Predictors of the Performance of Early Antireflux Surgery in Esophageal Atresia

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Objective To identify predictors of and factors associated with the performance of antireflux surgery during the first year of life in children born with esophageal atresia.

Study design All patients were included in a French registry for esophageal atresia. All 38 multidisciplinary French centers completed questionnaires about perinatal characteristics and one-year outcome for children born with esophageal atresia.

Results Of 835 infants with esophageal atresia born in France from 2010 to 2014, 682 patients, excluding those with long-gap esophageal atresia, were included. Three patients had type I, 669 had type III, and 10 had type IV esophageal atresia. Fifty-three children (7.8%) received fundoplication during the first year of life. The median age at the time of the end-to-end esophageal anastomosis was 1.1 day (range 0-15). Multivariate analysis identified three perioperative factors that predicted the need for early antireflux surgery: anastomotic tension ($P = .004$), associated malformations ($P = .019$), and low birth weight ($P = .018$). Six other factors, measured during the first year of life, were associated with the need for antireflux surgery: gastroesophageal reflux ($P < .001$), anastomotic stricture ($P < .001$), gastrostomy ($P < .001$), acute life-threatening event ($P = .002$), respiratory complications ($P = .045$), and poor nutritional status ($P < .001$).

Conclusions Gastroesophageal reflux disease, low birth weight, poor nutrition, and surgical anastomosis difficulties predicted the performance of antireflux surgery in the first year of life in infants with esophageal atresia. *(J Pediatr 2019;211:120-5)*.

Esophageal atresia is a rare congenital malformation characterized by a lack of continuity of the upper gastrointestinal tract with or without a tracheoesophageal fistula. Esophageal atresia occurs in 1 in 2400-4500 births.[1] The prognosis for esophageal atresia has benefited from recent advances in medical and surgical care; the survival rate is now >95%, and an increasing number of patients live to adulthood.[2–5] Gastroesophageal reflux disease (GERD) is the most frequent associated condition and occurs in the majority of patients with esophageal atresia.[6] The cause of GERD in esophageal atresia involves abnormal extrinsic and intrinsic innervation of the esophagus, which leads to dysmotility and anomalies in sphincter tone.[6–8] GERD can have

CHARGE	Coloboma, heart defects, atresia choanae—also known as choanal atresia—growth retardation, genital abnormalities, and ear abnormalities
ELBW	Extremely low birth weight
GERD	Gastroesophageal reflux disease
VACTERL	Vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities
VLBW	Very low birth weight

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potentially severe complications, such as peptic esophagitis, gastric metaplasia, Barrett esophagus, anastomotic stricture, aggravation of laryngomalacia, and asthma. GERD associated with esophageal atresia often is refractory to antireflux medication, and up to 40% of patients may require antireflux surgery.[6]

A prospective population-based register was initiated in 2008 and includes all centers that treat esophageal atresia in France.[2] About 10% of esophageal atresia cases are long-gap esophageal atresia,[3–5] and this form has a worse prognosis and greater morbidity than other forms of esophageal atresia.[1] The aim of this study was to identify predictors of and factors associated with the performance of antireflux surgery in the first year of life in patients included in the French register for esophageal atresia, excluding those with long-gap esophageal atresia.

Methods

Within the framework of the French national plan for rare diseases, a population-based registry of esophageal atresia was created and began to collect data prospectively on all infants born with esophageal atresia in France from January 1, 2008. The registry was approved by the National Informatics and Privacy Committee and was qualified by the National Committee of Register. All data were used anonymously, and the parents were informed of the aims of the registry.

Two specific questionnaires were used to collect information about the infants at birth and at 1 year of age. These questionnaires were reviewed by a multidisciplinary national committee of experts that included epidemiologists, obstetricians, neonatologists, surgeons, and pediatricians. The questionnaires were completed prospectively by the participating centers on a voluntary basis. All centers were tertiary care centers. A clinical research assistant helped to collect the information at each center when required. A physician and a research assistant checked each questionnaire and double-checked the data entered into the database. When inconsistencies or lack of information were found, the corresponding center was contacted to resolve the issue. The methodology of the registry have been reported elsewhere.[2,3]

The present study reports on the first-year outcomes of patients with esophageal atresia born between January 1, 2010, and December 31, 2014 (excluding those with long-gap esophageal atresia). Esophageal atresia was classified according to Ladd classification.[9] Long-gap was defined as an inability to perform end-to-end anastomosis within the first 15 days of life for anatomical reasons (excluding reasons such as extreme prematurity or severe cardiac malformation). Data collected included neonatal characteristics such as sex, birth weight, term, associated malformations (cardiac, costal, renal, anorectal, genital, neurologic, laryngeal cleft, others), associated syndromes (CHARGE [coloboma, heart defects, atresia choanae—also known as choanal atresia—growth retardation, genital abnormalities, and ear abnormalities] and VACTERL [vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities]), and information about esophageal atresia surgery (thoracotomy/thoracoscopy, laryngeal cleft, congenital stenosis, and anastomotic tension, which was subjectively assessed by the surgeon at the time of anastomosis). The outcomes were assessed at 1 year of age and included treatments (proton pump inhibitor and prokinetics), esophageal dilatation, complications (recurrent tracheoesophageal fistula), symptomatic anastomotic stricture (confirmed at endoscopy), respiratory complication, GERD, nutritional status at 1 year and feeding mode (oral or enteral nutrition), and the need for gastrostomy. Undernutrition was defined as a weight-for-height z score ≤−2.0 SDs. Low birth weight was defined as weight ≤1500 g and/or z score ≤–2 SD for gestational age. GERD was defined by positive pH-metry and/or esophagitis at endoscopy. Respiratory complications were defined as recurrent lung infections, chronic wheezing, or recurrent episodes of bronchiolitis.

We identified predictors of the performance of antireflux surgery, including factors existing since birth and the characteristics of esophageal atresia surgery. Associated factors were defined as other factors or complications occurring after esophageal atresia repair in the first year of life.

Statistical Methods

Continuous variables are expressed as mean ± SD or median (IQR). Categorical variables are expressed as numbers (percentages). The normality of distributions was assessed using histograms and the Shapiro–Wilk test. The cumulative incidence of antireflux surgery during the first year of life was estimated considering all-cause mortality as a competing risk using the Prentice and Kalbfleisch approach.[10]

The characteristics of infants and esophageal atresia surgery were compared between patients treated with and without antireflux surgery during the first year of life using the χ^2 test (or Fisher exact test when the expected cell frequency was <5) for categorical variables and Student t test for continuous variables.

The characteristics of infants and esophageal atresia surgery with $P < .10$ in bivariate analyses were included in a multivariable logistic model with a backward selection procedure at $P > .10$. To avoid case deletion in the multivariate analysis caused by missing data for the candidates' predictors, missing data were imputed by the multiple imputation procedure.[11]

A sensitivity analysis was conducted by considering the time of occurrence of the antireflux surgery using Fine–Gray models and treating death as a competing event.[12] Finally, for the infants alive after 1 year, we assessed the association between the performance of antireflux surgery and other treatments, complications, and nutritional status during the first year of life using χ^2 test (or Fisher exact test) for categorical variables, and ANCOVA for the change in weight from birth to 1 year. Logistic regression or ANCOVA models were used to adjust the associations for the characteristics of infants and esophageal atresia surgery identified as predictors in the previous multivariable logistic analysis.

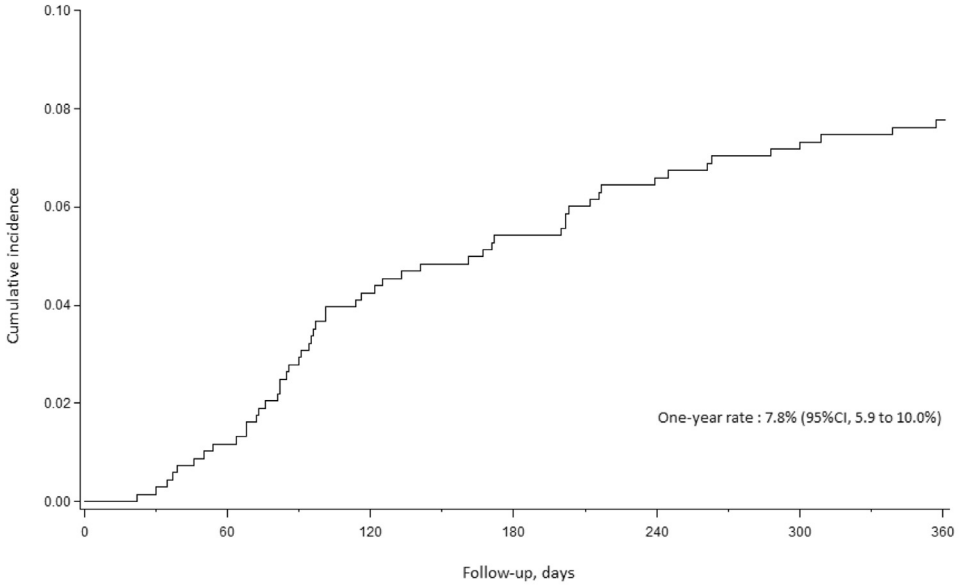

Figure. One-year cumulative incidence rate of antireflux surgery in infants with esophageal atresia.

Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed using the SAS software package (release 9.3; SAS Institute, Cary, North Carolina). Further details are presented in the **Supplementary Material** (available at www.jpeds.com).

Results

From the total population of 835 infants with esophageal atresia born in France between 2010 and 2014, 682 patients (male-female 1:1.49) received an esophageal atresia repair involving end-to-end esophageal anastomosis performed within the first 2 weeks of life. We excluded 153 patients with long-gap esophageal atresia as defined previously. Three patients had type I esophageal atresia, 669 patients had type III esophageal atresia, and 10 patients had type IV esophageal atresia. Neonatal characteristics, treatment, and complications in the first year of life are available in **Table IV** (available at www.jpeds.com) for the overall study population. Thirty-six percent of the infants were born at gestational age <37 weeks, and the mean birth weight z score was −1.70 ± 1.52 (median −1.6, IQR −2.7 to −0.60). The median age at the time of the end-to-end esophageal anastomosis was 1.0 day (IQR 0-1). Thirteen deaths occurred at a median age of 15 days (IQR 11-25). During the first year of life, 53 infants received antireflux surgery (1-year rate 7.8%, 95% CI 5.9-10.0; **Figure**), at a median age of 99 days (IQR 72-212). Very few antireflux surgeries were performed during the first month (2 patients). Thirty-eight centers enrolled at least 1 patient during the study period. The number of antireflux surgery per center varied between 0 and 6 (0%-26.1%).

Table I. Characteristics of infants and esophageal atresia according to the need of antireflux surgery during the first year of life

Characteristics	Antireflux surgery		*P* value
	Yes (n = 53)	No (n = 629)	
Male	30/53 (56.6)	378/628 (60.2)	.61
Birth weight, z score, mean (SD)	−2.28 (1.41)	−1.65 (1.52)	**.004**
Birth term <37 wk	26/53 (49.1)	214/613 (34.9)	**.040**
Associated malformation	39/53 (73.6)	316/629 (50.2)	**.001**
Cardiac	18/53 (34.0)	163/629 (25.9)	.20
Other(s)	18/53 (34.0)	98/629 (15.6)	**.002**
Costal	9/53 (15.1)	97/629 (15.4)	.95
Renal	9/53 (17.0)	58/629 (9.2)	.068
Anorectal	16/53 (30.2)	88/629 (14.0)	**.002**
Genital	3/53 (5.7)	36/629 (5.7)	1.00
Neurologic	3/53 (5.7)	31/629 (4.9)	.74
Laryngeal cleft	4/46 (8.7)	10/523 (1.9)	**.021**
Congenital esophageal stenosis	2/45 (4.4)	14/553 (2.5)	.34
Anastomotic tension	24/51 (47.1)	135/590 (22.9)	**<.001**
Thoracotomy	45/49 (91.8)	563/610 (92.3)	.78
VACTERL	11/53 (14.5)	91/629 (15.5)	.22
CHARGE	3/53 (5.7)	9/629 (1.4)	.059

Values expressed as number/total number (%), unless otherwise indicated.
Values in bold are statistically significant.

Perioperative Predictors of the Performance of Antireflux Surgery

The characteristics of the infants and esophageal atresia repair surgery, grouped according to the performance of antireflux surgery during the first year of life, are shown in **Table I**. Univariate analysis showed that infants needing antireflux surgery had a lower birth weight z score and were more likely to have been born at <37 weeks and to have various malformations (anorectal, laryngeal cleft, and other malformations including ear malformation, choanal

Table II. Multivariate analysis of perioperative predictors of the need for antireflux surgery during the first year of life in infants with esophageal atresia

Characteristics	OR (95% CI)*	*P* value*
Anastomotic tension	2.49 (1.34-4.59)	**.004**
Associated malformation	2.18 (1.13-4.17)	**.019**
Birth weight per z-score increase	0.79 (0.65-0.96)	**.018**

Values in bold are statistically significant.
*Calculated in backward stepwise multivariable logistic regression models after handling missing values using multiple imputation procedure. Candidate predictors were anastomotic tension, laryngeal cleft, birth weight, birth term, and at least 1 associated malformation.

atresia, tracheomalacia, cleft palate, chondroma, congenital diaphragmatic hernia, omphalomesenteric duct, single umbilical artery, arteriovenous malformation, cataract, coloboma, and microphthalmy) and anastomotic tension compared with infants who did not require antireflux surgery. Multivariate analysis (Table II) showed that anastomotic tension (OR 2.49; 95% CI 1.34-4.59), associated malformations (OR 2.18; 95% CI 1.13-4.17), and low birth weight (OR per 1-point z-score increase 0.79; 95% CI 0.65-0.96) were independent predictors of the performance of antireflux surgery during the first year of life. Similar results were found in the sensitivity analysis after considering death as a competing event; there was a significant association between the performance of esophageal atresia surgery and laryngeal cleft (subhazard ratio 2.89; 95% CI 1.00-8.29).

Factors Associated with the Performance of Antireflux Surgery during the First 12 Months of Life

Except for the use of proton pump inhibitor and prokinetics, all the symptoms and complications of GERD occurring during the first year of life were associated with antireflux surgery before and after adjustment for previously identified predictors of performance of antireflux surgery (Table III). Infants who underwent antireflux surgery were more likely to have needed enriched oral nutrition and enteral nutrition within the first year compared with those who did not need the surgery (Table III). Weight gain from birth was lower in infants treated with antireflux surgery (mean change in z score, 0.31 ± 0.17) than in those not treated with surgery (mean change in z score, 0.84 ± 0.05; $P = .003$). However, this difference was no longer significant after adjustment for previously identified predictors of antireflux surgery ($P = .071$).

Discussion

This prospective population-based study showed that antireflux surgery remains frequent in esophageal atresia during the first year of life. The information gained from this large population-based registry could help physicians to identify those children who require early antireflux surgery and therefore help care for this fragile population. A single-center, retrospective review of 767 patients undergoing fundoplication over a 20-year period, including 85 patients with esophageal atresia, found that median age at primary fundoplication was significantly lower in patients with esophageal atresia (7.2 months) than in those who did not have esophageal atresia (23.3 months).[13]

Three perioperative predictors of the performance of antireflux surgery were identified. Some of these factors have been reported as predictors of morbidity and mortality, but not specifically of the performance of antireflux surgery.[2,3,14,15] The predictors of the performance of fundoplication remain unclear.[1] GERD is more severe and frequent in infants born premature, and our study confirmed that low

Table III. Association of the need for antireflux surgery with other treatments, complications, and nutritional status during the first year of life of infants with esophageal atresia

	Antireflux surgery		Unadjusted	Adjusted
Characteristics	Yes (n = 53)	No (n = 616)	*P* value	*P* value*
Treatment and complications				
PPI treatment	45/50 (90.0)	540/586 (92.2)	.59	.90
Prokinetic treatment	12/48 (25.0)	132/574 (23.0)	.75	.87
Gastrostomy	33/50 (66.0)	29/566 (5.1)	**<.001**	**<.001**
Recurrent TEF	0/42 (0.0)	7/494 (1.4)	-	-
Anastomotic stricture	19/46 (41.3)	95/541 (17.6)	**<.001**	**<.001**
Acute life-threatening event	8/53 (15.1)	24/616 (3.9)	**<.001**	**.002**
Respiratory complication	16/53 (30.2)	113/616 (18.3)	**.036**	**.045**
Feeding difficulty	6/53 (11.3)	15/616 (2.4)	**<.001**	**.006**
Gastroesophageal reflux	25/42 (59.5)	42/434 (9.7)	**<.001**	**<.001**
Nutritional status at 1 y				
Oral nutrition	15/42 (35.7)	466/495 (94.1)	**<.001**	**<.001**
Enriched oral nutrition	22/35 (62.9)	52/415 (12.5)	**<.001**	**<.001**
Enteral nutrition	23/40 (57.5)	18/498 (3.6)	**<.001**	**<.001**
Weight gain from birth, z score, mean (SEM)†	0.31 (0.17)	0.84 (0.05)	**.003†**	**.071**
History of enteral nutrition	36/44 (81.8)	63/481 (13.1)	**<.001**	**<.001**

PPI, proton pump inhibitor; *TEF*, tracheoesophageal fistula.
Values are expressed as number/total number (%), except when otherwise indicated.
Values in bold are statistically significant.
*Adjusted for anastomotic tension, associated malformation, birth weight, and laryngeal cleft.
†Adjusted for weight at birth (available for 459 patients not treated with antireflux surgery and 42 treated with antireflux surgery).

birth weight is a predictor of GERD and the performance of antireflux surgery.[16,17] Infants of very low birth weight (VLBW; <1500 g) were recognized by Spitz in the early 1990s for having a lower survival rate.[18,19] It also was shown that birth weight <2500 g is associated with a greater morbidity risk in the first year of life.[19] Those with VLBW, and especially those with extremely low birth weight (ELBW), have an independent risk factor for mortality and morbidity.[20] Although this population has benefited from improvements in neonatal care, it remains a very fragile population, and the optimal surgical management of ELBW and VLBW with esophageal atresia is still debated.[20] In line with our results, Schmidt et al also found a greater rate of fundoplication in ELBW.[20]

Associated malformations were another independent perioperative predictor of the need for antireflux surgery in our patients. In the literature, cardiac malformations are associated with increased risk of morbidity and mortality.[14,21–23] However, Sulkowski et al[14] showed that other malformations also were associated with increased morbidity, consistent with the results of our study. The association between malformation and antireflux surgery was not previously reported and the reason for such an association remains unclear. One hypothesis is that GERD, which is caused by impaired esophageal motility, is more severe in infants with a more severe phenotype, including polymalformations. However, we could not find any manometric data showing that dysmotility was more severe in severe malformation syndromes such as CHARGE or VACTERL. We did not expect anorectal malformation to be associated with fundoplication, except as part of the VACTERL syndrome.[24] In the study by Rayyan et al, patients with VACTERL had more gastroenterologic and respiratory complications at 1 year,[17] and these patients have significant reflux in adulthood.[25] However, our study did not show that anorectal malformation frequency was related to VACTERL. In our study, neither VACTERL nor CHARGE were associated with the antireflux surgery. A less-surprising finding was that laryngeal cleft was a factor associated with a fundoplication, because it affects aspiration risk and could have a bearing on the child's indications for antireflux surgery (leading to some unnecessary fundoplication).

We found only one surgical perioperative predictor of the performance of antireflux surgery (esophageal anastomosis under tension), which probably diminished the efficiency of the antireflux barrier.[26] Pathophysiology of GER after repair of esophageal atresia involves inherent dysmotility due to abnormal extrinsic and intrinsic innervation of the esophagus, anomalies in sphincter tone, and a foreshortened intraabdominal esophagus, as well as possible damage to the vagus nerve during surgery or secondary to anatomic changes created at anastomosis.[27] These last 2 mechanisms could explain the association we found between esophageal anastomosis under tension and need for fundoplication.

Because of the lack of evidence in the literature, a recently published expert-based consensus noted that the indications for antireflux surgery in esophageal atresia include failure to thrive, failure of maximum conservative therapy for GERD, acute life-threatening events, esophagitis, and recurrent anastomotic stricture.[1] We confirmed that infants requiring fundoplication were more likely to have anastomotic stricture and to experience acute life-threatening events and to present with respiratory complications. Anastomotic stricture is one of the most common complications after esophageal atresia surgery and is associated with poor outcomes during the first year of life.[28,29] It is thought to be exacerbated by GERD.[30] Fundoplication generally is recommended when strictures are resistant to medical treatment.[28,31,32]

We also found that infants requiring fundoplication are more often malnourished and have feeding difficulties requiring gastrostomy feeding. Children with esophageal atresia may be undernourished,[33] and GERD can be responsible for feeding difficulties and failure to thrive. Our data are in line with the recently published expert-based consensus in which fundoplication was recommended for cases of failure to thrive.[1] However, because fundoplication was performed at various ages, from birth to 1 year, and weight gain (**Table III**) was measured between birth and 1 year, it was impossible to assess whether fundoplication per se improved the nutritional status or not.

We decided to exclude infants with long-gap esophageal atresia from this study because it is associated with more-severe GERD and a high rate of antireflux surgery.[34] These rare forms of esophageal atresia, in which end-to-end anastomosis must be delayed because it cannot be performed at an early age, lead to severe anatomic modifications and surgical trauma, which are associated with more severe GERD.[35] Factors associated with the performance of antireflux surgery might differ between patients with long-gap esophageal atresia and those with the classical form of esophageal atresia. During the first month of life, few of the infants underwent fundoplication, probably because of a medical antireflux treatment, progressive increase in feeding volume at this age, and the rarity of early GERD complications. One of the more striking findings of this study is that 50% of the antireflux surgeries in these infants were performed before 4 months of life, probably because of the presence of complications such as respiratory problems, acute life-threatening events, or anastomotic stricture.

Our study has some limitations and strengths. The limitations were the missing data for some infants, which increased the risk of bias, and that the outcomes were limited to the first year of life. We also did not compare the frequency of fundoplication by center or adjust according to the centers, which could have induced bias with our main criterion. Moreover, we did not have any information on success, repeat fundoplications, or weight gain after surgery because of the short follow-up.

The strengths were the prospective national-based register, which is unique, and the large number of patients included. To our knowledge, no similar national registry has been reported.[14,29,36,37]

Early antireflux surgery remains a frequent intervention in infants with esophageal atresia. Perioperative predictors of the performance of surgery were anastomotic tension at the

time of esophageal repair, associated malformations, and low birth weight. The performance of fundoplication also was associated with complications of GERD, such as anastomotic stricture, poor nutritional status and gastrostomy, acute life-threatening events, and respiratory complications. Identifying the predictors of and factors associated with the performance of antireflux surgery may help in the care of this fragile population. The outcomes of antireflux surgery in patients with esophageal atresia, particularly in regard to dysphagia, growth, and risk of Barrett esophagus, remain to be addressed by long-term follow-up of this cohort. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table IV. Characteristics of 682 infants with esophageal atresia and details of the surgery, treatment, and complications in the first year of life

Characteristics	Values	n
Male	408 (59.9)	681
Birth weight, z score, mean (SD)	−1.70 (1.52)	677
Birth term, <37 wk	240 (36.0)	666
Associated malformation	355 (52.1)	682
Cardiac	181 (26.5)	
Other(s)	116 (17.0)	
Costal	105 (15.4)	
Renal	67 (9.8)	
Anorectal	104 (15.3)	
Genital	39 (5.7)	
Neurologic	34 (5.0)	
Laryngeal cleft	14 (2.5)	569
Congenital esophageal stenosis	16 (2.7)	598
Anastomotic tension	159 (24.8)	641
Thoracotomy	608 (92.3)	659
VACTERL	102 (15.0)	682
CHARGE	12 (1.8)	682
Treatment and complications		
PPI treatment	585 (92.0)	636
Prokinetic treatment	144 (23.2)	622
Esophageal dilatation	119 (20.2)	*589*
Gastrostomy	62 (10.1)	616
Recurrence of tracheoesophageal fistula	7 (1.3)	536
Anastomotic stricture	114 (19.4)	587
Acute life-threatening event	32 (4.8)	669
Respiratory complication	129 (19.3)	669
Feeding difficulty	21 (3.1)	669
Gastroesophageal reflux disease	67 (14.1)	476
Nutritional status at 1 y*		
Oral nutrition	481 (89.6)	537
Enriched oral nutrition	74 (16.4)	450
Enteral nutrition	41 (7.6)	538
Weight gain from birth z score, mean (SD)	0.80 (1.50)	501
History of enteral nutrition	99 (18.9)	525

Values are expressed as number (%) unless otherwise indicated.
*Data for 669 neonates alive at 1 year.