Feeding and Growth Outcomes in Infants with Type C Esophageal Atresia Who Undergo Early Primary Repair

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Objectives To describe growth and feeding outcomes in patients with type C esophageal atresia who underwent early primary repair and to identify predictors for poor growth.

Study design This single-center, retrospective, cohort study included all patients with type C esophageal atresia who underwent early primary repair from 2013 to 2019. Weight-for-age z score (WAZ) was calculated at birth, and every 6 months until 3 years postoperatively. Longitudinal median regression was used to evaluate WAZ over time. A multivariable logistic regression model explored predictors of growth outcomes.

Results Of 46 infants who met the inclusion criteria, 72% were term. The median age at repair was 1.5 days of life (IQR, 1-2 days of life) and the hospital length of stay was 20 days (IQR-14, 30 days). Two patients had esophageal leak (4.3%). The median WAZ at birth was below average (-0.72; IQR, -1.37 to -0.40), but improved to reach average by 3 years (-0.025; IQR, -0.85 to 0.97, $P < .001$). At discharge, 72% of patients were receiving full oral nutrition, which improved to 95% by 3 years. The only independent predictor of poor growth at 1 year (WAZ < -1 [33%]) was WAZ at discharge ($P = .02$).

Conclusions Infants with esophageal atresia who undergo early primary repair are capable of achieving standard growth curves by 3 years of age. However, poor discharge WAZ score was predictive of poor WAZ score at 1 year. Efforts to identify at-risk patients and institute targeted inpatient and outpatient nutrition interventions are needed to improve their growth trajectory. *(J Pediatr 2022;241:77-82).*

Esophageal atresia occurs in 1:2500 to 1:4500 live births worldwide.[1] The spectrum of severity varies widely, partly owing to the type of a esophageal atresia. The most common type (85%) is esophageal atresia with a distal trachea-esophageal fistula (Gross type C), and typically with a short "gap," the distance between the upper and lower esophageal pouches (**Figure 1**). This usually allows for a primary repair, although studies on long-term outcomes are sparse.[2,3]

Studies focused on nutrition and growth are limited, and there is a perception that these patients are smaller than their peers without esophageal atresia in infancy, although they may catch-up by adulthood.[2-4] The current literature includes all types of esophageal atresia in the same cohort, which likely skews the data, because patients with long gap esophageal atresia are known to have significantly longer and more complicated hospital courses.

Examining specific pediatric surgical cohorts has revealed modifiable risk factors for impaired growth that could become targets for future nutrition optimization interventions in those populations.[5-8]

The aims of our study were to describe the growth of patients with type C esophageal atresia who undergo primary repair at our institution, examine factors associated with poor growth, and identify current feeding strategies. We hypothesized that these patients would be capable of achieving growth comparable with peers without esophageal atresia.

Methods

This is an institutional review board-approved, single-center, retrospective cohort study. We included all patients who presented to Boston Children's Hospital between 2013 and 2019 with type C esophageal atresia who were able to undergo primary anastomosis within the first week of life. Demographic, clinical, growth, operative, perioperative, and morbidity data were collected from the electronic medical record.
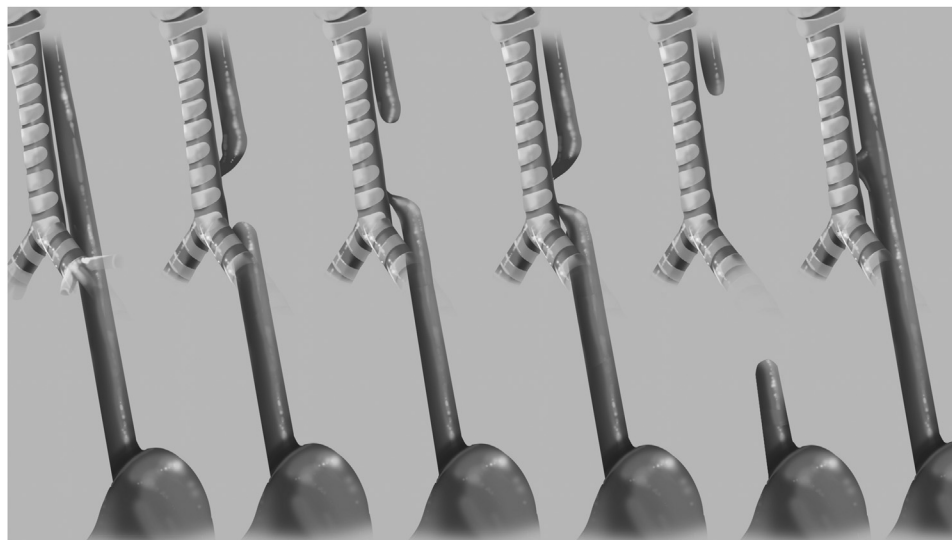
CHD	Congenital heart disease
CLABSI	Central line-associated blood stream infection
FOIS	Functional Oral Intake Scale
GT	Gastrostomy tube
UTI	Urinary tract infection
VACTERL	Association of vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities
WAZ	Weight-for-age z score
WHO	World Health Organization

Figure 1. Gross type classification and esophageal atresia (EA) and trachea-esophageal fistulas (TEF). From left to right: Normal anatomy, Gross type B (EA with proximal TEF; 2%), Gross type C (EA with distal TEF; 86%), Gross type D (EA with proximal and distal TEF; 1%), Gross type A (pure EA, 7%), and Gross type E (TEF without EA; 4%).

Our primary growth outcome measure was weight-for-age z score (WAZ), which is the SD above or below a statistical mean derived from population-based growth data (a z score of 0 corresponds with the 50th percentile of weight for a certain age).[9] The WAZ was collected at admission, time of operation, discharge, and every 6 months after the operation, until 3 years after repair or the date of last follow-up. WAZ was calculated from the Fenton growth chart for premature infants (≤40 weeks postmenstrual age), from the World Health Organization (WHO) growth chart for infants and children <2 years of age, and from the Centers for Disease Control and Prevention growth chart for children ≥2 years of age. Premature infants were corrected up to 3 years of chronological age on the WHO or Centers for Disease Control and Prevention growth charts per American Academy of Pediatrics recommendation.[10,11] The Functional Oral Intake Scale (FOIS) was used to determine feeding status at discharge and annually, until 3 years postoperatively, when available.[12]

Power and Sample Size

The sample of 46 patients with type C esophageal atresia, of whom 42 patients had complete data as measured by WAZ at 1 year, provides 80% power for detecting a standardized z score change from admission to 1 year of 0.50 (deemed clinically relevant), based on the nonparametric Wilcoxon signed-ranks test for repeated growth measures within the same patient over time and assuming a 2-tailed alpha of 0.05. Sample size calculations were performed using nQuery Advisor version 8.0 (Statistical Solutions Ltd).

Statistical Analyses

Demographic and nutritional variables were explored using appropriate descriptive statistics. Continuous data are presented as medians with IQRs and categorical data are presented as frequencies with percentages. Boxplots were created to show the distribution of WAZ at each measurement time-point. Longitudinal median regression was used to evaluate differences in WAZ over time while accounting for repeated measurements within patients over time.[13] Predictors of WAZ of <–1 at the 1-year follow-up were assessed using multivariable logistic regression modeling, with results presented as ORs with 95% CIs and P values.[14] Statistical significance was assessed at a P value of <.05 for all analyses. Data were analyzed using SAS (version 9.4, SAS Institute) and Stata (version 16.0, StataCorp LLC).

Results

Demographics

Forty-six consecutive patients met the inclusion criteria. All patients were Gross type C confirmed by bronchoscopy and operative exploration, as per our inclusion criteria. Median age at operation was 1.5 days (IQR, 1-2). Median gestational age was 39 weeks (IQR, 37-40). Median birth weight was 2.8 kg (IQR, 2.3-3.1), which corresponded with a WAZ of −0.72 (IQR, −1.37 to −0.30). One-third of the patients had congenital heart disease, but only 2 patients (4%) required operative intervention, which occurred after their esophageal atresia repair. More than one-half of the cohort had at least 1 other anomaly of an association of vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (VACTERL) (57%) (Table I).

Clinical Course

Hospital courses were generally unremarkable with a median length of stay of 20 days (IQR, 14-30), which included an initial intensive care unit stay of a median of 11 days (IQR, 8-14). Most patients were extubated in the operating room or on postoperative day 1, which corresponded with a median duration of mechanical ventilation of 2 days (IQR, 1-4). Complications included esophageal leak (radiographic

and resulting in a delay in initiating enteral nutrition; n = 2 [4.3%]), clinically significant or refractory esophageal stricture (defined as requiring >6 endoscopic dilations; n = 8 [17%]), central line-associated blood stream infection (defined by bacteremia; n = 1 [2.2%]), and urinary tract infection (n = 1 [2.2%]) (**Table I**).

Longitudinal Analysis of WAZ From Admission to 3 Years

The median (IQR) growth by WAZ over time is shown in **Figure 2**, with WAZ follow-up relative to timing of operation. Longitudinal median regression analysis of change in WAZ from admission to the 3-year follow-up, with discharge as the reference time-point, showed statistically significant differences in WAZ at all time-points except 6 months after discharge. There was a decrease in WAZ from admission to discharge, however WAZ consistently improved after discharge, with median WAZ reaching the 50th percentile for age (WAZ of 0) by 3 years (−0.025; IQR, −0.85 to 0.97), within the limitations of our follow-up (n = 14 at 3 years) (**Figure 2** and **Table II**).

Predictors of WAZ of less Than −1

Using multivariable logistic regression analysis, the only independent predictor of poor growth at 1 year (WAZ < −1 [33%]) was WAZ at discharge (*P* = .02). Prematurity, VACTERL, days intubated, total hospital length of stay, and esophageal leak were not associated with a low WAZ at 1 year (**Table III**; available at www.jpeds.com).

Feeding Outcomes

The majority of patients were quickly transitioned to enteral nutrition and were on full oral feeds by discharge (72%). Of the 28% patients with enteral access for nutrition support at discharge, 15% had temporary nasogastric tubes, which were no longer present by 1 year of follow-up. At the 1-year follow-up, there were 5 infants with surgical feeding tubes (gastrostomy tube [GT] [n = 4] or gastrojejunostomy tube [n = 1]) (**Table IV**[12]; available at www.jpeds.com). Of these, 3 were premature infants (gestational ages of 32, 33, and 34 weeks), with birthweights of 880, 2300, and 1550 grams, respectively.

Of the 4 patients with a GT, airway pexies to treat severe tracheobronchomalacia were required for 3. These patients were dependent on noninvasive positive pressure ventilation before tracheopexy and weaned to room air after operative intervention.

One patient's GT was removed by 2 years, and 2 others still had a GT in place at 3 years. One had an FOIS of 7, suggesting the tube was likely to be removed shortly after that visit. The remaining patient with a GT at 1 year was lost to follow-up.

The patient who was dependent on a gastrojejunostomy tube at 1 year was a full-term infant with a complicated course owing to an esophageal leak and an additional anomaly (cloaca). Still, this infant successfully reached full feeds and had no feeding tube in place by the 2-year follow-up.

By the 3-year follow-up, 95% of patients had no feeding restrictions; 1 patient had consistent oral intake but still used a GT for additional nutrition support (**Table IV**).

Table I. Demographics, clinical course, and postoperative complications*		
Characteristics	No. (%)	Median (IQR)
Female sex	19 (41.3)	
Gestational age (weeks)		38.9 (36.9-39.6)
>37	33 (71.7)	
34-36 6/7	8 (17.4)	
30-34 6/7	5 (10.9)	
<30	0 (0)	
Birth weight (kg)		2.8 (2.3-3.1)
Gross classification type C	46 (100)	
CHD	15 (33%)	
CHD requiring operative intervention	2 (4.3)	
Trisomy 21	0 (0)	
VACTERL	26 (56.5)	
Age at first operation (days)		1.5 (1.0-2.0)
Total length of stay (days)		20.0 (14.0-30.0)
Length of initial intensive care unit course (days)		10.5 (8.0-14.0)
Duration of mechanical ventilation (days)		2.0 (1.0-4.0)
Esophageal leak (any)	2 (4.3)	
Esophageal stricture*	8 (17)	
CLABSI	1 (2.2)	
UTI	1 (2.2)	

*Clinically significant (requiring >6 dilations).

Discussion

Patients with esophageal atresia who undergo early primary repair generally have short, uncomplicated hospital stays and demonstrate a positive growth trend after discharge, reaching an average WAZ by the 3-year follow-up. The discharge WAZ score is predictive of the 1-year WAZ score. The majority of patients are receiving full oral feeds by discharge and the few who require enteral access for nutrition support tend to be premature with lower birth weights or those with additional complex anomalies.

The WHO definitions of malnutrition include multiple anthropometric measurements (weight for age, length for age, weight for length, head circumference, mid-upper arm circumference); however, the principle is that a measurement with a z score between −1.0 and −1.9 indicates mild malnutrition, −2.0 to −2.9 suggests moderate malnutrition, and <−3 is considered severe malnutrition.[9] Our goal is to provide optimal nutrition for growth; therefore, our target for individual patients is a WAZ of >0. However, we recognize that some infants may be <50th percentile, but not malnourished; therefore, we defined adequate growth as a WAZ of >−1.

Using longitudinal median regression with discharge as the reference time-point, we found a statistically significant WAZ decrease from esophageal atresia repair to discharge. However, it is reassuring that the longitudinal analysis demonstrates a positive slope from discharge to the 3-year follow-up, with significant *P* values at each time-point, except at 6 months, which approaches significance.

These infants are capable of catching up to their peers, as demonstrated by an average WAZ by 3-year follow-up. It may be that optimizing nutrition and growth before discharge, or the enhancement of early postdischarge nutritional efforts, would help this cohort reach an average WAZ sooner.

We chose to analyze predictors of growth at 1 year both owing to follow-up attrition and the clinical benefit of
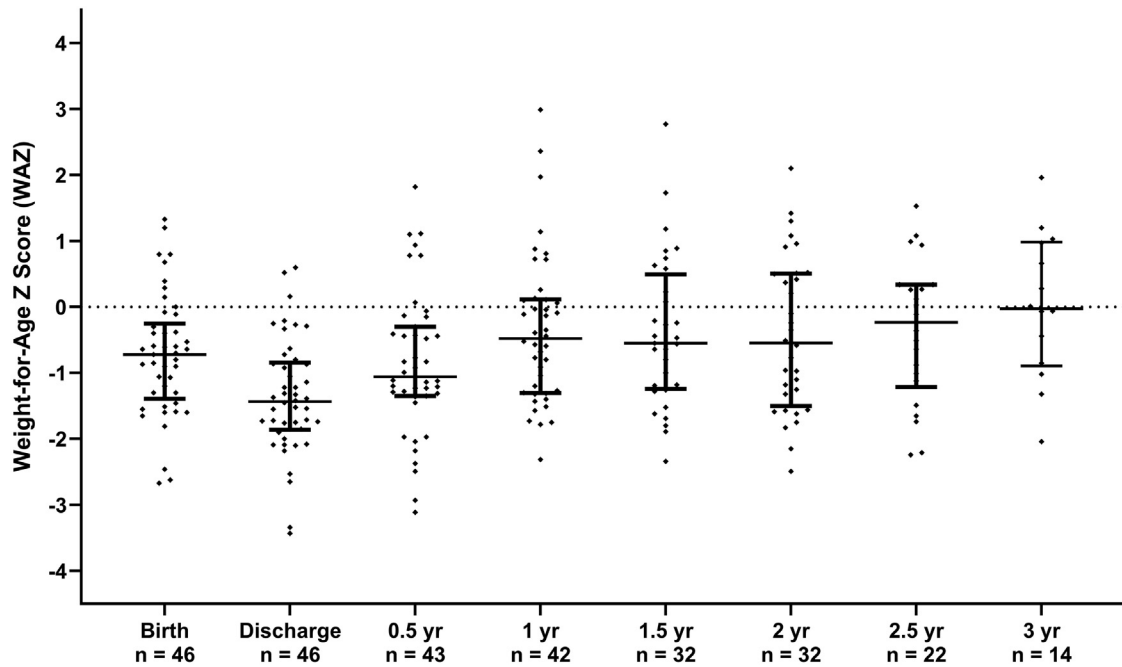
Figure 2. Growth as described by WAZ from admission to 3-year follow-up.

identifying poor growth earlier. We defined adequate growth as a WAZ of >−1; therefore, poor growth is defined as a WAZ of <−1. The only predictor of poor growth at 1 year was WAZ at discharge. Prematurity, VACTERL, days intubated, total hospital length of stay, and esophageal leak were not associated with a low WAZ at 1 year. In total, one-third of patients had a WAZ of <−1 at discharge. Further studies are needed to identify these at-risk patients.

A comprehensive review of feeding outcomes in infants with type C esophageal atresia reports 61% of patients were exclusively orally fed at discharge.[15,16] This outcome is comparable with our findings and supports the need to educate parents on postoperative expectations. The study is limited by there being no follow-up beyond 1 year. Additionally, we did not clarify what proportion of patients were discharged with a temporary feeding tube (nasogastric or nasojejunal) or surgical feeding tube (GT).

At discharge, one-third of our patients were reliant on a feeding tube to some degree, but of these, one-half had a tem-

porary nasogastric tube. All patients with a temporary feeding tube reached full feeds by 1 year.

Lees et al recommend placing a transanastomic tube at time of operation, to decrease the need for parenteral nutrition, allow enteral feeds sooner, and avoid the risk of placing a feeding tube across a new anastomosis.[16] Our institution does not favor placing transanastomic tubes because of the concern for an increased risk of anastomotic stricture. Although the use of transanastomic tubes remains controversial, there is growing evidence to support the association with strictures.[17] Our data suggest that these infants have good feeding outcomes without the need for a transanastomic tube.

After esophageal atresia repair, some degree of esophageal stricture or narrowing can occur. We defined our rate of clinically relevant strictures by those that required ≥6 endoscopic dilations based on our prior work with refractory esophageal strictures.[18] It is reassuring that, despite a proportion (17%) of infants requiring serial dilations for stricture development, the vast majority of the cohort was independent with oral intake by 1 year (90%) as described elsewhere in this article.

There is a perception that, after esophageal atresia repair, patients are small in infancy, and mixed evidence to support whether they remain small for age, have short stature, or are able to catch-up to their peers without esophageal atresia by childhood or adolescence.[2,4,19,20] Studies demonstrating that these patients are below average tend to include all types of esophageal atresia, which likely skews the data; patients with type C disease have lower rates of complications relative to other Gross types.[4] Studies describing poor growth in childhood and adolescence may also be biased because patients presenting for follow-up later in life are most likely symptomatic.[3]

Data are limited and further longitudinal studies are needed; however, our findings suggest that these patients

Table II. Longitudinal median regression analysis of change in WAZ from admission to the 1-year follow-up

Measurement timepoints	Change in WAZ*	95% CI	P value
Birth	0.70	(0.39-1.01)	<.001
Admission	0.65	(0.35-0.95)	<.001
Operation (first)	0.72	(0.44-1.00)	<.001
Discharge	Reference	-	-
6 months	0.36	(0.00-0.73)	.06
12 months after the operation	0.98	(0.53-1.43)	<.001
18 months after the operation	0.87	(0.35-1.39)	≤.001
24 months after the operation	0.91	(0.25-1.57)	.01
30 months after the operation	1.06	(0.54-1.58)	<.001
36 months after the operation	1.43	(0.48-2.38)	.004

The median regression modeling was implemented to assess changes in WAZ over time while accounting for repeated measures within the same patient over time.
*Change in WAZ from admission to 1 year.

are capable of obtaining growth comparable with peers without esophageal atresia by 3 years of age.[2,4,19,20]

We recommend that infants with an uncomplicated esophageal atresia type C undergo feeding and nutritional/growth evaluations every 3 months for the first year of life, with the goal that these patients meet the same growth metrics as their peers without esophageal atresia. Patients who fail to maintain growth metrics should be referred for evaluation of strictures or other anatomic barriers to meeting nutritional intake. Complicated patients, including infants with GTs or gastrojejunostomy tubes, should be followed frequently and until independent with oral intake.

Our findings support our hypothesis that practitioners should not be satisfied with low WAZ scores in infancy. Further studies should focus on long-term growth to establish whether z scores of >0 can be maintained.

This study examines data from a single center, with a high-volume multidisciplinary dedicated esophageal atresia and airway team. Despite trying to limit referral bias by focusing only on newborn patients with esophageal atresia type C repaired in their first week of life, many of these patients present to our referral center owing to other associated conditions diagnosed prenatally that required delivery at a tertiary care center, which could introduce certain referral bias. Similarly, not all centers manage concurrent pathology in a similar manner. For example, at our institution, we perform airway pexies on patients with symptomatic tracheobronchomalacia early in the course of their disease, because of our previous finding that suggests that these patients are at risk for failure to thrive secondary to increased metabolic demands from respiratory distress, which improves after the operation.[21-23] Furthermore, our rate of endoscopic surveillance of this cohort is likely greater than that of other centers because we have a lower threshold to evaluate and intervene in the setting of anastomotic stricture.

The study is retrospective with a relatively small cohort size and a degree of follow-up attrition, which limits statistical analysis.

Some FOIS and feeding tube data were collected from endoscopic documentation accounting for differences in follow-up for FOIS and WAZ time-points. Given the nature of our practice, more patients present for endoscopic follow-up rather than routine outpatient clinic follow-up at 2 and 3 years of age. This factor likely created a scenario where the patient weight at the time of their endoscopy was not entered into their growth chart, but their functional oral intake status was obtained by the endoscopic provider. Encouraging more routine clinic follow-up would have provided more data to better and more accurately track these patients' long-term growth. Additionally, we did not pursue active follow-up with either the patient's pediatrician (if outside of our healthcare system) or directly with the patients to inquire about their most recent weight.

After esophageal atresia repair, patients are capable of achieving standard growth curves. Practitioners should not assume that patients with esophageal atresia with straightforward courses will remain small for age in infancy. Further research is needed to evaluate long-term growth in childhood and adolescence in order to determine whether establishing normal growth curves in infancy can be maintained into adulthood. ■

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50 Years Ago in THE JOURNAL OF PEDIATRICS

Growing and Adapting Despite Intestinal Failure

Wilmore D. Factors correlating with a successful outcome following extensive intestinal resection in newborn infants. J Pediatr 1972;80:88-95.

In the early 1950s, infants who underwent massive surgical resections of bowel faced bleak prospects for survival. However, with the advent of parenteral nutrition (PN), there was now a life-sustaining therapy option that offered improved survival outcomes and quality of life. In 1972, Dr Douglas Wilmore reviewed the literature of the day regarding outcomes for infants who had undergone extensive intestinal resection during the neonatal period, and he defined factors that correlated with successful outcomes. Of the 50 infants who were reported, survival was related to remaining small bowel length and presence/absence of ileocecal valve—namely, there were no survivors reported in infants who had <15 cm small bowel remaining whether or not the ileocecal valve were present, nor any who had <40 cm small bowel remaining if the ileocecal valve were absent. Now nearly 50 years following the Wilmore study, we know that most of these children will survive for long periods.

We now use the term intestinal failure to describe the condition of those children who need PN to sustain growth and hydration. Following surgical resection, the intestines undergo an adaptive response to compensate for functional loss with the ultimate goal of achieving autonomy from PN. If children can be kept alive by minimizing blood stream infections, reducing the risk of liver disease, and maintaining vascular access, many survive and achieve emancipation from PN through full spontaneous adaptation or adaptation facilitated by teduglutide, a glucagon-like peptide 2 analog.[1] In the 1970s, many clinicians refused to provide enteral nutrition to infants with intestinal failure or they provided modular diets devoid of important nutrients. Now feeding strategies emphasize enteral nutrition that is balanced in types of nutrients provided.[2]

Although residual small bowel length remains a predictor of enteral autonomy, other factors are also important in permitting better outcomes. In infancy, retained small bowel has immense potential for growth and adaptation, regardless of the presence of colon. Presence of the terminal ileum remains essential given its role in absorption and endogenous release of a glucagon-like peptide 2.[3] Although the ileocecal valve acts as a barrier against reflux of colonic flora, its absence is mostly appreciated if also accompanied by the loss of terminal ileum. Lastly, presence of cholestasis may impact enteral autonomy negatively.[4] Therefore, although Wilmore's findings were applicable to those infants managed according to the standards of 1972, by today's standards, most of the children described by Wilmore will achieve better outcomes.

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Table III. Multivariable logistic regression analysis of predictors of poor WAZ (defined as WAZ < −1) at 1-year follow-up (n = 42)

Covariates	OR (95% CI)	P value
Discharge WAZ	0.24 (0.07-0.81)	.02
VACTERL	1.15 (0.22-6.14)	.87
Total length of stay (days)	0.99 (0.94-1.03)	.54
Mechanical ventilation (days)	1.04 (0.70-1.55)	.85
Esophageal leak	1.65 (0.01-374.56)	.86

Table IV. Feeding outcomes: FOIS[12] and need for enteral access

Variables	Discharge	1 Year	2 Years	3 Years
FOIS = 1, no oral intake	2 (4.3)	0 (0)	0 (0)	0 (0)
FOIS = 2, some oral intake	5 (10.9)	2 (4.7)	1 (2.9)	0 (0)
FOIS = 3, consistent oral intake	6 (13.0)	2 (4.7)	1 (2.9)	1 (5.0)
FOIS = 4, all oral intake, single consistency	0 (0)	0 (0)	0 (0)	0 (0)
FOIS = 5, all oral intake, special preparation	2 (4.3)	8 (18.6)	3 (8.8)	00 (0)
FOIS = 6, all oral intake, with restrictions	2 (4.3)	4 (9.3)	3 (8.8)	0 (0)
FOIS = 7, all oral intake, no restrictions	29 (63.0)	27 (62.8)	26 (76.5)	19 (95.0)
Nasogastric tube	7 (15.2)	0 (0)	0 (0)	0 (0)
GT	5 (10.9)	4 (9.3)	2 (5.9)	2 (10.0)
Gastrojejunostomy tube	2 (4.3)	1 (2.3)	0 (0)	0 (0)
Reliant on feeding tube (FOIS1-3)	13 (28.3)	4 (9.3)	2 (5.9)	1 (5.0)
All oral intake (FOIS 4-7)	33 (71.3)	39 (90.7)	32 (94.1)	19 (95.0)

Values are number (%).