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Primary repair of esophageal atresia is followed by multiple diagnostic and surgical procedures.

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ABSTRACT

Background: Children born with esophageal atresia (EA) face comorbidities and complications often requiring surgery and anesthesia. We aimed to assess all procedures performed under general anesthesia during their first 12 years of life.
Methods: We performed a retrospective cohort study about subsequent surgeries and procedures requiring general anesthesia in children born with type C EA between January 2007 and December 2017, with follow-up to March 2019.
Results: Of 102 eligible patients, 63 were diagnosed with comorbidities, of whom 18 had VACTERL association. Follow-up time for all patients varied between 14 months and 12 years (median 7 years). The patients underwent total 637 procedures, median 4 [IQR2-7] per patient. In the first year of life, 464 procedures were performed, in the second year 69 and in the third year 29. Thirteen patients underwent no other procedures than primary EA repair. In 57 patients, 228 dilatations were performed. Other frequently performed procedures were esophagoscopy (n=52), urologic procedures (n=44) and abdominal procedures (n=33).
Conclusions: Patients with EA frequently require multiple anesthetics for a variety of procedures related to the EA, complications and comorbidities. This study can help care providers when counselling parents of a patient with an EA by giving them more insight into possible procedures they can be confronted with during childhood.

1. Introduction

With an incidence of 1 in 4000 births, esophageal atresia (EA) is a rare congenital anomaly in which the upper esophagus is not connected to the lower esophagus and the stomach [1-3]. It is prenatally diagnosed in 24% to 32% of the cases [4-6]. Five types of EA are distinguished on the basis of the presence or absence of a tracheo-esophageal fistula (TEF) and the length of the present esophagus [1]. The type referred to as type C is the most common type, found in approximately 85% of individuals with a TEF.

The primary EA repair is a lengthy procedure, which often requires intraoperative anesthesia for over 3 hours and postoperative sedation for several days [7,8]. Moreover, most patients face hospital admissions and procedures at a young age for the management of comorbidities and complications. For some, these comorbidities might have a bigger impact on life than the primary surgery itself, and the procedures required to manage the comorbidities might negatively affect the long-term outcome. Studies have reported developmental problems, [9] behavioral problems, [10,11] motor functional impairment and attention deficits in children after primary EA repair [12]. The long-term outcome is mainly dependent on multiple interrelated variables, however, and the etiological determinants are hard to define. Therefore, prenatal and postnatal parental counselling should address possibly relevant variables and make clear that for many the comorbidities diagnostic or therapeutic procedures under general anesthesia are required. We hypothesize that the aggregate duration of anesthesia and the number of procedures performed under anesthesia during childhood have impact on this long-term outcome as well, while a direct correlation will be hard to find. To test this hypothesis, we evaluated the

Abbreviations: EA, esophageal atresia; TEF, tracheo-esophageal fistula; ICU, intensive care unit; PTS, primary thoracoscopic surgery; POS, primary open surgery; COS, converted thoracoscopic to open surgery; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities.

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aggregate duration and number of anesthesia exposures in EA patients treated in our hospital, and made a groupwise comparison of the type of primary surgery – open, thoracoscopic or converted thoracoscopic to open - performed in these patients.

2. Methods

2.1. Patients

In this retrospective cohort study, we included all patients who, from 1 January 2007 up to and including 31 December 2017, underwent repair of EA/TEF type C in a tertiary, specialized referral pediatric hospital (Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands). Patients with EA types A, B, D and E were excluded, as well as patients not primarily cared for in our hospital. Patients and procedures under anesthesia were identified from the hospital's electronic Anesthetic Information Management System (AIMS; Anesthesia Manager, PICIS Clinical Solutions S.A., Barcelona, Spain), ICU Patient Data Management System (PDMS, ChipSoft, Amsterdam, the Netherlands), and anesthesia charts (on paper until 2012 and electronically from 2012 onwards). Primary care was performed by our multidisciplinary team under direction of the pediatric surgical department, and all surgeries and consultations had taken place in our hospital. The end of the follow-up period for this study was March 1, 2019. All anesthetic events were supervised by a board-certified anesthesiologist with specific training in pediatric anesthesia. Anesthesia was not protocolized, sevoflurane and propofol were the most frequently used anesthetics, combined with an opioid and muscle relaxant. Neuroprotective measures such as brain monitoring were not taken. It is common practice in our hospital to combine procedures that require anesthesia, also from different specialties, where possible. Induction of anesthesia at the primary surgery encompassed various actions: intubation, insertion of an arterial line if possible, insertion of an intravenous drip, and bronchoscopy performed by an ENT doctor before the start of the surgery. In this study, the bronchoscopy before the start of primary surgery was considered part of the primary surgery, not as a separate procedure. Bronchoscopy after the first surgery was counted as a separate procedure. The end time of anesthesia of the primary surgery was defined as the moment when the patient left the operation room to be transported to the ICU, still intubated and sedated. The decision to extubate after primary EA repair was made by the surgeon and pediatric intensivist. We divided the patients into three groups: primary open surgery (POS), primary thoracoscopic surgery (PTS) and converted thoracoscopic to open surgery (COS). We did this with the aim to detect differences in numbers and length of procedures between these three groups, since there is no consensus on which surgical approach is superior to the other. We defined a surgical or diagnostic intervention requiring general anesthesia as an interventional procedure, e.g. esophagoscopy with balloon dilatation for an anastomotic stricture constitutes one interventional procedure. Additionally, general anesthesia for a diagnostic procedure is defined as diagnostic procedures, e.g. esophagoscopy without balloon dilatation. Altogether, all interventions are referred to as 'procedures' in this manuscript.

2.2. Procedures

All procedures performed during the follow-up period, including the primary EA repair, were included for analysis. All diagnostic procedures (e.g. esophagoscopy, bronchoscopy and MRI) and interventional procedures (e.g. esophageal balloon dilatation) under general anesthesia were defined as 'procedure'. Conscious sedation is not included in this study.

We distinguished three groups of procedures in this respect.

1. Direct EA-related procedures (e.g. leakage, reflux, stenosis, etc.).

This group includes all procedures that are directly related to the EA. The choice for a primary thoracoscopic surgical approach or primary open surgical approach, as well as a decision to convert from a thoracoscopic to an open surgical approach during surgery, had been made jointly by the surgeon and the anesthesiologist based on vital parameters (stability of the patient), surgical view/working space, and logistics. Other procedures included in this group are complications related to the primary repair, such as leakage of the anastomosis, stenosis of the anastomosis and gastroesophageal reflux, which had to be resolved surgically.

2. *EA-associated comorbidity-related procedures (e.g. cardiac anomaly, vesicourethral reflux, limb malformation, etc.).*

EA may be associated with multiple congenital comorbidities which might require interventions or surgeries. This group includes all procedures that can be directly related to a diagnosed comorbidity.

3. *Procedures for comorbidities that are not EA-related (e.g. intracerebral bleeding, etc.)*

Apart from congenital comorbidities, patients may suffer from comorbidities not directly related to the EA, but which may require procedural or surgical treatment. These procedures are part of the burden these children face.

2.3. Data collection and definitions

We collected information on the duration of anesthesia for primary EA repair, as well as the total number and aggregate duration of repeated exposures to anesthesia during follow-up. Procedures not requiring anesthesia were left out of consideration. If during an anesthetic session both a surgery and a procedure were performed, this session was defined as one procedure.

2.4. Statistics

All data presented are descriptive data, expressed as median [interquartile range] in the tables and in the text. Differences between surgical approach groups were tested with ANOVA and with Kruskal Wallis test for variables that were not normally distributed.

Multivariable ordinal logistic regression based on a proportional odds model was performed to find association between various variables and the total number of procedures the patients underwent. The total number of procedures was categorized into groups of 1-2 procedures, 3 procedure, 4-5 procedures, 6-8 procedures and >8 procedures. The number of procedures per patient was adjusted for confounders: the time of follow-up in each patient, which was log-transformed. Included variables are: premature (yes/no), surgical approach for primary EA surgery (thoracoscopic, open or converted thoracoscopic to open), number of diagnosed comorbidities, anastomotic leakage (yes/no) and stricture dilatation within the first year of life (yes/no). The odds ratios of the ordinal logistic regression can be interpreted as the relative change in the odds, due to a change in the independent variable, that the total number of procedures is in a given category or higher.

All statistical tests were two-sided with a significance level of 0.05. All analyses were performed with the SPSS 24.0 software package (SPSS Inc., Chicago, IL).

3. Results

In total, 117 children underwent a primary correction for EA between January 2007 and December 2017, of whom 102 had EA/TEF type C and were included in this study (Table 1). Five patients of the study group had died during the follow-up period: three of

Table 1
Baseline characteristics

	Total (n=102)	POS (n=34)	PTS (n=57)	COS (n=11)	p-value
Gender (male)	64 (63%)	21 (62%)	36 (63%)	7 (64%)	NS
Gestational age (weeks)	37.9 [36.3-39.6]	36.6 [33.8-38.4]	38.3 [37.0-40.0]	38.0 [36.9-39.9]	0.001
Weight at primary EA surgery (kg)	2.9 [2.2-3.2]	2.3 [1.8-3.1]	3.0 [2.6-3.3]	3.0 [2.5-3.4]	0.005
Age at primary EA surgery (days)	2.0 [1.0-2.3]	2.0 [1.0-3.0]	2.0 [1.5-2.0]	2.0 [1.0-3.0]	NS
Days ICU *	8 [4-17]	12.5 [6-47]	5 [3-10]	13 [10-19]	0.001
Days hospital*	18 [11-33]	29.5 [14-84]	15 [10-26]	21 [13-31]	0.002
Days to extubation*	1 [1-3]	2 [1-4]	1 [1-1]	2 [2-3]	0.005
Days to oral feeding*	6 [4-11]	8 [5-20]	5 [3-8]	11 [4-18]	0.002
Number of stricture dilatations**	3 [2-5]	3 [2-5]	2 [1-4.5]	5 [3-11]	0.026
Anastomotic leak***	22 (22%)	6 (18%)	12 (21%)	4 (36%)	NS

Data are presented as median with an interquartile range [IQR]
*after primary EA repair
** Number of stricture dilatations amongst infants who had to undergo a stricture dilatation
*** number of anastomotic leaks detected, no median [IQR]
POS: primary open surgery; PTS: primary thoracoscopic surgery; COS: converted thoracoscopic to open surgery
Strictures, recurrent fistula, anastomotic leak and pneumothorax are number of infants in each group

Table 2
Surgeries and procedures performed in all patients

Surgery/procedure	Total		POS (n=34)		PTS (n=57)		COS (n=11)		p-value
	Patients	number	patients	number	patients	number	patients	number	
Primary EA repair	102	102	33	33	58	58	11	11	NS
EA other (fistula, foreign body, tracheotomy)	11	14	4	6	6	6	1	2	NS
Esophageal stricture dilatations	57	228	21	76	28	102	7	50	0.026
Broncho*/laryngoscopy	22	35	11	22	9	11	2	2	NS
Esophagus/gastroscopy	35	61	13	23	19	35	3	3	NS
NISSEN fundoplication**	21	23	11	12	7	8	3	3	NS
Aortopexy	4	4	1	1	2	2	1	1	-
Pyloromyotomy	4	4	1	1	1	1	2	2	NS
Gastrostomy	3	3	2	3	0	0	0	0	NS
Abdominal***	17	33	9	23	6	6	2	4	NS
Urology	14	44	7	29	5	13	2	2	NS
Ears	6	9	4	4	2	4	1	1	NS
Cardiac****	8	9	5	6	3	3	0	0	NS
Hands	9	11	4	5	4	5	1	1	NS
MRI	10	14	4	7	6	7	0	0	NS
CT	2	2	1	1	1	1	0	0	-
Other (line, PAC, venflon)	19	41	7	12	10	24	2	5	NS
Total surgeries/procedures		**637**		**264**		**286**		**87**	**NS**
Median number of procedures [IQR]		**4 [2-7]**		**6 [2-11]**		**4 [2-6]**		**5 [3-13]**	**NS**
Median total duration anesthesia (hh:mm) [IQR]	7:11 [5:04 – 12:19]		7:56 [5:15 – 15:31]		6:16 [4:39 – 10:28]		8:03 [6:27 – 15:34]		NS
Median total duration surgery / procedure (hh:mm) [IQR]	5:07 [3:23 – 9:01]		5:55 [3:33 – 11:41]		4:15 [3:20 – 7:51]		6:18 [4:20 – 11:12]		NS

Anastomotic leak was found and cared for in 4 POS patients, 12 PTS patients and 3 COS patients.
* not including bronchoscopy during dilatation or during primary repair
** 1 patient in the POS group had an open procedure for NISSEN fundoplication. 1 patient in the COS group had open Nissen fundoplication, relaparotomy. All other 19 patients had a laparoscopic Nissen fundoplication.
***PTS: placement of gastric tube, gastroduodenal tube, gastric foreign body, malrotation, ileostomy, duodenal web
POS: reconstruction of peri-anal structures, ileus (2x), colostomy (2x), rectal examination under anesthesia, PSARP (4x), stoma, colon segment resection, feeding jejunostomy tube, gastric perforation, cholecystectomy, resection of the small intestine, duodenal tube, duodenal web, removal of gastric tube, jejunostomy, remove colostomy, repair of double chambered right ventricle in a patient with Fallot
COS: malrotation colon, exploratory laparotomy, pull through anorectal malformation, remove colostomy
****PTS: mitral valve, resection infundibulum, VSD
POS: ASD, clip patent ductus arteriosus, Fallot + resection infundibulum, ASD+PAPVR, resection infundibulum
Duration surgery is the time from the first incision until the last stitch.

these children were treated with an open approach, died at ages 17 days, 71 days and 225 days; and two were treated with a thoracoscopic approach, died at ages 57 days and 10.5 years. Details about cause of death are presented in Supplementary Table 1. There was a male predominance (63%), and 63/102 (62%) had been born full term; most of the 102 patients were mature for gestational age (66%) (Table 1).

The median duration of follow-up was 7y1m [IQR 3y8m-10y]. The total number of surgical, diagnostic or interventional procedures under anesthesia was 637, median 4 [IQR 2-7] per patient (Table 2). The total number of procedures during the follow-up period was 535. Thirteen patients (13%) did not have any surgeries or interventions besides the primary EA repair. The timing of the procedures is illustrated in Supplementary figure 1.

3.1. Direct EA-related procedures

All 102 infants underwent primary EA repair, at a median age of 2 [1-2.25] days (Table 1). Thoracoscopic surgery (PTS) was initiated in 68 cases but was converted to open surgery (COS) in 11 cases. Primary open surgery (POS) was performed in 34 patients. The median [IQR] duration of anesthesia for primary EA repair with thoracoscopic approach was 3:49h [3:20-4:27h], with open approach 3:06h [2:25-3:57h], and with converted approach 4:46h

[3:16-5:00h]. The anesthesia time for POS was significantly shorter than that for both PTS and COS (p=0.007). Both the induction time and surgery time were not significantly different between all three groups.

The gestational age in the POS group was lower than that in the other groups. The POS group differed on more aspects from the other groups: lower weight at the time of surgery (p=0.005) and more days in hospital (p=0.002). Both the time to extubation (p=0.005) and the time to oral feeding (p=0.002) were longer in the POS group than in the other groups.

Thirteen infants underwent primary surgery repair only (10 PTS, 2 POS, 1 COS).

One extremely premature infant (25 weeks, 750 grams) had undergone two separate surgeries prior to the primary EA repair: fistula ligation and a placement of a gastrostomy. Four others had undergone other surgeries in combination with primary EA repair: one underwent a duodenoduodenostomy; one a colostomy; one a gastrostomy and duodenostomy; and one a colostomy and duodenostomy.

Of the 535 procedures other than primary EA repair during the entire follow-up period, 338 were EA-related: stricture dilatations, fistula repair, removal foreign body from esophagus, esophagoscopy and broncho/laryngoscopy (See Figure 1: Flowchart, and Table 2).

Esophageal stricture dilatation was performed in 57 infants, with a median of 3 [2-5] dilatations per infant. The number of dilatations per infant ranged from 1 to 19. Twenty-three of these 57 infants (40%) underwent more than three dilatations. Significantly more dilatations had been performed in infants in the COS group compared to both other groups (5 [3-11] dilatations COS vs 3 [2-5] POS and 2 [1-4.5]) PTS, p=0.026).

Three infants were diagnosed with a recurrent fistula. One of them developed a second recurrent fistula. All three patients underwent a primary thoracoscopic repair. The recurrent fistulae developed several years after the primary repair. Two patients underwent thoracoscopic repair of the recurrent fistula, one was repaired via a neck incision.

Esophagoscopy/gastroscopy was performed 52 times in 32 infants after primary surgery, bronchoscopy/laryngoscopy was performed 35 times in 22 infants. Most of these procedures had been performed in the first year of life (Figure 2). The median number of broncho/laryngoscopies and esophagoscopies during follow-up was 2 [1-3].

Other EA-related procedures (n=14) were fistula repair of one re-fistula and three undetected fistulae during primary repair (n=4), tracheotomy (n=3), re-anastomosis (n=1), partial esophageal resection (n=1), delayed end to end anastomosis (n=3) and additional correction of the primary EA repair (n=2).

Tracheomalacia had been diagnosed in 55 infants by bronchoscopy or by clinical presentation; an aortopexy was performed in four of those. A Nissen fundoplication to treat gastroesophageal reflux with or without respiratory incidents was performed in 21 infants (21%). Eighteen infants underwent the Nissen fundoplication in their first year of life, two in their second year of life, and one after the age of 7 years (Table 2). Nineteen of these 21 surgeries were performed laparoscopically. In one case the surgery was combined with surgery of the colon; in another case it was performed with a laparotomy. Anastomotic leakage had been diagnosed in 22 infants, all managed by chest drainage and antibiotics. None required surgery for closure of the leak (Table 1).

3.2. EA-associated comorbidity-related procedures

One or more comorbidities were diagnosed in over half of the infants (n=63, 62%) (Supplementary table 2). Most of the comorbidities were of cardiological, anorectal or nephrological origin. The numbers of comorbidities did not significantly differ between the three surgical groups (p= 0.33). Fifty infants (49%) required surgical or procedural interventions to manage the comorbidities (Supplementary table 2); in total 229 surgeries, median 3 [IQR 1-5] per patient (besides primary EA repair and stricture dilatations). Most of the procedures targeted cardiological problems (n=64), followed by anorectal (n=58) and vertebral anomalies (n=24) (Figure 1: Flowchart, Supplementary table 2). Other procedures for associated comorbidities were brain surgery (n=1), hypertrophy of the pylorus (n=1), choanal atresia (n=1) and cleft palate (n=1). Some infants were diagnosed with syndromes and required other procedures as well: Down syndrome (n=2), CHARGE syndrome (n=2), Silver Russell (n=1), and 47XXX (n=3).

VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) was found in 18/63 infants (29%) with comorbidities. These 18 infants underwent in total 151 procedures besides primary EA repair (151 out of 542). The median number of procedures was 6 [4-14], which is significantly higher than that in infants without VACTERL (p=0.031). Fourteen of the 18 infants underwent procedures in the first year of life besides primary EA repair, a median number of 4 [2-9].

3.3. Procedures for comorbidities that are not EA-related

Twenty-five infants received anesthesia for an MRI, CT or procedure for a comorbidity that was not EA-related. Twelve infants underwent a total of 16 MRIs or CTs for various problems, such as tethered cord, lung agenesis and nerve problems in the shoulder. Chest CT for tracheomalacia and CT for feeding problems were EA-related, other MRI and CT procedures were not directly EA-related (Supplementary table 3).

The other 39 procedures requiring anesthesia involved, for instance, insertion of an intravenous drip (n=5) or central venous line (n=6), or dental cleaning (n=3) (Figure 1, Flowchart, Supplementary table 3).

3.4. Total numbers of procedures and associations

All 637 procedures together, had a median [IQR] total anesthesia duration of 7:11h [5:04h – 12:19h], and a median [IQR] total surgery duration of 5:07h [3:23h – 9:01h] per patient (Table 2). The median [IQR] number of procedures per patient was 4 [2-7]. The number of procedures did not significantly differ between the three surgical groups (thoracoscopic, open and converted groups). Infants with VACTERL underwent significantly more procedures (median 6 [4-14], p=0.031) than other infants. Of the total number of procedures, 464 (73%) had been performed in the first year of life (including the 102 primary EA repairs) (Figure 2). The 362 procedures performed in the first year following primary EA repair concerned 71 (70%) infants, who underwent a median of 3 [IQR 1-7] procedures besides primary EA repair. In total 69 procedures had been performed in 44 infants in their second year of life, and 29 in 17 infants in their third year of life (Figure 2).

For the multivariable ordinal logistic regression analysis, no data were missing. We did not find multicollinearity of variables (VIF $>$ 3.0). As we categorized the total number of procedures into five groups as discussed in the Methods, the number of patients per group were as follows: 1-2 procedures (n=33), 3 procedures (n=12), 4-5 procedures (n=19), 6-8 procedures (n=18) and $>$8 (n=20) procedures.

The odds for an increased number of procedures for the number of diagnosed comorbidities was 1.729 (OR, 95% CI 1.220 – 2.451, p=0.002). The odds for increased number of procedures when the patient underwent stricture dilatation within the first

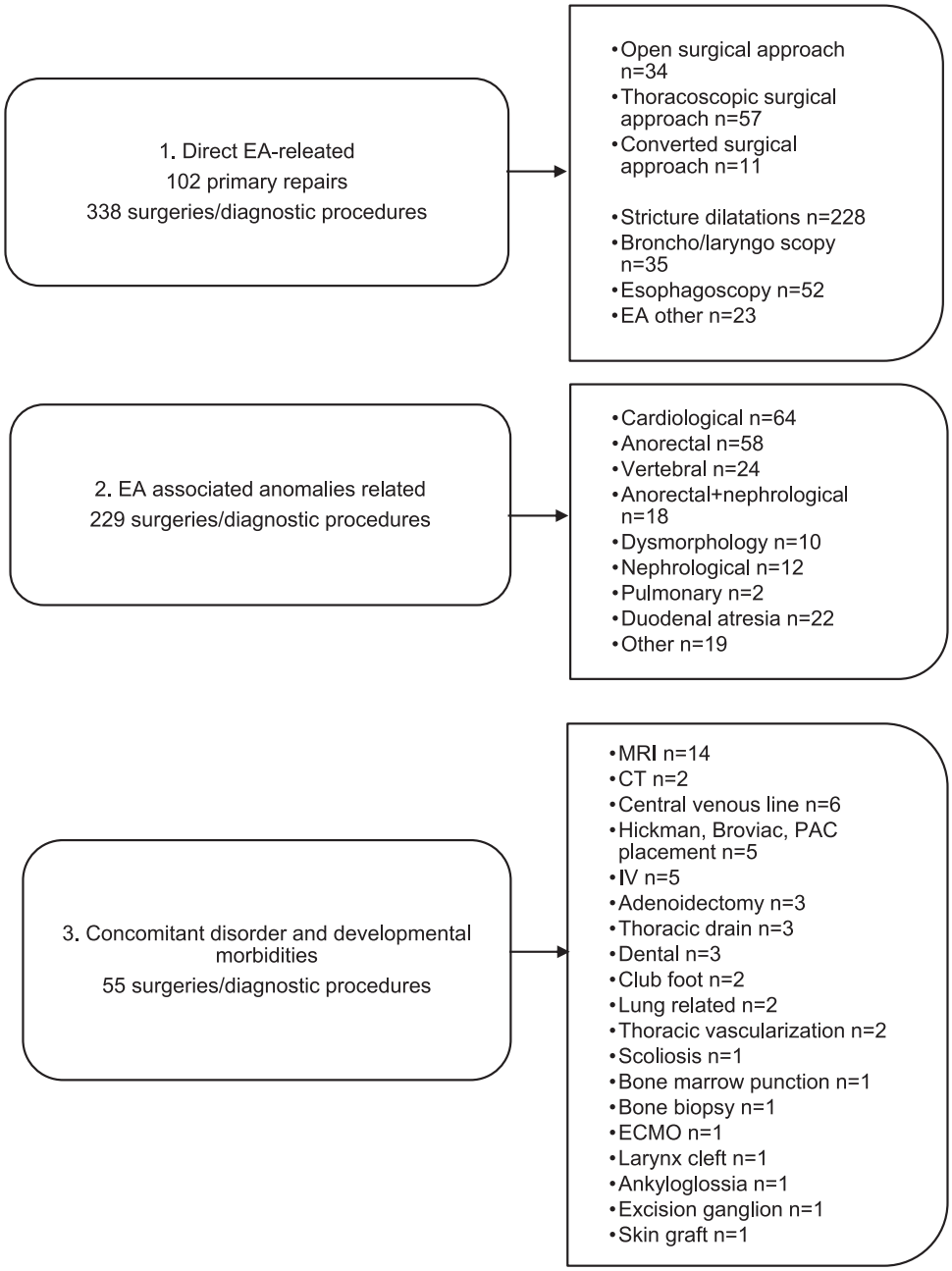

Figure 1. Flowchart

year of life was 0.029 (OR, 95% CI 0.011 – 0.079, $p<0.001$). Prematurity, surgical approach for primary esophageal atresia repair and anastomotic leakage did not show significant odds ratios.

4. Discussion

We found that 90% of study population had undergone multiple procedures, and had received anesthesia not only for primary EA repair, but even more frequently for procedures to manage complications and comorbidities. These children had undergone a median of 4 procedures in the maximum of 12 years follow-up, necessitating a median anesthesia time of 7:11h. Almost three quarters of the procedures had been performed in the first year of life, and a little more than half of all procedures were related to the EA. This information can be used to counsel the parents on the expected care path and the possible burden in the child's first years of life.

4.1. Primary EA repair

Since there is no consensus on the best surgical approach for primary EA repair – open or thoracoscopic– the choice of surgical approach is determined by the patient's condition and the surgeon's preference [13]. The approach chosen might affect the individual patient's outcome. Previous studies have not been able, however, to associate the type of surgical approach with number of complications and long-term outcome [8,14]. Regarding our study population, the open approach was preferred in more unstable infants, as reflected by these infants' lower gestational age, lower weight at surgery, and longer stay in the ICU and hospital for primary EA repair. Duration of the primary EA repair in this study was comparable with that reported by others, with a median anesthesia time of 3:42h [3:09-4:27h] [15-20]. The postoperative complications in our study population were mainly strictures and

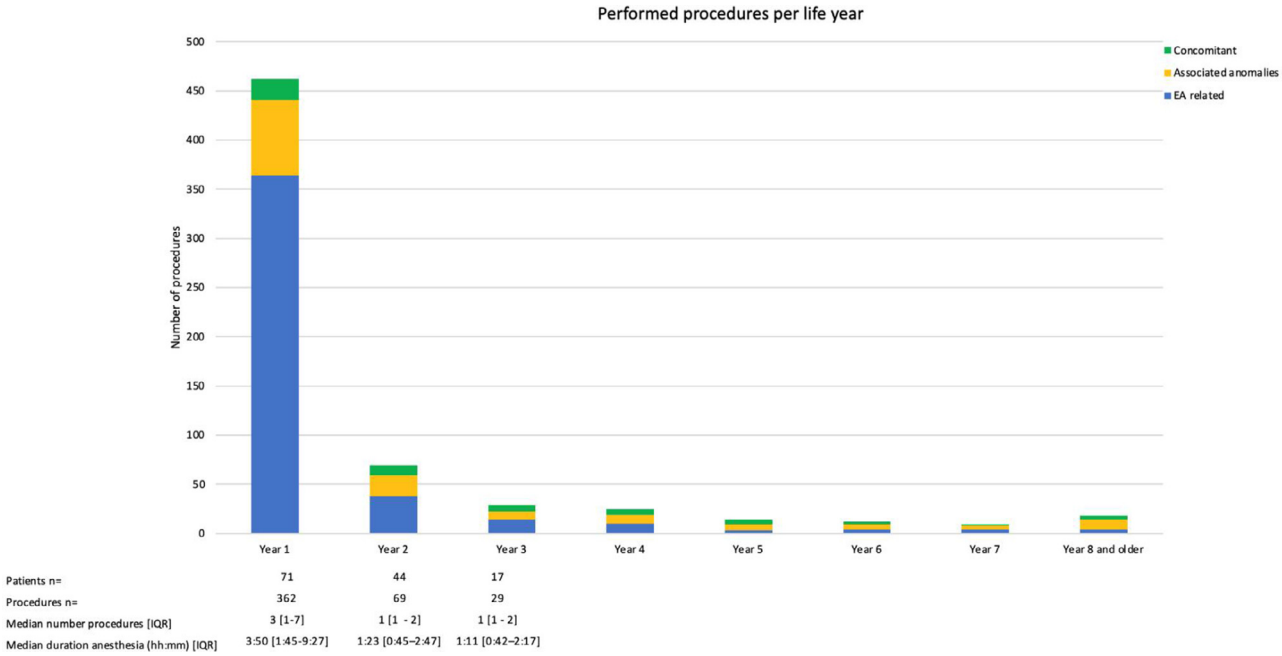

Figure 2. Procedures performed per life year

anastomotic leakage. Anastomotic leakage had occurred in 22 infants (22%), equally spread over all surgical groups. Of these 22 infants, none required surgical correction of the leakage. Other studies found comparable proportions of anastomotic leakage and emphasized that anastomotic leakage does not always require surgical intervention [21,22].

4.2. Dilatations

The percentage of infants with anastomotic strictures did not differ between the three surgical groups, whereas the number of dilatations differed significantly between groups: infants in the COS group underwent more dilatations compared to the other groups. The median number of dilatations in the entire cohort was 3 – the same as reported by others [23-26]. Anastomotic strictures have been reported for 37-58% of cases, comparative to the 56% found in our study [24,27]. The higher number of dilatations in the COS group might be due to more traction on the anastomosis, thus leading to more strictures. A previous study suggested that thoracoscopic repair was associated with stricture formation [28]. Nevertheless, a systematic review and meta-analysis did not find any differences in stricture formation between the thoracoscopic and the open approach [7,29]. Both these studies did not address a converted surgery group, because infants undergoing converted surgery had been included in the open surgery group [7,29]. Risk factors for dilatations reported in the literature are prematurity, VACTERL syndrome, isolated EA, first dilatation within 1 month after primary EA repair, anastomotic tension, and anastomotic leak [24,27]. In our study, the frequency of dilatations did not differ between infants with and without VACTERL. This might be related to the small number of infants with VACTERL who underwent 1 or more dilatations.

The logistic regression analysis showed that having an anastomotic dilatation within the first year of life had an OR of 0.029 for the number of procedures. Thus, patients that underwent stricture dilatation within the first year of life are prone to undergo more procedures during their youth compared to patients who did not. This finding can be addressed when counseling parents and show that clinical preventive studies on anastomotic strictures may be important.

4.3. Number of procedures

In this study, we found no difference between the overall number of procedures after primary open repair, primary thoracoscopic repair and converted repair. Over half of the procedures were EA-related. The literature contains no studies presenting data on the number of procedures performed in this patient population beyond the staged or primary EA repair; thus, we have no source of comparison in this respect. Infants with VACTERL underwent more surgeries ($p=0.031$) than infants without VACTERL. This was expected, since these infants born with EA had two additional comorbidities, possibly requiring surgery [30,31].

4.4. Comorbidities

Generally, 70% of infants with EA type C have diagnosed comorbidities for which surgical intervention might be needed [2,32-34]. In our cohort, this percentage was 62%. The majority of comorbidities were of cardiac or anorectal nature, in line with the VACTERL association presenting in association with EA [30]. VACTERL had been diagnosed in 18/102 infants (18%) in our study, which proportion is comparable to those reported by others [35,36].

Besides primary EA repair, comorbidities might require other surgical interventions, such as gastrostomy, colostomy or repair of a cardiac defect. Comorbidities may be diagnosed at birth but can also present later in life. For the present study, this implies that diagnosis and treatment could have taken place beyond the 12 years' follow-up period. The number of comorbidities provided in this study could therefore be an underestimation.

Our results indicate that we have to be aware that the amount of comorbidities may influence the number of procedures patients have to undergo during their childhood (OR 1.729). Parents should be well informed on this topic, in order to manage their expectations after the primary EA repair.

4.5. Long-term effects of the repeated hospitalization and anesthesia exposures

Concerns may be raised regarding the effect of anesthesia on the development of the immature brain. In the present cohort, the majority of the procedures (84%) had been performed in the first 2 years of life, when the brain largely is growing, and myelinization, white matter and grey matter increase significantly [37]. Studies on the long-term outcome of children born with EA show conflicting results. Some studies found significantly impaired long-term development compared to the reference population, [38,39] but others found the development to be normal [40,41]. The total anesthesia time has been found negatively associated with impaired long-term outcome in EA patients [12]. This would suggest that these patients are at risk of developmental impairments as a result of the repeated anesthesia periods in the first 2 years of life. A previous study on a part of this cohort showed impaired motor function at 5 years of age in children born with esophageal atresia, which was negatively associated with the number of days of postoperative endotracheal intubation, and was positively associated with intraoperative high blood pressure [42].

Hypoxia-ischemia, inflammation, exposure to anesthetics and stress in the period of neonatal critical illness has been suggested to be important factors for development of brain anomalies [43]. A case-control study indeed found that infants after EA repair had different brain structures at age 25.5 days compared to controls not exposed to neonatal surgery. However, their neurodevelopmental outcome scores at two years of age did not differ from the control population [44]. Long-term follow-up studies at older ages are still lacking.

The high number of procedures performed in infants with EA found in this study emphasizes that more procedures may be needed besides the primary EA repair and that lifelong management for various issues is inevitable [45]. Besides the possible negative impact of anesthesia expose on the brain development, frequent hospital admissions can have negative effects as well [46,47]. Hospital admissions may lead to anxiety and behavioral alterations, leading to multiple negative consequences presenting after the hospital admission [48,49]. The above mentioned problems may have a possible negative impact on the quality of life. An elaborate review on the health-related quality of life (HrQOL) of patients born with esophageal atresia showed that these patients experience a lower quality of life as compared to their peers [50].

4.6. Limitations

The present clinical study retrospectively included EA infants primarily cared for at the single hospital in which the primary EA repair took place. It cannot be excluded that in some cases emergency surgeries had been performed in other hospitals. Therefore, the number of surgeries could be underestimated. We expect, however, that the effect is nihil, as all children were regularly seen in our structured follow-up program at standardized time points between 6 months and 17 years of age [51]. During these consultations, admissions and procedures in other hospitals is asked for and would have been added to the patients' file. The scope of this study was limited in terms of selection of the patient population. We only included infants with EA type C, all other types of EA were not included. Children born with other types of EA, with different morphology, could encounter yet other problems during childhood.

4.7. Implementation of findings

Data provided on the number and length of anesthesia periods and procedures in patients with EA type C can be used to inform the parents. For example, primary EA repair is most likely not the sole procedure under general anesthesia the child has to undergo.

5.Conclusions

To conclude, infants with esophageal atresia are prone to undergo multiple anesthesia periods and procedures beyond the primary repair operation: in the first year of life, but also at later ages. This vulnerable patient population risks impaired quality of life due to the number of hospital admissions, procedures and potential effects on the brain development.

The information provided by this study can help caregivers when counselling parents of a patient with EA by giving them more insight into procedures they can be confronted with during childhood.

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Level of Evidence

Level 2

Type of Study

Prognosis Study

Declarations of Competing interest

None

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Supplementary materials

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