

Peer Review File

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Reviewer A

In this study, Florida Inpatient Discharge Dataset for patients who underwent thymectomy and had a primary diagnosis of Myasthenia Gravis were retrospectively evaluated, using ICD-9 and ICD-10 codes. This study included patients from January 1st, 2013, to December 31st, 2018. Outcomes of minimally invasive thymectomy versus open thymectomy were compared. Minimally invasive surgery group had a shorter length of stay (3.9 vs 8.9 days, $p < .001$) and had a non-significant lower total cost (\$20.1K vs \$29.8K, $p = .186$).

My concerns are as follows. Please clarify the followings:

1-The MIS group patients were younger (41.2 vs 48.5 years, $p = .031$) and had a lower Elixhauser Score (0.0 vs 0.5, $p = .015$). Please explain in details, how logistic regression analysis make it possible without propensity match.

Reply 1: The analysis used doesn't affect our initial patient demographics, which are reported in table 1. The assessment of outcomes could be conducted using either approach, both of which have strengths and weaknesses. In this case, we chose to use logistic regression to adjust for differences between the groups (including age and Elixhauser scores) as we have a small sample size, and propensity matching would risk eliminating patients and further reducing our sample size and ability to assess differences between the groups. According to Cepeda et al., logistic regression is the technique of choice when there are eight or more events per confounder, like in this case (1).

2- Please describe, what do you mean with minimally invasive thymectomy. Robotic, VATS, a right or left or subxiphoid. We need the details of the surgical techniques. Besides, technical details such as simple thymectomy vs extended thymectomy, requires clarification

Reply 2: We filtered patients by procedure using ICD-9 and ICD-10 codes. The codes that were considered as minimally invasive or open thymectomy are described on lines 85-91. As the information was obtained from an insurance database, we don't know precisely what minimally invasive surgical technique was used. Medicare surgical coding classifies minimally invasive as "thoracoscopic", which would include VATS and robotic. Transternal would be coded as "open" and transcervical, not included in our study, as "other and unspecified thoracoscopic operations on the thymus."

Moreover, ICD codes do not differentiate between extended and simple thymectomy. As for myasthenia, the standard teaching is to take all mediastinal tissue from phrenic nerve to phrenic nerve from the diaphragm to the thoracic inlet.

4- It is widely known that, in patients with MG, the clinical stage of the disease itself is the predictor of ICU and length of stay rather than the surgical component. Both groups need to be clarified in terms of Osserman Genkins or MG Scores.

Reply 4: We agree that the clinical stage of the disease itself is a predictor of ICU and length of stay, but the surgical component also contributes. We didn't mention MG scores as this information was not available in the database we used for this study. We added this information on line 186.

5- Preoperative medication is also an important predictor of length of stay. For instance patients with corticosteroids and immunosuppressants have sternal healing problems which may keep them longer in the hospital.

Reply 5: Although this information is important, it was not available in the database we used for this study. We mention this in the study limitations on lines 185-188.

6- Please prefer Medians in the length of stay. Please define the requirement for ICU stay and describe the length of ICU stay.

Reply 6: We can present the medians and IQR (Q1-Q3). We changed means to medians for length of stay and cost on lines 52-54 and 121. ICU length of stay was not analyzed as this information was not available in the insurance database we used for the study.

7 – The need for Ivig or plasmapheresis in the preoperative period needs to be clarified.

8- The duration of surgeries are important.

Reply 7-8: Although this information is important, it was not available in the database we used for this study. We mention this in the study limitations on lines 185-188.

9. Without understanding these factors it would not be appropriate to compare both groups.

Reply 9: We agree that the factors mentioned above are important and contribute to the outcomes. As we lack the data, we cannot include them in our study, which is discussed in the study limitations on lines 185-188. However, it is important to

mention that the main goal of this study is to look into direct outcomes depending on the type of surgery, not considering other clinical variables.

Reviewer B

The effectiveness of minimally invasive thymectomy is an important topic as thymectomy has become one of the mainstay treatments in seropositive generalized MG. The authors performed a simple retrospective big data analysis, using the Florida Inpatient Discharge Dataset. They compared admission period-related outcomes and costs of MG patients who had undergone a minimally invasive or open thymectomy. Those who underwent MIS had a significantly shorter stay and a lower overall cost. They adjusted the effect of confounders by including age and Elixhauser Comorbidity Index in their multivariable model. The authors have a strength in the data because they cover the entire region of Florida.

However, the implication of this study is limited. First of all, they could not discriminate MG-related outcomes (e.g. long-term MG severity or frequency of MG crisis) from those simply related to the extent of operation (e.g. wound recovery, infection). Second, considering the first limitation, the results of this study are not new and have been already reported previously.

I recommend the authors to

(1) State how further analysis can supplement the limitations of this study

Reply 1: Thank you for your comments. It would be challenging to gather all the information mentioned above from a database. Maybe it is possible if all the data was gathered from a specific hospital database, but that would reduce the cohort, and the sample would be less representative of the general population. The ideal scenario would be to carry out a RCT, but that would be difficult given the complexity of MG patients.

(2) briefly introduce what Elixhauser Comorbidity Index is.

Reply 2: We added a brief explanation of the score on lines 104-106.

Reviewer C

This study is important for the future Minimally Invasive surgery of another parts.

This study was analysed using only the Florida Inpatient Discharge Dataset for patients. Therefore we have to pay attention to the bias of each hospital data.

The Authors concluded that Patients who underwent minimally invasive thymectomy for Myasthenia Gravis had a significantly shorter length of stay and a lower, although not significant, overall cost.

This data didn't show the MG grade precisely.

The important thing is that the area of extended thymectomy. This data didn't show these data.

The importance of the MG patients is the therapeutic effect.

The hospital stay is uncertain information.

I think that we have to research the quality of the surgery methods.

MIS has some methods – subxyphoid approach, VATS approach and Robotic surgery etc. And these methods can see the detailed imaging.

Open surgery has the cosmetic disadvantage but it has the precise dissection area for extended thymectomy. The wound pain of open surgery is not inferior compared with MIS necessarily.

We cannot get these information from only the database.

This study has the uncertain results.

Reply 1: Thank you for your comments. Although we agree that our study has several limitations discussed on lines 185-188, we still think it has strengths that make our results relevant to the scientific community, mentioned on lines 177-183. Obtaining the information from a database allowed us to gather a more significant cohort and a more representative sample of the general population.

Reviewer D

The authors provide a well-constructed and appropriate report of their study, which assessed the length of stay and cost of minimally invasive versus open thymectomies in patients with myasthenia gravis in their state. The introduction and rationale for the study are clear. The methodology utilised is robust and reproducible. The results are clearly presented and easily accessible to readers. The discussion is strong and draws relevant literature together in order to place their findings into the context of previously published work. Limitations are discussed and appropriate conclusions reached. I have no concerns regarding this concise paper.

Reply 1: Thank you for your comments.

Reviewer E

Castillo-Larios and colleagues present an observational report of minimally invasive

vs open thymectomy for patients with MG in the state of Florida, USA. They present very limited data on length of stay and cost. I have several points of clarification.

- 1. The authors are not reporting any specifically new findings. It is already well known that the overall rate of minimally invasive thymectomy is increasing but adoption has been somewhat limited. Their results focus on what has been observed in Florida over the time period of interest, 2013 - 2018. While they note the rate of thymectomy by different techniques has not changed, it would be interesting to know if the number of thymectomies each year remained constant, especially since the results of the MGTX trial were released during this period.*

Reply 1: Although the results we obtained may not be new, we think our study is relevant as it covers the whole state of Florida, and it only includes patients with non-thymomatous MG, as we mentioned on lines 177-183. We agree that analyzing if the number of thymectomies each year remained constant would be interesting, but unfortunately we lack that information.

- 2. The only outcome on which the authors comment is length of stay. The last line of introduction suggests more than length of stay will be addressed. This is somewhat misleading to the reader.*

Reply 2: We clarified the outcomes of our study on lines 75-76: “This is the first statewide database study to compare hospital length of stay and charges of minimally invasive surgery (MIS) vs open thymectomy in patients with MG.”

- 3. In the discussion, the authors indicate their cohort only included patients with MG who did not have thymoma. The methods need to clearly state the population was restricted to non-thymomatous MG patients.*

Reply 3: We clarified that we only included patients with a primary diagnosis of “non-thymomatous MG” on lines 80 and 95.

- 4. The authors indicate they excluded Medicare patients under age 65 due to higher likelihood of comorbidities. If the Elixhauser Comorbidity Index was used to standardize risk, then this would have been controlled. Likewise, the more "sick" MG patients are the ones who may have the greatest benefit from thymectomy.*

Reply 4: Medicare patients under age 65 include those who require dialysis and have received social security disability checks for 2 years (2). We chose to exclude them since they are higher risk surgical candidates unrelated to their diagnosis of MG.

- 5. Which specific thymectomy techniques were assessed in the minimally invasive*

group (VATS, robotic VATS) vs open groups (transsternal, transcervical).

Reply 5: We filtered patients by procedure with ICD-9 and ICD-10 codes. The codes that were considered as minimally invasive or open thymectomy are described on lines 85-91. As the information was obtained from an insurance database, we don't know precisely what minimally invasive surgical technique was used. Medicare surgical coding classifies minimally invasive as "thoracoscopic", which would include VATS and robotic. Transternal would be "open" and transcervical, which was not included in our study, would be "other and unspecified operations on the thymus."

6. *While use of the Elixhauser Comorbidity Index is helpful to characterize patients, were there any specific differences among the items in the index that predominantly accounted for the choice of minimally invasive vs open thymectomy? For example, low FVC and obesity are two of the greatest factors limiting use of MIS due to poor tolerance of single lung ventilation.*

Reply 6: Although we agree that analyzing each factor separately would be interesting, we could not do it with the information available in the dataset.

7. *How do these results compare to the recent review of perioperative outcomes and LOS for non-thymomatous MG by Raja et al (PMID 34339670)?*

Reply 7: We think our results complement what was found by Raja et al., as their conclusions are similar to ours. Also, their study uses information from a database, so the limitations of their study are similar to ours. Nevertheless, their paper focuses on the complications of the different types of surgery, and ours focuses on the length of stay and cost of MIS vs open thymectomy.

8. *What new information does this manuscript add to the body of research on thymectomy in MG?*

Reply 8: Our study supports the published data with a robust cohort of patients. Currently, available data consists mainly of small and single-center studies with highly selected populations. This study is multi-center, and as information was gathered from an insurance database, this sample is more representative of the general population.

References:

1. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of Logistic Regression versus Propensity Score When the Number of Events Is Low and There Are Multiple Confounders. *American Journal of Epidemiology*. 2003;158(3):280-7

2. Medicare eligibility for those under 65 [Internet]. Medicare Interactive. 2022 [cited 25 February 2022]. Available from: [https://www.medicareinteractive.org/get-answers /medicare-basics/medicare-eligibility-overview/medicare-eligibility-for-those-under-65](https://www.medicareinteractive.org/get-answers/medicare-basics/medicare-eligibility-overview/medicare-eligibility-for-those-under-65)
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