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Original Article

Diagnosis and management of post-operative complications in esophageal atresia patients in China: a retrospective analysis from a single institution

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Abstract: Post-operative complications (PCs) remain a common morbidity of esophageal atresia (EA) repairs. Accurate diagnosis and appropriate treatments for these PCs remain a great challenge for pediatric surgeons. All EA patients admitted to our institution from 2010 to 2016 were retrospectively reviewed. Demographics, types of PCs, PC diagnosis, treatments, and follow-ups were recorded. Totally 157 of 172 patients with EA underwent primary repairs. PCs occurred in 65 patients (41.4%). Based on univariate analysis, the Gross classification significantly influenced the incidence of PCs ($P < 0.01$). The most frequent PCs were anastomotic strictures (23.7%), anastomotic leakages (11.1%), gastroesophageal reflux (5.9%), and recurrent tracheoesophageal fistulas (5.2%). Anastomotic strictures and leakages were confirmed by esophagography. Gastroesophageal reflux and recurrent tracheoesophageal fistulas were demonstrated with radionuclide scintigraphy and esophagoscopy, respectively. All of the patients with anastomotic strictures underwent esophageal dilatation. Conservative treatments were successfully performed in all of the patients with anastomotic leakages. Anti-reflux medications were prescribed to all of the patients with gastroesophageal reflux. All of the patients with recurrent tracheoesophageal fistulas underwent re-operations. In conclusion, Anastomotic strictures and leakages, gastroesophageal reflux, and recurrent tracheoesophageal fistulas are the most common PCs in patients undergoing EA repairs. Esophagography is the best option for diagnosing anastomotic strictures and leakages. Diagnosis of gastroesophageal reflux and recurrent tracheoesophageal fistulas requires radionuclide scintigraphy and esophagoscopy. Recurrent tracheoesophageal fistula is an indication for re-operation. Surgical outcomes are favorable in EA patients with PCs.

Keywords: Esophageal atresia, post-operative complications, esophagoscopy, esophageal dilation, re-operation

Introduction

Esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF) is the most frequent congenital malformation of the esophagus, with a prevalence ranging from 1 to 1.8 per 4500 live births [1, 2]. An increased number of neonates with EA have undergone successful surgical repairs during the past 3 decades. The prognosis of EA has improved from remarkable advances in both neonatal management and surgical care, and the survival rate is currently > 90% [3]. However, post-operative complications (PCs) remain a common morbidity in EA patients after esophageal repair [3, 4]. Post-operative morbidity mainly depends on the incidence of anastomotic leakages (ALs) and strictures (ASs), recurrent tracheoesophageal fistulas (RTEFs), and gastroesophageal reflux (GER). Accurate diagnosis and appropriate treatments for these PCs remain a great challenge for pediatric surgeons.

In the current study, we retrospectively reviewed our experience on the diagnosis and management of the most frequent PCs in EA patients, as well as the outcomes and potential causative factors associated with PCs in our institution from 2010 to 2016.

Materials and methods

Patient population

Approval was obtained from our Hospital Institutional Review Board prior to the initiation of

Table 1. Clinical features of esophageal atresia patients who underwent primary esophageal repair

		No.	%
Sex	Male	89	57%
	Female	68	43%
Gestational age	0-36 weeks	33	21%
	37-40 weeks	99	63%
	> 40 weeks	25	16%
Birth weight	1500-2499 g	41	26%
	2500-4000 g	105	67%
	> 4000 g	11	7%
Classification	Gross A	9	5.7%
	Gross C	139	88.5%
	Gross D	2	1.3%
	Gross E	7	4.5%

this study. A single institution retrospective review was performed on 172 EA neonates with or without a TEF between January 2010 and December 2016. The medical record, including demographics, Gross classification of EA, operative details, type of PCs, PC diagnosis and therapy, and prognosis, of each patient was reviewed. Follow-up information was collected from outpatient and inpatient records with telephone communications or questionnaires.

Statistical analysis

Data analysis was performed using SPSS version 20.0 statistical software (SPSS, Inc., Chicago, IL, USA). The parametric data are reported as percentages. The non-parametric continuous data are expressed as the mean ± SD. The differences between the non-parametric unpaired continuous data were analyzed using a chi-square or Fischer's exact test. A p-value < 0.05 was considered statistically significant.

Results

Patient demographics

One hundred seventy-two EA patients with or without a TEF were identified from January 2010 to December 2016. Primary surgery was performed on 157 EA patients (**Table 1**). The male-to-female ratio was 1.3:1. The gestational age ranged from 34 to 43 weeks (mean, 38 ± 2 weeks). The birth weights ranged from 1640-4260 g (mean, 2852 ± 515 g). The types of EA were classified according to the Gross classification [1], as follows: A (n = 9 [5.7%]); C (n = 139 [88.5%]); D (n = 2 [1.3%]); and E (n = 7 [4.5%]). EA-associated anomalies were diagnosed in 81 neonates (51.6%) and included congenital heart diseases, anorectal malformations, urogenital anomalies, and anomalies of limbs or vertebrae (**Table 2**); 70 neonates (86.4%) had 1 or 2 associated defects and 11 (13.6%) had > 3 associated malformations.

Primary esophageal surgical procedure in EA patients

157 of 172 neonates with EA underwent surgery by the same pediatric surgeon at our institution. The surgical procedures and approaches depended on the types of EA (**Table 3**). Patients with type A EAs underwent staged surgery, while a one-stage esophageal anastomosis with or without TEF ligation was performed for all of the other Gross types. The surgical methods were as follows: thoracotomies, n = 88 (56.0%); cervical, n = 6 (3.8%); thoracoscopies, n = 59 (37.6%); and combination open thoracotomies and cervical, n = 2 (1.3%). Two neonates (1.3%) required conversions from thoracoscopy-to-thoracotomy due to severe bleeding. Thirteen neonates with EAs died after the primary surgical procedure; the early post-operative survival rate in EA patients was 91.7%. The causes of death were respiratory distress, heart failure, severe sepsis, and treatment abandonment in 3, 2, 1, and 7 patients, respectively.

PCs and risk factors

PCs were observed in 65 operative cases (41.4%; **Table 4**). The most common PC was ASs (21.7%), followed by ALs (10.2%), GER (5.1%), and RTEFs (4.5%). Among the neonates with PCs, 56 had only 1 PC, whereas 9 patients had 2 PCs. Univariate and multivariate analyses with a logistic regression model were applied to investigate risk factors for PC occurrence and the results are summarized and shown in **Table 5**. Based on univariate analysis, demographic variables, such as gender, birth weight, gestational age, operation methods, operation staging, and associated anomalies had no significant association with the incidence of PCs (P > 0.05); however, the Gross classification significantly influenced the

Table 2. Malformations associated with esophageal atresia

	No. (%)
Congenital heart disease	63 (77.8%)
Patent ductus arteriosus	47
Atrial septal defect	25
Ventricular septal defect	15
Anomalous pulmonary venous connection	1
Cor triatriatum	1
Right aortic arch	1
Dextrocardia	1
Coarctation of the aorta	1
Anorectal malformation	12 (14.8%)
Rectoperinaeal fistula	5
Recto-urethral bulbar fistula	2
Rectovestibular fistula	5
Urogenital anomaly	8 (9.9%)
Hypospadias	4
Cryptorchidism	1
Hydronephrosis	1
Horseshoe kidney	1
Renal ectopia	1
Anomaly of limbs or vertebrae	10 (12.3%)
Polydactyly	7
Anomaly of rib cage	1
Anomaly of thoracic vertebra	3
Gastrointestinal malformation	3 (3.7%)
Annular pancreas	1
Esophageal duplication cyst	1
Hiatal hernia	1
Others	4 (4.9%)
Laryngeal cleft	1
Ear neoplasm	2
Cleft palate	1

incidence of PCs in EA patients ($P < 0.01$). Nearly 50% of EA patients with Gross A, C, and D EAs had PCs, whereas a lower incidence (14.3%) of PCs occurred among patients with Gross E EAs; however, not all factors were risk factors for PC occurrence in multivariate analysis ($P > 0.05$).

AS and AL

ASs and ALs were diagnosed in 34 and 16 operative cases with EAs, respectively. Contrast esophagography was used to determine whether or not AS or AL existed. All patients with ASs and ALs were confirmed by esophagography with barium or omnipaque (**Figures 1** and **2**). Regular endoscopic esophageal bougie or balloon dilatation was performed in all AS patients once every 1-3 months (**Figure 1C**, **1D**). The number of times esophageal dilatation was required in AS patients ranged from 1 to 10 (mean, 2.8 ± 2.2). The duration of dilatation treatments ranged from 1 to 24 months (mean, 6.5 ± 5.4 months). After endoscopic dilation, symptoms were relieved in all AS patients. Furthermore, all ALs were resolved with conservative treatment, including total parenteral nutritional support, trans-anastomotic feeding by nasogastric tube, use of broad-spectrum antibiotics, and chest tube drainage. The length of spontaneous healing of leaks ranged from 7 to 51 days (mean, 31.1 ± 16.3 days). The average length of chest tube drainage and post-operative hospital stay were 12.3 ± 6.7 days (range, 5-26 days) and 31.1 ± 16.3 days (range, 11-78 days).

Post-operative GER

Eight patients had post-operative GER, which were diagnosed with contrast esophagography and 24-hour esophageal pH monitoring or radionuclide scintigraphy. The severity of GER in EA patients was assessed with the Boix-Ochoa score according to the criteria developed by the Group of Digestive Diseases Branch of Pediatrics of the Chinese Medical Association [5]. Three GER patients (37.5%) had mild reflux (mean Boix-Ochoa score, 15.1 ± 3.7), and moderate reflux existed in 5 GER patients (62.5%; mean Boix-Ochoa score, 27.3 ± 4.1). All of the patients with GER received regular anti-reflux medications, including antacid and prokinetic agents during the post-operative period. The duration of anti-reflux medications among GER patients was variable, as follows: 3-6 months (5 cases [62.5%]); 6-12 months (2 cases [25%]); or > 12 months (1 case [12.5%]). No patient required a fundoplication procedure.

RTEF

Seven EA patients with RTEFs were identified. Diagnosing RTEFs relied on contrast esophagography and esophagoscopy (**Figure 3**). Only three RTEF cases (42.9%) were delineated with esophagography; however, the seven RTEF

Table 3. Initial operation for esophageal atresia

Gross classification	Operation type (n, %)					Operation staging (n, %)	
	Open thoracotomy	Cervical approach	Combination with thoracotomy and cervical approach	Thoracoscopic repair	Conversion	Primary repair	Staged repair
Gross A	9 (100%)	0	0	0	0	0	9 (100%)
Gross C	78 (56.1%)	0	0	59 (42.5%)	2 (1.4%)	138 (99.3%)	1 (0.7%)
Gross D	0	0	2 (100%)	0	0	2 (100%)	0
Gross E	1 (14%)	6 (86%)	0	0	0	7 (100%)	0
Total	88 (56.0%)	6 (3.8%)	2 (1.3%)	59 (37.6%)	2 (1.3%)	147 (93.6%)	10 (6.4%)

Table 4. Postoperative complications of esophageal atresia

Complications	No.	Incidence (%)
Anastomotic strictures (ASs)	34	21.7
Anastomotic leakages (ALs)	16	10.2
Gastroesophageal reflux (GER)	8	5.1
Recurrent TEFs (RTEFs)	7	4.5
Esophageal diverticulum	4	2.5
Tracheomalacia	3	1.9
Sepsis	2	1.3

TEF: tracheoesophageal fistula.

cases were all confirmed by esophagoscopy. All RTEF cases underwent re-operation 3-6 months after primary surgery for TEF resection and esophageal anastomosis. The surgical procedure has been described previously [6]. Re-operation was successfully performed in all RTEF cases. The operative time ranged from 1.75 to 3 hours, with an average of 2.2 ± 0.6 hours. Mechanical ventilation was maintained for 1-9 days, with an average of 3.5 ± 3.8 days. A chest drainage tube was used for drainage after re-operation for 2-11 days, with an average of 7.5 ± 4.4 days. The average length of post-re-operative hospital stay ranged from 10 to 26 days, with an average of 17.25 ± 7.5 days.

Follow-up

All of the EA cases with PCs were followed until December 2016. Follow-up ranged from 6 to 84 months, with an average of 34.2 ± 27.3 months. Barium swallow was performed in all cases during the follow-up period. For AS and AL cases, no specific therapies were required. Among the patients with RTEFs who underwent esophageal re-operations, 1 AS and 2 ALs were identified. The patient with an AS recovered after esophageal dilatation assisted with a pediatric gastroscope. The patients with ALs were cured with multiple conservative treatments described as above. In addition, 24-h esophageal pH monitoring or radionuclide scintigraphy was also applied in GER cases during the follow-up period. Medication management of GER was successful in relieving symptoms in all patients and further surgical intervention was not required.

Discussion

EA and TEFs are congenital malformations due to a defect in the development of the foregut into the esophagus and trachea at approximately the 5th week of gestation [7]. Recently, > 90% of EA patients have been cured with advanced surgical techniques; however, PCs still significantly impact the prognosis of patients with EA and TEFs [7]. Recent studies have reported that PC rates range from 20% to 60% and anastomotic complications, including ASs, ALs, RTEFs, and GER, are the most frequent PCs, and factors that determine the post-operative survival of EA patients [8, 9]. In the current study, the incidence of PCs was approximately 50% and most common PCs were ASs, ALs, post-operative GER, and RTEFs. The results were similar to other reports.

Multiple identified risk factors contribute to the incidence of PCs and the prognosis and survival of EA patients [10-13]. The incidence of PCs differs based on the EA type. Greater than 50% of newborns with EA have associated congenital anomalies, which is also a major factor that influences PC occurrence; however, other potential risk factors, including birth weight, gestational age, operation type, and operation staging, are controversial. The present study showed that these factors may not be related to the occurrence of PCs, although

Table 5. Univariate and multivariate analysis for postoperative complications

Variable	PC incidence	Univariate analysis	Multivariate analysis	
		P value	Odds ratio (95% CI)	P
Sex		0.709	1.027 (0.346, 3.046)	0.962
Male	36 (40.4%)			
Female	29 (42.6%)			
Birth weight (BW)		0.244	1.041 (0.404, 2.678)	0.934
Normal BW (2500-4000 g)	42 (40.0%)			
Low BW (< 2500 g)	18 (43.9%)			
High BW (> 4000 g)	5 (45.5%)			
Gestational age (GA)		0.290	0.983 (0.519, 1.862)	0.957
Preterm (< 37 weeks)	14 (42.4%)			
Full term (37-40 weeks)	42 (42.4%)			
Post term (> 40 weeks)	9 (36.0%)			
Classification		0.000*	1.138 (0.651, 1.989)	0.649
Gross A	3 (33.3%)			
Gross C	60 (43.2%)			
Gross D	1 (50.0%)			
Gross E	1 (14.3%)			
Associated malformation		0.330	0.519 (0.093, 2.884)	0.453
Yes	41 (50.6%)			
No	24 (31.6%)			
Operation type		0.118	1.695 (0.707, 4.061)	0.237
Open thoracotomy	43 (48.9%)			
Cervical approach	2 (33.3%)			
Combination with open thoracotomy and cervical approach	1 (50.0%)			
Thoracoscopic repair	17 (28.8%)			
Conversion	1 (50.0%)			
Operation staging		0.427	0.465 (0.088, 2.463)	0.368
Primary repair	60 (40.8%)			
Staged repair	5 (50.0%)			

*Statistically significant. PC: postoperative complication.

a significant different incidence was detected among different Gross types of EA based on univariate analysis. Therefore, additional studies with a high level of evidence are needed to confirm risk factors contributing to PCs.

The early and accurate diagnosis of the main PCs, including ASs, ALs, RTEFs, and GER, continues to be difficult, which results in delayed or incorrect therapies and poor prognoses. Because there are no specific symptoms for PCs, the diagnosis is mainly dependent on multiple imaging examinations. Contrast esophagography is the gold standard for diagnosing ASs and ALs; however, esophagography is not sufficiently sensitive for the diagnosis of GER and RTEFs [6-14]. Esophagoscopy or bronchoscopy is recommended to confirm the diagnosis of a RTEF [15]. In addition, determination of the severity of GER is dependent on 24-h esophageal pH monitoring or radionuclide scintigraphy [16]. All of the patients with ASs, ALs, and GER in the present study were independently confirmed by contrast esophagography. Only 42.9% of patients with RTEFs were independently confirmed by esophagography, whereas all of the RTEF patients were identified by esophagoscopy. The severity of GER depended on the data obtained from 24-h esophageal pH monitoring or radionuclide scintigraphy. Thus, contrast esophagography is able to determine the diagnosis of AS and AL. An esophagogram, which is combined with esophagoscopy, is recommended for RTEF confirmation. It is necessary to apply 24-h esophageal pH monitoring or radionuclide scintigraphy to determine the severity of GER.

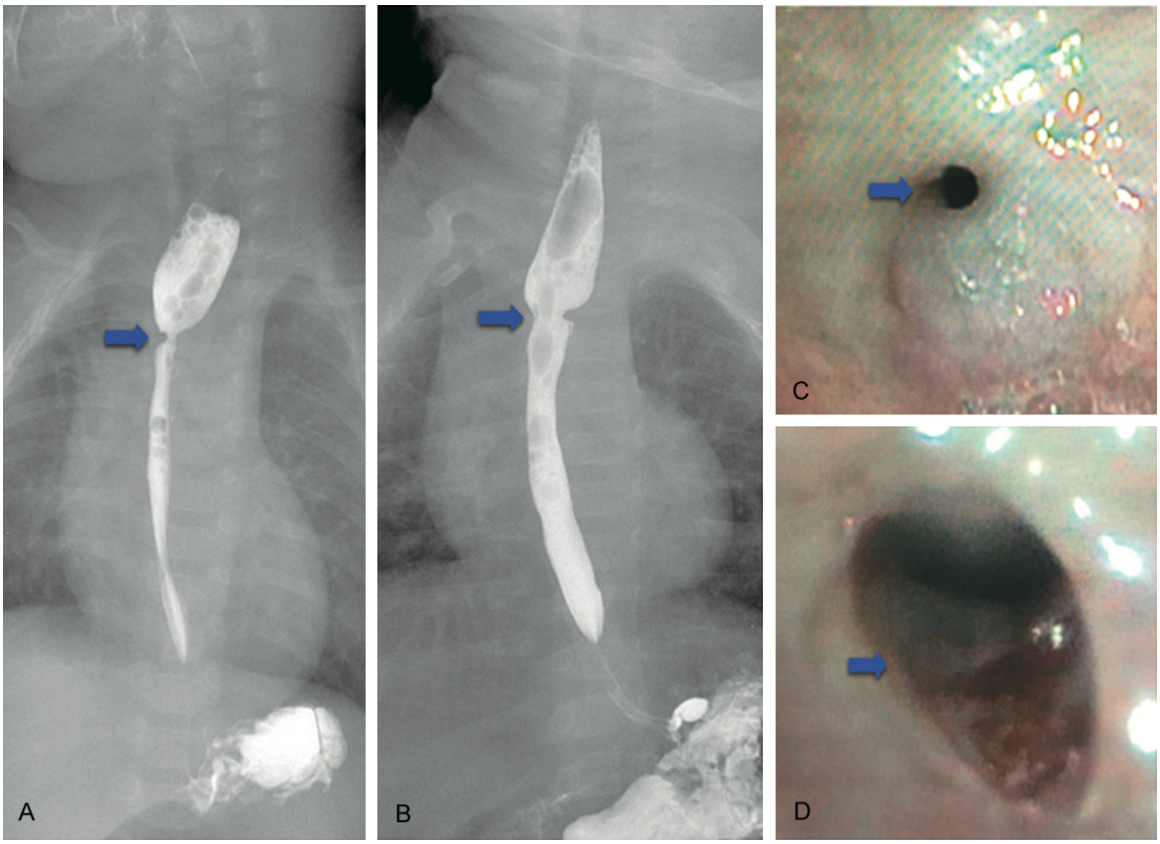

Figure 1. Diagnosis of anastomotic stricture. A. Esophagogram showing an anastomotic stricture (blue arrowhead). B. Esophagogram showing relief of an anastomotic stricture after endoscopic esophageal dilatation (blue arrowhead). C. Esophagoscopy revealing an anastomotic stricture (blue arrowhead). D. Esophagoscopy showing relief of an anastomotic stricture after endoscopic esophageal dilatation (blue arrowhead).

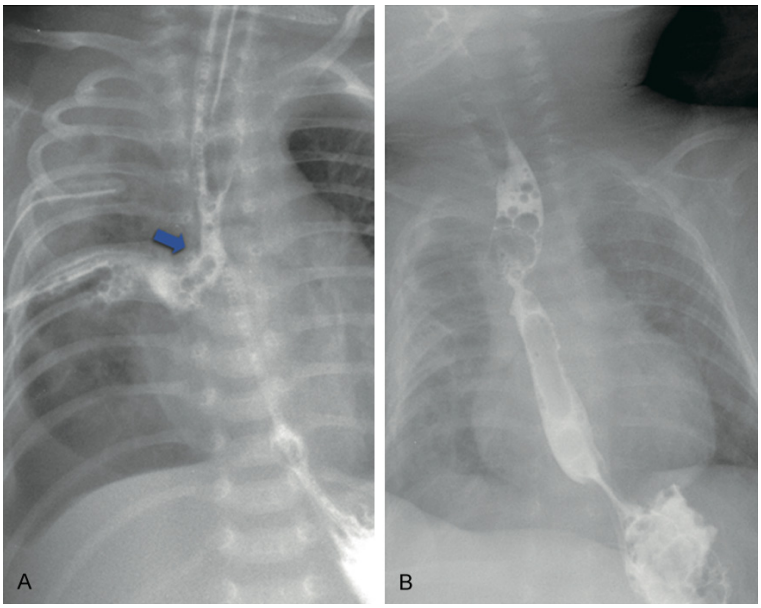

Figure 2. Diagnosis of anastomotic leakage. A. Esophagogram showing an anastomotic leakage (blue arrowhead). B. Esophagogram showing spontaneous healing of leakage.

According to the types of main PCs, various approaches are applied for treatment. For most patients with ASs and ALs, endoscopic dilatation and multiple conservative treatments are the first options, respectively [5-17]; however, esophageal re-operation is recommended for post-operative RT-EF [14, 15]. Patients with severe ASs and ALs, who fail treatment with endoscopic dilatation and conservative treatments, are also indications for re-operation [6]. Furthermore, post-operative GER is treated with anti-reflux medication or re-operation according to the severity of GER [16]. The results of the current study were not different from the results

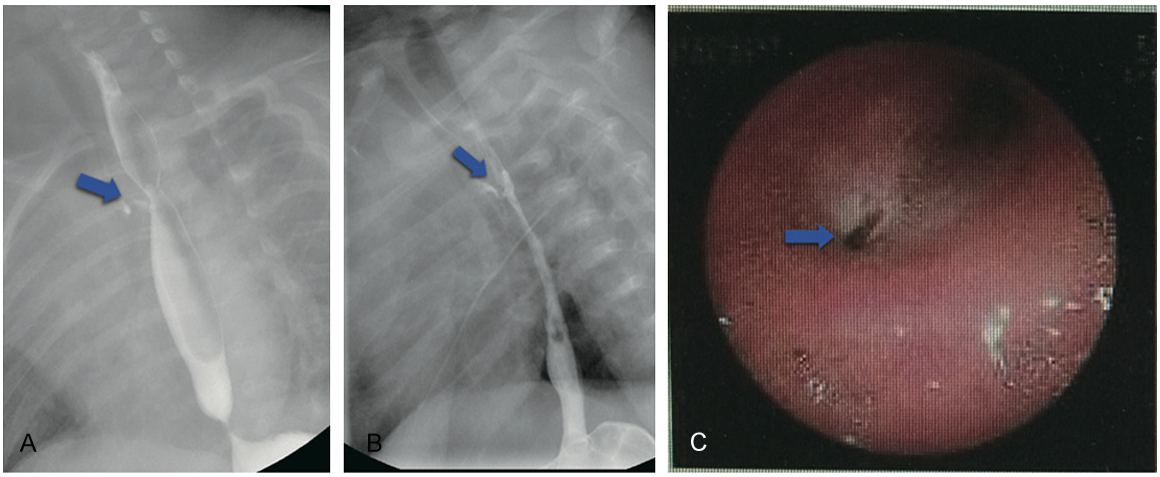

Figure 3. Diagnosis of a recurrent tracheoesophageal fistula. A, B. Esophagogram showing a recurrent tracheoesophageal fistula (blue arrowhead). C. Esophagoscopy revealing a recurrent tracheoesophageal fistula (blue arrowhead).

reported in the literature. All of the patients with ASs underwent esophageal bougie or balloon dilatation and the patients with ALs received multiple conservative treatments, including total parenteral nutritional support, trans-anastomotic feeding by nasogastric tube, use of broad-spectrum antibiotics, and chest tube drainage. Post-operative reflux was also controlled with anti-reflux medications in all of the patients with GER, who experienced relief of symptoms and no further re-operations were needed. Esophageal re-operations were performed in all of the patients with RTEFs and no additional severe complications occurred after re-operations Therefore, we recommend non-surgical therapy for AS and AL, as well as GER. RTEF is a significant indication for re-operation.

In conclusion, PCs are not rare in surgical EA patients; however, the risk factors for PCs have not been elucidated. Contrast esophagogram is the basic examination to diagnose major PCs. Confirmation of RTEFs and GER relies on esophagoscopy and 24-h pH monitoring combined with radionuclide scintigraphy, respectively. Re-operation is the fist-line treatment for RTEFs, but not for ASs, ALs, or GER. Patients with PCs have a low mortality rate, but need adequate post-operative follow-up.

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Disclosure of conflict of interest

None.

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