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Risk Factors of Early Mortality and Morbidity in Esophageal Atresia with Distal Tracheoesophageal Fistula: A Population-Based Cohort Study

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Objective To identify the risk factors for early mortality and morbidity in a population with distal esophageal atresia (EA)-tracheoesophageal fistula.

Study design Cohort study from a national register. Main outcomes and measures included early mortality, hospital length of stay (LoS), need for nutritional support at 1 year of age as a proxy measure of morbidity, and complications during the first year of life.

Results In total, 1008 patients with a lower esophageal fistula were included from January 1, 2008, to December 31, 2014. The survival rate at 3 months was 94.9%. The cumulative hospital LoS was 31.0 (17.0-64.0) days. Multivariate analysis showed that intrahospital mortality at 3 months was associated with low birth weight (OR 0.52, 95% CI [0.38-0.72], $P < .001$), associated cardiac abnormalities (OR 6.09 [1.96-18.89], $P = .002$), and prenatal diagnosis (OR 2.96 [1.08–8.08], $P = .034$). LoS was associated with low birth weight (-0.225 ± 0.035, $P < .001$), associated malformations (0.082 ± 0.118, $P < .001$), surgical difficulties (0.270 ± 0.107, $P < .001$), and complications (0.535 ± 0.099, $P < .001$) during the first year of life. Predictive factors for dependency on nutrition support at 1 year of age were complications before 1 year (OR 3.28 [1.23-8.76], $P < .02$) and initial hospital LoS (OR 1.96 [1.15-3.33], $P < .01$).

Conclusions EA has a low rate of early mortality, but morbidity is high during the first year of life. Identifying factors associated with morbidity may help to improve neonatal care of this population. *(J Pediatr 2021; ■:1-7)*.

Esophageal atresia (EA) is a rare congenital disease occurring in 1.8/10 000 live births in France.[1] Survival of this malformation has now reached the highest rate since first cases of successful treatment began to be reported in the late 1970s.[2] Studies from 1960-1990 have shown that in the most frequent form of EA with distal tracheoesophageal fistula (TEF), type C EA according to Ladd classification,[2] prematurity and associated congenital malformations were the major factors influencing mortality in all risk classifications described through time.[3-6] Improvements in the neonatal care of premature infants and associated malformations during the past decades have markedly increased early survival.[7] Although survival is now >90%, high morbidity has been reported, especially during the first year of life, and little is known about the risk factors for morbidity in infants with EA.[8-10] Moreover, prenatal suspicion is more frequently reported in isolated or polymalformative association. In this context, the objective of our study was to identify risk factors for early mortality and early morbidity in the population with EA with distal TEF.

EA	Esophageal atresia
GERD	Gastroesophageal reflux
LoS	Length of stay
TEF	Tracheoesophageal fistula

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Methods

Under the umbrella of the National Plan for Rare Diseases, an exhaustive population-based registry was set up in 2008 to prospectively record data for all live newborns with EA in France. The methods, quality assessment approach, and scope have been described in detail previously.[1] Briefly, 2 questionnaires are completed by the each of the 37 participating centers representing all academic hospitals in France plus 2 general hospitals. The first questionnaire is completed at the time of first discharge by the neonatal surgical wards and the second when the child is 1 year of age, usually by a pediatrician. All of the 37 centers performing neonatal surgery in France and overseas (35 academic centers) participate in the registry and completeness was assessed using 2 different sources to identify the patients (ie, surgical records in each center plus national health data recording system).

The registry was approved by the Advisory Committee on Information and Research in Health (CCTIRS no. 08.297) and by the National Commission on Informatics and Liberties (CNIL no. 908362). All data were used anonymously, and the parents were informed of what information was registered and why. The registry is recorded in ClinicalTrials.gov (NCT02883725).

The primary outcome of this study was the survival rate at age 90 days. Morbidity related to congenital abnormalities such as EA is difficult to assess and there is no agreed upon definition. In our previous study, the readmission rate for complications during the first year of follow-up was high,[8] which led us to define a priori for this study the total length of stay (LoS) during the first year as a good indicator of morbidity even if other medical conditions were present (associated abnormalities or acquired diseases). The second item we selected for assessing morbidity in this study was the rate of nutritional support at 1 year of age because dependency on prolonged enteral nutrition seems to be a good proxy for digestive and nutritional complications including dysphagia. Finally, data about all complications (surgical, digestive, and respiratory) occurring during the first year of life were collected during this first year as markers of EA severity.

The risk factors for mortality and morbidity studied included neonatal data (sex, birth weight, gestational age, associated abnormalities, place of birth, prenatal diagnosis-defined by an association of polyhydramnios, little or unseen stomach, and upper pouch sign); date of surgery; primary or delayed anastomosis (defined as anastomosis performed more than 7 days after birth excluding delays because of prematurity or severe cardiac diseases); surgical technique (open vs thoracoscopic); neonatal intensive care unit duration; duration of mechanical ventilation; and LoS. Complications before 1 year of age included all readmissions related to EA such as severe gastroesophageal reflux disease (GERD, defined as proven esophagitis, weight loss, or failure to thrive, uncontrolled regurgitation or vomiting, need for fundo plication); anastomotic stricture (defined as esophageal narrowing at the level of the anastomosis and associated symptoms requiring at least 1 esophageal dilatation)[8]; TEF recurrence; severe tracheomalacia (defined as collapse of >75% of the tracheal lumen); and respiratory distress or infection. Admission for associated abnormalities was included in the total duration of admission in the first year.

Statistical Analyses

Categorical variables are expressed as number (percentage). Quantitative variables are expressed as mean (SD) for data with a normal distribution or median (IQR) otherwise. The normality of distributions was assessed using histograms and the Shapiro-Wilk test. Using bivariate and multivariable analyses, we assessed the prognostic factors for mortality by censoring events after 90 days as recommended by Schoenfeld.[11] Among infants alive at 1 year of age factors associated with morbidity were tested. To reduce the skewness of the distributions, statistical analyses were performed on the log-transformed values for the cumulative LoS.

Bivariate comparisons according to the 3-month mortality or need for nutritional support at age 1 year were made using the Student t test for quantitative variables and the χ^2 test or the Fisher exact test when the expected cell frequency was <5 for categorical variables. Factors associated with 3-month mortality or the need for nutritional support at 1 year in the bivariate analyses ($P < .1$) were considered for inclusion in multivariable logistic models to assess the independent predictors of 3-month mortality and the need for nutritional support at 1 year, separately. Bivariate associations with cumulative hospital LoS at 1 year were identified using the Student t test for qualitative binary factors, analysis of variance for 3-level categorical factors, and the Pearson correlational coefficient for birth weight. Similarly, factors associated with hospital LoS in bivariate analyses ($P < .1$) were considered for inclusion in the multivariable linear regression model.

Before developing the multivariable regression models, we examined the log-linearity assumption for quantitative factors using restricted cubic spline functions for logistic regression models, and the absence of collinearity between candidate predictors by calculating the variance inflation factors for logistic and linear regression models.[12] Statistical testing was performed at the 2-tailed α level of .05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute).

Results

Study Cohort

A total of 1133 children were born alive with a diagnosis of EA in France from January 1, 2008 to the December 31, 2014, giving a prevalence of 1.96 per 10 000 live births for all types of EA. The population included in this study was 1008 patients with distal TEF.

Characteristics of the Population

Prenatal suspicion of EA was based on the association of different signs: polyhydramnios, and/or upper esophageal pouch visible on ultrasound and/or little or absent stomach. If one of these signs is present, a fetal magnetic resonance imaging was used in some cases; there has been an increased numbers of magnetic resonance imaging examinations in recent years. In our series, the diagnosis was suspected in 13.3% (n = 132) of patients; 8.6% (n = 51) of patients were from twin pregnancies, and 87% of infants were operated on within the first 48 hours. The male-to-female ratio was at 1.34:1. Associated abnormalities occurred in 53% of patients and included cardiac, genitourinary, central nervous system, and spinal abnormalities. Eight percent of patients were lost to follow-up at 1 year of age (**Table I**; available at www.jpeds.com).

Surgical Procedures

A right lateral thoracotomy by the axillary route is the most frequent type of thoracotomy (**Table I**). An extra pleural approach was used when possible and was performed in 93% of infants. A primary anastomosis was possible in 95% of infants; 26% of the surgeons defined the anastomosis as "difficult." This element is still subjective because no systematic measure of the defect is available. Six percent of patients received a delayed anastomosis after day 30 (maximum day 240). Preoperative tracheoscopy was performed in 29% of infants. During the first year of life, 8.6% of patients received an antireflux procedure, 13% had a gastrostomy, 20% developed a stricture requiring at least 1 esophageal dilatation, and 3% had recurrence of TEF confirmed at each time by double digestive and respiratory endoscopy with injection of a dye in the suspected fistula. Two patients received a colonic replacement at the age of 2 months and 6 received a gastric transposition before 1 year of age.

Outcomes

Mortality at 3 months was at 5.1% and included 13 children who died before any procedure was performed (**Table II**). All children who died had associated malformations and/or prematurity; 7 had a cardiac heart defect, 4 had vertebral defects, anal atresia, cardiac defects, TEF, renal anomalies, and limb abnormalities, 1 had coloboma, heart defects, atresia choanal, retardation of growth and development, genitourinary problems, ear abnormalities, and 3 had chromosomal anomalies. Eight children died between ages 3 and 12 months: 2 patients from causes directly related to EA complications, and the others from associated abnormalities. By age 1 year, 6% of patients had died. The total of death in this series was 48 deaths.

The mean cumulative LoS during the first year was 31.0 days, and the number of admissions ranged from 1 to 13 with a mean of 1.0. Ten percent of children needed artificial nutritional support at 1 year of age.

Risk Factors for Mortality

In the bivariate analysis, low birth weight, associated cardiac abnormalities, inborn birth, prenatal diagnosis, and difficult anastomosis were associated with increased intrahospital mortality at 3 months (**Table III**). In the multivariable analysis, low birth weight, associated cardiac abnormalities, and prenatal diagnosis remained significantly associated with intrahospital mortality at 3 months.

Risk Factors for Morbidity

Cumulative hospital stay was associated with a lower birth weight, associated abnormalities, prenatal diagnosis, surgical difficulties, and complications during the first year of life (**Table IV**). In the multivariate analysis, all of these factors except prenatal diagnosis remained associated with longer hospital stay. These factors explained 20.6% of variability in hospital length. The predictors of dependency on nutritional support at 1 year of age are shown in **Table V**. Complications before age 1 year and initial hospitalization duration were the only 2 factors that were independently associated with the need for nutritional support at age 1 year.

Discussion

Our study identifies the risk factors for both mortality and early morbidity of patients with EA at the population level. Our data show that, despite the marked improvement in neonatal care and the low rate of mortality, birth weight and cardiac malformations remain the major risk factors for mortality.

This study also helped to identify a new risk factor for mortality. In contrast to patients with an EA without TEF, for which prenatal diagnosis is frequent,[13] prenatal suspicion of EA associated with TEF was found in only 13% of patients in our study but was identified as an independent factor associated with a 3-fold higher risk of death. A possible, albeit unproven explanation for this new finding is an increased rate of therapeutic abortion in prenatally diagnosed cases that would lead to decrease the postnatal incidence of these severe cases.

Table II. Mortality, morbidity, and complications

	n (%)	n of data available
3-mo mortality	48 (5.0)	948
Complications (all)	285 (52.7)	541
Anastomotic leaks	20 (5.6)	359
Anastomotic stricture*	183 (19.9)	917
Recurrent TEF	28 (3.2)	868
Mechanical ventilation duration (d)	3.0 (2.0-5.0)	935
Age at first discharge (d)	23.0 (15.0-47.0)	953
Number of admission in the first y	1 (0-2)	599
Recurrent admission	371 (66.8)	555
Total duration of hospitalization in the first y (d)	31.0 (17.0-64.0)	1001

Values are number (percentage).
TEF for categorical variables, mean ± SD or median (IQR) for quantitative variables.
*Anastomotic stricture was defined by clinical signs and narrowing of the anastomosis requiring endoscopic dilatation.

Table III. Factors associated with 3-month mortality

	Univariate analysis			Multivariate analysis	
	Death (n = 48)	Alive (n = 900)	*P*	OR (95% CI)	*P*
Sex			.42	-	-
Male	26 (54.2)	538 (60.0)			
Female	22 (45.8)	359 (40.0)			
Prenatal diagnosis			**.001**		**.034**
Yes	**14 (29.2)**	**111 (12.5)**		**2.96 (1.08-8.08)**	
No	**34 (70.8)**	**774 (87.5)**		**1.00 (ref)**	
Inborn			**.027**		.95
Yes	**25 (52.1)**	**322 (36.2)**		1.03 (0.42-2.54)	
No	**23 (47.9)**	**567 (63.8)**		1.00 (ref)	
Birth weight (g)	**1683.5 ± 566.0**	**2595.6 ± 693.2**	**<.001**	**0.52 (0.38-0.72)***	**<.001**
Associated abnormalities			**<.001**		
None	5 (10.9)	442 (49.5)		1.0 (ref)	**.002**
Heart	30 (65.2)	198 (22.2)		**6.09 (1.96-18.89)**	**.002**
Other	11 (23.9)	253 (28.3)		1.78 (0.47-6.83)	**.40**
Difficult anastomosis			**.003**		.13
Yes	**14 (48.3)**	**213 (24.2)**		1.93 (0.83-4.46)	
No	**15 (51.7)**	**667 (75.8)**		1.00 (ref)	
Thoracotomy			.46	-	-
Yes	31 (91.2)	836 (94.0)			
No	3 (8.8)	53 (6.0)			
Thoracoscopy			1.00	-	-
Yes	2 (5.9)	61 (6.9)			
No	32 (94.1)	822 (93.1)			

Values are number (percentage) for categorical variables and mean ± SD for quantitative variables.
The significative values are in bold.
*OR per 500 g increase.

Table IV. Factors associated to the total length of hospitalization (days) during the first year

	Univariate analysis		Multivariate analysis		
	Values	*P**	β ± SE*	*P**	R^{2}*
Sex		.18	-	-	
Male	34 [19-67]				
Female	30 [17-59]				
Prenatal diagnosis		**<.001**		.56	0.0008
Yes	45 [23-100]		0.098 ± 0.168		
No	30 [18-61]				
Inborn		.056		.34	0.0020
Yes	36 [20-75]		−0.099 ± 0.103		
No	29 [18-58]				
Birth weight	−0.27	**<.001**	−0.225 ± 0.035†	**<.001**	0.0831
Associated abnormalities		**<.001**		**<.001**	0.0326
None	25 [15-45]				
Heart	42 [21-92]		0.082 ± 0.118		
Other	44 [23-85]		0.436 ± 0.114		
Difficult anastomosis		**<.001**		**.01**	0.140
Yes	45 [24-100]		0.270 ± 0.107		
No	28 [17-54]				
Thoracotomy		.30	-	-	
Yes	31 [18-62]				
No	40 [22-94]				
Thoracoscopy		.43	-	-	
Yes	37 [20-83]				
No	31 [18-64]				
Complication before 1 year‡		**<.001**		**<.001**	0.0968
Yes	52 [24-100]		0.535 ± 0.099		
No	23 [15-41]		Referential		

Values are median (IQR) of total length of hospitalization for categorical variables and Pearson correlation coefficient for quantitative variables.
The significative values are in bold.
*Calculated on the log-transformed values of cumulative hospital LoS.
†Beta per 500 g increase.
‡Complication before 1 year includes all readmissions for complications related to EA.

Table V. Factors associated with lack of oral autonomy at 1 year of age

	Univariate analysis			Multivariate analysis	
	Artificial nutrition at 1 y				
	Yes (n = 74)	No (n = 717)	*P*	OR (95% CI)	*P*
Sex				-	-
Male	50 (67.6)	423 (59.2)	.16		
Female	24 (33.4)	294 (40.8)			
Prenatal diagnosis					
Yes	15 (21.1)	75 (10.6)	**.009**	1.81 (0.67-4.85)	.24
No	59 (78.9)	642 (89.4)		1.00 (ref)	
Inborn					-
Yes	30 (41.7)	232 (32.8)	.13		
No	44 (58.3)	485 (67.2)			
Birth weight (g)	2253.1 ± 721.1	2647.7 ± 683.2	**<.001**	0.83 (0.61-1.13)*	.23
Associated abnormalities			**<.001**		.15
None	18 (24.7)	370 (52.0)		1.00 (ref)	-
Heart	25 (34.2)	148 (20.8)		1.93 (0.66-5.67)	.23
Other	30 (41.1)	193 (27.2)		2.83 (1.04-7.71)	.042
Difficult anastomosis					
Yes	33 (50.0)	163 (23.1)	**<.001**	1.59 (0.71-3.56)	.26
No	33 (50.0)	543 (76.9)		1.00 (ref.)	
Thoracotomy			.21		-
Yes	62 (89.9)	667 (93.7)			
No	7 (10.1)	45 (6.3)			
Thoracoscopy			.40		-
Yes	7 (10.1)	52 (7.4)			
No	62 (89.8)	655 (92.6)			
Complications before 1 year			**<.001**		**.02**
Yes	34 (82.9)	164 (44.4)		3.28 (1.23-8.76)	
No	7 (17.1)	205 (55.6)		1.00 (ref.)	
Initial hospitalization length (d)	86 [40-127]	23 [15-41]	**<.001**†	**1.96 (1.15-3.33)**†	**.01**†

Values are number (percentage) for categorical variables, mean ± SD for birth weight and median (IQR) for initial hospitalization length.
The significative values are in bold.
*OR per 500 g increase.
†OR and *P*-values calculated on the log-transformed values of initial hospitalization length.

One study showed a significant association between prenatal diagnosis and patients with long gap EA and positive testing for a genetic syndrome.[14] However, in our patients with prenatal diagnosis, the rate of associated abnormalities was much higher (95%) than in the global cohort and included genetic syndromes such as CHARGE (coloboma, heart defects, atresia choanal, retardation of growth and development, genitourinary problems, ear abnormalities) or trisomy 18 either if prenatal diagnosis of EA seems an independent risk factor of mortality. Another hypothesis is that prenatal diagnosis identifies more severe anatomic forms of EA that confer a higher mortality rate.

Associated abnormalities were present in more than one-half of the population. Cardiac malformations were the most frequently associated condition and the condition most strongly associated with mortality in patients with EA (6-fold higher risk of mortality). No other malformations influenced mortality. The mortality rate in children with congenital heart defects such as ductal-dependent heart disease after the first procedure is 1%-2%, and this defect in association with EA increases mortality by 2-fold.[15] Prenatal diagnosis of major cardiac defects is now the rule in most developed countries, and pregnancy termination may be considered in the context of prenatal bioethics legislation. In France, there is no limit on gestational age for termination of a pregnancy if the malformation is incurable and/or has an extremely poor prognosis. Despite this legislation, which probably led to a high rate of pregnancy termination in patients who would have been included in our study, infants born with EA and a cardiac heart defect have a worse prognosis than do those without cardiac abnormalities.

Birth weight remains an independent factor related to mortality as Waterston and Spitz reported in their risk classification for patients with EA.[5-7] However, some studies, mostly retrospective with low patient numbers, did not find any effect of birth weight.[8,16] The effect of birth weight seems to be continuous and not limited to the low birth weight population. This conclusion was confirmed by the finding that prematurity was not a risk factor for mortality in this population.

Mortality was not associated with surgical factors such as difficult anastomosis, leakage, or surgical approach. This probably reflects improvements in perinatal care, earlier diagnosis and treatment of complications, better medications to treat infections, and more efficient mechanical ventilation techniques. Our results identify opportunities for a greater focus in prenatal diagnosis, especially if this is associated with low birth weight and/or severe cardiac malformations.

The LoS is an important outcome variable for the assessment of operative outcomes when postoperative mortality is low, as in EA.[17] We considered the LoS as a good proxy for morbidity because it reflects hospitalizations, mainly for complications.

The initial duration of hospitalization and number of complications, which affected >66% of our population, were strongly associated with the total LoS during the first year. This finding confirms that these criteria reflect morbidity in the first year of life. Birth weight and associated abnormalities are known to increase the LoS in the neonatal intensive care unit population,[18] and we found in this study that this is also the case for patients with EA. Complications related to EA were the most frequent causes for readmission followed by associated abnormalities (surgery or complications). In our previous study of complications involving the respiratory and digestive systems, we also found a high frequency of anastomotic strictures requiring dilatation and severe GERD requiring fundoplication.[19]

Finally, only 1 surgical factor, difficult anastomosis, was a predictor of a longer LoS. Although "difficult" is a subjective item, it was recorded prospectively at the time of EA surgical repair, and we have recently shown that it is associated with the rate of fundoplication.[20] Gap measures was not an item on the questionnaire because its measurement is not a routine practice in primary possible anastomosis; in the long gap population, gap measure was recorded but too few data were available to be used.

The rate of full oral autonomy was correlated with number of complications and initial LoS during the first year. The initial LoS was related to birth weight, associated malformations, and difficult anastomosis. Ten percent of this population did not achieve full oral feeding at 1 year of age. Complications related to the EA pattern (stricture, TEF, severe GERD, pneumonia, tracheomalacia) and admission related to associated abnormalities leading to multiple surgical procedures and multiple readmissions are associated with abnormal oral feeding behaviors and dependence on artificial nutritional support to maintain adequate growth and avoid growth failure.[10] Anastomotic strictures, which can limit oral intake for days or weeks, occurred in 21% of patients in their first year. The incidence in our study justified the 20% rate of dilation under general anesthesia with bougies or the balloon technique.[20,21]

Severe GERD can also be responsible for alimentary reversion and/or a failure to thrive, and patients with GERD need a longer LoS for enteral nutrition adaptation and may need jejunal nutrition before GERD surgery. Severe GERD can be responsible for a long LoS with undernourished babies and can also be the source of respiratory complications. The indication of surgery is not universally acknowledged. Respiratory morbidity related to EA is multifactorial, occurs in 30%-40% of patients, and is related mainly to tracheomalacia. The importance of overlapping conditions (eg, stricture, GERD) in the management of tracheomalacia is difficult to analyze. In a study from Sydney, Australia, babies who benefitted from aortopexy were more likely to be operated on because of GERD.[20] The recurrence of TEF is low in our study compared with the 6%-10% rate in the literature. This low rate may be explained by the short follow-up in our series. Many patients present with respiratory symptoms lasting many months or years before the fistula recurrence is diagnosed.[22]

Our study has strengths and limitations. The limitations include the relative short follow-up, although most of the morbidity and mortality was seen during the neonatal period and first months of life. Other limitations are the absence of details about the types of cardiac malformation, and the lack of information about early termination of gestation. The strengths are the high quality of data, which were recorded prospectively in a population-based registry with a high degree of inclusion and completeness, common protocol of care,[23] and large number of patients who presented with the most frequent anatomical type of EA.

This study points the importance and the need for standardized and homogenous treatment and follow-up of these patients, to reduce early and long-term morbidity. Toward this end, a consensus from European Society for Paediatric Gastroenterology Hepatology and Nutrition-North American Society For Pediatric Gastroenterology, Hepatology & Nutrition,[9] National,[23] and European[24,25] recommendations have been published: Protocole National de Diagnostic et de Soins in France by the Health High Authorities and the European Reference Network for Rare Inherited and Congenital Anomalies.

In conclusion, this study shows good prognosis for infants with EA with distal fistula at the population level and identified a new factor—prenatal diagnosis—to predict mortality. The high rate of survival and the recent initiatives for better care and follow-up offered to these patients with rare diseases may help to identify and prevent the risk factors for morbidity related to EA. ■

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Table I. Characteristics of the population (n = 1008)

	n (%)	n of data available
Male	596 (59.3)	1005
Polyhydramnios	383 (42.4)	903
Little or not seen stomach	110 (14.4)	760
Prenatal suspicion of EA	132 (13.3)	991
Inborn patients	371 (37.3)	994
Familial history of EA	13 (1.4)	915
Spontaneous pregnancy	502 (92.5)	543
Birth weight (g)	2610 (2060; 3075)	1003
Gestational age (wk)	38 (35; 39)	988
Mother age (y)	30.0 (27; 34)	877
Primary anastomosis	958 (99.2)	965
Delayed anastomosis (>7 d of life)	61 (6)	975
Thoracoscopy	67 (6.9)	974
Preoperative tracheoscopy	268 (29.0)	924
Anastomotic stricture	182 (19.8)	888
Gastrostomy	131 (13.1)	999
Antireflux procedure	79 (8.6)	891
Aortopexy	15 (1.5)	996
Antisecretory treatment at first exit	831 (89.0)	934
Inhaled treatment	33 (6.4)	519
Oral autonomy at 1 y	722 (90)	805
Lost to follow-up at 1 y	83 (8.2)	1008
Associated malformations (all)	535 (53.1)	1007
Cardiac	250 (25.0)	1002
Spine and ribs	145 (14.5)	1000
Genitourinary	144 (14.4)	1000
Anorectal	90 (9.0)	998
Limbs	77 (7.7)	998
Congenital esophageal stenosis	19 (2.1)	873
Other malformations	144 (14.4)	994
VACTERL	191 (18.9)	1007
CHARGE	15 (1.4)	1007

CHARGE, coloboma, heart defects, choanal atresia, retardation of growth, genital/urinary and ear abnormalities, tracheoesophageal fistula; *VACTERL*, vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula/esophageal atresia, renal anomalies and limb defects. Values are number (percentage). For categorical variables and median (IQR) for quantitative variables.