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Pediatric thoracic surgery

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Pediatric thoracic surgery

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Editorial: Pediatric thoracic surgery

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Editorial on the Research Topic
Pediatric thoracic surgery

In the last decades pediatric thoracic surgery significantly developed, extending minimally invasive approaches such as thoracoscopy to infancy and childhood. This progress is mainly due to the introduction of specific devices for the management of little spaces and little anatomical structures. Pediatric thoracoscopic surgery has increasingly become important in clinical practice and now it represents a well-established approach for infants and children and it is considered, by most thoracic surgeons, as the best choice for many procedures. Pediatric thoracoscopic surgery allows to reduce pain and morbidity and to avoid the long-term consequences of a thoracotomy in an infant or a small child.

The introduction of Robot-assistance in pediatric thoracoscopic surgery has represented the latest instrumental innovation. Thus, innovations in minimally invasive surgery still need to be reported and validated. Furthermore, the development of this new minimally invasive approach requires a change in the modalities of training in pediatric thoracic surgery.

Nevertheless, there still are many unsolved questions on many conditions, like anesthetic approach during thoracoscopic surgery or management of congenital disease as cystic pulmonary malformations (CPM) or esophageal atresia (EA).

Thoracoscopy represents the most challenging area of pediatric minimally invasive surgery and a standardized training program would be advisable. Macchini et al. proposed a standardized training program is highly desirable to learn how to safely perform advanced pediatric thoracoscopy. It is based on a 2 year four-step program that consisted in: (1) theoretical part; (2) experimental training; (3) training in centers of reference; (4) personal operative experience.

Esophageal atresia (EA), although a rare congenital anomaly, represents one of the most common gastrointestinal birth defects. Due to its complexity, the scientific debate on the proper management of this condition and its consequences is still open. Recent developments in neonatal intensive care have significantly increased survival rates over the last decade also in premature babies and in those with associated malformations. Based on that Evanovich et al. proposed a need for a proper risk stratification in this unique population. In this study the authors addressed EA types, disease severity stratification (according to American Society of Anesthesiologists (ASA) and Pediatric Risk Assessment (PRAm) scores), and mortality in a retrospective cohort at a single institution. Despite a wider PRAm score distribution in infants born with EA, ASA scores remain the gold standard in assessing underlying disease severity stratification.

Thoracoscopic approach has been presented by Yong et al. as a valuable approach in managing esophageal diverticula after EA with tracheo-esophageal fistula. Esophageal diverticulum is an extremely rare complication of EA and is a clear indication for

diverticulectomy. In their series of 4 cases of esophageal diverticula thoracoscopy has been demonstrated to be a safe and effective approach for diverticulectomy.

In another article Ladefoged et al. aim to demonstrate whether the potential benefits of prophylactic intraoperative chest tube (IOCT) overweigh the potential harms. They conducted a systematic review and a meta-analysis on the most common research platform. Randomized clinical trials assessing the effect of a prophylactic IOCT during primary surgical repair of EA and observational studies were included. In their research the authors concluded that there is no evidence of a beneficial effect of placing a prophylactic IOCT during primary surgical repair of EA.

EA is strictly connected to different degrees of tracheomalacia (TM) in up to 87% of cases. Van Tuyll van Serooskerken et al. reported their own experience on performing primary posterior tracheopexy in EA in moderate and severe cases of ™ detected at first pre-operative bronchoscopy. The procedure has been performed in 36 cases and it impacted positively on the outcome of these patients by decreasing the rate of respiratory tract infections.

Moving forward to another congenital condition as pulmonary airway malformations we could appreciate the contribution given by Koga et al. In their research they would like to describe the use of an additional trocar (AT) in the lower thorax during thoracoscopic pulmonary lobectomy. Comparing two different populations based on the use or not of an AT they concluded that an AT and switching facilitated posterior dissection during TPL in children with congenital pulmonary airway malformation enhancing safety and efficiency.

Another crucial point in the management of congenital pulmonary airway malformations is whether to operate on asymptomatic patients. To answer this question Liu et al. proposed a novel point of view focusing on the proportion of hidden infection in congenital pulmonary airway malformations and its effect on surgery. In their study, patients with hidden infection accounted for 32% of all asymptomatic congenital pulmonary airway malformations patients. Hidden infection would increase the difficulty and risk of surgery and cause more surgical complications.

Oncology is one of the most promising frontier for pediatric surgeons who would like to extend the advantages of minimally invasive approaches also to those patients. Riccipetitoni et al. in their article give us a very interesting overview on their experience on application of thoracoscopy in pediatric malignancy. After reviewing 38 patients they concluded that thoracoscopy represents a valuable tool for diagnostic and therapeutic procedures in pediatric oncology that should be performed by expert surgeons. They also suggest that the advent of robotic surgery represents a new challenge that may further implement the advantages of the thoracoscopic approach.

Talking about tumors the key point of the treatment is the rate of survival. Ewing sarcomas of the chest wall represent an highly aggressive pediatric malignancies. Basharkhah et al. in their study reported a very promising results in terms of survival after an innovative multi-modal treatment. They sustain as specific oncological (neo)adjuvant treatment and multi-disciplinary surgery performing radical en-bloc resections and simultaneous chest wall repair contribute to a long-time survival of children and adolescents with Ewing sarcoma of the chest wall up to 89%. The main limit of the study is the small number of cases but the promising results should encourage many centers to this innovative multi-modal management of this tumor.

Last point of this research topic collection on thoracic surgery is congenital chest wall malformations. Nuss procedure is still considered a very challenging procedure to correct pectus excavatum. In their contribution McCoy and Hollinger focused on the anesthesiological point of view in the managment of these patients during operation. In particular they advocate as the use cryonalagesia, instead of epidural, and lung Isolation with the EZ-Blocker™, could improve surgical and clinical outcome of these patients.

The latest contribution is the one of Beigee at al. In this case report the authors present the first case of chest wall reconstruction by utilizing cryopreserved sternum in children. A 5-year old girl affected by hemangioma, receveid resection of the sternum; but the large anterior chest wall defect was reconstructed a by a cryopreserved sternal allograft. In the follow-up of the patient, there was no instability of the chest wall and acceptable cosmetic results.

Author contributions

ML has made a substantial contribution to the concept or design of the article; ML Drafted the article and revised it critically for important intellectual content, and approved the version to be published. All authors contributed to the article and approved the submitted version.

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Mentoring in Pediatric Thoracoscopy: From Theory to Practice

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Introduction: Thoracoscopy represents the most challenging area of pediatric minimally invasive surgery due to its technical difficulty. A standardized training program would be advisable. The aim of this study is to evaluate the results of our surgical training.

Materials and Methods: A retrospective, single-center, cohort study was performed. The following four-step program was tested: (1) theoretical part; (2) experimental training; (3) training in centers of reference; (4) personal operative experience. Particular attention was focused on the choice of mentor. Times and modality of adherence to the program were evaluated. The effectiveness and safety of the training were evaluated according to the surgical results of esophageal atresia (EA/TEF) repair and resection of congenital lung malformations (CLM). The study was conducted from January 2014 to May 2020. Attending surgeons with previous experience in neonatal and pediatric laparoscopy were selected for the training program after being evaluated by the head of Department.

Results: The training program was fully completed in 2 years. Twenty-four lobectomies, 9 sequestrectomies, 2 bronchogenic cyst resections and 20 EA/TEF repair were performed. Thoracoscopy was always feasible and effective, with no conversion. The operative times progressively decreased. Only three minor complications were recorded, all treated conservatively.

Conclusions: A standardized training program is highly desirable to learn how to safely perform advanced pediatric thoracoscopy. The 4-steps design seems a valid educational option. The choice of the mentor is crucial. An experience-based profile for pediatric surgeons who may teach thoracoscopy is advisable.

Keywords: thoracoscopy, training, mentoring, teacher education, congenital lung malformation, esophageal atresia

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INTRODUCTION

After the extensive diffusion of minimally invasive surgery (MIS) in the adult population, this surgical approach gradually involved the more challenging pediatric world (1).

In the last two decades MIS extended to an ever-growing number of indications in pediatric surgery and became the gold standard for certain diseases (2).

Among different applications of MIS in childhood, thoracoscopy is the most challenging as the thorax was the last area to be approached by MIS pediatric surgeons. Thoracoscopy is currently regarded by many pediatric surgeons as the last step in MIS training (1). In fact, it is technically more difficult than open surgery and requires a stepwise learning curve (LC). In particular, two factors are currently implicated to achieve competence: first case volume, but frequencies are typically low in pediatric surgery, so that a significantly longer time is required to reach a plateau of competence. Secondly, a standardized pediatric thoracoscopic training program does not exist yet (2, 3). As a consequence, only a limited number of pediatric surgeons are currently experts on this topic.

The recent development of instruments that are suitable for children has been crucial to making thoracoscopy feasible also in neonates and infants, so that even difficult procedures, such as esophageal atresia/tracheo-esophageal fistula (EA/TEF) repair and resection of congenital lung malformation (CLM), can be safely performed thoracoscopically (4).

In 2015, the European Society of Pediatric Endoscopic Surgeons (ESPES) published the guidelines for training program in pediatric minimally invasive surgery, recommending a four-steps training program (2).

The aim of our study is to evaluate the results of the surgical training in pediatric thoracoscopy in our Center, since the establishment of a new thoracoscopic program.

MATERIALS AND METHODS

We conducted a retrospective, single-center, cohort study at the Pediatric Surgery Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy. Parents gave written informed consent for surgical procedures and for the publication of this series in accordance with the Declaration of Helsinki. In 2012 we started a thoracoscopic training program.

The adherence of our training program to the ESPES guidelines for training program in pediatric minimally invasive surgery was evaluated, with the focus to verify the completion of all of the steps and the collection of the number of required procedures. In addition the surgical outcomes of our procedures were analyzed and also compared to the results of open surgery in our Center.

According to ESPES guidelines, a valid MIS training curriculum is represented by the "Peyton's Four-Step Approach" consisting in (5):

1. Theoretical part: attendance of at least 1 theoretical course in thoracoscopy;
2. Experimental training (MIS trainer, animal models, 3-D *ex vivo* models): spending at least 10–20 h of training on a pelvic trainer and at least 10 h of training on an animal model;
3. Training in a center of reference for pediatric MIS: attendance of 1–3 months of training in a center with high volume of MIS activity;
4. Personal operative experience: performing at least 30 procedures as assistant controlling the camera and more than 50 basic procedures as primary surgeon helped by a tutor (2).

Training Curriculum

Only attending surgeons with previous experience in neonatal and pediatric laparoscopy were selected for the training program after being evaluated by the head of department. The training process started with the delivery of educational material and attendance to national and international courses (6). High-fidelity simulation sessions were performed according to two different modalities. The "dry lab" was performed with the use of traditional and high-fidelity MIS trainers (7, 8). Next hands-on training was delivered through "wet labs," animal-based simulation sessions (9). An observership program at an international high volume referral center for pediatric thoracoscopy was the subsequent step (7). Professor S.S. Rothenberg from the Department of Pediatric Surgery of the Rocky Mountain Hospital for Children, Denver, Colorado (USA) was chosen as reference surgical mentor in view of his universally recognized experience in pediatric thoracoscopy (10, 11). Department directed by Prof. S.S. Rothenberg is a high-volume training center (>200 MIS procedures per year) (2) and trains pediatric surgeons from all over the world during the whole year. The first cases and the wider series of EA repairs and CLM resections come from this center, that published some of the most recent and updated papers (10, 11).

The next step consisted of performing a series of selected cases at our Hospital with the mentoring of Rothenberg (11). The first cases were performed by him with the training surgeons acting as first assistant. The following cases were managed by the local surgeons under his assistance and guidance. The last step was for the local team to manage the cases independently. For complex cases, pre-operative advice from the mentor was always required, by sharing through internet/web the history and images of patients. Patient's data were treated according to Data Protection Act.

The second end point of our study was the evaluation of the effectiveness and safety of our training according to our surgical results. This target was achieved focusing on two of the most difficult thoracoscopic procedures in pediatric surgery: EA/TEF repair in newborns and CLM resection during infancy (4). No modifications were made to the standard of care for newborns and infants requiring thoracoscopy for the studied diseases. Regarding EA/TEF, criteria for the thoracoscopic approach were: suspected standard type C EA/TEF, birth weight $\geq$2,000 g, absence of major associated malformations, and cardio-respiratory stability (no medical cardiac support and no mechanical ventilation). Reasons for conversion from thoracoscopy to open thoracotomy were any intraoperative adverse event or lack of progress for more than 15 min (12–14). According to the last step of our training program, the techniques recommended by Prof. Rothenberg in his last publications were selected as procedures of choice (10, 11).

Two additional aspects of our general approach deserve to be mentioned.

First, all cases are preoperatively evaluated by a multidisciplinary dedicated team, consisting of neonatologist, radiologist, pneumonologist, surgeon, anaesthesiologist.

Images are collectively evaluated, with 3D reconstructions when possible (15).

Secondly, the surgical team, including anesthetists and scrub nurses, always performs a preoperative meeting and a post-operative critical analysis of the procedures. During the first one, the surgical anatomy and the technical steps are revised in details, with the support of internal schemes and videos, e-learning (www.websurg.com; www.globalcastmd.com), and videos from the mentor. In the post-operative meetings, one soon after surgery and one a month later, an evaluation of the entire procedure and of the related criticisms and complications are carried out. Surgical criticisms are also evaluated on the basis of the analysis of video recordings of the procedures.

Surgical Outcome

To evaluate the impact of the surgical expertise on pediatric thoracoscopy, we retrospectively analyzed our case-series from the beginning of our surgical activity (January 2014) to present (May 2020). Only patients operated independently from the tutor were analyzed. We retrieved the following data: indications to thoracoscopy and demographic data; number of procedures performed with success; number of procedures needing conversion and reasons; length of surgery; perioperative, and postoperative complications.

A further comparison between the results of the thoracoscopic approach and the "open" traditional one was performed too, focusing on length of surgery and perioperative and postoperative complications. The population operated with the open technique was chosen among patients with characteristics similar to the thoracoscopic group, in terms of patients' age, indications for surgery and study period. It deserves to be specified that the open interventions were performed by a larger group of trained surgeons, including the surgeons selected for the thoracoscopic training.

The severity of every complication was assessed according to the Clavien-Dindo Classification of Surgical Complications (**Table 1**). It is a morbidity scale based on the therapeutic consequences of complications, that constitutes a simple, objective, and reproducible approach for comprehensive surgical outcome assessment (16).

The analysis of the results in terms of operative times and complications was limited to procedures with the higher number of patients and with the relatively lower variables, i.e., lobectomies, sequestrectomies and EA/TEF repairs.

Variables were expressed as mean ± standard deviation (SD) for demographic and baseline variables, and as median and range for length of follow-up. The learning curves were analyzed using linear regression.

Parametric variables were compared with the Student's *t*-test. Categorical variables were evaluated by Fisher exact test. Statistical analysis was performed using SigmaStat® (Systat Software Inc., San Jose, CA, USA). A $p < 0.05$ was considered significant.

RESULTS

Training Curriculum

Two surgeons previously trained in neonatal and pediatric laparoscopy and with experience in basic thoracoscopic procedures were selected. As regards laparoscopy, Nissen fundoplication, extra-mucosal pyloromyotomy, appendectomy, cholecystectomy, and surgery for Hirschsprung disease, were the most common and well-known performed procedures. Regarding previous thoracoscopic experience, neonatal removal of thoraco-amniotic shunts dislodged in thorax, treatment of pleural empyema and lung biopsies have been performed in a satisfactory number of patients. In particular, selected surgeons had a previous personal experience in more than 500 neonatal and pediatric minimally invasive procedures. The four-step training program was fully completed in 2 years (June 2012–2014).

Here following the details of every single step are reported.

- Theoretical knowledge: 4 theoretical national and 2 theoretical international courses were attended by the selected surgeons. All courses were focused on minimally invasive thoracic surgery and were organized under the sponsorship of national, European and international societies.
- Practice-based learning and improvement in experimental setting: 1 national and 1 international "dry lab" courses were attended, using both traditional and high-fidelity MIS trainers. Simulations were performed systematically even after treating the first patients in order to maintain a high level of technical ability. One national and 1 international "wet lab" courses were attended, both using young anesthetized piglets. During dry and wet labs, thoracoscopic lobectomies and esophageal anastomosis were performed. These steps were further developed by attending the post-graduate Master program in Pediatric Minimally Invasive Surgery at Alma Mater Studiorum—Università di Bologna—Italy.
- Stages in centers of reference: as previously described, a 15 day observer-ship was completed at the Department of Pediatric Surgery of the Rocky Mountain Hospital for Children, Denver, Colorado (USA), under the mentoring of Professor S.S. Rothenberg. During this period many thoracoscopic procedures were observed, such as pulmonary lobectomies, sequestrectomies, closures of patent ductus arteriosus, bronchogenic and pleural cysts resections, corrections of pectus excavatum.
- personal operative experience: within 6 months after the observership in USA, the first 10 cases of CLM were operated on as assistant with Professor S.S. Rothenberg working as main surgeon. In particular, trainees operated 5 pulmonary lobectomies, 1 bronchogenic cysts and 1 extra-lobar pulmonary sequestration as first assistant. The series included also 1 closure of patent ductus arteriosus and 1 esophageal duplication. Then, 2 pulmonary lobectomies and a resection of bronchogenic cyst were operated as first surgeon helped by the mentor. Finally the thoracoscopic procedures were approached without the presence of the tutor. In cases with challenging malformations, images, and advices were

TABLE 1 | Classification of surgical complications grades definition (modified from Clavien-Dindo Classification).

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for Grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic, or radiological intervention Grade III-a: intervention not under general anesthesia
Grade III-b	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)[‡] requiring IC/ICU-management
Grade IV-a	Single organ dysfunction (including dialysis)
Grade IV-b	Multi-organ dysfunction
Grade V	Death of a patient

[‡]*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks (TIA); CNS, Central Nervous System; IC, Intermediate care; ICU, Intensive care unit.*

shared by web the days before. The first neonatal thoracoscopy for EA/TEF correction was performed after almost 1 year since the first thoracoscopic CLM resection. Due to the urgent need for surgery, typical of this malformation, the procedure was done without the mentor. Also in this case images and videos were shared before surgery. As for the personal experience, dedicated surgeons were selected among those highly trained in neonatal and pediatric surgery and with previous high experience in minimally invasive pediatric surgery. At the end of the training period, more than 30 thoracoscopic procedures were performed as cameraman and more than 80 as primary surgeon.

Surgical Outcome

As regards the 2 thoracoscopic procedures selected for the present study, 35 CLM resections and 20 EA/TEF repairs were performed as main surgeons in the study period in Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy.

The CLM population received the following operations: 24 lobectomies, 9 sequestrectomies, and 2 bronchogenic cyst resections. Mean age at surgery was 7.6 ± 3.3 months, 19 patients were males. Thoracoscopy was feasible and effective in all cases, no conversion was observed. No major anatomical variants were detected in patients where a 3D CT scan reconstruction was possible. This data was consistent with the intraoperative findings. Mean operative time was 167 ± 65 min for lobectomies and 84 ± 27 min for sequestrectomies. As regards lobectomies, a significant reduction in operative times ($p = 0.0001$) was observed while increasing the surgical experience (**Figure 1**). Also operative times of sequestrectomies progressively reduced, though not reaching statistical significance probably due to the small number of patients ($p = 0.21$).

Regarding the comparison between traditional and MIS surgery, in the same study period 34 lobectomies, 2 sequestrectomies, and 2 bronchogenic cyst resections were performed in our Center with a thoracotomic approach. Mean operative time was 163 ± 45 min for lobectomies ($p = 0.83$). The mean surgery length was 110 min for sequestrectomies and 100 min for bronchogenic cyst resections but the limited numbers of both populations don't allow a statistical analysis.

The EA/TEF population consisted of 20 patients (13 males). Eleven newborns (55%) had a distal TEF (type C according to Gross classification), 5 (25%) an isolated TEF (type E), 3 (15%) had no fistulas and were classified as long gap (type A), and 1 (5%) proximal and distal fistulas (type D). The satisfactory results obtained with the first 5 EA/TEF cases prompted us to treat long gap forms too.

For EA with distal TEF (type C), mean gestational age at surgery was 38 ± 1.6 weeks, mean age was 1.7 ± 1 days and mean weight 2.763 ± 466,6 g.

Thoracoscopy was feasible and effective in all cases. No need for conversion was observed. Mean operative time was 134 25 min. The operative times rapidly decreased after the first case, though not reaching statistical significance ($p = 0.67$) probably due to the small number of patients, and remained stable for the subsequent procedures.

In the study period 18 type C EA were traditionally approached. Mean operative length was 126 ± 34 min ($p = 0.07$).

A total of 3 patients with a long gap malformation were operated on thoracoscopically. MIS was effective in performing a direct esophageal anastomosis in all cases and no conversion was recorded.

Regarding the MIS post-operative period, only 1 CLM patient (3%) developed an early complication. One male with an extralobar sequestration, that was prenatally ablated, had a post-operative bleeding that resolved after tranexanic acid iv therapy, probably as a consequence of the extensive blunt adhesiolysis between the lung and the ES (Grade II according to Clavien-Dindo Classification).

Two damages to the middle lobe requiring additional resections (Grade III b) occurred in the thoracotomic group.

Within C-type EA repair, 2 minor leakages were observed in both groups (MIS 18% vs. Open 11%; $p = 1$). Patients were treated conservatively with i.v. antibiotics and fasting, and presented a spontaneous resolution of the leakage. These complications were classified as Grade II according to Clavien-Dindo Classification. Six (50%) MIS vs. 9 (50%) open patients developed an anastomotic stricture ($p = 1$) requiring dilations (mean ± DS number of dilations: MIS 0.83 ± 1.0 vs. Open 0.94 ± 1.2; $p = 0.4$). These complications were classified as Grade IIIb according to Clavien-Dindo Classification. No significant

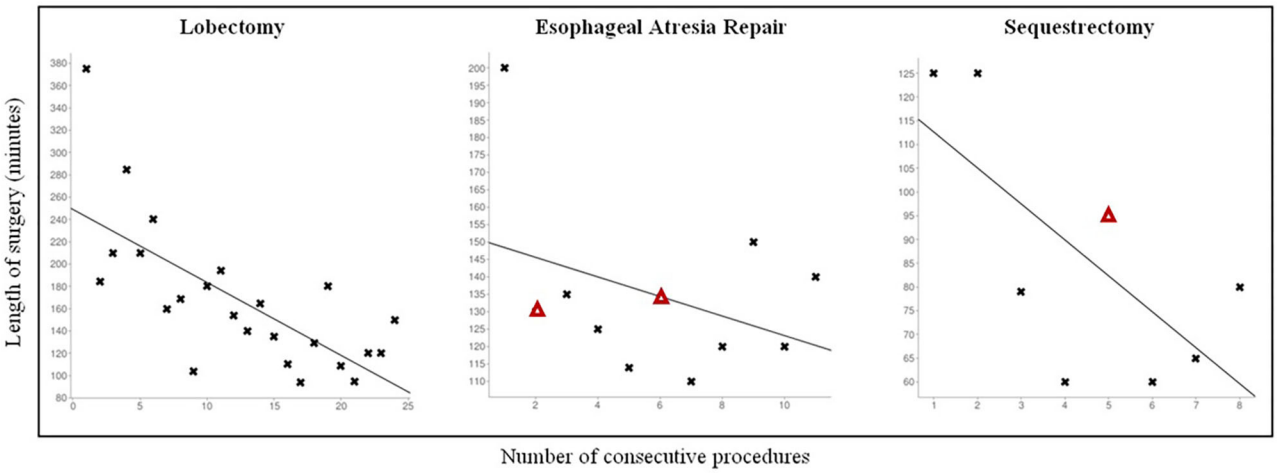

FIGURE 1 | Personal learning curve for different pediatric thoracoscopic procedures. Δ: Patients with Grade II complication according to Clavien-Dindo Classification.

differences in the prevalence of gastro-esophageal reflux disease was observed between the two studied groups (MIS 3/12–25% vs. Open 7/18–39%; $p = 0.69$).

As previously reported, all procedures were analyzed during the multidisciplinary post-operative meeting, where an evaluation of the entire procedure and of the related criticisms was done, and the follow-up was revised during the monthly meeting.

The mid-term follow-up was uneventful too. At follow-up (median time 24 months, range 1–46) children with CLM resection are clinically and radiologically healthy. Children with EA/TEF repair at a median follow-up time of 30 months (range 3–39) are clinically in good health. From an endoscopic point of view, 5 children (45%) developed a post-anastomotic stenosis that was successfully treated in the first 6 months of life with a mean of 1.8 ± 0.8 pneumatic dilations. In our series, the incidence of esophageal post-anastomotic stenosis is similar to the population operated with an open technique and to experiences from other centers (12, 17).

DISCUSSION

In the last few decades, MIS has significantly developed, extending to infancy and childhood. This progress was also due to the introduction of advanced techniques and specific devices for the management of little spaces and little anatomical structures.

However, among the different applications of MIS in childhood, thoracoscopy represented the last area to be reached. Although thoracoscopy represents a well-established approach for infants and children, reducing pain and morbidity and avoiding the long-term consequences of a thoracotomy (11), it is not still widely adopted, due to the fact that it is technically more difficult under different aspects. Main difficulties are due to anatomical features in children: pleural and mediastinal areas are minimal; intercostal spaces are limited, especially in neonates, not allowing the use of instruments >5 mm; the anatomy may be distorted by the original malformation; manipulated structures are thin and eventual complications may be fatal (1).

Technical aspects are involved in the delay in pediatric thoracoscopy too: the discrepancy between limited operative spaces and the large size of the available instruments, with a length and thickness of the jaws often disproportionate to the operative space of the infant (4). In addition, case volume and frequency are typically low in pediatric surgery, and a significantly longer time is required to reach competence. Finally, capnothorax is not always well-tolerated by neonates and infants, further reducing the number of procedures (18).

The final difficulties concern training. In many regions worldwide the training in pediatric surgery does not include a fellowship in adult cardio-thoracic surgery. Moreover, a standardized pediatric thoracoscopic training program does not exist yet (3).

Recently, the European Society of Pediatric Endoscopic Surgeons (ESPES) proposed guidelines for an European MIS training program for pediatric surgeons, with the aim to construct a curriculum that provides a safe, uniform, efficient and procedure-specific training program to gain experience, while maintaining patient safety. ESPES hoped that European countries would adopt this program so as to secure a standardized technical qualification in MIS for all future pediatric surgeons (2).

We tried to reproduce the suggestions by ESPES in our training program in pediatric thoracoscopy. The four-steps training program was fully completed in 2 years.

All steps reached high levels of satisfaction from the participants.

The basic knowledge of MIS procedures by the training surgeons was an important starting point, thanks to the acquired knowledge in handling thin structures and operating in limited spaces as in neonatal and infant thoracoscopic and laparoscopic procedures, as well as in doing intracorporeal knots. This

condition allowed to overcome the mentioned limits of pediatric MIS training, especially due to low volume and frequency of cases.

In our personal experience, the theoretical step represented a significant occasion to go deep into the topic.

According to the participants, the practice-based learning appeared more similar to reality and crucial from a surgical point of view to develop adequate technical skills.

Previous steps reached a high level of interest and utility, but we think that a special notice has to be given to the choice of the mentor that has to be highly accurate. In fact it represents not only the step immediately before the starting of surgery, but also the on-going support when the trained surgeons begin to operate independently.

We think that some points about this step need to be critically analyzed.

The first point is how to choose the mentor. At the moment there are a lot of training centers for MIS, but standardized essential requirement to certify them still does not exist. As suggested by ESPES guidelines, a training center should be able to offer a complete MIS training, with structured "dry" and "wet" laboratories. Trainees should participate in complex surgery and undergo structured training in all aspects of the procedure and then perform a designated number of cases under supervision (2).

In our experience some points of mentoring revealed crucial: to study the tutor's technique, reading his papers and watching the videos of his operations; to see and help him as assistant, trying to learn his tips and tricks; to operate with him as primary surgeon, following his live suggestions; to keep in strict connection even after the period of training. As regards tips and tricks, our mentor recommended us to introduce the use of miniaturized instruments, especially designed for neonates and infants. In our experience, these new instruments facilitated the thoracoscopic procedure and helped us to reduce the length of surgery (4).

As a general consideration, our experience shows that the surgical approaches suggested by Prof. S.S. Rothenberg are safe and reproducible, after an appropriate training. Results similar to other international centers (12) are achievable in a relatively short time frame.

Another important contribution to this last aspect may come from tele-mentoring: to overcome the lacking continuity in oversight by instructors, a remote teacher–student interaction is established through the web in different ways. Instructors use the connection to assess video recorded training sessions of students at distant locations and guide them through the MIS procedures with specific and personalized feedback. Tele-mentoring may be as effective as in-person instruction in teaching advanced MIS surgical skills, providing an effective method of teaching remotely and allowing expansion of robust simulation training curricula (19). We never adopted this tool but we think it may be very useful and will develop significantly in a near future.

According to all these considerations, we think that a step should be added to the training course, specifically dedicated to the choice and modalities of mentoring.

The results of our training program seem promising. Considerable numbers of thoracoscopic CLM resections and EA/TEF repairs were effectively performed in a relatively short period. Despite being still in training, the length of surgery did not significantly differ from the open group, thus not increasing the surgical and anesthesiological patient's exposure.

As regards the patients' safety, no major intra- and early post-operative complications, such as complications requiring surgical, endoscopic or radiologic intervention, life-threatening complications or death (16), were recorded. Focusing on CLM resection, the open group presented two major complications requiring additional surgery. One possible explanation of these results may be related to the magnification provided by the thoracoscopic approach that helps in a better anatomical vision. As regards EA/TEF repairs, no significant differences were recorded between the two groups, both in early and in late complication rate.

Pediatric thoracoscopy represents a fascinating and innovative technique, encountering in our experience a high level of satisfaction both for families and for the whole team.

The traditional "Master–Apprentice Model" revealed useful in the first part of our training, allowing us to reach the basic knowledge and technical competences to perform thoracoscopy in children. In this model, the apprentice first learns to perform a procedure by observing the master or surgeon how it needs to be done; then the trainee has to assist the surgeon several times; finally he will gradually be allowed to perform parts of the operation under the master's supervision until the apprentice can eventually perform it by himself (2, 20). The collaboration with the mentor in our experience also led to research projects and the organization of international workshops on pediatric thoracic surgery in 2017 and 2019.

In summary, in our experience a multistep training program as previously described seems effective to start pediatric thoracoscopy safely. A support to this consideration also comes from results we obtained following the same steps in other surgical areas, such as the fetoscopic correction of myelomeningocele (21) and the setting of a neonatal ECMO team (22).

We think that some further points of our method concurred to provide adequate surgical skills for an effective execution of thoracoscopy, especially in neonates and infants. A dedicated team including anesthetists, neonatologist, radiologist, pneumologist, and nurses, should be selected at the beginning of the training program and all steps should be shared with all the team. A multidisciplinary approach ensures a detailed preoperative assessment; a specific neonatal stabilization and study of the child; an appropriate intra-operative management; and a right post-operative and long-term follow-up.

A preoperative meeting and a post-operative critical analysis of the procedures are valuable. During the first one, the surgical anatomy and the technical steps are revised, and the intervention is planned in details. In our experience, an important help in deepening the anatomy and any anatomical variants of the lungs is guaranteed by the CT-scan images and, when possible, by the use of 3D reconstructions. In fact, as reported by previous studies (23), variations in lung anatomy are frequent and the benefits of

a precise pre-operative evaluation are currently stressed by many authors. In the post-operative meeting, the evaluation of the entire procedure and of the related criticisms and complications are always an opportunity to make steps forward. A significant help to this came in our experience from the systematic recording of the procedures, that were subsequently always reviewed and analyzed. This last step revealed useful also in our hospital to organize local and international meetings on this specific topic.

A last issue may be of some help in reducing the problem of low case volume and frequency and the subsequent slowness of the LC. Whenever possible, the opportunity to attend the operatory rooms of adult thoracic surgery may be useful for a constant revision of anatomy. Although the approaches in adult surgery are different from the pediatric ones, a significant improve may come from their experience and high volume activity. In addition, a centralization of the studied malformations in high level centers should be advisable. CLM and EA are considered rare diseases and need a dedicated training with high skill levels to provide the best management and outcome. Centralizing these patients would ensure higher volumes and accordingly better expertise.

After the completion of the described process, since 2018 the same training program involving other surgeons and trainees has started, being mentored by the already skilled local surgeons.

We think that the main limitation of the present study is represented by being a single center observational study. Despite this aspect provides uniformity of the studied population, we strongly advocate further multicentric studies to verify the reproducibility and safety of our training program.

CONCLUSIONS

Pediatric thoracoscopy represents the most challenging area of MIS. A standardized and certified training program is advisable. The 4-steps training seems a valuable educational proposal. The choice of the mentor is crucial.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

FM contributed conception and design of the study. FM and VG collected and analyzed the data retrospectively. FM, AM, EL, and SR wrote the first draft of the manuscript. All authors contributed to manuscript critical revision, read, and approved the submitted version.

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Interdisciplinary Radical "En-Bloc" Resection of Ewing Sarcoma of the Chest Wall and Simultaneous Chest Wall Repair Achieves Excellent Long-Term Survival in Children and Adolescents

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Introduction: Ewing sarcomas of the chest wall, historically known as "Askin tumors" represent highly aggressive pediatric malignancies with a reported 5-year survival ranging only between 40 and 60% in most studies. Multimodal oncological treatment according to specific Ewing sarcoma protocols and radical "en-bloc" resection with simultaneous chest wall repair are key factors for long-term survival. However, the surgical complexity depends on tumor location and volume and potential infiltrations into lung, pericardium, diaphragm, esophagus, spine and major vessels. Thus, the question arises, which surgical specialties should join their comprehensive skills when approaching a child with Ewing sarcoma of the chest wall.

Patients and Methods: All pediatric patients with Ewing sarcomas of the chest wall treated between 1990 and 2020 were analyzed focusing on complete resection, chest wall reconstruction, surgical complications according to Clavien-Dindo (CD) and survival. Patients received neo-adjuvant chemotherapy according to the respective Ewing sarcoma protocols. Depending on tumor location and organ infiltration, a multi-disciplinary surgical team was orchestrated to perform radical en-bloc resection and simultaneous chest wall repair.

Results: Thirteen consecutive patients (seven boys and six girls) were included. Median age at presentation was 10.9 years (range 2.2–21 years). Neo-adjuvant chemotherapy ($n = 13$) and irradiation ($n = 3$) achieved significant reduction of the median tumor volume (305.6 vs. 44 ml, $p < 0.05$). En-bloc resection and simultaneous chest wall reconstruction was achieved without major complications despite multi-organ

involvement. Postoperatively, one patient with infiltration of the costovertebral joint and laminectomy required surgical re-intervention (CD IIIb). 11/13 patients were treated with clear resections margins (R1 resection in one patient with infiltration of the costovertebral joint and marginal resection < 1 mm in one child with multiple pulmonary metastases). All patients underwent postoperative chemotherapy; irradiation was performed in four children. Two deaths occurred 18 months and 7.5 years after diagnosis, respectively. Median follow-up for the remaining patients was 8.8 years (range: 0.9–30.7 years). The 5-year survival rate was 89% and the overall survival 85%.

Conclusion: EWING specific oncological treatment and multi-disciplinary surgery performing radical en-bloc resections and simultaneous chest wall repair contribute to an improved survival of children with Ewing sarcoma of the chest wall.

Keywords: Askin tumor, Ewing sarcoma, chest wall reconstruction, tumor resection, multimodal therapy, chemotherapy

INTRODUCTION

Ewing sarcomas arising in the chest wall (historically known as Askin tumors) are small round cell sarcomas, molecularly defined by gene fusions involving one member of the FET family of genes and a member of the ETS family of transcription factors (1). They mainly arise from ribs, but paravertebral, sternal and scapular localizations have also been reported (2). In 1979, Askin et al. were the first ones to describe them in children, adolescents and young adults with a female preponderance (3, 4). Over the years, it became obvious that Askin tumor does not represent an separate tumor entity. In contrast, molecular studies showed identical molecular findings as seen in Ewing Sarcoma. Therefore, the terminology Askin tumor/primitive neuroectodermal tumor is not recommended by the resent WHO classification of bone and soft tissue tumors (1).

Clinically, children usually present late with a chest wall mass, chest pain or respiratory distress due to an intrathoracic mass (5). Unspecific symptoms such as fever, enlarged superficial lymph nodes, decreased general condition and nocturnal sweat may occur (6). Rarely, patients initially present with pathological fracture or metastasis related symptoms (7). Diagnostics reveal location and volume of the primary tumor as well as infiltrations e.g., into vertebral column, lung, pericardium, diaphragm or esophagus. Differential diagnoses include the group of undifferentiated small round cell sarcomas of bone and soft tissue, neuroblastoma, lymphoma, small-cell carcinoma, rhabdomyosarcoma, monophasic synovial sarcoma, and desmoplastic small round cell tumor.

Interdisciplinary and multimodal treatment of Ewing sarcoma is guided by the appropriate EWING protocols (8, 9). Aggressive treatment regimen have been shown to lead to longer relapse-free survival (6). Radical "en-bloc" resection remains crucial facing multiple challenges such as infiltrations e.g., into lung, spine, pericardium or diaphragm. Simultaneous chest wall reconstruction remains similarly challenging when covering large defects with prosthetic materials and viable tissue to prevent instability, flailing and infections. Thus, the question arises, which surgical specialties should build one team and join their comprehensive skills when approaching a child with Ewing Sarcoma of the chest wall. The present study elucidates the surgical and oncological outcome of children with Ewing Sarcoma of the chest wall treated by a multidisciplinary team of surgical specialists orchestrated according to the individual anatomical complexity.

PATIENTS AND METHODS

Following approval of the local ethics committee (EK 33-191 ex 20/21), we performed a retrospective analysis of all patients with Ewing Sarcoma of the chest wall treated at the Departments of Pediatric and Adolescent Surgery and Pediatrics and Adolescent Medicine between January 1990 and December 2020.

Patients received pediatric oncological management according to the currently valid protocol. Depending on the surgical complexity, a multidisciplinary surgical team was orchestrated to achieve radical "en-bloc" resections and simultaneous chest wall reconstructions. Pediatric surgeons or thoracic surgeons mainly performed en-bloc resections including resections of pulmonary, diaphragmatic, pericardial and esophageal infiltrations (**Figure 1**). They also inserted the prosthetic patches into the defect. Orthopedic surgeons took the lead for partial resection of a vertebral body and hemilaminectomy in one case with infiltration of the transverse process. Finally, plastic surgeons were responsible for covering the prosthetic patch with a muscle flap.

The diagnosis of Ewing Sarcoma of the chest wall was confirmed based on histological, immunohistochemical and molecular findings. Patient data were analyzed for presentation, tumor characteristics, oncological treatment, surgical outcome, surgical complications according to Clavien-Dindo (10), long-term follow-up and overall, progression free and relapse free survival.

RESULTS

From 1990 to 2020, 13 patients ($n = 7$ male, $n = 6$ female) underwent interdisciplinary multimodal therapy for Ewing

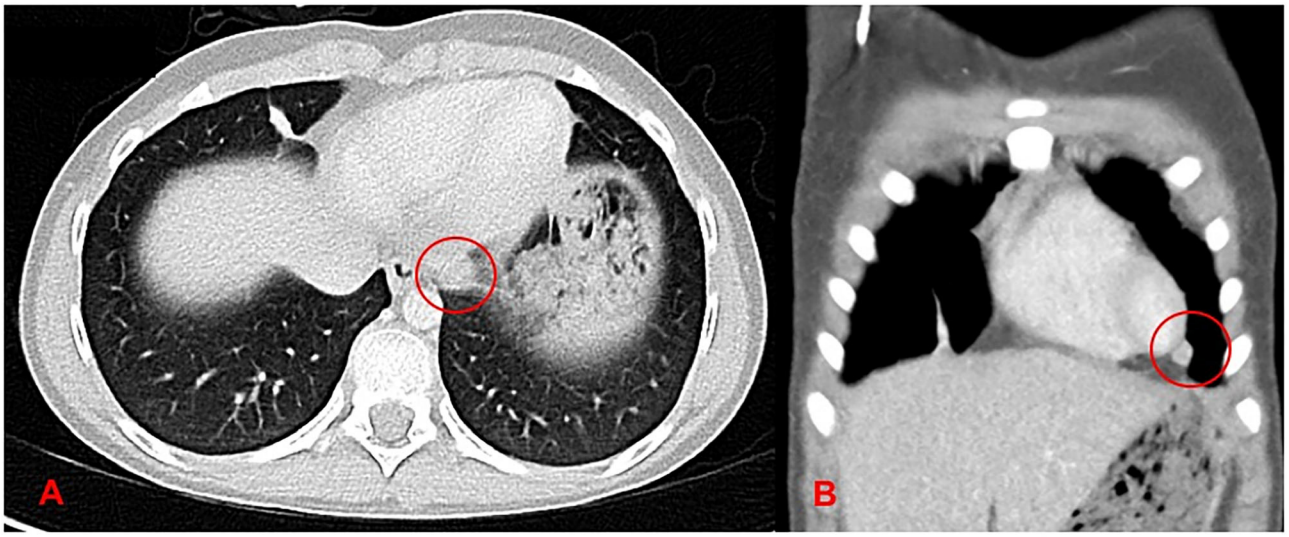

FIGURE 1 | Preoperative CT revealing multiple metastases: **(A)** shows a paraesophageal metastasis (red circle) and **(B)** demonstrates a pericardial metastasis (red circle). Both were removed surgically during initial resection (Patient #13).

Sarcoma of the chest wall. The median age of the patients at the time of presentation was 10.9 years ranging from 2.2 to 21 years.

Clinically, eight patients reported increasing thoracic pain. Three children had been treated for pneumonia. In two patients, the parents accidentally detected a thoracic swelling. One boy suffered from pneumothorax after a bout of laughter. Other unspecific symptoms included nocturnal sweating, fever, reduced general condition and collapse.

All patients underwent chest radiographs, bone scan, CT and MRI examinations revealing thoracic masses and the typical lytic bone destructions or cortical affection. Malignant pleural effusion was detected in four children, pleural seeding in three. At the time of presentation, two patients had pulmonary metastases. Detailed clinical data are presented in **Table 1**.

Neoadjuvant Treatment

All patients underwent diagnostic biopsies. On H&E morphology the tumors were composed of uniform small round tumor cells with fine chromatin, inconspicuous nuclei and scant clear or eosinophilic cytoplasm. The individual tumor cells were evenly spaced. Immunohistochemical examination revealed a strong membranous CD99 staining in all tumors. Tumors in the differential diagnosis were excluded using a broad immunohistochemical panel of antibodies. Molecular analyses were performed in 11/13 cases. Depending on the year of diagnosis FISH, RT-PCR and Archer fusion plex sarcoma panel were performed to confirm the diagnosis of Ewing Sarcoma. One boy had an additional tri-/tetrasomy of chromosome 8.

Chemotherapy was administered in all patients, i.e., two patients in the early nineties were treated according to the CESS 86 (11) and EICESS 92 (12), four and six according to the Euro-E.W.I.N.G. 99 (8) and EWING 2008 (9) protocols, respectively. In one patient (date of diagnosis 2009) initially diagnosed as desmoplastic round cell tumor, the diagnosis was revised after the patient developed a pulmonary metastasis. She was initially treated according to CWS 2002 (13) and postoperatively according to EURO-EWINGS 99. Three patients underwent irradiation additionally to their neoadjuvant chemotherapy due to malignant pleural effusion and pleural carcinosis.

Neo-adjuvant chemotherapy and irradiation led to a statistically significant reduction of the tumor volume from a median of 305.6 ml (ranging from 32 to 814 ml) to 44 ml (ranging from 2 to 215 ml) ($p < 0.001$, Wilcoxon Test) (**Table 2**).

Perioperative Course

En-bloc resection and simultaneous chest wall reconstruction was achieved in all cases without major complications despite multi-organ involvement. The affected rib and at least two adjacent ribs was removed in continuity with all infiltrations. Additional distant lesions were excised as well. In one case, orthopedic surgeons successfully performed partial vertebral body resection and hemilaminectomy for infiltrations into the transverse process (**Figure 2**). Pediatric and plastic surgeons could cover all chest wall defects with a prosthetic patch and muscle flaps. Postoperatively, the patient with infiltration of the costovertebral joint and hemi-resection of one vertebral body developed a liquor fistula requiring surgical intervention (placement of a lumbar drainage; CDC IIIb).

Table 2 summarizes detailed information concerning procedure, specialists of the team, chest wall reconstruction and short-term complications (30 days) according to CDC.

Histologically, complete resection was achieved in 11/13. R1 resection was found in one patient with infiltration of the costovertebral joint. Marginal resection of <1 mm was found in one child with multiple pulmonary metastases (**Table 3**).

Histologic evaluation of the tumor resection specimen after multimodal treatment revealed no viable appearing tumor cells in 9 cases therefore classifying them as Salzer-Kuntschik I grade

TABLE 1 | Clinical data of 13 patients treated with Askin tumors between 1990 and 2020.

ID	Year of diagnosis	Age	Sex	Primary tumor	Side	Complexity of disease
1	1990	7	M	6th−7th	Right	Adherent to lung
2	1994	21	M	8th	Right	Pleura, adherent to diaphragm
3	2001	16.5	M	6th	Right	Malignant pleural effusion
4	2001	2.5	F	11th	Right	Adherent to diaphragm
5	2001	10.5	M	4th	Right	Adherent to lung
6	2001	18	F	9th	Left	adherent to diaphragm
7	2009	12	F	4th−6th	Right	Left lower lobe, malignant pleural effusion
8	2012	16.5	M	7th	Left	Malignant pleural effusion, tumor embolism, adherent to diaphragm and the lung lower lobe
9	2014	11	M	4th	Left	Malignant pleural effusion, adherent to the lung lower and upper lobe
10	2017	3	F	7th	Left	Adherent to vertebral body and transverse process
11	2018	8	M	3th	Right	Adherent to lung
12	2019	9	F	6th	Right	Pleura
13	2020	11.5	F	3th	Left	Pleura, left lower lobe, diaphragmatic, paraesophageal, pericardial

of regression. In one case the regression grade was III (<10% vital tumor cells) and in the three remaining patients there were more than 50% vital tumor cell (regression grade V) (14).

All patients underwent adjuvant chemotherapy. Additional postoperative irradiation was administered in four cases, due to the above-mentioned marginal resection ($n = 2$), malignant pleural effusion ($n = 1$) and pulmonary metastases ($n = 1$). One patient with a histological confirmed invasion of tumor into a small pulmonary artery and malignant pleural effusion (patient #8) refused the advised radiotherapy.

Long-Term Outcome and Sequelae

Overall survival rate with multimodal therapy is 85% at a median follow-up of 8.8 years (ranging from 0.9 to 30.7 years). The 5-year survival rate is 89%. The median progression free survival was 7 years (range: 0.4–30.7 years). While one patient is still under the primary therapy and one patient passed away during primary therapy, the median relapse free survival in the remaining 11 patients was 8 years (0.4–30 years).

Eight out of the 13 patients had an uneventful oncological follow-up without signs of relapse or sequelae (**Table 3**). Patient #10, who required partial vertebral body resection developed postoperative scoliosis. A local relapse 2 years later necessitated radiotherapy. Three years after the primary diagnosis, a metastasis was found in the cervical vertebral column (C2) and she is currently under chemotherapy and radiotherapy. Two further patients had postoperative complications: Patient #1 developed postoperative scoliosis and pulmonary restriction with a tumor free interval of 30 years and patient #9 suffers from pulmonary restriction at a tumor free interval of 6.5 years.

Two patients died. In Patient #2 pulmonary metastasis occurred 5 years after the initial diagnosis. The metastasis was resected and chemotherapy including high-dose chemotherapy with autologous stem cell support was administered. However, two further relapses occurred, and he passed away 7.5 years after the initial diagnosis.

Patient #7 who initially presented with pleural effusion and pulmonary metastasis in the contralateral lower lobe developed six bilateral lung metastases later. Despite resection via sternotomy, chemotherapy and radiation the girl suffered from multiple recurrent metastases in both lungs and died 18 months after the first diagnosis.

DISCUSSION

With an aggressive multimodal interdisciplinary team approach with "targeted" surgical specialists we achieved an 85% overall survival rate at a median follow-up of 8.8 years and a 5-year survival rate of 89%. Two of the 13 patients treated during the last 30 years died 18 months and 7.5 years after diagnosis, respectively. Two patients are still under therapy.

Ewing sarcoma of the chest wall usually have a poor prognosis. Triarico et al. have reported a series of 9 patients with "Askin tumors," and their 5-year survival was 60% at a median follow-up of 53.1 months (15). Five-year survival of patients with localized extra-skeletal Ewing sarcomas has been described with 69.7% (16). Additionally, the overall survival rate after a median follow-up of 28 months was 45% in a study by Laskar (17).

Poor prognosis has been associated with tumor diameters > 5 cm, LDH levels > 240 U/l and late stage diagnosis (4). In another study, patients with poor histological response to chemotherapy and positive surgical margins had significantly worse event-free survival (18). Laskar et al. have shown that age at diagnosis higher than 18 years, poor response to induction chemotherapy, and presence of pleural effusion are indicators of inferior survival (17).

Cornerstones of current treatment protocols include neo-adjuvant chemotherapy, radical "en-bloc" resection

TABLE 2 | Treatment of 13 patients with Askin tumors.

ID	Preoperative therapy	Initial tumor volume (ml)	Tumor volume after CTX (ml)	Procedure performed	Surgical team	Material used for reconstruction	Complications CDC in 30 days
1	CESS 86/irradiation	32	4	Resection of the dorsal part of the 6th, the entire 7th rib, the transverse process and partial resection of the lung lower lobe	PS		
2	EICESS 92/irradiation	810	215	Partial resection of the 7th–9th ribs with adherent diaphragm	TS	Corium flap plastic and m. latissimus dorsi flap at a later time point autologous transplantation of the contralateral 7th rib and m. rectus abdominis flap at a later time point	
3	EURO EWING 99	148	2	Partial resection of the 5th–7th ribs	PS, OT	Vicryl® mesh and m. latissimus dorsi flap	
4	EURO EWING 99	246.5	16	Partial resection of the 10th–12th ribs with adherent diaphragm	PS, PL	Vicryl® mesh and m. latissimus dorsi flap	
5	EURO EWING 99	813.7	15.2	Partial resection of the 3rd–5th ribs with adherent lung	PS	Goretex® patch, Vicryl® mesh	
6	EURO EWING 99	199	5.2	Partial resection of the 8th–10th ribs with adherent diaphragm	PS	Goretex® patch, Vicryl® mesh	
7	CWS 2002 pilot	216	88.6	Partial resection of the 4th–7th ribs	PS	Tutomesh® plastic and m. latissimus dorsi flap	
8	EWING 2008	175	8.8	Partial resection of the 5th–9th ribs with adherent diaphragm and the lung lower lobe	OT, TS	Gore® Dualmesh®, Prolene® Mesh m. latissimus dorsi flap	
9	EWING 2008	310	37	Partial resection of the 3rd–7th ribs and the adherent lung lower and upper lobe	PS, TS, PL	Prolene® Mesh m. latissimus dorsi flap	
10	EWING 2008	72	15	Partial resection of 6th–8th with partial vertebral body resection/hemilaminectomy, resection of the transverse process and dorsal root ganglia	PS, OT, PL	Prolene® Mesh m. latissimus dorsi flap and m. trapezius	Liquor fistula lumbar drainage
11	EWING 2008	83	5.4	Partial resection of 2nd–4th ribs and adherent lung	PS, OT, PL	Prolene® Mesh m. pectoralis flap	
12	EWING 2008/ irradiation	53.1	2	Partial resection of the 4th–6th and pleural metastases	PS, OT, PL	Prolene® Mesh m. latissimus dorsi flap	
13	EWING 2008	814	158	Partial resection of the 1st–5th ribs with metastases to pericardium, lung, diaphragm	PS, OT, PL	Prolene® Mesh m. latissimus dorsi flap	

CTX, chemotherapy; PS, Pediatric Surgery; OT, Orthopedic Surgery; PL, Plastic Surgery; TS, Thoracic Surgery; CDC, Clavien-Dindo Classification.

and chest wall reconstruction as well as adjuvant chemotherapy/radiotherapy (19, 20).

Neo-adjuvant chemotherapy has been shown to prolong survival rates (21, 22). This may be attributed to the formation of a pseudo-capsule, which reduces the risk of intraoperative tumor rupture and tumor cell dissemination (21, 23, 24). By shrinking tumor volume it decreases vascularity and vulnerability and improves feasibility of complete removal with negative microscopic margins (4, 25–27). In our study, we confirmed the efficacy of neo-adjuvant chemotherapy with a significantly reduced tumor volume following preoperative chemotherapy (**Table 2**). Moreover, Demir et al. reported that neo-adjuvant chemotherapy significantly increased the complete resection rate with 5-year survival rates with or without neo-adjuvant therapy of 77 and 37%, respectively (28).

Following neo-adjuvant chemotherapy, complete "en-bloc" resection of the primary lesion and simultaneous reconstruction of the defect is mandatory. Radical surgical resection is associated with better survival; patients with complete resection have a higher 5-year survival rate compared to patients who had an incomplete resection (28). The surgical complexity primarily depends not only on tumor location and volume, but also on the extent of infiltrations into lung, pericardium, diaphragm, esophagus or spine. Thus, the question arises, which surgical

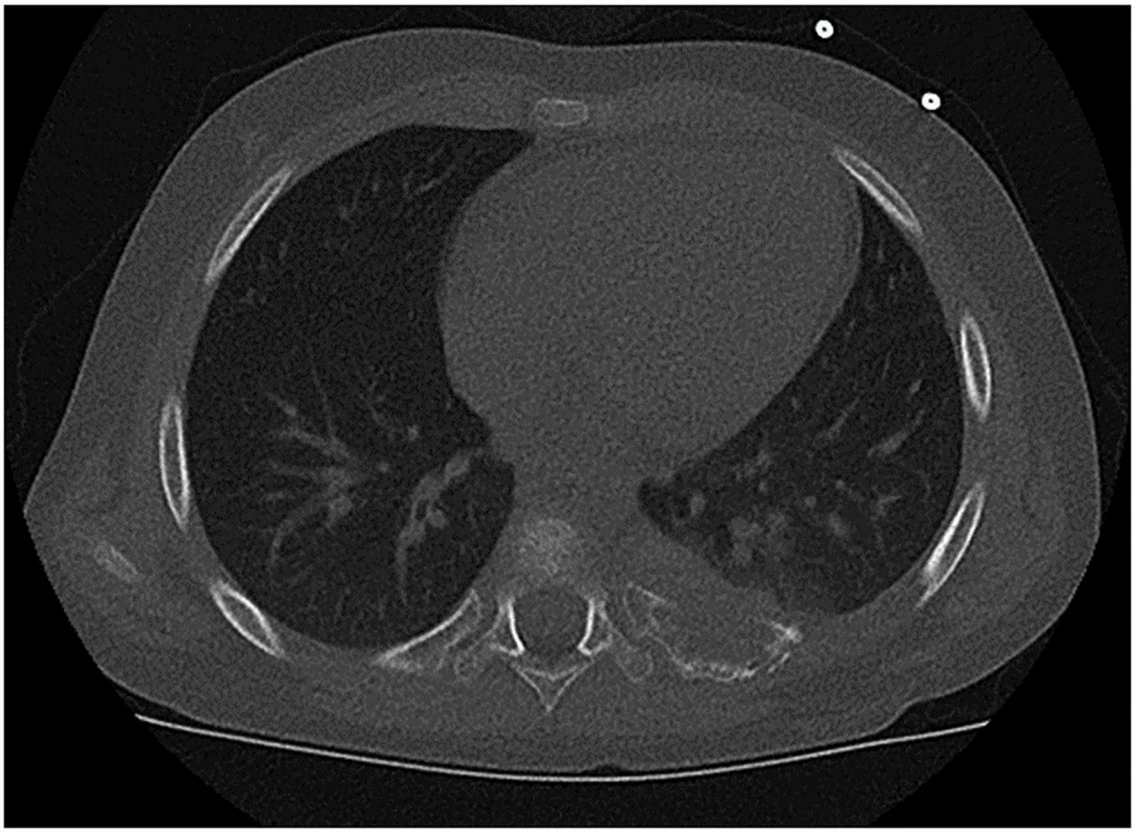

FIGURE 2 | Tumor arising from the paravertebral dorsal portion of the left 7th rib with infiltration of the transverse process and vertebral body. This extent required en bloc resection of the ribs 6–8 and additional removal of the costovertebral joint and hemilaminectomy (patient #10).

TABLE 3 | Outcome and complications of 13 patients treated with Askin tumors.

ID	Local resection status	Grade of regression	Postoperative therapy (CTX/irradiation)	Auto-PSCTx	Relapses	Outcome years	Sequelae
1	R0	1	+/–		–	30.7	Scoliosis, pulmonary restriction
2	R0	1	+/–	+	Lung/local	†7.5	
3	R0	1	+/+	–	–	20	
4	R0	1	+/–	–	–	19.9	
5	R0	3	+/–	–	–	19.5	
6	R0	1	+/–	–	–	19.4	
7	R0	5	+/+	+	Lung bilateral	†1.5	
8	R0	1	+/refused	+	–	8.8	
9	R0	1	+/–	+	–	7	Pulmonary restriction
10	R1	5	+/+	–	Local/cervical	3.4	Scoliosis
11	R0	1	+/–	–	–	2.9	
12	R0	1	+/–	+	–	1.2	
13	Marginal	5	+/+	+	–	0.9	

CTX, chemotherapy; PSCTx, peripheral stem cell transplantation. †deceased.

specialists should build one team and join their comprehensive skills when approaching a child with Ewing sarcoma of the chest wall. In the literature, there are some reports about the team approach (6, 15, 29), but the studies report lower survival rates than those achieved in ours. We orchestrated the team according to the surgical complexity and organ involvement, targeting

"en-bloc" resection with a preferably macroscopic safety margin of 1 cm. This strategy is technically more demanding when the first and second rib have to be removed. Care should be taken to avoid injury of subclavian vessels and brachial plexus.

Simultaneously, all distant metastases within the ipsilateral thoracic cavity must be managed requiring pulmonary, cardiac, esophageal and diaphragmatic expertise. In our setting pediatric surgeons or thoracic surgeons faced these challenges successfully with minor complications. Finally, simultaneous repair of the chest wall defect requires distinct surgical finesse. A variety of materials is available to cover the defect. This includes synthetic meshes, bioprosthetic materials, stainless-steel bars, osseo-integrated titanium systems, autografts, homografts or porcine or bovine xenografts. In 2020, Smelt et al. described the successful application of personalized three-dimensional (3D)-printed chest wall prostheses made of methylmetacrylate covered by expanded polytetrafluoroethylene for patients undergoing chest wall resection and reconstruction (30). However, due to residual growth and development, the choice of the optimal material is a major consideration in the pediatric and adolescent population. The material should be malleable enough to conform to the shape of the chest wall, rigid enough to prevent paradoxical motion and protective for the intrathoracal organs. Additionally, it should be durable, non-allergenic, non-toxic, biologically inert and radiolucent (31, 32). One advantage of synthetic meshes used in our patients is their permeability, which minimizes the amount of postoperative pleural effusion. The mesh is sutured tautly to the surrounding tissue allowing ingrowth of connective tissue and incorporation of the mesh into the body (33). Most centers also insert a prosthetic patch into the skeletal defect and cover it with viable tissue like a muscular flap. This dual layer technique offers the advantage that well-vascularized tissue facilitates integration of the underlying material into the surrounding tissue thereby minimizing the risk of infections (34). In our series no infection of the patches or flaps occurred.

Nevertheless, long-term sequelae such as scoliosis cannot always be prevented. In our series, two of the 13 patients developed scoliosis. In a recently published report, Marqués et al. describe the successful operative correction of four pediatric patients with scoliosis secondary to extensive chest resections due to Askin tumors (35). Moreover, female patients should be also observed regarding mammary sequelae. However, due to the rarity of the disease there is no real recommendation for mammary reconstruction in affected female patients.

Local relapse represents a major negative factor for mortality (36). Christiansen et al. described a series of 8 patients, in which 4 out of 5 patients with relapse died (6). In our series, we found similar mortality rates as two out of three patients with relapses died and the third one is still under treatment. In 2013, we have already published our experience with seven patients with Ewing sarcoma of the chest wall. We were able to achieve a 5-year survival rate of 86% and an overall survival of 71% (22). By adding another 6 patients in the current report, we support this relatively high survival rate.

Postoperative irradiation was applied in four of the patients. In two of them due to viable tumor cells with Salzer-Kuntschik grade V regression and marginal resection, in one boy with a malignant pleural effusion and in one girl with multiple pulmonary metastases. Patient #8 refused the recommended postoperative radiotherapy. Radiotherapy should only be reserved for individual patients with unfavorable non metastatic tumors or for patients with a high risk of recurrence, such as in an incomplete resection or viable tumor (26, 37), due to the late effects related to radiotherapy such as chest wall deformities, pulmonary fibrosis and risk of secondary malignancies (19).

Limitations of the present study include the relatively low number of patients and the short observation period of four patients (patients 10–13). However, due to the rarity of Ewing sarcomas in general and the location chest wall in particular large series in children and adolescents concentrating on the surgical approach are scarce in the literature.

In conclusion, Ewing sarcoma specific oncological (neo)adjuvant treatment and multi-disciplinary surgery performing radical en-bloc resections and simultaneous chest wall repair contribute to an improved long-time survival of children and adolescents with Ewing sarcoma of the chest wall.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Graz. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AB, CC, GS, and HT analyzed the data, wrote the manuscript and performed the statistics. AB, HL, AK, MBer, SS, CC, ES, MBen, BL-A, F-MS-J, CU, MH, and HT operated, treated and examined the patients and critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Thoracoscopy for Esophageal Diverticula After Esophageal Atresia With Tracheo-Esophageal Fistula

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Background: Esophageal diverticulum (ED) is an extremely rare complication of congenital esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) surgery. We aimed to investigate feasible methods for the treatment of this rare complication.

Methods: We retrospectively reviewed all patients with EA/TEF at Beijing Children's Hospital from January 2015 to September 2019. The clinicopathological features of patients with ED after EA/TEF surgery were recorded. Follow-up was routinely performed after surgery until December 2020.

Results: Among 198 patients with EA/TEF, ED only occurred in four patients (2.02%; one male, three female). The four patients had varying complications after the initial operation, including anastomotic leakage (3/4), esophageal stenosis (3/4), and recurrence of TEF (1/4). The main clinical symptoms of ED included recurrent pneumonia (4/4), coughing (4/4), and dysphagia (3/4). All ED cases occurred near the esophageal anastomosis. Patients' age at the time of diverticulum repair was 6.6–16.8 months. All patients underwent thoracoscopic esophageal diverticulectomy (operation time: 1.5–3.5 h). Anastomotic leakage occurred in one patient and spontaneously healed after 2 weeks. The other three patients had no peri-operative complications. All patients were routinely followed up after surgery for 14–36 months. During the follow-up period, all patients could eat orally, had good growth and weight gain, and showed no ED recurrence or anastomotic leakage on esophagogram.

Conclusions: ED is a rare complication after EA/TEF surgery and is a clear indication for diverticulectomy. During the midterm follow-up, thoracoscopic esophageal diverticulectomy was safe and effective for ED after EA/TEF surgery.

Keywords: esophageal diverticulum, esophageal atresia, tracheoesophageal fistula, thoracoscopic, children

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INTRODUCTION

Congenital esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a serious digestive malformation with an incidence of ∼1/2000–4500 (1). Esophageal diverticulum (ED) is a diverticulum of one or more layers of the esophageal wall. ED can be divided into two types; the true diverticulum includes the full layers of the

esophageal wall, and the pseudo diverticulum only includes the mucosa and submucosa (2). ED is relatively rare in adults, with an incidence of ∼0.06–4%, and mainly occurs in the elderly (3). Additionally, ED can occur as an extremely rare complication of EA/TEF surgery. Currently, only a few studies have reported the occurrence of ED after EA/TEF surgery. According to different reports, the incidence of ED is between 0.0% and 1.9% in patients who have undergone EA/TEF surgery (4–6). However, to the best of our knowledge, no reports have described the diagnosis and treatment of ED after EA/TEF surgery.

In this study, we retrospectively analyzed the diagnosis and treatment of patients with ED after EA/TEF surgery at our hospital. The objective of this study was to discuss feasible diagnostic and treatment methods for this rare complication after EA/TEF surgery.

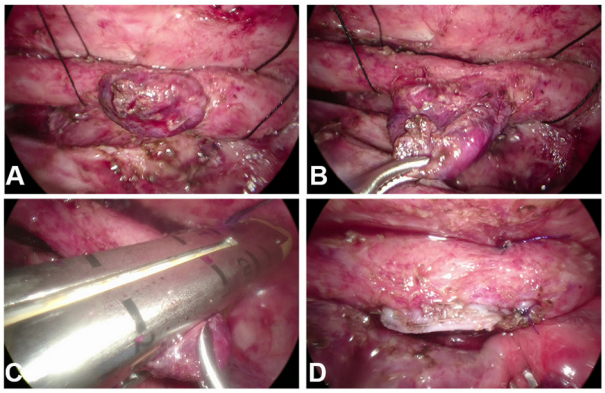

FIGURE 1 | (A,B) The neck of the esophageal diverticulum (ED) was fully exposed. **(C)** The linear cutter stapler was positioned at the neck of the ED and close to the esophagus. **(D)** The ED was excised by the stapler.

PATIENTS AND METHODS

Data Collection

We retrospectively reviewed all patients with EA/TEF at our institution between January 2015 and September 2019. Patients with ED after EA/TEF surgery were selected, and the clinicopathological features were recorded. Follow-up was routinely performed after surgery. This retrospective study was approved by the ethics committee of Beijing Children's Hospital (approval no. 2019-k-333), and the families of all patients provided written informed consent and agreed to participate in the study.

Diagnostic Method

Esophageal angiography was used to define the diagnosis of ED after EA/TEF and to evaluate the size and site of ED. Airway endoscopy, digestive endoscopy, and chest computed tomography (CT) were routinely performed to exclude other related diseases before diverticulectomy.

Surgical Method

Thoracoscopic esophageal diverticulectomy was routinely performed from the right side. A 5-mm thoracoscope was placed in the fifth intercostal space of the right infrascapular line. Two 3-mm trocars were placed in the second intercostal space in the mid axillary line and the fifth intercostal space in the posterior axillary line to establish operating channels. The intrathoracic pressure was maintained at 6–8 mmHg. The adhesion between the lung tissue and chest cavity was loosened, and the neck of the ED was fully exposed. The left-hand operating hole replaced with a 10-mm trocar, a surgical linear cutter stapler with a nail length of 30 mm, was inserted, and the diverticulum close to the esophagus was resected (**Figure 1**). The chest drainage tube was routinely indwelled. After the operation, patients were routinely transferred to the pediatric intensive care unit (PICU) under tracheal intubation.

Postoperative Follow-Up

Routine esophagogram was performed 7 and 14 days after the operation during hospitalization. Outpatient follow-up and esophagogram were routinely scheduled in the first month, third month and 6 month after surgery. Then outpatient follow-up was scheduled every 3 months during the first 1 year after surgery and every 6 months thereafter. If postoperative esophageal stenosis was found by esophagogram, endoscopy was used to detect and treat the stenosis with endoscopic balloon dilatation. All patients were followed up until the end of December 2020.

RESULTS

Among the 198 patients with EA/TEF at our institution between January 2015 and September 2019, ED only occurred in four patients (2.02%) during the follow-up period. Of these four patients, one was male, and three were female. EA repair surgery, including open or thoracoscopic ligation of the fistula and end-to-end anastomosis of esophageal segments, was performed in all patients 1 week after birth. The four patients had various complications after the initial operation, including anastomotic leakage (3/4), esophageal stenosis (3/4), and recurrence of TEF (1/4). Two patients also had malformations of other systems, including scoliosis (1/4) and vertebral deformities (2/4). The main clinical symptoms of ED included recurrent pneumonia (4/4), coughing (4/4), and dysphagia (3/4). All diverticula were located near the esophageal anastomosis, between T3 and T6, and all were therefore thoracic ED. Patient age at the time of diagnosing ED ranged from 2.5 to 9.3 months (median age: 6.2 months). The patient age of diverticulum repair was 6.6 to 16.8 months (median age: 9.5 months). By the time of diverticulectomy, the average long diameter of these EDs increased from 15.2 to 22.2 mm. Body weight at the time of operation was 6.5–9.5 kg (median weight: 7.3 kg). All four patients underwent a thoracoscopic esophageal diverticulectomy. Owing to recurrent TEF, patient 4 underwent thoracoscopic TEF resection at the same time. The operation time ranged from 1.5 to 3.5 h (average: 2.2 h). In all patients, intra-operative bleeding was <5 mL, and no blood transfusions were required during the operation. After the operation, patients were routinely transferred to the PICU. The postoperative time of invasive

ventilator use was 1–7 days (average: 3 days). The postoperative hospital stay time was 10–20 days (average: 14 days). In patient 4, anastomotic leakage occurred 1 week after surgery, as observed by esophagogram. After enteral nutrition via a nasojejunal tube and conservative supportive treatment were performed, the anastomotic leakage healed after 2 weeks, as demonstrated by radiography. The other three patients had no peri-operative complications. Clinicopathological data for the four patients with ED after EA/TEF are shown in **Table 1**.

All patients were routinely followed up after surgery for 14–36 months. During the follow-up period, all patients were able to eat by mouth and had good growth and satisfactory weight gain, without coughing, pneumonia, or dysphagia. Additionally, esophagogram revealed no ED recurrence or anastomotic leakage.

Illustrative Cases

Patient 1 was a 6.6-month-old girl who was diagnosed with congenital EA type IIIa after birth. Five days after birth, the patient underwent thoracoscopic ligation of the fistula and end-to-end anastomosis of the esophageal segments. Esophagogram indicated leakage of esophageal anastomosis at 2 weeks after surgery, which healed after conservative treatment. At 2.5 months, the patient visited our outpatient clinic for choking and repeated pneumonia. Esophagogram revealed a 14.8 mm diverticulum at the right posterior edge of the esophagus. The symptoms were not significantly relieved by conservative treatment. The esophagus re-examination 6 months after birth showed that the long ED diameter increased to 25.5 mm, compared to its initial examination. Airway endoscopy and digestive endoscopy showed that the ED did not communicate with the trachea; chest CT was performed to exclude inflammatory consolidation of the lung. The patient underwent thoracoscopic esophageal diverticulectomy, and postoperative pathology revealed a pseudodiverticulum, which only contained mucosa and submucosa tissues without muscle tissue involvement. After the operation, the coughing and pneumonia symptoms disappeared, and the patient was gradually able to consume a normal diet. The patient was followed up for 23 months without symptoms.

Patient 2 was a 9.5-month-old girl diagnosed with congenital EA type IIIb and underwent thoracotomy ligation of the fistula and end-to-end anastomosis esophageal segments 5 days after birth. At 2 months, the patient had recurrent TEF. After conservative treatment and enteral nutrition for 2 months, she underwent thoracoscopic ligation of recurrent TEF 4 months after birth. In 6.2 months, the patient had dysphagia, and the esophagogram revealed esophageal stenosis and an ED at the upper edge of the esophageal stenosis. Then, she underwent endoscopic balloon dilatation three times, which was expanded to 10 mm. However, the patient still exhibited choking and repeated pneumonia. Esophagogram and endoscopy revealed that the ED increased from 15.7 mm to 22.1 mm. The patient underwent thoracoscopic esophageal diverticulectomy, and postoperative pathology revealed a true diverticulum, which contained a thickened muscle layer in the diverticula wall. After the operation, the symptoms of coughing and pneumonia

TABLE 1 | Clinicopathological features of patients with esophageal diverticulum after esophageal atresia/tracheoesophageal fistula surgery.

ID	Gender	Age of diagnosis (months)	Age of surgery (months)	Body Weight (kg)	Symptoms	Long diameter (mm)	Site	Complications after the initial surgery	Combined deformity	Operation time (h)	Tracheal intubation time (d)	Postoperative hospital stay	Postoperative complications	Postoperative pathology
1	Female	2.5	6.6	6.5	Coughing, recurrent pneumonia	25.5	T3-5	Anastomotic leakage	None	2	3	12	None	Pseudodiverticulum
2	Female	6.2	9.5	8.0	Dysphagia, Coughing, recurrent pneumonia	22.1	T4-5	Esophageal stricture	Scoliosis, vertebral deformities	1.5	1	10	None	True diverticulum
3	Female	6.8	13.1	9.5	Dysphagia, Coughing, recurrent pneumonia	24.6	T4-6	Anastomotic leakage, esophageal stricture	None	1.5	5	14	None	Pseudodiverticulum
4	Male	9.3	16.8	6.0	Dysphagia, Coughing, recurrent pneumonia	16.7	T4-5	Anastomotic leakage, esophageal stricture, recurrent TEF	Vertebral deformities	3.5	7	20	Anastomotic leakage, esophageal stricture	Pseudodiverticulum

ED, esophageal diverticulum; EA, esophageal atresia; TEF, tracheoesophageal fistula.

disappeared. The patient was followed up for 33 months without symptoms.

Patient 3 was a 13.1-month-old girl. Three days after birth, the patient underwent thoracotomy ligation of the fistula and end-to-end anastomosis of the esophageal segments due to congenital EA type IIIb. Anastomotic leakage occurred 2 weeks after surgery and healed after conservative treatment of 4 weeks. At 6.8 months of age, the patient exhibited repeated vomiting, choking, and pneumonia. Esophagogram showed gastroesophageal reflux and right-side ED at the T4–6 level (**Figure 2**). The 24-h pH test confirmed pathological reflux in the lower esophagus. At 8 months of age, she underwent laparoscopic fundoplication to improve gastroesophageal reflux. After the operation, coughing and repeated pneumonia symptoms were still observed, and endoscopic balloon dilatation of the esophageal stenosis was performed several times, gradually expanding to 12 mm. She still had repeated pneumonia and choking, and re-examination of esophagogram and endoscopy revealed that the ED increased from 17.1 mm to 24.6 mm. Thoracoscopic esophageal diverticulectomy was performed, and the pathological response showed no muscle layer in the diverticula wall, indicating the presence of pseudodiverticulum. After the operation, the patient's coughing symptoms improved, and she gradually returned to a normal diet. The patient was followed up for 36 months without symptoms.

Patient 4 was a 16.8-month-old boy with congenital EA type IIIb who underwent thoracotomy ligation of the fistula and end-to-end anastomosis of esophageal segments 3 days after birth. Postoperative esophageal anastomotic leakage occurred, and complication was alleviated after conservative treatment. Recurrent TEF was diagnosed 5 months after birth, and conservative treatment for pneumonia and enteral nutrition were performed. In 9.3 months, esophagogram and endoscopy revealed an ED on the right side of the esophagus, except for recurrent TEF and esophageal stenosis (**Figure 3**). Then, he underwent thoracoscopic ligation of recurrent TEF. However, he still had repeated pneumonia and choking after surgery. At 16 months after birth, esophagogram showed the ED increased from 13.0 mm to 16.7 mm and a novel recurrent TEF on the left side. Thoracoscopic ligation of the recurrent TEF and esophageal diverticulectomy were performed. Pathological examination showed no muscle layer in the diverticula wall, indicating pseudodiverticulum. One week after surgery, anastomotic leakage occurred by esophagogram, which healed spontaneously after conservative treatment for 1 week. Two months postoperatively, the patient underwent endoscopic balloon dilatation due to esophageal stenosis, which gradually expanded to 12 mm. He slowly returned to his normal diet after the operation and was followed up for 14 months without symptoms.

DISCUSSION

ED is an extremely rare complication of EA/TEF surgery. Myers et al. reported that among 498 patients with EA/TEF after surgery, the incidence of ED was only 0.2% (6). Taghavi et al. found that among 56 patients with H-type treated by surgery, the incidence of ED was 1.9% (5). Additionally, in a study evaluating the postoperative complications of 92 patients with EA/TEF, ED did not occur in any of the 92 patients after surgery (4). Among the 198 patients with EA/TEF at our institution, ED only occurred in four patients after surgery, with an incidence rate of 2.02%. This was consistent with the results of these previous studies, confirming that ED was a rare complication after EA/TEF surgery.

According to its pathogenesis, ED is divided into two types, i.e., pulsion diverticulum and traction diverticulum. Most ED cases are pulsion diverticulum, which is related to esophageal dysmotility, functional or mechanical obstruction, or weakness of the esophageal wall. The esophageal sphincter cannot relax normally, resulting in compression of the esophageal cavity and forcing the mucosa and submucosa to herniate through the esophageal muscles (pseudodiverticulum). Traction diverticulum is relatively rare. The inflammatory reaction around the esophagus causes scarring of the esophageal wall, and local traction of the esophageal wall leads to the formation of a diverticulum (true diverticulum). The primary pulsion diverticulum commonly occurs at the proximal and distal ends of the esophagus and includes Zenker diverticulum and epiphrenic diverticulum. In contrast, traction diverticulum, including thoracic ED, commonly occurs in the middle of the esophagus (2, 7, 8). In all four patients in our series, ED was considered thoracic ED; however, the pathogenesis of ED after EA/TEF surgery is different from that of the primary ED. Our four patients had various complications after the initial operation. For example, anastomotic leakage occurred in three patients after the initial surgery, and the pathological results of these three cases after diverticulectomy showed no muscle structures involved, suggestive of pseudodiverticulum. The formation mechanism in these cases may be related to continuous saliva and esophageal secretions through the anastomosis, resulting in persistent pleurisy and local inflammation around the esophagus and thereby causing the formation of cavities and local fibrosis. Moreover, the distal esophagus combined with stenosis resulted in increased pressure in the proximal esophagus, forcing the mucosa and submucosa to herniate via the anastomotic fistula to form the ED. The pathology results for patient 2 after diverticulectomy revealed the involvement of muscular structures, indicating true diverticulum. The patient did not experience anastomotic leakage after surgery; however, recurrent TEF occurred in the patient after 2 months. In the second surgery for recurrent TEF, the fistula was ligated close to the trachea, resulting in an excessively long esophageal fistula. Additionally, these features combined with anastomotic stricture of the esophagus led to increased pressure in the proximal esophageal cavity, and the stump of the esophageal fistula gradually expanded to form a diverticulum. Livaditis esophageal myotomy can lead to ED after EA/TEF surgery (9). None of the children in our study underwent Livaditis esophageal myotomy during the initial operation. The pathogenesis of ED after EA/TEF surgery was different from that of the primary ED and may be related to esophageal anastomosis leakage, anastomotic stricture or the long esophageal fistula stump, especially for patients with multiple

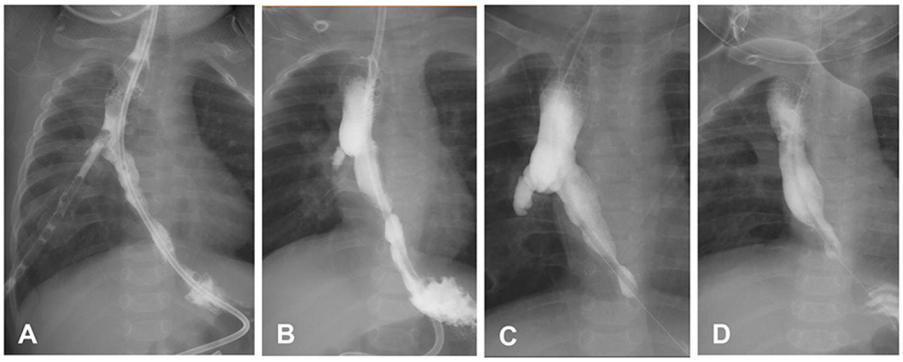

FIGURE 2 | Changes in the esophageal diverticulum (ED) of patient 3. **(A)** After esophageal atresia/tracheoesophageal fistula surgery, the contrast agent flowed into the chest drainage tube through the esophageal anastomosis leakage. **(B)** The thoracoscopic drainage tube was removed prematurely, and the ED appeared. **(C)** The ED was enlarged. **(D)** Two weeks after diverticulectomy, the esophagus was in good shape. In C and D, the patient underwent laparoscopic fundoplication, leading to postoperative distal esophageal stenosis.

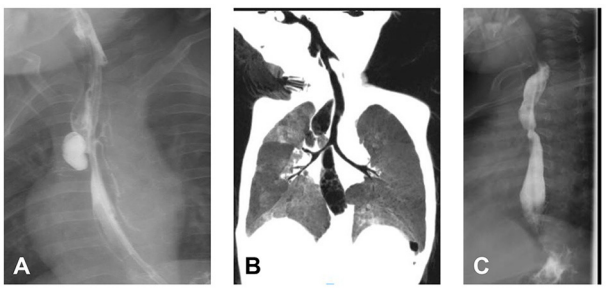

FIGURE 3 | The pre-operative and postoperative radiography of patient 4. **(A)** Esophagogram revealed esophageal diverticulum (ED) (on the right side of the esophagus) combined with recurrent tracheoesophageal fistula (on the left side of the esophagus). **(B)** ED on chest computed tomography. **(C)** Two weeks after diverticulectomy.

complications. For patients who had anastomosis leakage after surgery, early and aggressive endoscopic balloon dilatation for preventing anastomotic stricture might help in reducing the occurrence of ED. However, further studies are still needed to elucidate the detailed pathogenesis of this condition.

The common symptoms of thoracic ED in adults include dysphagia, gastroesophageal reflux, heartburn, aspiration pneumonia, and weight loss (10, 11). In our four patients, the main symptoms included recurrent pneumonia, dysphagia, coughing, and unsatisfactory weight gain. These symptoms were similar to the common symptoms of some complications after EA/TEF surgery, such as esophageal stenosis, gastroesophageal reflux, and recurrent TEF. Esophagogram is the preferred diagnostic method for ED; this approach can be used to confirm the diagnosis and evaluate the location and size of ED (12). Airway endoscopy, digestive endoscopy, and chest CT can be used to exclude other related diseases, such as recurrent TEF and inflammatory consolidation of the lung. Measurement of esophageal pressure is the gold standard for diagnosing esophageal dyskinesia. Studies have shown that more than 90% of ED patients may have abnormal esophageal motility; however, it is still unclear whether esophageal dyskinesia was the cause of ED or a symptom of ED (13). Some scholars have suggested that esophageal dyskinesia is always present in patients with ED, indicating that pressure measurement is not required (14). Gastroesophageal reflux is closely related to ED, and 24-h esophageal pH monitoring can confirm gastroesophageal reflux and guide surgical or drug treatment (12). All four patients underwent esophageal angiography to confirm the diagnosis of ED. All patients underwent airway endoscopy, digestive endoscopy, and chest CT, and recurrent TEF was diagnosed in patient 4. Moreover, 24-h esophageal pH monitoring was used to confirm the symptoms of gastroesophageal reflux in patient 3, which indicated pathological reflux, and laparoscopic fundoplication was performed. Esophagogram was a preferred diagnosis method for patients with ED after EA/TEF surgery. Moreover, airway endoscopy, digestive endoscopy, and chest CT should be performed to exclude surgical contraindications. Esophageal pH monitoring is a useful examination method for symptomatic patients. Comprehensive examination could contribute to the evaluation and provide direction for subsequent surgical approaches.

In adult thoracic ED, most surgeons agreed to surgical intervention in symptomatic patients; however, the treatment of patients with the mild or asymptomatic disease remains controversial (15–19). Altorki et al. reported that aspiration occurred in nine of 20 adult patients, and three experienced life-threatening complications (20). They strongly supported surgical intervention for all patients. Macke et al. summarized 15 years of experience in the treatment of thoracic ED in adults and concluded that surgical intervention should be carried out for patients with asymptomatic large diverticula or abnormal esophageal motility; additionally, asymptomatic patients, particularly those with a high risk of surgery, should be closely monitored (11). All four patients in this series had obvious clinical symptoms. Because infants and young

children are more prone to aspiration, coughing, and other symptoms, we recommend that active surgical intervention be performed for mild or even asymptomatic ED after EA/TEF. Notably, anastomotic stricture should be treated aggressively before esophageal diverticulectomy, which might be the cause of ED.

The surgical treatment of thoracic ED mainly included open surgical approaches and minimally invasive approaches. With advancements in minimally invasive techniques, the surgical linear cutter stapler has become widely used in pediatric gastrointestinal surgery (20–22). All four patients in this group underwent thoracoscopic esophageal diverticulectomy, and we identified four technical details related to the surgery. First, it was necessary to fully expose the neck of the diverticulum during the separation of the diverticula. The surgical linear cutter stapler must be inserted close to the esophagus to avoid leaving a residual diverticulum. Second, placing a gastric tube could help stabilize the esophagus and prevent esophageal cavity stricture. Third, the muscles or pleura around the staple line of the esophagus should be freed to reduce the incidence of anastomotic leakage. Finally, three of the four patients in this series had pseudodiverticulum, and the diverticula wall had no muscle tissue. The cutter stapler might be useful to cut the pseudodiverticulum but not hand-tied ligature. Additionally, using a cutter stapler could reduce the operation time and the incidence of postoperative anastomotic leakage. None of the patients in the study underwent transit thoracotomy. Anastomotic leakage and esophageal stricture occurred in one patient 1 week after surgery; this symptom was alleviated by conservative treatment and balloon dilatation. The other three patients had no peri-operative complications. During the follow-up period, none of the patients had any other complications. Thoracoscopic esophageal diverticulectomy proved to be a reliable and effective treatment method for ED after EA/TEF, but must be performed by surgeons experienced in open and minimally invasive esophageal surgery.

Currently, the use of routine or selective esophageal Heller's myotomy during diverticulectomy for ED in adults is controversial. Studies have reported that the incidence of esophageal dyskinesia in adults with ED is 45–100% (23–27). Simple mechanical obstruction or combined functional obstruction could lead to increased pressure in the esophageal cavity and the formation of the ED. Therefore, some surgeons tend to routinely perform Heller's myotomy, regardless of the presence or absence of distal esophageal dyskinesia (25). In contrast, other researchers have been more inclined to perform Heller surgery when distal esophageal dyskinesia is clearly diagnosed before surgery (18). Because the pathogenesis of ED after EA/TEF is different from that of adult ED, the main factor resulting in increased pressure in the esophageal cavity was esophageal stenosis, which could be eliminated by endoscopic balloon dilation. Therefore, we recommend that ED after EA/TEF surgery may not require routine Heller surgery. None of the four patients in this study underwent Heller surgery. During the follow-up period, none of the patients had shown symptoms such as distal esophageal stenosis or recurrence of ED. However, long-term follow-up is still needed to assess this issue.

However, the study also has several limitations. Due to the rarity of this complication, the number of patients is small, which is not suitable for statistical analysis. The possible risk factors for ED after EA/TEF still need to be confirmed by larger samples. Additionally, the study is a single-center retrospective research, and more clinical prospective studies are required to confirm our results.

In summary, ED is a rare complication after EA/TEF surgery and is a clear indication for diverticulectomy. Our results showed that thoracoscopic esophageal diverticulectomy was safe and effective for ED after EA/TEF surgery during mid-term follow-up. Further follow-up is needed to assess the reliability of these results. Additionally, surgical treatment is suggested to be performed by surgeons with extensive thoracoscopic experience.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Beijing Children's Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individuals, and minors' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZYo, WD, and HJ contributed to conception and design of the study. GY analyzed the data. HK and LJ processed the figures. ZYo and WD wrote the first draft of the manuscript. LS, WP, and ZYa wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Primary Posterior Tracheopexy in Esophageal Atresia Decreases Respiratory Tract Infections

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Background: Esophageal atresia (EA) is often accompanied by tracheomalacia (TM). TM can lead to severe respiratory complaints requiring invasive treatment. This study aims to evaluate if thoracoscopic primary posterior tracheopexy (PPT) can prevent the potential sequelae of TM in patients with EA.

Methods: A cohort study including all consecutive EA patients treated between 2014 and July 2019 at the Wilhelmina Children's Hospital was conducted. Two groups were distinguished: (group 1) all EA patients born between January 2014 and December 2016 and (group 2) all EA patients born between January 2017 and July 2019, after introduction of PPT. In the latter group, PPT was performed in EA patients with moderate (33–66%) or severe (67–100%) tracheomalacia, seen during preoperative bronchoscopy. Group differences were assessed using the Fisher's exact test for bivariate variables and the Mann–Whitney *U*-test for continuous variables.

Results: A total of 64 patients were included in this study (28 patients in group 1; 36 patients in group 2). In group 2, PPT was performed in 14 patients. Respiratory tract infections (RTIs) requiring antibiotics within the first year of life occurred significantly less in group 2 (61 vs. 25%, $p = 0.004$). Brief resolved unexplained events (BRUEs) seemed to diminish in group 2 compared to group 1 (39 vs. 19%, $p = 0.09$).

Conclusion: Thoracoscopic primary posterior tracheopexy decreases the number of respiratory tract infections in EA patients. The clinical impact of reducing RTIs combined with the minimal additional operating time and safety of PPT outweighs the risk of overtreatment.

Keywords: esophageal atresia, tracheomalacia, bronchoscopy, thoracoscopy, posterior tracheopexy, brief resolved unexplained event, respiratory tract infection

INTRODUCTION

In up to 87% of patients, esophageal atresia (EA) can be associated with some form of tracheomalacia (TM) (1). TM can be caused by flaccidity of the cartilaginous anterior rings, a floppy posterior membrane, or both and may lead to a dynamic collapse of the tracheal lumen (2, 3). This collapse of the trachea can result in a wide spectrum of symptoms and sequelae ranging from mild complaints, such as stridor or wheezing, to brief resolved unexplained events (BRUEs) (3). Furthermore, collapse of the trachea may lead to an ineffective cough and impaired clearance of secretions, increasing the risk of respiratory tract infections (4, 5). In severe TM, invasive treatment might be warranted (6, 7). Surgical treatment of preference depends on the type of TM and includes aortopexy to lift the aortic compression on the anterior flaccid cartilaginous rings (3, 8), or posterior tracheopexy of the floppy membrane to prevent posterior tracheal intrusion (9). In a previous study, we have introduced a new approach in which a posterior tracheopexy is performed during the thoracoscopic correction of EA. Results showed this approach to be feasible (10).

The aim of this study is to evaluate if thoracoscopic primary posterior tracheopexy (PPT) can prevent the potential respiratory sequelae of tracheomalacia in patients with EA and concurrent TM.

METHODS

Study Design and Participants

A cohort study including all consecutive EA patients between January 2014 and July 2019 was conducted at the University Medical Center Utrecht, Wilhelmina Children's Hospital. The variables of interest were collected prospectively at standardized time points for all children according to standard clinical practice. The comparative design was applied after data collection. Patients were excluded for follow-up if they had died before the age of 1 year. In January 2017 thoracoscopic PPT for moderate or severe TM was introduced in our hospital. Two patient subgroups were distinguished: (group 1) all EA patients born between January 2014 and December 2016 and (group 2) all EA patients born between January 2017 and July 2019, after the introduction of PPT. Data of patients that underwent thoracoscopic PPT were prospectively collected.

Surgical Procedure

Since 2014 almost all infants with EA underwent a rigid bronchoscopy prior to surgery to evaluate the presence of TM and to exclude a proximal fistula. Since 2017, a standardized scoring system for TM has been introduced (11). Patients with moderate to severe tracheomalacia were eligible for PPT. Tracheal obstruction, evaluated by bronchoscopy, was defined as collapse of the tracheal wall at three different levels, the upper third, middle third, and lower third of the trachea (11). TM was considered moderate when the tracheal lumen collapsed 33–66% and severe when 67–100%. The surgical procedure of thoracoscopic PPT during esophageal repair has been described previously (10). In short, during the procedure for thoracoscopic esophageal repair, the posterior tracheal membrane is fixed to the anterior spinal ligament with one to three non-absorbable sutures (**Figure 1**), prior to the anastomosis of the esophageal ends (**Figure 2**).

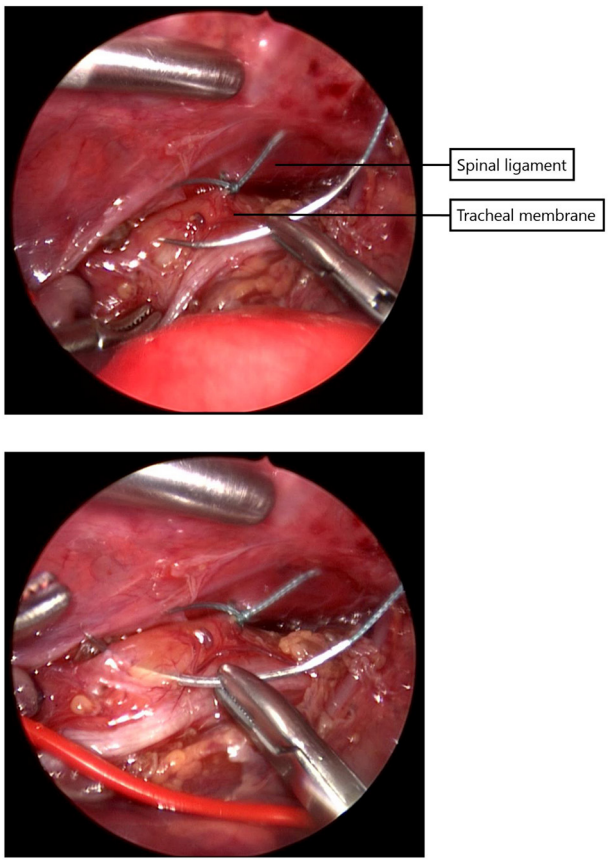

FIGURE 1 | The posterior tracheal membrane is fixed to the the anterior spinal ligament with one to three non-absorbable sutures.

Clinical Assessment

All baseline characteristics, including gender, type of EA and associated anomalies, and all surgical data including age at time of surgery, postoperative complications and length of hospital and NICU stay, were collected. Prospective data of patients that underwent PPT was obtained during standard EA follow-up in outpatient care at 4 weeks and 3, 6, 12 months of age.

Respiratory Outcome

Patients underwent standardized clinical assessment regarding respiratory symptoms. The primary outcome measures were respiratory symptoms, including respiratory tract infections (RTIs) requiring antibiotics within the first year of life and occurrence of BRUEs. Diagnosis of the RTIs was made by the pediatric pulmonologist. The pediatric pulmonologists based

Abbreviations: EA, esophageal atresia; TM, tracheomalacia; PPT, primary posterior tracheopexy; BRUE, brief resolved unexplained event; RTI, respiratory tract infection.

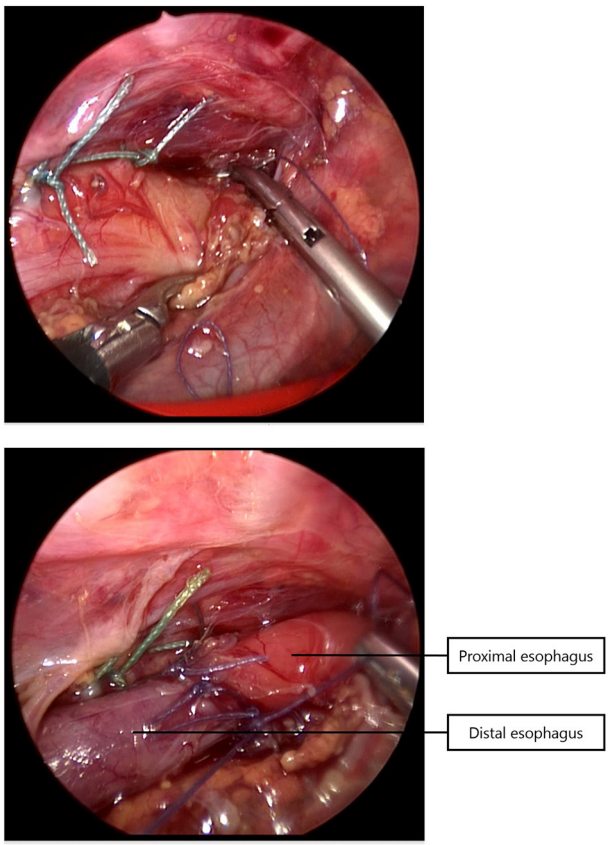

FIGURE 2 | After performing the tracheopexy, the proximal and distal esophagus are anastomosed.

TABLE 1 | Patient characteristics of group 1 and group 2.

Variable	Group 1 (2014–2016)	Group 2 (2017–2019)	*p*-value
	***n* = 28**	***n* = 36**	
Male	16 (57%)	24 (67%)	0.45
Gestational age (weeks)	39.2 (31.6–41.6)	37.3 (28.3–42.3)	0.08
Premature	7 (25%)	16 (44%)	0.12
Twin	3 (11%)	2 (6%)	0.65
Birthweight (g)	2,755 (1,585–4,170)	2,692 (1,050–3,950)	0.37
Apgar score			
1 min	8 (2–9)	9 (3–10)	0.17
5 min	9 (3–10)	9 (5–10)	0.48
Type EA			
A	3 (11%)	1 (3%)	0.38
B	1 (3.6%)	0	
C	23 (82%)	32 (89%)	
D	0	2 (5.6%)	
E	1 (3.6%)	1 (2.8%)	
Associated anomalies[#]			
Trisomy 21	2 (7%)	1 (3%)	0.57
VACTERL	6 (21%)	8 (22%)	1.0
Musculoskeletal	10 (36%)	15 (42%)	0.80
Urogenital	8 (29%)	5 (14%)	0.33
Cardiovascular	12 (43%)	15 (42%)	1.0
Gastrointestinal	4 (14%)	2 (6%)	0.40

EA, esophageal atresia.
All data are presented as median (range) or n (%).
[#]*Some patients had multiple anomalies.*

their decision on symptpoms and/or chest X-rays. Antibiotic treatment was prescribed by the pediatric pulmonologist. BRUE is defined as an event in which an infant younger than 1 year old presents with cyanosis, pallor, altered breathing, hypotonia or hypertonia and/or altered responsiveness (12).

Statistical Analysis

Continuous variables were presented as median and range and categorical data were presented as frequencies and percentage. To assess group differences for bivariate variables the Fisher's exact test was used. Group differences for continuous variables were assessed using the Mann-Whitney *U*-test. A $p < 0.05$ was considered significant. The analyses were performed with SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY).

Ethical Approval

This cohort study was submitted to the UMCU Ethics Committee. No ethical approval was required according to the Medical Research Involving Human Subject Act. The study was carried out in accordance with the Declaration of Helsinki.

RESULTS

In total, 67 consecutive EA patients were admitted at the Wilhelmina Children's Hospital between January 2014 and July 2019. Three patients that died within the first weeks after birth were excluded from further analysis. One patient died before esophageal repair due to severe prematurity with pulmonary bleeding. Two patients died after esophageal repair due to causes unrelated to surgery (cardiac anomalies and cerebral abscesses). The 64 remaining patients were all evaluated in our outpatient clinic at 4 weeks and 3, 6, 12 months. The patients were divided into two groups: the first group, before the introduction of PPT, consisted of 28 consecutive patients admitted between 2014 and 2016 (group 1). The second group, after the introduction of PPT, consisted of 36 patients admitted between 2017 and 2019 (group 2). Patient characteristics were comparable between the two groups, as shown in **Table 1**.

In group 2, a PPT was performed in 14 patients (39%). Of these 14 patients, 12 patients (86%) had EA Gross type C, and 2 patients (14%) type D. Patient characteristics are presented in **Table 2**. There were no relevant significant differences between the no-PPT patients and the PPT patients within group 2.

TABLE 2 | Patient characteristics of group 2 (2017–2019).

Variable	No-PPT, $n = 22$	PPT, $n = 14$	*p*-value
Male	14 (64%)	10 (71%)	0.73
Gestational age (weeks)	36.7 (29.1–42.3)	38.4 (28.3–41.4)	0.35
Premature	12 (55%)	4 (29%)	0.18
Twin	2 (9%)	0 (0%)	0.51
Birthweight (g)	2,249 (1,220–3,950)	3,008 (1,050–3,550)	0.22
Apgar score			
1 min	9 (4–10)	8.5 (3–9)	0.84
5 min	9 (7–10)	9 (5–10)	0.74
Type EA			
A	1 (4.5%)	0	0.20
C	20 (91%)	12 (86%)	
D	0	2 (14%)	
E	1 (4.5%)	0	
Associated anomalies[#]			
Trisomy 21	1 (4.5%)	0	1.0
VACTERL	3 (14%)	5 (36%)	0.22
Musculoskeletal	10 (45.5%)	5 (36%)	0.73
Urogenital	0	5 (36%)	0.005*
Cardiovascular	9 (41%)	6 (43%)	1.0
Gastrointestinal	1 (4.5%)	1 (7%)	1.0

PPT, primary posterior tracheopexy; EA, esophageal atresia.
All data are presented as median (range) or n (%).
[#]Some patients had multiple anomalies.
**Indicating statistical significance.*

TABLE 3A | Surgical data of group 1 and group 2.

Variable (median, range)	Group 1 (2014–2016) $n = 28$	Group 2 (2017–2019) $n = 36$	*p*–value
Age at EA surgery (d)	3 (0–58)	3.5 (1–54)	0.17
NICU time (d)	9 (3–126)	8 (3–81)	0.91
LOS (d)	20 (10–159)	25.5 (10–178)	0.14
Leakage	3 (11%)	6 (17%)	0.72

EA, esophageal atresia; LOS, length of hospital stay.

TABLE 3B | Surgical data of group 2 (2017–2019).

Variable (median, range)	No-PPT, $n = 22$	PPT, $n = 14$	*p*-value
Age at EA surgery (d)	3.5 (1–54)	3.5 (1–35)	0.28
NICU time (d)	8 (3–81)	11 (3–59)	0.83
LOS (d)	24 (13–178)	28 (12–93)	0.81
Leakage	3 (14%)	3 (21%)	0.66

PPT, primary posterior tracheopexy; EA, esophageal atresia; LOS, length of hospital stay.

TABLE 4 | Tracheomalacia evaluated during bronchoscopy before EA repair in group 2.

Variable	Group 2 (2017–2019) $n = 36$
No TM	5 (14%)
TM mild	15 (42%)
TM moderate/severe	13 (36%)
No TM evaluation possible	3 (8%)

EA, esophageal atresia; TM, tracheomalacia.

TABLE 5 | Respiratory outcome in group 1 and group 2.

Variable	Group 1 (2014–2016) $n = 28$	Group 2 (2017–2019) $n = 36$	*p*-value
BRUE	11 (39%)	7 (19%)	0.09
RTI <1 year	17 (61%)	9 (25%)	0.004*

BRUE, brief resolved unexplained event; RTI, respiratory tract infection requiring antibiotics.
**Indicating statistical significance.*

Surgical Outcome

Overall analyses of group 1 and group 2 showed no significant differences in age at EA surgery, postoperative NICU time, length of hospital stay or anastomotic leakage between the two groups (**Table 3A**). In group 2, moderate to severe tracheal collapse was diagnosed in 13 patients (**Table 4**). In two patients with mild TM (20% tracheal collapse) on bronchoscopy, increased flaccidity of the posterior tracheal membrane was seen during thoracoscopy after ligation and transection of the distal tracheoesophageal fistula. Therefore, a PPT was also performed in these two patients. The middle and distal third of the trachea were most often affected with a median tracheal collapse of 50% (range 20–90%). Thoracoscopic PPT was uncomplicated and successful in all patients with a median of 2 sutures (range 1–3). Median time per suture was 6 min (range 4–12 min). Anastomotic leakage occurred in 21% and could be treated conservatively in all patients. There were no significant differences in surgical outcome between patients with or without PPT in group 2 (**Table 3B**).

Patients that underwent PPT were operated at a median age of 3.5 days (range 1–35 days). Surgery was postponed due to respiratory instability in one patient of group 2, a premature neonate of 1,050 g (28.7 weeks). One patient of group 2 was operated in an emergency setting because of a gastric perforation and pneumothorax that occurred during CPR shortly after birth.

Overall Respiratory Outcome

In group 1, 11 patients (39%) experienced at least one BRUE, compared to seven patients (19%) in group 2 ($p = 0.09$). RTIs requiring antibiotics within the first year of life occurred

TABLE 6 | Respiratory outcome in group 2 (2017–2019).

Variable	No-PPT, $n = 22$	PPT, $n = 14$	p-value
BRUE	6 (27%)	1 (7%)	0.21
RTI <1 year	6 (27%)	3 (21%)	1.0

PPT, primary posterior tracheopexy; BRUE, brief resolved unexplained event; RTI, respiratory tract infection requiring antibiotics.

significantly less often after introduction of PPT (group 1 vs. group 2; 61 vs. 25%, $p = 0.004$; **Table 5**).

In group 1, three patients underwent an aortopexy at the median age of 12 days (range 12–29). In two of these three patients, severe TM was evaluated preoperatively with bronchoscopy. In one patient after aortopexy, TM persisted and consequently a posterior tracheopexy was performed.

In group 2, redo tracheopexy was not warranted in any of the PPT-patients. Bronchoscopy was incomplete in three patients of group 2 and TM could not be evaluated, because spontaneous breathing during bronchoscopy was impaired due to ventilation problems. Of these three patients, one had to undergo a secondary posterior tracheopexy and another patient was treated by aortopexy.

Four patients, two in each group, all with multiple comorbidities, needed a tracheostomy. One patient with a tracheostomy and Down's syndrome in group 1, died during follow-up due to accidental decannulation.

Respiratory Outcome After PPT Introduction

Subgroup analysis of group 2 showed occurrence of BRUEs in one patient (7%) in the PPT-patients group vs. 6 patients (27%) in the no-PPT patients group (**Table 6**). This difference, however, was non-significant. The one patient with BRUEs after PPT had two tracheoesophageal fistulas (the distal fistula was located in the carina, and the proximal fistula in the middle part of the trachea) and a severe TM in the middle part of the trachea on preoperative bronchoscopy. Therefore, this patient underwent selective PPT only at the level of this middle part of the trachea. Postoperative bronchoscopy in this patient with multiple comorbidities, including a subglottic stenosis and retrognathia, revealed a severe TM in the distal part of the trachea.

RTIs requiring antibiotics within the first year were seen in 21% in the PPT-patients vs. 27% in the no-PPT patients group. One patient in the PPT-patient group experienced postoperative respiratory distress caused by a suture granuloma. After removal of the granuloma by bronchoscopy, no further respiratory problems occurred.

DISCUSSION

This is the first prospective study to evaluate respiratory outcome after thoracoscopic primary posterior tracheopexy in EA patients with tracheomalacia.

This novel PPT technique decreases the number of respiratory tract infections (RTIs) in EA patients with moderate or severe TM. The number of BRUEs also seemed to decrease after introduction of PPT, although this was not statistically significant. Furthermore, the PPT-procedure takes only short additional operative time and there were no differences in hospital length of stay, NICU stay and postoperative leakage between the PPT-group and the no-PPT group.

Respiratory morbidity in EA is very common during early childhood (13). EA patients often suffer from RTIs during the first year of life (14–17). This is in line with our findings, showing 61% of patients with RTIs within the first year of life before introduction of PPT. After the introduction of PPT, RTIs requiring antibiotics were significantly decreased in both EA patients that underwent a PPT, as well as the entire EA cohort (EA patients with and without PPT between 2017 and 2019). Therefore, selecting EA patients with moderate to severe TM for PPT improves the respiratory outcome of EA patients as a whole. In a previous study on PPT (18), a decrease in RTIs was not seen. However, results are difficult to compare, since this study compared preoperative data to postoperative data within a group of 18 patients and follow-up duration was shorter (5 months).

Another possibly life-threatening aspect of respiratory morbidity is posed by BRUEs. Although the decrease in number of BRUEs after the introduction of PPT from 39 to 19% seemed evident, it was not statistically significant. However, this may be explained by the small number of patients. In the study by Shieh et al. (18), a decrease in BRUEs was shown ($p = 0.049$). However, in this study, almost 30% of patients were re-operated for persistent collapse of the trachea.

In a previous study (10), we showed thoracoscopic PPT to be feasible and safe, with favorable short-term outcome. During the longer follow-up in this study, one patient experienced respiratory problems, caused by a suture granuloma. After bronchoscopic removal of the granuloma, no more respiratory problems had occurred. Flexible bronchoscopic visualization during posterior tracheopexy may prevent this type of complication from occurring. Therefore, this has now been implemented as routine procedure during PPT in our center. Moreover, this may also optimize positioning of the sutures in the tracheal wall.

In three patients, TM could not be evaluated due to ventilation difficulties during bronchoscopy. In these patients, PPT was not performed since the extent of TM was unknown. In this study, in two out of three patients, a secondary surgical intervention for severe TM was warranted. In these patients posterior tracheopexy was challenging because of multiple adhesions and risk of damaging the esophageal anastomosis. Therefore, median duration of secondary tracheopexy takes significantly longer than PPT (hours vs. minutes) and can be associated with complications (3, 10).

Attention for respiratory morbidity in EA patients, and especially for TM, has raised over the past few years (1, 19, 20). Therefore, routine preoperative rigid bronchoscopy is performed in all EA patients in the University Medical Center Utrecht, Wilhelmina Children's Hospital since 2015. The introduction of a standardized scoring system for TM in 2017 (11) by the dedicated

congenital esophageal and airway team has led to increased awareness and improved recordings at our center.

A limitation of this study was that the rigid bronchoscopy was not repeated after PPT. In order to evaluate the effect of PPT, collapse of the trachea should be compared by rigid bronchoscopy before and after PPT. This would, however, require a second anesthesia for rigid bronchoscopy since spontaneous breathing is not possible directly after thoracoscopic EA repair and PPT. Therefore, our congenital esophageal and airway team has chosen not to evaluate the trachea by means of a second invasive procedure.

Although the data of the no-PPT patients was assessed retrospectively, the variables of interest were collected prospectively at standardized moments for all patients. Standardized questionnaires were not used, however, structured interviews regarding gastrointestinal and respiratory symptoms were conducted in every patient at our Congenital Esophageal and Airway outpatient clinic.

Another limitation is that no standardized scoring system was used during preoperative bronchoscopy in group 1. However, the baseline characteristics were similar within the two groups and therefore we expect that there are no significant differences on severity of tracheomalacia between the two groups.

Preferably, a prospective trial in EA patients with moderate or severe TM randomizing for PPT or no-PPT is needed to provide the best level of evidence. This comparative study shows the potential benefits of primary posterior tracheopexy in EA patients with concurrent moderate to severe tracheomalacia with a low complication rate.

CONCLUSIONS

In conclusion, this study shows that thoracoscopic primary posterior tracheopexy during esophageal atresia repair can significantly decrease respiratory tract infections that require antibiotics during the first year of life. The clinical impact of reducing respiratory tract infections combined with the relatively minimal additional operating time and safety of PPT may outweigh the risk of overtreatment. This, however, should be evaluated in an international, multicenter randomized controlled trial comparing PPT to no-PPT in neonates with EA.

Naturally, this advanced technique should only be performed in centers with a team of experienced pediatric upper GI- and airway surgeons, otolaryngologists, pulmonologists and anesthesiologists.

DATA AVAILABILITY STATEMENT

Requests to access these datasets should be directed to m.y.a.lindeboom@umcutrecht.nl.

AUTHOR CONTRIBUTIONS

ESTS conceptualized and designed the study, collected the data, carried out the initial analysis, drafted the initial manuscript, and reviewed and revised the manuscript. ML conceptualized and designed the study, contributed to the writing, supervised the data collection and the progress, and reviewed and revised the manuscript. ST and DZ provided input to the study, supervised the data collection and the progress, and reviewed and revised the manuscript. JV, AB, SC, and HA reviewed the study design, contributed to the interpretation of data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be 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.

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The Role of Video-Assisted Thoracoscopic Surgery in Pediatric Oncology: Single-Center Experience and Review of the Literature

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Aim: Video-assisted thoracoscopic surgery (VATS) has been widely used in the last decades. Nevertheless, the pros and cons of thoracoscopy vs. open surgery in pediatric oncology are still under debate. In literature, VATS has been applied for both diagnostic and ablative surgery to treat neurogenic tumors, thymic neoplasms, lung tumors and metastases, germ cell tumors, lymphoproliferative diseases, and other rare tumors. Recent reviews described excellent outcomes in pediatric oncology as well as in the treatment of adult lung cancer, with a significantly higher rate of mortality and complication in thoracotomy compared to VATS. We reviewed our experience on thoracoscopy in pediatric malignancy and compared it to the literature.

Materials and Methods: This was a retrospective cohort-study of pediatric oncological patients who underwent VATS at our institution from 2007 to 2020, and a review of the recent literature on the topic.

Results: A total of 43 procedures were performed on 38 oncological patients (18 males, 20 females). Median age was years 7.72 (0.35–18.6). Diagnosis: 10 neurogenic tumors, nine hematological diseases, five metastases, four lypoblastomas, three thymic pathologies, three germ cell tumors, two pleuropneumoblastomas, two myofibroblastic tumors, one myoepithelial carcinoma, one liposarcoma, and three suspected oncological mass. In three cases, a 3D model was elaborated to better plan the surgical approach. Diagnostic biopsies were 22 (51.1%), and ablative surgeries, 21 (48.9%). One neurogenic tumor was resected with the Da Vinci Robot. Median operative time was 120 min (30–420). A drain was left in place in 20 (46.5%) for a median of 4 days. Median length of hospitalization was 5 days (1–18). One case (2.3%) was converted (intraoperative bleeding). There were three post-operative complications (7.0%): one pneumonia, one pleural effusion, and one diaphragmatic paralysis (need for plication). Results were compared to recent literature, and morbidity and conversion rate were comparable to reviewed publications.

Conclusion: VATS represents a valuable tool for diagnostic and therapeutic procedures in pediatric oncology. Nonetheless, it is a challenging technique that should be performed by expert surgeons on oncological and mini-invasive surgery. Three-dimensional

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reconstruction can optimize the pre-operative planning and guarantee a safer and more targeted treatment. Finally, the advent of robotics-assisted surgery represents a new challenge that may further implement the advantages of VATS.

Keywords: thoracoscopy, pediatrics, oncology, mini-invasive surgery, robotic-assisted thoracoscopic surgery

INTRODUCTION

Minimally invasive surgery (MIS), including thoracoscopy, has been widely applied in the last few decades and has now become the gold standard approach for a variety of procedures for both adults and children (1–3).

The advantages of MIS compared to the open approach are well-known, as it reduces tissue trauma, decreases post-operative pain, shortens hospital stay, and guarantees better cosmetic and long-term functional results (4, 5). Moreover, among of the most important benefits of thoracoscopy are the virtually non-existing musculoskeletal complications such as chest wall deformities, rib fusion, shoulder girdle weakness, and scoliosis, which can occur in up of 30% of pediatric patients undergoing thoracotomy (6, 7).

Nevertheless, video-assisted thoracoscopic surgery (VATS) still represents a challenge due to the limitation of working space, the smaller body size of children, reduced tactile feedback, and the lack of three-dimensional vision.

As far as it concerns pediatric oncology, in the last decades, many reports and experiences have been published on the use of thoracoscopy to diagnose and resect intrathoracic neoplasms. Nonetheless, the role of VATS is still considered a developing field and no consensus exists regarding the details of its application. Specific limitations are an even lower exposure in pediatric oncological cases compared to general thoracoscopic pathologies and the inability to perform digital palpation.

In the last years, robotics has been applied to perform a wide variety of procedures, including thoracic surgery (8). Nonetheless, very few reports describe the use of robotics in pediatric oncological thoracic surgery and its use is not yet validated.

The aim of this study is to review our experience in VATS and robotics-assisted thoracoscopy in pediatric malignancy and to compare it to the most recent literature.

MATERIALS AND METHODS

We performed a retrospective review of all pediatric oncological patients who underwent video-assisted thoracoscopic surgery (VATS) and robotics-assisted thoracoscopic surgery (RATS) at our Institution from 2007 to 2020.

Patients over 20 years old and/or with thoracic pathologies treated with thoracotomy or endoscopic procedures were excluded.

We analyzed demographic data, including age at surgery, sex, pathology, and possible comorbidities; operation time (OT); length of hospital stays (LHS); perioperative complications; and post-operative outcomes. All complications were classified according to the Clavien–Dindo classification and graded from I to V. If present, length of chest drain aspiration was evaluated.

A specific search was performed in scientific database (PUBMED, MEDLINE, and EMBASE) to compare our experience with the most recent literature on the field. We selected articles reporting thoracoscopy in oncological pediatric patients between 2014 and March 2021 using the following key-words: (pediatric) or (children) and (thoracoscopy) or (VATS) and (oncology) or (tumor).

Inclusion criteria were:

- Articles published between January 2014 and March 2021
- Articles written in English
- Articles focusing on VATS in pediatric oncology
- Median/mean age <18 years old
- Case series with more than 10 patients
- Articles where data concerning demographics, surgical indications, complication rate, and conversion rate were clearly deductible

All data were elaborated using the statistical software "R", version 3.4.1.

Descriptive statistics was used to present findings, and quantitative variables were expressed as median (range) to express our data. Data elaborated from the literature review were expressed as median (range) or mean ± standard deviations depending on the reference found in the original articles.

Surgical Methods

Under general anesthesia, lung collapse has been achieved by single-lung ventilation. We routinely used a double lumen endotracheal tube in adolescent patients, mainly for ablative procedures. In small children (more than 6 months of age), we adopted a standard endotracheal intubation associated to the use of an endobronchial blocker. Low-pressure CO_2 insufflation (4–5 mmHg; flow 0.5 L/min) was employed in infants <6 months or when a quick biopsy of anterior mediastinal tumors was required. NIRS and BIS brain-monitoring were applied according to the age of the patients.

Patients were placed in lateral decubitus, with an angle ranging from 60 and 90° to 120°, depending on the mass localization.

A 10-mm one-trocar operative optic was employed for biopsy in three cases (one germ cell tumor, one pleuropneumoblastoma, and one myofibroblastic inflammatory tumor).

A three-trocar technique was adopted in most of the remaining cases, positioned according to the characteristics of the lesion. The optic (5 or 10 mm) was placed in the typical mid-axillary position under the shoulder angle, whereas the operative trocars were placed in a triangulation fashion anteriorly or posteriorly depending on the site of the mass.

In small children, a 3-mm operative trocar technique with 5-mm optic was carried out to perform biopsies, whereas in ablative surgery, one 5-mm operative trocar was reserved for Ligasure® or other vessel sealers. In recent cases, a 3-mm vessel sealer has been used, allowing a 3-mm operative VATS also for ablative procedures.

Pulmonary resection was safely performed with staplers (5 or 12 mm), which required an additional trocar. Specimens were retrieved using a 5 mm Endobag.

Regarding the use of chest drain, we tried to avoid drainage placement in diagnostic biopsies, except in case of complications such as intraoperative bleeding. A drain was normally applied at the end of any ablative surgery.

When possible, an early extubation of the patients was made a few hours after the VATS procedure.

About RATS, we performed one procedure using the Da-Vinci SI® Robot for a mass located on the supero-posterior mediastinum. Optic trocar was positioned in the sixth intercostal space on the midaxillary line. Operative trocars were positioned 8 cm away from the optic, in the fifth intercostal space on the anterior axillary line, and in the seventh intercostal space on the paravertebral line, respectively. Finally, a 5-mm auxiliary trocar was placed in the fourth intercostal space on the anterior axillary line.

RESULTS

A total of 43 procedures were performed on 38 oncological patients (18 males, 20 females). Median age was 7.72 (0.35–18.6). Patients were grouped according to diagnosis, and we observed high prevalence of neurogenic tumors and hematologic diseases, as shown in **Table 1**.

We performed diagnostic biopsies in 22 cases (51.1%), compared to 21 cases of ablative surgeries (48.9%); 42 out of 43 procedures were completed by VATS technique (97.7%); only one patient required an open conversion (2.3%).

The procedures were carried out by single-lung ventilation using a double-lumen endotracheal tube in 14 adolescent patients, and standard endotracheal intubation associated to the use of an endobronchial blocker was adopted in 16 cases. In the remaining 13 cases, lung collapse was obtained with low-pressure CO_2 insufflation.

One patient with growing ganglioneuroblastoma intermixed of the supero-posterior mediastinum in a 7-years-old girl with Horner's syndrome and positive image-defined risk factor (IDRF) (symptomatic encased subclavian vessels) was operated with the Da-Vinci SI® Robot-assisted thoracoscopic surgery. The robotic approach was chosen to achieve a safer and more precise dissection.

In the whole series, median OT was 120 min (30–420): 90 for diagnostic biopsies, 190 for ablative surgery.

Overall, a thoracic drain was left in place in 20 cases, for a median length of 4 days.

Only three diagnostic procedures required chest drainage due to intraoperative bleeding (one germ cell tumor), pneumothorax (one pleuropneumoblastoma), and pleural effusion (one myofibroblastic inflammatory tumor). As for ablative surgeries, a chest tube was positioned in 17 out of 21 procedures.

Median LHS was 5 days (1–18).

In two cases, we observed intraoperative bleeding (4.7%): one biopsy of a germ cell tumor managed thoracoscopically and one lung resection for nephroblastoma metastasis which required conversion to open surgery. The conversion rate to open surgery was 2.3% in the whole series.

In our series, we observed three post-operative complications (7.0%): one pneumonia (Clavien Dindo: grade II) 2 weeks after biopsy for a germ cell tumor; one pleural effusion a week after resection of a posterior mediastinal ganglioneuroma, which required a re-insertion of a thoracic drain for a further 7 days (IIIb); and one persistent right diaphragmatic paralysis after the excision of a giant cystic lymphangioma, treated with a laparoscopic diaphragmatic plication (IVa) 1 year later, which required intensive care assistance.

No tumor upstaging or trocar site recurrences occurred.

An advanced 3D virtual reconstruction and printing technology was recently applied in three complex cases (multiple immature teratoma metastases, multiple cystic lesions after pleuro-pneumoblastoma excision, vessel encasement in IDRF-positive ganglioneuroblastoma intermixed).

A review of the most recent literature on the topic was performed. From a total of 229 articles, seven were included in the review according to the inclusion criteria (**Table 2**) (9–15).

All papers were retrospective reviews and analyzed VATS to perform either tumor biopsy, ablative surgery, or both. A total of 423 children were included in the review, with a median age of 8.8 years. Among pulmonary lesions, metastases resulted as the most common indication for surgery. On the other hand, in case of a mediastinal lesion, neurogenic tumor was the most represented group. Conversion rate ranged from 0 to 15.1%, most commonly due to intraoperative bleeding or difficult dissection of the mass due to strong adhesions. Complications occurred in 2.1–20% of cases, pneumothorax being the most common post-operative one. No articles reported port-site recurrences, intraoperative tumor rupture, or tumor upstaging. Average LHS ranged from 2 to 10 days.

DISCUSSION

VATS in pediatric oncological surgery represents a great surgical achievement but still faces many challenges. Alongside the limitations of the technique, there are no guidelines on the details of the use of VATS or its contraindications. However, its application is expanding, and the experience reported in literature is growing.

Our study presents a large cohort of oncological patients undergoing VATS and proves the feasibility and effectiveness of the use of MIS in pediatric oncology; 97.7% of cases in our series were successfully treated by thoracoscopy.

As far as it concerns the use of VATS for diagnostic procedures, MIS has been effectively used to perform mediastinal mass biopsies as well as pulmonary masses (10, 13, 16–18). Reported advantages of thoracoscopy are the possibility

TABLE 1 | Summarized data of all oncological patients undergoing VATS (in chronological order).

ID*	Sex	Year	Age (y)	Pre-op Imaging	Diagnosis	Localization	Side	Intervention	Operative Time (min)	Peri-op compli-cations	Conversion	Drain (days)	LHS (days)	Post-op complications	Type of complication (Clavien Dindo Classification)
JM	M	2007	14.00	TC	Germ cell tumor	Complete invasion of all hemithorax	R	Biopsy (1 trocar)	30	No	No	No	2	No	
VG	M	2007	14.00	TC	T-cell lymphoma	Anterior mediastinum	L	Biopsy	60	No	No	No	3	No	
BL	F	2008	3.00	TC	Germ cell tumor	Complete invasion of all hemithorax	L	Biopsy	90	Yes (bleeding)	No	Yes (4)	7	No	
GD	M	2009	1.00	TC	Pleuropulmonary blastoma	Superior and medium lobe	R	Biopsy (1 trocar)	60	No	No	Yes (3)	4	No	
AL	F	2010	8.07	TC	Suspicion of renal carcinoma metastasis (not confirmed at histology)	Inferior lobe	L	Biopsy	105	No	No	No	14	No	
BA	M	2010	3.94	TC	Nephroblastoma metastasis	Inferior lobe	L	Mass excision (atypical pulmonary excision)	155	No	No	No	2	No	
ML (1)	M	2010	18.16	TC	Casteman's disease	Anterior mediastinum	R	Biopsy	75	No	No	No	1	No	
PC	F	2010	4.79	TC	Ganglioneuroma metastasis	Costophrenic recess	L	Mass excision	180	No	No	No	3	No	
ML (2)	M	2011	18,65	TC	Casteman's disease	Anterior mediastinum	R	Mass excision	330	No	No	No	2	No	
CA	F	2012	0.50	TC MRI	Neuroblastoma	Superior mediastinum	L	Biopsy	90	No	No	No	3	No	
CS	F	2010	14.11	TC	Diffuse large B-cell lymphoma	Antero-Superior mediastinum	R	Biopsy	80	No	No	No	–**	No	
HL	M	2012	16.53	TC	Neuroblastoma	Posterior mediastinum	R	Biopsy	60	No	No	No	3	No	
DM	M	2012	11.04	TC	Precursor T-cell lymphoblastic lymphoma	Retrosternal region	R	Biopsy	150	No	No	No	–**	No	
PG	M	2012	0.35	TC	Cystic lymphangioma	Superior mediastinum	R	Mass excision	165	No	No	Yes (4)	2	Yes	Diaphragmatic paralysis, need for laparoscopic diaphragmatic plication (IVa) 1 year later
BL	M	2014	6.00	TC	Classical Hodgkin's lymphoma	Anterior mediastinum	R	Biopsy	70	No	No	No	3	No	

(Continued)

TABLE 1 | Continued

ID*	Sex	Year	Age (y)	Pre-op Imaging	Diagnosis	Localization	Side	Intervention	Operative Time (min)	Peri-op compli-cations	Conversion	Drain (days)	LHS (days)	Post-op complications	Type of complication (Clavien Dindo Classification)
BR	F	2014	10.00	MRI	Ganglioneuroblastoma	Posterior mediastinum	L	Mass excision	120	No	No	Yes (3)	5	No	
SR	F	2019	1.25	MRI	Lipoblastoma (recidive)	Lateral chest wall, medullar invasion	R	Mass excision	240	No	No	Yes (7)	–**	No	
FE (1)	F	2014	1.19	TC	Neuroblastoma	Antero-Superior mediastinum	R	Biopsy	180	No	No	No	5	No	
FE (2)	F	2014	1.84	TC MRI	Neuroblastoma	Antero-superior mediastinum	R	Biopsy	90	No	No	No	2	No	
GD	M	2014	13.61	TC	Osteosarcoma metastasis	Inferior lobe	L	Mass excision	90	No	No	No	2	No	
PI	F	2014	10.00	TC MRI	Ganglioneuroblastoma	Posterior mediastinum	L	Mass excision	120	No	No	Yes (3)	18	Yes	Pleural effusion after drain removal, need for thoracic drain re-insertion for 7 days (IIIb)
RG	F	2014	11.96	TC MRI	Myofibroblastic inflammatory tumor	Pulmonary hilum	R	Biopsy	250	No	No	Yes (4)	7	No	
VA	M	2014	16.13	TC	Germ cell tumor	Costophrenic recess	R	Biopsy	115	No	No	No	11	Yes	Post-op pneumonia (II)
AA (1)	F	2015	7.67	TC	Suspicion of neoplastic mass (not confirmed at histology)	Middle mediastinum	R	Biopsy	95	No	No	No	5	No	
AA (2)	F	2015	7.72	TC	Suspicion of neoplastic mass (not confirmed at histology)	Middle mediastinum	R	Biopsy	105	No	No	No	2	No	
AA (3)	F	2015	8.18	TC	Suspicion of neoplastic mass (not confirmed at histology)	Middle mediastinum	R	Biopsy + Culture test	110	No	No	No	3	No	
LAn	M	2015	15.77	TC	Classical Hodgkin's lymphoma	Costophrenic recess	L	Biopsy	160	No	No	No	2	No	
PB	M	2015	5.44	TC	Nephroblastoma metastasis	Superior lobe	R	Mass excision (atypical pulmonary excision)	350	Yes (bleeding)	Yes	Yes (4)	7	No	
RA	F	2015	10.00	MRI	Thymic teratoma	Anterior mediastinum	L	Mass excision (thymectomy)	200	No	No	Yes (5)	7	No	
ZS	M	2015	7.00	MRI	Thymic teratoma	Anterior mediastinum	R	Mass excision (thymectomy)	195	No	No	Yes (4)	6	No	
TM	F	2016	11.00	MRI	Thymoma	Anterior mediastinum	R	Mass excision (thymectomy)	220	No	No	Yes (5)	7	No	

(Continued)

TABLE 1 | Continued

ID*	Sex	Year	Age (y)	Pre-op Imaging	Diagnosis	Localization	Side	Intervention	Operative Time (min)	Peri-op compli-cations	Conversion	Drain (days)	LHS (days)	Post-op complications	Type of complication (Clavien Dindo Classification)
TL	F	2017	16.47	TC MRI	Pleomorphic liposarcoma	Costophrenic recess	R	Biopsy	110	No	No	No	3	No	
BB	F	2018	7.00	TC MRI	Neuroblastoma	Posterior mediastinum	L	Mass excision	190	No	No	Yes (3)	5	No	
BF	M	2018	12.00	MRI	Lipoblastoma	Lateral chest wall	R	Mass excision	180	No	No	Yes (5)	7	No	
EZ	F	2018	6.00	TC MRI	Myofibroblastic inflammatory tumor	Superior and medium lobe, trachea and heart invasion	R	Biopsy (1 trocar)	60	No	No	No	3	No	
LAr	M	2018	2.00	TC MRI	Neuroblastoma	Posterior mediastinum	L	Mass excision	119	No	No	Yes (4)	6	No	
LM	M	2018	7.00	TC MRI	Cystic lesions after pleuropulmonary blastoma excision	Superior, medium, and inferior lobe (3 different lesions)	R	Masses excision (atypical pulmonary excision)	190	No	No	Yes (2)	7	No	
LN	F	2018	7.00	TC MRI	Myoepithelial carcinoma	Superior and inferior lobe, heart invasion	L	Biopsy (with associated bronchoscopic biopsy)	80	No	No	No	7	No	
BG	F	2019	5.00	MRI	Lipoblastoma	Posterior mediastinum	L	Mass excision	150	No	No	Yes (4)	6	No	
BM	F	2020	13.28	TC MRI	Lipoblastoma	Superior mediastinum	R	Mass excision	305	No	No	Yes (7)	6	No	
FE (3)	F	2020	7.59	MRI	Ganglioneuroblastoma intermixed	Anterior mediastinum	R	Robot-Assisted mass excision	290	No	No	Yes (6)	7	No	
PD	M	2020	14.80	TC	Classical Hodgkin's lymphoma	Anterior mediastinum	R	Mass excision (thymectomy)	285	No	No	Yes (3)	5	No	
SL	F	2020	7.00	TC MRI	Immature teratoma metastases	Superior, medium and inferior lobe (6 different lesions)	R	Mass excision (multiple lesions)	420	No	No	Yes (7)	8	No	

**If in the same patient, a different number of procedures is specified within brackets.*

***LHS was not considered as they started further therapy during the same hospitalization.*

TABLE 2 | Review of the most recent literature.

References	Year	Study	Number	Indication*	Median age (y)	Types tumor*	LHS (days)	Conversion	Complications**	Port-Site metastases	Intraoperative rupture
Lautz et al. (9)	2021	Retrospective	48	AS	13.9 ± 4.5	Metastatic osteosarcoma	2	0%	2.1% SSI; 2.1%; DVT or PE 6.3%	0	0
Abdelhafeez et al. (10)	2019	Retrospective	179	B (81.6%) AS (18.5%)	NA	B: 113 Pulmonary lesions, 30 Mediastinal tumors, 3 Pleural lesions; AS: 21 Pulmonary metastases, 7 Neurogenic tumors, Other: 5	NA	15.1%	7.8% (B: 10 PNX, AS: 3 PNX, 2 bleeding, 1 SSI, 1 other)	0	0
Da et al. (12)	2019	Retrospective	43	AS	3.7 ± 2.9	13 Neurogenic tumors, 5 Cystic Teratoma, 4 Lymphangioma, Other: 21	10.0 ± 5.5	0%	4.7% (not precisely specified)	0	0
McDaniel et al. (15)	2018	Retrospective	35	AS	11.25 (0.67–23.50)	6 Osteosarcoma, 5 Ewing sarcoma, 5 Hepatoblastoma, 3 Rhabdomyosarcoma, 3 Synovial cell Sarcoma, Other: 13	NA	0%	17.0% (6 PNX)	0	0
Acker et al. (13)	2015	Retrospective	77	B (72.3%) AS (27.7%)	10.7 ± 6.3	B: Lymphoma 21, Metastases 29, Other: 6 AS: Neuroblastoma 11, Metastatic disease 9, schwannoma 1	5.9 (±8.1)	5.2%	11.0% (not precisely specified)	0	0
Sato et al. (11)	2016	Retrospective	21	AS	6.9 ± 4.6	11 Neurogenic tumors, 6 Germ Cell Tumors, Other: 4	8.0 ± 3.7	0%	20% (1 brachial plexus palsy, 1 Horner's syndrome, 1 atelectasis, 1 palsy of upper limb)	0	0
Irtan et al. (14)	2015	Retrospective	20	AS	3.3 (0.3–11.6)	Neuroblastic tumors	5.2 (2–10)	15%	20.0% (3 Chlyothorax, 1 Horner's syndrome)	0	0
Riccipetitoni et al. (2021)	2021	R	43	B (51.1%) AS (48.9%)	7.72 (0.35–18.6).	10 Neurogenic tumors, 9 Hematological diseases, 5 Metastases, 4 Lypoblastomas, 3 thymic pathologies, 3 germ-cell tumors, Other: 9 (see **Table 1**)	5 (1–18)	2.3%	7.0% (see **Table 1**)	0	0

**B, biopsy; AS, ablative surgery.*

***SSI, surgical site infection; DVT, deep venous thrombosis; PE, pulmonary embolism; PNX, pneumothorax.*

of exploring the entire surface of the lung and pleura, and performing multiple biopsies if required (e.g., germinal tumors). Morbidity, mortality, and length of hospitalization are lower when compared to open surgery (19). Success rate of thoracoscopic-assisted biopsies have been reported in literature ranging from 96.7 to 100% for both histological and/or bacteriological diagnosis (12, 19–28). Nonetheless, different techniques have been proposed to further enhance the accuracy of MIS, such as intraoperative ultrasound localization (both trans-pleural and endoscopic) (29), CT-guided needle localization with methylene blue staining, or micro-coil application (15, 30, 31).

Our experience confirms the feasibility of VATS for diagnostic procedures. Among our cases, we performed three one-trocar site procedures, without complications. Nevertheless, indication for this technique in pediatrics is limited to procedures with low risk of bleeding.

Thoracoscopic surgery has been largely applied to excise mediastinal malignancies, and its use has been extended in pediatrics as well. Although in our cohort we did not record conversion to open surgery, in the most recent literature, conversion rate has been reported in up to 15% of cases (10–14) (**Figure 1**).

When performing mediastinal mass excisions ($n = 14$), we positioned a chest drain in 85.7% of patients. Nonetheless, its use is not mandatory, and in literature, chest drainage is not performed in up to 35% of procedures (29–31). A recent review of 2021 by Yu-Wei Liu reported how eliminating chest drain placement after mediastinal tumor resection can decrease post-operative pain and hospital stay without increasing complications or compromising patient safety (32).

In pediatrics, the most common mediastinal neoplasms are neurogenic tumors (neuroblastoma, ganglioneuroblastoma, and ganglioneuroma). Surgical approach has been evolving, and their resection is now often performed thoracoscopically, guaranteeing the well-known advantages of MIS (30). Different studies have found similar oncological outcomes and comparable rates of complication between the MIS and open approaches (30, 31, 33). Nonetheless, at least one port-site dissemination has been described (34). To date, VATS for neurogenic tumors does not yet have specific guidelines, although there are no contraindications. Nonetheless, literature still reports the frequent use of open approach in case of a large mediastinal tumor (35). In our series, seven patients with neurogenic tumor underwent a total of 10 procedures (four biopsies and six mass excisions). Among the excision group, five patients were submitted to a thoracoscopic surgery and one patient to a robotics-assisted procedure. All children presented IDRF-negative tumors except the case treated by RATS.

Pre-operative diagnostic workup and identification of IDRFs obtained by computed tomography (CT) and/or magnetic resonance are essential to precisely localize the lesion and identify the extent of the disease. A recent systematic review conducted by the APSA Cancer Committee confirmed how a pre-operative objective assessment by IDRFs and size criteria are recommended to guide the approach, in order to follow oncologic principles of surgical resection of neuroblastic tumors with the least possible morbidity (36).

In recent years, 3D virtual reconstruction and printing technologies have been increasingly applied to further implement the possibility of a more precise surgical planning (37, 38). These technologies enable surgeons to simulate beforehand the surgical procedure, potentially reducing the risk of intraoperative complications and allowing a conservative surgery when indicated (39–41) (**Figures 2** and **3**). In our experience, these techniques were chosen in complex cases with multiple lesions and vessel encasement and allowed the formulation of a personalized surgical strategy.

VATS is largely used to perform segmentectomies and lobectomies for pulmonary lesions in oncological adult patients. A recent meta-analysis reviewed 34 studies (183,426 patients), comparing open-approach, VATS, and robotics-assisted surgery. Their results showed how MIS seemed safer compared to open surgery, with reduced 30-day mortality, pulmonary complications, and overall complications with equivalent oncologic outcomes and 5-year overall survival (42). Nevertheless, use of VATS in pediatric lung tumors is not yet validated, and only small case-series can be found.

As far as it concerns metastatic disease, osteosarcoma represents one of the most relevant causes of metastases in children. Surgical management of osteosarcoma is still strongly debated, knowing that the most important prognostic indicator for this disease is the complete resection of all lesions (43). One of the main disadvantages of VATS is the impossibility to perform digital palpation to detect possible lesions not identified at imaging. Compared to other neoplasia, the higher calcification of osteosarcoma metastases allows for manual palpation at sizes below the resolution of CT. Nonetheless, many centers have started using thoracoscopy for osteosarcoma metastases due to the acknowledged advantages of MIS compared to open thoracotomy. A recent collaborative study on 202 patients showed that, in patients with limited metastases, both mortality and risk of pulmonary recurrence were similar when comparing VATS and thoracotomy (44). The risk of possible port-site metastases should not be neglected, as it has already been reported in the case of an 18-year-old female who presented with port site metastases within 4 months of pulmonary metastasectomy for osteosarcoma (45).

In the last decades, robotics-assisted surgery (RAS) has been increasingly employed in several complex procedures, and its use is now standardized for many interventions. The known advantages are the 3D vision, seven degrees of freedom, tremor filtration, and precise camera control (46). In pediatrics, its usage has more limitations due to the mismatch between the robotic arms and trocar dimensions compared to small children, the absence of haptic feedback, and the potential risk of tumor rupture and spillage. No guidelines or recommendations have yet been proposed from the main association of pediatric surgery in this field (47). Despite this, RAS is starting to be implemented in this field as well. In a recent review of 2020 (48), a total of 13 thoracic oncological neoplasias were treated (thymoma, neuroblastoma, inflammatory myofibroblastic tumor, bronchial carcinoid tumor). No tumor recurrence or port-site metastases

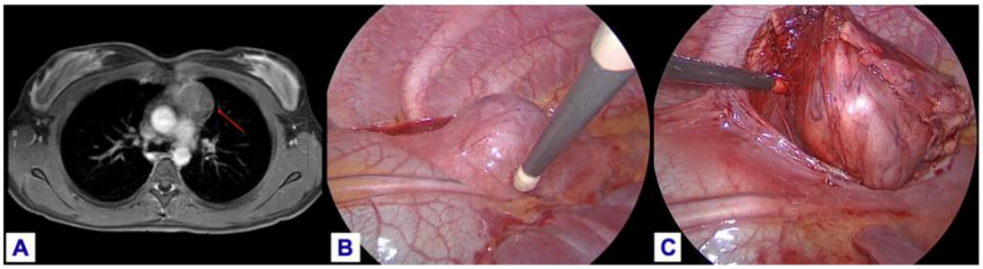

FIGURE 1 | Thymoma excision in an 11-year-old girl: **(A)** MRI pre-operative imaging. **(B)** Identification and preservation of the phrenic nerve. **(C)** Dissection of the thymus from the pericardium.

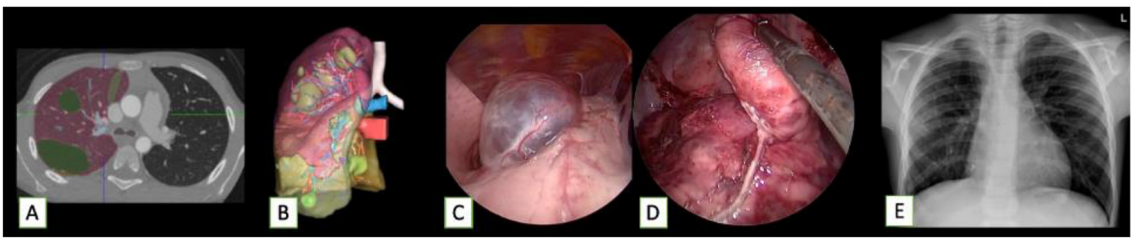

FIGURE 2 | Cystic lesions after surgery and chemotherapy for a pleuropulmonary blastoma in a 7-year-old boy, who then underwent MIS excision of multiple masses. **(A,B)** Reconstruction and 3D model of the lesions. **(C,D)** Intraoperative thoracoscopic view. **(E)** Post-operative X-ray.

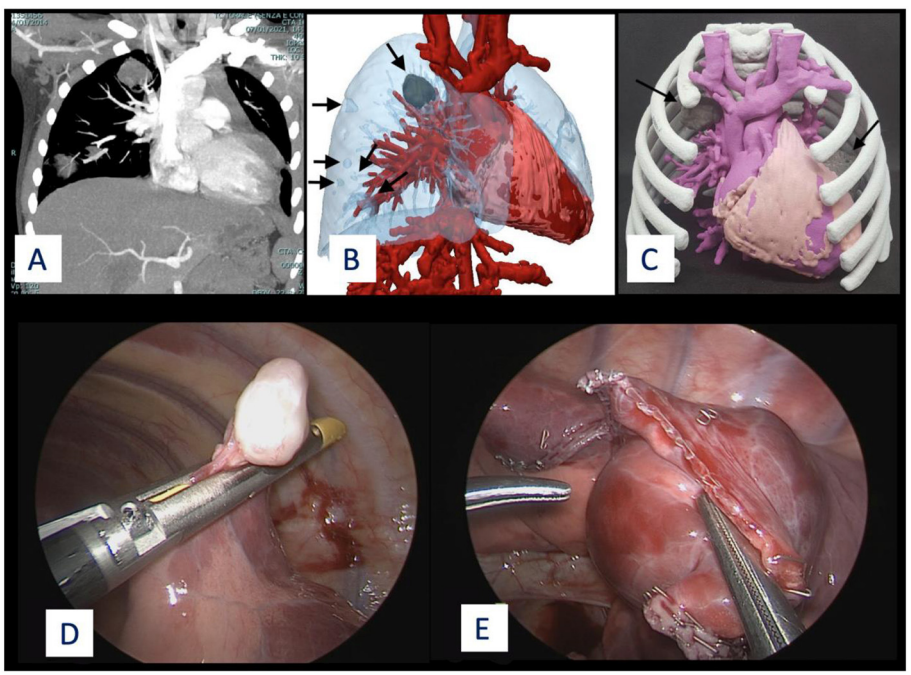

FIGURE 3 | Multiple metastases of immature teratoma in a 7-year-old girl. Left single metastasis was excised through an open procedure, due to dimension and site of the mass. The remaining lesions ($n = 6$, one solid, five cystic ones) on the right lobe were excised through VATS. **(A)** CT image. **(B)** 3D virtual reconstruction. **(C)** 3D printed model showing the two solid lesions (colored in gray). **(D,E)** Intraoperative view.

have been registered; two post-operative pneumothoraxes occurred, and one conversion due to difficult dissection of a neuroblastoma was recorded (48). In our single case, we did not observe any robot-related complications such as adjacent organ injury, positioning-related injury, or injury due to robotic arms. Despite some promising results of RAS reported in literature, its

use should be reserved to highly selected cases and, due to lack of recommendations, surgical indication should be discussed by an expert multidisciplinary team (48–50).

LIMITATIONS OF THE STUDY

We should recognize some limitations of the study, related to the predictable low case-volume and heterogeneity of rare diseases that we treated. The analysis of the recent literature faces the same challenge. In addition, the comparison of MIS to open surgery may be problematic in ascertainment with observational studies due to potential unmeasured selection bias, difficulty of retrospective patient-level comparison, and lack of randomized trials (10, 51).

CONCLUSION

VATS has now become a standardized tool in pediatric surgery. From our experience, it may be applied effectively in thoracic pediatric oncology for both diagnostic and therapeutic purposes with low complication and conversion rate.

It is a challenging procedure that requires a dedicated multidisciplinary team with competencies in pediatric oncology, radiology, anesthesiology, and mini-invasive thoracic surgery.

Pre-operative patient selection requires a strict adherence to tumor protocols; IDRF evaluation; and assessment of biology, stage, and dimension of the tumor. Recent technologies such as 3D virtual reconstruction and 3D printing may optimize this selection and guarantee a safer and more targeted treatment. The role of robotics-assisted surgery needs to be defined.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GR contributed to conception and design of the study. FV organized the database and performed the statistical analysis. FV, GR, and MB wrote the first draft of the manuscript. FV, MB, and GR wrote sections of the manuscript. MG and AR help the revision process and implemented sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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OPINION
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Cryoanalgesia and Lung Isolation: A New Challenge for the Nuss Procedure Made Easier With the EZ-Blocker™

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Keywords: Nuss, cryoanalgesia/cryoablation, pediatric, bronchial blockade, pectus excavatum

INTRODUCTION

Pain control modalities for minimally invasive repair of pectus excavatum (Nuss procedure) are evolving. While thoracic epidurals, regional anesthesia catheters, and patient-controlled analgesia effectively treat post-operative pain, each of these modalities bears their own unique set of benefits and challenges. In lieu of these, intercostal nerve cryoanalgesia has recently been adopted by pediatric surgeons performing the Nuss procedure, demonstrating decreased length of stay, hospital cost, and narcotic consumption as well as improved long-term pain control (1). Specifically, cryoanalgesia has been shown to provide equivalent analgesia to thoracic epidurals without the risks of epidural placement (2).

BACKGROUND

Cryoanalgesia is performed thoracoscopically by holding direct contact of the cryoprobe onto each intercostal nerve for a designated time period during extreme cooling, with additional time for defrosting and safe probe removal. The second through seventh intercostal nerves are typically targeted, or those which best correlate to the operative area. The cryoprobe is placed lateral to the parasympathetic chain and also excludes the first intercostal nerve to avoid developing Horner's syndrome. The probe cools to −40 to −65°C to ablate the distal nerve while leaving its essential framework intact for future regeneration. Lung isolation and controlled deflation are necessary to provide adequate exposure as well as prevent inadvertent lung injury by the actively cooled cryoprobe, adding a unique twist to a previously straightforward airway technique. We find bilateral trocar placement to be essential to deliver both the thoracoscope and the cryoprobe, as its extreme cold temperature needs to be protected from the patient's skin. Similar to others, we deliver these trocars through our standard Nuss procedure incisions, with the addition of a 5 mm trocar incision as necessary depending on patient anatomy (2). The Nuss procedure is performed in standard fashion.

Airway management options include placement of a double lumen endotracheal tube or bronchial blocker to achieve appropriate exposure. A double lumen endotracheal tube can safely and quickly achieve lung isolation but may be challenging in younger, smaller patients. Risks of double lumen tube placement include sore throat, hoarseness, and airway trauma (3, 4). Our institution has adopted the use of the EZ-Blocker™ Endobronchial Blocker (Teleflex, Inc., Wayne, PA, USA) for lung isolation in an effort to reduce these untoward effects while providing adequate surgical exposure.

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DISCUSSION

Cryoanalgesia is typically preformed thoracoscopically and, in our practice, prior to correction of the pectus defect. Lung isolation is facilitated by the EZ-Blocker™ and reinforced with intrathoracic insufflation pressure maintained during thoracoscopy. With the lung selectively deflated on the operative side, the probe is held in place for a number of minutes on each nerve while it cools to the designated temperature. It is important to avoid contact with the lung parenchyma while the probe is cooled to prevent inadvertent lung injury, which can result in pneumothorax or bleeding.

The benefits of EZ-Blocker™ placement for lung isolation include use of a single lumen endotracheal tube, ease of placement due to the bifurcated cuffs, and option for removal after lung isolation is complete. In our group, despite minimal provider experience with placement of this novel blocker, we encountered no issues with blocker dislodgement or inadequate surgical exposure. In 2018, a retrospective review concluded successful and stable lung isolation in a majority of patients 6 years of age and older when the EZ-Blocker™ was placed extraluminally (5). Our patients were 12 years of age and older; therefore, a standard intraluminal approach through a 7.0 endotracheal tube was used for placement.

To maximize success, here are a few lessons learned from EZ-Blocker™ use in our patient cohort. Attempt to keep your endotracheal tube midline during blocker placement. This allows for improved deployment of the bifurcated cuffs as they exit the endotracheal tube. Avoid water-based lubricants; opt instead for silicone-based spray to prevent the cuffs from drying and sticking to one another upon deployment. A fiberoptic scope should be used to confirm placement of the blocker straddling the carina and adequate cuff inflation. Lung deflation may take longer than expected, as compared to a double lumen endotracheal tube, due to the small channel within the blocker—have patience and ensure you have removed the cap for proper egress of air.

The use of the EZ-Blocker™ should be considered as a safe, effective, and efficient alternative to double lumen endotracheal tube placement in children undergoing minimally invasive repair of pectus excavatum. We encourage you to have confidence with this novel variation of the bronchial blocker as your surgeon requests lung isolation for intercostal nerve cryoanalgesia.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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ORIGINAL RESEARCH
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Congenital Pulmonary Airway Malformation in Children: Advantages of an Additional Trocar in the Lower Thorax for Pulmonary Lobectomy

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Aim: To present the use of an additional trocar (AT) in the lower thorax during thoracoscopic pulmonary lobectomy (TPL) in children with congenital pulmonary airway malformation.

Methods: For a lower lobe TPL (LL), an AT is inserted in the 10th intercostal space (IS) in the posterior axillary line after trocars for a 5-mm 30° scope, and the surgeon's left and right hands are inserted conventionally in the 6th, 4th, and 8th IS in the anterior axillary line, respectively. For an upper lobe TPL (UL), the AT is inserted in the 9th IS, and trocars are inserted in the 5th, 3rd, and 7th IS, respectively. By switching between trocars (6th⟷8th for the scope, 4th⟷6th for the left hand, and 8th⟷10th for the right hand during LL and 5th⟷7th, 3rd⟷5th, and 7th⟷9th during UL, respectively), vital anatomic landmarks (pulmonary veins, bronchi, and feeding arteries) can be viewed posteriorly. The value of AT was assessed from blood loss, operative time, duration of chest tube insertion, requirement for post-operative analgesia, and incidence of perioperative complications.

Results: On comparing AT+ ($n = 28$) and AT– ($n = 27$), mean intraoperative blood loss (5.6 vs. 13.0 ml), operative time (3.9 vs. 5.1 h), and duration of chest tube insertion (2.2 vs. 3.4 days) were significantly decreased with AT ($p < 0.05$, respectively). Differences in post-operative analgesia were not significant. There were three complications requiring conversion to open/mini-thoracotomy: AT– ($n = 2$; bleeding), AT+: ($n = 1$; erroneous stapling).

Conclusions: An AT and switching facilitated posterior dissection during TPL in children with congenital pulmonary airway malformation enhancing safety and efficiency.

Keywords: thoracoscopic surgery, pulmonary lobectomy, congenital pulmonary airway malformation, child, anterior approach, posterior approach

INTRODUCTION

Thoracoscopic pulmonary lobectomy (TPL) is now an accepted, well-described procedure for treating congenital cystic lung disease. Reports of TPL being used for congenital pulmonary airway malformation (CPAM) are increasing, because of improvements in prenatal diagnosis and better understanding of its prognosis. In infants and children, TPL has the advantages of better cosmetic outcome, less musculoskeletal chest wall sequelae, better shoulder motility, and unimpaired future breast development compared with conventional open thoracotomy (1–3).

Being minimally invasive, TPL is associated with less post-operative pain, shorter hospitalization, and decreased long-term morbidity (4, 5); the general consensus is that while it is a safe, efficient procedure, it can be technically challenging in children because everything is physically smaller, the anatomy is often anomalous, and the working space is limited. In particular, in neonates, the distance a trocar can be inserted is limited which compromises maneuverability and the visual field. In other words, the ability to correctly identify vital structures (both normal and anomalous), assess what can be preserved or not, then safely secure the large pulmonary vessels can be so daunting, that even well-experienced pediatric surgeons with expertise have opted to wait until patients are larger if possible, rather than operate during the neonatal period.

In order to address these limitations, the concept of adding an additional trocar (AT) in the lower thorax to allow instruments and hands to be switched between trocars as required for comfort and effectiveness during a task was trialed during TPL. Here, a comparison of TPL performed with and without an AT was used to assess the impact of using an AT.

MATERIALS AND METHODS

The medical records of 55 consecutive CPAM cases treated by TPL at a single institution between June 2009 and November 2019 were reviewed retrospectively. All procedures were performed by one of two senior board-certified pediatric surgeons (AY or HK) under the direct supervision of one of five thoracic surgeons with extensive experience of TPL (KeS, YW, KI, HU, and SH).

Conventional TPL performed with an AT (AT+; five trocars) was compared with TPL performed without an AT (AT–; four trocars) for prenatal diagnosis, incidence of pre-operative infections, age and weight at surgery, blood loss, operative time, duration of chest tube insertion, requirement for post-operative analgesia, and incidence of perioperative complications.

Thoracoscopic Pulmonary Lobectomy

Essentially, TPL involves the same principles as open lobectomy, namely, isolation and division of the pulmonary artery, vein, and bronchus to the affected lobe, with separation of lung parenchyma using a combination of sharp and blunt dissection and electrocautery to define and isolate the pathologic lesion. All subjects were treated using the same equipment and devices. Details of the TPL performed in this series are described elsewhere (6–8). Briefly, after induction of general anesthesia and tracheal intubation, the patient is placed in the lateral decubitus position to allow access to the hilum both anteriorly and posteriorly. For thoracoscopy, the surgeon and assistant stand facing the patient while viewing a monitor positioned behind the patient (**Figure 1**). A closed technique is used to place the initial 5 mm optical trocar 1 cm below the inferior angle of the scapula to prevent leakage around the trocar site when an artificial pneumothorax is established to complete collapse of the lung. The initial trocar is used to define the position and status of the fissure and evaluate the general condition of the lung parenchyma and later for lung retraction. Carbon dioxide insufflated at low flow (0.5–1.0 L/min) and under low pressure (4–6 mmHg) is used to collapse the lung. A Fogarty catheter is used for single-lung ventilation. A chest tube is placed under direct vision in all cases.

Lower Lobe TPL

The initial trocar is used to retract the lung. For a left lower lobe TPL (LL), 5-mm trocars for a 5-mm 30° scope, the surgeon's left hand, and the surgeon's right hand are placed in the 6th, 4th, and 8th intercostal spaces (IS) in the anterior axillary line, respectively. The AT is placed in the 10th IS in the posterior axillary line to dissect or view vital structures, such as the pulmonary veins, bronchus, and feeding artery from a posterior perspective as well as observe the entire pulmonary artery, aortic arch, and course of the vagus nerve by switching the scope between the 6th and 8th IS trocars, the left hand between the 4th and 6th IS trocars, and the right hand between the 8th and 10th IS trocars (**Figure 2**). For a right LL, the procedure is the same, but the left and right hand trocars are reversed.

Upper Lobe TPL

For upper lobe TPL (UL), trocar positions on either side are one IS higher than for LL; i.e., 5th IS for the scope, 3rd IS for the left hand, 7th IS for the right hand, and 9th IS for the AT (**Figure 3**). The scope is switched between the 5th and 7th IS, the left hand between the 3rd and 5th IS trocars, and the right hand between the 7th and 9th IS trocars.

Middle Lobe TPL

Trocars for the scope, left hand, and right hand are placed in the 5th, 4th, and 7th IS in the anterior axillary line, respectively. To create more space between the scope trocar and the right-hand trocar, the scope trocar can be placed slightly more anteriorly than the right-hand trocar, which will prevent the scope and right-hand instruments from colliding.

Statistics/Ethics

Data were expressed as mean ± standard deviation. The Student's *t*-test and chi-square test were used for statistical analysis. A p-value <0.05 was considered to be statistically significant. This study was approved by the Juntendo University School of Medicine Institutional Review Board (IRB number: 17-209) and complies with the Helsinki Declaration of 1975 (revised1983).

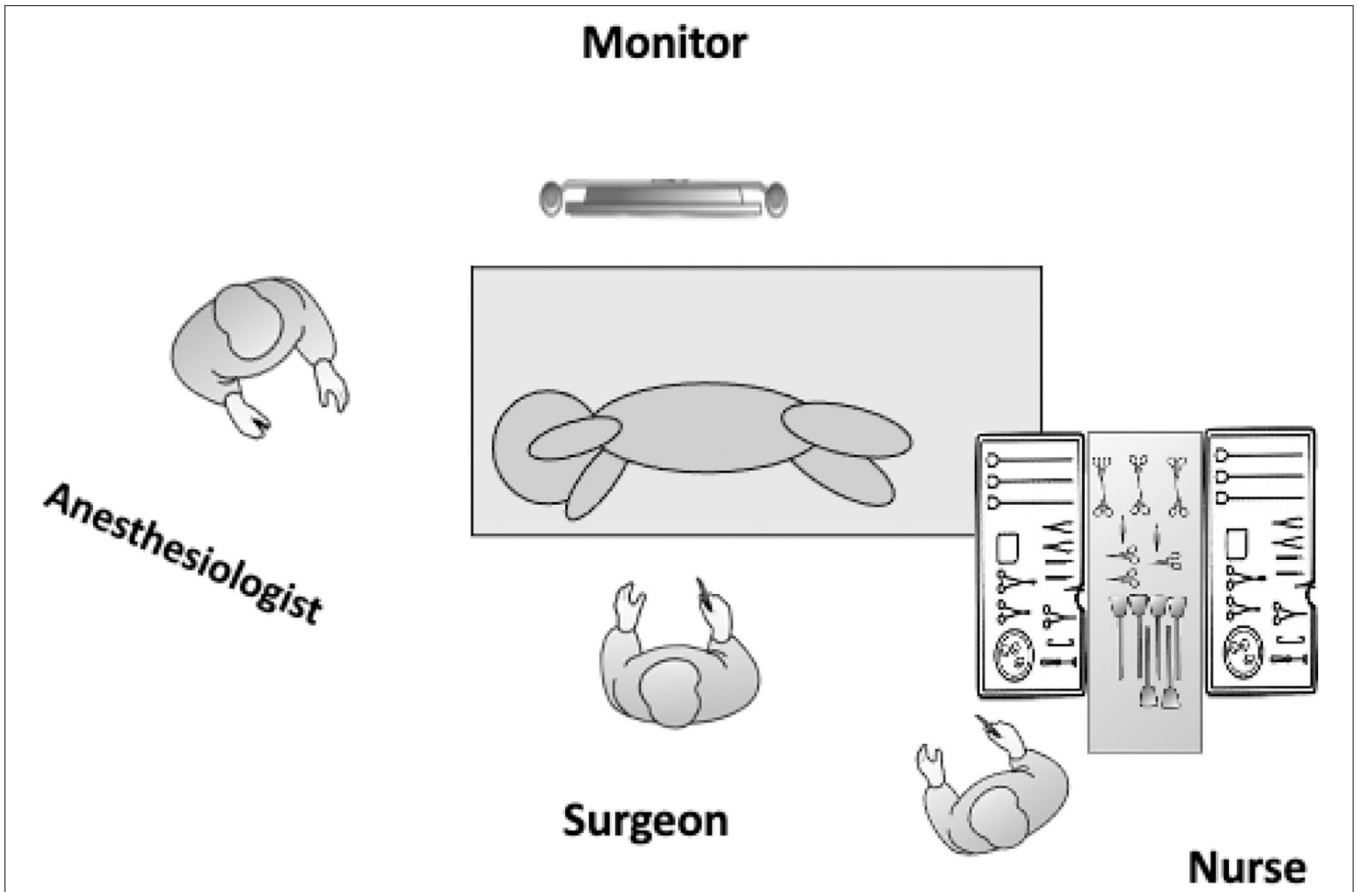

FIGURE 1 | Operating room layout and patient positioning for a left TPL. The patient is placed in the lateral decubitus position and should be placed toward the edge of the operating table in front of the operating surgeon to enhance maneuverability and prevent instruments from hitting the table. The operating surgeon stands facing the patient while viewing a monitor positioned behind the patient.

RESULTS

All 55 CPAM cases were Japanese. Groups were AT+ ($n = 28$) and AT– ($n = 27$). Both AT+ and AT– were similar for patient demographics and location of pathology. Prenatal diagnosis and incidence of pre-operative infections were not significantly different: 20 cases (71%) in AT+ vs. 20 cases (74%) in AT– for prenatal diagnosis ($p = 0.87$) and 7 cases (25%) in AT+ vs. 7 cases (28%) in AT– for pre-operative infections ($p = 0.93$), respectively. Mean ages and mean weights at TPL for AT+ and AT– were not significantly different (2.9 ± 2.3 vs. 2.6 ± 1.6 years old, $p = 0.57$, and 12.8 ± 5.1 vs. 12.0 ± 3.7 kg, $p = 0.80$, respectively). Pulmonary fissures were absent or incomplete in 13/28 (46%) cases in AT+ and 11/27 (41%) cases in AT–; these differences were not statistically significant ($p = 0.67$).

Types of TPL performed were the following: for AT+: left UL ($n = 4$), left LL ($n = 7$), right UL/right middle lobe TPL (ML) ($n = 1$), right ML/right LL ($n = 1$), right ML ($n = 2$), and right LL ($n = 13$); and for AT–: left UL ($n = 5$), left LL ($n = 10$), right UL ($n = 1$), right UL/right ML ($n = 1$), right ML ($n = 3$), and right LL ($n = 7$). There was no significant difference between AT+ and AT– for duration of post-operative analgesia (2.1 ± 1.1 vs. 2.6 ± 1.0 days; $p = 0.08$). However, differences for mean blood loss and mean operative time were significantly different between AT+ and AT– (5.6 ± 3.8 vs. 13.0 ± 5.6 ml, $p < 0.0001$ and 3.9 ± 1.5 vs. 5.1 ± 1.4 h, $p = 0.003$), respectively.

There were three intraoperative complications: bleeding from a bronchial artery during anterior-to-posterior dissection of a bronchus in AT– ($n = 2$) and accidental stapling of the Fogarty catheter used for single-lung ventilation in AT+ ($n = 1$). All three cases required conversion to open/mini-thoracotomy. Chest tubes were removed significantly earlier in AT+ than in AT– (2.2 ± 1.4 vs. 3.4 ± 2.0 days; $p = 0.01$). One case in AT– actually required a chest tube for 14 days post-operatively because of a persistent air leak from a sealed fissure.

DISCUSSION

To the best of our knowledge, this is the first report detailing the benefits of an AT in the lower thorax during TPL in children with CPAM. However, CPAM is rare (9–11), and the learning curve for TPL in children is steep. As with any surgical procedure, confidence comes from experience, and obtaining

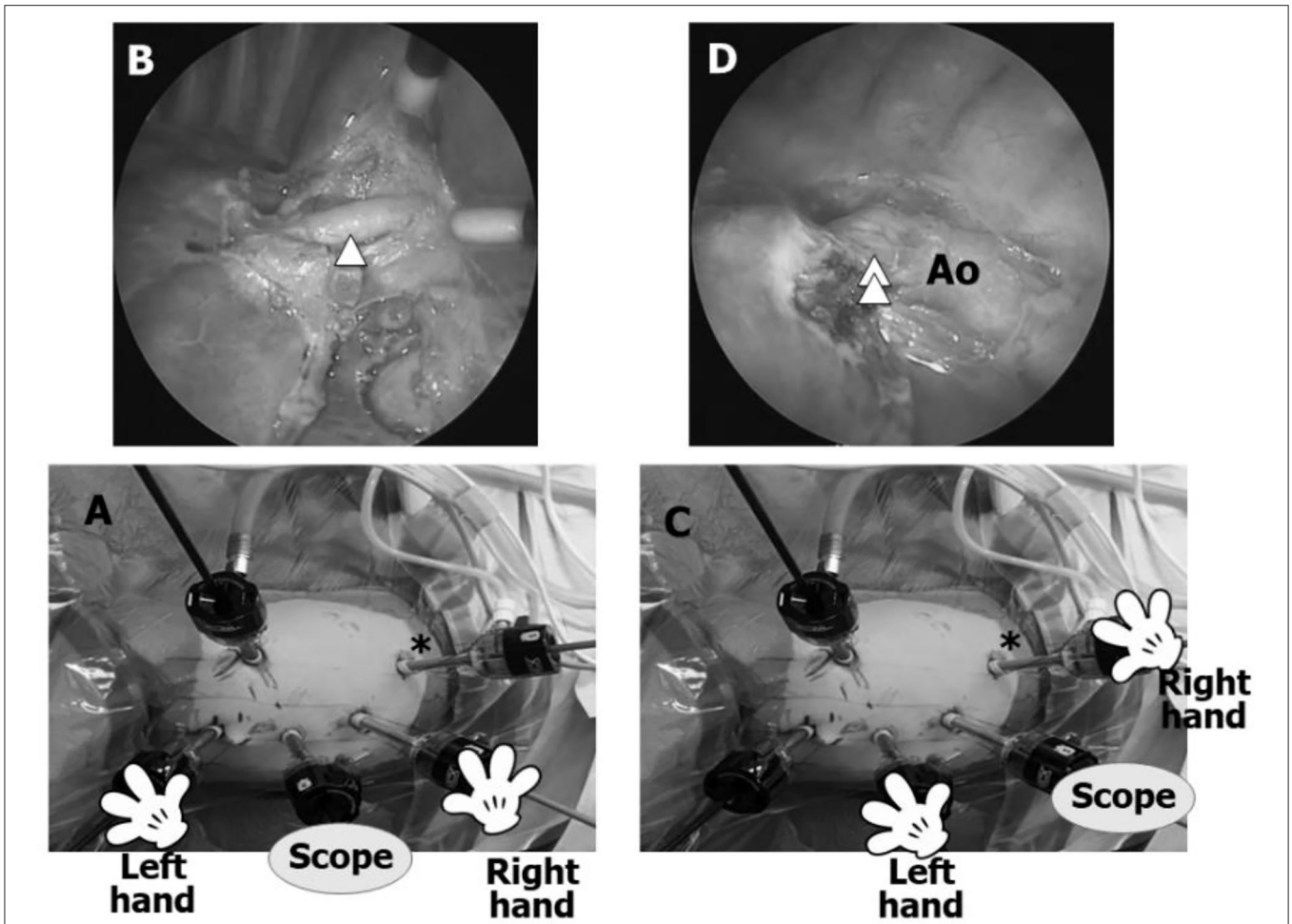

FIGURE 2 | Trocar positions for a left lower lobectomy TPL (left LL). **(A)** Most surgeons perform a LL with the scope in the 6th IS for the entire procedure without using an additional trocar (AT). **(B)** Anterior view using conventional trocar placement is adequate for dissecting the interlobar arteries, such as A8–10 (arrowhead), but dissection can only be viewed progressing in the anterior/posterior plane without viewing the posterior aspects of the bronchus and pulmonary vein and posterior mediastinum. By inserting an AT (asterisk) in the 10th IS, the same dissection can be observed from a different angle. **(C)** Asterisk shows the AT in the 10th IS. **(D)** Posterior view through the AT. The AT facilitates safe dissection of a feeding artery (double arrowhead) originating from the aorta (Ao) and visualization of the posterior aspects of the inferior pulmonary vein and left bronchus as well as the pulmonary artery, aortic arch, and course of the vagus nerve.

enough experience to perform TPL safely and efficiently is difficult. The literature reflects this, with most reports about TPL being from single specialist centers or, if they are from larger referral centers, involving few subjects. Despite improvements in technology and availability, TPL is generally considered too technically demanding for most pediatric surgeons to offer as a routine procedure. With this in mind, an AT in the lower thorax with switching between trocars as required was trialed during TPL in this series.

Conventional wisdom would dictate an anterior approach for TPL, particularly in children and especially in neonates because there is more space from the chest wall to the mediastinum where the pulmonary vessels arise. An anterior approach would also seem more logical because the visual field is easier to secure and allows hilar vascular structures to be viewed safely for orientation; dissection of bronchi and branches of pulmonary arteries could also be facilitated. However, an anterior approach is inadequate for viewing and understanding anatomic relationships in the mediastinum completely because the posterior aspects of bronchi and pulmonary veins, as well as the posterior mediastinum, cannot be viewed readily. AT trialed in this series expanded the visual field posteriorly to enable vital structures, such as the pulmonary veins, bronchi, and feeding vessels, to be inspected from a posterior perspective as well as allow the entire pulmonary artery, the aortic arch, and the vagus nerve to be viewed. Thus, by switching trocars using AT, the surgeon has access to the surgical field from all sides and can inspect and check progress from various angles, enhancing safety and reliability, especially during dissection of a feeding artery originating from the aorta and dissection of the posterior wall of the inferior pulmonary vein and bronchus during LL. During UL, A1+2, A3, and A6 branches located postero-lateral to the interlobar pulmonary artery can be

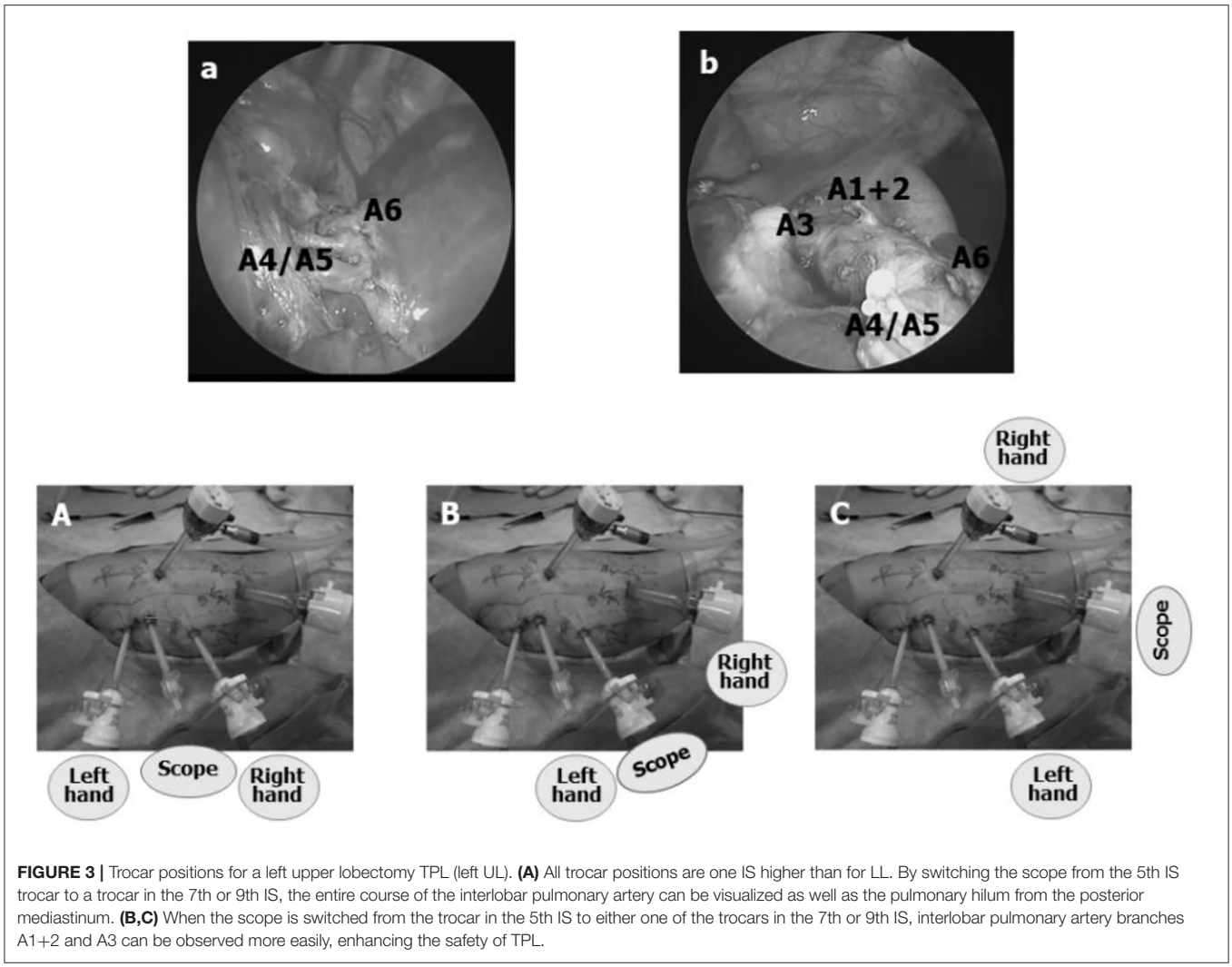

FIGURE 3 | Trocar positions for a left upper lobectomy TPL (left UL). **(A)** All trocar positions are one IS higher than for LL. By switching the scope from the 5th IS trocar to a trocar in the 7th or 9th IS, the entire course of the interlobar pulmonary artery can be visualized as well as the pulmonary hilum from the posterior mediastinum. **(B,C)** When the scope is switched from the trocar in the 5th IS to either one of the trocars in the 7th or 9th IS, interlobar pulmonary artery branches A1+2 and A3 can be observed more easily, enhancing the safety of TPL.

seen readily, ensuring added safety during TPL. In other words, without AT, the pulmonary hilum cannot be viewed from the posterior aspect throughout an entire TPL, with the result that a TPL can only be performed in the anterior–posterior plane which is stressful even for an experienced surgeon, because of the blind aspects, and further complicated if fissures are anomalous.

From experience, fissure cases can be handled with confidence by using an AT to switch instruments to view the same structures from a slightly different angle. In general, during TPL in infants and children, the view through the scope is from front to back and limited by the small size of the thorax, so treating an incomplete fissure located anteriorly, such as an incomplete fissure between S4+5 and S8 in the left lung, between the right UL and ML, or between the right ML and LL, is more difficult than treating an incomplete fissure located posteriorly, such as an incomplete fissure between S1+2 and S6 in the left lung or between the right UL and LL. Thus, by switching between trocars, there is less risk for injury because both anterior and posterior views are possible. As shown in this series, blood loss and operative time for AT+ were lower, although there were no significant differences in location or incidence of incomplete fissures between the two groups (AT+ and AT–). An AT with switching was crucial for preventing accidental injury to the pulmonary arterial wall during TPL with normal fissures but even more so when fissures were incomplete or absent.

Operator disorientation may also arise because of patient positioning during TPL. In conventional open thoracotomy, the surgeon and assistant usually stand behind the patient (5), but in TPL, they stand in front of the patient because the patient is in the lateral decubitus position. A thorough grasp of the anatomic relationships of each lobe cannot be overemphasized because intraoperatively, the three-dimensional relationships of vessels and bronchi to each lobe must be readily imaginable because the field of view through a scope is two-dimensional and everything may not be visible, so an operating surgeons must be completely comfortable with the anatomy of the lungs. In other words, anatomic relationships both normal and anomalous must be second nature, so the operating surgeon is always prepared and aware of the potential for the unexpected, especially important when no landmarks are present, for example, in cases

of absent or incomplete fissure. In such patients, incising lung parenchyma that otherwise lacks superficial landmarks can cause air leakage which is one of the commonest complications of lung surgery and can require chest tube insertion if prolonged. Chest tube insertion extends hospitalization resulting in higher costs and greater risks for pleural infections. While an AT alone will not prevent air leakage absolutely, having a better grasp of the operative field from additional perspectives will provide more information about anatomic relationships (or lack thereof) and allow operating surgeons to make decisions with greater confidence.

In this series, there were three intraoperative complications. Of these, two were bleeding from bronchial arteries that occurred in AT– cases and have not occurred again since AT use became routine. The third, accidental stapling of the Fogarty catheter used for single-lung ventilation, was due to operator carelessness. Although subject numbers are limited, AT should be considered as improving safety of TPL in children.

Although there are limitations to this study because of its retrospective nature and the small number of cases, the results obtained attest to the value of using an AT, and as a result, TPL in children should really be considered a five-trocar procedure henceforth. While the concept of an AT may seem somewhat unconventional because skilled experienced surgeons can perform TPL with just three trocars, an AT with switching is a simple technique that effectively enhances safety by facilitating visualization and as shown in this series improves TPL in children with CPAM.

In conclusion, AT could be applied to any minimally invasive procedure that is challenging technically, anatomically, or logistically.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

HK and AY designed the study. HK, TO, SH, YW, HU, KI, KaS, RK, KN, KeS, and AY were involved in clinical treatment. HK and TO collected and analyzed the data. HK and GL prepared and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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frontiers in Surgery

CASE REPORT
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Reconstruction of Chest Wall by Cryopreserved Sternum Allograft After Resection of Sternal Hemangioma: A Case Report

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A 5-year-old girl was referred to our department for a mass of sternum that was previously biopsied and diagnosed as hemangioma. Chest X-ray and CT scan confirmed a large sternal mass. We resected the sternum completely and reconstructed a large anterior chest wall defect by a cryopreserved sternal allograft. In the follow-up of the patient, there was no instability of the chest wall and acceptable cosmetic results.

Keywords: sternal tumor, hemangioma, sternal allograft, cryopreserved bone allograft, case report

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INTRODUCTION

Radical resection of the sternum is indicated in different situations, such as tumors, infection, radionecrosis, and trauma. In addition, it may be considered as an alternative surgical treatment in chest wall deformity (1). Sternum hemangioma is a rare benign bone tumor, and, to the best of our knowledge, about five cases have been reported in the literature, including adult and pediatric; meanwhile, any of them did not include pectus carinatum deformity coexisting with hemangioma of the sternum (2–5). In the case of sternal resection, reconstruction of the sternum is mandatory to prevent flail chest and ventilation impairment; besides, cosmetic consequences must also be considered. Due to mentioned difficulties, this procedure is challenging for most thoracic and reconstructive surgeons (6, 7).

Various techniques have been described previously, but there is no gold standard procedure for managing these defects (8). There is limited experience with a new method for the reconstruction of the sternum by utilizing cryopreserved sternal allograft; furthermore, no previous study was conducted in the pediatric group.

In this case report, we described a 5-year-old girl with the sternum hemangioma and pectus carinatum deformity, on whom reconstruction of the chest wall with a cryopreserved sternal allograft was conducted after complete surgical resection of the tumor (sternectomy).

CASE REPORT

A 5-year-old girl was referred to our thoracic surgery unit following diagnosis of hemangioma of the sternum (**Figure 1**). When she was 3 years old, following an attack of seizure, her brain MRI revealed a calcified hemangioma in addition to pectus carinatum deformity and thrombocytopenia (platelet count = 15,000/μL) in her primary evaluations. A chest CT scan was performed, which

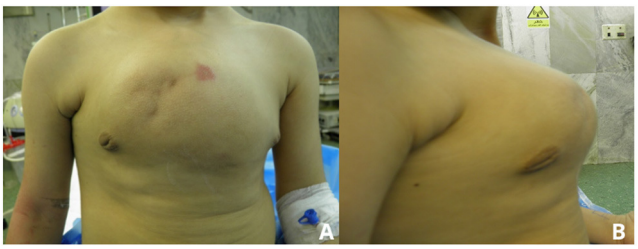

FIGURE 1 | Preoperative anterior **(A)** and lateral **(B)** view pictures showing a deformity and large mass.

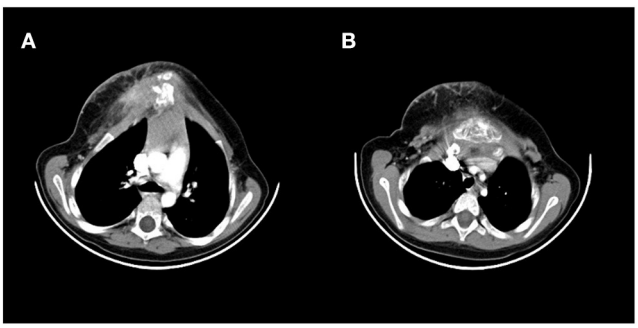

FIGURE 2 | Preoperative CT scan showing a large sternum mass. **(A)** Uppers segments, **(B)** lower segments.

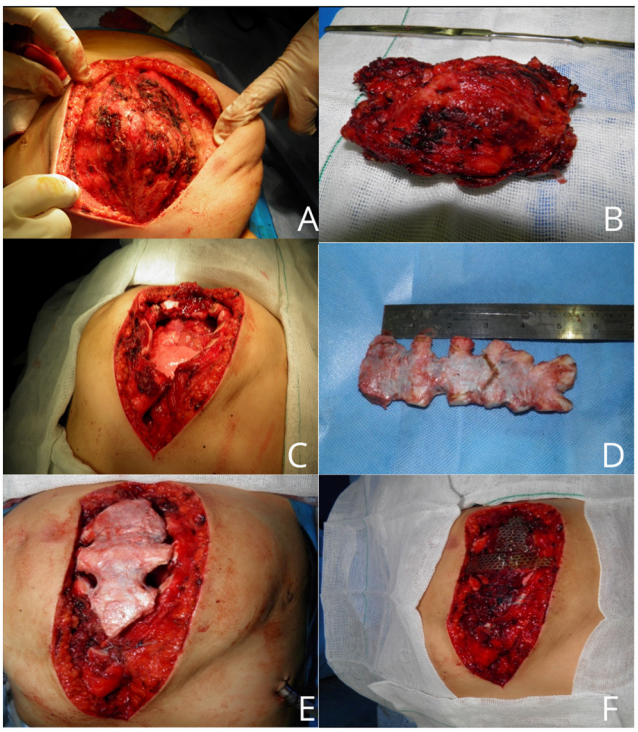

FIGURE 3 | An intraoperative picture of sternal mass **(A)**. Resected hemangioma with an acceptable margin **(B)**. Large chest wall defect **(C)**. Cryopreserved sternal allograft **(D)**. Covering of chest wall defect with graft **(E,F)**.

demonstrated a sternal expansile mass (**Figure 2**). Incisional biopsy of the mass was performed, and pathologic finding was compatible with hemangioma. Considering her thrombocytopenia, she underwent corticosteroid therapy. She experienced recurrent thrombocytopenia after corticosteroids withdrawal; therefore, she was referred for resection of sternal hemangioma as a potential genesis of thrombocytopenia. At the time of admission, she had a platelet count of 20,000/μL eventually; corticosteroid therapy was established before resection to normalize the platelet count.

According to CT findings, near-complete resection of the sternum was arranged. Based on predicted sternum size, measured according to anthropometric parameters and the resected area of the chest wall, a cryopreserved sternum was ordered from the tissue bank center. At the time of the surgery, a longitudinally elliptical midline incision was performed, which included a previous biopsy site. There was no infiltration or adhesion of mass to skin and subcutaneous tissue except the biopsied area, and a well-defined, capsulated but vascular mass was dissected from surrounding tissues. Due to the large dimension of the tumor, pectoralis major muscles were pushed laterally to nearly midclavicular lines (**Figures 3A,B**). The upper border of the manubrium seemed to be normal and preserved. The thoracic cavity was entered on the left side, and near-total sternectomy, including tumor and most parts of deformed cartilages, was achieved. Eventually, there was a 15 × 12-cm defect in the anterior chest wall. The previously preserved cryopreserved sternum allograft was prepared for the reconstruction (**Figures 3C,D**). The graft was dampened by 40°C normal salines, tailored gradually, fixed to the patient's ribs by titanium plates and screws, and fixed to remained manubrium (**Figures 3E,F**). Subsequently, the graft was covered by pectoralis muscles and after insertion of a bilateral chest tube and subcutaneous right side vacuum suction drainage; the skin was closed in the midline. The patient was extubated in the operation room. After surgery, the chest wall was completely stable, and there was no need for ventilator support. Chest tubes were removed on the 3rd day after the operation, and there was no evidence of wound infection. The patient was discharged after 7 days. In the 1st month after surgery, the defect was stable with no complications. The final pathologic finding was compatible with hemangioma (**Supplementary Figure 1**). Sixteen months after the operation, there was a minimal deformity in the anterior chest wall without any evidence of chest wall instability (**Figure 4**).

DISCUSSION

Hemangioma of the sternum is an extremely rare benign sternal tumor. To the best of our knowledge, <5 cases have been reported previously (2–5), and simultaneous occurrence of pectus carinatum and sternum hemangioma is a novel condition, although this type of anterior chest wall deformity

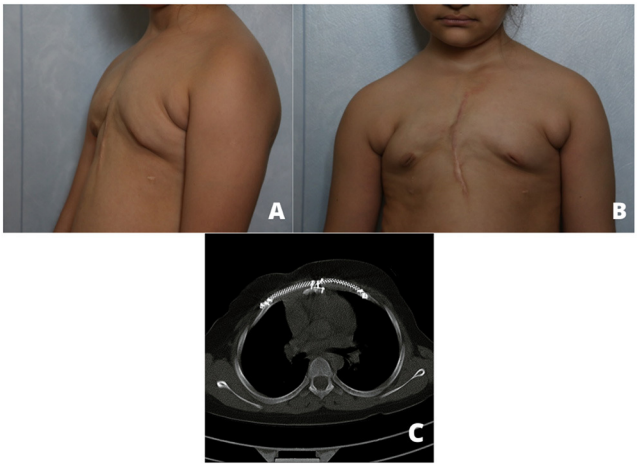

FIGURE 4 | An anterior, lateral photograph **(A,B)** and CT scan **(C)** 16 months after the operation.

may be acquired and secondary to abnormal overgrowth of the sternum (9). On the other hand, resection of sternum and repair strategies of the remained defect after resection based on different pathologies is challenging, especially in the pediatric. The most challenging part of the operation is the best reconstructive strategy selection for the reconstruction of the anterior chest wall. Reconstruction of soft tissue defects with various types of flaps is less challenging. The ongoing growth of a child and adverse effects of growth restriction following resection and reconstruction is the most important challenging points of pediatrics in contrast to adults.

Methyl methacrylate meshes and sandwiches, polytetrafluoroethylene (PTFE), and polypropylene patches are routinely used in thoracic surgery for reconstruction. The disadvantages of these prosthetic materials are the risk of infection, dislodgement, and long-term complications, including changes in thoracic morphology and function in pediatric patients (10). Metallic materials, such as titanium clips, plates, and moldable multi-hole plates, have been used for the stabilization of the chest wall (11, 12) and may have the same complications as other prosthetic materials. Turna et al. (13) described reconstruction of anterior chest wall defect after wide resection of this part with a well-designed patient-specific titanium implant. In addition, a hydroxyapatite tricalcium-phosphate compound (ceramic) that can be shaped has been introduced for reconstruction (11).

Due to complications related to using prosthetic material, such as infection, rigidity, and probable growth restriction in children, bone grafts have gained considerable attention in the reconstruction of the chest wall (14). Ribs can be harvested as autografts from the opposite surgical site or can be used as allografts. In extensive chest wall defects, as in sternum tumor resection, bone autograft harvest may lead to significant morbidity (15). A potentially inexhaustible source of bone for the reconstruction of chest wall defects in the human cadaver. The main advantage of bone grafts is their capability of integration with host tissue and chest wall stability without rejection, infection, and migration. Bone graft also acts as a scaffold for osteoprogenitor cells, which migrate within the graft, consequently, new bone will be formed (15). Some authors reported cryopreserved sternum allograft for a limited number of patients after sternum resection (15–18). Dell'Amore described this method and his experiences in fourteen patients, which is the largest group of patients (19). He has also described more limited experiences of other surgeons with this method in other centers (20). In all of these reports, no allograft complications have been reported.

Sternum allograft fixation by Titanium bridges and screws may result in a thoracic cage deformity in long term in a growing child; therefore, studies with longer follow-ups are mandatory to clarify this hypothesis.

Using an autologous flap in chest wall reconstruction is an option that is a complex but safe procedure; nevertheless, it may lead to inadequate functional and cosmetic results, especially in mid- and long-term follow-up. On the other hand, some surgeons have reported prosthetic material for reconstruction of the chest wall in this group of patients with acceptable results, but mid- and long-term results are not available and prosthetic material may interfere with the normal growth of the child (21); therefore, using bone allografts may be more beneficial for children.

In conclusion, in this case, we have reported three rare events occurring simultaneously. First, the rare occurrence of sternal hemangioma; second, the occurrence of sternum hemangioma with a pectus carinatum deformity (that most probably is acquired), and the last one is the use of a novel substitute for sternum reconstruction. Using cryopreserved sternum allograft for the reconstruction of the anterior chest wall after sternum resection is a simple and reproducible method.

To the best of our knowledge, this is the first report of chest wall reconstruction by utilizing cryopreserved sternum in children. The most important consideration in this reconstruction method is the restrictive effects on the sternum. Another question is why we did not try to repair pectus carinatum deformity completely? If we tried to resect more adjacent ribs and cartilages for cosmetic results, remained defect might have been as big as which could force us to use longer titanium bridges for sternum allograft fixation on the remained ribs. Still, we could repair the patient's carinatum deformity in the future to achieve more cosmetic results. Although, 16 months after the surgery, there was a minimal chest wall deformity in comparison with preoperative images. More studies with a larger sample size and longer follow up are mandatory to determine the long-term outcome of this type of transplantation, especially in children.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shahid Beheshti University Ethical Board. Written informed consent to participate in this study was provided by

the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

FS contributed in data gathering and drafting. AS contributed in revision and drafting. KS contributed in data gathering and final revision. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

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From the Ground Up: Esophageal Atresia Types, Disease Severity Stratification and Survival Rates at a Single Institution

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Esophageal atresia (EA), although a rare congenital anomaly, represents one of the most common gastrointestinal birth defects. There is a gap in our knowledge regarding the impact of perioperative critical care in infants born with EA. This study addresses EA types, disease severity stratification, and mortality in a retrospective cohort at a single institution. Institutional Review Board approved our retrospective cross-sectional study of term-born ($n = 53$) and premature infants (28–37 weeks of gestation; $n = 31$) that underwent primary surgical repair of EA at a single institution from 2009–2020. Demographic and clinical data were obtained from the electronic medical record, Powerchart (Cerner, London, UK). Patients were categorized by (i) sex, (ii) gestational age at birth, (iii) types of EA (in relation to respiratory tract anomalies), (iv) co-occurring congenital anomalies, (v) severity of disease (viz. American Society of Anesthesiologists (ASA) and Pediatric Risk Assessment (PRAm) scores), (vi) type of surgical repair for EA (primary anastomosis vs. Foker process), and (vii) survival rate classification using Spitz and Waterston scores. Data were presented as numerical sums and percentages. The frequency of anatomical types of EA in our cohort parallels that of the literature: 9.5% (8/84) type A, 9.5% (8/84) type B, 80% (67/84) type C, and 1% (1/84) type D. *Long-gap* EA accounts for 88% (7/8) type A, 75% (6/8) type B, and 13% (9/67) type C in the cohort studied. Our novel results show a nearly equal distribution of sex per each EA type, and gestational age (term-born vs. premature) by anatomical EA type. PRAm scoring showed a wider range of disease severity (3–9) than ASA scores (III and IV). The survival rate in our EA cohort dramatically increased in comparison to the literature in previous decades. This retrospective analysis at a single institution shows incidence of EA per sex and gestational status for anatomical types (EA type A-D) and by surgical approach (primary anastomosis vs. Foker process for *short-gap* vs. *long-gap* EA, respectively). Despite its wider range, PRAm score was not more useful in predicting disease severity in comparison to ASA score. Increased survival rates over the last decade suggest a potential need to assess unique operative and perioperative risks in this unique population of patients. Presented findings also represent a foundation for future clinical studies of outcomes in infants born with EA.

Keywords: ASA, EA, LGEA, mortality, term, term-born infant, PRAm, premature

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INTRODUCTION

Esophageal atresia (EA), although a rare congenital anomaly with a stable world-wide prevalence (1) represents one of the most common gastrointestinal birth defects with reported incidence of 1 in 3,000 to 1 in 4,500 live births (2). If esophageal lumen interruption is left unrepaired, infants are prone to inadequate nutrition and growth, as well as infections such as pneumonia (3). EA is classified into 4 types (type A, B, C, and D) based on the anatomical description in relation to the airway structures (4) (**Figure 1**), that does not take into account the complexity of underlying disease.

In addition to associated malformation, the EA gap length dictates the complexity of perioperative care. If the gap of the esophagus is too large to be repaired by direct anastomosis (>3 cm or >2 vertebral bodies in length), EA is defined as *long-gap* EA, which is more commonly found in anatomical types A and B of EA (9). At our institution, the latter cases undergo a unique type of EA repair, the Foker process (5–8). Compared to *short-gap* esophageal atresia, *long-gap* EA is also more likely to be an isolated defect and associated with trisomy 21 (9). In contrast, *short-gap* EA is more commonly found with VACTERL anomalies (vertebral, anorectal, cardiac, tracheo-esophageal fistula and/or esophageal atresia, renal, and limb defects/ malformations) relative to *long-gap* EA (9). Last but not least, CHARGE syndrome (coloboma, heart defects, choanal atresia, growth retardation, genital abnormalities, and ear abnormalities) (10) can further complicate the care of infants born with EA.

The complexity of underlying disease with and without other congenital anomalies in the case of EA is undeniable. Although *short-gap* EA is repaired with direct anastomosis and requires shorter pain management, infants are vulnerable to post-operative feeding challenges (11) in addition to the impact of associated anomalies. In cases of *long-gap* EA, the revolutionary Foker process (5–8) encourages the natural growth and lengthening of infant's existing esophageal pouches, but it requires at least two separate thoracotomies/thoracoscopies with a subsequent prolonged postoperative intubation (12, 13) associated with development of physical dependence to drugs of sedation (13–15). The primary goal of this study addresses the severity of EA disease as a blueprint for a subsequent myriad of caregiving conditions that might impose challenges to developing infants born with EA. Specifically, we conducted a retrospective analysis at a single institution to analyze incidence of EA by severity of disease using American Society of Anesthesiologists (ASA) (16) and Pediatric Risk Assessment (PRAm) (17–19) scores in the context of (i) sex, (ii) gestational age (term-born and premature), (iii) anatomical classification of EA types, and (iv) the type of surgical repair (viz. direct anastomosis vs. Foker process with prolonged sedation). Our secondary clinical end-point measures looked into mortality risk in the context of other co-morbidities according to Spitz et al. (20) and Waterson et al. (21) classifications that take into account co-existing pneumonia and cardiac disease, respectively. This study was, in part, previously published as thesis (22).

Abbreviations: ASA, American Society of Anesthesiologist; **EA**, Esophageal atresia; **CHARGE**, Coloboma, Heart defects, choanal Atresia, growth Retardation, Genital abnormalities, and Ear abnormalities; **PRAm**, Pediatric Risk Assessment; **TEF**, Tracheo-esophageal fistula; **VACTERL**, Vertebral, Anorectal, Cardiac, Tracheo-esophageal fistula and/or Esophageal atresia, Renal, and Limb defects/malformations.

METHODS

Study Design and Subjects Equations

Institutional Review Board at Boston Children's Hospital approved this retrospective cross-sectional research study (IRB-P000007855) of infants born with esophageal atresia (EA) that underwent primary surgical repair at a single institution. The study conformed to the standards set by the Declaration of Helsinki and Good Clinical Practice guidelines. The patient information was obtained from a prospectively maintained clinical database, *The Esophageal and Airway Treatment Center* REDCap database, established in 2009. Considering our institution is not a birthing center, all infants cared for at our institution are considered outborn. Eligibility criteria included: (1) term-born (defined as birth between 37 and 42 weeks of gestation) and premature infants (28–37 weeks of gestation) born with EA of any type, and (2) patients that received their primary surgical repair at Boston Children's Hospital. Cohort patients underwent surgery in the first month of life with exception of two patients that were born outside of the State and underwent primary surgical repair at our institution at 2 and 3 months of age. Exclusion criteria included: (1) extreme prematurity (<28 weeks of gestation), and (2) any surgical repair at other institutions (including but not limited to EA repair). Our retrospective study included a total of 84 patients ($n = 53$ term-born; $n = 31$ premature) over the period of 11 years (2009–2020).

Chart Review

Electronic medical record, Powerchart (Cerner, London, UK) was used to collect demographic data (viz. date of birth; gestational age at birth (weeks); birth weight (kg)) and clinical data. The latter included several end-point measures.

Esophageal Atresia Types

In addition to classification of EA into 4 anatomical types (type A, B, C, and D) based on the anatomical description in relation to the airway structures (4) – in particular to co-existence with tracheo-esophageal fistula (TEF), we also classified EA cases based on the length of EA gap into: *short-gap* (that was repaired by primary anastomosis) and *long-gap* that underwent repair by Foker process (5–8). Some of the patients with *long-gap* EA were managed with our newer minimally invasive Foker process which entails an internal adjustable traction system that is adjusted every 5–7 days via a thoracoscopy. As such, it leads to less postoperative muscle paralysis and sedation in comparison to the external traction Foker process via thoracotomy (8, 23, 24). For the purpose of this study, we identify *short-gap* EA with direct anastomosis repair, and *long-gap* EA with the Foker

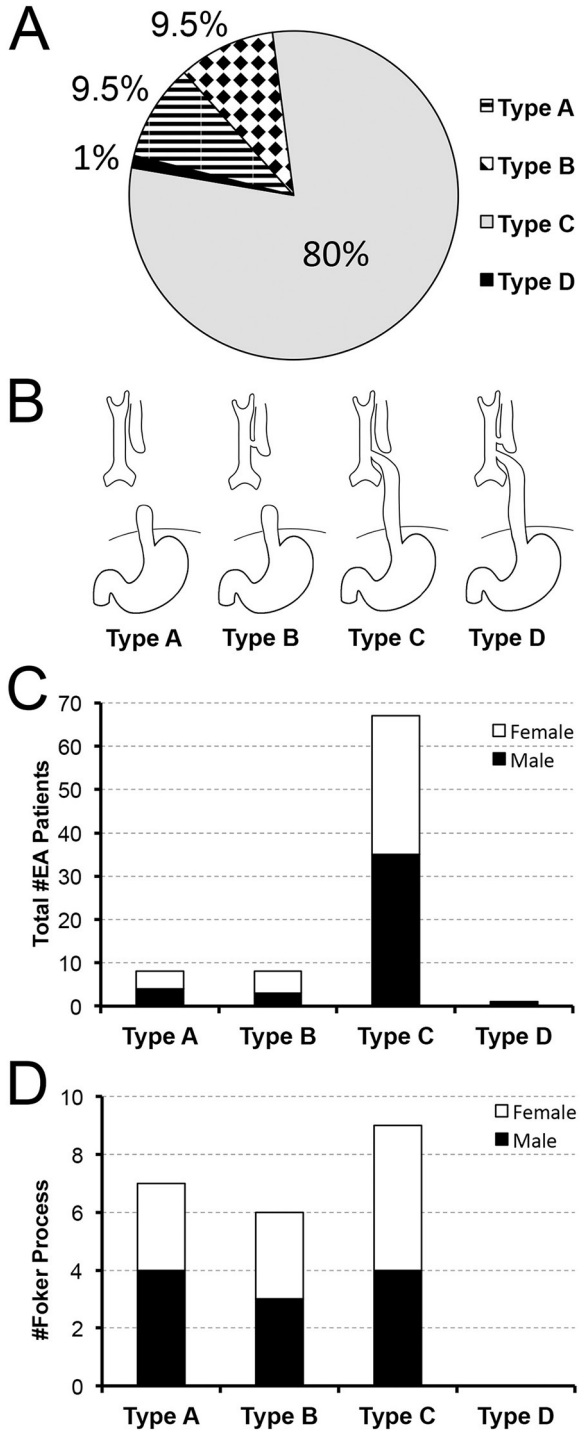


FIGURE 1 | Retrospective Analysis of Incidence of Primary Esophageal Atresia Repair at a Single Institution. Data was retrospectively collected from 2009–2020 ($n = 84$). Pie chart in **(A)** summarizes the percent (%) incidence of esophageal atresia (EA) by anatomical classification that is schematically illustrated in **(B)**. According to our retrospective data analysis, anatomical *type C* of EA is the most frequently encountered. Graph in **(C)** also illustrates nearly equal sex distribution per anatomical type with females found in 50% in *type A*, 62.5% in *type B*, and 48% in *type C*. Graph in **(D)** summarizes the incidence of *long-gap* EA patients ($n = 22$) that underwent Foker process (5–8). Incidence of *long-gap* EA follows the trend per anatomical type and sex, similar to the cohort as a whole (see Results for more detail).

process repair - as these are the two main surgical approaches at our Institution.

Medical/Surgical Comorbidities

As EA often presents with other congenital anomalies and/or co-morbidities, we collected clinical data regarding any other genetic or chromosomal anomalies (e.g., Trisomy 18, 21 etc.), and any other associated congenital anomalies (e.g., vertebral, cardiac, anal anomalies etc.), some of which are a part of the complex congenital syndromes associated with EA such as VACTERL (25) or CHARGE syndrome (26). Co-existing cardiac anomalies were classified as minor (not requiring surgical intervention such as patent foramen ovale, patent ductus arteriosus, atrial septal defect, ventricular septal defect, dextrocardia), or complex (requiring surgical correction such as large ventricular septal defect, large atrial septal defect, coarctation of the aorta, large patent ductus arteriosus, and Tetralogy of Fallow). We quantified the incidence of other associated co-morbidities such as: (i) pneumonia treatment, and (ii) cardiac surgeries, which both served as a basis for mortality risk evaluation (see below). Due to the retrospective study design, characterization of associated co-morbidities was obtained from the medical records as part of the clinical diagnostics and treatment.

Disease Severity

Complexity of clinical status in the context of other comorbidities was assessed using two scoring systems: American Society of Anesthesiologists (ASA) (16) and Pediatric Risk Assessment (PRAm) (17–19) scores at the time of EA repair surgery. Assigning an ASA Physical Status classification level is a clinical decision based on several factors (16) and represents the most commonly used assessment of system level disease severity by anesthesiologists (**Figure 3A**–*Table*). ASA scores are based on several factors and range from ASA I (normal healthy patient) to ASA VI (a declared brain dead patient) (16). In contrast, PRAm scoring is a relatively novel measure introduced in 2017 (17–19) that involves 5 scoring points: urgency of surgical procedure (+1), presence of at least one comorbidity (+2), presence of at least one indication of critical illness (+3), age <12 months at surgery (+3), and co-existing malignancy (+4) for a range of scores from 0 to 13. PRAm scoring has been designed as a less subjective assessment of disease severity for the use specifically in pediatric populations (scores 0 – 13; **Figure 3B**–*Table*).

Mortality Risk Assessment

Considering our retrospective data collection spans period of last 11 years (2009-2020), it was used for comparison to previously published survival rates in infants born with EA as per two different scoring systems: (i) Waterston et al. (21), and (ii) Spitz et al. (20). As originally described by Waterston et al. (21), this scoring system takes into account weight of the patient, co-existence of other congenital anomalies, and pneumonia. Scoring is described as low risk (**group A:** birth weight >2.5 kg with no or co-existing congenital anomaly or pneumonia), moderate risk (**group B:** birth weight 1.8–2.5 kg with co-existing mild pneumonia and mild congenital anomaly), or high risk (**group C:** birth weight 1.8–2.5 kg with co-existing severe pneumonia and severe congenital anomaly).

To improve clarity and transparency with scoring definitions, we modified the original scoring by Waterson et al. (21) for moderate and high risk groups. In this report, the moderate mortality risk group (group B) included infants with co-existing *moderate* pneumonia (defined as receiving antibiotics), and/or a *moderate* congenital anomaly (viz. limb anomalies, cleft lip or palate, atrial-septal defect or small patent ductus arteriosus). High mortality risk (group C) in this study referred to infants with *severe* pneumonia (defined as requiring mechanical ventilation) and/or a *severe* congenital anomaly (viz. defined as making survival difficult or impossible without surgical repair). The second scoring system, described by Spitz et al. (20), takes into account weight and co-existence of a severe cardiac congenital anomaly. The risk is described as low **(I)**, moderate **(II)**, and high **(III)** risk of mortality with major cardiac anomalies defined as one that required medical or surgical treatment.

Statistical Analysis

Data was presented as numerical sums and percentages for (i) sex and anatomical classification of EA, (ii) gestational age at birth, (iii) distribution of *long-gap* EA patients for sex and gestational age, (iv) distribution of congenital anomalies, (v) disease severity scores, and (vi) survival rate. PRAm scores were also presented as numerical sums and as boxplot distributions indicating median scores, first and third quartile ranges, and absolute values for minimum and maximum values.

RESULTS

The retrospective chart review included infants that underwent EA repair at a single institution over a period of 11 years (2009–2020; $n = 84$): 53 term-born, and 31 premature (born between 28 and 37 weeks of gestation).

Demographic Information and Incidence of Esophageal Atresia Types

Anatomical Types

Figures 1A,B illustrate incidence of EA patients according to the anatomical types of EA (4): type A (isolated EA; 8/84, 9.5%), type B (TEF at the upper esophageal pouch; 8/84; 9.5%), type C (the most common type of EA with TEF at the lower esophageal pouch; 67/84; 80%), type D (the rarest type of EA with TEF at each esophageal pouch; 1/84; 1%). Our novel data implicate equal distribution of sex for infants born with EA (**Figure 1C**) with 49% (41/84) female and 51% (43/84) male patients of nearly equal distribution per anatomical types of EA: 50% (4/8) female with type A, 62.5% (5/8) female with type B, and 48% (32/67) female with type C.

Esophageal Gap: Short-Gap vs. Long-Gap

We also distinguished between *short-gap* and *long-gap* EA (see Method's section). The latter is equated to Foker process repair (5–8), that represented 26% of the cohort (22/84). Unlike the cohort as a whole (**Figure 1C**), the incidence of *long-gap* EA cases showed nearly equal distribution by anatomical types (**Figure 1D**): type C (9/22; 41%), type A (7/22; 32%), and type B (6/22; 27%). However, *long-gap* EA accounted for 88% (7/8) of patients in type A, 75% (6/8) in type B, and 13% (9/67) in type C (not graphically shown). Importantly, infants born with *long-gap* EA showed exactly equal distribution of sex (50%; 11/22 female) with nearly equal distribution per anatomical types of EA (**Figure 1D**): 42% (3/7) female with type A, 50% (3/6) female with type B, and 56% (5/9 female) with type C.

Gestational Age

Taking into account exclusion of extreme prematurity, this retrospective cohort shows slightly higher frequency of term-born (53/84, 63%) than premature patients (31/84; 37%) with similar trend per anatomical classification of EA types: 75% (6/8) term-born with type A, 50% (4/8) term-born with type B, and 63% (42/67) term-born with type C (**Figures 2A,B**). There was only one term-born patient with type D EA. Similarly, infants that underwent Foker process for *long-gap* EA repair (**Figure 2C**) had a similar frequency of term-born and premature patients (11/22; 50%). However, term-born patients with *long-gap* EA were predominantly noted in type A (6/7; 86%) while premature infants with *long-gap* EA represented majority in type B (4/6; 67%) and type C (6/9; 67%) as illustrated in **Figure 2C**.

Incidence of Co-existing Congenital Anomalies

Syndromes Associated With Esophageal Atresia

Table 1 summarizes the incidence of other co-existing anomalies with EA. About 42% (35/84) of the cohort patients had complex EA disease as part of a syndrome or known chromosomal abnormality (**Table 1A**). Of those, the most frequent was VACTERL syndrome (31/35, 89%), although we also report cases of CHARGE syndrome (2/35, 6%), trisomy 21 (Down's syndrome; 1/35) and trisomy 18 (Edwards syndrome; 1/35). We also report a similar incidence of VACTERL syndrome in those that underwent primary repair (viz. *short-gap* EA; 24/62; 39%) compared to infants that underwent the Foker process for the repair of *long-gap* EA (7/22; 32%).

Esophageal Atresia in the Absence of Syndrome

For infants born with EA without associated syndrome (49/84; 58%), the majority had either 2 (17/49; 35%) or more than 2 (16/49; 33%) co-occurring congenital anomalies. Only a minority of patients had no co-existing congenital anomalies (6/49, 12%; **Table 1B**). Interestingly, a majority of patients – apart from syndromic patients (49/84; 58%) - had a cardiac anomaly (38/49; 78%) and no patients had a documented anorectal anomaly occurring outside of a syndrome (**Table 1C**).

Cardiac Co-anomalies

Of all the infants born with EA that had co-existing cardiac anomalies (72/84; 86%), only 18% (15/84) had congenital heart disease severe enough to require surgical repair (**Table 2A**). Of those that underwent cardiac surgery, 93% (14/15) had type C EA, and only one patient had type B EA. We report a similar pattern of co-existing congenital cardiac anomalies in

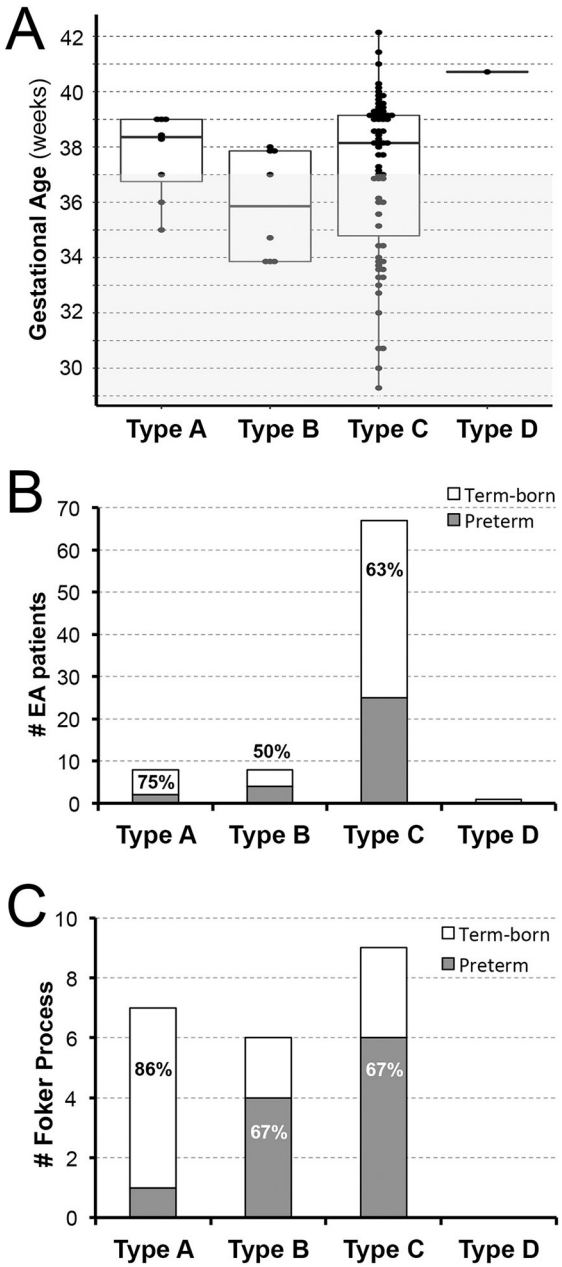


FIGURE 2 | Retrospective Analysis of Esophageal Atresia Classification by Gestational Age at Birth. Retrospective data of infants born with esophageal atresia (EA) was collected from 2009–2020 ($n = 84$) and included infants born ≥28 weeks of gestation that were classified as term-born (37–42 weeks gestation) or premature (28–37 weeks of gestation). **(A)** Illustrates individual distribution of gestational age at birth per EA type (dots), while gray area schematically marks prematurity (<37 weeks of gestation). **(B)** Summarizes percent (%) incidence of EA per anatomical type and gestational age groups with either equal (type B) or predominant incidence of term-born patients (type A and C). In this cohort of infants with primary surgical repair of EA at our institution, we report only one term-born infant with *type D* EA. For illustration of anatomical EA types, please see **Figure 1B**. **(C)** Summarizes incidence of infants that underwent Foker process (5–8) for *long-gap* EA repair. We report equal incidence of term-born and preterm patients. However, term-born patients with *long-gap* EA were predominantly noted in *type A* (6/7; 86%) while premature infants with long-gap EA represented majority in *type B* (4/6; 67%) and *type C* (6/9; 67%) anatomical EA type.

TABLE 1 | Incidence of esophageal atresia in the context of other congenital anomalies.

	Number	Percentage (%)
A. EA as part of complex congenital syndrome (cohort $n = 84$)		
VACTERL	31	37%
CHARGE	2	2%
Other	2	2%
None	49	58%
B. EA with other co-anomalies apart from syndrome ($n = 49$)		
None	6	12%
Isolated anomaly	10	20%
2 anomalies	17	35%
More than 2 anomalies	16	33%
C. Distribution of co-anomalies apart from syndrome ($n = 49$)		
Anorectal	0	0%
Vertebral	10	20%
Cardiac	38	78%
Laryngeal cleft	9	18%
Tracheo(broncho)malacia	23	47%
Limb	2	4%
Renal or Kidney	13	27%

Incidence of esophageal atresia with or without other congenital anomalies. (A) *shows that 42% (35/84) of EA was a part of complex syndrome: VACTERL syndrome (31/35, 89%); CHARGE syndrome (2/35, 6%); Trisomy 21 (Down's syndrome; 1/35); and Trisomy 18 (Edwards syndrome; 1/35). As illustrated in* ***(B)****, of those esophageal atresia (EA) infants with no complex congenital diagnosis (49/84; 58%), a majority had either 2 (17/49; 35%) or > 2 (16/49; 33%) co-occurring congenital anomalies not associated with the syndrome. Incidence of specific co-existing anomalies is listed in* ***(C)****. Interestingly, a majority of patients had a cardiac anomaly (38/49; 78%) and no patients had a documented anorectal anomaly occurring outside of a syndrome. Acronyms: CHARGE, Coloboma, Heart defects, choanal Atresia, growth Retardation, Genital abnormalities, and Ear abnormalities; VACTERL, Vertebral, Anorectal, Cardiac, Tracheo-esophageal fistula and/ or Esophageal atresia, Renal, and Limb defects/ malformations.*

infants with *long-gap* EA that underwent the Foker process repair (**Table 2B**): 86% (19/22) had co-existing cardiac anomalies, but only 14% (3/22) required cardiac surgery and were diagnosed with either type C EA (2/3) or type B EA (1/3). **Table 2** summarizes severity of cardiac findings in this cohort.

Severity Stratification of Underlying Disease

Figure 3 illustrates 2 different disease severity scores by anatomical EA types (types A-D; **Figure 1B**) and gestational age (term-born vs. premature).

American Society of Anesthesiologists Physical Status Classification

Half of the patients of this cohort were rated either ASA Physical Status III (49% (41/84) with severe systemic disease; 76% (31/41) term-born; 24% (10/41) premature), or ASA Physical Status IV (51% (43/84) with severe systemic disease that is a constant threat to life; 51% (22/43) term-born; 49% (21/43) premature). **Figure 3A** shows ASA Physical Status classification of the cohort infants per anatomical types of EA. For the most common type of EA – type C, the majority of term-born patients received ASA

TABLE 2 | Incidence of co-existing congenital cardiac anomalies.

EA type	Total number	Minor (no cardiac surgery)	Major (cardiac surgery)
A. Cohort (*n* = 84)	**72/84 (86%)**	**57/72 (79%)**	**15/72 (21%)**
Type A	6/8 (75%)	6/6 (100%)	0/6 (0%)
Type B	5/8 (63%)	4/5 (80%)	1/5 (20%)
Type C	60/67 (90%)	46/60 (77%)	14/60 (23%)
Type D	1/1 (100%)	1/1 (100%)	0/1 (0%)
B. Foker Process (*n* = 22)	**19/22 (86%)**	**16/19 (84%)**	**3/19 (16%)**
Type A	5/7 (71%)	5/5 (100%)	0/5 (0%)
Type B	5/6 (83%)	4/5 (80%)	1/5 (20%)
Type C	9/9 (100%)	7/9 (78%)	2/9 (22%)
Type D	none	N/A	N/A

Incidence of Congenital Cardiac Anomalies by Esophageal Atresia Types. *Table summarizes incidence of co-existing cardiac anomalies in infants born with esophageal atresia (EA) stratified by anatomical type in relation to the tracheo-esophageal fistula (See also **Figure 1**) for the entire cohort **(A)**, and in a subset of long-gap EA patients that underwent Foker process repair **(B)**. Incidence of cardiac anomalies is shown as total number (left column; n = 84). Of those that underwent cardiac surgery (n = 72), we summarize percent (%) of those with minor cardiac anomaly (not requiring surgery; central column; n = 57), and those that underwent cardiac repair (major anomaly; right column; n = 15).*

III status (27/42; 64%), while the majority of premature infants received ASA IV status (19/25; 76%).

Pediatric Risk Assessment Scores

Considering all patients in this retrospective cohort underwent surgical repair in infancy, and none had any associated malignancy, the PRAm score ranged from 3 to 9 across all anatomical types and gestational age groups (**Figure 3B**). For the cohort as a whole, we report Median PRAm score of 5 for both term-born (interquartile range of 4–6) and premature infants (interquartile range of 5–8). When classified according to anatomical EA types, premature infants had a higher median score for type B EA (Median 7; interquartile range of 4.75–9), but a lower median score for most frequent type C (Median 5; interquartile range 5–8) in comparison to term-born infants (Median 4; interquartile range of 3–5 for type B; Median 5; interquartile range of 4–6 for type C). While type B shows higher PRAm scores for premature infants, there is a limited number of patients in this group ($n = 8$) compared to type C ($n = 67$). Furthermore, we report a wide PRAm score classification (**Figure 4A**) for term-born patients with propensity for lower PRAm scores (25% (13/53) PRAm 3; 9% (5/53) PRAm 9), and premature infants with propensity for higher PRAm scores (10% (3/31) PRAm 3; 23% (7/31) PRAm 9).

Relationship Between ASA Physical Status and PRAm Scores

To better gauge individual relationship of two different scores, **Figure 4B** illustrates relationship between ASA physical status and PRAm scores. Despite wide distribution of PRAm scores irrespective of the gestational age (**Figure 4A**), patients with assigned ASA IV classification had about equal distribution per gestational age groups: premature (21/43; 49%) and term-born patients (22/43; 51%). However, we do not show that premature infants with ASA IV physical classification ($n = 21/43$) align with higher PRAm score distribution (**Figure 4B**).

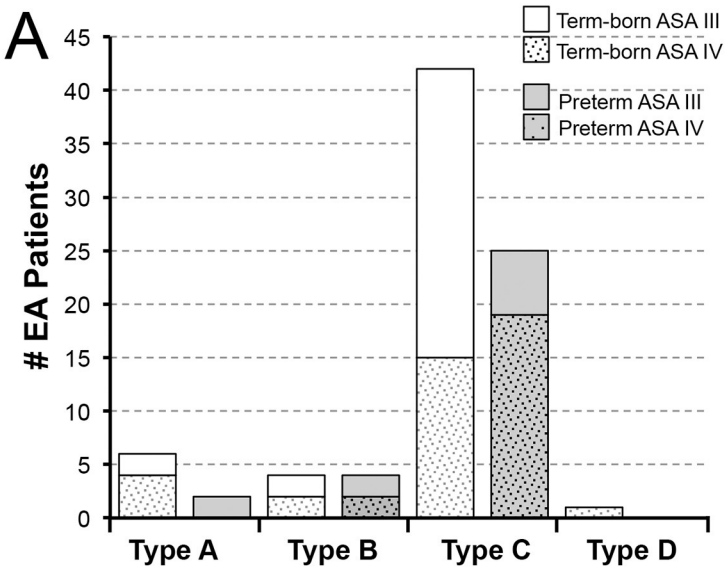
Disease Severity With Respect to Type of EA Surgical Repair

We also report a wide distribution of PRAm scores (scores 3-9) irrespective of the type of surgical repair (**Figure 5A**). However, infants born with *short-gap* EA undergoing direct anastomosis repair ($n = 62$) have a propensity for lower PRAm scores in term-born patients (62.5% (10/16) PRAm 3; 42% (5/12) PRAm 9) and higher PRAm scores in premature patients (12.5% (2/16) PRAm 3; 17% (2/12) PRAm 9) as illustrated in **Figure 5B**. Similarly, infants born with *long-gap* EA undergoing Foker process repair ($n = 22$) have a propensity for lower PRAm scores in term-born patients (19% (3/16) PRAm 3; 0% (0/12) PRAm 9) and higher PRAm scores in premature patients (6% (1/16) PRAm 3; 42% (5/12) PRAm 9) as illustrated in **Figure 5B**. Considering more premature patients with EA have ASA IV classification status (**Figure 3A**), prematurity should be considered a confounding factor for increased underlying disease severity. As such, other important aspects of prematurity, such as intra-uterine growth retardation and prematurity associated sequelae (e.g., respiratory distress syndrome) should be considered as potential indirect markers of prematurity in assessing outcomes following EA repair. Finally, when PRAm scores (with score range from 3–9) are graphed in relation to ASA physical status (**Figure 5C**), more infants with *long-gap* EA are scored as ASA IV classification (73%; 16/22) compared to *short-gap* EA patients (44%; 27/62). Future goals should include unique scoring system design that would include other potential confounders unique for EA repair, such as length of post-operative mechanical ventilation and antibiotic treatment as indirect markers of postoperative sedation and infections, respectively.

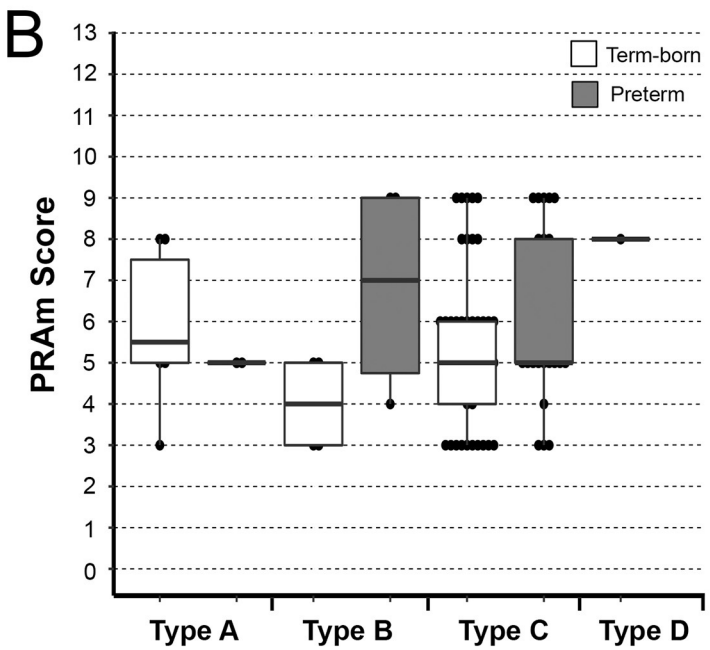
Mortality Risk Assessment of Infants Born With Esophageal Atresia

Mortality Risk Assessment I

Table 3 summarizes the mortality risk assessment as originally described by Waterston et al. (21) in EA patients according to the (i) birth weight, (ii) co-existing congenital anomalies (**Tables 1** and **2**), and (iii) co-morbidity with pneumonia into: low (group A), moderate (group B), and high mortality risk (group C). Indeed, our retrospective study is of similar population size of EA patients ($n = 84$) as in the original report ($n = 113$) (21). However, our cohort had smaller numbers of infants in low risk group and much higher number of infants in high mortality group, group C (**Table 4**). With that in mind, we also show striking survival rates especially in the moderate risk (group B; 100% (42/42) vs. 68% (29/43 in the Waterson's study) and high risk group [group C; 95% (38/40) vs. 6% (2/32) in the original study (21)].



Score	Definition
ASA I	Healthy
ASA II	Mild systemic disease
ASA III	**Severe systemic disease**
ASA IV	**Disease - a threat to life**
ASA V	Moribund patient



Value	Definition
+1	Urgent Surgical Procedure
+2	At least 1 comorbidity
+3	≥ 1 indication of critical illness
+3	<12 months age at time of surgery
+4	Surgical procedure with neoplasm or preoperative chemotherapy
* Values are added and scored 0-13.	

FIGURE 3 | Underlying Disease Severity Stratification in Esophageal Atresia Cohort. Graphs illustrate incidence of American Society of Anesthesiologists (ASA) Physical Status classification **(A)** and Pediatric Risk Assessment (PRAm) severity scores **(B)** in infants born with esophageal atresia (EA) that underwent primary repair at a single institution from 2009-2020 ($n = 84$). Definition of scoring is shown in summary tables on the right for both the ASA Physical Status (16) and PRAm scoring (17–19). Graphs show stratification by anatomical types of EA (type A-D) and gestational age (term-born and premature; see Methods section). Specifically, all patients in this study were rated as either ASA Physical Status III or IV **(A)**. For the most common *type C* EA, the majority of term-born patients had ASA III status (27/42; 64%), while the majority of premature infants were assigned ASA IV status (19/25; 76%) implicating premature infants were more critically ill in the most common type of EA, *type C*. Graph in **(B)** illustrates distribution of PRAm scores per anatomical type and gestational age. Considering all infants had surgery when <12 months of age, the minimal score was 3. Since none of the infants had co-existing malignancy, the highest score was 9. From the graph in **(B)**, one can infer that premature infants had higher median score for type B EA, but lower median score for type C (thick horizontal line). Individual values are represented as dots, boxes span the interquartile range (IQR) (first and third quartile), and whiskers represent maximum and minimum values.

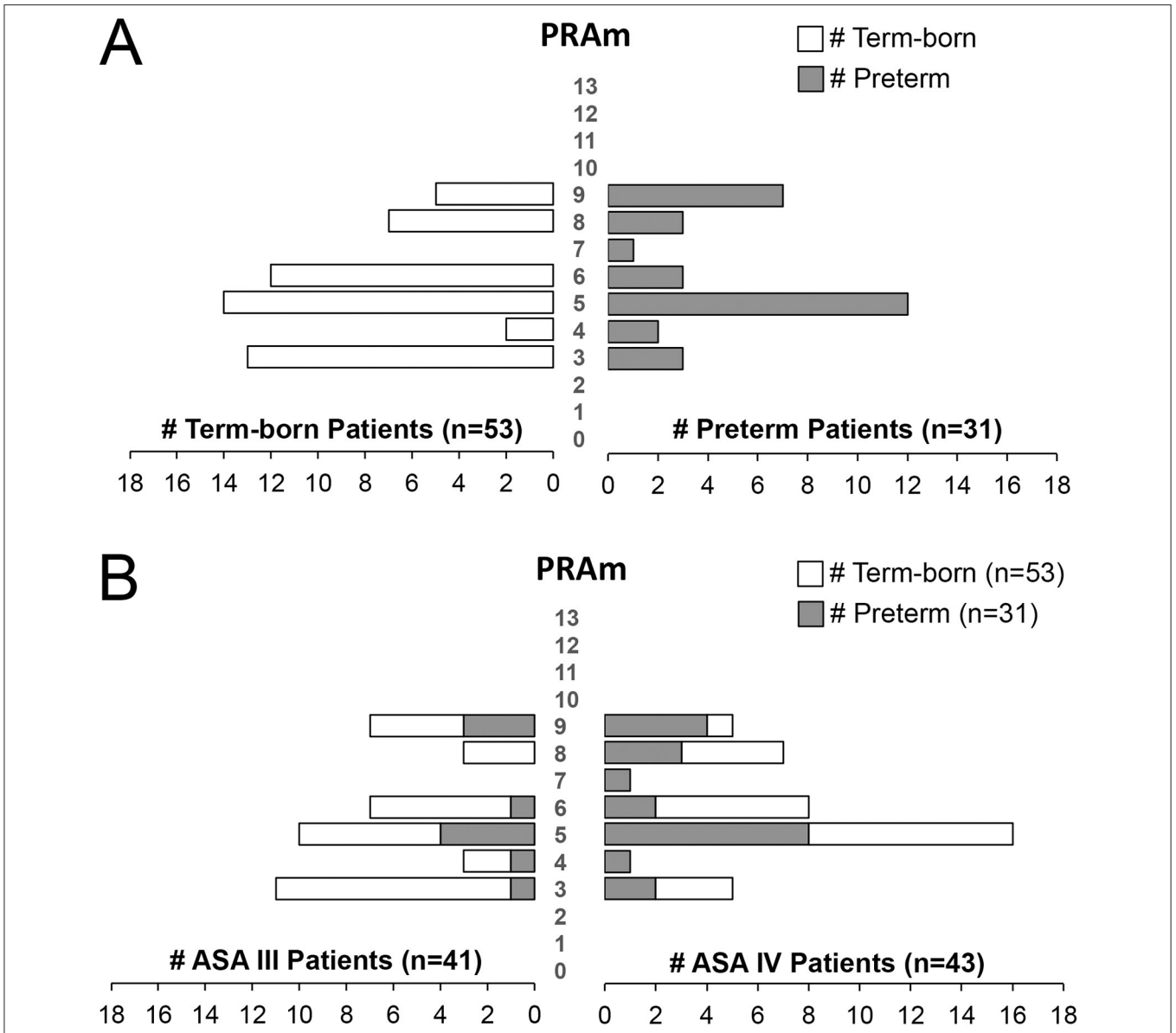


FIGURE 4 | Pediatric Risk Assessment (PRAm) Scores in a Retrospective Cohort of Infants Born with Esophageal Atresia. **(A)** Shows PRAm scores of term-born (left) and preterm patients (right) illustrating a wide range of PRAm score across gestational age of infants born with esophageal atresia (EA; $n = 84$). Note a subtle tendency of term-born patients for lower, and premature patients for higher PRAm scores. **(B)** Plots PRAm scores in relation to American Society of Anesthesiologists (ASA) Physical Status Classification. Despite more premature infants having had higher ASA IV classification (21/31; 68%) in comparison to term-born (22/53; 41%; see also **Figure 3A**), PRAm score shows wide distribution of scores between 3 and 9. Such outlining is in support of ASA and not PRAm scoring in assessing disease severity when gestational age is the primary factor.

Mortality Risk Assessment II

The second scoring system by Spitz et al. (20) takes into account (i) birth weight and (ii) co-existence and (iii) severity of cardiac congenital anomalies. The risk is described as low (I), moderate (II), and high (III) risk of mortality. Although our retrospective cohort has lower power ($n = 84$) in comparison to previous decades' reports: 1980–1992 ($n = 372$) (20) and 1993–2004 ($n = 188$) (27), we report improved survival rates (**Table 4**), especially for low risk group (I; 100%; 62/62) and moderate risk group (II) of 90% (19/21). This data are in stark contrast to moderate risk group (II) survival rates of 59% (41/70) during 1980s (1980–1992) (20) and 82% (41/50) survival rate in the following decade (1993–2004) (27). Since our cohort only had only one patient that met criteria for group III - in part due to the exclusion criteria of extremely premature patients (<28 weeks), future clinical studies are needed to evaluate group III survival rates at our institution.

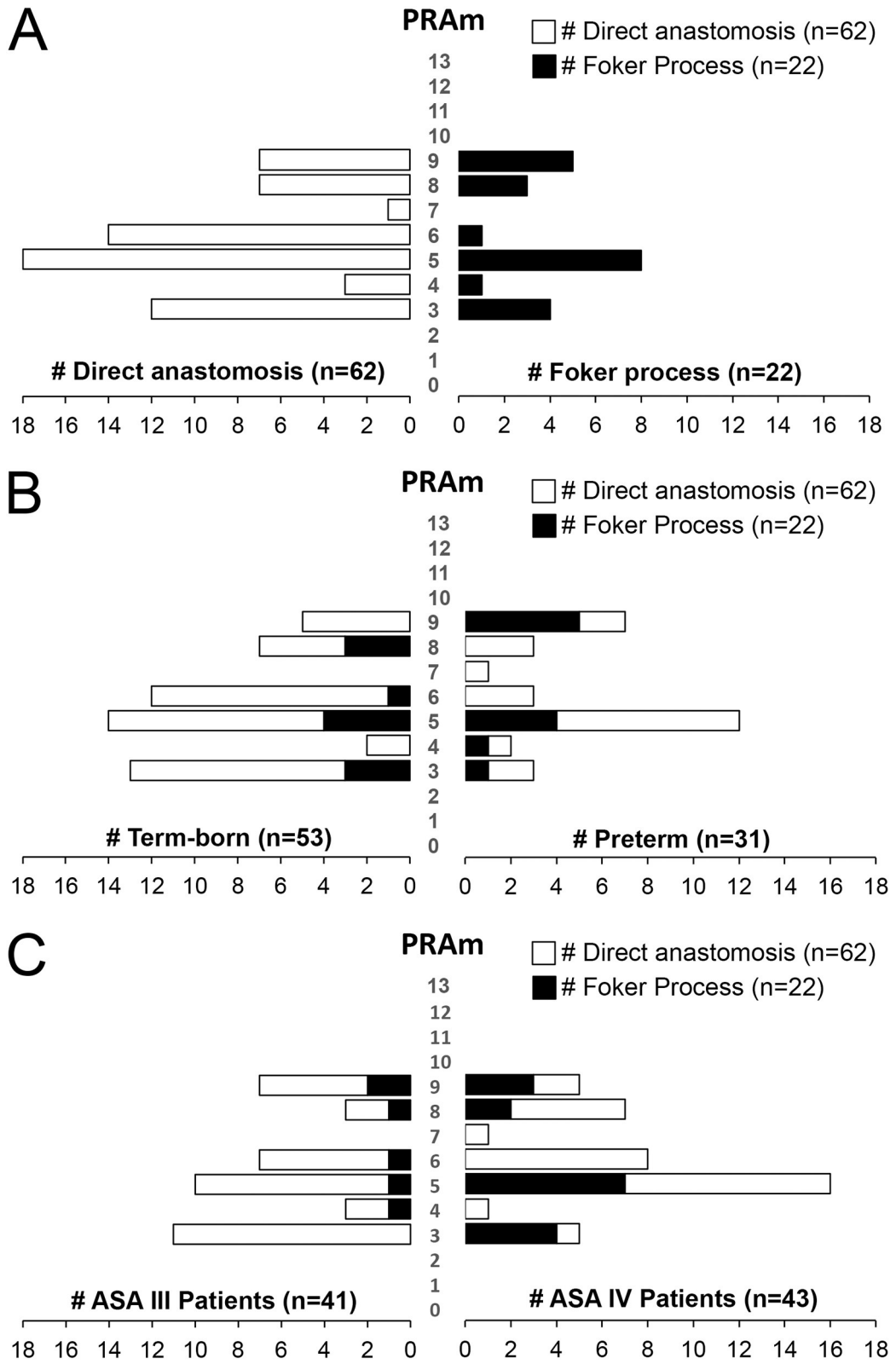


FIGURE 5 | Disease Severity Stratification of Infants Born with Esophageal Atresia by Type of Surgical Repair. **(A)** Illustrates wide distribution of Pediatric Risk Assessment (PRAm) scores (from scores 3–9) by the type of surgical repair: (i) direct anastomosis for *short-gap* esophageal atresia (EA) repair (left), and (ii) Foker process (5–8) for *long-gap* EA repair (right). **(B)** Summarizes severity of disease per type of surgical repair in relation to the gestation age at birth. Similar to data in **Figure 4A**, note the subtle tendency of term-born patients having had lower, and premature patients higher PRAm scores. When PRAm scores are graphed in relation to American Society of Anesthesiologists (ASA) physical status **(C)**, we report more infants with *long-gap* EA with an ASA IV classification (73%; 16/22).

TABLE 3 | Mortality risk assessment I.

Group	Definition	1951–1959 (21) ($n = 113$)	2009–2020 ($n = 84$)
A	Birth weight >2.5 kg	36/38 (95%)	2/2 (100%)
B	1.8 kg <Birth weight <2.5 kg or >2.5 kg with moderate congenital anomaly and/or pneumonia	29/43 (68%)	42/42 (100%)
C	Birth weight <1.8 kg or >2.5 kg with a severe congenital anomaly and/or pneumonia	2/32 (6%)	38/40 (95%)

Survival rates of infants born with esophageal atresia according to scores by Waterson et al*. Using a modified Waterston et al. protocol (21), patients born with esophageal atresia (EA) were stratified into 3 categories **(A–C)** of mortality risk based on birth weight, co-existing anomalies, and presence or absence of pneumonia. The risk is described as low **(A)**, moderate **(B)**, and high **(C)** risk of mortality. Previously reported incidence of survival rates for EA patients (1951–1959) (21) is shown along with the current cohort's survival rates (2009–2020). Our results demonstrate increased survival, especially for group with moderate and higher mortality risk, groups B and C, respectively.*

TABLE 4 | Mortality risk assessment II.

Group	Definition	1980–1992 (20) ($n = 372$)	1993–2004 (27) ($n = 188$)	2009–2020 ($n = 84$)
I	Birth weight >1.5 kg and no major cardiac anomaly	283/293 (97%)	130/132 (98.5%)	62/62 (100%)
II	Birth weight <1.5 kg or major cardiac anomaly	41/70 (59%)	41/50 (82%)	19/21 (90%)
III	Birth weight <1.5 kg and major cardiac anomaly	2/9 (22%)	3/6 (50%)	1/1 (100%)

Survival Rates Assessment of Infants Born with Esophageal Atresia According to Scores by Spitz et al. *Using the Spitz et al. protocol (20), patients born with esophageal atresia (EA) were stratified into three categories of mortality risk based on birth weight, and the presence and severity of cardiac anomaly. Major cardiac anomalies were defined as one that required medical or surgical treatment. The risk is described as low **(I)**, moderate **(II)**, and high **(III)** risk of mortality. Spitz's original incidence of survival rates of EA patients for two separate decades, (1980–1992) (20) and (1993–2004) (27), are shown along with the current cohort's survival rates (2009–2020). Our results demonstrate increased survival, especially for low and moderate mortality risk groups.*

DICUSSION

Our novel results using retrospective approach from a single institution show near equal distribution of sex and gestational age (term-born vs. premature) by anatomical type of EA (types A–D) and by type of surgical repair (direct anastomosis vs. Foker process). We also share the incidence of co-occurring congenital anomalies with EA, with special emphasis on cardiac anomalies that have been shown to be a major mortality risk factor for infants born with EA (20). Although PRAm score showed a wider range of disease severity (3–9), ASA scores (III and IV) are more useful in predicting disease severity. We also report increased survival rate in our EA cohort in comparison to the literature in previous decades.

Limitations of the Retrospective Chart Review

In keeping with the retrospective study design (28), data collected were originally intended for reasons other than research (29, 30). Due to the dependence of patient information stored for clinical practice, retrospective analysis may represent incomplete or missing documentation, poorly recorded or absent chart information, as well as difficult identification of desired patient data [e.g., attainment of PRAm scores (17) for cases of EA repair prior to 2017].

Study Size

Despite the exclusion of cases with extreme prematurity, and surgical repair at an outside institution, this study retained a moderate sample size with enough power to evaluate EA disease characteristics. The main challenges imposed with the exclusion criteria are that of generalizability since our institution represents a highly specialized level of care.

High-Risk Mortality Scores

Mortality risk assessment scores were quantified according to the scores previously described in the literature by Waterston et al. (21), and Spitz et al. (20). For both types of scoring, the high-risk groups used very low birth weights as surrogates for extreme prematurity. For this study, we defined Waterston risk assessment for the highest risk group (group C) as either (i) a low birth weight (associated with prematurity) or (ii) a standard birthweight with severe congenital anomaly or severe pneumonia. Therefore, analysis of Waterston et al. (21) group C was likely not significantly impacted by the exclusion of extreme prematurity. In contrast, the Spitz risk assessment required a birth weight <1.5 kg for the highest risk group (group III) for which only one patient from our retrospective cohort met criteria. Therefore, risk assessment of group III of the Spitz et al. (20) classification is not powered in our retrospective study.

Characteristics of Esophageal Atresia Cohort

Anatomical Types of Esophageal Atresia

We report similar distribution of EA patients according to the anatomical classification (**Figure 1A**) compared to the literature (4, 31, 32) although one should keep in mind that definition of long-gap EA might differ. Our slightly increased incidence for type A and type B EA could be explained by the fact that data was obtained from a single institution, which pioneered the Foker process (5–8) for repair of *long-gap* EA (9) and receives patients locally, nationally and internationally. Indeed, we report higher incidence of *long-gap* EA in more rare types of EA: types A and type B, despite type C having the highest number of *long-gap* EA patients in this cohort (**Figure 1D**). The definitions for *long-gap* EA have not been agreed upon and can confound the comparison of data within the literature. Currently, a common method of classification is to simply define types A and B as *long-gap EA* and all others as *short-gap* EA (33, 34). The presence of long-gap EA patients with type C EA (**Figure 1D**) is in direct contrast to those studies that classify *long-gap* EA by purely anatomical classification. However, Ure et al. in 1995 (35) reported a total of 9 long-gap EA patients and a majority of them having type C EA. Study by Donoso et al. in 2016 (34) reported that a single patient with type

C EA underwent *long-gap* EA repair despite being classified as *short-gap* in their study. Due to the inconsistency in the literature, we defined *long-gap* EA by surgical procedure [viz. Foker process (5–8)] implicating complex perioperative critical care instead of anatomical definitions based on the location of the EA gap.

Sex Distribution

We report nearly equal sex distribution for the entire cohort ($n = 84$), which is consistent with previous large retrospective reports (36–39). Since sex distribution for EA patients was only reported for the entire cohort (34, 39–41), we indicate – for the first time – that there is nearly equal sex distribution in EA patients by anatomical types (**Figure 1C**). We also report equal sex distribution for *long-gap* EA patients, which is in accordance with previous report in a larger cohort (9). Findings of equal sex distribution indicate that there is possibly no sex preference in infants born with EA – the subject of interest that continues to be investigated.

Distribution as Per Gestational Age

Our study found a slightly higher incidence of term-born patients in comparison to premature infants (28–37 weeks of gestation) with EA (**Figures 2A,B**). This finding stands in contrast to a large national cohort study of EA that included all gestational ages and found a higher prevalence of EA in premature patients (39). This discrepancy could be explained, in part, by our exclusion criteria that eliminated extremely premature patients from the cohort. However, our findings of higher incidence of term-born patients are consistent with the national studies in France (41) and Italy (40) reporting similar results. While the incidence of gestational age in *long-gap* EA patients are reported in the literature (6, 42), our novel results outline incidence of *long-gap* EA by anatomical types (**Figure 1B**). Discrepancy among gestational age within EA studies and novel findings of gestational age distribution in *long-gap* EA patients (with exclusion of extreme prematurity) suggests the need for future analysis to discern demographics of prematurity, as it represents an important risk factor in hospital mortality (43).

Incidence of Associated Congenital Anomalies and Comorbidities With Esophageal Atresia

Congenital co-anomalies with EA can present as a wide spectrum across multiple organ systems (26), and can pose a challenge for care of infants with EA with increased risk of mortality and morbidity (44).

VACTERL Syndrome

The incidence of VACTERL association in this cohort was high at 37% compared to the literature report at around 10% (44) (**Table 1A**). Higher incidences of VACTERL syndrome in our report has previously been recognized in other studies (9) and is likely due to recognized differences in VACTERL diagnostics (45). Our cohort was comprised of sicker infants due to the very low incidence of isolated EA at 12% (**Table 1B**) compared to very large cross-hospital findings of isolated EA at 45% (36), 57.3% (37), and 38.7% (38) at other institutions. Findings of increased incidence of VACTERL and other comorbidities in this study possibly reflects institutional reputation as a national and international referral center for infants born with EA. Our report of higher incidence of VACTERL patients in *short-gap* EA are in accordance with previous report from our institution (9). This is in contrast to the study from Tabriz Children's Hospital and Tehran Mofid Hospital in Iran that reported no difference in incidence of VACTERL spectrum defects irrespective of the type of surgical repair required (42). The analysis of etiology of VACTERL syndrome is outside the scope of this study but is described well in the literature (25, 45, 46) and continues to be investigated.

Congenital Cardiac Anomalies

It is well known that co-occurring cardiac anomalies can impact the length and complexity of care for EA patients (41). We identified that most EA patients had co-existing cardiac anomalies: 86% for the entire cohort (**Table 2A**) and 79% in the non-syndromic cases (**Table 1C**). This is consistent with literature report from the Children's Hospital of Chongqing Medical University, China (71.2%) (47) and a large multicenter study of EA patients across 43 hospitals (70%) (43). We and others (48) report that a great majority of co-existing cardiac anomalies were defined as simple. We also report, for the first time, that only about a fifth of EA patients with co-existing cardiac anomalies had undergone cardiac repair – of which majority were type C EA cases (**Table 2A**). Our novel data in infants with *long-gap* EA show having nearly equal incidence of cardiac co-anomalies compared to the entire cohort with a similar incidence of patients requiring cardiac surgery (**Table 2B**). Our results confirm that (i) non-syndromic patients with EA may present with additional and potentially life-threatening congenital anomalies and that (ii) infants with non-syndromic *long-gap* EA can have cardiac anomalies imposing additional risk to their care (20, 41).

Perioperative Risk Assessment

Underlying Disease Severity

Despite wider PRAm score variability (score 3-9; **Figure 4A**) and the same PRAm median score of 5 irrespective of the gestational age (**Figure 3B**), ASA Physical Status classification remains a golden standard in assessing underlying disease severity. We only noted a trend in term-born patients toward propensity for lower PRAm scores irrespective of the surgical type, while premature patients with *long-gap* EA showed propensity for higher PRAm scores (**Figure 5B**). Latter trends are in alignment with the seminal report in literature of a large cohort of infants undergoing non-cardiac surgery, validating PRAm scoring in predicting perioperative risk (17). Future work should also analyze unique risk factors related to surgical type of EA repair (viz. direct anastomosis vs. Foker process; open vs. laparoscopic approach) to expand on previous risk stratification of patients born with EA (49, 50). Morbidity risk assessment should also possibly include assessment of the neurological findings as our

recent pilot study of infants with *long-gap* EA reported incidental brain findings for not only premature but term-born infants following Foker process repair ($n = 13$/group) (12, 15, 51, 52).

Mortality Risk Assessment

We report increased survival rates in this cohort as per two different mortality risk assessment scores. Despite our modification to the scoring schema by Waterston et al. (21), we report the total survival rates have vastly improved in the last decade for each of the described Waterston risk groups (**Table 3**). In addition, Spitz et al. (20) extended Waterston's mortality risk score in 1994 by including co-existing cardiac anomalies with EA. Indeed, the latter mortality risk score represents the most widely used mortality risk stratification that continues to be used for assessing risk in EA patients (27, 34). According to the most recent study of mortality predictors, major congenital heart disease was a significant predictor, while birth weight <1.5 kg was not (53). Indeed, we report increased survival rates in the most recent decade (2009–2020; **Table 4**) when compared to 1980s (20) and 1990s (27, 34) as previously published by Spitz et al. (20, 27). Such data are in support of great improvements in perioperative critical care of EA patients and treatment of their comorbidities, which may account for our reporting of improved survival. As per literature recommendation, the preferred clinical management of infants born with EA should be aided by highly specialized multidisciplinary team at expert centers (54) to help increase survival and decrease the incidence of morbidities (55). Therefore, improved outcomes in this report may be explained – in part, by the highly specialized nature of *The Esophageal and Airway Treatment Center* at our institution. Increased survival rates over the last decade suggest a potential need to assess unique operative and perioperative risks in this unique population of patients, as well as non-survival metrics such as functional status and quality of life.

Last, but not least, previous reports also suggests that extremely low birth weight infants with EA patients are at a higher risk of mortality (56), while a recent study showed potentially improved outcomes for extremely low birth-weight infants that underwent a staged repair for EA (57). Analysis of survival rates of extremely low birth weight infants with EA, especially those that underwent the Foker process for *long-gap* EA repair is needed to validate and potentially expand on these and our findings.

CONCLUSIONS

We present a comprehensive analysis of EA patient classification by anatomical types (type A-D) and by surgical repair type (direct anastomosis vs. Foker process for *short-gap* vs. *long-gap* EA, respectively). Despite a wider PRAm score distribution in infants born with EA, ASA scores remain the gold standard in assessing underlying disease severity stratification. With increase in survival rates over the last decade, future studies should be directed toward assessing unique aspects of EA group in the context of (i) severity of underlying disease with and without comorbidities, (ii) unique complexities of perioperative critical care (with and without prolonged sedation, repeated procedures, and infection/sepsis assessment), and (iii) survival metrics such as functional status (e.g., neurobehavioral outcomes and quality of life). It is our hope that this retrospective study will be of service to research community when designing future clinical studies of risks and outcomes in this uniquely vulnerable population of infant patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The Institutional Review Board at Boston Children's Hospital approved this retrospective cross-sectional research study (IRB-P000007855) of infants born with esophageal atresia (EA) that underwent primary surgical repair at a single institution.

AUTHOR CONTRIBUTIONS

Authorship credit was based on substantial contribution to (1) the conception and manuscript design (DE, JW, and DB), (2) acquisition (DE, JW, RJ, and DB), analysis (DE and DB), or interpretation of data (all authors), drafting the article (DE and DB) or critical revision for important intellectual content (all authors), (3) final approval of the version to be published (all authors), and (4) 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 (all authors).

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Necessity of Prophylactic Extrapleural Chest Tube During Primary Surgical Repair of Esophageal Atresia: A Systematic Review and Meta-Analysis

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Background: Esophageal atresia is corrected surgically by anastomosing and recreating esophageal continuity. To allow the removal of excess fluid and air from the anastomosis, a prophylactic and temporary intraoperative chest tube (IOCT) has traditionally been placed in this area during surgery. However, whether the potential benefits of this prophylactic IOCT overweigh the potential harms is unclear.

Objective: To assess the benefits and harms of using a prophylactic IOCT during primary surgical repair of esophageal atresia.

Data Sources: We conducted a systematic review with a meta-analysis. We searched Cochrane Central Register of Controlled Trials (2021, Issue 12), MEDLINE Ovid, Embase Ovid, CINAHL, and Science Citation Index Expanded and Conference Proceedings Citation Index—(Web of Science). Search was performed from inception until December 3rd, 2021.

Study Selection: Randomized clinical trials (RCT) assessing the effect of a prophylactic IOCT during primary surgical repair of esophageal atresia and observational studies identified during our searches for RCT.

Data Extraction and Synthesis: Two independent reviewers screened studies and performed data extraction. The certainty of the evidence was assessed by GRADE and ROBINS-I.

PROSPERO Registration: A protocol for this review has been registered on PROSPERO (CRD42021257834).

Results: We included three RCTs randomizing 162 neonates, all at overall "some risk of bias." The studies compared the placement of an IOCT vs. none. The meta-analysis did not identify any significant effect of profylacitic IOCT, as confidence intervals were

compatible with no effect, but the analyses suggests that the placement of an IOCT might lead to an increase in all-cause mortality (RR 1.66, 95% CI 0.76–3.65; three trials), serious adverse events (RR 1.08, 95% CI 0.58–2.00; three trials), intervention-requiring pneumothorax (RR 1.65, 95% CI 0.28–9.50; two trials), and anastomosis leakage (RR 1.66, 95% CI 0.63–4.40). None of our included studies assessed esophageal stricture or pain. Certainty of evidence was very low for all outcomes.

Conclusions: Evidence from RCTs does not support the routine use of a prophylactic IOCT during primary surgical repair of esophageal atresia.

Keywords: chest tube, neonates, tracheoesophageal fistula, esophageal atresia, pediatric surgery

INTRODUCTION

Esophageal atresia refers to a group of congenital anomalies in which the continuity of the esophagus is interrupted (1). Tracheoesophageal anomalies are divided into subtypes depending on anatomy and the most prominent (85%) subtype has a tracheoesophageal fistula to the distal esophageal segment (1). The prevalence of esophageal atresia varies according to country and time period (2–8). Observational studies from 1981 to 2018 have estimated the prevalence to span from 0.88 to 4.55 per 10,000 births in China and in Germany, respectively. Recent European studies suggest that the prevalence is relatively stable over time (9–11) and that males are most affected with a male:female ratio of 1:0.74 (9).

At birth, the neonate presents with typical drooling of saliva, inability to swallow, choking, coughing, cyanotic attacks, and distended abdomen if the subtype involves a fistula to the trachea (11). The diagnosis is confirmed by the inability to pass a feeding tube into the stomach (11, 12) and a plain X-ray showing the non-progression of the feeding tube located in a blind-ending pouch (11, 12). Prenatal diagnostics having improved from 26 to 36% during the last 30 years (9). Postnatal diagnosis occurs on the first day after birth in 83% of cases, the remaining 15% of cases within the first week, and only in 1.2% after the first week (9).

Most cases seem to occur sporadically, therefore the etiology is likely to be multifactorial involving multiple genes and complex gene-environment interactions (13, 14). Despite observational studies suggesting various maternal risk factors (10, 13, 15), the exact etiology is still unclear (13, 14). Since esophageal atresia is an early organogenesis defect, associated anomalies are frequency found (9, 16–19). Isolated esophageal atresia occurs in ∼45–53% of the cases, whereas 32–47% have multiple anomalies, and 24–25% have an association or a syndrome, the most common being VACTERL association occurring in ∼10% (9, 16–21). Among the most common associated anomalies are congenital heart defects (23–29% of cases), other gastrointestinal anomalies (16–21%), urinary tract anomalies (15–16%), and limb anomalies (13–14%) (9, 16–19).

Left untreated, the condition is fatal due to starvation, infection, and respiratory complications and survival therefore relies on early surgical correction (1, 11). The surgery aims to reconstruct the continuity of the esophagus and eliminate any possible fistulae (11, 14), which can be done either as a transpleural thorascopical procedure, or as open surgery, most commonly extrapleural (11, 22).

The mortality rate in isolated esophageal atresia range from 4.3 to 8.1% (7, 8, 17, 23–25), but varies with the type of atresia (with higher mortality and morbidity in the long gap esophageal atresia presentation), and mortality increases furthermore in case of prematurity and/or low birth weight, and with the presence of associated abnormalities, notably major cardiac and chromosomal anomalies (2, 6, 9, 26, 27). Even after hospital discharge, the children have increased mortality with post-discharge mortality is primarily due to respiratory compromise, including sudden infant death, aspiration, tracheomalacia, and reactive airway disease (23, 28, 29).

The most common postoperative complications are anastomosis leakage, fistula recurrence, anastomotic strictures, respiratory complications, and infections (25, 30–40). Anastomotic leakage is one of the most common serious complications occurring in about 5–17% of cases (25, 34, 35). Leakage into the mediastinum result mainly from anastomotic tension (particularly in cases with increased gap length) leading to ischemia of the esophageal ends, particularly in the small, friable lower segment and sub-optimal surgical technique; sepsis and even use of prosthetic materials can contribute (36–38). Major leaks are uncommon and tend to present with acute deterioration associated with pneumothorax and sepsis, and may require emergency decompression with placement of a postoperative chest tube (35, 39, 40). Most leaks heal spontaneously given proper drainage and antibiotics and only few require surgical intervention (35, 39, 40).

Long-term complications include strictures of the anastomotic region [incidence 25–75% (25, 34, 41, 42)], gastroesophageal reflux [incidence 22–63% (43)], esophagitis, tracheomalacia, feeding difficulties [incidence up to 80% (30, 44)], pulmonary symptoms, and developmental challenges (30–33, 45). These long-term complications have an impact on quality of life (28) in both patients and parents, especially in the case of tracheal and esophageal complications (6, 31, 46–50).

During the esophageal repair a prophylactic intraoperative chest tube (IOCT) has traditionally been placed close to the anastomosis to drain access fluid and air through a one-way system (51, 52). The routine use of prophylactic IOCTs is now debated (11, 39, 40, 52) and at the European Reference Network for rare Inherited and Congenital Anomalies (ERNICA)

consensus conference, no consensus was found with only 21.4% of the members voting for the use of IOCTs (22). However, IOCTs are still used and reported as common as in 54% of the cases in the UK (53), 57% in Belgium (54), and 69% in an international survey, respectively (55).

IOCTs are not without drawback as they can cause insertion site infection (56) and when improperly placed, the tube can cause disruption of the site of anastomosis or penetration of proximal myotomy (57). IOCTs may also cause considerable postoperative pain, which would decrease inspiratory effort tand need for administration of more opoids, both leading to secondary effects such as atelectasis and pneumonia (58). Importantly, in some cases, IOCTs are insufficient to drain major leaks, necessitating the placement of a new chest tube (39, 40).

Whether the potential benefits of the prophylactic IOCT overweigh the potential harms is therefore unclear (22). Accordingly, the objective of this study was to examine the benefits and harms of prophylactic IOCT during primary surgical repair of esophageal atresia.

METHODS

We conducted a systematic review of the existing literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) and the Cochrane Handbook for Systematic Reviews of Intervention (59, 60). The predefined methodology, and method for this review in general, is described in our protocol, registered in June 2021 (61).

Eligibility Criteria

We searched for RCTs assessing the effect of a prophylactic IOCT during primary surgical repair of esophageal atresia and related observational studies identified during our searches for RCTs.

Search and Study Selection

We searched the Cochrane Central Register of Controlled Trials, MEDLINE Ovid, Embase Ovid, CINAHL, and Science Citation Index Expanded and Conference Proceedings Citation Index—(Web of Science). The search strategy was developed by an information specialist from the Cochrane Hepato-Biliary Group. The search strategy can be found in **Appendix 1**.

Studies were included irrespectively of publication type, publications status, and language. Two independent reviewers (MRL and SKK) screened and found relevant studies, performed data-extraction using an EXCEL data extraction sheet, and systematically checked risks of bias. We planned to contact trial authors if relevant data were unclear or missing. A description of the data collection process can be found in our protocol.

Risk of Bias Assessment

We followed the Cochrane Handbook for Systematic Reviews of Interventions to examine the risk of bias (62), including the ROBIN-I tool for non-randomized studies (63). Two authors, MRL and SKK, independently assessed the risk of bias in the included trials. In case of disagreements, a third author (ULT) would arbitrate.

Outcomes and Subgroup Analyses

The primary outcomes were: (1) all-cause mortality, (2) serious adverse events, and (3) pneumothorax - requiring intervention. Secondary outcomes were: (1) sepsis or mediastinitis, (2) anastomosis leakage, (3) esophageal stricture, and (4) pain (measured by any valid score). For every relevant outcome, the risk ratios (RRs) were calculated with a 95% confidence interval (CI).

Data Synthesis

We pooled the data from relevant studies that were estimated to be clinically homogeneous using the Review Manager 5.4.1 software. If more than one study provides usable data in any single comparison, we performed a meta-analysis. We used RR for dichotomous outcomes, and by utilizing the fixed-effect (Mantel-Haenszel model).

RESULTS

A systematic search done December 3rd, 2021, identified a total of 953 records from databases and registers. A total of 894 were excluded based on the title and abstract. We assessed 19 full-text original articles, of which following studies were included: three RCTs (64–66) and two case-control studies (51, 52) for narrative description in the discussion. See **Figure 1**: PRISMA flowchart and **Table 1**: Table of excluded studies regarding details on inclusion and exclusion of the studies.

Included Trials

We identified and included three RCTs randomizing a total of 162 neonates with esophageal atresia and distal tracheoesophageal fistula into intervention and control group. The trials compared mortality, serious adverse events, intervention-requiring pneumothorax, and anastomosis leakage (see **Table 2**: summary of findings). The risk of bias assessment is shown in **Figure 2**. All trials were assessed to be at overall "some concerns" for risk of bias. None of the trials adequately describe the randomization process or referred to a publish protocol.

Effects of Interventions

Primary Outcomes

All-Cause Mortality

A meta-analysis of three trials, randomizing 162 participants, showed that an IOCT might result in an increased risk of mortality compared to neonates undergoing surgery without an IOCT, but the confidence interval was compatible with no effect [RR 1.66, 95% CI 0.76–3.65; $P = 0.21$; 2.8% of optimal information size (OIS); very low certainty of evidence; **Figure 3**].

Proportion of Participants With One or More Serious Adverse Events

A meta-analysis of three trials, randomizing 162 participants, showed that an IOCT might result in an increased risk of having a serious adverse event compared with neonates with esophageal atresia undergoing surgery without an IOCT, but the confidence

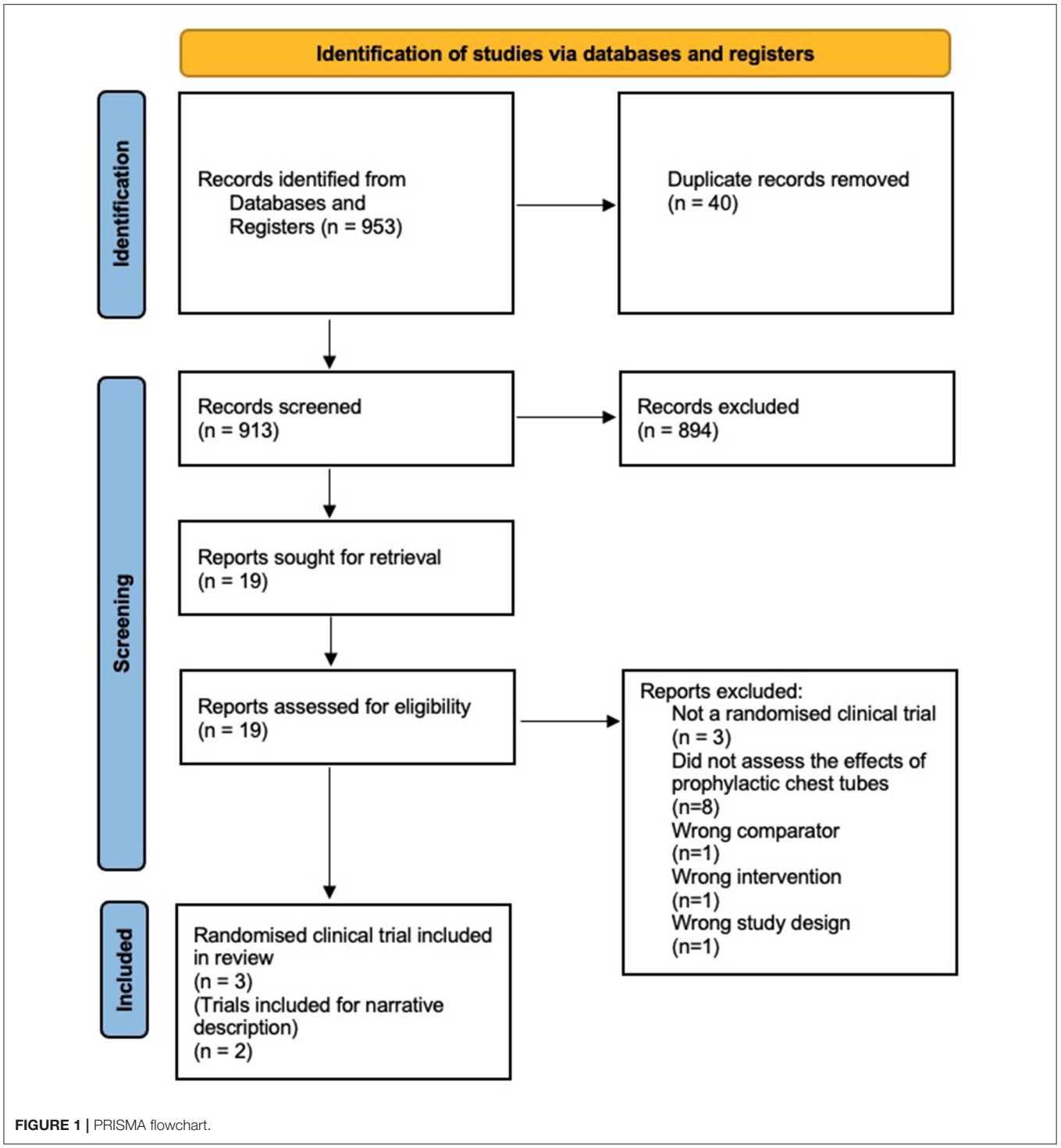

FIGURE 1 | PRISMA flowchart.

interval was compatible with no effect (RR 1.08, 95% CI 0.58–2.00; $P = 0.81$; 7.4% of OIS; very low certainty of evidence; **Figure 4**).

The serious adverse effects assessed in the trials were respiratory complications including respiratory distress, pneumonia, pneumothorax, lung collapse, and apnea as well as mortality.

Proportion of Participants With an Intervention-Requiring Pneumothorax

A meta-analysis of the two trials, randomizing 112 participants, showed that an IOCT might result in an increased risk of having an intervention-requiring pneumothorax compared with neonates with esophageal atresia undergoing surgery without an IOCT, but the confidence interval was compatible with no effect

TABLE 1 | Table of excluded studies.

Study id	Reason for exclusion	The authors's conclusion on IOCT (if any)
Brohi et al. (67)	Not a randomized clinical trial	NA
Castilloux et al. (68)	Did not assess the effects of prophylactic chest tubes	NA
Donoso et al. (69)	Did not assess the effects of prophylactic chest tubes	NA
Esteves et al. (70)	Did not assess the effects of prophylactic chest tubes	NA
Fasting and Winther (71)	Did not assess the effects of prophylactic chest tubes	NA
Grebe et al. (72)	Wrong intervention	NA
Johnson and Wright (57)	Wrong study design	An IOCT can perforate esophagus after primary repair.
Kay and Shaw (73)	Wrong comparator	An IOCT may not be necessary.
McCallion et al. (40)	Not a randomized clinical trial	IOCT unable to drain major leaks sufficiently, requiring placement of an additional drain.
Paramalingam et al. (74)	Not a randomized clinical trial	Drain appears not to be needed in all cases.
Vazquez et al. (75)	Did not assess the effects of prophylactic chest tubes	NA
Vercauteren et al. (76) Vol 8	Did not assess the effects of prophylactic chest tubes	NA
Zhang et al. (77)	Did not assess the effects of prophylactic chest tubes	NA
Zhang et al. (78)	Did not assess the effects of prophylactic chest tubes	NA

NA, not applicable.

(RR 1.65, 95% CI 0.28–9.50; $P = 0.58$; 0.46% of OIS; very low certainty of evidence; **Figure 5**).

Secondary Outcomes

Participants With Sepsis or Mediastinitis

One included trial (65), reporting sepsis, showed that an IOCT might result in an increased risk of having sepsis compared with neonates with esophageal atresia undergoing surgery without an IOCT, but the confidence interval was compatible with no effect (RR 3.00, 95% CI 0.14–64.26).

Participants With Anastomosis Leakage

Three trials, randomizing 162 participants, showed that an IOCT might result in an increased risk of anastomosis leakages compared with neonates with esophageal atresia undergoing surgery without an IOCT, but the confidence interval was compatible with no effect (RR 1.66, 95% CI 0.63–4.40; $P = 0.30$; 2.24 % of OIS; very low certainty of evidence; **Figure 6**).

Participants With Esophageal Stricture

None of the included trials reported on esophageal stricture.

Pain (Measured by Any Valid Score)

None of the included studies did a measurement of pain.

DISCUSSION

Summary of Main Findings

We identified and included three RCTs randomizing a total of 162 neonates with esophageal atresia and distal tracheoesophageal fistula into intervention and control group. The trials compared mortality, serious adverse events, intervention-requiring pneumothorax, and anastomosis leakage.

We found no evidence of a beneficial effect of placing a prophylactic IOCT during primary surgical repair from neither of the included studies. The evidence from RCTs shows potential harm when assessing all-cause mortality and serious adverse events, but the results were very uncertain. All studies were assessed to be at overall "some concerns" for risk of bias. The risk of bias assessment is shown in **Figure 2**. The statistical heterogeneity was low for all our meta-analyses. It was not possible to assess the preplanned subgroups regarding esophageal stricture and pain due to the lack of relevant data.

Two observational studies (51, 52) seem to support the overall results from the three RCTs in terms of mortality, serious adverse events, and anastomosis leakage that found no beneficial effect of placing a prophylactic IOCT. Furthermore, observational data from Nquyen et al. (51) suggest that the placement of a prophylactic IOCT may increase the risk of various complications such as an increase in the risk of developing esophageal stricture. These observational studies were assessed by ROBINS-I to be at overall serious (51) and critical risk of bias (52) and should therefore be interpreted with caution. Finally, we identified but excluded for various reasons (see **Table 1**) an additional 4 studies, no of which were in favor of routine ICOT (see **Table 1**).

Strengths and Limitations

This review draws strengths from the strict methodology, including following a protocol registered before the literature search began, systemically assessing for risk of bias, and adhering to all recommendations from the Cochrane Collaboration, including the use of ROBINS-I. The search strategy was developed by an information specialist from the Cochrane Hepato-Biliary Group. Our study also differs from a recent review by Anand et al. (79) on the topic by adding GRADE assessment of the included studies and abstaining from mixing RCTs with observational studies in the meta-analyses. In Anand et al., the meta-analysis included a mix of extrapleural and transpleural repair (51, 52) and an observation study, where some of the participants received IOCTs by a non-prophylactic indication (74). Although the overall conclusions in the present study are fairly similar to the study by Anand et al., inclusion of non-randomized studies with their inherently different study designs in a meta-analysis may severely compromise the validity of their results, as their lack of randomization makes them highly at risk for confounding bias resulting in an imbalance in prognostic factors associated with the outcome (80).

TABLE 2 | Summary of findings, randomized clinical trials.

Use of prophylactic chest tubes vs. control

Population: Neonates with esophageal atresia.

Intervention: Prophylactic chest tube in primary surgical repair.

Comparison: Control (no prophylactic chest tube).

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (No of studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk (controls)	Corresponding risk (chest tube)				
	Study population					
All-cause mortality						
Maximum follow-up	109 per 1,000	182 per 1,000 (83–398)	RR 1.66 (0.76, 3.65)	162 (3)	⊕⊖⊖⊖ **Very low**	OIS 5822 (alpha 5%, beta 20%, RR 0.8 and Pc 10.9%) Downgraded one level due to serious risk of bias and two levels due to very serious imprecision.
Serious adverse events						
Maximum follow-up	250 per 1,000	270 per 1,000 (145–500)	RR 1.08 (0.58, 2.00)	162 (3)	⊕⊖⊖⊖ **Very low**	OIS 2188 (alpha 5%, beta 20%, RR 0.8 and Pc 25%) The adverse events reported were respiratory complications. Downgraded one level due to serious risk of bias and two levels due to very serious imprecision.
Intervention-requiring pneumothorax						
Maximum follow-up	28 per 1,000	47 per 1,000 (8–271)	RR 1.65 (0.28, 9.50)	112 (2)	⊕⊖⊖⊖ **Very low**	OIS 24124 (alpha 5%, beta 20%, RR 0.8 and Pc 25%)
Sepsis or mediastinitis						
Maximum follow-up	NA	NA	RR 3.00 (0.14, 64.26)	16 (1)	⊕⊖⊖⊖ **Very low**	
Anastomosis leakage						
Maximum follow-up	89 per 1,000	148 per 1,000 (56–393)	RR 1.66 (0.63, 4.40)	162 (3)	⊕⊖⊖⊖ **Very low**	OIS 7240 (alpha 5%, beta 20%, RR 0.8 and Pc 8.9%) Downgraded one level due to serious risk of bias and two levels due to very serious imprecision.
Esophageal stricture						
Maximum follow-up	NA	NA				

**The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI, Confidence interval; Pc, Proportion in control group with outcome; RR, Risk ratio; NA, Not applicable.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

We only identified three RCTs, systematically comparing the intervention with an IOCT to no IOCT in 162 neonates undergoing primary repair for esophageal atresia. None of our meta-analyses reached the optimal information size. In addition to evaluate overall improvement in treatment techniques and clinical outcomes, future trials should also assess pain and esophageal stricture as this would be an important outcome for the children and parents. Importantly, the associated malformations and genetic aberrations often found in esophageal atresia and the difference in exact anatomical presentation [with or without fistula(e)] make this a relatively heterogeneous pathology. The patients included in these RCTs all presented with distal tracheoesophageal fistula, but with various details on pre-surgical gap length and on associated malformations; further complicating the comparison between studies and the transferability of the conclusion to other patient subgroups.

Esophageal atresia is a relatively rare condition; particularly considering the numerous subtypes with various possible

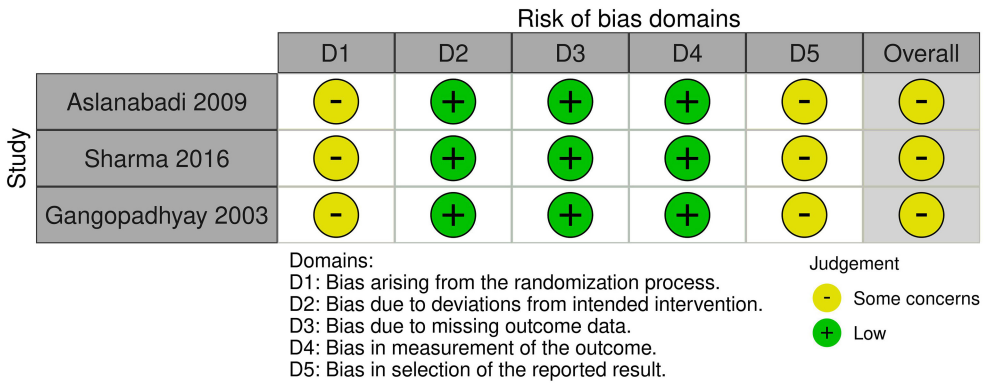

FIGURE 2 | Risk of bias assessment.

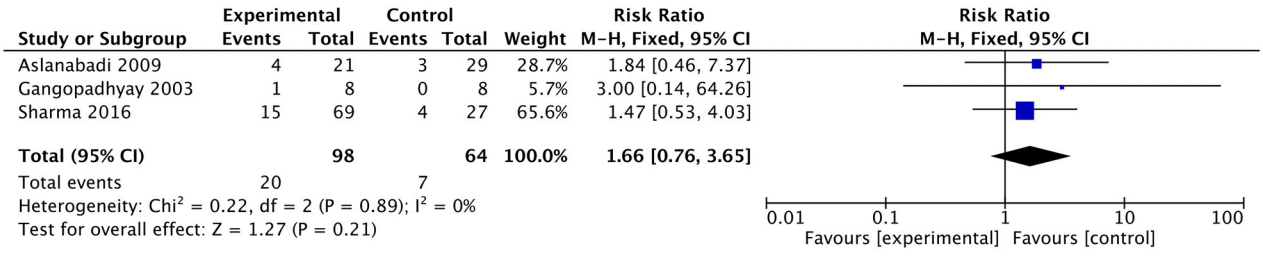

FIGURE 3 | Forest plot for all-cause mortality.

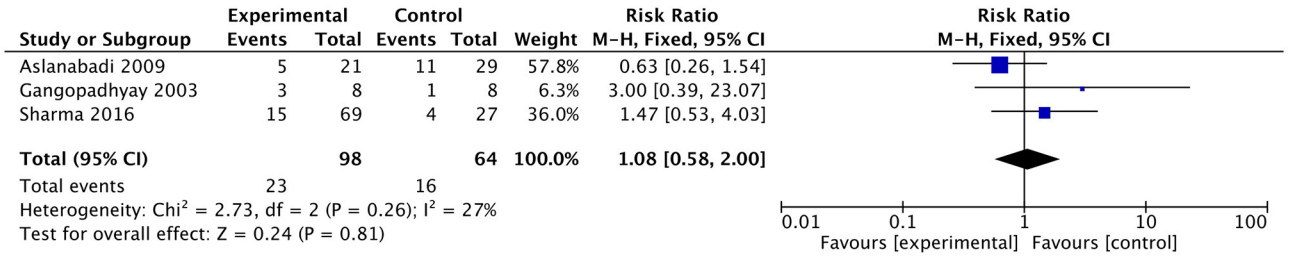

FIGURE 4 | Forest plot for serious adverse events.

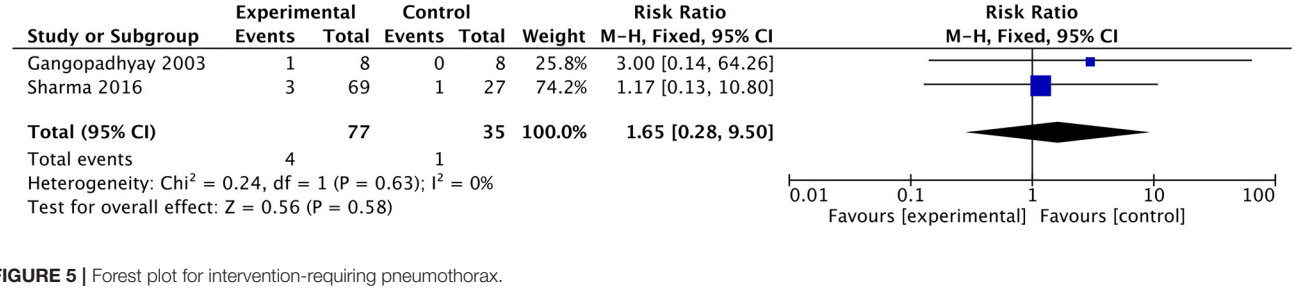

FIGURE 5 | Forest plot for intervention-requiring pneumothorax.

anatomical presentations and associated malformation. Rare diseases pose challenges to methodology when designing RCTs that are adequately powered to draw definitive conclusions, as small patient sample sizes are statistically vulnerable to small deviations in the observed number of outcomes (81). Innovative clinical trial methods minimizing sample size requirements

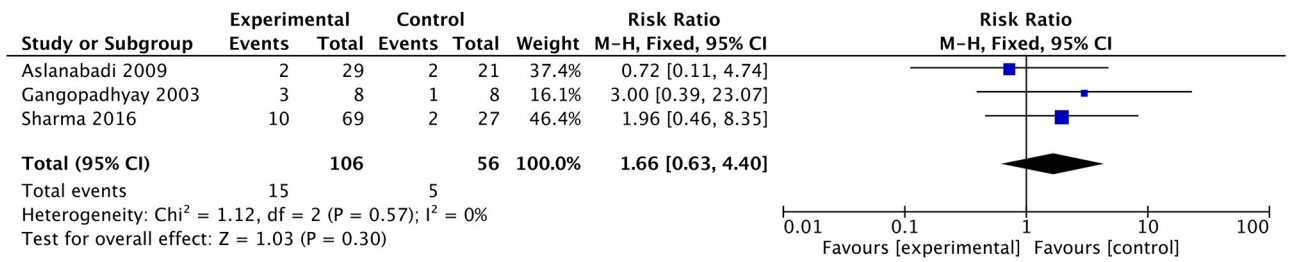

FIGURE 6 | Forest plot for anastomosis leakage.

(82) and optimal research infrastructure (83), possibly through international collaborations, may improve future productivity of robust research in esophageal atresia.

CONCLUSION

We did not identify any studies advocating for the use of prophylactic IOCTs. Based on the limited amount of research on this topic and results from the included studies, we did not find sufficient evidence to support or discontinue the routine use of prophylactic IOCTs for neonates undergoing surgical repair of esophageal atresia, as all confidence intervals were compatible with no effect. Further trials, ideally multicentric, are warranted to explore the effects of the prophylactic IOCT for neonates undergoing surgical repair of esophageal atresia. Importantly, future trials should adhere to SPIRIT guidelines (84).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

ML drafted the protocol and review, extracted data, co-ordinated the review, analyzed the data, and revised the review. SK drafted and revised the protocol, extracted data, analyzed the data, interpreted the data, commented on, revised the review, interpreted the data, provided supervision, and provided a methodological and statistical expertise. SH revised and commented on the protocol and review and provided supervision. JO and MF revised and commented on the protocol and review and provided clinical expertise. SP revised and commented on the review. UL-T drafted the protocol, conceived and designed the review, revised the protocol, commented on, revised the review, provided supervision, and clinical expertise. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX 1

Search Strategies (search performed 3rd of December 2021)
Cochrane Central Register of Controlled Trials [*via* Ovid Evidence-Based Medicine Reviews Database (EBMR)]

#1	MeSH descriptor: [Esophageal Atresia] explode all trees
#2	MeSH descriptor: [Esophagus] explode all trees
#3	(esophag∗ or oesophag∗)
#4	(artresia∗ or atretic∗)
#5	#1 or [(#2 or #3) and #4]
#6	MeSH descriptor: [Chest Tubes] explode all trees
#7	(chest tube∗ or catheter∗ or drain∗ or intubat∗ or artificial respirat∗ or suction∗ or IOCT∗)
#8	#6 or #7
#9	#5 and #8

MEDLINE Ovid

1.	exp Esophageal Atresia/
2.	exp Esophagus/
3.	(esophag∗ or oesophag∗).tw,kw.
4.	(artresia∗ or atretic∗).tw,kw.
5.	1 or [(2 or 3) and 4]
6.	exp Chest Tubes/
7.	(chest tube∗ or catheter∗ or drain∗ or intubat∗ or artificial respirat∗ or suction∗ or IOCT∗).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8.	6 or 7
9.	5 and 8

Embase Ovid

1.	exp esophagus atresia/
2.	exp esophagus/
3.	(esophag∗ or oesophag∗).tw,kw.
4.	(artresia∗ or atretic∗).tw,kw.
5.	1 or [(2 or 3) and 4]
6.	exp chest tube/
7.	(chest tube∗ or catheter∗ or drain∗ or intubat∗ or artificial respirat∗ or suction∗ or IOCT∗).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8.	6 or 7
9.	5 and 8

CINAHL

S9	S5 AND S8
S8	S6 OR S7
S7	TX (chest tube∗ or catheter∗ or drain∗ or intubat∗ or artificial respirat∗ or suction∗ or IOCT∗)
S6	MH chest tubes
S5	S1 or [(S2 or S3) and S4]
S4	TX (artresia∗ or atretic∗)
S3	TX (esophag∗ or oesophag∗)
S2	MH Esophagus
S1	MH Esophageal Atresia

Science Citation Index Expanded and Conference Proceedings Citation Index – (Web of Science)

#3	#2 AND #1
#2	TS = (chest tube∗ or catheter∗ or drain∗ or intubat∗ or artificial respirat∗ or suction∗ or IOCT∗)
#1	TS = [(esophag∗ or oesophag∗) and (artresia∗ or atretic∗)]

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ORIGINAL RESEARCH
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Hidden Infection in Asymptomatic Congenital Lung Malformations—A Decade Retrospective Study

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Background: Whether to operate on asymptomatic patients with congenital lung malformations (CLMs) remains controversial. Our study intended to find out the proportion of hidden infection in CLMs and its effect on surgery, to provide help for the management of asymptomatic CLMs patients.

Methods: A retrospective review of the medical records of patients with asymptomatic CLMs from January 2011 to December 2020 was performed in our center. Selected asymptomatic patients were divided into a non-hidden infection group (NHI) and a hidden infection group (HI).

Results: A total of 581 asymptomatic CLMs patients were included in this study. Thirty-two percent of asymptomatic CLMs patients had hidden infection in the lesion. Among various CLMs diseases, intralobular pulmonary sequestration had the highest percentage of hidden infection (48.8%). With age, the proportion of HI gradually increased. Patients in the HI and NHI groups were 223 and 121. The incidence of pleural adhesion and focal abscess in the HI group were 14.9 and 7.4%. Statistical significances were shown between the two groups in intraoperative blood loss ($p = 0.002$), operation time ($p = 0.045$), chest tube drainage time ($p < 0.001$), postoperative hospital stay ($p < 0.001$), and air leak ($p = 0.012$).

Conclusion: The proportion of HI detected by postoperative pathological results was high and they could increase the difficulty and risk of surgery. Therefore, early surgery may be a more appropriate choice for the management of asymptomatic CLMs patients.

Keywords: congenital lung malformations, hidden infection, congenital pulmonary airway malformation, bronchopulmonary sequestration, lobectomy, children

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INTRODUCTION

With the development of ultrasound technology and the frequent use of prenatal screening, the incidence of congenital lung malformations (CLMs) has been increasing in recent years (1, 2). Therefore, pediatric surgeons will encounter more asymptomatic CLMs patients. Over the past few decades, the understanding of the disease has deepened, but controversy still exists (3). The greatest controversy was whether to perform surgical treatment on asymptomatic CLMs patients

(4). Surgeons who did not support surgery believed that the trauma caused by surgery was relatively large, the rate of malignant transformation was low, a long-term follow-up would be more beneficial, and surgical intervention should be performed until symptoms appeared (5–7). Doctors who supported surgery believed that early surgery not only had a lower risk of postoperative complications but also had good postoperative lung function compensation in children. Duaa et al. showed that the postoperative exercise capacity of the patients was close to the normal children (8). The researches result from multiple centers have proved that postoperative lung function can be compensated to the normal level (9–11). And most importantly, the surgery eliminates the risk of infection and malignant transformation (12, 13). Such a large controversy makes it difficult for pediatric surgeons to choose strategies for children with asymptomatic CLMs.

Different studies had controversies about the proportion of asymptomatic patients who eventually developed symptoms. Wong et al. showed that 86% of asymptomatic patients eventually developed symptoms, with a median age of two years old (14). However, Thompson et al. found that only 13% of patients eventually developed symptoms through long-term clinical observation (15), which was the core argument over the management of the disease. If the proportion of patients with symptoms is low, conservative management seems to be better; if the proportion of patients with symptoms is high, early surgery may be better, because if the surgery is performed when symptoms occur, the risk and difficulty of surgery, length of hospital stay, and postoperative complications would greatly increase (12, 16). Infection is the most common complication of CLMs, and it is also the focal point for managing asymptomatic CLMs. Past studies have usually focused on children with symptomatic infection but have ignored children with hidden infection. Therefore, the real proportion of infection may be greatly underestimated. For the first time, our study retrospectively analyzed medical records through a large sample size of asymptomatic CLMs patients to provide help for clinical decision making.

TABLE 1 | Characteristics of the study population.

Variables		AP	AH
Gender	Female	232	69 (29.7%)
	Male	349	117 (33.5%)
Basic illness	CPAM	367	103 (28.1%)
	ILS	121	59 (48.8%)
	ELS	67	16 (23.9%)
	BC	14	5 (35.7%)
	CLE	12	3 (25.0%)
Total		581	186 (32.0%)

AP, aymptomatic CLMs patients; AH, asymptomatic CLMs patients who had hidden infection; CPAM, congenial pulmonary airway malformation; ILS, intralobar pulmonary sequestration; BC, bronchial cyst; ELS, congenital lobar emphysema.

TABLE 2 | Characteristics of hidden infection in patients with CPAM or ILS.

Variables	CPAM		ILS	
	AP	AH	AP	AH
Lobe				
LUL	49	12 (24.5%)	2	2 (100%)
LLL	101	37 (36.6%)	71	42 (59.2%)
RUL	46	10 (21.7%)	3	1 (33.3%)
RML	14	4 (28.6%)	2	0
RLL	134	29 (21.6%)	33	13 (39.4%)
ML	23	11 (47.8%)	1	1 (100%)
Stocker type				
0	0	0		
1	130	46 (35.4%)		
2	186	47 (25.3%)		
3	39	6 (15.4%)		
4	12	4 (33.3%)		
Total	367	103 (28.1%)	121	59 (48.8%)

LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; ML, multiple lobes.

MATERIALS AND METHODS

This retrospective study was approved by the Ethics Committee of West China Hospital of Sichuan University (file no. 2021-1306). We reviewed the cases of CLMs in our center from January 2011 to December 2020. Patient information and surgery-related information were retrieved from the electronic medical record system. Pathological pictures were obtained from slide scanner systems or reacquired original pathology slides from the pathology slide library. All specimens were routinely stained with hematoxylin and eosin. If the existence of inflammatory cell infiltration was uncertain, immunohistochemistry would be added (LCA, CD3, CD4, CD8, CD15, CD16, or CXCR were used for staining). The pathology pictures were reviewed by two senior pathologists, a third expert was invited when the opinions were inconsistent. The inclusion criteria for hidden infection were patients who had no symptoms related to CLMs since birth but had a pathologically significant number of inflammatory cell infiltration (neutrophils, macrophages, or lymphocytes) under the microscope. Exclusion criteria were CLMs patients who developed symptoms, age >14 years old or missing clinical data. Pathologists and surgeons worked independently, they did not know each other's results until all the work was done.

Since 2011, multiple surgical methods have been performed in our center, to ensure the consistency of the baseline, asymptomatic patients with CPAM or IPS who underwent thoracoscopic lobectomy were selected to evaluate the impact of hidden infection on surgery. Selected asymptomatic patients were divided into a non-hidden infection group (NHI) and a hidden infection group (HI). Appearances of lesion abscesses and pleural adhesions in the HI group were then recorded through surgical records.

Differences were compared using Pearson's chi-square test for non-continuous data, Wilcoxon test for continuous non-parametric data, and Student's *t*-test or Fisher's exact test for continuous parametric data. $p < 0.05$ was considered

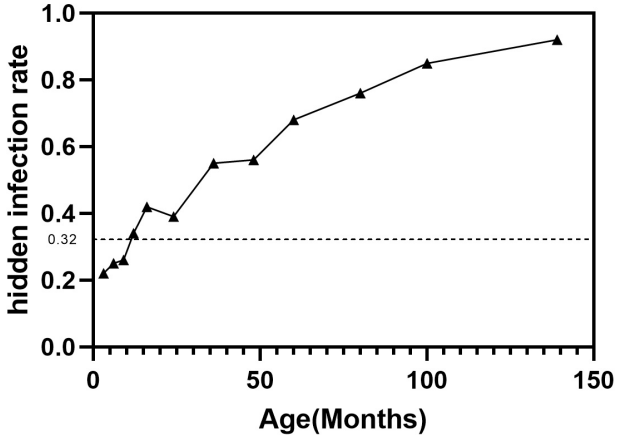

FIGURE 1 | The proportion of hidden infections gradually increased with age.

TABLE 3 | Characteristics of asymptomatic patients with CPAM or ILS who underwent thoracoscopic lobectomy.

Variables		NHI (n = 223)	HI (n = 121)	p
Basic illness	CPAM	167	80	0.084
	ILS	56	41	
Age (month)		8 (6–72)	10 (6–76)	0.048
Sex	Male	141	83	0.319
	Female	82	38	
Conversion to open		0	5	
Operation time (min)		57 (52–76)	61 (55–85)	0.045
Blood loss (ml)		5 (5–15)	10 (5–15)	0.002
Major bleeding		0	0	
Blood transfusions		13	9	0.560
Chest tube duration (day)		2.1 ± 1.2	2.7 ± 1.0	<0.001
Postoperative hospital stay (day)		3 (3–5)	4 (4–5)	<0.001
Air leak		11	15	0.012
Clavien–Dindo classification	None	71 (31.8%)	32 (26.4%)	0.179
	I	117 (52.5%)	43 (35.5%)	0.002
	II	35 (15.7%)	41 (33.9%)	<0.001
	IIIa/b	0	5 (4.1%)	
	IV/V	0	0	

statistically significant. SPSS 26.0 statistical software was used for statistical analyses.

RESULTS

A total of 581 asymptomatic CLMs patients met the criteria. The characteristics of the study population were shown in **Table 1**. A total of 186/581 (32%) asymptomatic CLMs patients had hidden infection in the lesion. Hidden infections that can be detected only by H&E staining accounted for 169/186 (90.9%) cases, different immunohistochemical methods were used in 17/186 cases (9.1%). The rate of hidden infection in males was higher than that in females (33.5% vs 29.7%), but the difference was not statistically significant (p = 0.338). The characteristics of CPAM and ILS in different lung lobes and stocker classification (17) were shown in **Table 2**. CLMs lesions located in the left lower lobe or multiple lung lobes had a relatively high proportion of hidden infection. Among CPAM classified by Stocker, the proportion of type 1 CPAM has the highest rate of hidden infection (35.4%). The rates of hidden infection in asymptomatic CLMs patients of different ages were plotted as a line graph (**Figure 1**). With age, the proportion of hidden infections in the lesions of asymptomatic patients increased.

Patients in the HI and NHI groups were 223 and 121. Through retrospective analysis of surgical records, intraoperative and postoperative comparisons of the two groups were shown in **Table 3**. The proportions of pleural adhesions and lesion abscesses in the HI group were 14.9% (18/121) and 7.4% (9/121). The differences in basic illness (p = 0.084) and sex (p = 0.319) were not statistically significant between the NHI group and the HI group. Five patients were converted to open in the HI group, while none were in the NHI group. There were statistical differences in operation time (p = 0.045), blood loss (p = 0.002), chest tube duration ($p < 0.001$), and postoperative hospital stay ($p < 0.001$) between the two groups. According to the Clavien–Dindo postoperative complications classification (18), no statistical difference was shown in patients with no complications (p = 0.179) between the two groups but were in grade I (p = 0.002) and II ($p < 0.001$) complications.

DISCUSSION

In our study, patients with hidden infection accounted for 32% of all asymptomatic CLMs patients, and the real proportion of infection in CLMs may be greatly underestimated. Compared with previous studies, our study systematically described the proportion of hidden infection on CLMs through a large series and evaluated the impact of HI on surgery. HI would increase the difficulty and risk of surgery and cause more surgical complications, so early surgery may be a better choice for asymptomatic CLMs patients.

Computed tomography (CT) is currently the most commonly used method for diagnosing CLMs disease after birth, and it has unique advantages compared to ultrasound or MRI (19, 20). In some asymptomatic patients, infection in the lesion could be found through preoperative CT, manifesting as fluid retention in the lesion, which appeared to be lung abscess (**Figure 2**). However, imaging tests cannot always detect this phenomenon, the pathogens in the lesions were not yet powerful to cause symptoms and imaging changes but could manifest in pathology (**Figure 3**). Neutrophil infiltration often represents acute infection, and macrophage or lymphocyte infiltration always represents chronic infection. Long-term chronic infection was more common in the HI group. Pelizzo et al. found that 50% (3/6) of asymptomatic CPAM patients had chronic inflammation through histopathologic examination (21). Durelle et al. found that eighteen asymptomatic CLMs patients (26%) had the microscopic disease (22). Microbial evidence has been suggested in asymptomatic CPAM infants for bacteria and fungi (*Pneumocystis jirovecii*, which is often found in

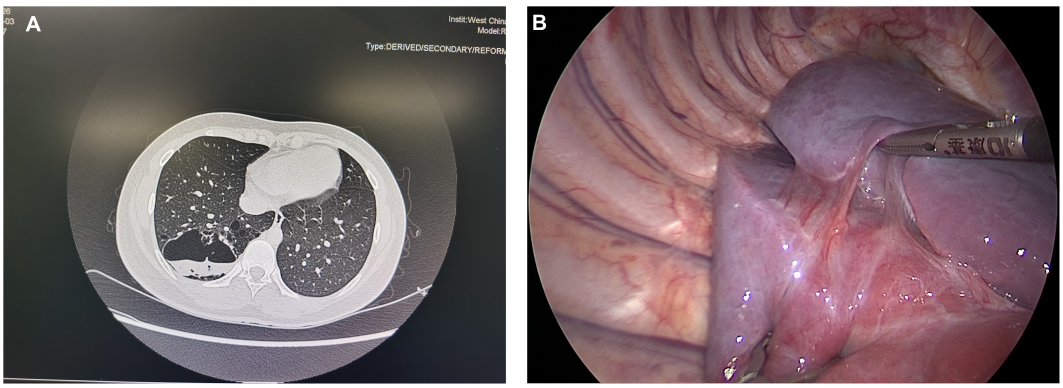

FIGURE 2 | (A) A typical CPAM patient with an abscess in the lesion. **(B)** Pleural adhesion in a 7-year-old asymptomatic CPAM patient. These two pictures showed the special situations in asymptomatic CLMs patients.

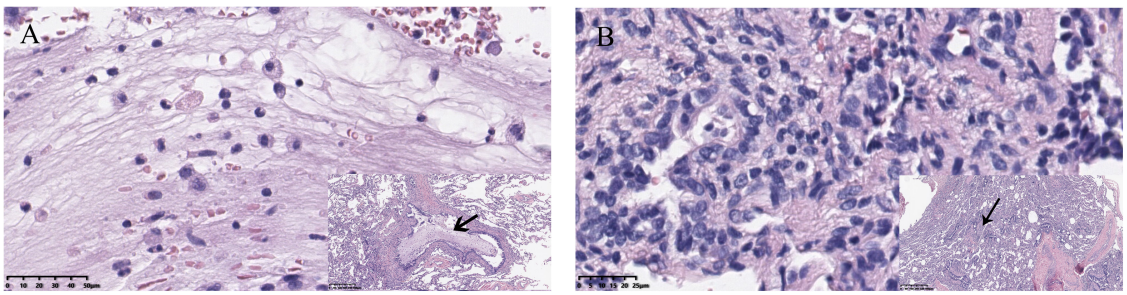

FIGURE 3 | (A) Neutrophil infiltration, which always indicates acute inflammation. Viscous exudate in the bronchioles was also found. **(B)** Lymphocyte infiltration, representing chronic infection, and thickening of blood vessel walls could also be seen.

immunodeficient patients) (23). Mycobacteria in CLMs lesions have also been reported by several studies (24–26). These opportunistic infections were unlikely to occur in the normal lung, it indicated that there could be immunodeficiency limited in the CLMs lesions, which made the CLMs lesions prone to infection, but the patients did not develop any symptoms. This may be the reason for the high rate of hidden infections in our study, it could also explain the reason of the increasing chance of developing an apparent infection with age.

Different types of CLMs diseases showed different proportions of hidden infections. ILS often appears as lung infection or other CLMs-related symptoms. Zhang et al. showed that up to 71% of ILS patients developed an infection (27). Our study also found that ILS had the highest proportion of hidden infection among various CLMs diseases, while ELS was lower. This was probably because ILs is always connected to normal lung tissue and communicate with the vitro environment, and easier to be invaded by microorganisms. Our study showed that the proportions of asymptomatic infections involving the left lower lobe or multiple lung lobes were higher in children with CPAM. Therefore, when the routine postnatal CT examinations of asymptomatic CPAM patients find that the lesions are located in the above positions, pediatric surgeons should be particularly vigilant. There was an obstruction hypothesis about the etiology of CPAM, which was believed to be the obstruction of the trachea and bronchus in different regions caused the occurrence of CPAM (28). Stocker type 1 CPAM manifests as a cyst diameter greater than 5 mm, so it is also called macrocystic type CPAM (29). Macrocystic CPAM tends to accumulate gas or liquid due to poor drainage and large cavities, which may be the reason why type 1 CPAM is susceptible to hidden infection. A study from Japan showed that the proportion of patients with CLMs-related symptoms gradually increased with age, similar to their research results. Our study found that the proportion of hidden infections also gradually increased with age (30). Older patients were often admitted to the hospital because of symptoms, and the remaining asymptomatic patients had a higher proportion of hidden infections, which indicated that CLMs may have the characteristics of asymptomatic stage and symptomatic stage, patients with hidden infections would gradually develop symptoms as they age.

In our study, patients with hidden infections sometimes presented with pleural adhesions or empyema. Mineo et al. showed that the existence of these two situations may enhance the difficulty and risk of surgery (31). In our study, patients in the HI group had a higher operative time, intraoperative blood loss, and postoperative drainage time and a higher risk of postoperative complications than those in the NHI group. Although no patients had Clavien–Dindo grade IV/V complications, such as organ

failure and death, there were statistical differences in grade I–III complications between the two groups, suggesting that more serious complications occurred in the HI group. The hidden infection could lead to larger surgical injury and more exudates, causing longer drainage time and hospital stay, meanwhile, enhancing the risk of air leakage.

Postoperative air leak is the most common complication of thoracic surgery. In our center, the criteria for removing the chest tube are no obvious bubble exudates in the water-sealed bottle when the baby cries, and postoperative CT (X-rays for ELS and BC which the surgery does not involve lung parenchyma) shows good lung recruitment without obvious pneumothorax or pleural effusion. In patients with hidden infections, the surgery was more likely to cause more exudates and leakage in tiny airways or alveoli, resulting in prolonged postoperative drainage time and increasing suffering for the young patients. It is believed that thoracotomy could lead to musculoskeletal deformities (32) and cause acute or chronic pain. Five patients in the HI group experienced conversion to open, while the NHI group did not. Tong et al. found that the most common reason for conversions was vascular injury (33). Pleural adhesion or abscess shielded the pulmonary arteries or veins, increasing the risk of vascular damage during thoracoscopic lobectomy and finally leading to conversions. Therefore, early surgery has a lower risk of hidden infection, reducing the difficulty and risk of surgery, more importantly, eliminating the risk of overt infection and malignant transformation.

With the increasing understanding of CLMs and the maturity of pediatric thoracic surgery, the number of centers supporting surgery on asymptomatic patients has gradually increased in recent years (28, 34). Based on the above reasons, in our center, we also recommend that children with asymptomatic CLMs prenatally diagnosed should undergo thoracoscopic surgery between 6 months and 1 year of age. At this age, children can tolerate the surgery and anesthesia well (35), and the lung can continue to develop to get better compensation (36). Future research should focus on the analysis of the microbial population in the lesion of hidden infection based on next-generation sequencing and immunological research to clarify the mechanism of hidden infection in CLMs patients. Our research was only a single-center retrospective study and lacked monitoring of postoperative lung function. It was unknown whether there was a difference in the long-term prognosis of patients between the NHI and HI groups, but for the first time, our study aimed at the hidden infection of CLMs through a large sample size and analyzed the influence of hidden infection on the operation, which may help pediatric surgeons make clinical decisions about whether to perform an early surgical intervention on asymptomatic CLMs patients.

CONCLUSION

We performed a retrospective study on hidden infections of CLMs. The proportion of hidden infections detected by pathology was high, they increased the difficulty and risk of surgery. Therefore, early surgery may be a more appropriate choice for the management of asymptomatic CLMs patients.

DATA AVAILABILITY STATEMENT

The data for this article are not publicly available according to the hospital and government regulations. Requests to access partial information of these datasets should be directed to CL, lcy_medical@qq.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee on Biomedical Research, West China Hospital of Sichuan University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CL participated in the whole research process. XY provided pathological support. KC, DL, MY, and TH participated in data collection and graph production. CX provided guidance and supervised the conduct of research. All authors read and approved the final manuscript.

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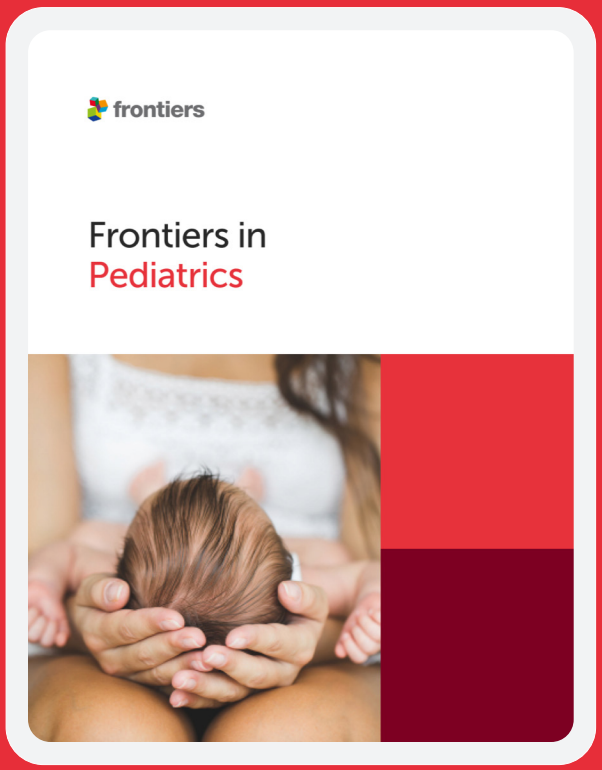

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