoma [6]. However, the da Vinci Robotic System has emerged as an effective alternative to open surgery with better perioperative outcomes like reduced postoperative pain and hospital stay, fewer postoperative complications and fewer deaths compared to open sternotomy [7, 8]. These benefits are more pertinent and relevant if the patient is myasthenic.

The prognostic significance of the WHO histological and Masaoka staging systems in the long-term outcomes of thymectomy has been well studied [9]. However, the role of MG (being the most common paraneoplastic syndrome associated with thymoma) as a prognostic factor in the short- and long-term outcomes is largely unknown and has not been studied extensively, particularly in relation to robotic surgery. Our goal was to fill this gap by evaluating the role of MG as a prognostic factor in patients who underwent robotic extended thymectomy for thymoma.

MATERIAL AND METHODS

Study population

This is a retrospective analysis of 111 patients with or without MG who underwent robotic thymectomy for thymoma from March 2012 to December 2019 at a tertiary level thoracic surgery centre. Consent for the study was obtained from all patients. This study was approved by the institutional ethics committee.

Preoperative evaluation

Each patient provided a detailed history, and a physical examination was done to enable us to assess their general condition and comorbidity status. A contrast-enhanced computed tomography (CT) scan of the chest was performed routinely to assess the tumour size, extent, involvement of surrounding structures and presence of pleural nodules. In our practice, positron emission tomography CT was not performed routinely [10]. Anti-acetylcholine receptor antibody levels were measured in all patients with thymoma to rule out MG. A neurology consultation was sought for optimal analysis of the myasthenic symptoms before the surgical intervention. Contraindications for robotic-assisted thymoma resection were invasion of major vascular structures (superior vena cava, innominate veins, aorta, pulmonary artery) by the tumour and pleural and pericardial metastases.

Surgical technique

Surgical procedures were performed using the da Vinci Si System (Intuitive Surgical, Sunnyvale, CA, USA). The side of the surgical approach depended on the location and extension of the mass. If the mass was located predominantly to the left of the midline, we used a left-sided approach and vice versa. In cases where the epicentre of the mass was in the midline, we preferred the left-sided approach. All patients were operated on in the supine position with the operative side elevated 30°. A diagnostic thoracoscopy was performed in all patients to rule out unsuspected pleural or pericardial deposits and to assess the feasibility of the robotic approach. An extended thymectomy involving removal of the entire thymus gland along with all mediastinal/pericardial fat between the 2 phrenic nerves from the thyro-thymic ligaments down to the pericardiophrenic recess was performed in all cases. If the tumour was densely adherent to the lung, the pericardium or the phrenic nerve, a wedge of the adherent lung/patch of pericardium/segment of the phrenic nerve was resected *en bloc* with the mass. If patients required emergency/elective conversions, a midline sternotomy was used. A pericardial defect was always repaired with polyglactin mesh. In the case of a phrenic nerve resection, the ipsilateral diaphragm was always plicated. The specimen was placed in a plastic bag and removed *en bloc*.

Postoperative care

Patients were extubated at the end of the operation whenever possible. Those requiring postoperative ventilation were kept on

a ventilator until they were extubated. They were mobilized on the first postoperative day, and early oral nutrition was started. If the patient was myasthenic, we watched carefully for worsening of myasthenic symptoms or signs of a myasthenic crisis. The intercostal drains were removed when there was no air leak and when the drainage was not purulent/haemorrhagic and was <100 ml in 24 h. The duration of the postoperative air leak (if >5 days), duration of chest tube, hospital stay, wound infection, worsening of myasthenia and other complications were monitored and recorded.

Adjuvant therapy

Adjuvant therapy was advised based on operative findings and on the final histopathology report. The histological diagnosis was based on the WHO histological classification system. In an AB thymoma, if B1 was the major combined component, it was reported as an AB thymoma; if B2 or higher was the predominant component, it was classified according to the highest B component. In a combined B category (B1/B2 or B2/B3), the type of thymoma was determined according to the higher grade of B category. Type C thymoma (previously thymic carcinoma) was not included in this study. Tumour clinical stage was decided as per the modified Masaoka–Koga classification system. Postoperative radiotherapy was advised for all stage II, III and IVA tumours, regardless of histological diagnosis, and all R1/R2 resections. Adjuvant chemotherapy was also suggested for patients with pleural metastases.

Follow-up

Initial follow-up was done on an out-patient basis 1 month after discharge. A detailed physical evaluation including history of myasthenic symptoms was carried out at every visit. We routinely advise a contrast-enhanced CT scan every year for 10 years.

Statistical analyses

Statistical testing was conducted with the Stata software 15.0 (StataCorp LLC, College Station, TX, USA). Continuous variables are presented as mean ± standard deviation. Categorical variables are expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using the Student's *t*-test. Nominal categorical data between the groups were compared using the χ^2 test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using the Mann–Whitney *U*-test. The survival probabilities were calculated by the Kaplan–Meier method from the date of the operation until death. The differences in survival were evaluated with the log-rank test. Univariable Cox regression analysis was used to investigate the effect of MG on survival, and the proportional hazards assumption test was assessed based on Schoenfeld residuals (phtest). The correlation of MG with the Masaoka stage and the WHO histological grade was assessed using linear regression analysis. For Masaoka stage and WHO histological classification, ordinal regression analysis was used. The odds ratios mentioned are per point and are the same between successive grades and stages. For all statistical tests, a *P*-value <0.05 was considered significant.

RESULTS

Overall demographic characteristics

A total of 111 patients had a robotic radical thymectomy for thymoma. There were 74 men (66.7%) and 37 women (33.3%), with a mean age of 48.4 years (range 18–72 years). Sixty-eight patients (61.3%) had MG associated with thymoma. Patients with myasthenic thymoma had earlier onset of symptoms than those with non-myasthenic thymoma (5.4 ± 5.1 vs 8.3 ± 7.6 months) (Table 1).

Thymoma with myasthenia versus thymoma without myasthenia

Intraoperative variables.. The mean tumour diameter was larger (6.5 ± 3.1 cm) in the non-myasthenic thymoma group, but the difference was not statistically significant ($P = 0.07$). Duration of surgery and intraoperative blood loss were similar in both groups. However, the requirement for resection of the surrounding structures (pericardium, lung, phrenic nerve and left brachiocephalic vein) was greater in the myasthenic thymoma group, and this difference was statistically significant ($P = 0.02$). For this reason, 7 patients needed conversion to sternotomy or thoracotomy in the myasthenic thymoma group and none in the non-myasthenic thymoma group ($P = 0.04$). Among 7 conversions in the myasthenic thymoma group, 5 were elective and 2 were emergency conversions in view of iatrogenic vascular injury (Table 1). No conversions were required in the non-myasthenic thymoma group.

Postoperative variables and complications.. No difference was observed between the 2 groups regarding variables such as the need for ventilation, postoperative stay in the intensive care unit, duration of intercostal drains and total hospital stay. However, the total number of postoperative complications was significantly higher in the myasthenic thymoma group (14 vs 2; $P = 0.02$). Aggravation of myasthenic symptoms postoperatively was the most common complication, which was managed with upgrading of myasthenic medications as per the neurologist's advice. After excluding the myasthenic crisis ($n = 3$) from the total complications in the myasthenic group ($n = 14$), the difference in the overall complications was still higher, though statistically non-significant ($P = 0.07$). Cardiac arrhythmias, postoperative pleural collection and chyle leak were other complications. Pleural collections were managed with a pigtail drainage catheter. One patient with a chyle leak was managed conservatively with a medium-chain triglyceride diet and injection octreotide therapy, whereas the second patient required re-exploration and video-assisted thoracic surgery (VATS) thoracic duct ligation. Postoperative bleeding occurred in 1 patient who was also re-explored for control of the bleeding source. The left internal mammary vein was the culprit in this case (Table 1).

Mortality

There were no perioperative deaths (<90 days). However, in the median follow-up of 4.2 years, 7 deaths (6.3%) occurred: 5 in the myasthenic thymoma group and 2 in the non-myasthenic thymoma group. Of the 5 patients in the myasthenic thymoma group who died, 3 had a myasthenic crisis and 2 had sudden cardiac

Table 1: Comparison of perioperative variables between myasthenic and non-myasthenic thymomas

	Thymoma with MG (*n* = 68)	Thymoma without MG (*n* = 43)	*P*-value
Age (years), mean ± SD	45.7 ± 17.8	51.7 ± 17.9	0.08
Number of patients with comorbidities, *n* (%)	23 (34)	17 (40)	0.55
Duration of symptoms (months), mean ± SD	5.4 ± 5.1	8.3 ± 7.6	**0.02**
Method of surgery, *n* (%)			
Transthoracic robotic thymectomy	68 (100)	43 (100)	
Mean tumour diameter (cm), mean ± SD	5.6 ± 3.9	6.5 ± 3.1	0.07
Preoperative MGFA status, *n* (%)			
I	8 (12)		
II A	17 (25)		
II B	16 (24)		
III A	12 (18)		
III B	12 (18)		
IV	3 (4)		
V	None		
MGFA therapy status, *n* (%)			
CH	24 (35)		
CH, IM (Azathioprine)	2 (3)		
CH, IM (MMF)	3 (4)		
CH, PR	14 (21)		
CH, PR, IM (Azathioprine)	22 (32)		
CH, PR, IM (MMF)	3 (4)		
Mean dosage of medications (mg), *n*			
Pyridostigmine bromide	206		
Prednisolone	26.5		
Azathioprine	131		
Mycophenolate mofetil	1333.3		
Additional structures resected, *n* (%)	32 (47)	11 (26)	**0.02**
Wedge of lung	11 (16)	4 (9)	
Pericardium	14 (21)	6 (14)	
Left phrenic nerve	5 (7)	1 (2)	
Right phrenic nerve	1 (1)	0	
Left brachiocephalic vein	1 (1)	0	
Mean duration of surgery (min), mean ± SD	13 8 ± 110	149 ± 102	0.71
Mean intraoperative blood loss (ml), mean ± SD	110 ± 45	101 ± 38	0.27
Total number of conversions, *n* (%)	7 (10)	0	**0.04**
Postoperative variables			
Need for postoperative ventilation, *n* (%)	2 (3)	0	0.52
Mean duration of postoperative ICU stay (days), mean ± SD	1.15 ± 0.9	1.02 ± 0.7	0.42
Postoperative air leak, *n* (%)	2 (3)	3 (7)	0.37
Postoperative ICD duration (days), mean ± SD	3.4 ± 2.1	2.9 ± 1.8	0.19
Mean hospital stay (days), mean ± SD	5.1 ± 4.9	4.3 ± 4.1	0.37
Complications, *n* (%)			
Total number of overall complications, *n* (%)	14 (21)	2 (5)	**0.02**
Re-exploration for bleeding	1 (1)	0	
Wound infection	1 (1)	0	
Atelectasis and pneumonia	2 (3)	1 (2)	
Cardiac arrhythmias	3 (4)	0	
Postoperative pleural collection	2 (3)	0	
Postoperative chyle leak	2 (3)	1 (2)	
Postoperative myasthenia aggravation	3 (4)	0	
Follow-up mortality (%), *n* (%)	5 (7)	2 (5)	
<3 months	0	0	
<12 months	2 (3)	0	
<24 months	1 (1)	1 (2)	
<48 months	2 (3)	1 (2)	
Number of complications according to preoperative MGFA status, *n* (%)			
Class I	0		
Class II A	0		
Class II B	2 (3)		
Class III A	7 (10)		
Class III B	4 (6)		
Class IV	1 (1)		
Stage of disease (modified Masaoka staging), *n* (%)			
I	20 (29)	23 (53)	0.10
II A	15 (22)	9 (21)	0.80
II B	21 (31)	7 (16)	0.11
III	11 (16)	3 (7)	0.24
IV A	1 (1)	1 (2)	1.00

CH: cholinesterase inhibitors; ICD: intercostal drain; ICU: intensive care unit; IM: immuno-suppression therapy other than prednisolone; MG: myasthenia gravis; MGFA: Myasthenia Gravis Foundation of America; MMF: mycophenolate mofetil; PR: prednisolone; SD: standard deviation.

P -value < 0.05 depicts the significant difference between the two groups (Thymoma with MG & Thymoma without MG).

arrest where the cause could not be ascertained. In the non-myasthenic thymoma group, 1 patient died of acute decompensation of chronic liver failure and another patient had sudden cardiac arrest. No disease-related mortality was noted in either group during the median follow-up of 49 months (Table 1).

Adjuvant treatment

Sixty patients (54%) received adjuvant radiation according to the criteria mentioned previously. Adjuvant chemotherapy was also advised in addition to radiotherapy in 2 patients with pleural metastases.

Correlation of myasthenia gravis with Masaoka staging and the World Health Organization histological grade

A high Masaoka stage [OR 1.96, 95% confidence interval (CI) 1.22–3.15] and aggressive WHO histological grade (OR 1.58, 95% CI 1.10–2.26) were more likely in patients with MG. When we considered the Masaoka stage as the outcome variable, the presence of myasthenic status (OR 3.17, 95% CI 1.39–7.21) was more likely; however, no linear relationship was found with the WHO grade. If the measured outcome variable was the WHO histological grade, again, the presence of myasthenic status [OR 2.84, 95% CI 1.27–6.35) is more likely and there is no significant correlation with Masaoka stage. The odds ratios mentioned are per point and are the same between successive grades and stages. Therefore, our results indicate that higher histological grade thymomas and higher Masaoka clinical stage are correlated with a myasthenic status (Table 2).

Survival analysis

There was a gradual decline in the survival percentages with increments in the Masaoka stage and the WHO histological grade. On testing the equality of survival functions using the log-rank test, the Masaoka stage was the only significant factor affecting survival ($P < 0.001$) (Fig. 1). On univariable Cox regression analysis, there was insufficient evidence to draw any conclusions regarding the effect of MG on survival (hazard ratio 0.51, 95% CI 0.09–2.71; $P = 0.43$).

Table 2: Ordinal and logistic regression analysis with the variables myasthenia gravis, Masaoka stage and World Health Organization histological classification

	Odds ratio	95% confidence interval	*P* value
Outcome variable: myasthenia gravis			
Masaoka stage	1.96	1.22–3.15	0.005
WHO grade	1.58	1.10–2.26	0.012
Outcome variable: Masaoka stage			
Myasthenia gravis	3.17	1.39–7.21	0.006
WHO grade	1.08	0.80–1.45	0.608
Outcome variable: WHO grade			
Myasthenia gravis	2.84	1.27–6.35	0.011
Masaoka stage	1.09	0.78–1.54	0.590

WHO: World Health Organization.

DISCUSSION

Thymoma is the most common anterior mediastinal tumour arising from thymic epithelial cells. Prognosis of these tumours is directly related to its complete surgical excision with negative margins. Trans-sternal thymectomy has been the standard approach for thymoma resection [11]. The extent of surgery should be extended thymectomy, defined as resection of the tumour *en bloc* with the remnant gland, surrounding fatty tissue in the mediastinum and bilateral pericardial fat pads and dissection into the neck up to the thyrothymic ligament [12]. However, the extent of resection is still under debate, particularly for non-myasthenic thymoma, for which few authors have advocated the role of subtotal/partial thymectomy for stage I and II thymomas [13]. In our practice, we always perform extended tumour resection with clear margins.

Surgeons increasingly use minimally invasive approaches like thoracoscopic and robotic-assisted thoracoscopic surgery for performing extended thymectomy to achieve better short-term outcomes and similar oncological efficacy. The da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA, USA) provides extra advantages to the surgeon over the conventional thoracoscopic approach. These include 3-dimensional vision, greater freedom of movements, endowrist technology, elimination of hand tremors and improved dexterity [14]. There is evidence to support the better immediate postoperative outcomes with the robotic method compared to sternotomy. Two retrospective analyses by Cakar *et al.* [15] and Renaud *et al.* [16] analysed the outcomes of open versus robotic extended thymectomy in non-thymomatous myasthenia and showed lower complication rates, better clinical outcomes and reduced hospital stays in the robotic group. Marulli *et al.* [17], in a recent propensity score matched comparative analysis in early stage thymoma, concluded that robotic thymectomy has the advantages of fewer complications, shorter hospital stay and lower total cost. A meta-analysis by O'Sullivan *et al.* [18] also revealed significantly fewer postoperative complications in the robotic thymectomy group. In our study, however, patients with thymoma and MG had significantly more complications compared to those without thymoma, even after having the robotic approach. Even when myasthenic complications were ignored, the complication rate was still higher in the myasthenic group though not statistically significant.

The higher number of complications in the myasthenic group in our study can be attributed to 2 factors. First, MG itself is a predisposing factor for more complications compared to no MG [19], whereby surgical stress acts as a trigger for aggravated myasthenic symptoms. A postoperative myasthenic crisis has been reported to be as high as 10% [20]. In addition, myasthenic patients on prolonged steroids and immune-suppressive drugs are prone to development of surgical site infections, lung atelectasis and pneumonia [21]. Second, in 47% of the myasthenic patients with thymoma in our study, there was a need for resection of 1 or more of the surrounding adherent structures. Of these, 14.4% ($n = 16$) of tumours were grouped in stage III and higher. The pericardium was the most common adherent structure followed by the lung and the left phrenic nerve. Complications such as lung atelectasis and pneumonia and postoperative fluid collection occurred in patients with phrenic nerve resection, where immobility of the diaphragm could be the

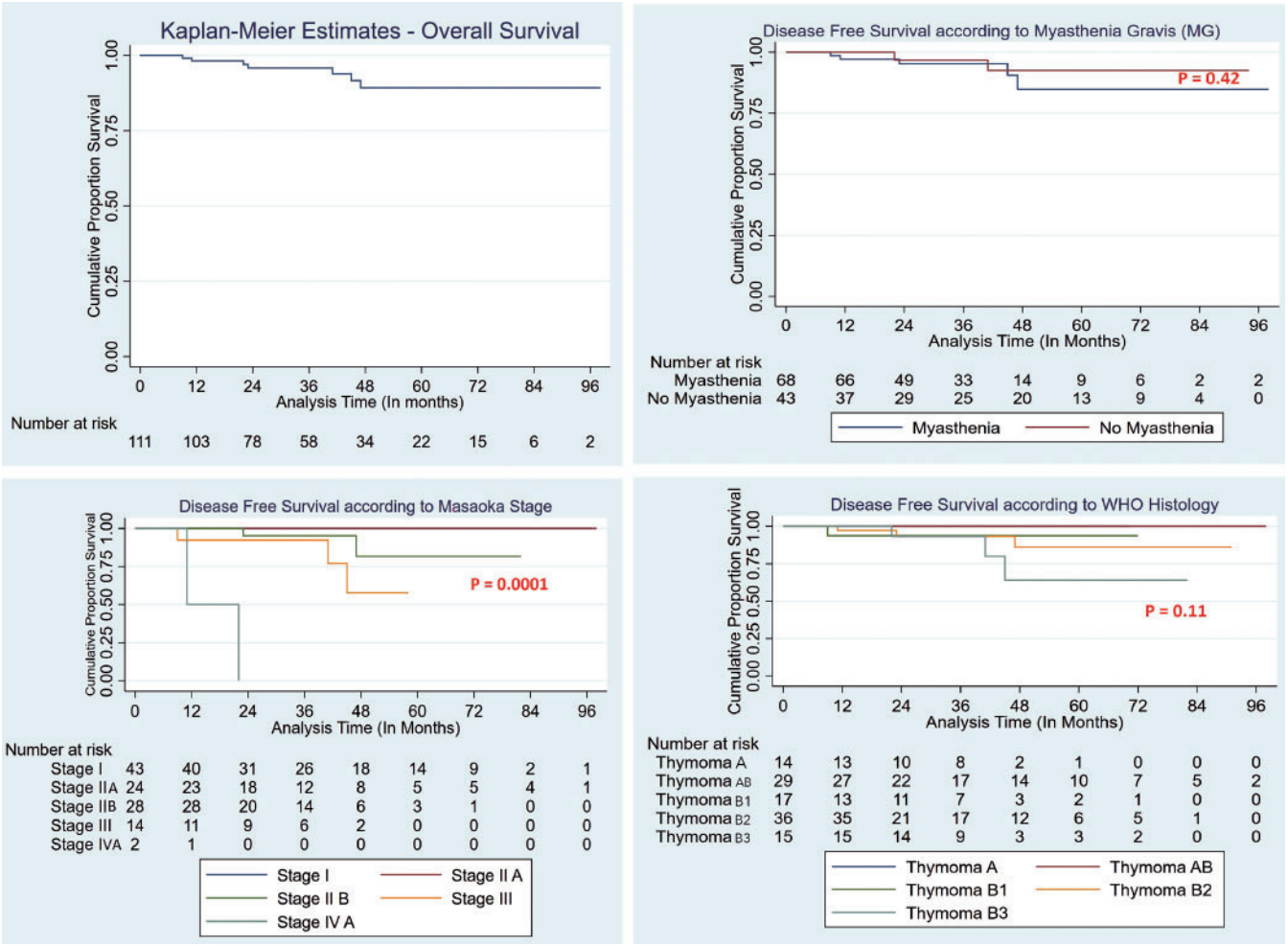

Figure 1: Kaplan–Meier graphs: analysis of overall and disease-free survival.

underlying cause. All cardiac arrhythmias occurred in patients with pericardial resection and reconstruction with Vicryl mesh. In their study on the feasibility of VATS thymectomy for patients with thymoma, Toker *et al.* [22] analysed how Masaoka stage, tumour size, the presence of MG and WHO histological subtypes affected surgical resection by VATS. They similarly reported significantly more unsuccessful outcomes at a higher Masaoka stage. So, higher stage tumours in the myasthenic group that required resection of additional structures may have contributed to increased complications in our study. In light of these facts, the conventional trans-sternal appoach may be a better option for patients with higher Masaoka–Koga stage (III and above) and severe myasthenic symptoms (Osserman stage IIA and above). Therefore, if there is a reasonable doubt about the radicality of surgery and the resectability of the tumour on diagnostic thoracoscopy, especially in patients with MG, who are prone to more postoperative complications, adopting a trans-sternal approach may be prudent.

Aggressive efforts to control MG should be the approach, particularly in cases of generalized MG with bulbar symptoms. Perioperative use of plasmapheresis and intravenous immunoglobulin may be required to reduce myasthenia-related complications [23, 24]. It is important to emphasize that good case selection is of paramount importance.

In our series, MG was associated with thymoma in 61.2% ($n = 68$) of cases, which is higher than the reported rate of 25% association [25]. This result can be explained by the referral bias. The relation between thymoma and MG is complex. Few studies report MG as a poor prognostic factor with higher operative mortality in patients with thymoma [26] in contrast to findings reported by many recent surgical series in which myasthenic thymomas were equally or less malignant than those without MG [27]. The better outcomes in patients with thymoma and MG were explained by the earlier diagnosis of the disease in the myasthenic thymoma group and improvements in the treatment of MG. Ruffini *et al.* [28], reported that the presence of MG is associated with early Masaoka stage thymomas. In contrast, we found that if the patient was myasthenic, the probability was greater of a higher Masaoka stage and a WHO histological grade of the tumour with greater need for resection of surrounding structures and a greater number of conversions. The association of MG with higher Masaoka stages in our study could indicate a delayed surgical referral for patients with MG and small thymomas in our country or could be due to a referral bias wherein MG patients with an early stage lesion were operated on in peripheral centres and only later stages were referred to our tertiary care centre.

Limitations

The limitations of our study were its retrospective nature and the relatively shorter follow-up time. Considering the indolent nature of this tumour, the follow-up required to comment confidently on recurrence or survival should ideally be 10 years.

CONCLUSIONS

The present study is one of the largest single-centre series of robotic extended thymectomy for thymoma. Patients with myasthenic thymoma had significantly more postoperative complications and conversions compared to the non-myasthenic group. Due to the small number of deaths, there is insufficient evidence to draw any conclusion about the effect of MG on survival after surgery. Myasthenic status correlated with higher Masaoka stage and WHO grade B thymoma. Patients with advanced stage thymoma with moderate to severe MG may not be good candidates for the robotic approach.

Conflict of interest: none declared.

Author contributions

Arvind Kumar: Methodology; Project administration; Resources; Supervision; Validation; Writing—original draft; Writing—review & editing. **Belal Bin Asaf:** Data curation; Resources; Visualization; Writing—review & editing. **Mohan Venkatesh Pulle:** Conceptualization; Data curation; Formal analysis; Methodology; Software; Writing—original draft. **Harsh Vardhan Puri:** Data curation; Investigation; Writing—review & editing. **Nitin Sethi:** Resources; Supervision; Validation; Writing—review & editing. **Sukhram Bishnoi:** Resources; Writing—review & editing.

Reviewer information

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