

## Peer review file

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### Reviewer A

The authors retrospectively studied the efficacy and potential benefit of ABPP for PAL after lung resection. They found that after propensity-score matching, ABPP was associated with shorter time to chest tube removal and less risk of readmission or empyema. The results are in accordance with previous reports, showing that ABPP is helpful in dealing with PAL.

**Major comments:** What do the authors think is new in this study? The discussion part of the manuscript is very long. The authors should try to make it more focused on what they could provide in addition to the existing literature.

**Reply:** Historically, clinicians cite older data that ABPP can be associated with empyema development. This has led to hesitancy among providers in more routinely using ABPP in PAL. Although studies have demonstrated the efficacy of ABPP, a majority of the literature consists of small patient populations and indications for ABPP vary. This study specifically looks at a post-surgical population and the utility of ABPP in the postoperative period. For example, this study excluded spontaneous pneumothoraces in the setting of bullous disease or COPD whereas previous studies include this population.

Our study finds that empyema risk does not increase with ABPP and may help with decreasing complications such as readmission and reoperation. By demonstrating ABPP safety and efficacy, this study allows us to confidently proceed with establishment of a randomized control trial to gain a better understanding of ABPP utility and its potential impact in removing chest tubes and facilitating discharges earlier.

Based on the reviewer's suggestions, we have narrowed the focus of our discussion and made major edits in order to help address the concerns mentioned.

**Changes in the text:** See discussion.

Minor comments:

**Comment 1:** It seems that ABPP was not applied on POD 5 in all patients with PAL. Details should be provided in the Results.

**Reply 1:** Correct, not all patients underwent ABPP application on POD 5 with PAL. This decision was based on individual surgeon preferences. At this time, there is no department wide protocol for when ABPP should be utilized in PALs. In fact, this question was a motivating factor to conduct this study and better understand that safety and efficacy of ABPP. Ultimately, we hope to create an algorithm in order to more consistently manage PALs leaks in this population.

**Changes in the text:** “The remaining 76 patients did not undergo ABPP as dictated by surgeon preference and comprised the control group in this study, Figure 2”

**Comment 2:** The amount of blood used is said to be 90cc +/- 30cc. There has been literature arguing for a higher amount of blood with better outcome. Detailed results on amount of blood used should be presented.

**Reply 2:** The +/- 30cc was described in case the lab technician is unable to draw the full amount of blood in each syringe during the ABPP procedure. This small variation is usually a negligible volume but we initially had included +/- 30cc to account for potential variation. None of the patients had recorded an ABPP blood volume that significantly varied from 90cc. To clarify this further, we have made the following changes in the text.

**Changes in the text:** Results section, paragraph 1 “Of these, 34 patients underwent ABPP for PAL using 90cc of autologous blood.” Methods section, paragraph 1: “A laboratory technician then draws 90cc of autologous blood into three equal 30cc unheparinized syringes. The autologous blood sample is directly injected into the chest tube through a connector with stopcock followed by saline flush solution. Occasionally, the syringes are not completely full and thus the volume may vary to a minor degree.”

**Comment 3:** In fact, it would be interesting and clinically relevant if the authors could study potential risk factors for successful/unsuccessful ABPP for PAL. This would provide useful guide for future practice. Although the authors claimed there

were not enough patients enrolled in this study for such analysis, at least they could make some efforts in comparing the amount of blood, timing of application, etc.

**Reply 3:** Correct, there were not enough patients in this study for such analysis. The amount of blood was consistently 90cc for all patients in the study and therefore could not be analyzed. We made an effort to compare timing of application as shown in table 1. The patients labeled ABPP (all) included those who had ABPP administration prior to POD 5 (most typically POD 3 or 4). For instance, as the table shows, successful air leak resolution on the first attempt with ABPP in the all ABPP group compared to the group with ABPP for PAL (on or after POD5) was 59% vs 64%. Changes in the text: addition to results section, paragraph 2. “Table 1 additionally describes results for all ABPP treated patients, which includes those with ABPP administration prior to POD 5. In this group, there was a 59% air leak resolution with the first ABPP compared with 64% when ABPP was used after POD 5.”

**Comment 4:** From Table 2 it seems that increasingly more patients with PAL were managed with ABPP. Maybe a time-trend figure would help better show that ABPP has been increasingly accepted by surgeons at their unit.

**Reply 4:** Correct, ABPP was increasingly utilized by surgeons. Thank you for your suggestion, we have added changes to the text to bring attention to this point.

**Changes in the text:** Results paragraph 4 addition: “It should be noted that over time, there was increase in surgeon preference to utilize ABPP in managing air leaks as its effectiveness became more evident. [Table 2]”

**Comment 5:** All abbreviations should be fully spelled out upon first appearance in the text, including the Abstract.

**Reply 5:** Agree, this has been completed

**Changes in the text:** length of stay (LOS), chest tube (CT), hazard ratio (HR) all spelled out in the abstract

## **Reviewer B**

Prevention of postoperative air leaks with a careful intraoperative management of pulmonary parenchyma and use of numerous sealants and glues routinely used to

cover lung parenchyma to avoid PAL, should be stressed because it represents the most efficient strategy to prevent PAL.

**Comment 1:** Did you use any intraoperative protocol or sealant? And did you find any difference in the two groups?

All surgeon knows that a complete pulmonary parenchyma expansion promotes air leak resolution

**Comment 2:** Did you analyze if there are any difference in pulmonary expansion in the two group, comparing at chest x-ray the length of residual pleural space?

Please add these informations in the manuscript.

**Reply 1:** Thank you for bringing this point up. In the patients selected for this study, sealants were not utilized for any of the patients and we have added this to the text.

**Reply 2:** We did collect data of pulmonary expansion as visualized on chest x-ray prior to administration of ABPP. This was done by measuring the residual pleural space on chest x-ray and categorizing results by size into none/tiny (0.5cm or less), small (0.5cm to 1cm), moderate (2-4 cm), and large (>4cm). These groupings were based on the correlation of size measured with Radiologists interpretation of small/moderate/large. There were not enough patients in each group for analysis however we have now included the descriptive data in table 2 and additionally in the text.

### **Changes in the text:**

#### Methods

Methods, data collection, paragraph 1: "If sealants were used at the time of surgery, these patients were excluded from the study."

Methods, data collection, paragraph 3: "The degree of pulmonary expansion was documented radiographically prior to ABPP, and then was re-reviewed by an expert thoracic-focused radiologist. Residual pleural space was measured in centimeters (cm) from the apex of the lung to the highest extent of chest wall apex on upright chest x-ray. The radiologist's interpretation of the residual pleural space size was used to correlate the measurements into categories, (none/tiny= $\leq 0.5$ cm, 0.5-2cm=small, 2-4cm=moderate, and  $>4$ cm=large)."

Results, paragraph 3: “Residual pleural space size prior to administration of ABPP is described in Table 1. If a tiny or small space was present on chest x-ray prior to administration of ABPP, the success rate for air leak resolution within 72 hours was higher than if a moderate or large residual pleural space was present. This study was underpowered to delineate a benefit based on remaining pneumothorax measured as pleural space size.”

**Comment 3:** “CT” abbreviation in the Abstract must be written in full words.

**Reply 3:** Thank you, this has been corrected

Changes in the text: CT changed to chest tube (CT)

**Comment 4:** At page 5 line 32 and page 8 line 9 type error are present (ABPP) correct them please.

**Reply 4:** We are unsure as to what the reviewer is specifically referring to but we have made numerous edits and hope this has addressed your concern.

## **Reviewer C**

**Comment 1:** The full name should be used in the abstract. LOS(P1 L34), CT (P2 L3), etc. And the sequence of HR and P value should be unified (P2 L3).

**Reply 1:** Thank you, this has been corrected

**Changes in the text:** length of stay (LOS), chest tube (CT) and P value and HR sequence unified.

**Comment 2:** I didn't see any description of Propensity-matched analysis in the method part. Does the Propensity-matched analysis mean Propensity Score Matching (PSM)? If so, please add this procedure in the flow chart (figure 1). how did you conduct the PSM? How many patients were included in ABPP group and control group after matching?

Moreover, which software was used for statistical analysis?

**Reply 2:** Yes, the propensity-matched analysis means propensity score matching. This was described in the methods portion under the subheading “Data Analysis” starting on page 5. Patients missing one of the variables used in the IPTW estimation

of weights were not included in the analysis. This left us with 34 patients in the ABPP treatment group and 71 patients in the no ABPP group. This is reflected in figure 3 and we have added this explanation in the text under results as well. Software description also added to the methods portion.

**Changes in the text:**

Methods, data analysis, paragraph 1: “Using SAS version 9.4 software, a logistic regression model was utilized to obtain the predicted probabilities of treatment with ABPP.”

Results, effectiveness of ABPP, paragraph 4: “Patients with missing variables used in IPTW estimation of weights were not included in the analyses, which left 34 patients in the ABPP group and 71 patients in the no ABPP treatment group.”

**Comment 3:** I suggest the author separate the results part using several subheadings.

**Reply 3:** We have added subheadings per your suggestion to the results portion

**Changes in the text:** addition of subheadings (Patient selection, Effectiveness of ABPP, and Follow-up).

**Comment 4:** Why ABPP could cause pneumothorax?

**Reply 4:** An ABPP itself does not cause a pneumothorax. However as described in the supplemental methods and figure, during the procedure after the blood is inserted via the chest tube, the chest tube is clamped. In the setting of an air leak a patient may not be able to tolerate clamping of the chest tube, leading to increased accumulation of air within the intrathoracic cavity and worsening pneumothorax. We did not **observe this phenomenon specifically in this patient population that led to discontinuation of the ABPP.**

**Changes in the text:** None.

**Comment 5:** The patient number in Figure 2 is 71, but in other figures and tables, the number is 76.

**Reply 5:** Figure 2 illustrates the inverse probability weighting results as described in the methods portion, under the subheading Data Analysis. Incomplete data for 5 patients led to those patients being excluded for this portion of the analysis. (see response to comment 2)

**Changes in the text:**

Results, effectiveness of ABPP, paragraph 4: “Patients missing one of the variables used in IPTW estimation of weights were not included in the analyses, which left 34 patients in the ABPP group and 71 patients in the no ABPP treatment group.”

**Reviewer D**

Major remarks:

The study attempts to describe a small and heterogeneous group of patients treated with different protocols with ABPP for PAL. The idea of presenting the results of this kind of a retrospective study deserves attention. However, the study population is very difficult. We cannot even discuss the selection biases as it seems there is no evident selection at all. This data may be interesting to practicing clinicians under the condition of a clear presentation. Authors should try to concentrate on a narrower and more homogenous population to reveal a clear message. Currently, the paper is difficult to understand due to the wide inclusion criteria.

**Comment 1:** I would like the authors to improve the Figure 1. The abbreviations d/c w/ CT should be explained. This Figure is the most important part of the results section and should be self-explainable. Maybe there is too much data in the Figure and it should be split. Please consider that.

**Reply 1:** The abbreviations in the abstract and figures/tables have been clarified; additional corrections have been made to hopefully be more self-explanatory.

**Changes in the text:** See figures/tables

**Comment 2:** I do not support the use of the name of the group – “control group”. According to methodology, this is not a control study. This study represents a comparison of three different treatment protocols. I would rather propose “no ABPP group”.

**Reply 2:** Thank you for your suggestion. The “control group” has been renamed “No ABPP group” throughout the text.

**Changes in the text:** see figures/tables.

**Comment 3:** Please exactly describe the drain withdrawal criteria.

**Reply 3:** This has been added to the data collection portion under methods, page 5.

**Changes in the text:** Methods, data collection, paragraph 2. “Chest tube removal criteria included transition to waterseal for at least 4-6 hours, lack of an air leak with forced expiratory maneuvers, less than 200-300cc of non-infected fluid output per 24 hours, and expansion of the lung on chest x-ray.”

**Comment 4:** In Table 1 and Figure 3 there is a group ABP (all). The study describes the results of ABPP in PAL. Reconsider the removal of this group from the Figure and Table.

**Reply 4:** Thank you for your suggestion. You are correct; this study focuses on the results of patients undergoing ABPP specifically for PAL. However, given that outcomes of interest included complications such as empyema development we feel it is important to demonstrate that ABPP itself does not lead to such complications. Some may argue that administering ABPP prior to postoperative day 5 may not be useful to determine resolution of air leak since an air leak may have spontaneously resolved regardless of the ABPP prior to day 5. This is why we chose to set a cutoff of postoperative day 5 to define prolonged air leak, consistent with the current literature. However, it is important to note that if ABPP was to be administered prior to day 5, the patients are not at an increased risk of complications such as an empyema.

**Changes in the text:** None.

**Comment 5:** There is no statement concerning the ethics of the study.

**Reply 5:** There is a statement that the authors have no conflicts of interest to disclose on the title page. An additional ethical statement has been added to the manuscript.

**Changes in the text:**

Methods, data collection, paragraph 1. “The study was conducted in agreement with ethical standards and approval obtained by the Mayo Institutional Review Board (IRB #16-005562).”

Footnote added: “The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.”



Minor remarks:

**Comment 6:** Please explain abbreviations in Tables and Figures. Part of the abbreviations is not defined in the appropriate section of the text.

**Reply 6:** The abbreviations in the abstract and figures/tables have been clarified  
Changes in the text: see figures/tables

#### **Reviewer E**

**Comment:** My only issue is the format of figure 3, I strongly suggest to use a bar format, the circular graphics do not match the overall quality of your paper.

**Reply:** Thank you for your suggestion, we have made this change.

**Changes in the text:** See figure 4 (now in bar format rather than a circular graphic)

#### **Reviewer F**

**Comment 1:** I read this paper with great interest from the title. This paper contains certain useful information. The incidence of empyema, which is a concern after ABPP for PAL, does not increase significantly. And also, it is clinically useful information that the risk of discharge with the Heimlich valve without ABPP is also relatively high.

However, there are some inaccurate descriptions and difficult sentences to understand in this paper. For example, in abstract, abbreviations that are not spelled out (CT, LOS) are used, and Figure 1,2,3 and Tables 1,2,3 are also somewhat confusing and should be more self-explanatory. Abbreviations in the figures are also incorrect.

**Reply 2:** The abbreviations in the abstract and figures/tables have been clarified; additional corrections have been made to hopefully be more self-explanatory  
Changes in the text: see figures/tables

**Comment 2:** There would be general lacks of readability throughout the text.

Although the content of the paper is interesting, I am hesitant to accept this paper as a scientific English paper.

Taking above points into consideration, if the Editor encourages authors to revise, I think major revisions are needed, otherwise, recommendation is considered to submit to other journals.

**Reply 2:** Thank you for your suggestion and comments. We have made numerous changes to improve the readability throughout the text.

**Changes in the text:** See numerous edits throughout the text.