Peer Review File

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Reviewer A

This is a case series of 12 infants with CPAM who were managed by thoracoscopic resection at a single hospital in Shanghai. All of the patients underwent surgery before 3 months of age without a conversion to thoracotomy and there were no complications. My major concerns include the very small number of patients and the lack of novelty in this approach given what is already discussed in the literature.

1 The feasibility of doing a thoracoscopic lung resection in early infants is already well described. For example, the 2015 study by Laje and colleagues at CHOP in the USA reviewed 100 cases with a fairly low conversion rate. The mean age of surgery was 7 weeks. The mean hospital length of stay was 3 days.

Reply 1: In our study, the mean age of surgery was 60 days (about 8 weeks), the mean postoperative hospital length of stay was 8.42 days. All these children were hospitalized for a few more days because of their young age, and they were discharged after ensuring that there were no signs of discomfort.

We have modified our text as advised (see Page 5, line 153-154).

2 The authors suggest that all of the patients in their series were symptomatic (usually tachypnea) but there are no details in terms of whether they have these symptoms at birth. Was surgery delays beyond the neonatal period to enable resection? Based on the relatively high CVR values reported, the answer might be yes. Similarly, recurrent pneumonia in infants at that young age seems implausible given the existing literature.

Reply 2: As the huge CPAM was discovered in utero, all these children were admitted to the neonatal intensive care unit directly after they were born in the local hospitals. Most of them were born with symptoms such as tachypnea. Due to lack of medical conditions for surgery in those local hospitals, the parents of these children chose our hospital for surgery. Four children had a history of repeated cough and fever, and chest X-ray suggested pulmonary inflammation. One of them suffered from lung consolidation owing to repeated infections in the lower lobe of the right lung.

We have modified our text as advised (see Page 2, line 68-76).

3 The reasons for the long length of stay are unclear as the manuscript is currently written. The the USA, the length of stays are almost always less than 5 days.

Reply 3: In our study, the mean postoperative hospital length of stay was 8.42 days. All these children were hospitalized for a few more days because of their young age, and they were discharged after ensuring that there were no signs of discomfort.

We have modified our text as advised (see Page 5, line 153-154).

4 Was a single surgeon and an anesthesiologist involved in all of these cases? This would be important to document given the steep learning curve associated with the operation.

Reply 4: All cases were completed by the same surgeon and the same chief anesthesiologist.

We have modified our text as advised (see Page 4, line 137-138).

5 The paper is generally well written but might benefit from English language editing. One example is the use of the term "fetal edema" instead of "fetal hydrops." Another is a reference to the author as "Timothy" instead of his surname "Crombleholme".
Reply 5: Thank you very much for your advice. We have modified our English language as advised.

Reviewer B

Summary:
Chen et al provide a single institutional experience on management of CPAM lesions via VATS at an age that is younger than typical. Their report provides insight into the favorable outcomes seen postoperatively when using specific operating room surgical and anesthesia methods. This series provides a compelling report that may be of help to medical decision making related to surgical approach and timing for infants with CPAM under 3 months of age that are experiencing cardiorespiratory complications.
Concepts to Consider in Revision:

There are a number of recommended areas to revise with small administrative changes related to semantics and grammar though the article reads reasonably well. I would suggest the following:
-Please share with the reader what factored into decision to perform lobectomy, segmental resection or irregular (lung -sparing) resection. Was this all based on CT imaging or driven by intraoperative findings? In the operative method section, mention is made of a pneumonectomy though I don't believe a full lung resection was performed in any patients and this led to some confusion.
Reply 1: The three-dimensional CT imaging was carefully analyzed before the operation to determine the resection range, which may be adjusted according to intraoperative findings during the operation. No cases underwent pneumonectomy.
We have modified our text as advised (see Page 3, line 105-107 and line 123-127).
-Standard deviations for the results section would be of help to include.
Reply 2: We added standard deviations of results section (see Page 4, line 139 and Page 5, line 148,152,153).
-"Recovered well" is somewhat vague aside from the findings of improved chest CT (the column in Table 1 seems unnecessary). Did all children receive repeat chest CTs? What types of questions were provided in clinic to assure adequate cardiorespiratory health in follow up?
Reply 3: All the children had no serious respiratory infection or pneumonia except occasional slight upper respiratory infection during the follow-up. All of them received chest CTs for about 1 year after operation. Besides, ECG, echocardiography and pulmonary ventilation function test were performed if necessary. The column "Outcome" in Table 1 was deleted.
We have modified our text as advised (see Page 5, line 164-171).
-Any comments on ventilatory weaning parameters would help the reader apply this approach to their own institution to see if mechanical ventilator time is comparable.
Reply 4: Ventilatory weaning was performed when the children were awake from anesthesia, spontaneous breathing resumed, and arterial blood gas analysis showed that there was no

carbon dioxide retention (arterial carbon dioxide partial pressure lower than 50mmHg).
We have modified our text as advised (see Page 5, line 148-150).

-Any comments on preterm infants? Will this practice change their surgical management if born with CPAM? Were preterm infants excluded from this assessment due to any concern about thoracic size/development?

Reply 5: All cases were born at full term. So far, we haven't treated preterm infants with CPAM who had severe respiratory symptoms under 3 months old. In case of treating similar preterm infants, I think we will perform early surgery.

-The CVR information was included but did this impact medical decision making at all for the 12 patients in this series?

Reply 6: CVR value is not the primary factor to determine the timing of operation but it is an important factor, and we rely more on clinical symptoms and CT imaging.
We have modified our text as advised (see Page 7, line 253-254).

-CPAM types (based on Stocker classification) should be included earlier in the manuscript with reference to Figures 1-4. Comments on type of lesion in each of the examples used in the Figures here would be of benefit (especially Figure 4). I would imagine that post operative complications are different based on CPAM type. Also consider placing the Stocker type as a column in Table 1.

Reply 7: We added CPAM types in Figures 1-4 and placed the Stocker type as a column in Table 1.

-The authors refer to clinical indications for surgery and also indicators of high risk. Can this be clarified a bit as it relates to medical decision making? Did all patients that underwent surgery at this earlier time point have clinical deterioration? Or, were other risk indicators enough to prompt the decision to operate? Were all surgeries “emergent”?

Reply 8: When the children have persistent tachypnea or recurrent pneumonia, early surgery can be considered. Additionally, a few children were born with serious respiratory and circulatory disorders due to the compression of the heart and lungs and mediastinal deviation. Most of these children have huge cystic lesions and emergency surgery should be carried out in time after birth. In our study, all the children had severe respiratory symptoms. Some of them had persistent tachypnea owing to the compression of the heart and lungs; some had recurrent pneumonia; some even required mechanical ventilation because of respiratory failure. So all the surgeries were emergent.
We have modified our text as advised (see Page 6, line 189-196).

-The authors nicely factor in aspects of the methods used to gain the advantage of space in the thoracic cavity for an effective operation. I think this warrants additional detail to replicate in these small, very young infants that are at risk. For example, how were cystic lesions cauterized (would use this terminology in place of “destroys”)? How was the bronchial occluder placed (under endoscopy or other) to achieve such good outcomes since one-lung ventilation was felt to be important? Were all patients in the lateral position since this impacts bronchial occluder migration and the use of artificial pneumothorax?

Reply 9: The electric hook will be used to cauterize the huge vesicles which look like balloons under the enlarged visual field of thoracoscope, so as to reduce the volume of the lesion and increase the operating space. However, attention should be taken not to touch the blood vessels to avoid bleeding affecting the surgical visual field. Usually, the anesthesiologist will first keep

the children in the supine position and place the bronchial occluder under endoscope, then make them in the lateral position. It is important to observe the bronchial occluder under endoscope immediately after changing the body position to ensure that there is no migrations. Even if it is displaced, it is relatively easy to adjust. It is difficult to place bronchial occluder in the lateral position. We suggest setting the pressure of artificial pneumothorax to below 5mmHg.
We have modified our text as advised (see Page 6, line 220-225 and Page 7, line 234-237).
-The symptoms described in the final, summative paragraph are somewhat vague though the degree of symptoms along with which symptoms/complications are present are amongst the most important pieces of information related to the decision to operate. This paragraph, along with the final claims, seem to include any symptoms as driving the decision to perform a VATS when in reality, there are more subjective factors that are considered. I feel this should be discussed a bit more.
Reply 10: In short, infants with CPAM accompanied by severe clinical symptoms less than 3 months of age as discussed in the preceding content should be operated as soon as possible. VATS is an alternative surgical approach. With the improvement of minimally invasive technology and anesthesia management, VATS is relatively safe and effective in treating children with such conditions.
We have modified our text as advised (see Page 7, line 261-265).
Specific Line Corrections:
-Title. Would strongly consider changing the end of the title to "…Airway Malformation in Infants Less Than 3 Months of Age"
Reply: We have modified our title as advised (see Page 1, line 2).
-Line 28. Would write out "days" in place of d.
Reply: We have modified our text as advised (see Page 1, line 20,21).
-Line 29-30. Obvious respiratory symptoms seems very vague and non-descriptive. Consider more descriptive terms like "persistently tachypneic" or "showing evidence of respiratory failure" based on the group's experience.
Reply: We have modified our text as advised (see Page 1, line 22).
Line 35 and elsewhere. Would change any usage of "ventilator-assisted ventilation time" to "mechanical ventilation time".
Reply: We have modified our text as advised (see Page 1, line 27).
Line 40. "Recovered well" is fairly non-descriptive and should include something more objective such as "were all discharged within 10 days of hospitalization without need for readmission" or something to that extent.
Reply: We have modified our text as advised (see Page 1, line 32-33).
Line 59. Use person-centric language here. Say "children with CPAM" instead of "CPAM children".
Reply: We have modified our text as advised (see Page 2, line 50).
Line 79. Not sure why tachypnea is in quotes.
Reply: We have modified our text as advised (see Page 2, line 71).
Line 80. "Triconcave Syndrome" is not widely used in the literature or common semantics. Triple concave inspiratory sign is used sparingly. If wanting to include this descriptor, please place in parentheses what the three findings are to be included for the sake of the reader.
Reply: We deleted this word "Triconcave Syndrome".

Line 84. “…transferred by ambulance to our hospital for treatment.”

Reply: We have modified our text as advised (see Page 2, line 79).

Line 88. As mentioned above, the column of good outcomes is non-specific and seems unnecessary.

Reply: The column"Outcome" in Table 1 was deleted.

Line 88. Would include types of CPAM in this Table.

Reply: We added the Stocker type as a column in Table 1.

Lines 93-108. Consider including the types of CPAM found with the imaging shown for each Figure.

Reply: We added CPAM types in Figures 1-4.

Line 117 and elsewhere. Would change “destroying” in all locations to cauterizing or a more specific surgical term.

Reply: We have modified our text as advised (see Page 4, line 112; Page 7, line 234 and Page 8, line 271).

Line 123. “We chose two 5 mm Trocars…”

Reply: We have modified our text as advised (see Page 4, line 117).

Line 124. Please be mindful of proprietary names and trademarks and make mention of this related to LigaSure.

Reply: We added the name of the registered company.

We have modified our text as advised (see Page 4, line 118).

Line 133. Concern for use of pneumonectomy in this section though that is not described elsewhere.

Reply: No cases underwent pneumonectomy.

We have modified our text as advised (see Page 4, line 126-127).

Lines 156-160. Consider including standard deviations for these results.

Reply: We added standard deviations of results section (see Page 4, line 139 and Page 5, line 148,152,153).

Line 172. Can it be clarified how it was determined that “inflammation dissipated” was determined?

Reply: We have modified our text as advised (see Page 5, line 167-169).

Line 183. “…Kulaylat reports that children…”

Reply: We have modified our text as advised (see Page 5, line 179).

Line 183-185. I believe the authors are trying to convey that follow up imaging is indicated for those with prenatally identified lesions by ultrasound but this should be mentioned.

Reply: We have modified our text as advised (see Page 5, line 180-182).

Line 196-200. These 2 sentences are unclear. They should either be revised or removed. If the intent is to outline risk factors influencing decision to operate that are separate from clinical indications, those should be described in that fashion.

Reply: We have modified our text as advised (see Page 6, line 189-196).

Line 205. Should probably not include the 3 month threshold related to “development stage” because skeletal muscles are developing well after 3 months as well. Would refer to more general early infancy.

Reply: We have modified our text as advised (see Page 6, line 199).

Line 207-208. Would remove language about lingering shadow.

Reply: We removed “and the long incision scar has become a lingering shadow in the hearts of children and parents”.

Line 215-217. Specifics on how cystic lesions were cauterized would be of value to the reader.

Reply: The electric hook will be used to cauterize the huge vesicles which look like balloons under the enlarged visual field of thoracoscope. But care should be taken not to touch the blood vessels to avoid bleeding affecting the surgical visual field.

We have modified our text as advised (see Page 7, line 234-237).

Line 223. Would remove “This process requires the anesthesiologist” and replace with “Anesthesiology collaboration is required”

Reply: We have modified our text as advised (see Page 6, line 214-215).

Line 224. Change to under 3 months of age.

Reply: We have modified our text as advised (see Page 6, line 215).

Line 225. “occlude easily migrates into different aspects of the airway.”

Reply: We have modified our text as advised (see Page 6, line 216-217).

Line 244. The term “focus” is a bit unclear. Just say “CPAM”.

Reply: We have modified our text as advised (see Page 6, line 220).

Line 250. “Timothy reports…”

Reply: We have modified our text as advised (see Page 7, line 245).

Line 302: Is there supposed to be something after “See:”?

Reply: Sorry, this needs to be filled in by the editorial department.

Reviewer C

This is an interesting study.

Furthermore I made additional suggestions for the references.

This is a multicentric study (https://doi.org/10.1089/lap.2020.0596) with 102 patients.

Reply: Thank you very much. We studied this article carefully. It really inspired us a lot and we have quoted it to our article.

Reviewer D

This article is well written and reports the Center experience with minimally invasive treatment of symptomatic CPAMs in infants younger than 3 months. While 12 cases may seem a small sample, one should consider that CPAM patients are rarely symptomatic in the first months of life, so the sample results more than adequate. Some technical aspects of the operation could be improved (the use of 3mm instruments, for example), but generally the surgical and anesthesiological aspects described are impressive and show the Center’s experience in treating CPAMs (successful single lung ventilation in such small infants or the tricks used to increase operation space, for example).

Here are some comments or corrections to your article:

1. Line 59-60: how can you say that the appropriate age for operation in asymptomatic patients is above 3 months old? Please cite a paper. I think that it would be more accurate to state that

the consensus (or the tendency) is to operate between 3-6 months.

Reply 1: Kulaylat reports that children with CPAM operated before 3 months of age have a higher incidence of complications than those operated after 3 months of age. Verhalleman indicated that in his university hospital, if possible, the first 3 months of life are preserved for lung growth and general development.

We have cited papers as advised (see Page 2, line 51).

2. Line 62-63: remove the word "consequently" because you are not stating a consequence. You can write: "Generally, these children tend to have larger cystic lesions."

Reply 2: We have modified our text as advised (see Page 2, line 53-54).

3. Line 65: write "on the use of VATS to treat CPAM"

Reply 3: We have modified our text as advised (see Page 2, line 56).

4. Line 80: do you mean triconcave sign? Otherwise please explain.

Reply 4: As another reviewer said, "Triconcave Syndrome" is not widely used in the literature or common semantics. We deleted this word "Triconcave Syndrome".

5. Line 115: why do you use a pressure of 5-10mmHg (which in my opinion is very high) even if you stated that you use one-lung ventilation? This kind of ventilation should allow you to perform a gasless procedure or at least to use a pressure of 3-4mmHg. Even in the discussion (line 234) you state that the pressure should be below 5mmHg. Please explain.

Reply 5: Sorry, this is a writing mistake.

We have modified our text as advised (see Page 4, line 110).

6. Line 123: you are using two 5mm and one 10mm ports. In smaller infants there is also the possibility to use 3mm instruments (like the 3mm vessel sealer) and 5mm one (like the hem-o-lok or the 5mm stapler), this could grant you a better use of the operating field. Try to look at these papers:

a. Rothenberg SS, Kuenzler KA, Middlesworth W, et al. Thoracoscopic lobectomy in infants less than 10 kg with prenatally diagnosed cystic lung disease. J Laparoendosc Adv Surg Tech A. 2011;21(2):181-184. doi:10.1089/lap.2010.0138

b. Macchini F, Zanini A, Morandi A, Ichino M, Leva E. Thoracoscopic Surgery for Congenital Lung Malformation Using Miniaturized 3-mm Vessel Sealing and 5-mm Stapling Devices: Single-Center Experience. J Laparoendosc Adv Surg Tech A. 2020;30(4):444-447. doi:10.1089/lap.2019.0589

Reply 6: Thank you, because as to the surgical instruments, we had been using two 5mm and one 10mm ports in the past. We will improve it in the future as you advised.

7. Line 124-125: the combined use of a clip and an energy device could be potentially dangerous, as stated by:

a. "Use of clips and a sealing device on the same vessel may lead to weakening at the level of the clip and disruption" (Lai SW, Rothenberg SS. Culture of safety and error traps in pediatric thoracoscopy. Semin Pediatr Surg. 2019;28(3):178-182. doi:10.1053/j.sempedsurg.2019.04.021)

b. "We hypothesize that the heat from the sealing device may have weakened the tissue, and we have abandoned the combined use of clips and a sealing device as a result of this case" (Hall NJ , Chiu PP , Langer JC . Morbidity after elective resection of prenatally diag- nosed asymptomatic congenital pulmonary airway malformations. Pediatr Pul- monol. 2016;51(5):525–530.)

Reply 7: Thank you for your suggestion. We will improve the safety of using surgical materials and device in the future.

8. Line 150-154: why did you decide to perform one segmental and one irregular resection? Many reports indicate that there may be microscopical residual disease, and therefore indicate the lobectomy as the safest approach for this kind of lesions.

Reply 8: AS many reports indicate that lobectomy is the safest approach for CPAM. Therefore, 83.3% of the children in our study used this approach, but one patient's lesion was located in the posterior segment of the upper lobe of the left lung, and the scope of the lesion was limited and segmentectomy could be performed. Another patient's lesion was located both in the left upper lung and in the left lower lung, and pneumonectomy would make the child lose one side of lung function, so lung-saving surgery was performed.

We have modified our text as advised (see Page 4, line 140-143).

9. Line 171: do you routinely perform a follow-up chest CT scan in your institution, or only in infants younger than 3 months old?

Reply 9: All the children received chest CTs for about 1 year after operation in our institution regardless of the age.

We have modified our text as advised (see Page 5, line 166-167).

10. Line 211: write “less drainage time.”

Reply 10: We have modified our text as advised (see Page 6, line 204).

11. Line 210-212: please cite the source for the claim you make.

Reply 11: We have modified our text as advised (see Page 6, line 205).

12. Line 255-256: intrauterine laser ablation is a treatment used for pulmonary sequestration. For CPAM the intrauterine treatment, when needed, should be thoraco-amniotic shunt placement.

Reply 12: We have modified our text as advised (see Page 7, line 250).