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A scoring system to predict mortality in infants with esophageal atresia

A case–control study

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Abstract

Esophageal atresia (EA) is a rare anomaly that mandates surgical intervention. Patients with EA often have complicated medical courses due to both esophageal anomalies and related comorbidities. Although several prognostic classification systems have been developed to decrease the mortality rate in EA, most systems focus only on the influence of the major anomaly, and external risk factors that could be influenced by the neonatal caregivers to a certain extent are not included. The aim of this study was to investigate the risk factors for in-hospital mortality in neonates with EA and develop a scoring model to predict mortality.

In total, 198 infants with EA who were treated with surgical intervention at the Children's Hospital of Chongqing Medical University between March 2004 and June 2016 were included. The demographic information, clinical manifestations, laboratory testing, and outcomes during hospitalization were analyzed retrospectively. A predictive scoring model was developed according to the regression coefficients of the risk factors.

The mortality rate was 18.1% (36/198). In the univariate analysis, higher incidences of prematurity, low birth weight, long gap, anastomotic leak, respiratory failure, postoperative sepsis, respiratory distress syndrome, pneumothorax, and septic shock were found in the nonsurvivor group than in the survivor group ($P < .05$). In the logistic regression analysis, anastomotic leak (OR: 10.75, 95% CI: 3.113–37.128), respiratory failure (OR: 4.104, 95% CI: 2.292–7.355), postoperative sepsis (OR: 3.564, 95% CI: 1.516–8.375), and low birth weight (OR: 8.379, 95% CI: 3.357–20.917) were associated with a high mortality rate. A scoring model for predicting death was developed with a sensitivity of 0.861, a specificity of 0.827, a positive predictive value of 0.524, and a negative predictive value of 0.963 at a cutoff of 2 points. The area under the receiver-operating characteristic curve of the score was 0.905 (95% CI, 0.863–0.948, $P = .000$) for death from EA. The mortality rate increased rapidly as the scores increased, and all patients with scores ≥5 died.

Anastomotic leak, respiratory failure, postoperative sepsis, and low birth weight are independent risk factors for mortality in EA. Infants with a predictive score of 5 had a high risk of death.

Abbreviations: AUC = area under curve, CHD = congenital heart disease, EA = esophageal atresia, NRDS = neonatology respiratory distress syndrome, ROC = receiver-operating characteristic curve.

Keywords: congenital esophageal atresia, mortality, neonate, predictive scoring model, risk factors

1. Introduction

Esophageal atresia (EA) is a life-threatening congenital malformation of the esophagus that is associated with significant neonatal morbidity and mortality. The incidence of EA appears to be 1.27 to 4.55 per 10,000 live births.[1,2] Due to improvements in surgical techniques and neonatal intensive care, the mortality rate has recently decreased. In most current reports excluding neonates with lethal congenital anomalies, neonates with EA have an expected survival rate of more than 90%.[3,4] In addition to fatal malformations, factors such as prematurity,[3] low birth weight,[3–7] sepsis,[8–10] respiratory system complications,[6,8,11,12] anastomotic leak,[6,13] chromosome abnormality disorders,[14] low socioeconomic status, and delayed diagnosis [6] are associated with high mortality in EA.

To decrease the mortality rate in EA, several prognostic classification systems, including the Spitz et al,[15] modified Spitz,[7] Waterston,[16] and Matthew [17] classification systems, have been developed to guide diagnostic and treatment strategies. However, most of these systems only focus on the influence of major anomalies, such as major cardiac malformation and/or renal deformity, on the prognosis of EA, and external risk factors, such as sepsis and respiratory failure that could be influenced by the neonatal caregivers to a certain extent are not included. Undoubtedly, any efforts to reduce the incidence of the above-mentioned external risk factors may actually decrease the mortality rate in EA.

The aim of this study was to investigate the risk factors for in-hospital mortality in infants with EA without major cardiac and renal malformations and develop a predictive scoring system to

Editor: Jing Liu.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:32(e7755)

Received: 26 April 2017 / Received in final form: 20 July 2017 / Accepted: 24 July 2017

http://dx.doi.org/10.1097/MD.0000000000007755

assess the influence of external risk factors on the prognosis of EA, which could provide more effective treatment strategies in clinical practice.

2. Methods

2.1. Ethics statement

This retrospective case–control study was approved by the Institutional Review Board (IRB) of the Children's Hospital of Chongqing Medical University. The data were collected, reviewed, deidentified, and analyzed anonymously by the authors, and permission to use the data in the patient database was granted by the Ethics Committees of the Children's Hospital of Chongqing Medical University. The IRB/Ethics Committee waived the requirement for informed consent because of the anonymous data analysis and scientific purpose of the present study.

2.2. Study population and data collection

All infants with EA who were treated with surgical interventions at the Children's Hospital of Chongqing Medical University between March 2004 and June 2016 were preliminarily included. Infants who died before the surgical intervention or those with major cardiac malformations and/or renal defects were excluded from the present study. All medical records were reviewed to collect data regarding demographic information, clinical manifestation, laboratory testing, imaging examinations, treatment protocols, and outcomes during hospitalization.

The diagnosis of EA was based on the clinical manifestations and chest X-rays using air as the contrast in the proximal pouch to avoid aspiration of the contrast fluid (esophagography) or chest computed tomography with 3-dimensional reconstruction.[6,18] The classification of the EA anomalies was based on the Gross classification system.[18]

The gap length between 2 esophageal pouches was classified as a short gap (<1 cm or 1 vertebral body), an intermediate gap (1–3 cm or 1–3 vertebral bodies), or a long gap (>3 cm or 3 vertebral bodies).[6] Congenital heart disease (CHD) was diagnosed by 2-dimensional echocardiography performed by pediatric cardiologists who were also responsible for the categorization of the cardiac defects. Major CHD was defined as disease that might have an impact on the patient's well-being or the surgical course. CHD includes defects for which the likelihood of cardiovascular surgical intervention was high or anesthetic risk was greatly increased.[19,20] Minor CHD was defined as disease that was less likely to alter the surgical course or required no cardiovascular intervention in the near future.[19,20] The diagnosis of neonatology respiratory distress syndrome (NRDS) was primarily based on clinical findings, blood gas analysis, and chest radiography before pulmonary surfactant replacement therapy.[21] Sepsis was diagnosed according to the international criteria of the Centers for Disease Control for the diagnosis of neonatal sepsis.[22] All infants with sepsis had postnatal signs of sepsis and a positive blood culture from a sample of peripheral or central venous blood. Neonatal respiratory failure was diagnosed if the infant required intubation and mechanical ventilation.[23,24] We defined survival as an infant who was discharged and was able to effectively feed. The infants were divided into the survivor group and the nonsurvivor group, and the risk factors for mortality during hospitalization were compared between the 2 groups.

2.3. Statistical analysis

Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed data, such as gestational age and birth weight, are presented as the mean ± standard deviation (mean ± SD), and these data were analyzed using *t* tests as applicable. Skewed data are presented as the median and interquartile range (P_{25}–P_{75}); these data were analyzed using the Mann–Whitney *U* test as applicable. Classification data, such as the incidence of complications, were analyzed using the chi-square test or Fisher exact test. Statistical significance was established at $P < .05$. The risk factors for mortality were evaluated in a bivariate analysis, followed by a stepwise logistic regression. Different score values were developed for the variables according to their regression coefficients. A receiver-operating characteristic curve (ROC) was constructed, and the cutoff was determined based on the analysis. All data were analyzed using SPSS 13.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Baseline information

In total, 222 neonates with EA were admitted to the Children's Hospital of Chongqing Medical University. Eleven infants were excluded due to death before the surgical intervention, and the parents of 5 patients refused further treatment due to multiple congenital anomalies during the study period. In addition, 6 infants with major CHD (1 with tetralogy of Fallot, 1 with aortic stenosis, 2 with single atrium, and 2 with pulmonary artery stenosis) and 2 infants with severe renal defects were excluded. Therefore, 198 infants were further analyzed; of these infants, 120 (60.6%) were male, and 33 (16.7%) were preterm infants. Forty-nine patients were low birth weight infants (<2500 g); the age at admission was 1.69 (1–3.3) days of life.

The types of EA included types A (5.1%; n = 10), B (8.6%; n = 17), C (65.2%; n = 129), and D (21.2%; n = 42). A short gap was found in 12 (6.1%) cases, an intermediate gap was found in 172 (86.9%) cases, and a long gap was found in 14 (7.1%) cases. Other observed malformations are listed in Table 1. The majority of the anomalies were simple cardiovascular malformations, followed by anorectal anomalies.

The main combinations and complications included respiratory failure (21.2%, n = 42), pneumothorax or mediastinal emphysema (10.1%, n = 20), postoperative sepsis (6.1%, n = 12), anastomotic leak (4.5%, n = 9), neonatal respiratory

Table 1

Total number of associated anomalies in infants with esophageal atresia (n = 198).

Malformations	n, %
Cardiovascular malformations	141 (71.2)
ASD	54 (38.3)
PDA	20 (14.2)
VSD	1 (0.7)
PDA + ASD	58 (41.1)
ASD + VSD	5 (3.5)
PDA + ASD + VSD	3 (2.1)
Other anomalies	12 (6.0)
Anorectal anomaly	6 (50)
Bronchial stenosis	5 (41.7)
Intestinal malrotation	1 (8.3)

ASD = atrial septal defects, PDA = patent ductus arteriosus, VSD = ventricular septal defect.

distress syndrome (3.5%, n=7), pulmonary hemorrhage (1.5%, n=3), atelectasis (2.5%, n=5), bilirubin encephalopathy (1.5%, n=3), necrotizing enterocolitis (1%, n=2), and septic shock (1%, n=2).

All infants received surgical interventions. Of the 33 preterm infants, primary closure was delayed by 2 or 3 months in 7 infants because their gestational age was less than 37 weeks. Of the 14 infants with long gap EA, repair was performed using jejunal segments as a neo-esophagus in 12 cases within 7 days of hospital admission. For another 2 infants with long gap EA, the operation was delayed by temporizing with fistula ligation and gastrostomy tube placement because of prematurity, and an esophageal replacement operation was performed 3 months later. Infants with NRDS were treated by pulmonary surfactant. Other treatment protocols, such as the administration of antibiotics and intensive care therapy (cardio-respiratory support and transfusion of blood or blood products), were performed as necessary. The mortality rate while in the hospital was 18.1% (n=36), and among the infants whose birth weights were less than 2500 g, the mortality rate was 34.7% (17/49).

3.2. Identification of risk factors by univariate analysis

3.2.1. Prematurity, low birth weight, and a long gap were associated with a high mortality rate. The influence of gestational age, birth weight, and other demographic factors on the mortality rate are shown in Table 2. Compared with the incidence in the survivor group, a higher incidence of prematurity, low birth weight (<2500 g), and long gap length were found in the nonsurvivor group ($P<.05$). No significant differences in gender, age at admission, type of EA, incidence of asphyxia, anorectal anomalies, and bronchial stenosis were found between the 2 groups ($P>.05$).

3.2.2. Severe combinations and complications influenced the mortality rate. Table 3 shows the higher combinations, such as NRDS, found in the nonsurvivor group ($P<.05$); meanwhile, the higher complications of EA, such as respiratory failure, anastomotic leak, postoperative sepsis, pneumothorax, and shock, were also found in the nonsurvivor group ($P<.05$).

3.3. Determination of risk factors by logistic regression analysis

All significant variables identified by the univariate analysis were investigated further by a logistic regression analysis (forward stepwise). Table 4 shows that anastomotic leak, respiratory failure, postoperative sepsis, and low birth weight were associated with the high mortality rate in EA.

3.4. Development of the scoring system

To develop a scoring system for the mortality risk in EA, different score values were established for the variables according to their

Table 2

Influence of demographic factors on the mortality rate in infant with esophageal atresia (EA).

	Nonsurvivor group (n=36)	Survivor group (n=162)	Statistics	P
Variables	%(n), M (P_{25}–P_{75})			
Gender (male)	58.3 (21)	61.1 (99)	$\chi^2=0.095$	.758
Prematurity (<37 wk)	33.3 (12)	13 (21)	$\chi^2=8.8$	.003
Low birth weight (<2500 g)	47.2 (17)	19.8 (32)	$\chi^2=11.934$	.001
Asphyxia	8.3 (3)	3.7 (6)	$\chi^2=0.584$	.445
Age at admission, d	1.94 (1–3.43)	1 (1–2.75)	Z=0.92	.358
Atrial septal defect	72.2 (26)	58 (94)	$\chi^2=2.487$	.115
Ventricular septal defect	8.3 (3)	3.7 (6)	$\chi^2=0.584$	.445
Patent ductus arteriosus	38.9 (14)	41.4 (67)	$\chi^2=0.074$	.758
Type of esophageal atresia			$\chi^2=3.548$	.351
Gross A	2.8 (1)	5.6 (9)		
Gross B	11.1 (4)	8 (13)		
Gross C	75 (27)	63 (102)		
Gross D	11.1 (4)	23.5 (38)		
Long gap	16.7 (6)	4.9 (8)	$\chi^2=4.51$	.034
Anorectal anomalies	2.8 (1)	3.1 (5)	$\chi^2=0.000$	1.000
Bronchial stenosis	0	3.1 (5)		.587*

* Fisher exact value.

Table 3

Influence of severe combinations and complications on the mortality rate in esophageal atresia (EA).

Variables	Nonsurvivor group (n=36)	Survivor group (n=162)	χ^2	P
Respiratory failure, % (n)	52.8 (19)	14.2 (23)	26.232	.000
Sepsis after operation, % (n)	19.4 (7)	3.1 (5)	11.12	.001
Respiratory distress syndrome, % (n)	13.9 (5)	1.2 (2)	10.369	.001
Anastomotic leak, % (n)	22.2 (8)	0.6 (1)	26.903	.000
Atelectasis, % (n)	2.8 (1)	2.5 (4)		1.00*
Pulmonary hemorrhage, % (n)	5.6 (2)	0.6 (1)		.086*
Necrotizing enterocolitis, % (n)	2.8 (1)	0.6 (1)		.331*
Pneumothorax, % (n)	22.2 (8)	7.4 (12)	5.581	.018
Shock	5.6 (2)	0		.032*

* Fisher exact value.

Table 4

Independent risk factors of mortality in EA.

Variables	β	*P*	OR	95% CI	Range/grade	Scoring
Anastomotic leak	2.375	.000	10.75	3.113–37.128	Yes	3
					No	0
Postoperative sepsis	1.271	.004	3.564	1.516–8.375	Yes	2
					No	0
Respiratory failure	1.412	.000	4.104	2.292–7.355	Yes	2
					No	0
Birth weight <2500 g	2.126	.000	8.379	3.357–20.917	<1800 g	2
					1800–2500	1
					>2500 g	0
Score maximum						9

CI = confidence interval, EA = esophageal atresia, OR = odds ratio.

OR and 95% CI (Table 4). The infants were categorized into 3 groups based on their birth weight using the 1800 and 2500 g cutoff points in the Waterston classification systems,[16] and we further assigned the variable of birth weight with scores of 0, 1, and 2 based on the Waterston classification systems. The area under the ROC curve (area under curve [AUC]) of the score was 0.905 (95% CI, 0.863–0.948, $P = .000$) for death from EA (Fig. 1). At the cutoff point of 2, a sensitivity of 0.861, a specificity of 0.827, a positive predictive value of 0.524, and a negative predictive value of 0.963 were obtained using this model. To facilitate the application of this predictive model in the clinic, we categorized the infants with these risk factors into the following 3 groups: "low" risk group (≤1 score), "moderate" risk group (2–4 score), and "high" risk group (≥5 score). The mortality rate increased rapidly as the scores increased. The mortality rate was significantly higher in the "high" risk group (6/6, 100%) than that in the "low" (5/139, 3.6%) or "moderate" risk groups (25/53, 47.2%, $\chi^2 = 76.814$, $P = .000$). All the patients with scores ≥5 died.

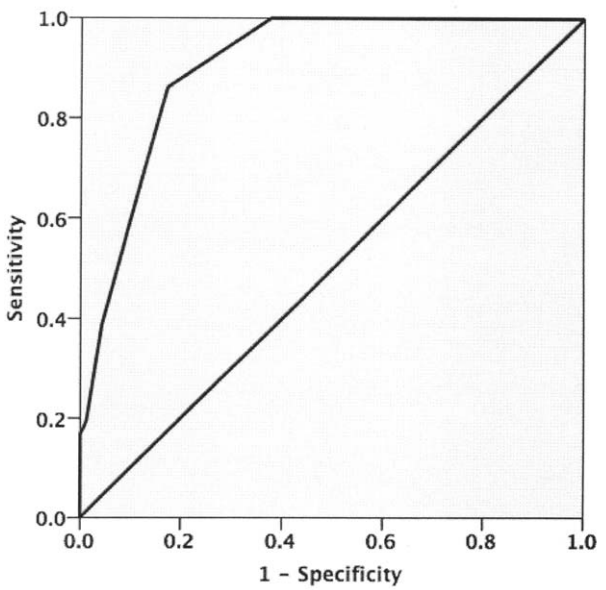

Figure 1. The receiver-operating characteristic curve.

4. Discussion

Many studies have indicated that CHD is the most common congenital malformation associated with EA,[3,15,25] and major CHD is considered an important risk factor for mortality in EA.[2,8,13] However, in a large sample survey conducted by Rokitansky et al.,[25] the most common malformations in neonates with EA were cardiac defects (23.3%, 72/309), and a majority of the defects were simple CHD (83.3%, 60/72). In a nationwide survey conducted in the United States, most cardiovascular malformations were also simple CHD.[3] Therefore, compared with the prevalence of complex CHD, simple CHD in EA infants is more common, and identifying the risk factors for mortality in EA infants without major CHD may provide useful strategies for the treatment of EA.

Anastomotic leak was identified as one of the risk factors for mortality in the present study. Anastomotic leak might increase the incidence of pneumonitis or sepsis and is associated with a higher mortality rate.[6] McKinnon et al[26] reported that only 20% of infants with anastomotic leaks survived. The incidence of anastomotic leak in EA patients after primary repair was observed in 9 (4.5%) patients, and 8 of these patients died in the present study. Anastomotic leaks occur in 10% to 20% of patients with EA.[6,7,27] Several factors are involved in the incidence of anastomotic leaks, including sepsis, poor suturing techniques, ischemia of the esophageal ends, friable lower segment, the type of suture, and excess anastomotic tension.[28,29] Therefore, there is no doubt that adequate preoperative assessments, superb surgical skills, and postoperative care may be helpful in reducing mortality in patients with EA.

Postoperative sepsis was also associated with a poor prognosis in the present study. This finding was consistent with other reports.[13,30] Another independent risk factor for mortality in the present study was respiratory failure, which was consistent with other findings.[4,26] Respiratory failure caused by gastric fluid reflux into the lungs could increase the risk of mortality.[6,30] A low birth weight has already been considered one of the substantial risk factors for mortality in many studies.[2–6] A birth weight less than 1500 g was considered one of the risk indicators in the prognostic classification system established by Spitz et al.[15] A nationwide investigation performed in 2014 indicated that a birth weight less than 1500 g remains an independent predictor of mortality in infants with EA in the United States, and the survival rate in infants whose birth weight was greater than 1500 g was more than 92%.[3] However, authors from developing countries have shown in their studies that birth

weight <2500 g remains a high risk factor, and babies with a birth weight <1.8 kg had the lowest survival rate.[6]

Birth weights of 2500 and 1800 g were used as cutoff points in the Waterston classification systems.[16] Among infants whose birth weight was less than 2500 g, the survival was only approximate 65%, and a low birth weight (<2500 g) significantly affects the mortality rate in EA patients in our study. Therefore, strengthening care in these patients is strongly recommended for decreasing their mortality.

In the present study, an effect of prematurity and NRDS on survival was not observed in the logistic regression analysis most likely because of their strong correlation with low birth weight, which continued to be an independent risk factor for increased in-hospital mortality ($P = .000$, OR: 8.379, 95% CI: 3.357–20.917). A long gap was also identified as a risk factor in the univariate analysis ($P = .034$) because it could increase the risk of anastomotic leak, which was associated with a higher mortality rate.[6,15] The long gap variable was excluded from further multivariate analysis perhaps because of its strong correlation with anastomotic leak in the present study. Our findings suggested that CHD was not associated with a poor prognosis, which is markedly inconsistent with other studies.[5,10–13] This inconsistency might be because all CHD defects were minor defects in the current study, and only major CHD defects, such as single atrium/ventricle and transposition of the great arteries, were considered risk factors.[5,10,11,13]

In the present study, we established a predictive scoring model by using logistic regression to quantify these risk factors. We further validated this model by using the ROC curve. It indicates that the predictive model has a low diagnostic value if the AUC is 0.5 to 0.7; the diagnostic value is moderate if the AUC is 0.7 to 0.9; and the diagnostic value is high if the AUC is greater than 0.9.[31] In this study, our model had a high predictive value because it had an AUC of up to 0.905 for predicting mortality. According to this predictive scoring model, higher scores represented more severe medical conditions, and the mortality rate increased rapidly as the scores increased. Therefore, we recommend applying this predictive scoring model to all infants with EA as a routine clinical practice. Infants with high scores should be prioritized for treatment and management.

The limitations of our retrospective study include inherent errors and bias. First, all patients had only minor CHD in the present study, which does not reflect the actual situations of EA. However, this study reflects the profiles of risk factors for mortality in those patients without major heart anomalies, and further studies focused on these factors might be necessary. Second, this study was conducted at a level III neonatal intensive care unit in a large tertiary teaching facility in Southwest China; therefore, the results might not be representative of all neonates with EA in China, and multicenter studies are recommended. Third, the infants with EA were not followed up after hospital discharge, which prevented us from determining the long-term outcomes of these babies, and large-scale research studies are also recommended in the future.

5. Conclusion

A low birth weight, anastomotic leak, respiratory failure, and postoperative sepsis were independent risk factors for poor outcomes. The latter 3 variables can be influenced, to some extent, by neonatologists. Notably, any efforts to reduce these risk factors may reduce the mortality rate in EA. Infants with high scores on this predictive scoring system should be given management and treatment priority.

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