

Epidemiology and Outcomes of Congenital Esophageal Atresia in Croatia: A Retrospective Population-Based Study

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Abstract

Purpose

Esophageal atresia (EA) serious congenital gastrointestinal anomalies with variable birth prevalence and outcomes worldwide. This population-based study aimed to examine the birth prevalence, epidemiological features, associated anomalies, prenatal diagnosis, and early outcomes in Croatia.

Methods

Medical records of live-born neonates with EA treated at four Croatian tertiary centers between 2010 to 2020 were retrospectively reviewed. Data collected included demographics, prenatal findings, associated anomalies, and 30-day outcomes. Prevalence was calculated per 10,000 live births; χ^2 and trends were analyzed with Cochran-Armitage tests.

Results

A total of 101 EA cases were identified. Prevalence remained stable at 2.64 per 10,000 live births despite declining national birth rates ($\chi^2 = 17.79$, $p = 0.0585$; trend $p = 0.167$). Type C EA accounted for 88.1% of cases. Associated anomalies occurred in 57.4% of newborns, most commonly cardiac and great vessel anomalies (21.8%). Prenatal diagnosis was established in only 3%. Thirty-day mortality was 11.9%.

Conclusion

Birth prevalence and early outcomes of EA in Croatia align with European data; cardiac anomalies were less common, and VACTERL was more prevalent compared to other studies. One-month mortality is low and comparable to European data. Prenatal detection remains low, highlighting the need for improved prenatal screening.

1. Introduction

Esophageal atresia (EA) is a rare congenital condition characterized by a discontinuity in the esophagus, often accompanied by a trachea-esophageal fistula (TEF). This developmental defect arises during early embryogenesis due to abnormal division of the foregut into the trachea and esophagus. The malformation impedes normal swallowing, necessitating urgent intervention after birth. EA often appears as part of a spectrum of anomalies, most frequently associated with the VACTERL association (vertebral, anorectal, cardiac, trachea-esophageal, renal, and limb anomalies), and is linked with chromosomal abnormalities [1, 2].

The global birth prevalence of EA is estimated to be between 1,27 and 4,55 per 10000 live births, with slight geographic variation and no consistent gender predilection [3, 4]. Although most cases are sporadic, population-based studies suggest a multifactorial etiology, involving both genetic and environmental factors. An increased prevalence has been reported in the offspring of mothers with gestational diabetes and those exposed periconceptually to cigarette smoking and alcohol consumption, although causal links remain uncertain [5, 6]. Advances in prenatal imaging have improved detection rates, especially when polyhydramnios and an absent or small gastric bubble are observed on second-trimester ultrasound [7].

Anatomically, EA is classified using the Gross classification, with the most common subtype being Type C (EA with distal TEF), accounting for approximately 78–90% of cases [3]. Less frequent variants include isolated EA (Type A), EA with proximal TEF (Type B), and the H-type fistula (Type E), which can present more subtly and thus evade early diagnosis [8].

Surgical repair remains the main treatment and is usually performed within the first days of life. Thanks to advances in neonatal intensive care, anesthesia, and surgical techniques, overall survival rates in developed countries now exceed 90% [9]. However, postoperative morbidity remains considerable. Long-term complications such as anastomotic stricture, recurrent fistula, gastro-esophageal reflux disease (GERD), and esophageal dysmotility are common and can significantly affect quality of life [10, 11].

Despite improved outcomes, recent population studies indicate that EA survivors have increased healthcare utilization and a higher prevalence of chronic comorbidities throughout childhood and into adulthood [12]. Consequently, multidisciplinary long-term follow-up and research into the pathophysiology of esophageal dysmotility and respiratory sequelae are increasingly recognized as priorities in the care of this patient group.

The aim of this study is to analyze the epidemiological characteristics and short-term outcomes of live-born neonates with EA in Croatia over an eleven-year period (January 2010-December 2020), as such research has not been previously conducted in this area. Additionally, it seeks to determine the percentage of positive prenatal diagnoses. The study's hypothesis is that the results will align with those from studies conducted in Europe. The overall goal of this work is to identify factors that may help reduce morbidity and mortality in neonates with EA.

2. Materials and Methods

This retrospective cohort study included all live-born neonates with congenital EA in Croatia from January 2010 to December 2020. The data source consisted of patient medical records from four neonatal and pediatric intensive care units (NICUs and PICUs) that provide comprehensive tertiary surgical and neonatal intensive care across Croatia. There are two centers in Zagreb (serving the northern and eastern regions), one in Rijeka (covering the western region), and one in Split (serving the southern region). Neonates born with EA in regional hospitals are transferred to the nearest tertiary center, usually after diagnostic evaluation and initial stabilization. In each tertiary center, a principal

investigator was appointed to oversee data collection (two pediatric intensivists, a neonatologist, and an anesthetist).

To standardise the collected data, the principal investigators were provided with a Microsoft Access Data Collection Database featuring a “drop-down menu”. The following demographic data were entered into the database and made available to investigators: gender (male/female), birth weight (< 1500 g, 1500–2499 g, > 2500 g), gestational age (< 32 weeks, 32–36 weeks, > 37 weeks), and mother’s age (< 25 years, 25–35 years, > 35 years). Regarding AE, the following data were offered: prenatal diagnosis established (yes/no), type of atresia (A, B, C, D, E), and associated anomalies (yes/no). The investigator could select one or more associated anomalies from the following: cardiac/big vessels, skeletal, intestinal, renal/urogenital, VACTERL, CNS, other. Regarding outcome, the following options were offered: operated (yes/no), survived after 1 month, died within 1 month of surgery.

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and with all relevant institutional and national guidelines for ethical research. Ethical approval was received from the Ethics Committees of Clinical Hospital Centre Rijeka (2170-29-02/1-20-2), Children’s Hospital Zagreb (02–23/8-1-22), Clinical Hospital Centre Zagreb (8.1.-25/234-2 02/013AG), and Clinical Hospital Centre Split (2181-147-01/06/M.S.-20-02).

3. Results

During the study period, 101 live-born infants with congenital EA from four centers in Croatia were documented. During this time, Croatia's birth rate declined; in 2020, 7,405 fewer children were born than in 2010 [13]. However, the number of live-born neonates with EA did not change significantly during this period. The total number of live births with confirmed EA during the study was 101, which corresponds to a rate of 2.64 per 10,000 live births (Table 1).

Table 1
Live-born infants and birth prevalence of esophageal atresia in Croatia during the study period
(2010–2020) per 10,000 live births

Year	Live born infants in Croatia (N)	Live born infants in Croatia with EA¹ (N)	Birth prevalence of EA per 10 000 live births
2010	43361	4	0,92
2011	41197	4	0,97
2012	41771	13	3,11
2013	39939	9	2,25
2014	39566	18	4,55
2015	37503	9	2,40
2016	37537	8	2,13
2017	36556	8	2,19
2018	36945	8	2,17
2019	36135	12	3,32
2020	35956	8	2,22
Total	383105	101	2,64
¹ Esophageal atresia			

Over the eleven-year period in Croatia, between 4 and 13 live births with EA were recorded each year, except in 2014, when 18 cases were reported. Analysis of the annual birth prevalence of EA demonstrated notable year-to-year variability. Overall heterogeneity across the study period was weakly significant ($\chi^2(10) = 17.79$, $p = 0.0585$), suggesting slight, but not conclusive, differences between individual years. However, the Cochran–Armitage trend test showed no evidence of a linear temporal trend ($\chi^2 = 1.91$, $p = 0.1670$), indicating that the observed fluctuations represent random annual variation rather than a systematic increase or decrease in prevalence (Fig. 1).

The epidemiological characteristics of newborns with EA are presented in Table 2.

There was no statistically significant difference between the genders ($P = 0.76$). Most newborns with EA weighed more than 2,500 grams (60.4%, $P < 0.01$) and were born after more than 37 weeks of gestation (66.0%, $P < 0.01$). Associated congenital anomalies were present in 57,4%, with heart and great vessel malformations observed in 21,8% of newborns.

Table 2
Characteristics of mothers and newborns with esophageal atresia in Croatia in the study period (2010–2020)

Characteristics of mothers/ newborns	Newborns with EA (N)	%	χ ²	P
Survived after 1 month	89	88	58,70	< 0,001
Died within 1 month	12	12		
Mothers age (years)				
< 25	9	9	42,39	< 0,001
25–35	61	60		
> 35	28	28		
Missing data	3	3		
Male	52	51	0,089	0,765
Female	49	49		
BW < 1500 g	6	5,9	44,93	< 0,001
BW 1500–2449 g	34	33,7		
BW > 2500 g	61	60,4		
GA < 32 weeks	5	5	55,86	< 0,001
GA 32–36 weeks	30	30		
GA > 37 weeks	66	65		
Isolated EA	43	43	2,23	0,136
EA with associated anomalies	58	57,4		
Associated anomalies:				
heart and Wessels	22	21,8		
VACTRL	19	18,8		
renal, urogenital	10	9,9		
skeletal	6	5,9		
intestinal	5	4,6		
CNS	2	2,0		

The most common type of atresia was Type C – EA with distal fistula (in 88,1% of infants, Table 3).

Table 3
Types of esophageal atresia (EA) in newborns in Croatia in the investigation period (2010–2020).

Type of EA (Gross)	N	%
A	6	5,9
C	89	88,1
D	5	4,9
E	1	1
Total	101	100

Prenatal diagnosis was reported as normal in 57 pregnancies (56.4%). Polyhydramnios was detected in 42 (41,6%) and a small or absent stomach was observed in only three (3%). The results are presented in Table 4.

Table 4
Prenatal diagnosis in newborns with esophageal atresia (EA) in Croatia in the investigation period (2010–2020).

Prenatal diagnosis	N	%
Polyhydramnios	41	40,6
Small/absent stomach	3	3
Normal	57	56,4
Total	101	100

The one-month mortality rate during the study period was 11,9% (N = 12) (Fig. 2).

4. Discussion

Although rare, congenital EA is among the most common major gastrointestinal anomalies. Birth prevalence varies across different regions worldwide. The most recent global meta-analysis reported a prevalence of EA of 2.46 cases per 10,000 births, with the highest prevalence in Oceania (3.07/10,000) and the lowest in North America (1.98/10,000) [4, 14]. A study conducted across Europe in 2012 (European Database for the Surveillance of Congenital Anomalies, EUROCAT) from 23 registries reported a similar prevalence of 2.43 per 10,000 [3].

After that period, several large studies on the prevalence of EA at birth were carried out across various European countries. These studies ranged from five to thirty years and focused either on the entire country or specific larger regions within it. The results of a study conducted in Italy (Veneto region and

Trento province) show a prevalence of EA of 2.87 per 10,000 births [15]. Another study carried out in Germany reports an almost identical prevalence of EA (2.88 per 10,000 births) [16]. However, a similar study performed in Finland reports a higher prevalence of 3.73 per 10,000 births [17].

Two studies on the prevalence of EA have been conducted in Croatia to date. The first study took place in Zagreb and covered the period from 1987 to 2006. The prevalence of EA during this period was surprisingly low (1.27/10,000 births) [3]. The second study was recently conducted at a single center in southern Croatia (Clinical Hospital Centre Split) over a 30-year period (1991–2020); the birth prevalence of EA was 2.44/10,000, consistent with European findings [18].

Our research was conducted throughout Croatia over 11 years. These are the initial results from Croatia, showing an EA prevalence of 2.64 per 10,000 births, which aligns with findings from Split and is slightly lower than the prevalence reported in Italy and Germany [16–18].

The reasons for variation in EA prevalence remain unclear. Likewise, the cause of EA is not well understood. However, environmental factors may contribute to it during fetal development. The most mentioned factors include older maternal age (over 35 years), maternal gestational diabetes, alcohol consumption during pregnancy, and passive smoking [19]. In our study, 30% of mothers were over 35 years old.

Associated anomalies significantly affect mortality rates in neonates with EA. EAs with associated anomalies are slightly more common than isolated ones; according to EUROCAT data, associated anomalies are identified in 55.3% of cases. The most frequent are congenital heart defects (29.4%), urinary system anomalies (16.4%), and other gastrointestinal defects (15.5%). The VACTERL association was observed in 9.6% of cases [3]. In the Finnish study, associated anomalies were found in 58.8% of cases, although their distribution varied. The most common were also congenital heart defects (35%), followed by VACTERL association in 16.6% of cases [18]. In our study, associated anomalies were present in 57.4%. The most frequent was a congenital heart defect (21.8%), followed by VACTERL association, found in 18.8%. Our findings show a different distribution of associated anomalies: congenital heart defects occur less frequently, and the VACTERL association is more common than in the EUROCAT study and the Finnish newborn population.

There are variations in the diagnosis and in the preoperative, operative, and postoperative management of EA across tertiary centers worldwide [19]. Consequently, in 2018, members of the European Reference Network for Rare Inherited Congenital Anomalies (ERNICA) in Berlin established widely accepted guidelines for diagnosing and treating EA. In diagnostics, due to the high prevalence of associated anomalies, particularly cardiac ones, it was agreed that thoracoabdominal X-ray and echocardiography should be performed routinely as part of the preoperative assessment in all newborns with EA [20]. In our study, all four centers conducted thoracoabdominal X-ray and echocardiography on all examined newborns before deciding to proceed with surgery.

Type C malformation, according to Gross, refers to EA with a lower tracheo-esophageal fistula and is the most common type of anomaly, accounting for about 85% [3]. In our study, Type C anomaly was also the most common, representing 88% (N = 89), followed by Type A (N = 6, 5,9%).

Mortality among infants born with EA in European countries ranges from 5–15%, with the highest mortality primarily occurring within the first month of life in neonates with associated anomalies [16–18]. In our study, the overall mortality of neonates with EA within the first month was 11.9% (N = 12). Four newborns (4%) died without surgery due to prematurity and severe associated congenital anomalies. This finding is consistent with published European data.

Despite significant improvements in prenatal detection of congenital anomalies, the prenatal diagnosis rate of EA remains low, at about 30% of cases, depending on the type of atresia and gestational age [21]. According to the EUROCAT registry, prenatal diagnosis rates ranged from over 50% to less than 10% [3]. Polyhydramnios (defined as an amniotic fluid index (AFI) greater than 18 cm or a deepest vertical pocket (DVP) greater than 8 cm) can be detected in about 56% of cases, and a small or absent stomach in about 50% [22]. In our study, the prenatal diagnosis rate for EA was surprisingly low; only 3 fetuses (2.97%) had a small or absent stomach detected prenatally. Although polyhydramnios was found in 40.6% of pregnancies, EA was neither suspected nor further investigated, and MRI was not performed, despite its specificity and sensitivity of more than 90% [22].

Newborns with postnatal diagnosis of EA, compared to those with prenatal detection, have a higher morbidity rate, but this does not appear to affect the 1-year survival outcome [23]. However, prenatal diagnosis avoids postnatal transfer to tertiary centers and allows for counselling and psychological support for the family. Congenital EA has chronic, sometimes very severe, lifelong complications that significantly affect the quality of life of the child and the entire family and should therefore be understood as a lifelong disease. Some complications that survivors with EA experience in adulthood include esophageal adenocarcinoma, GERD, malnutrition, and various respiratory complications [24]. Therefore, timely prenatal diagnosis would help parents to prepare in advance for surgery and, subsequently, ongoing treatment and monitoring of the child.

This study has some limitations. Although our study group was large enough for statistical analyses, a larger sample over a longer study period would make the results more reliable. Also, our study is retrospective; a prospective study would yield more precise data. The follow-up period in this study is only one month, so the outcome after this period may differ. These statements need further investigation.

However, this study has several important strengths. It is the first national study in Croatia on the prevalence of EA, involving all tertiary hospital centers. The epidemiological data, like associated anomalies and prenatal diagnosis of EA, have never been investigated before in this area. It has raised awareness of the need to create a national registry for patients with EA to facilitate easier follow-up.

5. Conclusions

The first epidemiological study on birth prevalence and one-month outcomes of neonates with congenital EA in Croatia aligns with reports from other European countries (2.64/10,000 live births; one-month mortality 11.9%). Our findings reveal a different distribution of associated anomalies: congenital heart defects are less common, while the VACTERL association is more prevalent than in other studies. Prenatal diagnosis remains very low (< 3%). Improved prenatal diagnostics could enable transfer to tertiary centers before birth and assist parents in preparing emotionally for ongoing treatment and potential short-term and long-term complications.

Declarations

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Ethics Committees of Clinical Hospital Centre Rijeka (2170-29-02/1-20-2), Children's Hospital Zagreb (02-23/8-1-22), Clinical Hospital Centre Zagreb (8.1.-25/234-2 02/013AG), and Clinical Hospital Centre Split (2181-147-01/06/M.S.-20-02).

Informed Consent

Statement: Patient consent was waived since the research is retrospective and the identities of the respondents have not been revealed.

Conflicts of Interest:

The authors declare no conflicts of interest.

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Author Contribution

Conceptualization, K.L.T and A.B.V.; methodology, K.L.T; software, A.V; validation, B.P., J.M., and R.G.; formal analysis, A.V.; investigation, K.L.T., A.B.V., B.P., and Br.P. and S.K.,; resources, S.K., J.M., and R.G.; data curation, A.B.V, Br. P; writing—original draft preparation, K.L.T. and A.B.V.; writing—review and editing, A.B.V., A.A., and J.M.; visualization, K.L.T. and A.B.V.; supervision, R.G. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement:

Not applicable.

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Figures

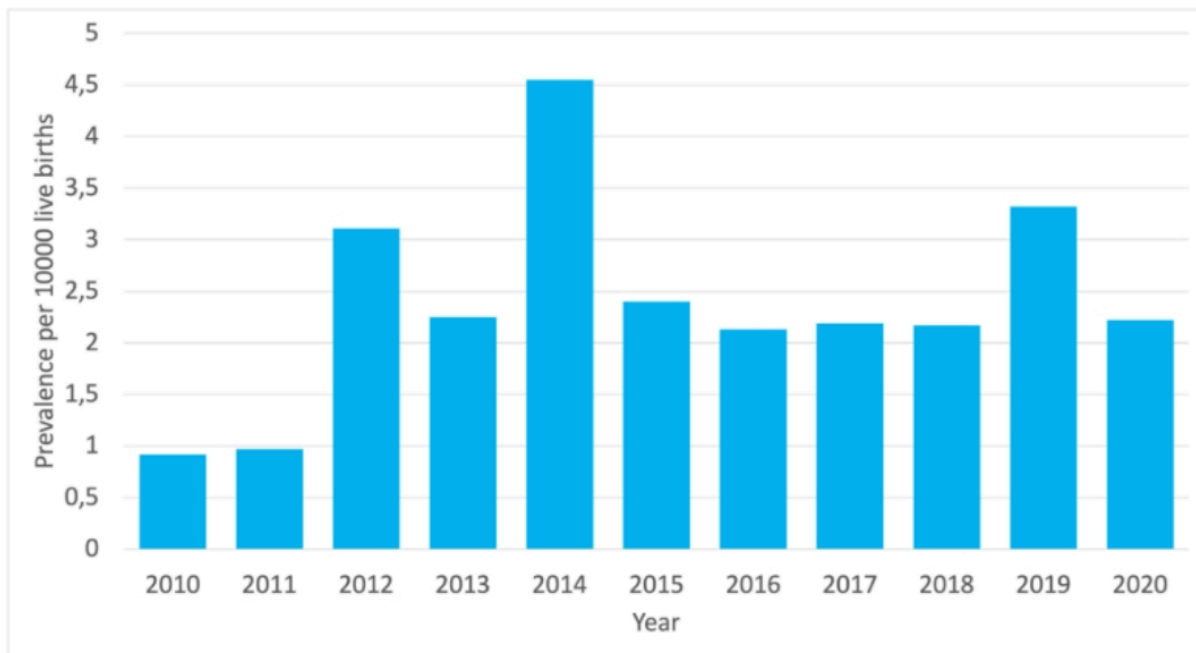


Figure 1

Birth prevalence of infants with esophageal atresia in Croatia during the study period (2010–2020).

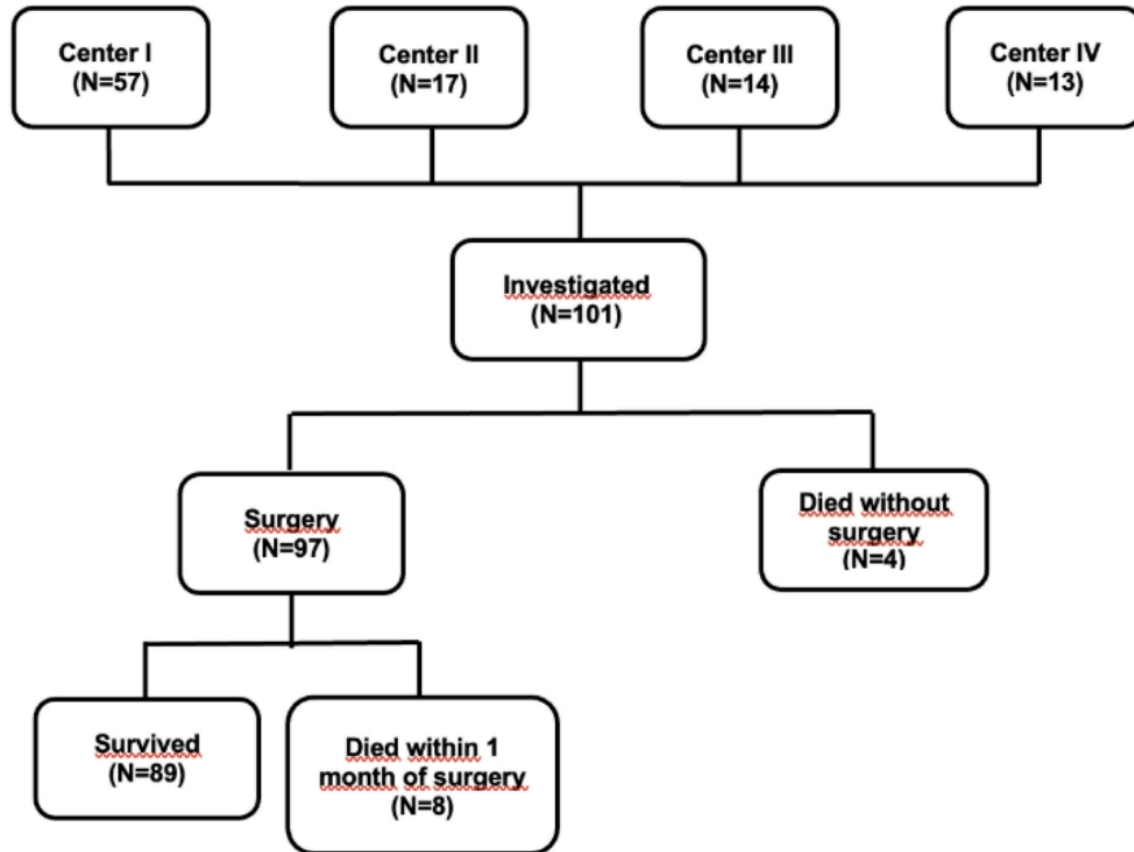


Figure 2

Flow chart: outcome of newborns with esophageal atresia in Croatia during the study period (2010–2020)