Analysis of mortality and long-term outcomes of pediatric patients with tracheoesophageal fistula/esophageal atresia

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BACKGROUND/PURPOSE: *This study analyzed factors that affect mortality in patients surgically treated for EA, then explored the long-term problems encountered by these patients.*
MATERIALS AND METHODS: *Among 252 patients with EA who were either diagnosed, treated, and subsequently followed at the Department of Pediatric Surgery, Dicle University Medical Faculty Hospital, or were treated surgically elsewhere but followed at our center, between January 2010 and January 2020,214 patients were included in the study.*
RESULTS: *Early complications:One or more early complications were observed in 132(62.5%) of the 211 patients who underwent surgical EA repair. The most common early complication was AS, which developed in 106(50.2%) patients. Anastomosis leakage. Was detected in 48 (22.7%) patients. Late complications: The late findings of 161 patients who underwent definitive surgery and had a mean follow-up period of 68 months (range, 6-120 months) were evaluated. The most common late complication was GER. Mortality: Of the 214 patients in our study, 63(29.4%) died, including 48(76.2%) during the early period after the first surgery. Of the 10(15.9%) patients who died during the late period.*
CONCLUSION: *In our study, the most common early complication was anastomotic stenosis in patients with esophageal atresia. We recommend balloon dilation in the treatment of anastomotic stenosis.Gastroesophageal reflux is the most common long-term complication. Most of these can be treated conservatively and medically. The association of low birth weight, cardiac anomalies, prematurity and VACTERL increased mortality in patients with esophageal atresia in our study.*

KEY WORDS: Esophageal Atresia, Morbidity, Late Period, Mortality, Tracheoesophageal Fistula

Introduction and Objective

Esophageal atresia (EA) is an anomaly that occurs at a rate of one in 3,500-4,500 live births [1]. In the most common form of EA, the proximal end of the esophagus terminates bluntly and the distal end is fistulized into the trachea [2]. Haight developed the first successful treatment of EA, in 1941. Since then, survival rates have risen; in some reports, they have reached 90%. Today, EA patients with severe prematurity and cardiac malformation may survive [3]. The improved survival rates can be attributed to advances in surgical techniques and neonatal care; however, there have been increasing rates of long-term complications, including gastroesophageal reflux (GER), anastomotic stenosis (AS) and dysmotility, lung problems, and musculoskeletal issues. Because these conditions affect nutrition, the child's growth and development may also be negatively impacted [4,5].
This study analyzed factors that affect mortality in patients surgically treated for EA, then explored the long-term problems encountered by these patients.

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Materials and Methods

Need for respiratory support, clinical findings, time to surgery, drug treatments, imaging results, bronchoscopy and surgical findings, surgical technique, distance between the two atretic ends (detected during surgery), postoperative clinical findings, endoscopy findings, effects of postoperative clinical features on morbidity and mortality, and clinical results. Early (anastomotic stenosis, anastomosis leakage, and recurrent tracheoesophageal fistula) and late (GER, growth and developmental retardation, dysphagia, respiratory system problems, scoliosis, and thoracic deformity) complications were also investigated.

The patients were evaluated according to the Waterston, Okamoto, and Spitz classifications, the mortality rate differed depending on the classification group [6-8].

Early Complications

Anastomotic Stenosis: Contrast-en Approval for this retrospective study was obtained from the Dicle University Ethics Committee (approval no. 229, dated 07/05/2020). Among 252 patients with EA who were either diagnosed, treated, and subsequently followed at the Department of Pediatric Surgery, Dicle University Medical Faculty Hospital, or were treated surgically elsewhere but followed at our center, between January 2010 and January 2020, 214 patients were included in the study. Patients with isolated tracheoesophageal fistula (TEF) and congenital esophageal strictures were excluded.

The data analyzed for each patient included sex, birth weight, prenatal findings, gestational age at birth, time of diagnosis, time of admission to our clinic, accompanying anomalies, chromosome analysis results (for patients with chromosomal anomalieshanced radiofluoroscopic esophagography was performed in patients who were operated for EA and had nutritional complaints after the operation, and it was examined whether there was a narrow segment in the anastomosis line. Endoscopy and, if necessary, dilatation were planned for patients with stenosis.

Anastomotic Leakage: Patients who were operated for EA and saliva came from the chest tube after the operation, patients with suspected AL and admitted to an orally administered methylene blue chest tube, or patients who were found to have passed into the thorax by esophagography under the scope available in our clinic were defined as patients with AL.

Recurrent Tracheoesophageal Fistula: Patients who were operated for EA and had recurrent lower respiratory tract complaints after surgery, cough and cyanosis after feeding, and abdominal distension with crying, straining and coughing were evaluated for recurrent TEF.

Radiofluoroscopic esophagography was performed by experienced people in these patients.

Late Complications

Gastroesophageal Reflux Disease: All patients followed up were evaluated for GER disease. especially in patients who were operated for EA and patients who had recurrent pulmonary infection, recurrent aspiration pneumonia, AS who did not respond adequately to dilatation therapy, growth retardation, treatment-resistant reactive airway, recurrent pulmonary infection, recurrent aspiration pneumonia dysphagia, and vomiting in postoperative follow-ups. Patients with symptoms that are significant enough to require medical treatment after the first 6 months, those with GER findings in the endoscopic evaluation, findings consistent with GER (reflux index over 4.2%) in 24-hour esophageal pH monitoring, or patients whose reflux scintigraphy is compatible with GER disease. He was defined as a GER patient.

Growth and Development Retardation: In the outpatient clinic controls of the patients who were operated for EA, height and weight measurements were routinely performed to be evaluated for growth and developmental retardation. Patients with height or weight below the 25% percentile were considered to have growth retardation.

Difficulty in Swallowing: Patients who were operated for EA and who had a history of difficulty in swallowing and feeling of strangulation while feeding although there was no evidence of AS, congenital esophageal stenosis and esophagitis in the postoperative follow-up were considered as patients with dysphagia.

Respiratory System Problems: Patients who were operated on for EA, who had repeated lower respiratory tract infections evaluations in the postoperative follow-ups and who were diagnosed with reactive airway or chronic lung disease by pulmonary function tests were considered to have respiratory problems.

Scoliosis and Thoracic Deformity: Patients with asymmetry in the thoracic wall and size difference between the two hemithorax were considered as patients with thoracic deformity.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Qualitative data were summarized as numbers (n) and percentages; quantitative data were summarized as means, standard deviations, and ranges. The distributions of the data were investigated using Kolmogorov–Smirnov and Shapiro-Wilk tests, as well as histogram plots.

The chi-squared test was used to compare qualitative data between groups. Relative risks and odds ratios were calculated for groups with significant findings according to the chi-squared test. For comparisons of quantitative data between independent groups, a t-test was used when assumptions were met; the Mann-Whitney U test was

used when these assumptions were not met. For comparisons of quantitative data among more than two groups, an analysis of variance was performed when assumptions were met; the Kruskal-Wallis test was used when these assumptions were not met. Statistical significance in all tests was defined as $p < 0.05$.

Results

Early Complications

One or more early complications were observed in 132 (62.5%) of the 211 patients who underwent surgical EA repair.

Anastomotic stenosis: The most common early complication was AS, which developed in 106 (50.2%) patients. Most cases of AS occurred in patients with EA Gross type C (52%). Dilatation was performed only once in 47 of 106 (44.3%) patients; the mean number of dilatations was 2.94, with a success rate of 99%. AS was accompanied by GER in 66 of 106 patients. The relationship between AS and GER was statistically significant ($p < 0.01$).

Anastomosis leakage: AL was detected in 48 (22.7%) patients, including 35 (72.9%) in the low birth weight group, 27 (56.3%) in the premature group, and 20 (41.6%) in the long-gap atresia group.

In all patients with AL, the leak closed spontaneously with conservative follow-up. Among the patients with AL, 33 (68.8%) developed GER, 30 (62.5%) developed AS, 24 (50%) developed growth and developmental retardation, 18 (37.5%) developed recurrent, lower respiratory tract infections (LRTIs), and 5 (10.4%) developed recurrent TEFs. Among the 24 patients with growth and developmental retardation, the causes included weight loss, sepsis, oral intake disorder, and AS. The development of leakage increased the risk of growth and developmental retardation ($p < 0.05$). The risk of AL was 2.5-fold greater in patients with long-gap EA. The relationships of AL with atresia type and long-gap EA were statistically significant ($p<0.05$).

Sepsis: Sepsis developed in 45 (21.3%) of our EA patients; it was significantly more common in patients with Gross types A (44%) and B (50%) ($p< 0.05$). The causes of sepsis were AL or concomitant disease. Thirteen patients who developed sepsis died in the early period. Sepsis occurred in 23 (47.9%) of the 48 patients with AL and 22 (15.8%) of the 139 patients without AL. Patients with AL had a significantly greater risk of developing sepsis ($p < 0.01$). Recurrent tracheoesophageal fistula and tracheal stump Recurrent TEFs were detected in 8 (3.79%) patients who underwent definitive surgery. All of these patients had Gross type CEA.

Late complications: The late findings of 161 patients who underwent definitive surgery and had a mean follow-up period of 68 months (range, 6-120 months) were evaluated. In this group of patients, 11 had Gross type A, 2 had Gross type B, 145 had Gross type C, and 3 had Gross type D EA. The most common late complication was GER.

Gastroesophageal reflux disease: GER was detected in 84 (52.2%) patients during late follow-up, including in 67.6% of patients with early AL, 62.3% of patients with AS, 58.5% of patients with long-gap atresia, and 41.5% of patients requiring postoperative mechanical ventilation support. Among the patients with GER, growth and developmental retardation occurred in 41 (45%) and recurrent LRTIs occurred in 27 (32.1%). The relationships of GER with AS, AL, long-gap atresia, recurrent TEFs, and growth and developmental retardation were statistically significant ($p < 0.01$). Fifteen (17.8%) patients with GER underwent antireflux surgery.

Growth and developmental retardation: During late follow-up, the height and/or weight of 55 (34.2%) patients was below the 25% percentile. Among the patients with developmental delay, 42 (76.6%) had GER, 41 (74.5%) had AS, 23 (41.8%) had AL, 22 (40%) had a history of recurrent LRTIs, and 10 (17.2%) underwent repeat thoracotomy because of recurrent TEFs or tracheal stump.

Thirty-six patients had a low birth weight; a vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (VACTERL) association was identified in 15 (25.9%). The relationships of growth and developmental retardation with GER, AS, AL, birth weight, and prematurity were statistically significant ($p < 0.05$).

Respiratory system problems: During late follow-up, 38 (23.6%) patients had recurrent LRTIs, including 18 (47.4%) who developed AL in the neonatal period, 11 (28.9%) with long-gap EA, 8 with recurrent TEFs, and 3 with a tracheal stump. Among the patients with recurrent LRTIs, 30 (78.9%) had AS, 27 (71%) had GER, and 21 (55.3%) had growth and developmental retardation; all of these conditions worsened postoperatively.

Table I

Early Complications	**Total (n: 211)**
Anastomotic Stenosis	106 (50 %)
Anastomotic Leak	48 (22,7 %)
Sepsis	45 (21,3 %)
Pneumothorax	36 (17 %)
Atelectasis	18 (8,5 %)
Tracheoesophageal Fistula	8 (3,8 %)
Tracheal stump	4 (1,9 %)
Late Complications	**Total (n: 161)**
Gastroesophageal Reflux	84 (52,2 %)
Growth and Development Retardation	55 (34,2 %)
Respiratory System Problems	41 (25.5 %)
Swallowing Difficulty	23 (14.3 %)
Scoliosis and Thorax Deformity	20 (12.4 %)
Esophageal Diverticulum	9 (5.6 %)

Three of the patients with recurrent LRTIs died during the late period because of pneumonia + sepsis; two other patients with recurrent LRTIs died because of major cardiac anomalies. Tracheomalacia was detected in 18 patients during late follow-up, including 15 (83.3%) with GER and 13 (72.2%) with recurrent LRTIs. In the early period, AS developed in 13 (72.2) patients and AL developed in 8 (44.4%) patients. Five of the patients subsequently developed asthma, and one patient had bronchiectasis.

The relationships of AL with AS and GER in the groups with and without respiratory system problems were statistically significant ($p<0.05$).

Dysphagia: During late follow-up, 23 patients had dysphagia. Esophagus stomach duodenum radiographs showed that GER accompanied esophageal dysmotility in 13 patients. Most of the patients with esophageal dysmotility had long-gap atresia and had undergone a Livaditis procedure. Gastric transposition surgery was performed in two patients.

Scoliosis and thoracic deformities: Eleven patients had a thoracic deformity; this was treated by repeat thoracotomy in 7 patients. Nine patients had scoliosis, including 5 who were premature, and 4 who underwent repeat thoracotomy. The difference between groups with and without scoliosis in terms of prematurity frequency was statistically significant ($p<0.05$).

Esophageal diverticulum: Esophageal diverticulum was detected in 9 patients based on their esophagography findings. Of these 9 patients, 8 had a low birth weight, 6 were premature, and 3 had undergone Livaditis myotomy. The rate of diverticula among all EA patients was

TABLE II - *Comparative relationship between gastroesophageal reflux disease (GÖR) and risk factors in operated patients (n=161)*

Groups	GÖR Total (%)	Antireflux surgery N	P
Anastomotic Stenosis	66/106(62.3%)	13	<0.01
Birth Weight (<2500 g)	42/87(48.3%)	11	>0.05
Postop Mechanical Ventilator Support	49/118 (41.5%)	7	>0.05
Heart Anomaly	36/84 (42.9%)	4	>0.05
Extrapleural approach	36/83(43.4%)	6	>0.05
Transpleural approach	28/64 (43.8%)	5	>0.05
Prematurity	26/61 (42.6%)	6	>0.05
Long Intermittent Atresia	24/41 (58.5%)	5	<0.05
Anastomotic Leak	23/34 (67.6%)	4	<0.01
Genitourinary system anomaly	10/27 (37%)	2	>0.05
Sepsis	11/19 (57.9 %)	3	>0.05
Recurrence tracheoesophageal fistula	7/8(87.5%)	3	<0.05

TABLE III - *Relationship between preoperative clinical features and mortality (n=214)*

Groups	Total	Died	%	p
Birth Weight (<2500 g)	130	51	39,2	<0.05
Heart Anomaly	111	54	48,6	<0.05
Prematurity	95	38	40	<0.05
VACTERL Collaboration	61	36	59	<0.01
Genitourinary system anomaly	61	34	55,7	<0.01
Mechanical Ventilator Support	42	26	61,9	<0.01
Skeletal System Anomaly	40	24	60	<0.01
Gastrointestinal anomaly	35	22	62,8	<0.01
Hypothyroidism	28	15	53,6	<0.05
ARDS-BPD	25	18	72	<0.01
Trisomy 18+Trisomy 13	11	11	100	<0.01
CHARGE Collaboration	5	2	40	>0.05
Relationship between postoperative clinical features and mortality in patients who underwent definitive surgery (n=211)				
Mechanical Ventilation Support	118	51	43,2	<0.01
Long Range	59	26	44,1	<0.05
Anastomotic Leak	48	17	35,4	>0.05
Postoperative Sepsis	45	24	53,3	<0.01
Pneumothorax	36	12	33,3	>0.05
Atelectasis	18	6	33,3	>0.05

4.3%; the rate among patients treated with a Livaditis procedure was 18.7%.

Mortality: Of the 214 patients in our study, 63 (29.4%) died, including 48 (76.2%) during the early period after the first surgery. The causes of death were prematurity, low birth weight, sepsis, accompanying chromosomal anomalies, VACTERL association, severe lung problems, or a major cardiac anomaly.

Five patients died during the early period after late repair. Of the 10 (15.9%) patients who died during the late period, the causes of death were aspiration pneumonia and sepsis in 3, cardiac anomaly in 2, anal atresia surgery in 1, Di George syndrome in 1, and a traffic accident in 1. The other two patients died after surgery performed at other institutions for accompanying anomalies.

Of the 111 patients with cardiac anomalies, 46 (41.4%) died. The correlation between cardiac anomaly and mortality was statistically significant ($p < 0.05$). Forty (36%) of the 111 patients had a major cardiac anomaly. Twenty-nine (72.5%) of those patients and 17 (23.4%) patients with minor cardiac anomalies died. The correlation between mortality and cardiac anomaly was statistically significant ($p < 0.05$).

Of the 74 patients with syndrome-association conditions (eg, VACTERL; coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities [CHARGE]; trisomy 18; and trisomy 13), 43 (58.1%) died. This patient group comprised 68.3% of the 63 patients lost during follow-up. The correlation between syndrome-association and mortality was statistically significant ($p<0.01$).

When mortality was evaluated according to the Waterston (risk) classification, the survival rates were 100% in group A, 89% in group B, and 50% in group C. According to the Okamoto classification, the survival rates were 80% in group 1, 73% in group 2, 26% in group 3, and 29% in group 4. According to the Spitz classification, the survival rates were 84% in group 1, 57% in group 2, and 23% in group 3.

An analysis of relationships between preoperative clinical features and mortality showed statistically significant differences between the surviving and deceased groups in terms of birth weight, cardiac anomaly, prematurity, VACTERL association, genitourinary system anomaly, mechanical ventilation support, skeletal system anomaly, gastrointestinal system anomaly, hypothyroidism, acute respiratory distress syndrome-bronchopulmonary dysplasia, and chromosomal anomalies ($p<0.01$).

In the analysis of birth weight, mean body weight was lower in deceased patients (2,054 g) than in survivors (2,429 g). The difference was statistically significant ($p < 0.05$).

Based on the gestational age at birth, the mean age was lower in deceased patients (35.1 weeks) than in survivors (36.6 weeks). This difference was also statistically significant ($p < 0.05$).

Discussion

The incidence of EA is one in every 3,500-4,500 live births. Developments in anesthesia and neonatal care have reduced but not eliminated morbidity and mortality in EA [1,2,5] such that both remain high before, during, and after surgical treatment. Low birth weight, prematurity, accompanying major cardiac anomalies, other organ and system anomalies, and lung infections increase the mortality risk in EA patients [8-13]. Thus, the early diagnosis and treatment of EA are important for reducing mortality and morbidity. However, the improved survival rate has also revealed age-related problems, which are detected during late follow-up.

Approximately 90% of the patients in our study were born in other hospitals; 56% of the patients were born in other cities and then referred to our clinic. This often resulted in a delayed diagnosis, aspiration of secretions during transfer, and worsening of the clinical condition in patients with distal TEF related to chemical pneumonia after GER. The mean diagnosis time of patients who came to our hospital after birth was 37 h, whereas it was 1 h for patients born in our hospital ($p<0.01$). This difference may reflect inexperience, carelessness, or a lack of antenatal diagnostic capability at other hospitals. A late diagnosis may also occur in infants born at home, or in infants discharged from the hospital and then re-admitted with the complaint of cough and cyanosis after each breast feeding. Very few studies have examined the relationship between EA and thyroid function. In our patients, hypothyroidism was identified in 30% of patients with thyroid function tests. The 53% mortality among patients with hypothyroidism might have been related to accompanying VACTERL, hydrocephalus, or chromosomal anomalies.

Potential preoperative risk factors include low birth weight and prematurity [10,14]. In our study, these conditions were present in 60.7% and 44.4% of the patients, similar to the percentages previously reported. Our study also identified birth in another city and subsequent referral to our clinic (resulting in a delayed diagnosis; 56.1% of patients) as a risk factor. Prematurity and low birth weight are also critical risk factors for mortality [11,12]. In our study, mortality was 40% among premature patients, 39.2% among patients with low birth weight, and 66.6% in patients with birth weight < 1,500 g. The large majority (80.9%) of patients who required respiratory support before surgery had a low birth weight; 64.3% of such patients were premature. These results are consistent with previous studies in which low birth weight and prematurity were risk factors that increase mortality and the need for mechanical ventilator support (associated with morbidity). Long-gap atresia is not well-defined in the literature, with 2 cm, 3 cm, or 2 or 3 vertebral lengths regarded as long intervals. In our study, long-gap atresia was defined as a distance of ≥3 vertebral lengths after the release of both esophageal ends.

Accordingly, 62 (29%) of our patients had long-gap atresia. In the repair of EA, the preferred approach is primary or delayed primary repair, depending on the anatomical type and the distance between the ends [5]. Alternative options for patients who can not undergo primary repair vary according to patient characteristics and surgeon preference [15].

The preferred alternatives are various forms of Livaditis myotomy, tubularized flap of the upper pouch, staged repair, graded intrathoracic lengthening, and esophageal replacement techniques [15,16,17]. In our clinic, primary repair is preferred, including in patients with isolated EA. Of the patients in our study, 181 had their initial surgery in our clinic; of those 181 patients, thoracotomy was performed in 180 (99.4%) and primary esophago-esophagostomy was performed in 176 (97.8%). Primary repair was performed in 122 patients (69.3%) without the need for additional procedures except fistula separation and upper pouch dissection.

When long-gap atresia is detected during the first thoracotomy, the preferred method is to stretch both atretic ends during surgery using maximum traction [18,19]. In our study, intraoperative stretching was the most common approach (63.6%), while intraoperative stretching + Livaditis myotomy were used in long-term primary early repair. In our clinic, Kimura's extra thoracic elongation and Foker's staged intrathoracic esophageal lengthening were attempted in one patient; both were later abandoned. Because our goal in EA patients is to preserve esophageal anatomy and physiology, we prefer the intraoperative stretching method; it causes less damage than direct disruption of esophageal wall integrity during surgery. In patients for whom primary anastomosis could not be performed, we did not disable the esophagus; instead, we prioritized its protection with delayed or secondary repair, such that esophago-esophagostomy was performed in 98.9% of our patients.

Displacement of the cardia into the thorax and an overtensioned anastomosis have been suggested to increase the frequencies of early and late complications; in our study, neither increased the rates of complications (eg, AL, AS, and GER). This result supports the primary use of esophageal-sparing surgical techniques.

The incidences of early postoperative complications in our patients were similar to the reported values [13], including our finding that AS was the most common complication during the early period [13,20,22]. In the literature the rate of AS was 33%; moreover, AS was diagnosed in patients who required multiple dilatations [21]. In our study, AS occurred in 106 (50.2%) patients; this high rate included 47 (44.3%) patients who underwent dilatation only once.

In the literature the mean number of dilatations was 3.2, and the success rate was 87% [23]; in our study, the mean number of dilatations was 2.94 and the success rate was 99%. The slightly higher incidence of AS in patients with long-gap EA might have been related to the anastomosis tension. During late follow-up, 62.3% of GER patients, 40.6% of growth and developmental retardation patients, and 28.3% of recurrent LRTI patients developed AS.

These results support the need for a careful evaluation of potential AS in EA patients. The development of AS might be avoided by refraining from the use of excessive suturing, inclusion of the mucosa in each suture of the anastomosis, meticulous treatment of the esophageal ends, and the creation of a wide anastomosis.

In primary repair, anastomoses can be single-row, double-row, or telescopic. In single-row end-to-end anastomoses, the reported rate of AL is 21.4% [22,24]. All patients in our study underwent single-row end-to-end anastomosis, and the frequency of AL was 22.7%. Additional conditions also increase the risk of AL [20,22]. Among our patients with AL, 72.9% had a low birth weight, 56.3% were premature, 41.6% had long-gap EA, and 70.8% had at least one additional anomaly. These were considered risk factors in our study. Furthermore, in all of our patients who developed AL, their condition improved with conservative treatment. Therefore, we recommend that AL patients be breastfed by insertion of a nasojejunal tube; routine total parenteral nutrition should be avoided. Our patients who developed AL were at greater risk of sepsis and subsequent mortality.

During late follow-up of the patients with AL, 68.8% developed GER, 62.5% developed AS, 50% developed growth and development retardation, 37.5% developed recurrent LRTIs, and 10.4% developed recurrent TEFs. According to these results, patients with AL should be followed up for late complications.

Recurrent TEFs or tracheal stump may be present in patients who develop recurrent LRTIs during late follow-up of EA. The incidence of recurrent TEFs reported in the literature is 3–15% [25]. Although most cases occur in the early period, a fistula can develop months or years later in some patients. In our study, the rate of relapse TEF was near the low end of the range reported in the literature (3.79%); 75% of the patients who developed recurrent TEFs had a low birth weight. Rethoracotomy was performed in 7 of the 8 patients with recurrent TEFs. After fistula ligation and excision, the patients' complaints resolved, as determined in the follow-up examinations. In our patients with recurrent TEFs, 100% had growth and developmental retardation, while 87.5% had GER; both conditions improved after recurrent TEF repair. The tracheal stump was excessively long in 3 patients with recurrent LRTIs, presumably because it facilitated the accumulation of secretions.

GER is the most common complication in the late postoperative period [26].

In the meta-analysis conducted concerning the late results of patients with EA, the frequency of GER was 40.2% [26]. In the study by Koivusalo et al., the frequency was 45.9% [25] In our study, the frequency of GER was similar to the value reported in the literature (52.2%).

Koivusalo et al. reported the need for antireflux surgery in 64.3% of patients with EA [27], whereas antireflux surgery was performed in only 17.8% of such patients in our study. However, because antireflux surgery is controversial, medical treatment and nutritional control should be the initial approach [29]. Indeed, the low rate of antireflux surgery in our study may have been related to our insistence on medical treatment. Considering the significant relationships of GER with AS, AL, long-gap atresia, recurrent TEFs, and growth and developmental retardation in our study, EA patients with these conditions should undergo long-term follow-up.

Growth and developmental retardation is a notable late complication in patients with surgically treated EA; it occurred in 55 (34.2%) of our patients during late follow-up. The relation ships of growth and developmental retardation with GER, AS, AL, birth weight, and gestational age at birth were statistically significant.

However, growth and developmental retardation improved after these conditions were satisfactorily resolved.

In the meta-analysis, the frequency of respiratory system problems ranged from 10% to 52% [26,28,30], whereas the rate was 25.5% during late follow-up in our study. Recurrent LRTIs constituted the most common respiratory condition, occurring in 76.9% of our patients. Respiratory conditions in our patients were generally attributed to aspiration pneumonia. Recurrent LRTIs were also associated with growth and development retardation, involving 53.8% of those patients.

Therefore, patients with growth and developmental retardation during follow-up should be examined for underlying disease. Tracheomalacia is an important late period problem in EA patients [26,28]; in our study, it was identified in 8.5% of patients during late follow-up. In this group of patients, 83.3% had GER, 72.2% had recurrent LRTIs, and 72.2% had AS. The relation ships of respiratory system problems with AS and AL were statistically significant.

There is no clear definition of dysphagia in the literature; thus, the reported rates are difficult to compare [26]. In the meta-analysis, the mean frequency of dysphagia was 50.3-84% (range, 18-84%) [26,31]; while it was 10.9% (23 patients) in our study. Based on the finding that most of our patients with dysphagia had long-gap EA and had undergone a Livaditis procedure, the presence of dysphagia should be assessed during long-term follow-up of similar EA patients.

In the meta-analysis, which included 1,338 patients, the rate of scoliosis was 13%, but there were substantial differences among included studies. Additionally, most of the cases were mild and did not require intervention [32]. In our study, the rate of scoliosis was 5.6%; most patients with scoliosis had undergone repeat thoracotomy. The low rates of scoliosis and thoracic deformity in our study are presumably because muscles were not cut during thoracotomy.

The high rate of scoliosis in patients who underwent repeat thoracotomy may have been related to tissue adhesions caused by the first operation.

Esophageal diverticulum is another complication encountered in patients with surgically treated EA. In the study by Porcaro et al.,it was detected in 14% of the patients [33]; it was detected in 4.3% of patients in our study and in 18.8% of patients who underwent a Livaditis procedure. Notably, the Livaditis procedure may increase the risk of diverticulum.

When our patients were evaluated based on the Waterston, Okamoto, and Spitz classifications, the mortality rates differed among classification groups [6-8]. According to these data, body weights of < 2,500 g or < 1,500 g substantially affected mortality. According to the Waterston classification, the survival rates were as expected (100%) in class A, better than expected (89.2%) in class B, and considerably lower than expected (50%) in class C. These results indicate that a low birth weight and accompanying additional anomalies influence the survival rate of EA patients.

According to the Okamoto classification, the survival rates in our study were lower than expected for classes 1 and 2, whereas they were close to the expected rates for classes 3 and 4. In the Spitz classification, our rates were lower than expected for class 1 and close to the expected rates for classes 2 and 3. The lower than expected survival rates for Okamoto classes 1 and 2 and Spitz class 1 may be explained by the limited access to echocardiography data for patients who underwent surgery before 2014.

The suboptimal survival rates of our patients, according to these classifications, indicate that our clinic's infrastructure and neonatal care conditions remain below the targeted level. In two studies conducted in developed countries, the mortality rates in EA patients were 7.5% and 11.3%; in three studies conducted in Balkan, Asian, and African countries, they were 28%, 56%, and 59%, respectively [10,13]. In two series published in our country, mortality rates in EA patients were 31% and 60% [4,34]. In an evaluated three consecutive time periods in their own clinics between 1978 and 2000. Their results highlight the infrastructure and care conditions in our country. Those authors reported a mortality rate in EA patients of 80% between 1978 and 1985; it decreased to 29.5% between 1992 and 2000, following improvements in intensive care infrastructure conditions, the number of healthcare personnel, and the quality of medical education [34].

Factors recently shown to affect infant mortality include the detection of fetal atresia during the prenatal period and the need for resuscitation and mechanical ventilation support [5,34]. However, there have been substantial differences between series in terms of the effects of those factors on mortality, compared with low birth weight, major cardiac anomaly, and severe preoperative pneumonia. Among our patients, relevant factors were low birth weight, prematurity, VACTERL association, need

for mechanical ventilator support, long-gap atresia, and sepsis. Most large series have determined that the presence of a cardiac anomaly in EA patients increases the risk of mortality [10-12,35-42]; this result is consistent with our current findings. In our study, preoperative clinical features associated with mortality were low birth weight, prematurity, mechanical ventilator support, VACTERL association, chromosomal anomalies, hypothyroidism, acute respiratory distress syndrome, gastrointestinal system anomaly, and genitourinary system anomaly; postoperative features included mechanical ventilator support, long-gap atresia, and sepsis.

Conclusion

In our study, the most common early complication was anastomotic stenosis in patients with esophageal atresia. We recommend balloon dilation in the treatment of anastomotic stenosis. In the treatment of anastomotic leakage, we recommend conservative treatment by feeding with a nasojejunal tube.
Gastroesophageal reflux is the most common long-term complication. Most of these can be treated conservatively and medically.
The association of low birth weight, cardiac anomalies, prematurity and VACTERL increased mortality in patients with esophageal atresia in our study.

Riassunto

In questo studio sono stati analizzati i fattori che influenzano la mortalità nei pazienti trattati chirurgicamente per atresia esofagea (EA), ed i problemi a lungo termine incontrati da questi pazienti.
Materiali e metodi: sono stati inclusi nello studio 214 pazienti dei 252 pazienti con EA che sono stati diagnosticati, trattati e successivamente seguiti presso il Dipartimento di Chirurgia Pediatrica, Dicle University Medical Faculty Hospital, o sono stati trattati chirurgicamente altrove ma seguiti presso il nostro centro, tra gennaio 2010 e gennaio 2020.
Risultati: Una o più complicanze precoci sono state osservate in 132 (62,5%) dei 211 pazienti sottoposti a riparazione chirurgica di EA. La complicanza precoce più comune è stata la stenosi dell'anastomosi, che si è sviluppata in 106 (50,2%) pazienti. La deiscenza dell'anastomosi è stata riscontrata in 48 (22,7%) pazienti.
Sono stati valutati i risultati tardivi di 161 pazienti sottoposti a intervento chirurgico definitivo e con un periodo medio di follow-up di 68 mesi (range, 6-120 mesi). La complicanza tardiva più comune è stata il reflusso gastroesofageo.
Per quanto riguarda la mortalità, dei 214 pazienti nel nostro studio, 63 (29,4%) sono deceduti, inclusi i 48 (76,2%) in relazione al primo periodo dopo il primo intervento chirurgico. 10 (15,9%) pazienti sono deceduti durante il periodo tardivo,
Conclusione: Nel nostro studio, la complicanza precoce più comune è stata la stenosi anastomotica nei pazienti con atresia esofagea. Raccomandiamo la dilatazione con palloncino nel trattamento della stenosi anastomotica. Il reflusso gastroesofageo è la complicanza a lungo termine più comune. La maggior parte di questi può essere trattata in modo conservativo e medico. L'associazione di basso peso alla nascita, anomalie cardiache, prematurità e complesse malformazioni ocngenite combinate (VACTERL) ha aumentato la mortalità nei pazienti con atresia esofagea nel nostro studio.

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