The optimal timing of surgery for asymptomatic congenital pulmonary airway malformation in children: a meta analysis

Jiachi Liao[1], Minhua Lin[1], Jinan Chen[2], Jiamin Liang[2], Tingting Cui[2], Xingfei Chen[2], Xinyu Xu[2], Yudan Chen[2], and Le Li[1]

[1]Guangzhou Women and Children's Medical Center
[2]Guangzhou Medical University

July 13, 2022

Abstract

Aims: We conducted a meta-analysis of trials in when is prefectly to conduct a surgery for asymptomatic congenital pulmonary airway malformation (CPAM) in children. **Methods:** We searched the PubMed, Embase, Scopus and Cochrane Library databases to identify related articles published prior to April 2022 that conduct the surgery for asymptomatic congenital pulmonary airway malformation in children in different ages. **Results:** The results showed that operating the surgery between 3 months to 6 months old in patients can decrease the length of hospital stay. The younger the age of operation, the shorter the operation time. As for get rid of the ventilation as soon as possible and lower major complications, the surgery should be performed no more than 6 months old. Whereas, the chest tube duration as well as the number of deaths didn't have statistically significant change. **Conclusions:** As for asymptomatic CPAM patients, we suggested that surgical treatment should be performed less than 6 months old.

The optimal timing of surgery for asymptomatic congenital pulmonary airway malformation in children: a meta analysis

Jiachi Liao[a#], Minhua Lin[a#], Jinan Chen[b], Jiamin Liang[b], Tingting Cui[b], Xingfei Chen[b], Xinyu Xu[b], Yudan Chen[b], Le Li[a*]

[a]Department of Pediatric Surgery, Guangzhou Women and Children's Medical Center, Guangzhou, China

[b]Paediatrics School, Guangzhou Medical University, Guangzhou, China

#These authors contributed equally to the article, and they are both the first author.

*Correspondence to: Le Li, Department of Pediatric Surgery, Guangzhou Women and Children's Medical Center, Guangzhou, China (e-mail: doctorlile@aliyun.com)

Abstract

Aims: We conducted a meta-analysis of trials in when is prefectly to conduct a surgery for asymptomatic congenital pulmonary airway malformation (CPAM) in children.

Methods: We searched the PubMed, Embase, Scopus and Cochrane Library databases to identify related articles published prior to April 2022 that conduct the surgery for asymptomatic congenital pulmonary airway malformation in children in different ages.

Results: The results showed that operating the surgery between 3 months to 6 months old in patients can decrease the length of hospital stay. The younger the age of operation, the shorter the operation time. As for get rid of the ventilation as soon as possible and lower major complications, the surgery should be performed

no more than 6 months old. Whereas, the chest tube duration as well as the number of deaths didn't have statistically significant change.

Conclusions: As for asymptomatic CPAM patients, we suggested that surgical treatment should be performed less than 6 months old.

Keywords: asymptomatic congenital pulmonary airway malformation; children; surgery; meta-analysis

Systematic review registration: PROSPER CRD42022321457

Abbreviations

CPAM Congenital pulmonary airway malformation

RCT Randomized controlled trial

SD Standard deviation

95% CI 95% confidence interval

MD Mean Difference

OR Odds Ratio

NOS Newcastle-Ottawa Quality Assessment Scale

Objectives

CPAM is an uncommon fetal lung anomaly characterised by the presence of multiple cysts within the lung parenchyma due to hyperproliferation and dilation of terminal bronchioles without normal alveoli[1]. With the increasing awareness of clinicians and the widespread use of the latest ultrasound technology, The incidence of CPAM has increased in recent years, with an incidence of approximately 1 in 7200 live births[2, 3], and more than 90% of the lesions involved a single lobe of the lung[4]. CAMP classification scheme has been revised in 2002 by Stocker and categorized them as: type 0, trachea-bronchial; type 1,bronchial/bronchiolar; type 2, bronchiolar; type 3, bronchiolar/alveolar duct; and type 4, distal acinar[5]. These cysts are connected to the normal bronchial system potentially leading to the development of various respiratory diseases including pneumothorax, pneumonia, hemoptysis and the development of malignancies, and it can even lead to death[6]. Therefore,the surgical intervention is very important. The appearance of these symptoms indicates the need for immediate surgical resection, however, the treatment plan for patients with prenatal diagnosis of CPAM who are asymptomatic is less clear. The study by Liu Chenyu et al[7]found that 32% of 581 asymptomatic Congenital Lung Malformations patients had hidden infection(HI) in postoperative pathology, and the proportion of HI was high, which would increase the difficulty and risk of surgery,so early surgery was advocated. Stanton et al.[8], Laberge et al.[6]and Esposito et al.[9]recommend surgery in patients with congenital lung malformations by the first year of life,and the consensus of experts in China recommend surgery should be performed between 3 months and 1 year old[10], because patients who undergo early resection are thought to experience compensatory lung growth to reduce the risk of complication,to make the procedure technically easier and decrease radiation exposure and related risks[9, 11].However,some scholars believe that delaying surgery to later in infancy is beneficial as older children have a decreased anaesthetic and surgical risk[12, 13].The primary objective of our systematic review is to evaluate if age at surgical treatment of asymptomatic paediatric CPAM patients is associated with outcomes to determine the optimal age for surgical intervention and optimize treatment.The primary objective of our systematic review was to assess whether age at surgical treatment is associated with outcome in asymptomatic pediatric CPAM patients to determine the optimal age for surgical intervention and optimize treatment.

Data sources

Information sources

The systematic literature search was performed in the PubMed, Embase, Scopus and Cochrane library, which was conducted by two investigators independently by using medical subject headings and search terms: 'Cystic Adenomatoid Malformation of Lung, Congenital', 'Asymptomatic Diseases' and 'Surgical Procedures, Operative'. A combination of MeSH words and Entry terms was used in our search. Other potential studies were identified through manual searching of the eligible studies. Two researchers independently reviewed the publications and studies and selected the articles identified with specific inclusion criteria presented. Disagreement was resolved by consensus involving a third reviewer. To improve the transparency, accuracy and completeness, this meta-analysis is written and conducted in accordance with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) guidelines for conducting and reporting systematic reviews.

The inclusion criteria were as below:

1. Research type: Randomized controlled trials (RCTs), controlled clinical trial, prospective/retrospective cohort study or studies that have at least two arms of comparison;
2. An object of study: Patients must have been <=18 years of age, who diagnosed with CPAM while asymptomatic;
3. Intervening measure: Patients received surgical treatment for CPAM in different operation timing;
4. Outcome indicator: The study included at least one of the following information was reported: complications, length of hospital stay, pleural drainage/chest tube duration, ventilation outcomes, mortality;
5. Written in English only;

The exclusion criteria were as below:

1. Repetitive literature, individual case reports, review articles, empirical perspectives, conference abstracts and studies without available data:
2. Baseline characters were incomplete;
3. In repeated reports by the same institution.

Data extraction

The study was evaluated by two researchers, and a third researcher was consulted if there was disagreement. We used Microsoft Excel to extract and categorize the necessary information from the included studies. The information included basic information (age, country, etc.), type of surgery, the number of deaths, the number of diagnosed prenatally, major complications and etc.

Missing data management

If the data contained in the literature is incomplete, attempts were made to contact the corresponding authors to obtain the necessary data. When the secondary classification data in the study is incomplete or missing, we conduct sensitivity analysis to determine whether the study can be excluded. When the mean change of continuous data does not report the standard deviation (SD), but the 95% confidence interval (95% CI) or P value of both groups are reported at the same time, the data will be converted and included in the meta-analysis.

Data items

Data extraction was executed by two authors on their own, with divergence resolved by consensus. We included the relevant data for all selected articles, which were extracted into Microsoft Excel to analyze. The following data will be extracted:

The characteristics of included literature: country, study year, sample size, standard baseline patient characteristic (sex, age).

Outcomes: age at surgery, length of stay, operative time, chest tube duration, length of ventilation, number of deaths, major complications.

Measures of treatment effect

Continuous data were represented by the Mean Difference (MD) and 95% Cl. Dichotomous data were represented by the Odds Ratio (OR) and 95%Cl. All the units of the data were consistent.

Quality assessment

The quality of the included studies was evaluated independently by two authors using the Newcastle-Ottawa Quality Assessment Scale (NOS). The NOS scale includes three domains, the maximum scores are four points for selection(representativeness of the exposed cohorts, selection of the non-exposed cohorts, ascertainment of exposure, and demonstration of the absence of an outcome of interest at study initiation), and two points for comparability (comparability of cohorts based on the design or analysis), and three for outcome assessment (assessment of outcome, follow-up long enough to produce results and adequacy of cohort follow-up). One point is awarded for each item that is satisfied by the study, except for the second part of the scale (comparability of Cohorts on the Basis of the Design or Analysis), which is capped at two points. The scale is scored out of 9, with a cumulative score of >=6 being a high-quality study and less than 6 stars being a low-quality study. The study was evaluated by two investigators, and a third investigator was consulted if there was disagreement.

Quantitative synthesis

The data of included literature was undertaken using Review Manager V.5.4. Random effects models were used as a measure of the outcomes with high heterogeneity, otherwise, use the fixed effects models. We calculated the MD with a 95% CI and pooled the means and SD from continuous results, OR with a 95% CI from dichotomous data. I2 value and Q test was used to assessed the heterogeneity between all statistical tests, which was showed with the forest plots. Heterogeneity was regarded as to be low if I2<=30%, high if I2>30%[14]. Galbraith's diagram performed the heterogeneity created by the circle beyond the lower and upper lines. Subgroup sensitivity analysis was executed by excluding one study for the purpose that evaluated the effect on the result. We applied STATA V.12.1 to subsequent operations. The publication bias was assessed with Egger's test and funnel plot. All the reported p values were two-side and it was considered statistically significant merely it less than 0.05.

Results

Literature search

A total of 559 articles were retrieved from PubMed (n=146), Embase (n=232), Cochrane Library (n=1), Scopus (n=180) and other resources (n=15). Apart from the repeated publications, 322 articles were expected for a further review. Then 313 studies were excluded by thoroughgoing screening; these consisted of letters (n=2), book section (n=3), adult patients (n =21), review articles (n =27), not comparisons (n =31), not original published (n=3), conference abstracts (n=69), irrelevant interventions (n=137) and not report outcome of interest (n=20). Eventually, 10 qualified articles were included for a systematic analysis (including one unpublished article). The specific search and selection process is represented in Figure 1.

Quality assessment

According to the NOS scale (in Table 1), six studies with scores >=7 were considered to be of high quality with low risk of bias, while the remaining three studies were of moderate quality with a score of 6, with some risk of bias. This was mainly due to the fact that four of the nine included studies were single-centered and not representative in terms of patient selection. Two studies did not conduct heterogeneity analysis on other characteristics other than age. Six studies did not mention the postoperative follow-up rate or did not have a long enough follow-up time, which may be the source of information bias.

The characteristics of studies

In the ten retrospective studies, which involved 1606 patients in total, seven studies were performed at a single center, the other three studies were performed at multiple centers. No RCT was identified. These studies were published between 2011 and 2020, and five of them were conducted in America (n=1353), two in Italy (n=172), one in China (n=81), one in England (n=13), and one in Canada (n=15). The minimum

follow-up time in the study was 2 years and the maximum was 14 years. The gender ratio (male/female) ranged from 12/23 to 48/34, and the mean age at surgery varied from 0.59 to 32.00 months. Meanwhile, the mean length of hospital stay (days) ranged from 1.64 to 19.09, the mean operative time (min) ranged from 105.77 to 187.62 and the mean chest tube duration (days) ranged from 1.53 to 7.6. The main characteristic of each study included is summarized in the following Table 2.

Primary outcome

Length of hospital stay (days)

Definition 1: <3 month vs. >=3 month

There was no discrepancy in length of stay (MD, 0.84; 95% Cl, -0.40 to 2.09; P=0.18), with very high heterogeneity (I2=86%). The sensitivity analyses revealed noteworthy heterogeneity in the two studies from Eric2018 and Gulack2017. Furthermore, when we omitted them, the heterogeneity decreased from 86% to 0% with a statistically significant p-value (P<0.0001). The heterogeneity may have resulted from the experiments in different countries. Publication bias was assessed and not detected.

Definition 2: <6 month vs. >=6 month

There was no significant difference in length of hospital stay (MD, -0.09; 95% Cl, -0.54 to 0.37; P=0.70), with high heterogeneity (I2=62%). The sensitivity analysis indicated that noteworthy heterogeneity existed in two studies by Conforti2009 and Duron2020. Furthermore, when we omitted them, the heterogeneity decreased from 62% to 0% with a statistically significant p-value (P=0.005). The heterogeneity may have resulted from the small sample size in both trials. The heterogeneity may have resulted from the small sample size in both trials.

Definition 3: <12 month vs. >=12 month

No difference in length of stay was showed (MD, 1.32; 95% Cl,-3.80 to 6.44; P=0.61) with very high heterogeneity (I2=95%). Deleting the Dukleska2017, the heterogeneity droped from 95% to 0%, the p-value was statistically significant (P < 0.00001). But the reason can't be found. The publication bias of the length of stay was assessed. None was detected.

In sum, to decrease the length of stay, it's well to operate the surgery between 3 months to 6 months old, no more than 12 months old in patients.

Operative time

Definition 1: <3 month vs. >=3 month

There was discrepancy in operative time (MD, -41.35; 95% Cl, -58.86 to -23.85; P <0.00001), with moderate to high heterogeneity (I2=37%). When omitting Li2022, the heterogeneity decreased to 0%, the p-value was still statistically significant (P<0.00001). The heterogeneity may have resulted from the article didn't published. Publication bias was assessed and not detected.

Definition 2: <6 month vs. >=6 month

Operating surgery when patient more than 6 months old did not significantly decrease the operative time (P=0.95), with high heterogeneity (I2=89.5%). The publication bias was assessed and not detected. When we performed he subgroup analysis, we found that in groups with sample size >=200, patient younger than 6 months old could decrease the operative time (p=0.004), with low heterogeneity (I2=0%).

Definition 2: <12 month vs. >=12 month

There was statistically significant in operating time (MD, -27.05; 95% Cl, -51.11 to -2.99; P=0.03), with high heterogeneity (I2=75%). The sensitivity analysis didn't show the noteworthy heterogeneity in the included article. The publication bias was assessed and not detected.

In sum, to decrease the operating time, it may be well to perform the surgery as soon as possible.

Length of ventilation(days)

Definition 1: <3 month vs. >=3 month

There was no pronounced difference in the number of major complications (MD,

-0.02; 95% Cl, -0.20 to 0.16; P= 0.84), with very low geneity (I2 = 0%).

Number of major complications

Definition 1: <3 month vs. >=3 month

There was no pronounced difference in the number of major complications (OR,

0.80; 95% Cl, 0.16 to 4.10; P=0.79), with high geneity (I2=70%). The sensitivity analysis indicated that noteworthy heterogeneity existed in Gulack2017. When they were omitted, the heterogeneity decreased from 70% to 0%, but still with no statistically significant (P=0.32). The reason can't be found. Publication bias was assessed and not detected.

Definition 2: <6 month vs. >=6 month

There was pronounced difference in the number of major complications (OR, 1.51; 95% Cl, 1.03 to 2.22; P=0.04), with very low geneity (I2=0%). The publication bias of the length of stay was assessed. None was detected.

In sum, operating the surgery when patient no more 6 months old, it maybe decrease the number of major complications happen.

Chest tube duration(days)

None showed a significant difference (P=0.63) and with low heterogeneity (I2=0%). The time operate surgery <6 month vs. >=6 month (MD, 0.14; 95% Cl, -0.42 to 0.70).

Number of deaths

None showed a significant difference (P > 0.05) and both with low heterogeneity (I2=0%). The time operate surgery <3 month vs. >=3 month (OR, 1.91; 95% Cl, 0.26 to 14.26);The time operate surgery <6 month vs. >=6 month (OR, 0.73; 95% Cl, 0.10 to 5.35).

Discussion

Nowadays, most CPAMs are diagnosed prenatally, with an 85.7% prenatal diagnosis ate for CPAM[15].The exact etiology and pathogenesis of CPAM are still unclear, and current studies suggest that some potential genes and expressions are related to the formation of lung cysts. The difference of Thyroid Transcription Factor 1, Fibroblast Growth Factor 7, Fibroblast Growth Factor 9, Clara cell marker 10, SOX 2, SOX10, COL2A1, Hoxb-5, hMSH-2 and other transcription factors and expression appear to play a role in the pathogenesis of CPAM[16, 17].In addition, the positive rate of Transcription Factor 1 in CPAM type I, II, and III is significantly different, and it can be used as an important marker for CPAM tissue typing[18].In severe cases, the lesion continues to grow and ultimately may cause severe lung compression, mediastinal shift, hydrops fetalis, and/or fetal demise. Management options include observation, maternal antenatal steroid administration, and fetal surgical intervention[19, 20]{Aziz, 2021 #37;Loh, 2012 #38;Aziz, 2021 #35}.In children with symptoms after birth, it is recommended to surgically remove the lesions as soon as possible. For asymptomatic children with prenatal diagnosis of CPAM, most experts still recommend early elective surgery, but the exact timing of surgery is still controversial. Early surgical resection can help early compensatory growth of the lung and reduce the possibility of repeated infection and malignant transformation[21], but some doctors are concerned about the increased risk of surgical complications and anesthesia sequelae in children[8, 22].Therefore, exploring the optimal timing of early surgery, that is, exploring the timing of compensatory lung growth and reduction of lung-related diseases in children with good tolerance to surgery and anesthesia is very important to weigh the risks of surgery.

The purpose of this study was to evaluate the efficacy of surgery in children of different ages,which is reflected in the indicators of length of hospital stay, operative time, chest tube duration, length of ventilation, number of deaths, number of major complications. We found that the indicators of length of hospital stay, operative time, the length of ventilation and number of major complications contain statistical significance.

Notably, some researchers[23] used surgical time as a proxy for technical difficulty, which means the shorter duration of surgery reflects fewer problems and accidents during surgery. In addition, studies[24, 25] have shown that shortening surgical time can shorten the length of hospital stay, as well as reducing the incidence of surgical site infection within 30 days after surgery, the use of air drainage tube, the possibility of readmission and reoperation[23]. Especially for children, shorter procedures mean less time spent on anesthetics, which can stunt brain development and damage the nervous system[26]. In addition, shortening the operation time can enable children to resume normal eating time earlier[27], which is of great significance to help the early recovery of growth and development of children.

Some studies have shown that mechanical ventilation is associated with the occurrence of complications, and the incidence of complications increases with the duration of respiratory support[28]. Shortening the length of ventilation can not only reduce pulmonary complications[28, 29], such as postoperative pneumonia, atelectasis, pulmonary edema, acute respiratory failure, tension pneumothorax, and also can reduce extrapulmonary complications, such as gastric insufflation, fistula, anastomotic leakage, bleeding, hospital infection, mask discomfort, damaged skin, eye irritation, sinus congestion, oronasal drying, and patient-ventilator asynchrony[30, 31]. It is worth noting that several studies have shown that mortality associated with lung disease is largely related to complications of postoperative re-intubation and mechanical ventilation. This means that reducing the duration of ventilation can reduce postoperative mortality by reducing the incidence of ventilator-related complications[32]. In particular, children's lung development is not yet perfect, and changes in forced ventilation, normal pulmonary respiration physiology and respiratory mechanics will lead to respiratory dysfunction and decreased airway clearance ability. Therefore, shortening mechanical ventilation time is of great significance for children's postoperative recovery[33].

Interestingly, one study[34] found that the incidence of complications increased with the age of the patient at the time of surgery, and most of the complications were related to pleural problems, mainly including air leakage and fluid accumulation[35]. Air leakage at the surgical site can lead to surgical emphysema and pneumothorax, while fluid accumulation can lead to chylothorax, and in severe cases they may lead to accidental re-intubation or even reoperation.

In addition, major complications include transient unilateral phrenic nerve palsy, hemorrhage, pneumonia, deep incision or inter-organ space infection, deep wound dehiscence, pulmonary embolism, renal failure or insufficiency, sepsis, and deep venous thrombosis. Minor complications include superficial surgical site infection, superficial wound rupture, and urinary tract infection. In particular, musculoskeletal complications including breast deformity, rib fusion,chest wall asymmetry,pterygoid scapulae and scoliosis are the major long-term complications of thoracotomy[36], which have a bad effect on children in skeletal development during growth[35]. A cohort study published by Markel M et al demonstrated that compared with the general population, children experience more frequent respiratory infections after resection of congenital lung malformations, and Resection does not eliminate the increased risk of pneumonia[37].

Extubation time is also one of the perioperative indicators. Ko HK et al. believed that delayed extubation after surgery was significantly associated with a higher proportion of other pulmonary complications, reintubation, mortality, and prolonged intensive care unit and hospital stays[38]. Studies also have shown that early extubation is beneficial to reduce the pain and stress response of patients, promote early activities, and speed up postoperative recovery, and it is feasible and safe[39].However, the clinical extubation time mainly depends on the amount of postoperative thoracic hemorrhage and the surgeon's assessment, which has individual differences and a certain degree of subjectivity. Our study shows no meaningful difference in extubation time by surgical age.

Postoperative mortality is an important indicator for evaluating the postoperative prognosis of children.

Postoperative death may be caused by complications such as heart failure, respiratory failure, infection, etc., which are closely related to the surgical skill of the operator and the conditions of the medical institution. But deaths from lung resections are rare. In center with expertise and experience, CPAM lesions can be safely resect with virtually no mortality[40, 41]. However, due to the lack of data that can be included at present, larger multi-center clinical trials are needed to further improve the conclusions, and more comprehensively assess the effect of age on clinical outcomes.

Limitations:

There are several limitations to our meta-analysis. The number of articles included is low in number and quality, and the articles we include may be potentially biased in the review process. We included only one unpublished article, the rest were published articles, which means there may be publication bias. Moreover, only English language studies are included, so relevant studies published in other languages may be missing. The literature was all retrospective, with no RCTs, allowing for the introduction of error due to confounding and bias. In addition, due to the insufficient number of cases, factors that cannot be controlled consistently may have an impact, such as different types of surgery (thoracotomy or thoracoscopy), lesion size, gender, etc., and further evaluate whether it affects the results. For lack of long-term prognostic indicators in the literature makes it difficult to fully assess how age affects patient outcomes after elective CPAM resection.

Conclusion:

In consideration of the lower length of hospital stay as well as major complications, shorter operation time and getting rid of ventilationa, we suggest that surgical treatment should be performed when asymptomatic CPAM patients are no more than 6 months old, which can provide more options for surgical strategies.

Author contributions

Conception and design: Jiachi Liao,Minhua Lin,Le Li

Analysis and interpretation: Jiachi Liao,Minhua Lin;Yudan Chen

Data collection: Jinan Chen,Xingfei Chen,Jiamin Liang,Tingting Cui,Xinyu Xu

Writing the article: Jiachi Liao,Minhua Lin,Yudan Chen,Jinan Chen,Xingfei Chen,Jiamin Liang,Tingting Cui,Xinyu Xu

Critical revision of the article: Jiachi Liao,Minhua Lin,Le Li

Final approval of the article: Jiachi Liao,Minhua Lin,Le li,Yudan Chen,Jinan Chen,Xingfei Chen,Jiamin Liang,Tingting Cui,Xinyu Xu

Statistical analysis:Minhua Lin,Jinan Chen,Xingfei Chen,Jiamin Liang,Tingting Cui,Xinyu Xu

Overall responsibility: Jiachi Liao,Minhua Lin,Le Li

Funding

This work was funded by Featured Clinical Technique of Guangzhou (NO.2019TS57)

Conflict of interest

The authors have no conflict of interest.

References

1. Wong, K.; Flake, A. W.; Tibboel, D.; Rottier, R. J.; Tam, P. J. L. C.; Health, A., Congenital pulmonary airway malformation: advances and controversies. *Lancet Child Adolesc Health* **2018,***2* (4), 290-297.

2. Laberge, J. M.; Flageole, H.; Pugash, D.; Khalife, S.; Blair, G.; Filiatrault, D.; Russo, P.; Lees, G.; Wilson, R. D. J. F. D.; Therapy, Outcome of the prenatally diagnosed congenital cystic adenomatoid lung malformation: a Canadian experience. *Fetal Diagnosis & Therapy***2001,** *16* (3), 178-186.

3. Lau, C. T.; Kan, A.; Shek, N.; Tam, P.; Wong, K. K., Is congenital pulmonary airway malformation really a rare disease? Result of a prospective registry with universal antenatal screening program. *Pediatric surgery international* **2017,** *33* (1), 105-108.

4. Xia, B.; Yu, G.; Liu, C.; Hong, C.; Tang, J. J. J. o. M.-F. M., Surgical treatment of congenital cystic adenomatoid malformation: a retrospective study of single tertiary center experience. *J Matern Fetal Neonatal Med* **2016,** *30* (4), 416-419.

5. Stocker, J. T., Congenital pulmonary airway malformation: A new name for and an expanded classification of congenital cystic adenomatoid malformation of the lung. *Histopathology* **2002,** *41*(2), 424-430.

6. JM, A.; P, P.; H, F., Asymptomatic congenital lung malformations. *Seminars in Pediatric Surgery* **2005,** *14* (1), 16-33.

7. Liu, C.; Yu, X.; Cheng, K.; Luo, D.; Yuan, M.; He, T.; Xu, C., Hidden Infection in Asymptomatic Congenital Lung Malformations-A Decade Retrospective Study. *Frontiers in pediatrics* **2022,***10* , 859343.

8. Stanton, M.; Njere, I.; Ade-Ajayi, N.; Patel, S.; Davenport, M., Systematic review and meta-analysis of the postnatal management of congenital cystic lung lesions. *J Pediatr Surg* **2009,***44* (5), 1027-1033.

9. C, E.; A, B.; H, T.; E, L.; N, K.-D.; A, Z.; L, M.; S, S.; M, E., Thoracoscopic Management of Pediatric Patients with Congenital Lung Malformations: Results of a European Multicenter Survey. *J Laparoendosc Adv Surg Tech A* **2021,** *31* (3), 355-362.

10. General thoracic surgery group, p. s. b., Chinese Medical Association; care, W. s. a. c. s. h. c. B. o. C. A. f. t. p. o. i. e. i. h., National Expert Consensus on Diagnosis & Treatment of Congenital Pulmonary Airway Malformations in China. *Chinese Journal of Pediatric Surgery* **2021,** *42* (8), 679-687.

11. DP, F.; LF, D.; NS, R., Computed tomography and radiation risks: what pediatric health care providers should know. *Pediatrics***2003,** *112* (4), 951-7.

12. E, E., Antenatal Diagnosis of Congenital Thoracic Malformations: Early Surgery, Late Surgery, or No Surgery? *Semin Respir Crit Care Med* **2007,** *28* (3), 355-366.

13. A, I.; M, T.; A, S.; S, K.; K, M.; M, I.; K, U., Introduction of thoracoscopic surgery for congenital pulmonary airway malformation in infants: review of 13 consecutive surgical cases. *J Thorac Dis***2019,** *11* (12), 5079-5086.

14. Higgins, J.; Thompson, S. G.; Deeks, J. J.; Altman, D. G., cochrane handbook for systematic reviews of interventions version 5.1.0. the cochrane collaboration. *Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie* **2008,** *5*(2), S38.

15. S, H.; L, T.; CT, S.; RA, C.; J, C.; RA, M., Congenital Cystic Lung Lesions: Evolution From In-utero Detection to Pathology Diagnosis-A Multidisciplinary Approach. *Pediatr Dev Pathol.* **2017,***20* (5), 403-410.

16. Soriano, V.; Chia, D.; Aronin, S. I., Congenital Pulmonary Airway Malformation (CPAM) with Malignant Transformation. In *American Thoracic Society International Conference* , American Journal of Respiratory and Critical Care Medicine: American, 2016; Vol. 193, p A7752.

17. M, D.; R, L.-P.; T, H.-C., Prenatal and Postnatal Management of Congenital Pulmonary Airway Malformation. *Neonatology***2016,** *110* (2), 101-115.

18. Liqun, W.; Lingling, Z.; Linli, Z.; Huifang, W.; Yalou, W.; Wei, Q.; Zongmin, W., Expression of TTF-1 and hMSH-2 in conqenital pulmonary airway malformation and their implication. *Chinese Journal of Diagnostic Pathology* **2016,** *23* (1), 43-46.

19. Aziz, K.; Jelin, A. C.; Keiser, A. M.; Schulkin, J., Obstetrician patterns of steroid administration for the prenatal management of congenital pulmonary airway malformations. *Journal of neonatal-perinatal medicine* **2021,** *14* (2), 213-222.

20. Loh, K. C.; Jelin, E.; Hirose, S.; Feldstein, V.; Goldstein, R.; Lee, H., Microcystic congenital pulmonary airway malformation with hydrops fetalis: steroids vs open fetal resection. *Journal of Pediatric Surgery* **2012,** *47* (1), 36-39.

21. Calvert, J. K.; Lakhoo, K., Antenatally suspected congenital cystic adenomatoid malformation of the lung: postnatal investigation and timing of surgery. *Journal of Pediatric Surgery* **2007,** *42*(2), 411-414.

22. Papagiannopoulos, K.; Hughes, S.; Nicholson, A. G.; Goldstraw, P., Cystic lung lesions in the pediatric and adult population: surgical experience at the Brompton hospital. *Ann Thorac Surg***2002,** *73* (5), 1594-1598.

23. BJ, D.; W, C.; PC, C.; JB, C.; OD, G., How Slow Is Too Slow? Correlation of Operative Time to Complications: An Analysis from the Tennessee Surgical Quality Collaborative. *Journal of the American College of Surgeons* **2015,** *220* (4), 550-558.

24. NJ, I.; R, A.; L, M.; E, L.; KJ, T.; JL, I., Operative Time Is Independently Associated With Morbidity in Pediatric Complicated Appendicitis. *Journal of Surgical Research* **2022,***276* , 143-150.

25. Jackson, T. D.; Wannares, J. J.; Lancaster, R. T.; Rattner, D. W.; Hutter, M. M., Does speed matter? The impact of operative time on outcome in laparoscopic surgery. *Surgical Endoscopy***2011,** *25* (7), 2288-2295.

26. JL, W.; MG, P., Review of preclinical studies on pediatric general anesthesia-induced developmental neurotoxicity. *Neurotoxicol Teratol* **2017,** *60* , 2-23.

27. A, S.; G, M.; H, M.; E, S.; EC, P.; J, M.; RP, B., Laparoscopic colon surgery: does operative time matter? . *Dis Colon Rectum***2009,** *52* (10), 1746.

28. SX, X.; CS, W.; SY, L.; X, L., High-flow nasal cannula oxygen therapy and noninvasive ventilation for preventing extubationfailure during weaning from mechanical ventilation assessed by lung ultrasound score: A single-center randomized study. *World J Emerg Med***2021,** *12* (4), 274-280.

29. D, D.; G, S., Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* **1998,***157* (1), 294-323.

30. HK, S.; EF, A.; Y, T.; H, V.; OK, D., Efficacy of continuous positive airway pressure and incentive spirometry on respiratory functions during the postoperative period following supratentorial craniotomy: A prospective randomized controlled study. *Journal of Clinical Anesthesia* **2017,** *42* , 31-35.

31. DA, F.; EM, D. S.; ÁN, A.; FM, V., Noninvasive positive pressure ventilation for acute respiratory failure following upper abdominal surgery. *Cochrane Database Syst Rev* **2015,** *2015*(10), CD009134.

32. S, J.; A, D. J.; A, C.; E, F.; G, C., Non-invasive ventilation after surgery. *Ann Fr Anesth Reanim* **2014,** *33* (7-8), 487-91.

33. X, Y.; PF, X.; L, S.; LG, L.; L, D.; FY, J., Advances in respiratory assessment and treatment in children undergoing invasive mechanical ventilation. *Chinese journal of contemporary pediatrics***2019,** *21* (1), 94-99.

34. Kim, Y.; Kim, J.; Park, J.; Kang, C.; Sung, S.; Kim, J., Treatment of congenital cystic adenomatoid malformation-does resection in the early postnatal period increase surgical risk? *Eur J Cardiothorac Surg* **2005,** *27* (4), 658-661.

35. Xie, J.; Wu, Y.; Wu, C., Is thoracoscopy superior to thoracotomy in the treatment of congenital lung malformations? An updated meta-analysis. *Therapeutic Advances in Respiratory Disease***2020,** *14* , 175346662098026.

36. Lau, C. T.; Leung, L.; Chan, I. H.; Chung, P. H.; Lan, L. C.; Chan, K. L.; Wong, K. K.; Tam, P. K., Thoracoscopic resection of congenital cystic lung lesions is associated with better post-operative outcomes.*Pediatric Surgery International* **2013,** *29* (4), 341-345.

37. Markel, M.; Derraugh, G.; Lacher, M.; Iqbal, S.; Balshaw, R.; Min, S.; Keijzer, R., Congenital lung malformation patients experience respiratory infections after resection: A population-based cohort study. *Journal of pediatric surgery* **2022,** *57* (5), 829-832.

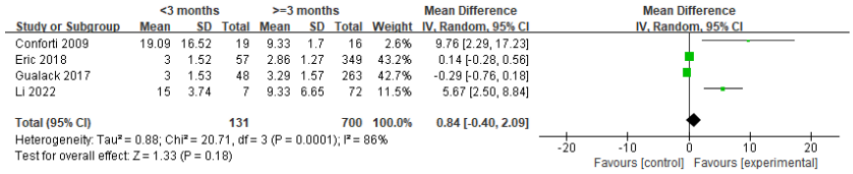
38. Ko, H. K.; Liu, C. Y.; Ho, L. I.; Chen, P. K.; Shie, H. G., Predictors of delayed extubation following lung resection: Focusing on preoperative pulmonary function and incentive spirometry. *Journal of the Chinese Medical Association* **2021,** *84* (4), 368-374.

39. Chao, Z.; Yiqing, L.; Xiaofeng, P.; Faming, X.; Mingxing, L.; Wentao, L., Early enhanced recovery after lung surgery: early ambulation 1 hour after extubation. *Annals of palliative medicine***2021,** *10* (9), 9732-9741.

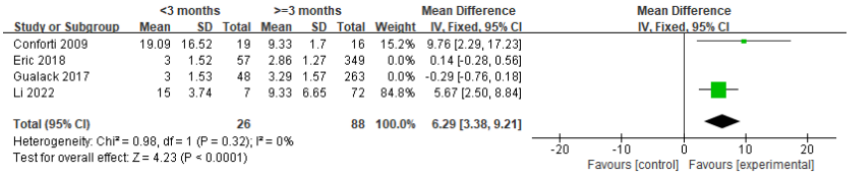
40. RG, A.; TM, C., Congenital cystic lung disease: contemporary antenatal and postnatal management. *Pediatr Surg Int***2008,** *24* (6), 643-657.

41. Chen, H. W.; Hsu, W. M.; Lu, F. L.; Chen, P. C.; Hsieh, W. S., Management of Congenital Cystic Adenomatoid Malformation and Bronchopulmonary Sequestration in Newborns. *Pediatrics Neonatology* **2010,** *51* (3), 172-177.

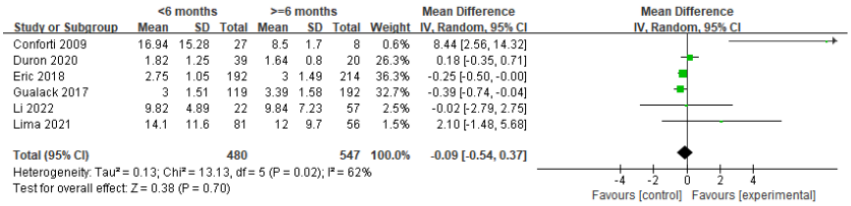
A1



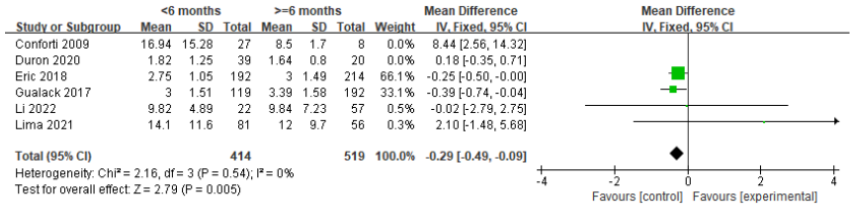
A2



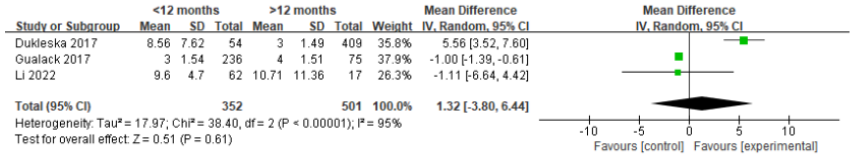
A3



A4



A5



A6

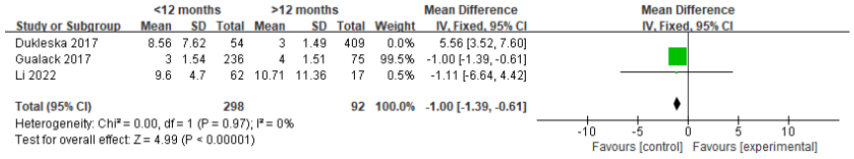
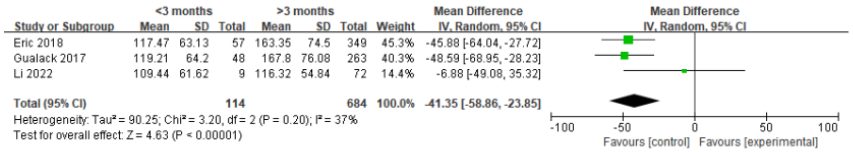
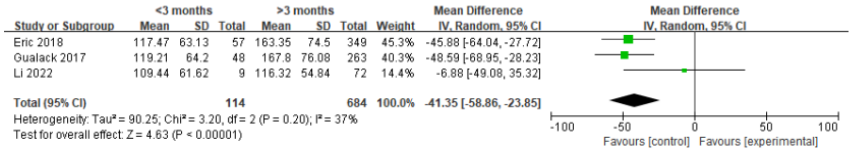


Figure 1: the forest plots of the length of hospital stay (days). A1: <3 month vs. >=3 month;A2: <3 month vs. >=3 month excluding Eric2018 and Gulack2017;A3: <6 month vs. >=6 month;A4: <6 month vs. >=6 month excluding Conforti2009, Duron2020;A5: <12 month vs. >=12 month;A6: <12 month vs. >=12 month excluding Dukleska2017.

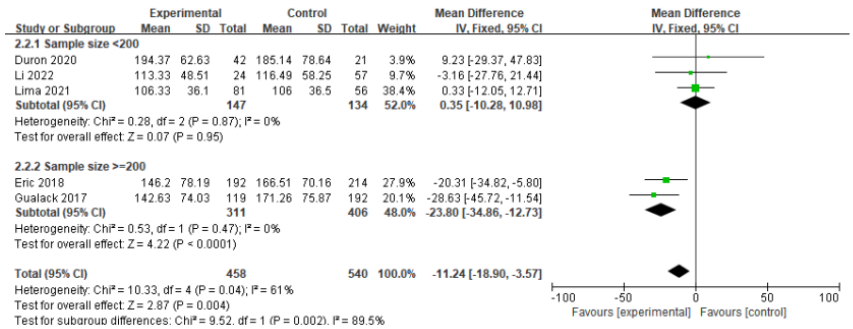
B1



B2



B3



B4

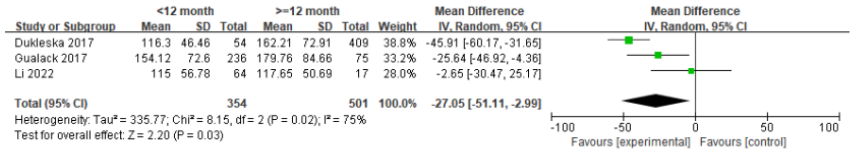


Figure 2: the forest plotsof the operative time. B1:<3 month vs. >=3 month;B2:<3 month vs. >=3 month excluding Li2022;B3:the subgroup analysis of the definition:<6 month vs. >=6 month;B4: <12 month vs. >=12 month.

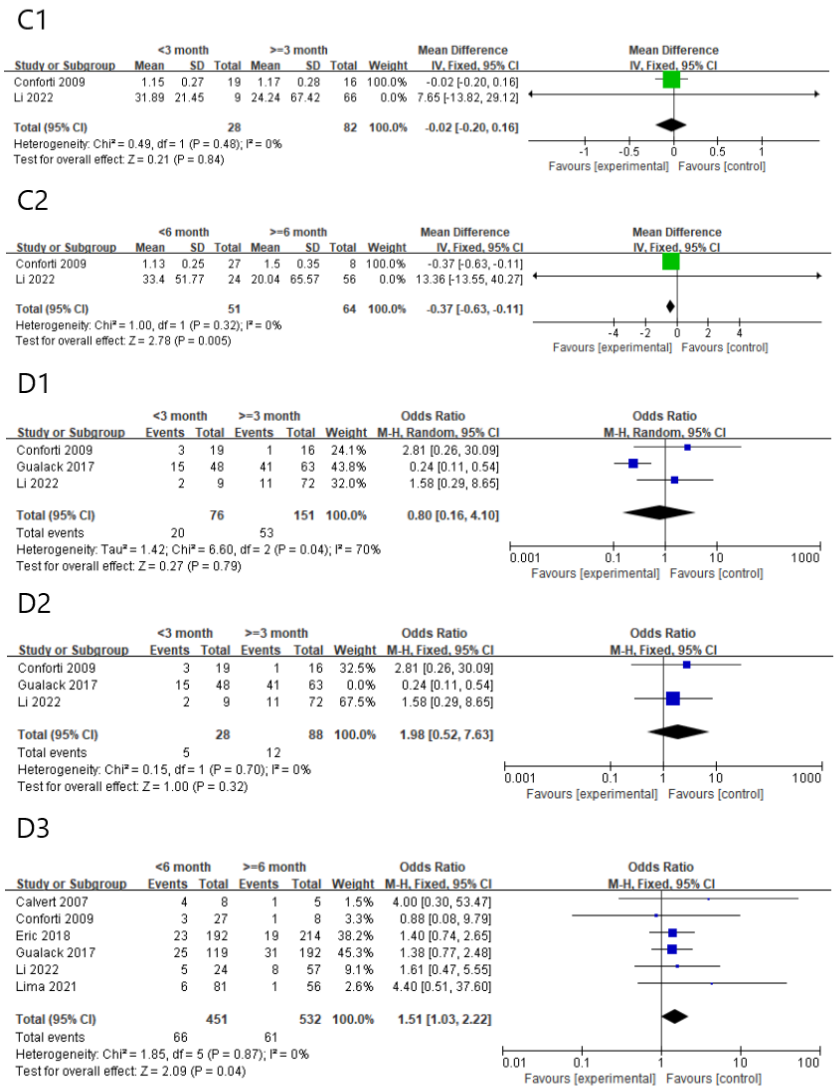


Figure 3: the forest plots of length of ventilation(days)(C) and number of major complications(D). C1:<3 month vs. >=3 month;C2:<6 month vs. >=6 month;D1:<3 month vs. >=3 month;D2:<3 month vs. >=3 month excluding Gulack2017.

Hosted file

Table 1.xlsx available at https://authorea.com/users/494924/articles/576820-the-optimal-timing-of-surgery-for-asymptomatic-congenital-pulmonary-airway-malformation-in-children-a-meta-analysis

Hosted file

Table 2.xlsx available at https://authorea.com/users/494924/articles/576820-the-optimal-timing-of-surgery-for-asymptomatic-congenital-pulmonary-airway-malformation-in-children-a-meta-analysis

Hosted file

Table 3.xlsx available at https://authorea.com/users/494924/articles/576820-the-optimal-timing-of-surgery-for-asymptomatic-congenital-pulmonary-airway-malformation-in-children-a-meta-analysis