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Statistical modelling of survival for babies with oesophageal atresia☆,☆☆

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ABSTRACT

Aim of study: We examined variables associated with survival for oesophageal atresia between 1996 and 2014.
Methods: Possible explanatory variables: birth weight, gestation, cardiac anomalies (any or major), renal anomalies (any or severe), primary anastomosis, leak, secondary oesophageal surgery, tracheomalacia, aortopexy, tracheostomy, gastrostomy, fundoplication, karyotype, neurological status. Variables were assessed with logistic regression and a new model assessed with Kaplan–Meier graphs.
Results: 104/120 (87%) babies survived. Median gestation 37 weeks, 4 (3%) born before 28 weeks. Mean birth weight 2.3 (SD 0.7) kg, 17 (14%) less than 1500 g. Frequency (%) of explanatory variables: Major cardiac anomaly 21 (18%), any cardiac anomaly 48 (40%), severe renal anomaly 10 (8%), any renal anomaly 25 (21%), primary anastomosis 105 (88%), anastomotic leak 16 (13%), symptomatic tracheomalacia 28 (23%), aortopexy 17 (14%), tracheostomy 12 (10%), neurological anomaly 7 (6%), fundoplication 15 (13%), gastrostomy 30 (25%), secondary oesophageal surgery 8 (7%), abnormal karyotype 6 (5%). Multivariate analysis showed only renal (OR 0.04, 0.007 0.2) $p = 0.001$, cardiac (OR 0.1, 0.002 0.6) $p = 0.01$ and a primary anastomosis (OR 12.2, 1.8 81.6) $p = 0.01$ ($R2 = 0.48$), or major cardiac (OR 0.04, 0.007 0.29) $p = 0.001$ and severe renal anomalies (OR 0.009, 0.001 0.12) $p<0.001$ alone were significant ($R2 = 0.57$).
Conclusions: Survival is dependent on cardiac and renal anomalies. Birth weight is not significant. We propose a new classification system: 1: neither severe renal nor major cardiac anomaly, 2: either severe renal or major cardiac anomaly, 3: severe renal and major cardiac anomaly.

The survival rate of babies born with an oesophageal atresia with an associated tracheooesophageal fistula in a recent national survey is now 97% [1]. Waterston, reporting a 50% mortality in 1962, noted three variables which were associated with death: birth weight, additional congenital anomalies and presence of significant pneumonia [2]. The classification of babies into three categories based on these factors allowed a calculation of prognosis and comparison of outcome between centres. Advances in surgery and neonatal care made this classification redundant [3,4] and it was replaced in 1994 by the Spitz classification based more simply on birth weight and presence of major cardiac anomalies [5].

The aim of this study was to identify those variables associated with mortality in a contemporary population and to develop an alternative classification of babies born with oesophageal atresia to better stratify risk of mortality.

1. Methods

We identified a consecutive series of babies treated for oesophageal atresia over 18 years in our tertiary centre institution. We included all cases of oesophageal atresia with a tracheal fistula, and all cases of pure atresia without fistula, but excluded H type fistulas without atresia, since we believe these cases should have no mortality. Case note review was performed and the outcome was classified as survival or death.

Variables which we thought might be associated with survival were as follows: birth weight, gestation, major cardiac anomaly (which we defined as any congenital cardiac anomaly requiring surgery, including patent ductus arteriosus), minor cardiac anomaly (which we defined as any cardiac anomaly), severe renal anomaly (which we defined as either bilateral structural renal anomalies, or unilateral structural with elevated serum creatinine within one week of birth), any renal anomaly, neurological anomaly, chromosomal anomaly, the occurrence of anastomotic leak, whether a primary anastomosis was performed (which we defined as the performance of an oesophageal anastomosis at the first procedure, secondary oesophageal surgery (which we define as any procedure other than an initial oesophagooesophageal anastomosis usually either oesophageal replacement or resection of structured anastomosis), the presence of symptomatic tracheomalacia, the need for aortopexy, the use of a tracheostomy, the need for fundoplication and the use of a gastrostomy.

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Table 1
Table of anomalies in babies who died.

Child number	Cardiac anomaly	Renal anomaly	Other anomalies	Cause of death
1	VSD	Nil	Down's syndrome, duodenal atresia	Tracheomalacia
2	ASD. Small right ventricle. Dextrocardia. Abnormal drainage of SVC to left atrium	Single kidney with intrarenal reflux	Severe neurological impairment. Imperforate anus. Multiple vertebral and rib anomalies	Pulmonary hypertension
3	PDA ligated	Bilateral renal dysplasia	Cloaca. Hypothyroid. Long gap atresia with oesophagostomy	Not known
4	PDA. VSD	Nil	Necrotising enterocolitis	Klebsiella septicaemia
5	AVSD. PDA. Hypoplastic aortic arch	ATN	Gastric perforation	Sepsis
6	Nil	Right hydronephrotic kidney drained in utero at 25 weeks. Left multi-cystic dysplastic kidney		Pulmonary hypoplasia
7	Tetralogy of Fallot, double outlet right ventricle, pulmonary stenosis	Vesico-ureteric reflux		Tracheomalacia
8	Hypoplastic left heart	Nil		Died during cardiac surgery
9	Tetralogy of Fallot	Nil	Long gap atresia with oesophagostomy	Pulmonary hypoplasia
10	Nil	Renal failure	Long gap atresia. Fistula ligated only. Severe hydrocephalus. Ascites	Renal failure
11	Severe pulmonary trunk hypoplasia. VSD.	Bilateral renal dysplasia	Pulmonary hypoplasia. Imperforate anus. Limb anomalies. Vertebral anomalies	Care withdrawn
12	Nil	Single dysplastic kidney	Imperforate anus. Cleft palate. Structurally abnormal brain.	Care withdrawn
13	VSD	Nil	Diffuse lymphatic leak	Uncontrollable lymphatic losses
14	Tetralogy of Fallot	Nil	Limb and vertebral anomalies. Failed initial anastomosis	Post mortem inconclusive.
15	Nil	Bilateral renal dysplasia	Delayed primary anastomosis	Renal failure
16	PDA. Coarctation. Right ventricular hypertrophy. Aortic stenosis.	Absent right, hydronephrotic left kidney	Trisomy 20	Care withdrawn

PDA: patent ductus arteriosus, VSD: ventricular septal defect, SVC: superior vena cava AVSD: atrioventricular septal defect,

Table 2
Univariate analysis of possible influential variables on survival of babies with oesophageal atresia.

Variable	Survival	Odds ratio (95% CI)	p value*
Any cardiac anomaly	36/48 (75%)		
No cardiac anomaly	68/72 (94.5%)	0.17 (0.053 0.587)	0.005
Major cardiac anomaly	11/21 (52.4%)		
No major cardiac anomaly	93/99 (93.9%)	0.071 (0.022 0.233)	<0.001
Birth weight >1500 g	91/103 (87%)		
Birth weight < 1500 g	13/17 (76.5%)	0.429 (0.12 1.52)	0.19
Birth weight as a continuous variable		0.33 (0.14 0.77)	0.010
Any renal anomaly	15/25 (60%)		
No renal anomaly	89/95 (94%)	0.1 (0.032 0.32)	<0.001
Severe renal anomaly	2/10 (20%)		
No severe renal anomaly	102/110 (93%)	0.02 (0.004 0.1)	<0.001
Primary anastomosis	96/105 (91%)		
No primary anastomosis	8/15 (53%)	9.3 (2.74 31.7)	<0.001
Secondary oesophageal surgery	15/16 (94%)		
No secondary oesophageal surgery	97/104 (94%)	1 (0.1 9.4)	0.9
Symptomatic tracheomalacia	24/28 (86%)		
No symptomatic tracheomalacia	80/92 (87%)	0.9 (0.26 3.0)	0.86
Aortopexy	14/17 (82%)		
No aortopexy	90/103 (87%)	0.67 (0.17 2.66)	0.57
Tracheostomy	9/12 (75%)		
No tracheostomy	95/108 (88%)	0.41 (0.09 1.71)	0.22
Fundoplication	14/15 (93%)		
No fundoplication	90/105 (86%)	2.33 (0.28 19.07)	0.42
Gastrostomy	22/30 (73%)		
No gastrostomy	82/90 (91%)	0.26 (0.09 0.79)	0.018
Abnormal karyotype	4/6 (67%)		
Normal karyotype	100/114 (88%)	0.28 (0.05 1.65)	0.16
Abnormal neurology	5/7 (71%)		
Normal neurology	99/113 (88%)	0.35 (0.06 2)	0.24
Anastomotic leak	15/16 (94%)		
No anastomotic leak	89/104 (86%)	2.5 (0.3 20.5)	0.3
Gestation < =28 weeks	2/4 (50%)		
Gestation > 28 weeks	102/116 (88%)	0.13 (0.01 1.05)	0.05
Gestation as a continuous variable		0.8 (0.7 0.9)	0.005

* Wald p value.

We examined the effects of birth weight both as a continuous variable and as a dichotomous variable above or below 1500 g. We similarly examined gestation as a continuous and dichotomous variable, above and below 28 weeks.

For each patient we calculated both the Spitz criteria and the modified Spitz criteria [6].

Data were recorded on an access database, which we programmed to calculate Spitz criteria as follows: Original Spitz criteria: 1 birth weight >1500 g and either no or minor cardiac anomaly, 2 birth weight < 1500 g or major cardiac anomaly, 3 birth weight < 1500 g and cardiac anomaly major. Modified Spitz: 1 birth weight >1500 and cardiac anomaly either absent or minor, 2.1 birth weight < 1500 g and cardiac anomaly absent or minor, 2.2 birth weight >1500 g and cardiac anomaly major, 3 birth weight < 1500 g and cardiac anomaly major.

1.1. Statistical analysis

We constructed a statistical model using logistic regression analysis of the listed variables. Covariates with a Wald's p value ≤ 0.05 on univariate analysis were entered into multivariate analysis using a forced entry blockwise design. Variables which have previously been shown to be of prognostic significance (major cardiac anomalies and birth weight) were entered as the first block. Because of the collinearity between cardiac anomaly and major cardiac anomaly, and between renal anomaly and severe renal anomaly, the multivariate analysis was performed twice, using renal and cardiac anomalies, then severe renal and major cardiac. The two models so produced were compared using Nagelkerke's R^2 using this to decide on the best fit.

Variables which were significant on multivariate analysis were then used to construct a final model. The model was assessed for outliers and observations with unusual influence by examination of standardised residuals and calculation of Cooks distance. Collinearity was assessed by calculation of tolerance and variance inflation factor.

We then constructed further models using the Spitz and modified Spitz criteria, comparing them to the new model again using Nagelkerke's R^2.