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Original Article

Comparison of Mortality Classifications and Prediction of Morbidity Risk Factors in Esophageal Atresia/Tracheoesophageal Fistula Patients

Özofagus Atrezisi/Trakeoözofageal Fistül Olgularında Mortalite Sınıflandırmalarının Karşılaştırılması ve Morbidite Risk Faktörlerinin Belirlenmesi

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ABSTRACT

Objective: The aim of the study is to compare the mortality rates in cases with esophageal atresia/tracheoesophageal fistula (EA/TEF) using Spitz and Okamoto prognostic classifications as the predictive power of the presence of major cardiac anomalies alone, and to reveal specific risk factor indicators predicting early-stage postoperative morbidities.

Method: Archive files of the patients with the diagnosis of EA/TEF admitted between between January 2000 and May 2020 were retrospectively reviewed. Archive files of the patients were reviewed in terms of their demographic information, disease characteristics, the surgeries they had undergone, postoperative outcomes, early complications, and morbidities developed during follow-up and secondary surgical interventions. Morbidities were divided into three groups as gastrointestinal, respiratory, and developmental complications.

Results: The Okamoto and Spitz classifications were valid in predicting mortality, but the Okamoto classification provided statistically more significant prognostic data. The presence of major cardiac anomalies alone was not significant in predicting mortality. All morbidities were found to be at a higher rate in cases with prematurity and in the presence of accompanying congenital syndrome. The time to removal of postoperatively inserted thoracic and nasogastric tubes, length of hospital stay, and duration of postoperative mechanical ventilation were positively correlated with the development of all morbidities. Anastomotic leakage and development of recurrent fistula were found to worsen especially respiratory morbidities. However, among all morbidities, long-gap EA was not a significant risk factor.

Conclusion: The presence of a major cardiac anomaly, regardless of birth weight, is insufficient to predict mortality. Although Okamoto and Spitz classifications remain valid for predicting mortality, Okamoto classification was a more powerful predictor of mortality. Knowing morbidity-specific risk factors for each of them will guide the follow-up of EA/TEF patients in order to reduce the incidence rates of gastrointestinal, respiratory, and developmental morbidities.

Keywords: Esophageal atresia, tracheoesophageal fistula, mortality, morbidity

ÖZ

Amaç: Bu çalışmanın amacı, özofagus atrezisi-trakeoözofageal fistül (ÖA/TÖF) tanılı olgularda, Spitz ve Okamoto mortalite sınıflamaları ile yalnızca majör kardiyak anomali varlığının mortaliteyi öngörmedeki yeterliliğinin karşılaştırılması ve erken postoperatif morbiditeyi öngören özgül risk faktörlerinin belirlenmesidir.

Yöntem: 2000-2020 yılları arasında ÖA/TÖF tanısı ile izlenen hastalar retrospektif olarak değerlendirildi. Demografik veriler, hastalık özellikleri, cerrahi süreç, postoperatif erken komplikasyonlar, morbiditeler ve sekonder cerrahi girişimler incelendi. Morbiditeler gastrointestinal, solunum ve gelişimsel olmak üzere üç grupta sınıflandırıldı.

Bulgular: Okamoto ve Spitz sınıflamalarının her ikisi de mortalite öngörüsünde geçerliliğini korumakla birlikte, Okamoto sınıflamasının prediktif gücünün istatistiksel olarak daha yüksek olduğu gösterildi. Sadece majör kardiyak anomali varlığı, mortaliteyi öngörmede belirleyici olmadığı görüldü. Prematürite ve eşlik eden konjenital sendrom varlığı, tüm morbiditeler ile anlamlı ilişkili bulundu. Postoperatif toraks tüpü ve nazogastrik sonda çekilme süresi, uzun hastanede yatış ve mekanik ventilasyon süresi tüm morbiditelerin gelişimiyle pozitif korelasyon gösterdi. Özellikle anastomoz kaçağı ve rekürren fistül gelişimi respiratuar morbiditeleri anlamlı düzeyde arttırdığı ortaya kondu. Bununla birlikte, tüm morbiditeler arasında uzun segmentli ÖA anlamlı bir risk faktörü olarak saptanmadı.

Sonuç: Majör kardiyak anomalilerin varlığı tek başına mortaliteyi öngörmek için yetersizdir. Okamoto sınıflaması, Spitz'e kıyasla daha güçlü olmakla birlikte her ikisi de mortalite öngörüsünde geçerlidir. Her bir morbiditeye özgü risk faktörlerinin bilinmesi, gastrointestinal, solunum ve gelişimsel morbiditelerin azaltılması amacıyla EA/TEF hastalarının takibine yön verecektir.

Anahtar kelimeler: Özofagus atrezisi, trakeoözofageal fistül, mortalite, morbidite

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INTRODUCTION

Esophageal atresia (EA) represents the most frequently observed congenital malformation of the esophagus, which occurs in 1/2500 to 1/4000 live births[1]. The most typical form of anomaly is characterized by proximal EA and distal tracheoesophageal fistula (TEF) in 85-88% of the cases[2]. Besides, 30-60% of the cases with EA/TEF were most commonly accompanied by cardiac (35%), vertebral, anorectal, renal, and extremity anomalies[1,2]. In these cases, the presence and severity of additional congenital anomalies are among the key determinants influencing both mortality and morbidity.

The principle of surgery in EA is to provide esophageal continuity by anastomosing the cut ends of the esophagus. The most accepted anatomical classification today is the Gross anatomical classification[2]. In terms of reducing and preventing mortality and morbidity in EA cases, it is important to correct the accompanying anomalies besides primary surgical repair.

In 1994, Spitz et al.[3] developed a mortality risk classification by categorizing patients into three risk groups according to their birth weights and the presence of major congenital heart disease (MCHD). Later in 2009, Okamoto et al.[4] re-evaluated and revised this classification dividing patients into four groups[3,4]. MCHD is defined as cyanotic or atrioventricular ductal and as well as left-to-right shunt pathologies that require surgery before the age of 1 year[3]. Finally, in 2020, Lazow et al.[5] reported that low birth weight was not a determining factor in mortality classification. The Spitz mortality classification allocated patients into low, medium, and high risk groups based on a birth weight limit of 1.5 kg and the presence of major cardiac anomalies[3]. In the Okamoto classification, the birth weight threshold was increased to 2 kg and patients were allocated into:low, medium, relatively high, and high risk groups depending on the presence of a major cardiac anomaly[4].

There isn't any accepted classification that predicts morbidity. However, Lazow et al.[5] presented male gender, prematurity, prenatal diagnosis, and the need for preoperative mechanical ventilation as markers for index admission morbidity.

Recent developments in neonatalogy and surgical technique have led to changes in causative factors that decrease mortality. However, the survival rates have increased, in parallel with a decrease in the incidence rates of late complications and morbidities.

Postoperative morbidities include respiratory problems, dysphagia; need for nutritional support; esophageal stricture; gastroesophageal reflux (GER); additional postoperative surgical interventions; enteral nutrition (tube feeding); need for gastrostomy as causative factors for gastrointestinal morbidity and developmental delay[6].

On esophagography, adequate anastomotic width, the absence of significant dilation in the proximal esophagus, and minimal peristaltic waves in the distal esophagus suggest the presence of a motility disorder. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines define benign refractory esophageal anastomotic strictures in children as strictures that cause dysphagia despite at least five dilations performed at intervals of no more than four weeks, in the absence of endoscopically observed inflammation[6,7]. Hospital readmissions due to pneumonia within the first two years following surgical repair are common, and patients experiencing two or more episodes are classified as having recurrent pneumonia[8]. During surgical procedures, a "long gap" is defined when, after mobilizing both esophageal segments, the distance between the two cut ends measures 2 cm or more, or exceeds the length of two thoracic vertebrae[9,10]. Secondary surgeries include anti-reflux procedures (most frequently Nissen fundoplication), gastrostomies, and gastric pull-up.

This study aims to evaluate the predictive power of the Spitz and Okamoto classifications, as well as the presence of major cardiac anomalies per se in foreseeing hospital mortality in patients with EA/TEF. Additionally, the study aims to identify individually independent risk factors for early postoperative morbidities by analyzing ample and detailed data regarding EA/TEF.

MATERIALS and METHODS

After obtaining Institutional Ethical Board of University of Health Sciences Turkey İzmir Dr. Behçet Uz Child Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee approval (approval number: 444, dated: 07.02.2020), data of 211 patients diagnosed with EA/TEF and treated primarily at our institution between January 2000 and May 2020 were retrospectively collected. Patients operated at external centers, misdiagnosed cases, those without accessible medical records, patients died before being operated, or had been followed up for less than two years were excluded from the analysis. The demographic

and basic clinical data related to the presence of prematurity polyhydramnios, a major or minor cardiac anomaly, the type of delivery, the gender of the patient and the concomitancy with either V- Vertebral anomalies (omurga anomalileri) A, Anal atresia, C, Cardiac defects, T, Tracheo-esophageal fistula, E,Esophageal atresia, R, Renal anomalies, L, Limb anomalies (VACTERL) or non-VACTERL syndromes (presence of two or more components associated with VACTERL) were collected. Data regarding disease characteristics and surgery performed, included type of EA (according to Gross classification A, B, C, D, E, and F), length of gap between esophageal cut ends, presence of esophageal elongation procedure, and postnatal age at operation (days). Data on the postoperative period encompassed duration of postoperative invasive mechanical ventilation; feeding with a nasogastric catheter (N/G); follow-up with a chest tube; time to the first oral feeding; first symptomatic stricture and dilation performed; need for prokinetic and inhaled medical treatment; presence of early complications (re-canalization of fistula or anastomotic leakage); total number of dilations perfomed; presence of GER; need for secondary operations (anti-reflux, colonic pull-through, gastric pull-up procedures); and long-term morbidity outcomes (follow up results are limited to two years because of high burden of immigrant patients).

Morbidities that occurred during follow-up period were divided into three groups as gastrointestinal (dysphagia, GER, anastomotic leak, anastomotic stenosis), respiratory (asthma-like symptoms, recurrent pneumonia, cyanotic spells), and developmental (nutritional supplement need, percentile growth charts) morbidities.

In the mortality group, patients who were diagnosed and operated upon during their first hospitalizations were included in the study. Deceased patients after discharge were not included. Patients were evaluated according to their birth weights, and the presence of MCHD (if any).

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation, median, and range (minimum-maximum) based on the distribution characteristics of continuous variables. Categorical variables were expressed as frequencies and percentages. The normality of numerical variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For comparisons between two independent groups, the Independent Samples t-test was applied to normally distributed variables, whereas the Mann-Whitney U test was used for non-normally distributed variables. The Pearson's chi-square test and Fisher's exact test were used to compare categorical variables between groups. Factors associated with mortality were examined through univariate logistic regression analysis. All statistical analyses and graphical outputs were performed using Jamovi (Version 1.6.3) and JASP (Version 0.13.1) softwares. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 152 patients who did not meet the exclusion criteria were included in the study. Data of 79 (52%) male, and 73 (48%) female patients were included in the statistical analysis. The mean birth weight, and birth age of the patients were 2509.7±653.2 g, and 37±2.7 weeks, respectively. An accompanying syndrome was detected in 87 (57.2%) patients, and morbidities of 74 (85.1%) syndromic patients were associated with VACTERL (Table 1). Ninety percent (n=136) of the cases had type C EA/TEF according to the Gross classification. The median hospital stay was 22 days.

Mortality

In our study, the index admission mortality rate for EA/TEF patients was found to be 25% (n=38).

The Spitz classification placed 65.8% (n=100) of the patients in the low mortality risk group. While 32.2% (n=49) of the cases were in the medium, and only 2% (n=3) of them in the high risk groups. Based on the Okamoto classification system, 53.3% (n=81), 16.4% (n=25), 23.0% (n=35), and 7.2% (n=11) of the cases were in the low, medium, relatively high, and high mortality risk groups, respectively (Table 2).

While statistical analysis confirmed the validity of both the Spitz and Okamoto mortality classifications, logistic regression analysis showed that the Okamoto classification exhibited greater predictive accuracy for mortality ($p<0.001$). The isolated presence of a major cardiac anomaly showed no statistically significant association with mortality prediction. ($p=0.156$) (Table 2).

Morbidity

The morbidity analysis was performed on 95 patients, excluding those with isolated TEF, esophageal web, and patients who died during the initial hospitalization. Early complications were observed in 27.1% of the patients, including recanalization of arteriovenous fistula (n=7) and anastomotic leakage (n=25). The esophagus-

Table 1. Patient demographics and basic clinical data	
	Numerical, and categorical variables
Gender, n (%)	
Male	79 (52)
Female	73 (48)
Mean (±SD) birth weight (g)	2509.7±653.2
Gestational age (weeks) (mean ±SD)	37±2.,7
Antenatal diagnosis, n (%)	9 (5.9)
Prenatal consultancy, n (%)	133 (87.5)
Polyhydramnios, n (%)	39 (25.7)
Family history of EA/TEF, n (%)	2 (1.3)
Prematurity, n (%)	36 (23.7)
Presence of a syndrome, n (%)	87 (57.2)
Syndromic entities, n (%)	
VACTERL	74 (85.1)
Others	13 (14.9)
Mortality, n (%)	38 (25)
EA type (Gross classification), n (%)	
A	9 (6)
C	136 (90.1)
E	6 (4)
Esophageal gap, n (%)	
Short	98 (75.4)
Long (>2 vertebrae, >2cm)	32 (24.6)
Gap Length (cm) (min-max)	1.5 (0.0-7.0)
Need of preoperative mechanical ventilation , n (%)	33 (21.7)
Age at the time of definitive surgery (days) median (min-max))	3.0 (0.0-90.0)
Anastomosis, n (%)	
Tension-free	121 (80.1)
Tensioned	30 (19.9)
Placement of thoracic tube, n (%)	148 (97.4)
Perioperative placement of nasogastric tube, n (%)	151 (99.3)
Lengthening procedure (myotomy/flap from upper pouch), n (%)	11 (7.2)
Bronchoscopy and esophagoscopy, n (%)	152 (100)
Time to thoracic tube removal (days), median (min-max)	8.0 (0.0-55.0)
Time to nasogastric tube removal (days) median (min-max)	12.0 (0.0-270.0)
Length of hospital stay (days) median (min-max)	22.0 (3.0-270.0)
Postoperative duration of mechanical ventilation (days) median (min-max)	6.0 (0.0-86.0)
Duration of noninvasive ventilation (days) median (min-max)	3.0 (0.0-10.0)
Time to the first postoperative oral feeding (days) median (min-max)	10.0 (3.0-100.0)
Gastrostomy, n (%)	15 (10.0)
Colonic transposition, n (%)	1 (0.7)
Gastric pull-up procedure, n (%)	6 (3.9)
Total oral feeding at discharge, n (%)	100 (87.7)

stomach-duodenum passage radiographs of only 4 cases revealed the existence of anastomotic stenosis, However, 52.7% (n=59) of patients manifested symptoms of anastomotic stenosis. Respiratory morbidities were detected in 57.7% of these patients.

Gastrointestinal Morbidities

Development of symptomatic anastomotic stenosis (56.8%), application of esophageal dilatation (60%), enteral tube feeding during follow-up (4.2%), presence of dysphagia (36.8%), and development of GER (54.7%) detected in respective percentages of patients were defined as gastrointestinal morbidities. Prolonged mechanical ventilation, delayed removal of the N/G and chest tubes, presence of associated syndromes, and long-gap EA were identified as statistically significant risk factors indicating gastrointestinal morbidities (p<0.001). Polyhydramniosis, prematurity, and long-gap atresia were found to be the risk factors for the development of GER (p<0,001) (Table 3).

Respiratory Morbidities

Respiratory morbidities were seen in 52.6% of patients. Prolonged mechanical ventilation, and hospital stay, delayed removal of the N/G and thorax tubes, early need for esophageal dilatation, and requirement for additional oxygen were statistically significant risk factors (p<0.001) (Table 4).

Developmental Morbidities

Developmental delay was detected in 4.2% of the cases during follow-up. Accompanying syndromic

Table 1. Continued

	Numerical, and categorical variables
Inhaler usage at discharge, n (%)	61 (55.0)
Early complications (anastomotic leak/fistula recanalization), n (%)	32 (27.1)
Esophageal dilatation, n (%)	57 (60)
Anastomotic stenosis, n (%)	54 (56.8)
Need for additional dietary supplements	87 (77.7)
Respiratory problems, n (%)	50 (52.6)
Dysphagia, n (%)	35 (36.8)
Gastroesophageal reflux, n (%)	52 (54.7)
Postoperative follow-up period (years) median (min-max)	5.0 (0.0-17.0)

EA/TEF: Esophageal atresia and tracheoesophageal fistula, VACTERL: Vertebral defects, A, Anal atresia, C, Cardiac defects, T, Tracheo-esophageal fistula, E,Esophageal atresia, R, Renal anomalies, L, Limb anomalies

Table 2. Mortality Data

	Survival status		**p-value**	**Odds ratio (95 % CI)**	**p-value*** **
	Survived (n=114)	**Deceased (n=38)**			
Major cardiac anomaly, n(%)					
None	83 (72.8)	23 (60.5)	0154*	1.75 (0.81-3.77)	0.156
Present (Ref.)	31 (27.2)	15 (39.5)			
Okamoto risk classification, n(%)					
Low risk (Ref.)	69 (60.5)	12 (31.6)			
Medium risk	14 (12.3)	11 (28.9)	<0001*	4.52 (1.66-12.28)	**0.003**
Relatively high risk	29 (25.4)	6 (15.8)		1.19 (0.41-3.47)	0.751
High risk	2 (1.8)	9 (23.7)		25.87 (4.97-134.77)	**<0.001**
Spitz risk classification, n(%)					
Low (Ref.)	80 (70.2)	20 (52.6)	0007**		
Medium	34 (29.8)	15 (39.5)		1.76 (0.81-3.85)	**0.154**
High	0 (0)	3 (7.9)		N/A	

Ref.: Reference, *: Pearson's chi-square test, **: Fisher-Freeman-Halton test, ***: Logistic regression test, CI: Confidence Interval, N/A: Not applicable

anomalies, prolonged postoperative mechanical ventilation, delayed removal of the N/G and chest tubes, and extended hospital stay were determined to be significant risk factors (p<0.001). Prematurity, gastroesophagel reflux and cardiac anomalies did not demonstrate a statistically significant association with developmental morbidities (p>0.001) (Table 5).

Secondary Surgical Interventions

Forty percent of the patients in the study group required secondary surgery. While anti-reflux (Nissen fundoplication) was the most common surgical intervention performed, 14 patients underwent gastrostomy, and 4 cases underwent both procedures. A gastric pull-up procedure was performed in six patients (Table 6).

Table 3. Gastrointestinal morbidities

	None	Present	p-value
	Anastomotic stricture		
Duration of postoperative mechanical ventilation (days) median (min-max)	4 (0-68)	6 (0-60)	**0.050****
Anti-reflux procedure, n (%)	6 (15)	19 (35.2)	**0.026***
	Esophageal dilation		
Duration of postoperative mechanical ventilation (days) median (min-max)	4 (0-68)	6 (0-60)	**0.026****
Anti-reflux procedure median (min-max)	5 (13.2)	20 (35.1)	**0.017***
Presence of a gap between esophageal cut ends, n (%)	28 (73.7)	52 (91.2)	**0.044***
Gap length, n (%)			
Short Long	23 (82.1) 5 (17.9)	41 (78.8) 11 (21.2)	0.953*
	Dysphagia		
Total number of dilations median (min-max)	0 (0-6)	3 (0-16)	<0.001**
Presence of accompanying syndrome, n (%)	20 (33.3)	22 (64.7)	0.003*
Gap length, n (%)			
Short Long	37 (78.8) 10 (21.3)	26 (81.3) 6 (18.8)	0.784*
Gender, n (%)			
Male Female	36 (60) 24 (40)	11(32.4) 23 (67.6)	**0.010***
Prematurity, n (%)	8 (133)	4 (11.8)	0.999*
	Gastroesophageal reflux		
Polyhydramnios, n (%)	16 (37.2)	8 (15.4)	**0015***
Prematurity, n (%)	10 (23.3)	2 (3.8)	**0005***
Cardiac anomalies, n (%)	38 (88.4)	49 (94.2)	**0461***
Accompanying syndromes, n (%)	18 (41.9)	25 (48.1)	**0545***
	Need for enteral tube feeding		
Time to thoracic tube removal (days) median (min-max)	7 (2-55)	21.5 (13-23)	**0.003****
Time to nasogastric tube removal (days) median (min-max)	10 (0-270)	112.5 (40-251)	**0.002****
Length of hospital stay (days) median (min-max)	24 (8-270)	121.5 (60-251)	**0.004****
Duration of postoperative mechanical ventilation (days) median (min-max)	5 (0-68)	39 (26-60)	**0.001****
Time to the first postoperative oral feeding (days) median (min-max)	10 (0-65)	35 (0-72)	**0.161****
Time to the first esophageal dilation (months) median (min-max)	5 (1-96)	1.5 (0.5-3)	**0.027****
Presence of accompanying syndromes, n (%)	39 (42.9)	4 (100)	**0.039***

*: Pearson chi-square or Fisher's exact test, **: Independent samples t-test, ***: Mann-Whitney U test

DISCUSSION

Improvements in neonatal intensive care, advancements in surgical methods, and preoperatively applied technical innovations, combined with multidisciplinary postoperative follow-up, have been shown to enhance survival rates and quality of life in these patients.

The male-to-female patient ratio in our study was determined to be 1.08, which is consistent with the literature[11]. We observed polyhydramnios in 39 cases (25.7%) during antenatal follow-ups, whereas Lazow's[5] study reported a higher rate (31.2%) of polyhydramnios. Leibovitch's[11], 21-year retrospective study revealed a prematurity rate of 36.2% in their cases, while Sulkowski's[12] national cohort discosed a prematurity rate of 37% in EA/TEF cases. However, our study found a lower prematurity rate of 23.7% in comparison with previously published data. This discrepancy may be attributed to differences in referral patterns, regional variations in perinatal care, and the characteristics of the study population.

Thanks to modern advancements in mechanical ventilation and monitoring protocols in neonatal

Table 4. Respiratory morbidities

	None	Present	p-value
Birth weight (g) (mean ± SD)	2569.1±540.9	2730.7±628.3	0.191***
Age at surgery (days), median (min-max)	2 (1-20)	3 (0-85)	0.160**
Time to thoracic tube removal (days) median (min-max)	7 (2-17)	8 (3-55)	0.037**
Time to nasogastric tube removal (days) median (min-max)	10 (0-31)	12 (3-270)	**0.037****
Length of hospital stay (days) median (min-max)	20 (8-115)	33.5 (8-270)	**0.004****
Duration of postoperative mechanical ventilation (days) median (min-max)	3 (0-26)	6 (0-68)	**0.014****
Time to the first postoperative oral feeding (days) median (min-max)	10.5 (1-60)	3.5 (0.5-96)	**0.050****
Total duration of postoperative O_2 requirement (days) median (min-max)	6.5 (3-28)	9.5 (2-98)	**0.036****
Cardiac anomalies, n (%)			
Minor **Major**	30 (71.4) 12 (28.6)	30 (71.4) 12 (28.6)	0.999*
Gender n (%)			
Male Female	26 (59.1) 18 (40.9)	22 (45.8) 26 (54.2)	0.204*
Prematurity n (%)	5 (11.4)	7 (14.6)	0.647*
Accompanying syndromes n (%)			
VACTERL Others	19 (86.4) 3 (13.6)	17 (85) 3 (15)	0.999*
EA type (Gross classification) n (%)			
A C	1 (2.3) 43 (97.7)	5 (10.4) 43 (89.6)	0.206*
Gap length n (%)			
Short Long	33 (82.5) 7 (17.5)	28 (75.7) 9 (24.3)	0.461*
Early complications (anastomotic leak/fistula recanalization) n (%)	8 (18.2)	16 (33.3)	0.098*
Anti-reflux procedure, n (%)	10 (22.7)	15 (31.3)	0.359*
Preoperative need for mechanical ventilation, n (%)	7 (15.9)	6 (12.5)	0.639*
Inhaler need at discharge, n (%)	4 (9.1)	40 (83.3)	**<0.001***
Antisecretory need at discharge, n (%)	4 (9.1)	40 (83.3)	**<0.001***
Gastroesophageal reflux, n (%)	19 (43.2)	30 (62.5)	0.064*

*: Pearson chi-square or Fisher's exact test, **: Independent samples test, VACTERL: Vertebral defects, A, Anal atresia, C, Cardiac defects, T, Tracheo-esophageal fistula, E,Esophageal atresia, R, Renal anomalies, L, Limb anomalies, EA: Esophageal atresia

intensive care units, low and/or very-low-birth-weight patients can survive at a higher rate. In 1994, Spitz modified the risk classifications based on the presence of cardiac anomalies and birth weight, and since then, it has been recognized as the most frequently preferred prognostic classification system[2]. In 2009, Okamoto introduced a new prognostic classification, emphasizing that major cardiac anomalies serve as a more reliable predictor of survival compared to low birth weight. In the literature various index admission mortality rates have been reported for patients with EA/TEF by Okamoto et al.[4] (19.8%), Leibovitch et al.[11] (13.8%), Lazow et al.[5] (5.1%). In our study, the overall index admission mortality rate for EA/TEF patients was found to be higher, at 25%. The higher prevalence of accompanying major cardiac anomalies and late presentation of high burden of immigrant patients escaping from the war prevailing in the Middle East countries could explain the relatively high mortality rates observed in our clinic. An analysis of recent data reveals a decline in mortality rates, decreasing to 20% over the past decade and further reducing to 14.8% in the last five years. The diversity in mortality rates observed in this study and the literature raises questions about the validity of the defined classifications and the importance of the presence of cardiac anomaly regardless of birth weights. We conducted a regression analysis to confirm our hypothesis that being low birth weight is a less important factor for the prediction of survival. In our study we have considered the presence of major cardiac

Table 5. Developmental morbidities

	None	Present	p-value
Birth weight (g) (mean ±SD)	2690.5±536.6	2639.9±595.8	0.732***
Age at surgery (postnatal days) median (min-max)	3 (1-20)	21.5 (13-23)	0.930**
Time to thoracic tube removal (days) median (min-max)	7 (2-55)	112.5 (40-251)	**0.003****
Time to nasogastric tube removal (days) median (min-max)	10 (0-270)	121.5 (60-251)	**0.002****
Length of hospital stay (days) median (min-max)	24 (8-270)	21.5 (13-23)	**0.004****
Duration of postoperative mechanical ventilation (days)	5 (0-68)	39 (26-60)	**0.001****
Time to first postoperative oral feeding (days) median (min-max)	10 (0-31)	10 (0-72)	0.552**
Cardiac anomalies, n (%)			
Minor Major	14 (73.7) 5 (26.3)	48 (70.6) 20 (29.4)	0.792*
Gender, n (%)			
Male Female	12 (60) 8 (40)	36 (48) 39 (52)	0.34*
Prematurity, n (%)	3 (15)	9 (12)	0.712*
Presence of accompanying syndrome, n (%)	5 (25)	38 (50.7)	**0.04***
Associated anomalies, n (%)			
VACTERL Others	3 (60) 2 (40)	33(86.8) 5 (13.2)	0.180*
EA type (Gross classification), n (%)			
A C	3 (15) 17(85)	3 (4) 72 (96)	0.105*
Gap length, n (%)			
Short Long	12 (75) 4 (25)	52 (81.3) 12 (18.7)	0.727*
Early complications (anastomotic leak/ fistula recanalization), n (%)	21(23.1)	3 (75)	**0.048***
Anti-reflux procedure, n (%)	4 (20)	21(28)	0.470*
Preoperative need for mechanical ventilation, n (%)	6 (30)	8 (10.7)	0.068*
Gastroesophageal reflux, n (%)	11(55)	41(54.7)	0.979*

*: Pearson chi-square or Fisher's exact test, **: Independent samples test,***: Mann-Whitney U test, VACTERL: Vertebral defects, A, Anal atresia, C, Cardiac defects, T, Tracheoesophageal fistula, E,Esophageal atresia, R, Renal anomalies, L, Limb anomalies, EA: Esophageal atresia

Table 6. Secondary surgical interventions	
	n (%)
Gastrostomy	14 (9.2)
Anti-reflux procedure	25 (16.4)
Colonic transposition	1 (0.7)
Gastric pull-up	6 (3.9)

disease alone to assess the predictive power of the Spitz and Okamoto mortality risk classifications. The results showed that both the Spitz and Okamoto mortality risk classifications remain valid for EA/TEF patients treated at our hospital, but the Okamoto classification was more effective in predicting mortality. Furthermore, it was found that the presence of a major cardiac anomaly alone, independent of birth weight, was not an adequate predictor of mortality in these patients, differing from the findings reported by Lazow et al[5]. After analyzing the results, we have confirmed that birth weight remains a significant factor in predicting risk of mortality among EA/TEF patients. Our study population of 152 cases consisted of 2 extremely low birth weight, 14 very low birth weight, and 80 low birth weight patients. Although the prematurity rate in our study (23.7%) was lower than those reported in other series, the presence of low birth weight should be emphasized as a significant predictor of mortality.

In our study, major cardiac disease was present in our 46 (30.2%) patients. In their study Lazow et al.[5] reported major cardiac anomalies in 20.9% of their cases. The literature demonstrates that associated anomalies occur in 30-70% of cases with EA/TEF. In Sulkowski's[12] national cohort, 83.5% of the cases had been reported to have at least one accompanying anomaly. In our study, 87 (57.2%) patients had accompanying syndromes. Among these anomalies, 85% of them were VACTERL associations.

Although significant progress has been made in preoperative and postoperative management, along with advancements in surgical techniques used for the treatment of EA/TEF, both early and long-term gastrointestinal, respiratory, and developmental morbidities continue to be reported. To better predict the course of clinical outcomes in this patient group, potential neonatal, preoperative, intraoperative, and postoperative risk factors for the development of complications were evaluated. Since the disease is an anatomical defect affecting the functional and anatomical integrity of the gastrointestinal system, all cases had morbidities related to the gastrointestinal system.

In our study, we observed long-gap EA in 24.6% (n=32) of cases. considerably higher than those reported in the literature (i.e., Spitz et al.[13], 9.4%, and Lazow et al.[5] 12.6%). However, long-gap EA wasn't a statistically significant predictive factor for postoperative morbidity, as expected.

Anastomotic stricture and esophageal dysmotility are common complications that develop following surgical repair. Stricture and dysmotility often indicate significant morbidity, requiring repeated interventions and multiple dilatations before achieving a satisfactory outcome. Approximately 50% of cases with EA/TEF require esophageal dilations[14]. In our study, 55.3% of patients underwent esophageal dilations.

Various studies have reported the incidence of postoperative anastomotic stricture—despite the lack of a universally accepted definition—to range between 17% and 60%[15]. In the present study, its incidence was identified as 52.7%.

Between 53% and 92% of the patients with EA/TEF experience dysphagia during the postoperative period[16]. Dysphagia occurred in 35.8% of patients in our cohort, representing a lower incidence compared to prior reports in the literature. Factors identified as significant contributors to gastrointestinal morbidities included polyhydramnios, prematurity, associated syndromic anomalies, prolonged hospitalization, the esophageal gap length (regardless of its size), extended duration of postoperative mechanical ventilation, prolonged retention of the N/G and chest tubes, and the need for early esophageal dilatation.

Respiratory problems in cases of EA/TEF encompass many underlying mechanisms that begin to take effect in the early years of life. Therefore, early detection and treatment of pulmonary morbidity are important to prevent development of pulmonary dysfunction and serious long-term complications. Generally, respiratory problems in the early period, seen in about 10-20% of the cases, develop due to anastomotic leakage, recurrent fistula, and anastomotic stricture[9]. In our study, early stage complications (recurrent fistula and anastomotic leakage) were present in 27.1% of our cases.

We found that having other concomitant health problems, significant delay in removing both N/G catheter and chest tubes following surgery, prolonged hospital stay and postoperative mechanical ventilation, requirement for esophageal dilation at an early stage, and inhaler drug requirement after discharge were risk

factors for developing respiratory morbidities. Lazow et al.[5] reported that preoperative mechanical ventilation was required in 14.6% of their patients, whereas our study revealed a higher rate of 21.7%. Chetcuti and Phelan.[17] found that respiratory problems affected 46% of EA/TEF cases, both in the short and long-term (1-37 years of age). In the short term, we observed respiratory morbidity in 57.7% of our patients. In our study, developmental retardation was observed at a rate of 78.9%, exceeding the rates previously reported in the literature. In Leibovitch's[11] study, developmental retardation was observed in 41.3-43.5% of cases within the first two years of life, and it was shown that with advancing age, this developmental delay disappeared, and these patients caught up with their peers in the age range of 16-21 years. Consistent with risk factors for respiratory morbidities, the presence of syndromic anomalies, prolonged postoperative mechanical ventilation, delayed withdrawal of N/G catheters and chest tubes, recurrence of fistula or anastomotic leakage in the short term, and prolonged hospitalization were identified as contributing factors of growth retardation during the first two years of follow-up.

Published studies have shown that the incidence rates of GER in individuals with EA/TEF range from 34% to 58%[16,18-20]. Our study detected GER in 52.3% of cases, in line with the literature. In our clinic, although 52.3% of operated cases of EA/TEF had GER, half of these patients responded to medical treatment. A secondary surgical intervention was performed in 40% (n=38) of patients postoperatively. Anti-reflux surgery was the most common procedure which was performed on 48% of patients with GER disease. In 23% of cases, gastrostomy was performed, while anti-reflux surgery combined with gastrostomy surgery was performed in 10% of cases. Besides, 7.8% (n=3) of cases underwent a gastric pull-up surgery.

Study Limitations

A key limitation of our study is its retrospective design covering 20 years, during which evolving medical and surgical practices resulted in formation of a heterogeneous study population. Secondly, the study relies on data obtained from medical record files. It was observed that all operated cases were not consistently followed up at our clinic. Therefore, considering the average durations of follow-ups, the results of the patients' two-year follow-ups have been taken into account for evaluation.

In this study, it was proven that having a major cardiac anomaly alone, regardless of birth weight, was not sufficient to predict mortality in patients with EA/TEF. Regression analysis demonstrated that the currently used mortality classifications separately proposed by Spitz and Okamoto were still valid; however, the Okamoto classification was more powerful in terms of mortality prediction.

By elaborating postoperative gastrointestinal, respiratory, and developmental morbidites in cases with EA, specific risk factors for predicting each of these morbidities have been revealed in detail.

CONCLUSION

In conclusion, the risk factors predicting all three morbidities have been identified as the presence of polyhydramnios, prematurity, associated syndromes, prolonged duration of postoperative mechanical ventilation and hospital stay, delayed removal of the N/G and chest tubes, and the need for early esophageal dilation. Anastomotic leakage, recurrent fistula development, and the requirement for inhaler therapy at discharge were found to increase, especially respiratory morbidities. Nevertheless, the long gap between esophageal cut ends wasn't a significant risk factor among all morbidities.

Identifying these risk factors in patients with EA/TEF will assist in counseling families during the neonatal period. Early identification of potential morbidities and prompt initiation of treatment may improve the quality of life of these patients.

Ethics

Ethics Committee Approval: Institutional Ethical Board of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee approval with approval number: 444, dated: 07.02.2020.

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept: A.E.B., M.H., Design: A.E.B., M.H., Data Collection or Processing: A.E.B., Analysis or Interpretation: A.E.B., M.H., Literature Search: A.E.B., Writing: A.E.B.

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