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Gastro-esophageal and respiratory morbidity in children after esophageal atresia repair: a 23-year review from a single tertiary institution in Asia

Jayne Chiang[1*†], Te-Lu Yap[1†], Shaista Arif[2], Candy S. C. Choo[1], A. K. Pugalenthi[3], Biju Thomas[3], Anette S. Jacobsen[1] and Lin Yin Ong[1]

Abstract

Background Improved survival of neonates with esophageal atresia with/without tracheoesophageal fistula (EA/TEF) has resulted in increased prevalence of gastro-esophageal and respiratory-related morbidities. However, long-term outcome data on these patients remains limited, making it difficult to substantiate any guidelines on their chronic care. The purpose of our study is to report on their post-operative outcomes especially the long-term gastro-esophageal and respiratory morbidities.

Methods This was a retrospective review of 65 patients (39 males, 26 females) who underwent EA/TEF repair from 1996 to 2019 at a single tertiary institution. Follow up data pertaining to clinical characteristics, operative management and long-term gastro-esophageal and respiratory morbidities was analyzed.

Results Fifty-seven patients (87.7%) had Gross Type-C anatomy, followed by 5(7.7%) patients with Type-A, 1(1.5%) with Type-B and 1 with Type-D. One patient had a late diagnosis of H-type fistula (Type-E). Thirteen (20%) patients had long-gap EA.

Median age at first surgery was day 1 (IQR 1–2) of life. All patients underwent bronchoscopy at their index surgery. All 52 non-long gap EA (LGEA) patients underwent primary anastomosis, while most (76.9%) LGEA patients underwent staged repair. Post-operatively, 4(6.2%) developed anastomotic leak which resolved with conservative management. Three (4.6%) had recurrent TEF, 2 underwent re-do ligation. Twenty (30.8%) patients developed anastomotic strictures, with 15 requiring serial dilatation.

Long-term burden of gastro-esophageal and respiratory morbidity was high (63.1%; 64.6% respectively). The majority ($n=39$,60%) of patients required active follow-up for a median duration of 5 years (IQR 1.5–10 years). Predominant conditions were gastroesophageal reflux disease ($n=28$, 43.1%), dysphagia ($n=20$, 30.8%), recurrent respiratory infections ($n=23$, 35.3%), chronic cough ($n=19$, 29.2%), and pneumonia ($n=19$, 29.2%). Tracheomalacia was diagnosed in 22(33.8%), 2 of whom required tracheostomy for severe disease. Overall mortality rate was 10.8% ($n=7$): 5 demised due to chronic respiratory failure, while 2 demised intra-operatively during the index surgery.

†Jayne Chiang and Te-Lu Yap are joint first authors as both have contributed equally to this paper.

*Correspondence:
Jayne Chiang
Jaynechiang19@gmail.com
Full list of author information is available at the end of the article

Conclusion Despite successful surgical repair for EA/TEF, our data demonstrated significant morbidities among EA/TEF survivors, thus highlighting the importance of long-term multi-disciplinary care with collaboration between respiratory, gastroenterology, and otolaryngology specialists.

Level of evidence Prognostic, Level IV.

Keywords Esophageal atresia, Tracheoesophageal fistula, Esophageal strictures, Gastro-esophageal reflux, Tracheomalacia

Background

Esophageal atresia with or without tracheoesophageal fistula (EA/TEF) is an important surgically correctable congenital foregut anomaly with an estimated incidence of 1 in 2500 to 4500 live births [1, 2]. Early diagnosis and intervention to establish esophageal continuity and perform ligation of the fistula, are crucial to prevent life-threatening events of atelectasis, pneumonia, and respiratory distress from aspiration of feeds or saliva from the upper esophageal pouch into the airways. Advances in surgical and neonatal intensive care have substantially improved survival rates up to 95%, with patients undergoing successful surgical repair within a few days of birth [3, 4]. However, many patients continue to suffer long-standing gastroesophageal and respiratory morbidities which may persist into adulthood. Late manifestations of gastro-esophageal morbidities include anastomotic strictures, recurrence of TEF, gastro-esophageal reflux disease (GERD) and dysphagia, while long-term upper and lower respiratory sequelae encountered in EA/TEF patients include tracheomalacia, airway hyperreactivity, recurrent pneumonia, and bronchiectasis. The focus of management should therefore be shifted to prevention, early detection and treatment of such complications. However, reports on regular and consistent long-term assessments of EA/TEF survivors have been extremely limited. As such, it has been challenging to justify any guidelines on extended follow-up for this group of patients, especially commitment to multi-disciplinary team-care.

The aims of our study are therefore two-fold: firstly, to review the epidemiology, peri- and post-operative outcomes of patients with EA/TEF in our institution; and secondly, to evaluate the early and long-term incidence of gastro-esophageal and respiratory morbidities.

Methodology

Study design

Our retrospective review comprised of patients who underwent surgical repair for EA/TEF over a 23-year period from year 1996 to 2019 at KK Women's and Children's Hospital. Patients who were transferred to us from other hospitals after failed primary repairs or who had significant missing data were excluded. The study was approved by our institutional review board (CIRB Ref: 2019/2040).

The following data were obtained from review of both hard-copy and electronic medical records: (i) demographic and clinical characteristics including pre and post-natal parameters, associated congenital anomalies; (ii) type of EA/TEF, gap length, mode of repair from operative notes; (iii) surgical complications (anastomotic stricture or leak, recurrent TEF); (iv) early and long-term gastro-esophageal and respiratory morbidities and functional evaluations by multi-disciplinary follow-ups; (v) use of medications (anti-reflux medications, inhalers); (vi) mortality.

Definitions

EA/TEF was classified according to the gross anatomic subtypes, as determined at the time of surgery [5]. There is currently no accepted standard length, between the proximal and distal ends of esophagus, for the definition of long gap esophageal atresia (LGEA). For the purposes of our study, LGEA will be defined as a gap length exceeding 2 vertebral bodies (VB) in height, or 3 cm in length [6].

Major congenital cardiac anomaly was defined as either cyanotic heart disease requiring palliative or corrective surgery, or non-cyanotic heart disease requiring treatment for cardiac failure [5]. Atrial septal defect (ASD)/patent foramen ovale (PFO) or patent ductus arteriosus (PDA) with spontaneous closure were excluded.

Anastomotic tension was defined as longitudinal stress on the anastomotic junction, the degree of which was ascertained by the operating surgeon.

Anastomotic stricture was defined as symptomatic narrowing on contrast study at the level of esophageal anastomosis [7, 8].

Peri-operative management

All patients had a chest, abdominal and spine radiograph, and 2D echocardiography prior to surgery. Ultrasound imaging of the spine, kidneys and bladder was performed peri-operatively. Upper esophageal pouch decompression was performed via nasogastric or Replogle tube on suction. All patients routinely underwent bronchoscopy at

their initial surgery from the year 2006 onwards. A standard right postero-lateral thoracotomy was performed. Following identification and division of the fistula, the tracheal end was sealed by one of two methods: either by placing running or interrupted sutures as close to the trachea as possible without causing stenosis; or by suture transfixion and ligation of the tracheal stump. Esophageal gap length was assessed following mobilization of the proximal and distal esophageal pouches. Gap length was recorded in terms of vertebral body height on X-rays [6]. Definitive esophageal repair was performed either at the primary operation or as a staged procedure. For primary repair, end-to-end single layer esophageal anastomosis was achieved with interrupted sutures over a trans-anastomotic feeding tube in all patients. Upon completion of the anastomosis, a chest drain was routinely placed for all patients.

Post-operative care and follow-up

All patients were kept mechanically ventilated in the immediate post-operative period, with regular pharyngeal suctioning. Since 2006, a post-operative contrast study has been routinely performed to document integrity of the anastomotic repair. Upon confirmation of esophageal integrity, patients were weaned from nasogastric tube feeding to oral feeds. Early and late onset of post-operative complications, gastro-esophageal and respiratory morbidity were monitored. Mortality and readmission data were analyzed.

Follow-up outpatient appointments were arranged with pediatric surgery and other relevant sub-specialties at 3-monthly intervals, or earlier as guided by the nature and severity of their symptoms. Asymptomatic patients were seen yearly after the first year. Patients who were compliant with follow-up past their sixteenth birthday were transitioned to respective adult sub-specialist care.

Statistical analysis

Descriptive analysis of patients' demographic and clinical variables were expressed as medians with ranges or interquartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables. Statistical comparison between groups was performed using the Mann–Whitney *U* test for continuous variables and either chi-squared test or Fisher's exact test for categorical variables. Univariate analysis was utilized to verify associations between demographic, peri- and post-operative variables, outcomes, and mortality. This data was reported as odds ratio (OR) with 95% confidence interval (CI). A p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistical software version 19 (SPSS Inc. Chicago, IL).

Results

Demographic characteristics

A total of 83 patients were managed from the time of their initial surgery at our institution between 1996 and 2019. Eighteen patients admitted between 1996 and 2000 had to be excluded as they were either lost to follow-up or had substantial missing data. Of the remaining 65 patients, there were 39 males and 26 females, giving a male–female ratio of 1.5:1. Median gestational age was 37 weeks (range 30–41), with 25 (38.5%) born prematurely prior to 37 weeks. Median birth-weight (BW) was 2.49 kg (range 1.05–3.42). The ethnicity was predominantly Chinese ($n=34$, 52.3%).

According to Gross anatomic classification for the 65 patients: the predominant variant was EA with distal TEF (Type C) in 57 (87.7%), followed by isolated EA (Type A) in 5 (7.7%) (Table 1). Thirteen (20%) had long-gap EA (LGEA) of which 7 patients were of Type C and 5 were Type A variant. There was no significant difference in demographic characteristics between the LGEA and non-LGEA groups (Table 2).

EA/TEF was suspected or diagnosed prenatally in only 23 (35.4%) patients; with 100% detection of isolated esophageal atresia (Gross Type A) infants, but only 31.6% of infants with associated TEF (Gross B–E; $p<0.05$). Diagnosis was based on ultrasonographic findings of an absent or small stomach bubble in association with polyhydramnios. Interestingly, the blind-ending upper esophageal pouch was not visualized in any of our patients' prenatal ultrasounds. The most frequently encountered post-natal presentation was the classic pooling of secretions with coiling of the feeding tube in the upper esophageal pouch ($n=52$, 82.5%). Majority ($n=36$, 55.4%) of the patients were born in our institution; 26 (40.0%) were transferred from other local hospitals, and 3 (4.6%) were referred from overseas centers.

Associated anomalies

The incidence of associated congenital anomalies was high in our cohort, present in 37 out of 65 patients (57.0%), with 20 (30.8%) having more than one anomaly.

Table 1 Types of esophageal atresia (EA) by Gross anatomic classification

Gross type of EA	All infants ($n=65$)	(%)	Infants with LGEA ($n=13$)	(%)
A	5	7.7	5	38.5
B	1	1.5	1	7.7
C	57	87.7	7	53.8
D	1	1.5	–	–
E	1	1.5	–	–

Table 2 Demographic characteristics

	All patients ($n=65$)	LGEA ($n=13$)	Non-LGEA ($n=52$)	p value*
Gender ratio (M:F)	1.5:1	1.6:1	1.47:1	0.899
Ethnicity, Chinese	34 (52.3%)	8 (61.5%)	26 (50%)	0.542
Gestational age (week), median (range)	37 (30–41)	37 (33–40)	37 (30–41)	0.868
Birth weight (kg), median (range)	2.50 (1.05–3.42)	2.53 (1.23–3.1)	2.49 (1.05–3.42)	0.967
Plurality	5 (7.7%)	0	5 (9.6%)	0.315
Antenatal diagnosis	23 (35.4%)	8 (61.5%)	15 (28.8%)	0.055
Associated anomalies	61 (93.8%)	12 (92.3%)	49 (94.2%)	1.000
Major CHD	29 (44.6%)	4 (30.8%)	25 (48.1%)	0.355
VACTERL	20 (30.8%)	3 (23.1%)	17 (32.7%)	0.739

CHD congenital heart defect (congenital cardiac anomaly)

* p value is for comparison between LGEA and non-LGEA

The most common associated anomalies were cardiac defects ($n=29$, 44.6%) of which 21 (32.3%) were defined as major cardiac anomalies. This was followed by anorectal anomalies ($n=9$, 13.8%), vertebral ($n=9$, 13.8%), and renal anomalies ($n=7$, 10.8%).

Twenty (30.8%) patients met the criteria for VACTERL association (vertebral anomalies, anal atresia, cardiac malformations, TEF, renal, and limb malformations) [9]. There was no difference in the proportion of VACTERL association between the LGEA and non-LGEA groups. Two patients were diagnosed with CHARGE syndrome (coloboma, cardiac defects, choanal atresia, growth retardation, genital hypoplasia, and ear deformities).

Peri-operative management

Eighteen (27.7%) patients needed to be intubated preoperatively in the Neonatal ICU. The median time to the initial surgery in our cohort was 24 h (Table 3). This excluded 1 patient with H-type TEF who had delayed presentation and was diagnosed at 19 months of age. Routine pre-operative bronchoscopy identified laryngeal cleft in 2 patients (3.1%) and tracheomalacia in 3 patients

Table 3 Peri- and post-operative management

	All patients ($n=65$)	LGEA ($n=13$)	Non-LGEA ($n=52$)	p value*
Pre-operative and operative management				
Pre-op intubation	18 (27.7%)	5 (38.5%)	13 (25%)	0.489
Duration to first op, median (IQR)	1 (1–2)	1 (1–10)	1 (1–1)	**0.025**
Bronchoscopy performed	65 (100%)	13 (100%)	52 (100%)	1.000
Gap length, VB, median (range)	1.3 (0.4–8.0)	3.9 (1.3–8.0)	1.0 (0.4–3.0)	**<0.001**
Gap length, CM, median (range)	2 (0.6–12.0)	5.9 (2.0–12.0)	1.5 (0.6–4.5)	**0.001**
Open repair	57 (87.7%)	9 (69.2%)	48 (92.3%)	**0.026**
Extrapleural dissection	48 (73.8%)	7 (53.8%)	41 (78.8%)	**0.005**
Trans-anastomotic tube placement	58 (89.2%)	10 (76.9%)	48 (92.3%)	0.142
Catheterization of TEF	16 (25%)	5 (41.7%)	11 (21.2%)	0.156[a]
Chest drain placement	61 (95.3%)	11 (91.7%)	50 (96.2%)	0.470[a]
Tension at anastomosis	17 (26.2%)	6 (46.2%)	11 (21.2%)	0.060
Post-operative management				
Days intubated, median (IQR)	5 (4–9)	4 (2.5–7.5)	6 (4–9)	0.106
Days to contrast study, median (IQR)	8 (7–9.75)	9 (7.5–12.5)	8 (7–9)	0.233[a]
Days to feeds initiation, median (IQR)	8 (6–9)	9.5 (7.25–12.75)	8 (6–9)	0.069[a]
LOS[b], median (IQR)	27 (15.75–52.25)	45 (30.25–132.00)	22 (14.00–43.25)	**0.018**
Discharged on oral feeds	38 (64.4%)	3 (30%)	35 (71.4%)	**0.022**[a]

[a] Missing values excluded from analysis

[b] *LOS* length of stay (excluding patients who demised)

* p value is for comparison between LGEA and non-LGEA

(4.6%). The decision for placement of an occluding Fogarty catheter into the distal fistula was made as per surgeon's preference ($n=16$, 25%), to optimize ventilation and identification of the fistula prior to ligation.

The median esophageal gap assessed intra-operatively was 4VB (range 1.3–8.0) or 5.9 cm (range 2.0–12.0) in the LGEA group, and 1VB (range 0.4–3.0) or 1.5 cm (range 0.6–4.5) in the non-LGEA group ($p<0.001$). An extra-pleural dissection was preferred in our cohort ($n=48$, 73.8%), to avoid potentially severe complications of empyema and mediastinitis associated with transpleural dissection [10]. All non-LGEA patients ($n=52$) deemed clinically stable at surgery underwent primary anastomosis. Most of the LGEA group ($n=10/13$, 76.9%) underwent staged repair with open gastrostomy creation at their initial surgery. Surgical techniques employed at eventual esophageal reconstruction were delayed primary anastomosis (DPA) in 5 patients (38.5%), gastric transposition in 2, and colonic interposition in 1 patient. Anastomotic tension was documented in 6 (46.2%) LGEA patients and 11 (21.2%) of non-LGEA patients. Of those who underwent definitive repair, surgery was performed via an open right thoracotomy in 57 ($n=87.7$%). Minimally invasive surgery was attempted in 5 (7.7%) patients from year 2009, however 3 required conversion to open thoracotomy due to difficult mobilization. Our patient with H-type TEF underwent ligation via a cervical approach at 19 months of age.

The median duration of peri-operative intubation was 5 days (IQR 4–9). From the year 2006 onwards, a post-operative contrast study to document integrity of anastomosis was routinely performed in our institution, at a median of 8 days (IQR 7–9.8) after surgery. Upon verification of esophageal integrity, the median time to initiation of feeds, either orally or via naso-gastric tube, was 8 days (IQR 6–9) post-operatively. Patients in the non-LGEA group had a shorter median length of stay when compared to the LGEA group ($n=22.5$ v 48 days), and were more likely to be weaned to oral feeds by the time of discharge ($p<0.02$, Table 3).

Post-surgical complications

Our overall post-operative surgical morbidity rate was 32.3%. The most common complication was esophageal strictures ($n=20$, 30.8%) with 85% ($n=17$) presenting within the first year of life. Fifteen (75%) required serial (3 or more) dilatations. The cumulative number of mechanical dilatations across our cohort was 122, with 67 balloon dilatations (54.9%) performed by interventional radiologists and 55 endoscopic dilatations (45.1%) performed by pediatric surgeons. There was no significant difference in stricture rate, or the median number of dilatations between the LGEA (4.5, IQR 2.8–8) and non-LGEA group (5.5, IQR 3.3–8). The highest number of dilatations for a single patient was 38, who was also the only patient in our cohort to receive adjunct therapy with intralesional triamcinolone and mitomycin injections for recalcitrant esophageal stricture. The rate of perforation post-dilatation ($n=3/122$, 2.4%) was low; all were treated conservatively with a period of nasogastric decompression and bowel rest. None of our patients with esophageal stricture required surgical resection and re-anastomosis.

Four patients (6.2%) developed anastomotic leak confirmed on routine contrast study within 2 weeks post-surgery. All were managed conservatively: kept nil by mouth with total parenteral nutrition, nasogastric stenting and intravenous antibiotics. Anastomotic leak was significantly associated with LGEA ($p<0.05$, Table 4). Recurrent TEF occurred in 3 (4.6%) patients, 2 of whom were LGEA patients and required redo ligation via open thoracotomy at 5- and 35-months old. No patients developed post-operative vocal cord paralysis or symptomatic tracheal diverticulum.

Gastro-esophageal morbidity

In the immediate post-operative period, 42 patients (66.7%) were started on anti-reflux medications. Majority ($n=41$, 63.1%) suffered dysmotility-related symptoms, with GERD in 28 (43.1%) and dysphagia in 20 (30.8%), most of whom were diagnosed before their first year of age ($n=16/28$, 82.1% and $n=16/20$, 80.0% respectively). Within this sub-group of patients on anti-reflux medications, 21 remain symptomatic, requiring long-term medications (range 2–23 years). There was no significant difference in incidence of these complications between the LGEA and non-LGEA groups.

GERD in our patients was diagnosed on impedance/pH study and/or contrast imaging demonstrating reflux up to the proximal or mid-esophageal level [11]. Nine were co-managed with a gastroenterologist. Reflux was deemed severe enough to require Nissen's fundoplication in 9 (13.8%) patients (age range 2–43 months). Two patients had radiologic evidence of persistent reflux post-fundoplication although none had wrap disruption or required re-operation.

Esophagogastroduodenoscopy (OGD) was performed in 18 patients from our cohort (28.1%), 4 of whom were diagnosed with esophagitis. One demonstrated features of eosinophilic esophagitis. None were found to have Barrett's metaplasia or esophageal malignancy.

Respiratory morbidity

Tracheomalacia was diagnosed by visual assessment via bronchoscopy of reduction in the cross-sectional tracheal luminal area during the expiratory phase of quiet breathing. Severity is classified as mild (50–75% reduction),

Table 4 Post-operative and long-term complications

	All patients ($n=65$)	LGEA ($n=13$)	Non-LGEA ($n=52$)	p value*
Mortality	7 (10.8%)	1 (7.7%)	6 (11.5%)	1.00
Surgical complications	21 (32.3%)	7 (53.8%)	14 (26.9%)	0.096
Anastomotic stricture	20 (30.8%)	7 (53.8%)	13 (25.0%)	0.089
Anastomotic leak	4 (6.2%)	3 (23.1%)	1 (1.9%)	**0.023**
Recurrent TEF	3 (4.6%)	1 (7.7%)	2 (3.8%)	0.494
Gastro-esophageal complications	38 (58.5%)	10 (76.9%)	28 (53.8%)	0.209
GERD	28 (43.1%)	8 (61.5%)	20 (38.5%)	0.210
Dysphagia	20 (30.8%)	2 (15.4%)	18 (34.6%)	0.314
Esophagitis	4 (6.2%)	0	4 (7.7%)	0.576
Respiratory complications	42 (64.6%)	7 (53.8%)	35 (67.3%)	0.518
Chronic cough	19 (29.2%)	0	19 (36.5%)	0.007
Pneumonia	19 (29.2%)	7 (53.8%)	12 (23.1%)	**0.042**
Recurrent RTI	23 (35.3%)	4 (30.8%)	19 (36.5%)	0.758
Asthma/BHR	13 (20%)	1 (7.7%)	12 (23.1%)	0.438
Bronchiectasis	3 (4.6%)	1 (7.7%)	2 (3.8%)	0.494
Tracheomalacia	22 (33.8%)	1 (7.7%)	21 (40.4%)	**0.046**
Interventions				
Dilatations for AS, median (IQR)	5 (3–5)	4.5 (2.75–8)	5.5 (3.25–8)	0.671
Anti-reflux medications[a]	48 (73.8%)	12 (92.3%)	36 (69.2%)	0.157
Fundoplication performed	9 (13.8%)	4 (30.8%)	5 (9.6%)	0.070
Bronchodilators[b]	15 (23.1%)	1 (7.7%)	14 (26.9%)	0.268

RTI respiratory tract infections, *BHR* bronchial hyper-reactivity, *AS* anastomotic strictures

[a] Current and previous use of anti-reflux medications

[b] Current and previous use of bronchodilators

* p value is for comparison between LGEA and non-LGEA

moderate (75–90% reduction), or severe (>90% reduction) [12, 13]. Twenty-two (33.8%) patients were diagnosed with tracheomalacia (17 mild, 5 severe) in our cohort, of which only 3 were identified at initial surgery. The remaining 19 patients were diagnosed within the first year of life when they became symptomatic, commonly presenting with persistent barking cough, stridor or wheezing. Thirteen had follow-up with flexible bronchoscopy. Two patients with severe tracheomalacia necessitated tracheostomy though none required aortopexy.

Respiratory symptoms were frequently encountered in our cohort ($n=42$, 64.6%), of which the most common manifestation was recurrent lower respiratory tract infections ($n=23$, 35.3%), defined as 3 or more episodes requiring hospitalization in a year. This was followed by chronic cough with recurrent pneumonia ($n=19$, 29.2%), and asthma/bronchial hyper-reactivity ($n=13$, 20%). Pneumonia and tracheomalacia were associated with LGEA in our cohort ($p<0.05$).

Eighteen (27.7%) patients were co-managed with paediatric respiratory physicians. Bronchodilator use was recorded in 15 (23.1%) patients, with 8 currently on active treatment (duration of treatment ranging 3.25–23 years). Fifteen patients (23.1%) underwent flexible bronchoscopy, 13 of whom were on follow-up of tracheomalacia. Bronchoscopy was performed in 2 children as an adjunct investigation for reflux esophagitis and symptomatic esophageal pseudodiverticulum. Eleven (16.9%) children had computed tomography (CT) thorax for follow-up assessment of airway disease. Bronchiectasis was diagnosed in 3 (4.6%) patients.

Long-term follow-up

Among the surviving patients, 29 were 5 years or older at the time of the study, 21 were between 1 to 5 years old, and 8 were less than 1 year old. Median duration of follow-up for the overall cohort was 5 years (IQR 1.5–10), while 5.5 years (IQR 1.75–9.25) for those remaining on active follow-up ($n=39$, 60%; Table 5). Majority ($n=53$, 82.8%) required multiple readmissions for EA/TEF-related issues with a median of 3 admissions (IQR 1–6) across the cohort. Six patients (13.8%) have been discharged or transferred to overseas specialist care, while 10 (15.4%) have defaulted from all follow-up. Three of 9 adolescent patients have complied with transition to adult care. There was no significant

Table 5 Follow-up data

	All patients ($n=65$)	LGEA ($n=13$)	Non-LGEA ($n=52$)	p value*
Follow-up duration				
Years of active follow-up, median (IQR)[a]	5.5 (1.75–9.25)	4.54 (0.80–9.25)	5.5 (1.87–9.75)	0.508
Years of overall follow up, median (IQR)[b]	5 (1.5–10)	15 (1.04–20)	5 (1.75–9.25)	0.922
Readmissions	53 (81.5%)	9 (69.2%)	44 (84.6%)	0.237
Number of readmissions, median (IQR)	3 (1–6)	3 (0–9.5)	3 (1–6)	0.735

[a] Patients remaining on active follow-up ($n=39$)

[b] Overall duration of follow-up for all patients

* p value is for comparison between LGEA and non-LGEA

difference in median years of follow-up and readmissions, between the LGEA and non-LGEA group.

Survival

Overall survival of our operated patients was 58/65 (89.2%). All 7 mortalities were of the Gross Type C anatomical subtype, with a median birth weight of 2460 g. Two of them acutely deteriorated and died at their initial surgery: Sudden lung re-expansion followed by severe cardiorespiratory collapse occurred in one during thoracoscopic dissection of the upper esophageal pouch; in the other, acute cardiorespiratory collapse occurred peri-bronchoscopy. One patient with LGEA, concomitant type 2 laryngeal cleft and broncho-esophageal fistula required intensive care unit care from birth for recurrent respiratory infections, and eventually demised at 14 months old. Four patients died of late respiratory failure secondary to pneumonia and GERD-related complications at a median age of 8 months (range 5–32 months).

Table 6 compares survival by Spitz classification: majority of our infants ($n=34$, 52.3%) belonged to the low risk (Class I: birth weight > 1500 g with no major congenital cardiac defect) group, with 97% survival [14]. All our infants in the high-risk (Class III: BW < 1500 and major congenital cardiac defect) group survived, although this group was limited to 5 patients. Mortality in our patients was associated with presence of major congenital cardiac anomaly on univariate analysis ($p=0.028$; OR 15.9; 95% CI).

Discussion

Since the late 1970s, overall survival of EA/TEF infants has increased up to 95%. However, long-term gastroesophageal and respiratory morbidities are still highly prevalent in EA/TEF survivors despite advances in perinatal and surgical care. Hence there is an increased need to optimize management of this subset of patients based on updated evidence [15, 16]. Our retrospective study provides a contemporary description of the epidemiology, management, and post-operative outcomes of infants with EA/TEF treated at the main pediatric teaching hospital in Singapore over a 23-year period. Our study reports a significant burden of long-term gastroesophageal and respiratory complications in the EA/TEF survivors, and is the first in the existing literature to address these outcomes in an Asian population. In particular, we found a high prevalence of anastomotic strictures, dysmotility-related symptoms, GERD, recurrent lower respiratory tract infections, chronic cough, and bronchial hyper-reactivity.

Parallel to published studies from other continents, our cohort comprises of predominantly male patients, and the Gross Type C configuration of EA and distal TEF. Antenatal ultrasound diagnosis of EA/TEF can be challenging, with only 35.4% being diagnosed or suspected antenatally in our series. In a meta-analysis of 73,426 fetuses, Pardy et al. reported that prenatal ultrasound performed better in identification of cases with EA alone, than in cases with an associated TEF (77.9% vs 21.9%) [17]. The pick-up rate of associated anomalies on antenatal ultrasonography in our cohort was likewise low, with

Table 6 Survival comparison using Spitz classification

Group definition	Cohort, n (%) ($n=65$)	Deceased ($n=7$)	Survival rate, %
I: BW > 1500 g AND no major cardiac anomaly	34 (52.3%)	1	97%
II: BW < 1500 g OR major cardiac anomaly	26 (40.0%)	6	77%
III: BW < 1500 g AND major cardiac anomaly	5 (7.7%)	0	100%

detection in only 35.0% of our VACTERL patients and 26.5% of the overall cohort.

Congenital anomalies are frequently seen in EA/TEF children, sometimes occurring as part of a syndrome or association. The VACTERL association is the most well recognized, occurring in 30.8% of our cohort. Our incidence of major congenital cardiac anomalies is high ($n=21$, 32.3%), comparative to a reported 17–34.6% in the literature [18–20]. Performing a detailed workup to screen for associated cardiac anomalies and laterality of the aortic arch is of paramount importance.

Our study further evaluates the outcomes for LGEA and non-LGEA separately. LGEA presents a unique challenge within the EA/TEF spectrum with variable definitions and surgical approaches described in the literature, making parallel comparisons of clinical outcomes difficult. In addition, there is limited follow-up data on post-operative morbidity and recommendations from the available literature are generally derived from expert opinion rather than supported by evidence-based practice [6, 21]. Most authors believe 'the native esophagus is the best esophagus', and support a period of observation with interval gap assessments, followed by delayed primary anastomosis—which resonates with our department's practice. Where esophageal substitution is required, gastric transposition or intestinal interposition have been shown to be successful [22]. Of those who underwent esophageal substitution at our institution ($n=3$), none suffered complications of graft necrosis, anastomotic leak or strictures that have been described in the literature [23, 24]. When compared with non-LGEA, LGEA in our cohort was associated with longer hospital stay, prolonged tube feeding, anastomotic leak, pneumonia, and tracheomalacia ($p<0.05$).

All patients in our institution underwent rigid bronchoscopy pre-operatively prior to EA/TEF repair, by either a pediatric surgeon or otolaryngologist. Pre-operative screening bronchoscopy enables identification and localization of TEF, and has the advantages of excluding concomitant pathologies such as tracheomalacia and laryngeal cleft [25]. Tracheomalacia is the commonest tracheal anomaly among children with EA/TEF, with varying incidences of between 10 and 78% reported in existing literature [26]. Our series reports a 33.8% ($n=22$) prevalence, with majority diagnosed within the first year of life. Interestingly only 3 patients were diagnosed with tracheomalacia at pre-EA/TEF repair bronchoscopy. Among the remaining patients, tracheomalacia was diagnosed on repeat bronchoscopy in 12 patients, via clinical assessment for respiratory distress in 5 patients, and on esophagogram in 1 patient. This supports the theory that tracheomalacia can be a delayed event, related to surgical dissection of the upper esophageal pouch or persistent upper pouch dilatation due to stricture or dysmotility. Persistent chronic cough, and asthma or airway hyper-reactivity ($p<0.05$) were significantly associated with tracheomalacia in our study. Only 1 patient experienced an acute life-threatening event (ALTE). None had congenital or acquired vocal cord paralysis or hypo-motility diagnosed on initial or repeat bronchoscopy. We feel this provided us with quality assurance of our peri-operative management.

Overall incidence of gastro-esophageal and respiratory morbidity was 38 (58.5%) and 42 (64.6%) respectively, with only 10 having isolated gastro-esophageal symptoms and 14 having isolated respiratory symptoms. The proportion of patients with dual pathologies is explained by the multi-factorial nature of the underlying disease processes: a common underlying pathophysiology is impairment of mucociliary transport in a malacic tracheal segment or abnormal presence of non-ciliated squamous epithelium in the trachea around the site of repair [27, 28]. This is further exacerbated by esophageal dysmotility due to strictures or GERD, which increases the risk of chronic microaspiration-related lung injury, leading to sequelae of chronic cough, aspiration pneumonia, airway hyper-reactivity, chronic lung disease, and bronchiectasis. Respiratory morbidity was reported in the literature to have a overall higher incidence of up to 78% [12, 29]. This may be explained by consistent long-term follow-up of our patients, with early involvement of pediatric respiratory physicians in the care of persistently symptomatic patients. There is currently no established guideline on respiratory management for EA/TEF patients. Our findings concurred with some studies which suggested infancy and childhood to be the most vulnerable period for these patients, and recommend early routine specialist review, alongside surveillance with pulmonary function tests or radiologic imaging [30].

In the literature, anastomotic strictures are the most frequent post-operative complication in EA/TEF, with reported incidence in the literature varying from 6 to 49%, and is predominantly diagnosed in the first year of life [31–34]. In our cohort, significant anastomotic tension due to long gap and limited use of anti-reflux medications were associated with development of anastomotic stricture ($p<0.05$), but not anastomotic leak and GERD, unlike in other studies. The mainstay of treatment for anastomotic stricture is esophageal dilatation, with the aim of achieving an adequate capacity for oral feeding without developing aerodigestive complications. In general, 50% of esophageal strictures resolve after 6 months of age. However, 85% of our patients presented within their first year, with the majority requiring serial dilatations, though none required stricture resection. There is no consensus on the role of prophylactic dilatation as

opposed to a "wait-and-see approach" for symptomatic patients [33].

Abnormal anatomical development in infants with EA/TEF leads to primary innervation disorders with resulting intrinsic dysmotility, impaired peristalsis and dysfunction of the lower esophageal sphincter [27]. Incidence of dysphagia ranges from 10 to 60% throughout the literature, with 30.8% of our cohort affected. GERD is commonly encountered despite EA/TEF repair and tends not to improve over time, with a reported incidence in 35 to 60% of post-operative patients [32, 35]. Eosinophilic esophagitis is an increasingly recognized entity that has overlapping symptoms with GERD, but is best treated with an elemental diet and topical corticosteroids [36].

ESPGHAN-NASPGHAN consensus guidelines have recommended prophylactic treatment of all EA/TEF infants with anti-reflux medications in their first year of life, and thereafter in accordance with clinical symptoms [31]. In our cohort, 32.3% of our cohort remain on long-term treatment with proton-pump inhibitors or histamine-2 receptor antagonists. Nine patients (13.8%) underwent anti-reflux surgery for persistent GERD refractory to medical therapy, classically a Nissen's fundoplication in our institution. Other studies reported a 13 to 32% fundoplication rate among their patient cohorts [37]. Fundoplication is effective in reducing esophageal acid exposure without altering motility; however, definitive conclusions on its effectiveness in the subset of patients with EA remains limited due to the lack of a standardized framework for reporting outcomes [38]. Nevertheless, the benefit of long-term acid suppression presides, as chronic acid exposure of the esophageal mucosa can lead to esophagitis, Barrett's metaplasia, even esophageal adenocarcinoma. Long-term follow-up beyond childhood with endoscopic surveillance is recommended in patients with GERD and eosinophilic esophagitis to prevent development of these late complications, and increasingly advocated even in asymptomatic patients [39, 40].

Our study is limited firstly, by its retrospective design and small number of study subjects derived from a single institution. Secondly, a significant number of patients born in the earlier years of the study period were excluded from our study due to several missing data points. These factors limited our ability to perform more meaningful sub-group analysis. Thirdly, advances in surgical techniques over a considerably long study period could have had an impact on long-term outcomes. Despite these limitations, to our knowledge, this is the first study from Asia reporting post-operative outcomes and long-term morbidity in children with EA/TEF derived from a unique multi-racial population. Comprehensive multidisciplinary follow-up and our institution's use of integrated electronic medical records (EMR) in recent years enabled us to review detailed longitudinal data from our cohort.

Recommendations

EA/TEF is best regarded as a chronic disease requiring long-term multi-disciplinary care beyond childhood and adolescence, regardless of symptoms, in order to avoid missed diagnosis and resultant morbidity. This should include paediatric surgeons, gastroenterologists, pulmonologists, otolaryngologists, as well as dietitians and speech therapists. In particular, persistent GERD can lead to esophageal metaplasia and malignancy, warranting systematic transition to adult sub-specialist care for continued cancer surveillance.

International networks, such as ERNICA (European Reference Network of Rare Inherited and Congenital Anomalies), have developed guidelines for long-term follow-up of EA/TEF patients, however these are tailored to a different patient demographic [41]. Furthermore, it is recognized that the management of EA/TEF can differ substantially between institutions. The limitations imposed by retrospective evaluation of outcomes as encountered in our study emphasize the need for a standardized registry for prospective capturing of patient data, and monitoring of long-term morbidity. In due course, multi-institutional cooperation on a national or regional level to combine databases can contribute to developing a framework of best practice management guidelines for EA/TEF infants. An in-depth understanding of the local epidemiology and outcomes associated with EA/TEF can also guide antenatal and post-operative counseling of patient's parents.

Conclusion

With the privilege of consistent follow-ups within the same institution, our longitudinal series demonstrates significant post-operative burden of gastro-esophageal and respiratory morbidity in EA/TEF survivors. This highlights the importance of multi-disciplinary specialist care and long-term follow-up. Developing a transitional care program from pediatric to adult sub-specialist services is imperative, especially for esophageal cancer surveillance. With standardized post-operative management and follow-up protocols, even a low-volume center can achieve good outcomes and establish best practice models of care.

Abbreviations

AS	Anastomotic strictures
BHR	Bronchial hyper-reactivity
CHD	Congenital heart defect
DPA	Delayed primary anastomosis
EA/TEF	Esophageal atresia with or without tracheoesophageal fistula

GERD	Gastro-esophageal reflux disease
IQR	Interquartile ranges
LGEA	Long gap esophageal atresia
LOS	Length of stay
OGD	Esophagogastroduodenoscopy
RTI	Respiratory tract infections
VB	Vertebral bodies

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Authors' contributions
Study conception and design: JC, YTL, OLY. Data acquisition: JC, SA, CC, YTL. Analysis and data interpretation: JC, CC, YTL, OLY. Drafting of the manuscript: JC, YTL, OLY. Critical revision: JC, AP, BT, AJ, YTL, OLY. JC and YTL have contributed equally to this manuscript and are listed as co-first authors. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and analyzed during the current study are not publicly available, however are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Our study was approved by our institutional review board (CIRB Ref: 2019/2040). No human or animal tissue was used in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Paediatric Surgery, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore. [2]Temasek Polytechnic School of Applied Science, Singapore, Singapore. [3]Department of Respiratory Medicine, KK Women's and Children's Hospital, Singapore, Singapore.

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References

1. Nassar N, Leoncini E, Amar E, Arteaga-Vázquez J, Bakker MK, Bower C, et al. Prevalence of esophageal atresia among 18 international birth defects surveillance programs. Birth Defects Res Part A - Clin Mol Teratol. 2012;94:893.
2. Malmström K, Lohi J, Lindahl H, Pelkonen A, Kajosaari M, Sarna S, et al. Longitudinal follow-up of bronchial inflammation, respiratory symptoms, and pulmonary function in adolescents after repair of esophageal atresia with tracheoesophageal fistula. J Pediatr. 2008;153:396.
3. Koivusalo AI, Pakarinen MP, Rintala RJ. Modern outcomes of oesophageal atresia: single centre experience over the last twenty years. J Pediatr Surg. 2013;48:297.
4. Cartabuke RH, Lopez R, Thota PN. Long-term esophageal and respiratory outcomes in children with esophageal atresia and tracheoesophageal fistula. Gastroenterol Rep. 2016;4:310.
5. Spitz L. Oesophageal atresia. Orphanet J Rare Dis. 2007;2:24.
6. Baird R, Lal DR, Ricca RL, Diefenbach KA, Downard CD, Shelton J, et al. Management of long gap esophageal atresia: a systematic review and evidence-based guidelines from the APSA outcomes and evidence based practice committee. J Pediatr Surg. 2019;54:675.
7. Baird R, Laberge JM, Lévesque D. Anastomotic stricture after esophageal atresia repair: a critical review of recent literature. Eur J Pediatr Surg. 2013;23:204.
8. Stadil T, Koivusalo A, Pakarinen M, Mikkelsen A, Emblem R, Svensson JF, et al. Surgical repair of long-gap esophageal atresia: a retrospective study comparing the management of long-gap esophageal atresia in the Nordic countries. J Pediatr Surg. 2019;54:423.
9. Bairdain S, Zurakowski D, Vargas SO, Stenquist N, McDonald M, Towne MC, et al. Long-gap esophageal atresia is a unique entity within the esophageal atresia defect spectrum. Neonatology. 2017;111:140.
10. Batikhe M. Transpleural versus extrapleural approach in treatment of esophageal atresia. Ann Pediatr Surg. 2020;16(1):8. https://doi.org/10.1186/s43159-019-0015-7.
11. Vergouwe FWT, van Wijk MP, Spaander MCW, Bruno MJ, Wijnen RMH, Schnater JM, et al. Evaluation of Gastroesophageal Reflux in Children Born With Esophageal Atresia Using pH and Impedance Monitoring. J Pediatr Gastroenterol Nutr. 2019;69(5):515–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31490855
12. Shah R, Varjavandi V, Krishnan U. Predictive factors for complications in children with esophageal atresia and tracheoesophageal fistula. Dis Esophagus. 2015;28:216.
13. Fayoux P, Sfeir R. Management of severe tracheomalacia. J Pediatr Gastroenterol Nutr. 2011;52:S33.
14. Lopez PJ, Keys C, Pierro A, Drake DP, Kiely EM, Curry JI, et al. Oesophageal atresia: improved outcome in high-risk groups? J Pediatr Surg. 2006;41:331.
15. Mousa H, Krishnan U, Hassan M, Dall'Oglio L, Rosen R, Gottrand F, et al. How to care for patients with EA-TEF the known and the unknown. Curr Gastroenterol Rep. 2017;19:65.
16. Séguier-Lipszyc E, Bonnard A, Aizenfisz S, Enezian G, Maintenant J, Aigrain Y, et al. The management of long gap esophageal atresia. J Pediatr Surg. 2005;40:1542.
17. Pardy C, D'Antonio F, Khalil A, Giuliani S. Prenatal detection of esophageal atresia: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2019;98(6):689–99. https://doi.org/10.1111/aogs.13536.
18. Lal DR, Gadepalli SK, Downard CD, Ostlie DJ, Minneci PC, Swedler RM, et al. Perioperative management and outcomes of esophageal atresia and tracheoesophageal fistula. J Pediatr Surg. 2017;52:1245.
19. Leonard H, Barrett AM, Scott JES, Wren C. The influence of congenital heart disease on survival of infants with oesophageal atresia. Arch Dis Child Fetal Neonatal Ed. 2001;85:F204.
20. Pedersen RN, Calzolari E, Husby S, Garne E. Oesophageal atresia: Prevalence, prenatal diagnosis and associated anomalies in 23 European regions. Arch Dis Child. 2012;97:227.
21. Shieh HF, Jennings RW. Long-gap esophageal atresia. Semin Pediatr Surg. 2017;26:72.
22. Liu J, Yang Y, Zheng C, Dong R, Zheng S. Surgical outcomes of different approaches to esophageal replacement in long-gap esophageal atresia. Medicine (United States). 2017;96:e6942.
23. Spitz L. Gastric transposition in children. Semin Pediatr Surg. 2009;18:30.
24. Chowdhary SK, Kandpal DK, Agarwal D, Balan S, Jerath N, Sibal A, et al. Endoscopic esophageal substitution for pure esophageal atresia and wide gap esophageal atresia: a report of five cases with minimum follow-up of twelve months. J Pediatr Surg. 2016;51:360.
25. Parolini F. Role of preoperative tracheobronchoscopy in newborns with esophageal atresia: a review. World J Gastrointest Endosc. 2014;6:482.
26. Deurloo JA, Ekkelkamp S, Schoorl M, Heij HA, Aronson DC. Esophageal atresia: historical evolution of management and results in 371 patients. Ann Thorac Surg. 2002;73:267.
27. Fragoso AC, Tovar JA. The multifactorial origin of respiratory morbidity in patients surviving neonatal repair of esophageal atresia. Front Pediatr. 2014;2:39.
28. Emery JL, Haddadin AJ. Squamous epithelium in respiratory tract of children with tracheooesophageal fistula. Arch Dis Child. 1971;46:236.
29. Porcaro F, Valfré L, Aufiero LR, Dall'Oglio L, De Angelis P, Villani A, et al. Respiratory problems in children with esophageal atresia and tracheoesophageal fistula. Ital J Pediatr. 2017;43:77.
30. Sadreameli SC, McGrath-Morrow SA. Respiratory care of infants and children with congenital tracheo-oesophageal fistula and oesophageal atresia. Paediatr Respir Rev. 2016;17:16.

31. Krishnan U, Mousa H, Dall'Oglio L, Homaira N, Rosen R, Faure C, et al. ESPGHAN-NASPGHAN guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with esophageal atresia-tracheoesophageal fistula. J Pediatr Gastroenterol Nutr. 2016;63:550.
32. Acher CW, Ostlie DJ, Leys CM, Struckmeyer S, Parker M, Nichol PF. Long-term outcomes of patients with tracheoesophageal fistula/esophageal atresia: Survey results from tracheoesophageal fistula/esophageal atresia online communities. Eur J Pediatr Surg. 2016;26:476.
33. Lévesque D, Baird R, Laberge J-M. Refractory strictures post-esophageal atresia repair: what are the alternatives? Dis Esophagus. 2013;26(4):382–7. https://doi.org/10.1111/dote.12047.
34. Donoso F, Kassa AM, Gustafson E, Meurling S, Lilja HE. Outcome and management in infants with esophageal atresia – A single centre observational study. J Pediatr Surg. 2016;51:1421.
35. Little DC, Rescorla FJ, Grosfeld JL, West KW, Scherer LR, Engum SA. Long-term analysis of children with esophageal atresia and tracheoesophageal fistula. J Pediatr Surg. 2003;38:852.
36. Krishnan U. Eosinophilic esophagitis in esophageal atresia. Front Pediatr [Internet]. 2019;7:497. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31850292
37. Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. Chest. 2004;126:915.
38. Jancelewicz T, Lopez ME, Downard CD, Islam S, Baird R, Rangel SJ, et al. Surgical management of gastroesophageal reflux disease (GERD) in children: A systematic review. J Pediatr Surg. 2017;52:1228.
39. Hsieh H, Frenette A, Michaud L, Krishnan U, Dal-Soglio DB, Gottrand F, et al. Intestinal metaplasia of the esophagus in children with esophageal atresia. J Pediatr Gastroenterol Nutr. 2017 Jul;65(1):e1–4. Available from: https://journals.lww.com/00005176-201707000-00005
40. Schneider A, Michaud L, Gottrand F. Esophageal atresia: metaplasia Barrett. Dis Esophagus. 2013;26(4):425–7. https://doi.org/10.1111/dote.12057.
41. Dingemann C, Eaton S, Aksnes G, Bagolan P, Cross KM, De Coppi P, et al. ERNICA consensus conference on the management of patients with esophageal atresia and tracheoesophageal fistula follow up and framework. Eur J Pediatr Surg. 2019;30:475.

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