Pulmonary function in children and adolescents after esophageal atresia repair

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Abstract
Introduction: Respiratory morbidity after esophageal atresia (EA) is common. The aims of this study were to assess pulmonary function, to identify risk factors for pulmonary function impairment (PFI), and to investigate the relations between respiratory morbidity, defined as medical treatment for respiratory symptoms or recent pneumonia and PFI after EA repair.

Material and Methods: Single center retrospective observational study including patients with EA who participated in the follow-up program for 8- or 15-year old patients from 2014 to 2018 and performed pulmonary function testing by body plethysmography, dynamic spirometry, impulse oscillometry, and diffusing capacity of the lungs. Univariate and multiple stepwise logistic regression with PFI as outcome were performed. Anastomotic leak, episodes of general anesthesia, extubation day, birth weight, age at follow up, gross classification, and abnormal reflux index were independent variables.

Results: In total, 47 patients were included. PFI was found in 19 patients (41%) and 16 out of 19 patients (84%) had an obstructive pattern. Respiratory morbidity was found in 23 (52%, NA = 3) of the patients with no correlation to PFI. Birth weight, age at follow-up, and episodes of general anesthesia were identified as risk factors for PFI.

Conclusion: Respiratory morbidity and PFI were common in children and adolescents after EA repair. The major component of PFI was obstruction of the airways. The risk for PFI increased with lower birth weight and older age at follow up. The poor correlation between respiratory morbidity and PFI motivates the need of clinical follow up including pulmonary function tests.

Keywords
esophageal atresia, pulmonary function, respiratory morbidity

1 | INTRODUCTION
Esophageal atresia (EA) is a congenital anomaly of the foregut affecting about 1:3000 life births. Although the prognosis for infants born with EA has improved over the years with survival rates approaching 90%, there is significant respiratory morbidity in survivors affecting physical function and health-related quality of life (HRQoL). Respiratory morbidity in 5-year old children with EA is
comparable to children with congenital diaphragmatic hernia, a condition with lung hypoplasia and pulmonary hypertension.7

Persistent respiratory symptoms in children with EA are chronic cough, recurrent pneumonia and bronchitis, asthma-like wheezing, vocal cord dysfunction, dyspnea, apneic, and cyanotic attacks.8–10 Some of the respiratory symptoms may be related to gastroesophageal reflux (GER), esophageal dysmotility, dysphagia, tracheomalacia, bronchiectasis, chest wall deformities, and surgical complications.2,3,7,11,12 However, the cause of pulmonary dysfunction is not fully understood as a significant proportion of survivors have obstructive and/or restrictive pulmonary function impairment (PFI) not related to these conditions.4,8

Pulmonary function tests from body plethysmography, dynamic spirometry, impulse oscillometry (IOS), and the diffusing capacity of the lungs for carbon monoxide (D_LCO) are well-established pulmonary function tests; validated in children with reference values for the growing child13–15 and they have been conducted in children after EA repair with good correlation to disease and other tests.10,16

Knowledge of pulmonary function in children and adolescents with EA is still scarce and most of the available studies are small-sized including patients at various ages.7,10,11,16–21

The aims of this study were to assess pulmonary function and eventual differences between 8- and 15-year-old patients after EA repair. We also aimed to identify risk factors for PFI and to investigate the relations between respiratory morbidity, defined as medical treatment for respiratory symptoms or recent pneumonia, and PFI after EA repair.

2 MATERIALS AND METHODS

2.1 Study participants

The use of patient’s data in this study was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2014/060, 2014/119/1, and 2014/1191/3). This was a retrospective observational study including patients who had undergone surgical correction of EA at our tertiary pediatric surgical center from 1994 to 2013 and participated in the follow-up program for 8- or 15-year-old patients between 2014 and 2018.

2.2 National follow-up program after EA repair

Since 2011 there has been a national follow-up program after EA repair in Sweden and from 2014 we have added pulmonary function tests to the follow-up program in our unit. The program is a multidisciplinary approach with a team consisting of a pediatric surgeon, a pediatric pulmonologist, and a dietitian. The patients underwent an examination and an interview was carried out with the parents and patients. Pulmonary function tests were performed the day before upper endoscopy and pH/impedance measurements.

2.3 Pulmonary function tests

Body plethysmography, dynamic spirometry, IOS, and D_LCO were performed by a trained pulmonary technician using Jaeger MasterScreen Body and MasterScope PFT system with IOS (Erich Jaeger AG, Würzburg, Germany).

The following variables were analyzed:

- Total lung capacity (TLC) from body plethysmography measurements
- D_LCO adjusted for hemoglobin from diffusion capacity measurements (D_LCO)
- Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), FEV₁/FVC ratio (VC) alternatively FEV₁/FVC from dynamic spirometry
- IOS parameters:
  1. Reactance (X) at 5 Hz (reflecting elastic properties of the lungs and small airways),
  2. Resistance (R) at 5 Hz (reflecting resistance in the whole airways tree),
  3. R at 20 Hz (reflecting resistance of central airways).

All pulmonary function testing reports were analyzed by two clinical physiologists (AM, HH) and measurements that did not fulfill quality criteria were excluded. Furthermore, a consensus review was carried out, based on the American Thoracic Society (ATS)/European Respiratory Society (ERS) lung function assessment strategies22 with regard to PFI, describing it as obstructive and/or restrictive and/or diffusion capacity impairment.

For comparative purposes the values were analyzed and presented as a percent of predicted or z-score based on the predicted value from the reference population. The reference values were obtained from Solymar et al,23 Polgar and Promadhat,24 Quanjer et al,25 the Global Lung Function Initiative (GLI),13,15 and Nowowiejska et al.14 For guidance in interpreting these values see ATS/ERS lung function assessment strategies.22

The anthropometric data was compared with the reference values provided by the WHO Child Growth Standards26–28 and the extension of this data published by Rodd et al29 using the online CPEG shiny app “WHO Z-scores 0 to 19 years.”30

2.4 Data collection and definitions

Data were obtained from the medical records of the patients that met the inclusion criteria described above and was analyzed according to age groups (8 or 15 years) and pulmonary function (normal or impaired).

The dichotomous variable PFI was defined based on the assessment of pulmonary function by the clinical physiologists (obstructive, restrictive, and/or diffusion capacity impairment) and reflected abnormal results in any of these categories. We defined respiratory morbidity as medical treatment for respiratory symptoms with β-agonists and/or inhaled steroids and/or history of pneumonia during recent years. Abnormal reflux index was defined as DeMeester score greater than 14.7 or Boix-Ochoa score greater than 12. The pH/impedance probe was placed during a gastroesophagoscopy and measurements were conducted for 24 hours.
Use of inhaled medication and history of pneumonia in the study population are presented in Table 1.

2.5 Statistical analysis

For descriptive statistics, the Fisher exact test was performed on qualitative variables and the Kruskal-Wallis rank sum test on quantitative parameters.

Univariate logistic regression and multiple stepwise logistic regression with impaired pulmonary function as outcome were performed. We included the following independent variables in the multiple regression: anastomotic leak, episodes of general anesthesia, extubation day, birth weight, age at follow up, and gross classification and used P value based selection. Abnormal reflux index was excluded from the main multiple regression model due to missing data in 12 cases but was added in a separate multiple regression model.
Statistical significance was set at values of $P < 0.05$. Statistical analyses were performed using R version 3.5.2 Copyright (C) 2018 The R Foundation for Statistical Computing with R Commander v 2.5-1 and the EZR v1.37 plug-in.

3 RESULTS

During the period from 1994 to 2013, 133 patients underwent EA repair at our unit. In total, 47 patients participated in the follow-up program between February 2014 and September 2018. Four patients were excluded from the multiple regression analysis; the pulmonary function of one patient could not be evaluated due to incomplete tests, one patient received a tracheostomy and two patients were considered outliers regarding episodes of general anesthesia (27 and 53 episodes). All patients underwent surgical repair with thoracotomy. Seven of the participants (14.9%) had long gap EA (Gross type A/B and a gap of three or more vertebral units). Five (10.6%) of them were reconstructed with delayed primary anastomosis, one (2.1%) with a gastric tube and one with gastric transposition. Gross C malformation was found in 38 participants (80.9%).

The median gestational age (GA) was 38 weeks and our cohort comprised 21 girls (45%) and 26 boys (55%). The median birth weight was 2.80 kg ($Q_1 = 1.99; Q_3 = 3.29$) and the median birth length was 48 cm ($Q_1 = 46; Q_3 = 50$). The infants were extubated on the second postoperative day ($Q_1 = 1; Q_3 = 3$). The median number of episodes of general anesthesia before the pulmonary function tests was 6 ($Q_1 = 2.5; Q_3 = 12$). Compared with the reference population the z-scores for birth weight and length were $-1.05$ ($-3.19; 0.03$) and $-0.81$ ($-2.05; 0.46$), respectively. The corresponding scores at follow up were $-0.24$ ($-1.09; 0.66$) and $-0.15$ ($-0.94; 0.68$), respectively. PFI was found in 19 patients (41%) and 16 of those patients (35% of total) had an obstructive component. Respiratory morbidity at follow up was found in 23 (52%, NA = 3) of the patients. Medical treatment with a combination of $\beta$-agonists and inhaled steroids were found in 19 patients. Two more patients received inhalatory medicines: one was treated with only $\beta$-agonist and one with only inhaled steroids.

The study population was divided into two groups according to age: 8-years old ($n = 25$) and 15-years old ($n = 22$). Patients' characteristics by age groups are presented in Table 1. There were no statistically significant differences between the age groups.

When the study population was grouped according to PFI, significantly lower birth weight, length, and GA were observed in the group with PFI compared with those who had normal pulmonary function. No difference, regarding respiratory morbidity was observed ($P = .157$). Patients' characteristics by pulmonary function are presented in Table 2. The pulmonary function of one patient could not be evaluated due to incomplete tests.

The percent of predicted values or z-scores for TLC, FEV$_1$ (both with Solymar et al$^{23}$ and GLI$^{13,15}$), FEV$_1$/VC, and FEV$_1$/FVC did not vary between the age groups; however FEV$_1$ and FVC were notably lower in both groups compared with the reference population (Table 3). The values for X at 5 Hz were significantly higher in group 15 compared with group 8 and the diffusion capacity of the lungs was lower than the reference population, particularly in the adolescent group (Table 3).

Both the univariate and multiple risk factor analyses showed an increased risk of PFI with decreasing birth weight. No other variable was significant in the univariate analysis (Table 4). The multiple risk factor analysis also showed increased risk for PFI for every additional year in age at follow up and a reduced risk for each episode of general anesthesia (Table 5). We found no correlation between impaired pulmonary function and abnormal reflux index ($n = 34$).

4 DISCUSSION

In the current study we found that PFI was common in children and adolescents after EA repair. The dominant pattern of PFI was airway obstruction. Restrictive ventilatory impairment was found in a minority of our subjects and only among the 15-year old patients. The risk for PFI increased with lower birth weight and older age at follow up. Respiratory morbidity was common both among 8- and 15-year old patients without any correlation with PFI. PFI affected a considerable proportion of our study population. Obstructive ventilatory impairment was the main cause of limitation of pulmonary function and was found in 35% of the study population, this lies within the range given by other studies of 12% to 57%.$^{8,11}$ Earlier studies have reported an association between obstructive ventilatory impairment in patients with EA and bronchial hyperresponsiveness comparable with asthma. However, only minor improvement was achieved after treatment with $\beta$-agonists.$^{8,18}$ Tracheomalacia is another condition that has been proposed as a cause behind obstructive ventilatory impairment.$^{10,17,31}$ However only five of the patients in our study underwent tracheobronchoscopy and four of them were diagnosed with tracheomalacia. The patients in this study underwent repair of EA before peroperative tracheobronchoscopy was routinely performed.

The restrictive ventilatory impairment of 12% in the current study was lower compared with other studies of 17% to 35%.$^{11,18}$ Congenital or acquired vertebral or chest wall abnormalities (i.e., scoliosis or postoperative rib fusions), surgical trauma, aspiration due to GER, and/or recurrent chest infections are all factors that have been associated with restrictive lung disease.$^{8,32}$ All patients in our study underwent thoracotomy. We found no relation between abnormal reflux index and PFI indicating that there are other factors involved in the restrictive impairment in our study population.

Impaired diffusion capacity was also found in a low proportion of our subjects, especially among the adolescents. There was a tendency towards lower diffusion capacity values in the adolescents compared with 8-year old children. Pedersen et al$^{18}$ also investigated the diffusion capacity of the lungs in children with EA and could not find a significant difference compared with healthy controls.

Changes in reactance were present to a larger degree in the adolescents than in the children. In theory, reactance can be affected by both peripheral obstruction$^{33}$ as well as restrictive disorder$^{33}$, which limits the conclusions that can be made from this observation.
Birth weight was identified as a variable influencing pulmonary function. This variable has strong correlation with GA and is likely a reflection of lung maturity at birth. Neonates with low GA have more pulmonary complications, such as broncho-pulmonary dysplasia, which in turn has been associated with impaired pulmonary function, both regarding obstructive disorder, suggesting involvement of small airways, and diffusion capacity.34 Similar findings were found for extremely preterm and extremely low birth weight infants with obstructive patterns at 8 and 18 years of age.35

The multiple risk factor analysis also identified age at pulmonary function test as being a risk factor for PFI. This is likely due to insufficient lung development at birth, but probably also impaired pulmonary growth during childhood. Impaired pulmonary growth during childhood was also suggested by our findings with a trend towards lower FEV1 and diffusion capacity, according to GLI, in the older group compared with the younger group. Among other factors, GER and recurrent pneumonia have been proposed as being processes that drive impaired pulmonary growth. In our study population, neither GER nor recurrent pneumonia were found to be risk factors, which is supportive of the results of Pedersen et al18 but in contrast to Dittrich et al.19 Larger series are needed to bring clarity to what drives the PFI in patients treated for EA.

### TABLE 2  Patients’ characteristics by pulmonary function (n = 46a)

|                                | Impaired pulmonary function (n = 19b) | Normal pulmonary function (n = 27) | P value |
|--------------------------------|-------------------------------------|-----------------------------------|---------|
| Birth length z-score (Q1; Q3)  | −1.69 (−5.61; −0.27)                | −0.20 (−1.52; 0.89)              | .018*   |
| Birth weight z-score (Q1; Q3)  | −2.02 (−5.14; −0.56)                | −0.93 (−1.50; 0.10)              | .02*    |
| Gestational age w (Q1; Q3)     | 37.9 (30.6; 38.7)                   | 38.6 (37.3; 40.3)                | .036*   |
| Female, n (%)                  | 11 (57.9)                           | 9 (33.3)                         | .135    |
| Gross, n (%)                   |                                     |                                   |         |
| A                              | 1 (5.3)                             | 4 (14.8)                         | .803    |
| B                              | 1 (5.3)                             | 1 (3.7)                          | ...     |
| C                              | 17 (89.5)                           | 20 (74.1)                        | ...     |
| D                              | 0 (0.0)                             | 1 (3.7)                          | ...     |
| E                              | 0 (0.0)                             | 1 (3.7)                          | ...     |
| Associated malformations, n (%)| 12 (63.2)                           | 12 (44.4)                        | .245    |
| VACTERL, n (%)                 | 3 (15.8)                            | 6 (22.2)                         | .716    |
| Major cardiac anomaly, n (%)   | 4 (21.1)                            | 2 (7.4)                          | .213    |
| Surgical method, n (%)         |                                     |                                   |         |
| PDA                            | 17 (89.5)                           | 20 (74.1)                        | .27     |
| DPA                            | 1 (5.3)                             | 5 (18.5)                         | .377    |
| GT                             | 1 (5.3)                             | 0 (0.0)                          | .413    |
| GTrans                         | 0 (0.0)                             | 1 (3.7)                          | 1       |
| H                              | 0 (0.0)                             | 1 (3.7)                          | 1       |
| Extubation day (Q1; Q3)        | 2 (1; 3)                            | 2 (1; 2.5)                       | NA = 1  |
| Anostomotic leak, n (%)        | 2 (10.5)                            | 3 (11.1)                         | 1       |
| Episodes of general anesthesia (Q1; Q3) | 4 (1.5; 10.5) | 7 (3; 13) | .066    |
| Weight follow up z-score (Q1; Q3) | −0.19 (−1.07; 0.73) | −0.48 (−1.01; 0.48) | .858    |
| Height follow up z-score (Q1; Q3) | 0.03 (−0.62; 0.74) | −0.30 (−1.19; 0.32) | .26     |
| Age at follow up (Q1; Q3)      | 14.50 (8.10; 15.45)                 | 8.40 (7.81; 14.92)               | .39     |
| Abnormal reflux index, n (%)   | 9 (56.2)                            | 11 (61.1)                        | 1       |
| Respiratory morbidity at follow up, n (%) | 7 (36.8) | 16 (66.7) | NA = 3  |
| Medical treatment              | 2 (10.5)                            | 8 (33.3)                         | ...     |
| Pneumonia                      | 1 (5.3)                             | 1 (4.2)                          | ...     |
| Both medical treatment and pneumonia | 4 (21.1) | 7 (29.2) | ...     |

Abbreviations: PDA, primary direct anastomosis; DPA, delayed primary anastomosis; GTrans, gastric transposition; GT, gastric tube; H, H-fistula; VACTERL, VACTERL association with at least three of the following conditions: vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities

*aThe pulmonary function of one patient could not be evaluated due to incomplete tests.

*bTwelve patients had an isolated obstructive impairment. One patient had isolated impairment of D_{LCO}. Two patients had both obstructive and restrictive impairment; two had obstructive and D_{LCO} impairment; and two patients had restrictive and D_{LCO} impairment.

*statistical significance.
The role of episodes of general anesthesia or mechanical ventilation in lowering the risk of PFI needs confirmation in larger series but could reflect a positive effect of mechanical ventilation on lung development (at the alveolar stage and the stage of microvascular maturation) and growth.

In contrast to others, we found no relation between Gross type/esophageal gap length, anastomotic leak, abnormal reflux index, longer periods in mechanical ventilation, and impaired pulmonary function. This could be explained by the limited number of patients and the results may change with the inclusion of more patients over time in the follow-up program.

A considerable proportion of patients in both age groups had respiratory morbidity at follow up, this finding has been described earlier by others, as well as its negative impact on quality of life.

### TABLE 3

| Parameter                        | Group 8 (n = 25) | Group 15 (n = 22) | P value |
|----------------------------------|-----------------|------------------|---------|
| TLC (% pred)                     | 100.44 (96.12; 109.67) NA = 13 | 94.49 (85.15; 102.81) NA = 2 | .15     |
| FEV1 (% pred)                    | 82.58 (71.25; 89.61) NA = 3 | 75.67 (65.83; 93.27) NA = 2 | .497    |
| FEV1 (% pred)                    | 88.84 (75.65; 96.03) NA = 2 | 73.14 (64.57; 94.36) NA = 2 | .08     |
| FEV1 (z-scores)                  | 0.90 (−2.00; −0.34) NA = 2 | −2.26 (−2.93; −0.47) NA = 2 | .093    |
| FEV1/FVC (% pred)                | 98.62 (91.31; 106.34) NA = 2 | 95.32 (87.14; 105.15) NA = 2 | .381    |
| FEV1/FVC (z-scores)              | 0.23 (−1.17; 1.12) NA = 2 | −0.69 (−1.60; 0.76) NA = 2 | .342    |
| FEV1/VC (% pred)                 | 98.02 (92.78; 101.83) NA = 2 | 96.06 (88.02; 105.14) NA = 2 | .472    |
| FVC (% pred)                     | 81.90 (70.91; 101.18) NA = 2 | 93.13 (75.36; 103.49) NA = 2 | .364    |
| FVC (% pred)                     | 86.39 (74.58; 99.23) NA = 2 | 83.93 (70.49; 93.85) NA = 2 | .401    |
| FVC (z-scores)                   | −1.11 (−2.12; −0.06) NA = 2 | −1.37 (−2.58; −0.54) NA = 2 | .276    |
| X5 (% pred)                      | 96.16 (84.22; 119.30) NA = 3 | 141.51 (92.94; 182.18) NA = 3 | .028*   |
| R5 (% pred)                      | 117.31 (105.53; 123.01) NA = 3 | 116.67 (105.13; 151.21) NA = 4 | .605    |
| R20 (% pred)                     | 111.18 (103.40; 122.87) NA = 2 | 115.87 (103.61; 155.62) NA = 4 | .198    |
| Resonant fr (% pred)             | 122 (113; 134) NA = 2 | 118.90 (106.72; 154.57) NA = 4 | .733    |
| DLCO (%)                         | 96.05 (92.92; 110.35) NA = 11 | 90.47 (81.65; 98.98) NA = 11 | .064    |
| DLCO (z-scores)                  | −0.22 (−0.41; 0.59) NA = 11 | −0.63 (−1.39; −0.07) NA = 11 | .051    |

Abbreviations: TLC, total lung capacity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; R, resistance; GLI, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; R, resistance; TLC, total lung capacity; X, reactance.

| Odds ratio 95% CI | P value |
|------------------|---------|
| Gross A/B vs C   | 0.47 (0.08-2.74) | .87 |
| Gross D vs C     | 0.00 (0.00-Inf) | ... |
| Gross E vs C     | 0.00 (0.00-Inf) | ... |
| Extubation Day 2-4 vs Day 1 (n = 45) | 1.82 (0.50-6.68) | .62 |
| Extubation Day 5+ vs Day 1 (n = 45) | 1.00 (0.14-7.10) | ... |
| Birth weight, kg | 0.35 (0.16-0.79) | .01* |
| Anastomotic leak | 0.94 (0.14-6.26) | .95 |
| Abnormal reflux index (n = 34) | 0.82 (0.21-3.22) | .77 |
| Episodes of general anesthesia (n = 43) | 0.89 (0.80-1.01) | .06 |
| Age at follow up | 1.10 (0.95-1.27) | .22 |
| Pneumonia (n = 43) | 0.71 (0.19-2.69) | .62 |

Note: Patients excluded from the risk factor analyses: the pulmonary function of one patient could not be evaluated due to incomplete tests, one patient received a tracheostomy and two patients were considered outliers regarding episodes of general anesthesia (27 and 53 episodes); 3 cases of missing data for pneumonia and 12 for abnormal reflux index.

Abbreviation: CI, confidence interval.

*statistical significance.
life,11,16,31,26,37 Our definition comprised the medical treatment of their respiratory symptoms and/or at least one episode of pneumonia during recent years. The majority of our patients classified as having respiratory morbidity were using inhaled medicine.

In the current study, neither pulmonary function nor respiratory morbidity improved in the older patients. This observation is contrary to other reports of improvement of clinical symptoms such as recurrent pneumonia and bronchitis over time.6 Furthermore, the multiple risk factor analysis identified age at pulmonary function test as a variable that increases the risk of PFI, indicating that the PFI is acquired or cannot be compensated to the same extent as the children grow. This is in contrast to earlier reports11 but supportive of more recent ones,18,19,21,31 indicating that the PFI does not improve over time.

When we analyzed the study population according to pulmonary function, there was no difference in respiratory morbidity between the group with normal pulmonary function and the group with impaired pulmonary function. This supports earlier reports16,19 on the lack of correlation between respiratory symptoms and PFI. Follow-up programs including pulmonary function tests seem to be required to detect and treat respiratory morbidity early, to try to prevent impairment in pulmonary function and improve HRQoL.

The main strength of this study was the assessment of pulmonary function and the relations between respiratory morbidity and PFI in an ongoing follow-up program according to a pre-established protocol in well-defined age groups of children and adolescents after EA repair which thus allowed us to compare the degree of PFI in different age groups. Another strength of the current study is that we incorporated the relatively recent GLI reference values for pulmonary function.13,15

A limitation of the current study is the relatively small study groups. However, the study population is within the upper range of previously published reports of pulmonary function testing after EA repair10-12,16-21,32 and represents patients recruited over a period of 6 years. Furthermore, the study population was representative of the EA-population in terms of patient characteristics, according to other reports.3,38,39 As our study is based on data from a clinical follow-up program that has to be feasible to be implemented, we were not able to include bronchial challenge test, imaging, or bronchoscopies.

5 | CONCLUSION

Respiratory morbidity and PFI were common in children and adolescents after EA repair. The major component of PFI was obstruction of the airways. The risk for PFI increased with lower birth weight and older age at follow up. The poor correlation between respiratory morbidity and PFI justifies the need of clinical follow up including pulmonary function tests in patients with EA.

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TABLE 5 Multiple stepwise logistic regression (n = 43)a

| Independent variable | Odds ratio  | 95% CI     | P value |
|----------------------|------------|-----------|---------|
| Episodes of general anesthesia | 0.84       | (0.72-0.98) | .025*   |
| Birth weight         | 0.30       | (0.11-0.77) | .012*   |
| Age at follow up     | 1.27       | (1.02-1.58) | .029*   |

Note: Four patients were excluded from the risk factor analyses. The pulmonary function of one patient could not be evaluated due to incomplete tests, one patient received a tracheostomy and two patients were considered outliers regarding episodes of general anesthesia (27 and 53 episodes).

Abbreviation: CI, confidence interval.

aThe dependent variable was impaired pulmonary function and the independent variables were: anastomotic leak, episodes of general anesthesia, extubation day, birth weight, age at follow up, and Gross classification.

*statistical significance.
