

## Peer Review File

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### Reviewer A

**Comment 1:** Costs (lines 131 to 139) should be removed as they are confusing and not helpful. I think a reference was missing, which is a systematic review that shows that thymectomy is more effective than clinical treatment for NTMG: <https://doi.org/10.1186/s13023-018-0837-z>. I suggest that this systematic review be placed to encourage thymectomy,

**Reply 1:** Thank you so much for your comment. We have added the text with the aim to alleviate any confusion surrounding these results. However, we believe that providing costs highlighting the beneficial aspect of thymectomy in this population is meaningful and novel. Moreover, feedback from other reviewers suggests these data may be important to readers. We hope that the revised paragraph addresses the concern of the reviewer. We have also added the citation shared by reviewer A, and thank them for providing us with this important systematic review.

### Changes in Text

- Please see lines 136-137 in the extensively revised manuscript, for clarification surrounding the cost results.
- The reviewer's citation was added in our discussion, on lines 156-157.

### Reviewer B

**Comment 1:** Very well-designed study. Benefits of thymectomy in terms of symptomatic control usually does not occur until at the least 4 to 6 months postoperatively. Should there be discussion or analysis looking at the costs at 1 year? Would that data set show a clearer benefit in terms of costs, NSIS, rescue therapy, or even steroid use? It may not be possible because of the use of national databases, but if able, I would include a brief analysis/chart to see if steroid and rescue usage was within the immediate postoperative period and then decline with time (at 6 months, 1 year, etc).

**Reply 1:** The authors thank reviewer B for their kind comments regarding our study. As the reviewer alludes to, one limitation of the database used is longitudinal follow up, as patients may change insurance provider frequently. While we agree that such an analysis would be meaningful, we are unfortunately limited by sample size considerations when extending the analysis out to a longer time period as noted within our limitations. We have noted that a "long-term analysis in a larger population" would be valuable within our discussion, on line 177.

### Reviewer C

**Comment 1:** It's a good paper overall, well written and clear. However, the paper's focus should be changed as there are already many studies with more significant populations and longer follow-up times analyzing the same variables. If the direction is changed to the cost of NTMG therapy before and after thymectomy or why many patients are not undergoing thymectomy even if they have an indication, it would be a much more interesting and innovative study.

**Reply 1:** The authors thank reviewer C for their insightful comments, and minor edits that follow. We aimed to provide the readership of the *Journal of Thoracic Diseases* with a broad overview of the capabilities afforded by this novel database. As such, we decided to include both use of treatment, as well as their associated costs, and the rate of thymectomy. We have added the discussion section to ensure that the focus of this manuscript includes the cost analysis.

#### **Changes in Text**

- Please kindly see line 153 of the revised manuscript

**Comment 2:** Authors state in the introduction (lines 76-77), "... little is known as to how this evidence has translated into clinical practice". However, there are already many retrospective studies published about thymectomy in NTMG. There are even a couple of systematic reviews and meta-analyses on the topic. So, I would not say that little is known about the clinical outcomes of thymectomy in NTMG.

**Reply 2:** Thank you so much for bringing this concern to our attention. With that statement, we aimed to signal that "real-world" evidence surrounding the use of thymectomy for NTMG is lacking. While retrospective cohort studies have been published, we feel that broad multi-institutional / national data on the topic are not well-described regarding utilization of thymectomy in this setting.

#### **Changes in Text**

- Please kindly see the changes made in the text on line 79-81 that clarify this important distinction.

**Comment 3:** Lines 82-83: Authors extract their data from an insurance database. If their goal is to translate the evidence into clinical practice, using data from an insurance database is not ideal, as much specific patient information may be missing.

#### **Reply 3:**

Thank you very much for sharing this concern. The goal of our report was to highlight that using a "real-world" database, the rate of thymectomy was low, despite obvious advantages, supported by level 1 evidence (MGTX trial). The reviewer is certainly correct in that clinically captured variables are not available for reporting purposes. However, we do benefit from complete capture of cost data, as the reviewer notes is valuable, as well as information related to prescriptions / rescue therapy.

**Comment 4:** Inclusion criteria are well-explained and clear. Adding a wash-out period and only including patients undergoing thymectomy within 12 months of MG diagnosis is a great way to avoid bias.

**Reply 4:** Thank you so much for this kind comment. We aimed to design this study in a way that minimized bias, while producing novel and meaningful results.

**Comment 5:** Line 101: study period is only 6 months. Again, there is already literature on the topic with far longer follow-ups.

**Reply 5:** Thank you for bringing this up to our attention. There is literature on this topic with longer follow up, and these have been cited in our introduction and discussion. However, the novel aspect of this manuscript is the use of a national insurance database with complete capture of costs and treatment data. We have included the reviewer's concern as a limitation in the Discussion.

**Comment 6:** Line 116: Only 45 patients underwent thymectomy and had the 6-month follow-up. Compared to the published literature, the study population seems small.

**Reply 6:** This finding surprised us as well, considering that the advantages of thymectomy in this cohort are well accepted across societies, including that of Neurology. This is an important finding of this study, highlighting the low rate of resection.

**Comment 7:** Line 131: comparing the cost of NTMG therapy before and after thymectomy makes this study different and adds to the already available literature. I would add a paragraph about this in the introduction, as this is the "innovation" of the study. This should be the main focus of the study and the main finding.

**Reply 7:** Thank you so much for highlighting this finding. We agree that this is an valuable aspect of our manuscript and may differentiate it from prior work. As such, we have edited both the Introduction to highlight / set up the importance of this analysis and included in our discussion increased attention on the cost data in our study.

#### **Changes in Text**

- The introduction has been revised on lines 79-81 to reflect the thoughtful comment from Reviewer C
- Please see changes in the discussion section, on lines 153.

**Comment 8:** Discussion first paragraph: "we found that few patients with NTMG underwent thymectomy despite guidelines and clinical trial evidence suggesting benefit in this patient population." This is an important finding that has not been mentioned before. Although you say some possible causes of this in the discussion, it needs further development.

**Reply 8:** Thank you very much for bringing attention to the nuances reported in this manuscript.

This is one of our key findings, and we appreciate your suggestion to develop this further.

**Changes in Text**

- Please see lines 168-171 which develops this novel finding.

**Comment 9:** The limitations part is good. But what are the benefits of this study? What does it add to the literature? I would add a paragraph about this because although it has many limitations, it also has good and innovative things (comparing the costs and the finding that not many patients are undergoing thymectomy even though they have indications).

**Reply 9:** The reviewer brings good suggestions relating to the novelty and benefits associated with this study.

**Changes in Text**

- Kindly see the changes made in the limitation section, on lines 172-174

**Comment 10:** On table 2: It is unnecessary to add a \* indicating what statistical test you used for the analysis. You already mention it in the methods, and adding more legends makes the tables confusing.

**Reply 10:** The authors would like to thank reviewer C for their thoughtful review of our manuscript, and with comments that undoubtedly have strengthened our manuscript. Table 2 has been revised and simplified.

**Changes in Text**

- See table 2

**Reviewer D**

**Comment 1:** In the manuscript "Outcomes after Thymectomy in Non-Thymomatous Myasthenia Gravis" the authors address the important issue of what is the rate of thymectomy in NTMG patients and the economic output of the operation, which has been proven beneficial by an RCT and is included in practically all clinical guidelines for the management of NTMG in patients aged 18-50 years. However, the study design has some major difficulties. The patients were selected from a certain commercial insurance database, which likely affects the demographic and socioeconomic features of the patients. Moreover, clinical relevant data, such as information on the severity of disease based on for example MGFA rating, is thereby lacking.

**Reply 1:** The authors would like to thank reviewer D for taking the time to thoroughly review our manuscript and to provide thoughtful comments. We acknowledge the limitations of this novel database in our discussion, and while the database limits some analyses, it permits an evaluation of real-world data, specifically, investigating costs of NTMG-related treatment, and rate of thymectomy in this cohort.

**Comment 2:** To manage these issues, I suggest selecting a comparison cohort from those

patients with NTMG that did not undergo thymectomy, for example 3 times the number of thymectomized patients, age- and sex-matched. How does the need for IVIG and plasmapheresis, use of steroids, compare to these patients during the same follow-up time? Could propensity-score matching be applied to select a control group with similar disease severity based on these parameters? With such a low rate of patients thymectomized, I find it likely that the patients undergoing thymectomy had a more severe disease. The authors should try to address this issue with the afore-mentioned means, and discuss the effect of disease severity on increase in use of steroids after thymectomy. Cost calculations should also take into account the relative change in cost compared to a matched control cohort.

**Reply 2:** Thank you for this compelling suggestion that would undoubtedly complement the current analysis. The authors reviewed the possibility of undertaking such an analysis just as the Reviewer has described. Unfortunately, after much discussion and preliminary analyses, we felt that, to the Reviewer's point, there was no meaningful way to account for disease severity in a matched analysis of surgical vs non-surgically managed patients. Any attempt at comparing these two groups would be limited and fraught with selection bias. Thus, we felt the most appropriate and compelling analysis would be to review surgical outcomes, medication use, and costs within a single arm "real world" study of surgical patients. Though limited by the use of an insurance database, this methodology is commonly used in studies of other payer databases, including Premier, etc, as well as Medicare studies which restrict analyses to elderly patients.

**Comment 3:** Was there a change in frequency of thymectomy after MTGX trial was published in 2016?

**Reply 3:** This is a very good question. The rate of receipt of thymectomy in this cohort is very low and prevents meaningful longitudinal assessment that could otherwise be afforded by a Cochran-Armitage test.

**Comment 4:** Is there an insurance-based limitation on the availability of thymectomy for these patients?

**Reply 4:** This is a very plausible phenomenon and we have added our discussion to include this hypothesis.

#### **Changes in Text**

- Please kindly see lines 165.

**Comment 5:** What was the mean delay between diagnosis and thymectomy? Was there a correlation between delay and benefits of the procedure?

**Reply 5:** This is another excellent question that would be more significantly answered with a larger analysis, perhaps via a retrospective institutional cohort study. In this study, we intentionally restricted the time period between diagnosis and thymectomy to be 12 months for purposes of a more concrete, robust analysis with less confounding (ie patients leaving the

database or lost to follow up, etc). As such, any reporting of mean delay from diagnosis to thymectomy we feel would be limited in interpretation.

**Minor comments on language:**

row 64: quality life -should state: quality of life

row 66: nonglucorticoid steroids? do the author's mean corticosteroids?

**Reply:**

Thank you so much for your close review of our manuscript. This is very kind, and we appreciate it. The minor comments have been addressed in the text.

**Changes in Text**

- Line 66 and 68 of the heavily revised manuscript