Clinicodemographic characteristics and prognostic role of myasthenia gravis in thymoma: Experience from a Saudi population

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Abstract:

OBJECTIVES: The objectives of the study were to determine the clinicodemographic characteristics and the prognostic role of myasthenia gravis (MG) in thymoma.

METHODS: The records of patients who underwent surgical resection of thymoma at King Faisal Specialist Hospital and Research Center in the past 23 years were reviewed. Seventy thymoma patients were finally included and were then categorized based on MG status into the MG group (39 patients) and the non-MG group (31 patients). Collected data included patients' demographic characteristics, tumor characteristics, and postoperative clinical outcomes. All analyses were conducted using SPSS. The comparison between both groups was tested using the Student t-test and Chi-square test for continuous and categorical variables, respectively. A $P = 0.05$ or less indicated statistical significance.

RESULTS: Patients' age ranged from 11 to 76 years, and female predominance was observed (55.7%). Compared to the non-MG group, no difference in patients' gender was observed ($P = 0.058$); however, MG patients had a younger age (39.30 vs. 48.77, $P = 0.0095$). No difference was noted between both groups based on the World Health Organization classification ($P = 0.398$), but MG patients tended to present with less-advanced tumors based on the TNM classification ($P = 0.039$) and lower stage based on the MASAOKA staging system ($P = 0.017$). No significant change in tumor size ($P = 0.077$), resectability ($P = 0.507$), and adjuvant therapy ($P = 0.075$) were observed. MG was not significantly associated with postoperative complications, morbidity, or mortality. However, it exhibited a prognostic protective role in terms of lower recurrence (2.56% vs. 35.48%, $P = 0.0001$) and longer survival duration (18.62 vs. 10.21 years, $P < 0.001$) as compared to non-MG patients.

CONCLUSIONS: MG occurrence in thymoma patients is more likely to occur at a younger age, higher TNM classification, and advanced MASAOKA stage. Although no significant association was noted between MG and complications and mortality, MG exhibited a protective role in thymoma by providing a lower recurrence rate and longer survival duration.

Keywords:

Myasthenia gravis, recurrence, Saudi Arabia, surgery, thymoma

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Thymomas are neoplasms with a rare occurrence. Thymomas arise from the thymus' tissue elements and develop in the anterior mediastinum.[1] Thymomas may be associated with various autoimmune and systemic disorders, including pancytopenia, pure red cell aplasia, collagen-vascular disease, hypogammaglobulinemia, and in most cases, myasthenia gravis (MG).[2-5] It

should be noted that thymomas are uncommon, with an annual incidence of about 0.15 cases per 100,000 person-years.[6] However, despite this low figure, thymomas double as the only tumor of the anterior mediastinum with the most diagnoses.[7]

Thymomas may show benign or aggressive behavior in affected patients. However, it is a malignant neoplasm despite its inconsistent histology and clinical advancement. Thymomas are characterized by their thymic epithelial differentiation. On a molecular level, it has been suggested that the thymoma affects the functionality of the thymus in performing the negative selection for incompetent T-cells.[8]

Therefore, thymoma generates autoreactive cells that can cause any autoimmune disease.[9] Up to half of thymoma, patients have developed MG.[10] Numerous studies over the past decade studied the clinical presentation and prognostic role of MG in thymoma; however, these findings were widely variable and inconclusive. Therefore, there was a need for studies to examine the correlation and the behavior of thymoma and MG with respect to each other. In this regard, we conducted a retrospective cohort study done based on thymoma patients' data from a tertiary center in Riyadh, Saudi Arabia, to determine the clinicodemographic characteristics and prognosis of MG in thymoma patients as compared to non-MG controls.

Methods

Patient population and study design
This retrospective comparative cohort study included the records of prospectively collected records of thymoma patients who underwent surgical resection at King Faisal Specialist Hospital and Research Center from 1996 to 2019. Initially, 125 patient records were reviewed, of whom 55 were excluded due to missing data or the presence of nonthymomatous tumor [Figure 1]. Finally, 70 thymoma patients were included and analyzed. These patients were divided into two groups: those with concurrent MG (MG group) and those without MG (non-MG group). The diagnosis of MG was confirmed from the medical records based on neurologists' assessment of clinical presentation, antiacetylcholine receptor antibody titers, and edrophonium test/low-frequency repetitive nerve stimulation results. Of note, the ethics committee of our institutional review board approved the study protocol and related materials before the initiation of this research.

Study outcomes
Data were gathered from our electronic medical record system. Patients' data were classified into three main
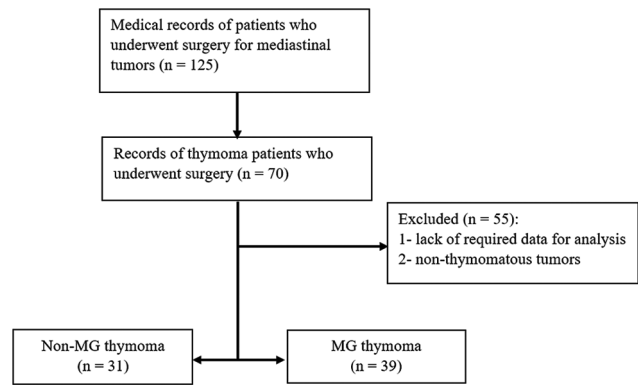

Figure 1: This study enrolled 125 patients who underwent surgical excision of mediastinal tumors at our institution. However, due to the lack of required data and the absence of thymomatous tumors, 55 records were excluded from the study. Finally, 39 patients in the myasthenia gravis (MG) group and 31 in the non-MG group were included in the study. MG = Myasthenia gravis

domains. The first part included patients' demographic characteristics (age and gender), while the second part included tumor characteristics in terms of tumour, node, metastasis (TNM) classification, MASAOKA stage, the World Health Organization (WHO) histology, tumor size, resection extent (R0, R1, and R2), and adjuvant therapy (chemotherapy or radiotherapy either as standalone or combined). The final part included patients' clinical outcomes in terms of prognosis (survival time and 10-year disease-free survival [DFS]) and postoperative complications, morbidity, mortality, and recurrence.

Statistical analysis
All of the performed statistical tests were done using IBM SPSS Statistics (Version 25). Categorical variables were presented as frequencies and percentages, while continuous variables were presented as mean ± standard deviation. The normal distribution of the data was confirmed by observing the histograms and using the Kolmogorov–Smirnov test. The differences between MG and non-MG thymoma groups were tested by the Student *t*-test for continuous variables (i.e., age) and the Chi-square test for categorical variables (i.e., recurrence). Meanwhile, we used the Kaplan–Meier curve to determine the change in DFS between studied groups. A $P < 0.05$ was used to highlight statistically significant differences.

Results

Baseline demographic characteristics
A total of 70 patients were analyzed, the majority of whom were females (55.7%), and only 34 (48.6%) patients had comorbid conditions [Table 1]. The whole population had a mean age of 43.5 (15.37) years, ranging from 11 to 76 years. Most patients were in the 31–40 years age group (24.3%). Among patients with thymoma, 39 (55.71%) cases had MG. Patients with

MG were predominantly females (53.85%), while the majority in the control group were males (67.74%); however, no statistically significant difference was noted (*P* = 0.058). Age differed significantly between both groups (*P* = 0.005), where most patients in the MG group were in the 31–40 years age group (35.89%), while those in the control group were in the 41–50 years age group (35.48%).

Thymoma characteristics among included patients

The tumor size was bigger in the MG group as compared to the control group (8.08 cm vs. 6.37 cm); however, this difference did not reach statistical significance (*P* = 0.077). We used three different classification systems (TNM, MASAOKA, and WHO)

to determine the grade of thymoma among included patients [Table 2]. Based on TNM classification, most patients had grade I thymoma (54.3%). The same was observed based on MASAOKA classification where most patients had grade 1 thymoma (31.42%). Meanwhile, based on the WHO classification system, the majority had grade B2 thymoma (48.58%). In terms of comparison between MG and controls, only the TNM (*P* = 0.039) and MASAOKA (*P* = 0.017) classification systems showed statistically significant differences. Based on TNM classification, patients with MG had lower grade thymoma than control. For instance, MG patients were more likely to present with grade I thymoma (69.23% vs. 35.48%), while controls tended to present with grade IV (A and B) thymoma (10.24% vs. 38.71%), respectively.

Table 1: Baseline demographic characteristics of included patients (*n*=70)

Variables	Category	Total, *n* (%)	MG (*n*=39), *n* (%)	Control (*n*=31), *n* (%)	*P*
Gender	Male	31 (44.3)	18 (46.15)	21 (67.74)	0.058#
	Female	39 (55.7)	21 (53.85)	10 (32.26)	
Age group (years)	Mean±SD	43.5±15.37	39.30±2.56	48.77±2.31	0.0095^
	10–20	5 (7.1)	5 (12.82)	0	0.005*
	21–30	9 (12.9)	6 (15.38)	3 (9.67)	
	31–40	17 (24.3)	14 (35.89)	3 (9.67)	
	41–50	15 (21.4)	4 (10.25)	11 (35.48)	
	51–60	11 (15.7)	4 (10.25)	7 (22.58)	
	>60	13 (18.6)	6 (15.38)	7 (22.58)	

*Chi-square test, #Fisher's exact test, ^Student's *t*-test. MG=Myasthenia gravis, SD=Standard deviation

Table 2: The clinical characteristics of thymoma patients with and without myasthenia gravis

Variables	Category	Total, *n* (%)	MG (*n*=39), *n* (%)	Control (*n*=31), *n* (%)	*P*
TNM classification	I	38 (54.3)	27 (69.23)	11 (35.48)	0.039
	II	7 (10)	4 (10.25)	3 (9.67)	
	IIIA	8 (11.4)	3 (7.69)	5 (16.13)	
	IIIB	1 (1.4)	1 (2.56)	0	
	IVA	9 (12.9)	2 (5.12)	7 (22.58)	
	IVB	7 (10)	2 (5.12)	5 (16.13)	
MASAOKA stage	1	22 (31.42)	13 (33.33)	9 (29.03)	0.017
	2a	8 (11.42)	4 (10.25)	4 (12.90)	
	2b	2 (2.85)	1 (2.56)	1 (3.22)	
	3	20 (28.57)	10 (25.64)	10 (32.26)	
	4a	6 (8.57)	3 (7.69)	3 (9.67)	
	4b	8 (11.4)	4 (10.25)	4 (12.90)	
WHO histology	A	4 (5.71)	3 (7.69)	1 (3.22)	0.398
	AB	11 (15.71)	4 (10.25)	7 (22.58)	
	B1	10 (14.28)	4 (10.25)	6 (19.35)	
	B2	34 (48.57)	21 (53.84)	13 (41.93)	
	B3	11 (15.71)	7 (17.94)	4 (12.90)	
Tumor size, mean±SD		7.32±3.66	8.08±4.03	6.37±2.94	0.077
Resection	R0	52 (74.3)	31 (79.49)	21 (67.74)	0.507
	R1	12 (17.1)	5 (12.82)	7 (22.58)	
	R2	6 (8.6)	3 (7.69)	3 (9.67)	
Adjuvant therapy	Chemotherapy	3 (4.29)	0	3 (9.67)	0.075
	Radiotherapy	20 (28.57)	12 (30.77)	8 (25.81)	
	Both	10 (14.29)	3 (7.69)	7 (22.58)	
	Total	33 (47.14)	15 (38.46)	18 (58.06)	

SD=Standard deviation, WHO=World Health Organization, MG=Myasthenia gravis, TNM=Tumour, Node, Metastasis

Most thymoma patients underwent R0 resection (74.30%), and although patients with concomitant MG were more likely to undergo R0 resection as compared to controls (79.49% vs. 67.74%), no significant difference was observed (*P* = 0.507). Less than half of thymoma patients had adjuvant therapy (47.14%), with radiotherapy being the most commonly indicated intervention accounting for 28.57% of all cases. Patients with MG were less likely to take adjuvant therapy as compared to controls (38.46% vs. 58.06%). This was similar in those who took adjuvant chemotherapy or combined chemoradiotherapy; however, MG patients were more likely to take radiotherapy as compared to controls (30.77% vs. 25.81%). That being said, no significant difference between MG and controls was noted regarding adjuvant therapy (*P* = 0.075).

Postoperative clinical outcomes

The postoperative clinical outcomes of recruited patients are summarized in Table 3. Overall, 10 (14.28%) patients experienced complications, the most common of which was atelectasis (4.28%). Noteworthy, the rate of postoperative complications in the control group was substantially higher than that of the MG group (25.81% vs. 5.12%); however, this difference did not reach statistical significance (*P* = 0.241). In the whole population, only four had morbid conditions and two patients in the MG and the control group (5.13% vs. 6.45%, *P* = 0.815), respectively. Six (8.57%) patients died throughout the follow-up period 4 (10.26%) in the MG group and 2 (6.45%) in the control group. Importantly, 12 (8.57%) patients experienced recurrence; the rate was significantly higher in the control group than in the MG group (35.48% vs. 2.56%, *P* = 0.001).

The overall mean survival time for the whole population was 14.21 years. The survival time was significantly higher in patients with MG than in non-MG controls (18.62 vs. 10.21, *P* < 0.001). Consistently, 58 (82.85%) patients had 10-year DFS; the rate was significantly higher in patients with MG than in non-MG controls (100% vs. 61.29%, *P* < 0.001) [Figure 1].

Discussion

The temporal association between MG and thymoma has been long studied; however, its aspects are poorly defined, particularly when it comes to its incidence, presentation (in terms of clinicodemographic characteristics), management, and prognosis. Based on empirical evidence, MG can be observed in 10%–15% of thymoma patients.[11] Furthermore, MG is expected to occur as one of the most common paraneoplastic syndromes during the course of
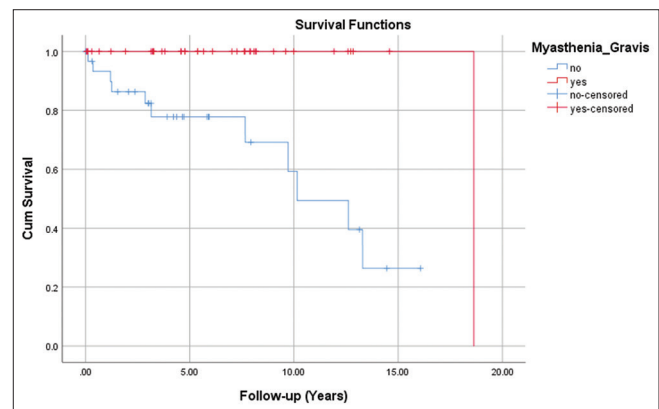

Figure 2: Kaplan–Meier survival plot showing probability of survival in relapsed thymoma

Table 3: Postoperative outcomes of thymoma patients with and without myasthenia gravis

Variables	Category	Total, *n* (%)	MG (*n*=39), *n* (%)	Control (*n*=31), *n* (%)	*P*
Postoperative complications	Atelectasis	3 (4.28)	2 (5.12)	1 (3.22)	0.241
	Pulmonary embolism	2 (2.85)	0	2 (6.45)	
	Phrenic nerve injury	1 (1.42)	0	1 (3.22)	
	Pleural effusion	2 (2.85)	0	2 (6.45)	
	Vocal cord paralysis	1 (1.42)	0	1 (3.22)	
	Cardiac arrhythmia	1 (1.42)	0	1 (3.22)	
	Total	10 (14.28)	2 (5.12)	8 (25.81)	
Morbidity	MG exacerbation	1 (1.42)	1 (2.56)	0	0.815
	Lung fibrosis	1 (1.42)	0	1 (3.22)	
	Postthoracotomy pain	1 (1.42)	0	1 (3.22)	
	Vocal fold paralysis	1 (1.42)	1 (2.56)	0	
	Total	4 (5.71)	2 (5.13)	2 (6.45)	
Mortality	Sepsis	5 (7.14)	4 (10.26)	1 (3.22)	0.124
	Respiratory failure	1 (1.42)	0	1 (3.22)	
	Overall	6 (8.57)	4 (10.26)	2 (6.45)	
Recurrence		12 (17.14)	1 (2.56)	11 (35.48)	0.0001
Survival (years)	OS duration, mean±SE	14.21±1.179*	18.62±1.236	10.21±1.093	<0.001
	10 years DFS	58 (82.85)	38 (100)	19 (61.29)	<0.001

*Data are presented as SE not SD. DFS=Disease-free survival, OS=Overall survival, SE=Standard error, SD=Standard deviation, MG=Myasthenia gravis

thymoma.[11] In the literature, the rate of MG occurrence in thymoma has been widely variable, ranging from as low as 14.28% to as high as 64.28%. In our institution, MG thymoma accounted for 55.71% of our thymoma patients. However, in a recent systematic review of 49 studies, the rate of MG in thymoma was 21%.[12] This rate is the closest to the true value given the narrow confidence interval (CI) (95%CI: 22%–23%). This discrepancy might be, in part, related to patients' characteristics at baseline. The rate of MG thymoma is reported to be higher in surgery-based populations, accounting for potential sampling bias, which goes in line with our observation.[13,14]

According to demographic characteristics, MG thymoma has been reported to occur more frequently among men, especially those above 40 years of age.[12] Controversy, in our center, we noted male predominance (67.74%) in the non-MG group and female predominance (53.85%) in the MG thymoma group. This finding is consistent with the observations reported in the literature.[15,16] For instance, Kondo and Monden[15] reported that 20.90% and 79.10% of MG and non-MG thymoma patients were males, respectively. In terms of age, we noted that MG thymoma patients were significantly younger than their non-MG peers. This observation is consistent across all other studies in the literature.[15-17]

Regarding tumor characteristics, in our study, we noted that non-MG patients were more likely to present with higher TNM stage as compared to MG thymoma patients. This point has been scarcely studied in the literature and the only study that investigated this variable reported no significant difference across studied groups.[18] However, this can be attributed to the propensity score matching process that was implemented in the latter study. Similarly, according to the MASAOKA staging classification, we observed that MG thymoma patients tended to present with lower stage as opposed to non-MG patients who were more likely to present with higher stages. This finding is similar to that of numerous studies,[14,19] where MG occurrence was noted to be higher in the early stages of thymoma (MASAOKA Stage I-II) with an increased incidence of advanced Stages (III-IV) in the non-MG group. On the other hand, we noted no significant difference between MG and non-MG thymoma patients in terms of WHO histology. This contradicts with other reports in which it was observed that MG had an increased likelihood of presenting in patients with advanced WHO classification.[13,14,16,17,19,20] This difference could be attributed to the small sample size in our study where statistical significance could not be reached due to the lack of power to detect minimal differences between studied groups.

The association between tumor size and MG occurrence has been rarely investigated. MG patients tend to present with significantly smaller tumors as compared to non-MG patients.[19] However, in our study, we noted a contradicting observation where MG thymoma patients had larger tumor size, but this difference did not reach statistical significance. This point still warrants further investigation given preoperative management (in terms of standalone or combined chemotherapy and radiotherapy) affects tumor size and subsequently the prognosis.[21,22] This coincides with our observation given the small percentage of MG patients who received adjuvant chemo/radiotherapy; hence, the size could be larger. In addition, we found no significant difference between MG and non-MG thymoma patients regarding resection (R0, R1, and R2).

The prognostic impact of MG on thymoma-associated clinical outcomes has long been controversial. In the past, MG was recognized as a negative prognostic factor leading to poor survival and increased morbidity/mortality, particularly due to MG-related postoperative complications.[23] That being said, this impact was, in part, related to the lack of advanced technologies and management protocols. Now, the prognosis in these patients is thought to have turned favorable.[18] MG thymoma patients have been reported to be more likely to experience postoperative complications as compared to non-MG patients (63.6% vs. 3%).[24] However, our observation was different; MG thymoma patients were less likely to experience complications but this difference did not reach statistical significance. This difference in our observation could be explained by two things. The first is the small sample size included, which overestimates the actual complication rate. For instance, in the study of Wu *et al*.,[24] 63.6% of MG thymoma patients experienced complications; however, it should be noted that the MG group comprised only 11 patients, while the non-MG group consisted of 66 patients. The second thing is the follow-up time point; we hypothesize that the longer the follow-up period, the increased rate of complications. In terms of mortality, we observed no significant difference between MG and non-MG patients. This goes in line with other reports.[17,18,25] Meanwhile, in our study, MG thymoma patients were significantly less likely to have recurrence as compared to non-MG patients. This finding is consistent with that reported in other studies.[15,19]

In terms of survival, we noted a significant prognostic protective value of MG in thymoma, and this has been observed similarly in another report where MG thymoma patients were less likely to experience recurrence.[19] In addition, in our study, MG thymoma patients had higher survival duration as compared to non-MG thymoma patients. Consistently, all of our MG 54 thymoma patients had 10-year DFS, while only 61.29% 55 of non-MG patients had 10-year DFS [Figure 2]. However, other reports in the literature found no significant difference

in survival between both groups.[18,20] This discrepancy in survival could be explained by the difference in the stage of thymoma and WHO classification, where in the latter study, no significant difference in thymoma stage was observed between studied groups.

Limitations

This study is the first to highlight the patterns and prognostic role of MG in thymoma in a Saudi population. However, our findings should be carefully interpreted and not be generalizable to the whole populations given the several limitations related to our study. First, our sample size was not large enough to detect clinically-defined small differences between studied groups. Second, we did not consider the role of disease severity, immunological parameters (such as acetylcholine receptor antibody and muscle autoantibody assays), and preoperative management protocols on the prognosis in such cases. Therefore, future studies are still warranted to fill these gaps and to provide high-certainty evidence on the role of MG in thymoma.

Conclusions

MG occurrence in thymoma patients is more likely to occur at a younger age, higher TNM classification, and advanced MASAOKA stage. Although no significant association was noted between MG and complications and mortality, MG exhibited a protective role in thymoma by providing a lower recurrence rate and longer survival duration.

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Conflicts of interest
There are no conflicts of interest.

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