ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Esophageal Atresia: Comparison of Mortality Classifications and Factors Affecting Mortality

Trakeoözofageal Fistül/Özofageal Atrezili Hastalarda Mortalite Skorlarının ve Mortaliteye Etki Eden Faktörlerin Karşılaştırılması

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Abstract

Introduction: Esophageal atresia (EA) is a disease that is accompanied by other concomitant systemic anomalies in 30-70% of cases. In this study, we aimed to evaluate the antenatal and postnatal factors that influence mortality in patients with EA, examine the relationship between these factors and mortality and compare the effectiveness of mortality classification defined in the literature in assessing mortality.

Materials and Methods: This retrospective study examined records of patients diagnosed with EA who were hospitalized between 2010 and 2020 in the NICU. Patient demographics, additional congenital anomalies, and Montreal, Bremen, and Spitz mortality classifications were evaluated.

Results: A total of 71 patients were included in the study. The mean gestational week of the patients was 35.7 ± 2.5, and the mean birth weight was 2382 ± 715 g. The mortality rate was 29.5% (21/71).

All patients with three or more concomitant anomalies had died. All mortality classifications were significant in predicting mortality. Low birth weight, prematurity, low APGAR score, presence of preoperative pneumonia, and presence of preoperative intubation were concluded to be significant in predicting mortality. The highest correlation between mortality and classification systems was found for the Montreal classification.

Conclusion: The identification of risk factors determining mortality remains controversial. Prematurity, a low APGAR score, the presence of more than three anomalies, preoperative pneumonia, and the need for invasive mechanical ventilation have been found to increase mortality in EA. In conclusion, there is a need for new classification systems that evaluate various parameters that affect mortality, including multiple congenital anomalies.

Keywords
Esophageal atresia (EA), tracheoesophageal fistula, mortality, neonates, mortality classification

Anahtar kelimeler
Özafagus atrezisi, trakeoözofageal fistül (TÖF), mortalite, yenidoğan, mortalite skorlaması

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Öz

Giriş: Trekeo-özofagial fistül (TÖF), %30-70'inde eşlik eden başka sistem anomalileri olan bir hastalıktır. Hastalarda mortaliteyi belirlemek için farklı risk skorlamaları kullanılmaktadır. Bu çalışmada, TÖF olan hastalarda mortaliteyi etkileyen prenatal ve postnatal faktörleri, bu faktörler ile mortalite ve morbiditeler arasındaki ilişkiyi değerlendirmeyi, literatürde tanımlanmış mortalite skorları ile bu skorların mortalite ve morbiditenin değerlendirilmesinde ne kadar etkin oldukları ve birbirlerine üstünlüklerinin karşılaştırılması amaçlandı.

Gereç ve Yöntem: Bu retrospektif çalışmaya 2010 ile 2020 yılları arasında yenidoğan yoğun bakım ünitesine yatırılarak izlenen TÖF tanısı alan hastaların kayıtları

incelenmiştir. Hastaların demografik özellikleri, ek konjenital anomalileri yanında Montreal, Bremen ve Spitz mortalite skorları kaydedildi.
Bulgular: Çalışmaya toplam 71 hasta dahil edildi. Hastaların ortalama gestasyon haftası 35.7 ± 2.5, doğum ağırlığı 2382 ± 715 gr idi. Mortalite oranı %29.5 (21/71) idi.
Eşlik eden anomali sayısı üç ve üzeri olan tüm hastalar kaybedildi. Düşük doğum ağırlığı, prematürite, APGAR skorunun düşük olması, operasyon öncesi pnömoni ve invaziv mekanik ventilasyon ihtiyacı mortaliteyi öngörmede anlamlı saptandı ($p<0.001$, $p= 0,035$, $p=0.03$, $p<0,001$, $p<0.001$). Mortalite skorlarının hepsi mortaliteyi ön görmede anlamlı saptandı. Mortalite ve skorlama sistemleri arasında en yüksek korelasyon ise Montreal sınıflamasında bulundu ($r=0.71$, $p <0,001$).
Sonuç: TÖF'lü hastalarda, mortaliteyi belirleyen risk faktörlerinin tanımlanması tartışmalı olmaya devam etmektedir. Prematüre doğum, düşük APGAR skoru, üçten fazla konjenital anomalinin varlığı, ameliyat öncesi pnömoni ve invaziv mekanik ventilasyon ihtiyacının TÖF'te mortaliteyi arttırdığı bulunmuştur. Sonuç olarak, çoklu konjenital anomaliler dahil olmak üzere mortaliteyi etkileyen çeşitli parametreleri değerlendiren yeni sınıflandırma sistemlerine ihtiyaç vardır.

Introduction

Esophageal atresia (EA)/tracheoesophageal fistula (TEF) is a disease first described in 1670 and can present with multiple anomalies (1). Its etiology is largely unknown; however, it is thought to be multifactorial (2). Although different incidences are reported in different countries, it is considered to occur in 1 in 2500 live births (2).

There are other concomitant systemic anomalies in 30-70% of infants with TEF. These are congenital heart disease (CHD), urinary system anomalies, gastrointestinal system anomalies, neurological system anomalies, and skeletal system anomalies (2). One of the most common associated congenital anomalies is VACTERL association (vertebral, anorectal, cardiac, tracheoesophageal, renal, and limb anomalies). Various mortality risk classifications have been used to determine patient mortality (3).

The Waterston classification was first defined in 1962, after which the Montreal, Bremen, and Spitz classifications were introduced (4). These classifications evaluate the patient's birth weight, cardiac pathology, congenital anomalies, and inability to wean from the ventilator and may sometimes fail to adequately predict mortality in most patients. In this study, in addition to these parameters, we also assessed the effectiveness of antenatal and postnatal characteristics of patients, operative time, clinical conditions such as preoperative pneumonia and sepsis, duration of invasive mechanical ventilation before and after surgery, and concomitant neonatal morbidities in predicting mortality.

We aimed to evaluate the aforementioned factors that influence mortality in patients with TEF, examine the relationship between these factors and mortality and morbidity, and compare the mortality classifications defined in the literature. Thus, we aimed to establish what parameters could be considered when creating a novel mortality classification.

Materials and Methods

This retrospective study included patients diagnosed with EA who were hospitalized between January 2010 and September 2020 in the Neonatal Intensive Care Unit (NICU) of the Pediatrics and Pediatric Surgery Departments of Bursa Uludag University Faculty of Medicine.

The study received approval from the institution's ethics committee (Bursa Uludağ

University Faculty of Medicine Clinical Research Ethics Committee (decision no: 2011-KAEK-26/620, date: 13.11.2020).

Gestational age, birth height-weight-head circumference and percentiles, mode of delivery, sex, multiple pregnancies, number of pregnancies, number of births, maternal age, antenatal steroid history, maternal diabetes history, prolonged premature rupture of the membranes, pre-eclampsia/eclampsia, presence of chorioamnionitis, polyhydramnios, oligohydramnios, antenatal diagnosis, and in vitro fertilization information were recorded for all patients.

At clinical follow-up of the infants, APGAR scores of the 1st and 5th minute, sepsis findings, pneumonia findings, oxygen requirement, mechanical ventilation requirement, day of transition to full enteral feeding, length of hospital stay, height-weight-head circumference and percentiles at discharge, CHD, central nervous system anomaly, presence of coloboma, urinary system anomaly, gastrointestinal tract anomaly, ear anomaly, choanal atresia, genital anomaly, chromosomal anomaly, esophageal atresia type, status of intraventricular hemorrhage, presence and stage of retinopathy of prematurity, presence and stage of bronchopulmonary dysplasia, presence of necrotizing enterocolitis, operative day (time), presence of preoperative pneumonia and intubation, and presence and day of mortality were recorded.

The mortality classification systems of the patients according to Waterston, Montreal, Bremen, and Spitz were calculated (4). The effectiveness of these scores in assessing mortality and morbidity was compared.

Statistical Analysis

Characteristics, mortality classifications of discharged and deceased (exitus) patients, and their relationship to mortality were calculated using the SPSS version 22 program (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The Shapiro-Wilk test was used to examine the fit of the data to the normal distribution. Comparisons between two groups were performed with t-tests for normally distributed parameters. For parameters that did not have a normal distribution, comparisons between the two groups were made using the Mann-Whitney U test, and multiple comparisons were made using the Kruskal-Wallis test. Data with a normal distribution are shown as the mean ± standard deviation (SD), and those without a normal distribution are shown as a percentage (%). Pearson chi-square analysis was used to analyze the cross-tabulations. Spearman correlation analysis was performed for the variables that did not have a normal distribution to determine the strength and direction of the relationship between the variables. Multivariate logistic regression analysis was applied to identify risk factors for mortality. A p-value of <0.05 was considered statistically significant for all tests.

Results

During the ten years studied, a total of 71 infants with a diagnosis of EA were admitted to the NICU. The mean gestational age was 35.7±2.5, and the mean birth weight was 2382 g ± 715. Nine (12.6%) patients had a birth weight below 1500 g, and 41 (57.7%) patients were premature. Only 6 (8.5%) patients had an antenatal diagnosis (Table 1). Thirty (42%) patients were diagnosed after admission to the NICU, 27 (38%) patients were diagnosed by radiography after suspicion in the delivery room, and 6 (8.5%) patients were diagnosed by the onset of symptoms after handover to the mother. The most common EA type was EA+distal TEF (Type C) in 66 (93%) patients.

Concomitant Anomalies

Fifty-seven (80.3%) patients had additional concomitant anomalies, with the most common concomitant anomaly being cardiovascular in 52 (73.2%) patients. The most common cardiac anomalies were patent ductus arteriosus (PDA), atrial septal defect (ASD), and ventricular septal defect. The most common skeletal anomalies were butterfly vertebrae and hemivertebrae (5/71). Anal atresia was present in 7 (9.8%) patients, undescended testis in 3 (4.2%) patients, and diaphragmatic hernia in 2 patients. Two (2.8%) patients had VACTERL association, 1 (1.4%) patient had CHARGE syndrome, 4 (5.6%) patients had trisomy 18, and 3 (4.2%) patients had trisomy 21 (Table 2). Among the patients who died following the operation, 3 had trisomy 18, 1 had Down syndrome, 1 had a diaphragmatic hernia, 2 had anal atresia, and 1 had VACTERL association. A common feature among all these patients was the presence of a congenital heart anomaly.

Mortality

Of the 71 patients, 21 (29.5%) died in the neonatal period. Seven (9.8%) of the exitus patients died before they could be operated on. Of the 64 operated patients, 51 (71.8%) were discharged after successful surgery. The characteristics of the exitus and discharged patients are given in Table 2. Of the 21 patients who died, 20 (28.1 %) had type C esophageal atresia and 1 (1.4 %) had type H esophageal atresia. All patients who died before the operation had severe congenital heart anomalies.

Birth weight and 1-minute APGAR scores were lower ($p<0.001$, $p=0.03$) in exitus patients than in discharged

Table 1. Patients' demographic and clinical characteristics

Birth weight (gr), mean ± SD	2382 ± 715
Gestational week, mean ± SD	35.7 ± 2.5
Birth weight < 1500 gr n (%)	9 (12.6)
Prematurity n (%)	41 (57.7)
Male n (%)	34 (47.8)
Caesarean n (%)	46 (64.8)
APGAR 1st minute, median (min-max)	6.5 (1-10)
APGAR 5th minute, median (min-max)	8 (1-10)
Antenatal diagnosis n (%)	6 (8.5)
Polyhydramnios n (%)	25 (35)
Presence of preoperative pneumonia n (%)	19 (26.8)
Presence of preoperative intubation n (%)	16 (22.5)
Operated patients n (%)	64 (90.1)
The age at which the operation was done (day), median (min-max)	3 (1-16)
Duration of invasive mechanical ventilation (day), median (min-max)	3 (0-166)
Mortality n (%)	21 (29.5)

patients. In addition, prematurity and birth weight less than 1500 grams were identified as factors that increased mortality (p=0.035, p=0.016). Among the exitus patients, 14 (87.5%) had preoperative intubation, and 15 (78.9%) had preoperative pneumonia. In addition, it was found that the presence of preoperative intubation and pneumonia and the long duration of invasive mechanical ventilation (before and after surgery) were among the important factors that significantly increased mortality (p<0.001 for each parameter) (Table 2).

When all anomalies associated with TEF were evaluated, it was concluded that concomitant isolated CHD did not increase mortality, whereas the number of concomitant anomalies of two or more significantly increased mortality. While all 4 patients with trisomy 18 anomaly and all patients diagnosed with CHARGE and VACTERL died, only one of the 3 patients diagnosed with Down syndrome died (Table 3). The most common cause of mortality was infection in 13 (65%) patients. The patient with type H esophageal atresia had severe congenital heart disease, specifically type 4 truncus arteriosus, along with choanal atresia, hemivertebrae, various skeletal anomalies, and cerebral ischemic infarction. Unfortunately, this patient passed away before surgery could be performed.

Mortality Classification Systems

The distribution of patients by group within the Waterston, Montreal, Bremen, and Spitz classification systems is given in Table 4. All mortality classification systems were significant in predicting mortality (Tables 5, 6). The highest correlation between mortality and classification systems was found for the Montreal classification (Table 5, 6) (p <0.001, r=0.70).

Discussion

TEF is a congenital anomaly that requires early diagnosis, surgical treatment, and a multidisciplinary approach (5). Mortality rates vary between 9-59.7% in the literature (4,6-9). Of the 71 patients included in our study, 21 (29.5%) died in the neonatal period. The wide range of mortality rates by country suggests that they vary according to the level of a country's development.

The mean birth weight of the exitus patients in the current study was 2400.9±639.4 g. Birth weight below 1500 g and prematurity were found to be significant risk factors for mortality, similar to those reported in the literature (p 0.001) (10-12). Moreover, the APGAR scores of the exitus patients were calculated as 5-8 in the 1st and 5th minutes, respectively, and the low APGAR score was determined to be significant in predicting mortality (p=0.03, p=0.02). Similar studies in the literature reported that a low APGAR score was significant in predicting mortality (10,13).

Additional congenital anomalies may accompany TEF. The most common accompanying congenital anomalies are anomalies of the cardiovascular system. In two retrospective

Table 2. Comparison of demographic-characteristics of death and discharged patients

	Death n=21 (%29.5)	**Discharged n=50 (%70.4)**	**p**
Birth weight (gr) mean ± SD	2400.9±639.4	2661.04±665.2	**<0.001**[a]
Birth weight <1500 gr n (%)	6 (28.5)	3 (6)	**0.016**[a]
Gestational week mean ± SD	34.5±2.2	36.2±2.5	0.1[a]
Prematurity n (%)	16 (76)	25 (50)	**0.035**[b]
Male n (%)	7 (35)	27 (52.9)	0.197[b]
Caesarean n (%)	14 (70)	32 (62)	0.783[b]
APGAR 1st minute, median (min-max)	5 (1.9)	8 (1.10)	**0.03**[c]
APGAR 5th minute, median (min-max)	8 (3.10)	8 (1.10)	**0.02**[c]
Antenatal diagnosis n (%)	3 (15)	3 (5.8)	0.118[b]
Polyhydramnios n (%)	10 (50)	15 (29)	0.258[b]
Presence of preoperative pneumonia n (%)	15 (78.9)	4 (21)	**<0.001**[b]
Presence of preoperative intubation n (%)	14 (87.5)	2 (12.5)	**<0.001**[b]
Operated patients n (%)	16 (25)	48 (75)	**0.021**[b]
The age at which the operation was done, median (min-max)	5 (1-16)	3 (2-10)	0.06[c]
Duration of invasive mechanical ventilation (day), median (min-max)	15 (2-59)	3 (0-166)	**<0.001**[c]

[a]: T-test, [b]: Chi-square, [c]: Mann-Whitney U Test

Table 3. Concomitant anomalies of death and discharged patients			
Clinical characteristics of patients	**Death n=21 (%29.5)**	**Discharged n=50 (%70.4)**	**p**
Anomaly present	**12 (25)**	**36 (75)**	0.09[a]
CHD*	3 (14.2)	18 (85.7)	**0.048**[a]
Urinary System Anomaly	-	2	
Limb-Vertebra Anomaly	-	1	
Central Nervous System Anomaly	-	1	
Gastrointestinal Tract Anomaly	-	2	
CHD + Limb-Vertebra Anomaly	3	-	
CHD + Genital System Anomaly		2	
CHD + Gastrointestinal Tract Anomaly	1 (50)	1 (50)	
CHD + Urinary System Anomaly	-	2	
Genital System Anomaly + Ear Anomaly	-	1	
CHD + Central Nervous System Anomaly	-	1	
CHD + Urinary System Anomaly + Gastrointestinal Tract Anomaly	-	3	
CHD + Limb-Vertebra Anomaly + Urinary System Anomaly	-	2	
CHD + Urinary System Anomaly + Limb-Vertebra Anomaly + Central Nervous System Anomaly	1	-	
CHD+ Urinary System Anomaly + Limb-Vertebra Anomaly + Gastrointestinal Tract Anomaly	2	-	
Diaphragmatic Hernia +CHD	1	-	
Diaphragmatic Hernia + CHD + Limb-Vertebra Anomaly	1		
Anomaly absent	1 (7.6)	12 (92.3)	
Chromosomal anomaly	5 (71)	2 (29)	
Syndromic patients	3	-	
[a]: Chi-square, *CHD: Congenital heart disease			

cohort studies in the literature, the incidence of cardiac anomalies was reported to be 33-47% (6,14). In our study, the most common concomitant anomaly was cardiovascular system anomaly.

Considering the parameters used to predict mortality when evaluating mortality classification systems in patients with TEF, the presence of cardiac anomalies and concomitant severe anomalies are included in the classifications. Few studies have examined the association between mortality and anomalies, except for CHD. In our study, concomitant anomalies were present in 12 of the 21 exitus patients, and the most common isolated anomaly was severe CHD. It has been reported that when a concomitant systemic anomaly was added to TEF, the mortality rate was 3.2%, but the addition of two or more systems increased mortality up to 40%. Our study also found that the mortality rate was higher in patients with two or more systemic anomalies. In the study by German et al. (15), the presence of two or more anomalies was emphasized to increase mortality.

The presence of preoperative pneumonia was significant for mortality in our study (p 0.001), which is similar to the literature (16). In addition, in line with the literature, the presence of preoperative intubation was also identified as significant for mortality ($p < 0.001$) (17,18).

Syndromes of known genetic etiology with additional malformations are present in approximately half of the cases. A genetic cause is present in 11-12% of patients diagnosed with TEF. Nonsyndromal TEF is generally considered a multifactorial disorder, suggesting that epigenetic and environmental factors also contribute to the disease (2). In our study, 2 (2.8%) patients had VACTERL association, 1 (1.4%) patient had CHARGE syndrome, 4 (5.6%) patients had trisomy 18, and 3 (4.2%) patients had trisomy 21. All patients diagnosed with trisomy 18 died. In the study by Sparey et al. (19), an increased mortality

Table 4. Mortality classifications and their relationships with reported mortality			
Mortality classification	**Discharged n (%)**	**Death n (%)**	**Total**
Waterston			
A	18 (94.7)	1 (5.3)	19
B	23 (92)	2 (8)	25
C	9 (33.3)	18 (66)	27
Montreal			
1	44 (91.6)	4 (8.3)	48
2	6 (26)	17 (73.9)	23
Bremen with complication			
1	1 (50)	1 (50)	2
2	7 (38)	11 (61)	18
3	0	4 (100)	4
Bremen without complication			
1	40 (95.2)	2 (4.7)	42
2	3 (60)	2 (40)	5
0	0	1 (100)	1
Spitz			
1	40 (93)	3 (7)	43
2	10 (43.4)	13 (56.5)	23
3	0	5 (100)	5

Table 5. Correlation of mortality classification with reported mortality					
Mortality	**Waterston**	**Montreal**	**Bremen with complication**	**Bremen without complication**	**Spitz**
p	<0.001	<0.001	0.13	<0.001	<0.001
r	0.55	**0.70**	0.31	0.50	0.62

Table 6. Relative values of mortality classifications in predicting mortality			
	Waterston	**Montreal**	**Spitz**
Odds ratio	0.392	160	14.54
%95 Confidence interval	0.01-0.264	15.2-1683.26	3.48-60.8
p-value	<0.001	<0.001	<0.001

rate was determined in patients with TEF diagnosed with a genetic disease (19).

Perioperative classification systems have been established to determine prognosis in patients with TEF based on preoperative clinical factors and patient characteristics (4). In 1962, Waterson et al. (20) identified the presence of low birth weight, congenital anomalies, and pneumonia as major risk factors and developed a classification system based on these factors. However, this classification system did not take into account the nature of the patients' congenital anomalies, length of stay on the ventilator, or other factors affecting mortality (11). The Montreal classification was developed in 1993 by Poenaru et al. (11) as an alternative to the Waterston classification (11). This classification system is based on whether the patient is ventilator dependent or not and whether the accompanying congenital anomaly is

mild or severe. On the other hand, in 1994, Spitz et al. (21) created a new classification system based on the patients' birth weight and the degree of CHD. In 2000, Yaygu et al. (16) created a new classification system as an adaptation of the Spitz classification by adding an assessment of the patient's pulmonary status before surgery.

There are few studies in the literature that evaluate each system and its relationship to mortality. A retrospective study by Peters et al. (4) in England, which included 248 patients over a 20-year period, compared the Waterston, Spitz, and Montreal classifications, and all were significant in predicting mortality, similar to our study. The study by Teich et al. (22) compared the Waterston and Montreal classifications and concluded that the Montreal classification was more successful in identifying high-risk patient groups. In our study, the Montreal classification system was found to be the system with the highest correlation scores.

In a study conducted between 1999 and 2012 by Sulkowski et al. (17) in the USA with 3479 patients, the evaluation of mortality factors showed that birth weight, CHD, genetic anomalies, and being on an invasive mechanical ventilator before surgery were factors that increased mortality. Similarly, in our study, the presence of preoperative intubation, low birth weight, and genetic anomalies (urinary system anomaly) were found to be factors that increased mortality.

TEF may be associated with many congenital anomalies, with CHD being the most common (6,17,23). Bremen and Spitz classifications assessed the presence of severe CHD as a parameter that affected mortality (12,16).

In the study by Sulkowski et al. (17), the presence of concomitant anomalies was found to be a factor in predicting mortality. However, there is no study in the literature that evaluates multiple mortality-affecting independent risk factors, including all congenital anomalies. When considering the presence of multiple anomalies in cases diagnosed with TEF, the question of which anomaly is the main factor influencing mortality remains controversial. In our study, all 5 patients who died without surgery had severe congenital heart disease. With the exception of patients with severe CHD or multiple anomalies incompatible with life, the life expectancy of these patients has increased with advances in medicine. Therefore, there is a need for new classification systems that will incorporate patient CHD and other associated risk factors when determining mortality risk. The prenatal factors need to be considered and actually a prenatal score calculated based on the prenatal signs could be a great help to predict the postnatal mortality and decide or not to interrupt the pregnancy.

Study Limitations

The relatively small number of patients and their retrospective evaluation from patient records are the limitations of our study. In addition, surgical techniques that may influence mortality were not evaluated in this study.

Conclusion

The survival rate of patients with TEF/EA has increased in recent years. The identification of risk factors that determine survival remains controversial. We believe that a new system that assesses mortality risk with a scoring system rather than a classification and evaluates birth weight, prematurity, low APGAR score, length of stay on an invasive mechanical ventilator, number of concomitant anomalies, preoperative intubation, presence of preoperative pneumonia, presence of syndromes, and chromosomal anomalies is needed. Large-scale studies may contribute to the development of new mortality classification system.

Ethics

Ethics Committee Approval: The study received approval from the institution's ethics committee (Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee (decision no: 2011-KAEK-26/620, date: 13.11.2020).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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