ORIGINAL ARTICLE

Outcomes and prognostic factors for survival of children with oesophageal atresia

Andi Lestiono, MD[1], Aditya Rifqi Fauzi, MD[1], Nunik Agustriani, MD[1,2], Tunjung Wibowo, PhD[3], Gunadi, PhD[1]

[1]Pediatric Surgery Division, Deartment of Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia, [2]Pediatric Surgery Division, Department of Surgery, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Hospital, Surakarta, Indonesia, [3]Neonatology Division, Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia

ABSTRACT

Introduction: Oesophageal atresia (EA) is a life-threatening congenital oesophageal deformity that causes considerable newborn morbidity and death. Many prognostic variables have been linked to the survival of infants with EA, although the results of the studies are still conflicting. Furthermore, studies on EA effects in developing countries still need to be included. Here, we aimed to determine the survival of children with EA and link it to prognostic variables in a particular developing country.

Materials and Methods: A cross-sectional observational retrospective study was conducted using medical records of paediatric patients with EA at our institution from January 2014 to December 2020.

Results: A total of 53 children with EA were included in the study. Log-rank analysis showed that definitive surgery and thrombocytopenia were significantly associated with the survival of children with EA, with a p-value of 0.007 and 0.002, respectively, whereas, sex, EA type, pneumonia and sepsis were not (p = 0.898, 0.919, 0.255, and 0.499, respectively). Multivariate analysis revealed that thrombocytopenia and definitive surgery were strongly associated with the survival of children with EA with a p-value of 0.014 (hazard ratio (HR) = 2.67 [95% confidence interval (CI) = 1.22–5.85]) and 0.022 (HR =0.39 [95% CI = 0.17–0.87]), respectively.

Conclusion: Our study shows that thrombocytopenia might increase mortality, while definitive surgery might be beneficial for the survival of paediatric patients with EA. It implies that definitive surgery should be performed as early as necessary to prevent further morbidity and mortality. Our study comprehensively provides the survival of children with EA and links it to prognostic variables in a particular developing country. It serves as a potential research project that can be applied to the clinical setting to help clinicians manage EA better.

KEYWORDS:
Oesophageal atresia, prognostic factors, survival, thrombocytopenia, pneumonia, definitive surgery

INTRODUCTION

Oesophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a life-threatening congenital oesophageal deformity that causes considerable newborn morbidity and death. This abnormality occurs in one in every 2,500 to one in every 4,500 live births.[1] Over time, the treatment of EA with or without TEF has improved dramatically. Early diagnosis, better newborn critical care and anaesthesia and improved surgical methods have all contributed to this progress. As a result, the survival rate of these children is around 95% in developed countries when other serious congenital abnormalities do not accompany EA.[2–4] Unfortunately, the survival rate of infants with EA, with or without TEF, is not as favourable in developing countries. Prematurity, low birth weight and severe related congenital abnormalities have a proportionally higher impact on EA morbidity and mortality in developing countries due to a lack of adequate medical facilities.[5–7]

Several studies about the prognostic variables linked to the survival of infants with EA, including those from developing countries; however, have shown conflicting results.[5,8-10] This is why we have embarked on this study intending to examine the prognostic variables associated with a better survival of infants with EA in a developing country in Southeast Asia.

MATERIALS AND METHODS

Subjects

From January 2014 to December 2020, we conducted a cross-sectional observational retrospective study utilising the medical records of children with EA at our hospital. We examined 53 infants with EA who had surgery at our institution and had the ICD X code Q.39.1.[11] Incomplete medical records were an exclusion criterion.

The study was approved by the Institutional Review Board of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital (KE/FK/0963/EC/2020).

Prognostic Factors

We evaluated following prognostic factors for the survival of paediatric patients with EA: sex, birth weight, gestational age, associated anomaly, EA type, sepsis, thrombocytopenia

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Corresponding Author: Gunadi
Email: drgunadi@ugm.ac.id

Table I: Haematological score in neonatal sepsis

Haematological criteria	Abnormality	Score
Immature: Total neutrophil (I/T) ratio based on age	Increased	1
Neutrophil count	Increased or decreased	1
Immature: Mature neutrophil (I/M) ratio	≥ 0.3	1
Immature neutrophil	Increased	1
Leucocyte count		
• Decreased to ≤ 5,000/mm^3		
• Increased:		
√ At birth ≥25,000/mm^3		
√ 12-24 hours ≥30,000/mm^3		
√ Day 2 ≥21,000/mm^3	Increased or decreased	1
If degenerative neutrophils are present:		
• Vacuolisation or Dohle bodies		
√ 0 if not present		
√ 1+ if ≤ 25%		
√ 2+ if 25 to 50%		
√ 3+ if 51 to 75%		
√ 4+ if ≥ 75%		
• Toxic granulation		
√ 0 if normal granulation		
√ 1+ if few toxic granulations		
√ 2+ if 50% of the neutrophils contain dark granulation		
√ 3+ if most cells contain granulation		
√ 4+ if toxic granulation blurs nuclei	≥3+	1
Platelet count	≤ 150,000/mm^3	1

and pneumonia. Gestational ages were classified as preterm, at term and post-term.

Sepsis was defined as clinical sepsis in our hospital. Clinical diagnosis of neonatal sepsis is based on one or more signs/symptoms in at least four of the below listed groups of signs and symptoms:

a. General symptoms/signs: Ill-looking infant, infant refuses to drink, increase or decrease in body temperature, sclerema
b. Central nervous system: Lethargy, irritability, seizures
c. Cardiovascular system: Tachycardia, oedema, dehydration
d. Respiratory system: Dyspnoea, tachypnoea, cyanosis
e. Gastrointestinal system: Hepatomegaly, splenomegaly, abdominal distension
f. Haematological system: Jaundice, petechiae or bleeding, leukopenia,or the haematological score as follows: ≤ 2 very unlikely to be sepsis, 3-4 possible sepsis, ≥5 very likely to be sepsis (Table I)

Survival was defined as patients being discharged from the hospital alive or death before discharge from the hospital.

Statistical Analysis

The survival of neonates with EA was determined using a log-rank test, while the probabilities of children's survival were plotted using the Kaplan–Meier curve. The IBM SPSS Statistics version 24 (SPSS Chicago, USA) was utilised to perform all statistical analyses.

RESULTS

Baseline Characteristics

We evaluated 53 children with EA, with an overall survival rate of 18.9%. Most of them were male (52.8%), post-term (50.9%), low weight (52.8%), had thrombocytopenia (58.5%), sepsis (94.3%), pneumonia (90.6%) and had atresia with distal TEF (83%) (Table II).

Multivariate Analysis of Prognostic Factors for Survival of Children with EA

Multivariate analysis revealed that thrombocytopenia and definitive surgery were strongly associated with the survival of children with EA with a p-value of 0.014 (hazard ratio (HR)=2.67 [95% confidence interval (CI)= 1.22–5.85]) and 0.022 (HR=0.39 [95% CI=0.17–0.87]), respectively (Table IV).

DISCUSSION

Our study shows our EA children had a relatively low overall survival rate. Late diagnosis, delayed transport to tertiary care, and a lack of infrastructure are some of the causes of the high mortality rate in developing countries.[6,8,12] In contrast, the overall survival of EA patients in developed countries is 87%.[13] Some variables might have contributed to a high survival rate of children with EA, including advances in neonatal anaesthesia and intensive care and antibiotics.[12,13]

We reveal that thrombocytopenia is a strong prognostic factor for the survival of children with EA. In patients with sepsis, thrombocytopenia is caused by ingestion of platelets against direct pathogens and activation of pathogen-produced mediators, induction of apoptosis, lysis and increased clearance of phagocytes.[14] However, sepsis did not become a significant prognostic factor in our study. This finding is not compatible with previous studies that showed sepsis to be a strong prognostic factor for outcomes of children with EA.[8,15,16] Moreover, notably, thrombocytopenia can also be a surrogate marker for sepsis.

Table II: Baseline characteristics of children with EA in our institution

Characteristics	n (%)
Sex	
• Male	28 (52.8)
• Female	25 (47.2)
Weight at diagnosis (gram)	
• Normal weight (≥ 2500)	22 (41.5)
• Low weight (< 2500)	28 (52.8)
• Very low weight (< 1500)	3 (5.6)
• Extremely low weight (< 1000)	0
Gestational age	
• Preterm	15 (28.3)
• At term	11 (20.8)
• Post-term	27 (50.9)
EA type	
• Isolated EA without TEF (Gross A)	9 (17)
• EA with distal TEF (Gross C)	44 (83)
Thrombocytopenia (< 150,000/mm3)	
• Yes	31 (58.5)
• No	22 (41.5)
Pneumonia	
• Yes	48 (90.6)
• No	5 (9.4)
Sepsis	
• Yes	50 (94.3)
• No	3 (5.7)
Definitive surgery (oesophageal anastomosis)	
• Yes	17 (32.1)
• No	36 (67.9)
Outcome	
• Survived	10 (18.9)
• Died	43 (90.1)
Associated anomaly	
• VACTERL	27 (51)
• VACTERL, undescended testis	1 (1.9)
• VACTERL, Opitz G/BBB syndrome	1 (1.9)
• VACTERL, Down syndrome, clubfoot	1 (1.9)
• VACTERL, Meckel diverticulum	1 (1.9)
• VACTERL, hypospadias, undescended testis, left radial clubhand	1 (1.9)
• VACTERL, dextrocardia	2 (3.8)
• VACTERL, cholestasis	1 (1.9)
• Tracheomalacia	1 (1.9)
• No associated anomaly	14 (26.4)
• Unknown	3 (5.7)

EA: Oesophageal atresia; TEF: Tracheoesophageal atresia

Table IV: Multivariate analysis of survival of children with EA in our institution

Variables	HR (95% CI)	p-value
Sex	0.82 (0.42–1.63)	0.578
EA type	0.69 (0.23–2.02)	0.496
Thrombocytopenia	2.67 (1.22–5.85)	0.014*
Pneumonia	3.67 (0.84–16.04)	0.084
Sepsis	0.80 (0.12–5.41)	0.817
Definitive treatment	0.39 (0.17–0.87)	0.022*

*, $p < 0.05$; CI: Confidence interval; HR, hazard ratio; EA, oesophageal atresia

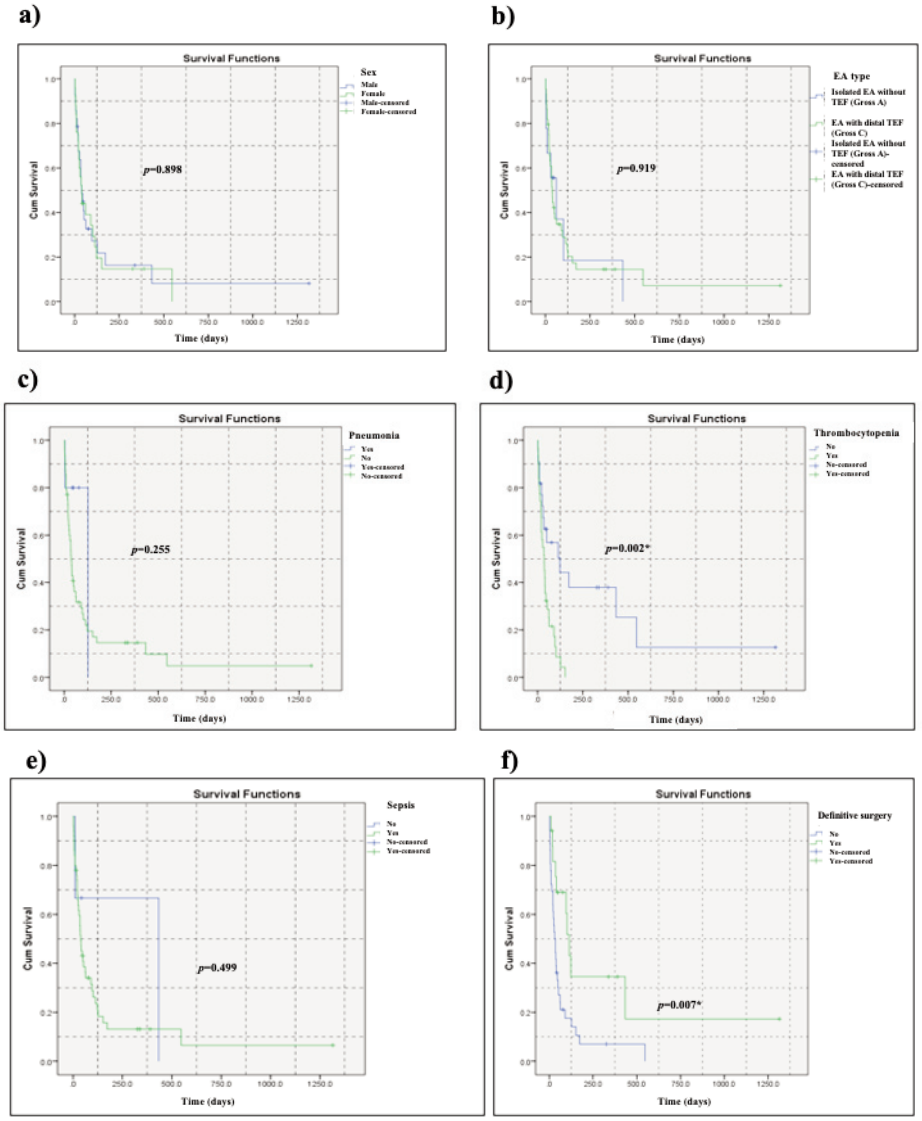

Fig. 1: Kaplan-Meier analysis for the association between prognostic factors: a) sex, b) EA type, c) pneumonia, d) thrombocytopenia, e) sepsis, f) definitive surgery, and EA patients' survival. A log-rank test showed that thrombocytopenia and definitive surgery had a significant association with the survival of EA patients, with a p-value of 0.002 and 0.007, respectively. Whereas, sex, EA type, pneumonia and sepsis were not (p = 0.898, 0.919, 0.255 and 0.499, respectively).

We fail to show pneumonia as a significant prognostic factor for the survival rate of children with EA which is different from previous study.[17] When air passes through the fistula, it causes stomach distension and subsequent reflux of gastric contents through the same TEF, causing aspiration pneumonia.[18] Airway abnormalities such as tracheomalacia, tracheobronchial malformations and lung hypoplasia, according to a previous study, contribute to recurrent respiratory exacerbations by impairing mucociliary transport.[19]

Interestingly, our finding shows that children with EA who underwent definitive surgery have a higher survival rate than subjects who did not undergo oesophageal anastomosis. However, previous reports revealed that definitive surgery did not affect the overall survival of EA patients.[6]

Our study provides new evidence of the association between the survival rate of EA patients with several prognostic factors, including thrombocytopenia and definitive surgery, from a particular developing country in Southeast Asia, Indonesia.

Several limitations have been noted in our study, including a single centre study, which would lead to an inadequate sample size. We also have difficulties analysing the long-term consequences of EA because of its retrospective design. In addition, we associated the outcomes of EA patients with prognostic factors according to overall means without considering other variables that might impact this association, including surgery experiences, late diagnosis and delayed transport to tertiary care.

CONCLUSION

Our study shows that thrombocytopenia might decrease the survival of children with EA, while definitive surgery might be beneficial for the survival of children with EA. It implies that definitive surgery should be performed as early as necessary to prevent further morbidity and mortality. Our study comprehensively provides the survival of children with EA and links it to prognostic variables in a particular developing country. It serves as a potential research project that can be applied to the clinical setting to help clinicians manage EA better.

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This study was approved by the Institutional Review Board of the Faculty of Medicine, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia (KE/FK/0963/EC/2020). Written informed consent was obtained from all parents who participated in this study. The research has been performed following the Declaration of Helsinki. Some results for the manuscript are from Andi Lestiono's thesis.

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