

Peer review file

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Reviewer A

Comment 1: This is a well written study exploring the use of thoracotomy for treating invasive pulmonary aspergillosis. Because it uses the NIS database, there are many relevant questions that cannot be answered. For example, the diagnosis can be elusive without pulmonary and infectious diseases diagnosis. HIV is identified as a risk factor for mortality; however, HIV disease is no longer a fatal disease and patients who take their medication have no evidence of immune suppression. Consequently, including that observation suggests that HIV patients were not taking their meds.

The paper is basically a negative study assessing the role of surgery which is less than 5% of cases in their database. The most interesting observation is the improved outcome with VATS. It might be valuable to look at the data from 2017 where VATS was the preponderant modality in surgical treatment and compare outcome to medical management.

This study addresses an uncommon, serious and complicated medical condition and while the study showed no difference between medical and surgical treatment it does provide insight.

Reply 1: We thank the reviewer for this thoughtful comment. As the reviewer mentioned, there are several limitations to the NIS database that preclude us from commenting on the extent or severity of a patient's existing comorbidity, and whether the patient is compliant with their medications. This important point and the excellent example provided by the reviewer have been incorporated in the limitations section of the discussion within this manuscript.

Furthermore, the reviewer proposes an interesting comparison; to selectively use the 2017 NIS dataset to compare outcomes, medical management vs. surgery (predominantly VATS). Unfortunately, this analysis is not feasible within our existing study resources, as we have selectively utilized the 2007-2015 (through the 3rd quarter)

NIS data in order to maintain consistency in data entry with ICD-9 coding. As the tenth edition (ICD-10) coding was utilized in the 4th quarter of 2015 onwards. Additionally, as surgical management is so infrequently utilized in the treatment for pulmonary aspergillosis (please see Figure 2 in manuscript), a comparison would be underpowered with only a single year of data, and highly unlikely to elucidate any differences.

Changes in the text:

Discussion, Lines 257-261

The lack of detail within the dataset pertaining to a patient's baseline pulmonary function or pre-existing medical comorbidities limit us from commenting on the extent and severity of a patient's condition. For instance, a patient with HIV treated with the appropriate antiviral therapy will not possess the same immune deficiencies as a patient non-compliant with medications.

Reviewer B

The authors evaluated factors associated with inpatient mortality and surgical intervention in patients with pulmonary aspergillosis using the NIS database with ICD-9 coding. The study sample size was large and the manuscript was generally well-written. However, several major methodological concerns, largely related to the limitation of NIS database design, were noted in the manuscript:

Comment 1: Pulmonary aspergillosis encompasses a heterogeneous disease entity. IPA and CPA represent distinct clinical manifestations, and therefore prognosis. Between the IPA-CPA spectrum, this current cohort looks more like IPA cohort, given the much higher mortality in this cohort than that in the reported CPA cohort. The exact type of pulmonary aspergillosis may be a more important predictor of survival, than types of intervention. Failure to incorporate this parameter will make the prediction model for mortality less accurate.

Reply 1: As the reviewer astutely points out, pulmonary aspergillosis encompasses a wide spectrum of varying manifestations, ranging from Allergic Bronchopulmonary Aspergillosis (ABPA) to Invasive Pulmonary Aspergillosis (IPA). The distinct type of

pulmonary aspergillosis is unable to be accounted for with the NIS dataset. However, we did attempt to exclude the more benign manifestations within the pulmonary aspergillosis spectrum by excluding patients with Allergic Bronchopulmonary Aspergillosis (ABPA) or sinusitis, in order to focus our study on patients with invasive pulmonary aspergillosis. We have clarified this in the limitations section. Additionally, we have elaborated on this important limitation in the discussion of the manuscript.

Changes in the text:

Discussion, Lines 261-265

Lastly, given the limited granularity in ICD-9 codes, we are unable to distinguish IPA from more subacute or chronic forms of pulmonary aspergillosis, this will invariably limit the accuracy of our multivariable model predicting mortality. However, we have excluded ABPA and sinusitis to focus on non-allergic pulmonary manifestations of *Aspergillus* infection, such as IPA (16, 32, 33).

Comment 2: What was the indication for surgical resection? Only patients receiving surgical resection as a “treatment modality” for pulmonary aspergillosis should be enrolled for analysis. Whether pulmonary aspergillosis was the primary discharge diagnosis may be helpful for clarification.

Reply 2: We appreciate the reviewer’s important comment. Patients with a primary or secondary procedure code describing an open or VATS surgical resection with an admission diagnosis for pulmonary aspergillosis was used to identify the surgical cohort in this study. Given the limitations of the dataset, we are unable to delineate the specific indication for surgery. However, we were able to identify specific patient diagnoses associated with receipt of surgery during admission – the strongest predictor was hemoptysis. Likely a consequence of the necrotizing bronchopneumonia with invasion of pulmonary parenchyma and nearby blood vessels characterized by invasive pulmonary aspergillosis. This limitation has been further clarified in the discussion section.

Changes in the text:

Discussion, Lines 250-251

Further, beyond the operation performed, indications for surgery and operative details are not reported within the NIS dataset.

Comment 3: Given the low percentage of patients with hemoptysis or receiving bronchial artery embolization (only 2-6%), the purpose of surgical management may reside in better long-term infection control. Therefore, inpatient mortality with a relative short hospital stay (median 9-12 days) may not be a suitable outcome measurement.

Reply 3: We thank the reviewer for this valuable comment, and we agree that the primary benefit of surgical management may be an improvement in long-term infection control. Some have suggested that surgical intervention may decrease the risk of fungal reactivation or life-threatening angioinvasion from occurring several months after discharge. Unfortunately, the NIS does not include any long-term data, thus we can only speculate on the long-term benefits of surgical management. However, given the paucity of data regarding the perioperative outcomes for patients with pulmonary aspergillosis undergoing surgery, we do believe this study adds value by aggregating a large number of surgical patients that would not be otherwise possible using single institutional data. We have used the reviewer's comment to add this limitation to the discussion.

Changes in the text:

Discussion, Lines 244-246

As the NIS is a collection of admissions data, longitudinal data is not available and prevents this study from examining the long-term benefits of surgical resection.

Comment 4: Compared to detailed surgical procedures, the presence and components of medical anti-fungal treatment for pulmonary aspergillosis were completely unknown, no matter during or before admission. Lacking this information would definitely influence the analysis of factors associated with the need for surgery.

Reply 4: We appreciate the reviewer for this important comment. Unfortunately, detailed information regarding the medical management for pulmonary aspergillosis is not captured within the NIS dataset. As anti-fungal treatment is the standard of care, this study is based on the assumption that all patients were on some type of anti-fungal treatment, however, we are unable to elucidate the exact anti-fungal regimen or duration using the NIS dataset. We have added this important point to the discussion.

Changes in the text:

Discussion, Lines 241-243

Furthermore, the database does not include the type or duration of antifungal treatment regimens used, which would certainly affect prognosis and surgical decision making (31).

Comment 5: The CONCLUSION section: seemed like DISCUSSION section.

Reply 5: We thank the reviewer for this comment. We have retitled this section as the DISCUSSION, and have placed our concluding remarks at the end as a CONCLUSIONS section.

Changes in the text: Lines 190, 269

Comment 6: In CONCLUSION section LINE 205: the authors evaluated patient factors including prior tuberculosis. Was “tuberculosis” in TABLES “active tuberculosis” or “prior tuberculosis”?

Reply 6: We appreciate the reviewer bringing this important point to our attention. We have now clarified the TABLES to state “Prior Tuberculosis” to indicate a patient’s previous diagnosis with tuberculosis.

Changes in the text: Tables 1, 2, 3 edited as stated above

Comment 7: In CONCLUSION section LINE 216-225: the study finding could not support the hypothesis of benefits of early surgical intervention in patients with pulmonary aspergillosis, because the exact time interval between diagnosis and surgery was unknown in this study.

Reply 7: We thank the reviewer for this insightful comment. As the NIS dataset does not include data pertaining to the time between diagnosis and surgery, we attempted to indirectly investigate this point by delineating the role of surgery in the elective and non-elective admission setting. Patients undergoing surgery during a non-elective admission were more likely to have worse outcomes, additionally we found that these patients were more likely to undergo more extensive operations (for instance a pneumonectomy), rather than a wedge resection in the elective setting for infectious source control. We have clarified this important point in the discussion.

Changes in the text:

Discussion, Lines 223-242

Furthermore, non-elective admission and pneumonectomy were important risk factors for inpatient mortality among those who underwent surgery in our study, which supports several previous studies that have reported the benefits of early surgery (9, 16, 18). Haibicht and colleagues demonstrated a significant 6-month survival advantage in those treated with early surgical intervention (defined as surgical resection within a few days of establishing clinical diagnosis) over those treated with medical management only (27). A trend towards lower mortality was noted in a surgically managed cohort of patients with pulmonary aspergillosis when compared to those treated medically at 3 months post-treatment (28). Early surgical resection may decrease the risk of fungal reactivation or life-threatening angioinvasion from occurring months after discharge (6, 29, 30).

In patients admitted non-electively, the extent of damage caused by the invasive nature of pulmonary aspergillosis may result in significantly more extensive pulmonary

resections. We found that patients who were admitted non-electively were more likely to undergo a pneumonectomy. Similar trends have been identified in a study comparing emergent and elective surgery for pulmonary aspergillosis, reporting increased need for lobectomies rather than partial resections in the emergent setting (28). Avoiding surgery in the non-elective setting may be advisable, as it can lead to larger, more morbid resections, and is associated with higher mortality. Certainly, there are situations in which non-elective admission and surgery is unavoidable. However, in the context of a patient with a history of SOT, liver disease, HIV, or hematologic disease, one may consider intervening with surgery sooner rather than later.

Discussion, Lines 250-255

Further, beyond the operation performed, indications for surgery and operative details are not reported within the NIS dataset. Data pertaining to the time of diagnosis and surgery is also lacking, and if available would have provided insight into the potential benefits of early surgical intervention. Although, we did indirectly attempt to address the impact of timing and surgery by characterizing non-elective admissions for pulmonary aspergillosis requiring surgical intervention as described above.

Comment 8: In TABLE 3 and SUPPLEMENTARY TABLE 2, tuberculosis was a poor prognostic factor (AOR 3.25 for mortality) in surgical management group, but a good prognostic factor (AOR 0.55 for mortality) in overall group. The contradictory role of tuberculosis deserves further discussion.

Reply 8: We thank the reviewer for this valuable comment. Given the retrospective nature of this database study, it is difficult to explain this contradictory finding with any reasonable certainty. We speculate patients undergoing surgery were more likely to have had an underlying history of cavitary tuberculosis, whereas patients treated medically were less likely to have large cavitary lesions as a sequelae of possibly more mild tuberculosis.

Changes in the text:

Discussion, Lines 205 - 210

Interestingly, prior tuberculosis was found to be a beneficial prognostic factor in terms of inpatient mortality in multivariable analysis examining the entire study cohort (including medical and surgically managed patients). This contradictory finding may be a result of surgical patients more likely to have had an underlying history of cavitary tuberculosis, whereas patients treated medically were less likely to have large cavitary lesions as a sequelae of possibly more mild tuberculosis.

Reviewer C

The authors performed a clinical study using the National Inpatient Sample dataset to investigate the influence of preoperative patient comorbidities on inpatient mortality and need for surgery in patients with pulmonary aspergillosis. While this study is interesting, there are some points to be elucidated.

Comment 1: Methods, Page 5, Line 122-123. It would be needed to describe more detailed process for multivariable analysis. How did you choose clinical factors for multivariable analysis? Even if there is no significant difference in the univariate analysis, it would be also better to consider including factors that have been previously reported or are clinically important in your multivariable analysis.

Reply 1: We thank the reviewer for this valuable comment. The clinical factors selected for the multivariable analysis were those that were statistically significant in univariate analysis, and the variables that were considered to be clinically important based on our clinical experience and previous literature. We have clarified this in the methods section.

Changes in the text:

Methods, Lines 127-130

The clinical factors selected for the multivariable analysis were those that were statistically significant in univariate analysis, and the variables that were considered to be clinically important based on our experience and previous literature.

Comment 2: Results, Page 6, Line 166. It would be needed to clarify how you adjusted for confounding variables.

Reply 2: We appreciate the reviewer bringing this important point to our attention. Our multivariable model was adjusted based on patient and operative factors that were statistically significant on univariate analysis and clinically important based on our clinical experience and previous literature. We have clarified this in the methods section.

Changes in the text:

Methods, Lines 127-130

The clinical factors selected for the multivariable analysis were those that were statistically significant in univariate analysis, and the variables that were considered to be clinically important based on our experience and previous literature.

Comment 3: Conclusions, Page 7, Line 205, Table 1 and 2. What kinds of pulmonary diseases are included in “chronic pulmonary disease” or “underlying pulmonary disease”? Does “Tuberculosis” in Table 1 and 2 mean extra-pulmonary TB?

Reply 3: We thank the reviewer for this important comment. Chronic pulmonary disease encompassed patients with α 1AT deficiency, pulmonary sarcoidosis, COPD, asthma, bronchiectasis, occupational and other exposure based lung diseases, interstitial lung disease, and chronic respiratory failure. We have now added a footnote to Tables 1 & 2 to clarify this point. “Tuberculosis” was used to characterize patients with a history of pulmonary tuberculosis – this has now been more clearly stated in the tables.

Changes in the text:

Tables 1, 2, 3 edited

Comment 4: If possible, it would be better to mention other pulmonary clinical findings such as pulmonary function or radiological findings before surgery.

Reply 4: We thank the reviewer for this thoughtful comment, and agree that pulmonary function testing or radiographic findings would certainly add to the strength of this study. Unfortunately, this level of granularity is not available in the National Inpatient Sample (NIS) dataset. Despite these limitations, one of the greatest strengths of the NIS dataset is the ability to aggregate a large number of surgical patients that would otherwise not be possible using single institutional data. Nonetheless, we have added this important limitation to the discussion of our manuscript.

Changes in the text:

Discussion, Lines 257-259

The lack of detail within the dataset pertaining to a patient's existing baseline pulmonary function or medical comorbidities limit us from commenting on the extent and severity of a patient's condition.

Discussion, Lines 265-267

Despite these limitations, one of the greatest strengths of the NIS dataset is the ability to aggregate a large number of surgical patients that would otherwise not be possible using single institutional data.

Comment 5: If possible, it would be better to analyze the data in a hierarchical manner by timing of surgery (the duration from establishing clinical diagnosis through surgery).

Reply 5: We appreciate the reviewer's insightful suggestion, similar to Reviewer B, Comment 7. Unfortunately, this level of granularity is not available in the NIS dataset. As the reviewer astutely points out, the ability to examine timing of surgery may provide a greater understanding of the utility of performing surgery in patients with invasive pulmonary aspergillosis. We indirectly attempted to delineate the impact of timing by examining the role of surgery in the elective setting versus non-elective setting. We found in this study that patients undergoing surgery during a non-elective admission were more likely to have worse outcomes, additionally we found that these patients were more likely to undergo more extensive surgery (i.e. pneumonectomy), rather than a wedge resection in the elective setting for infectious source control. We

speculate patients undergoing surgery in a non-elective admission were secondary to an emergency, such as uncontrollable hemoptysis. Nonetheless, we have added this important limitation to the manuscript.

Changes in the text:

Discussion, Lines 244-246

As the NIS is a collection of admissions data, longitudinal data is not available and prevents this study from examining the long-term benefits of surgical resection.

Discussion, Lines 244-246

Further, beyond the operation performed, indications for surgery and operative details are not reported within the NIS dataset. Data pertaining to the time of diagnosis and surgery is also lacking, and if available would have provided insight into the potential benefits of early surgical intervention. Although, we did indirectly attempt to address the impact of timing and surgery by characterizing non-elective admissions for pulmonary aspergillosis requiring surgical intervention as described above.