

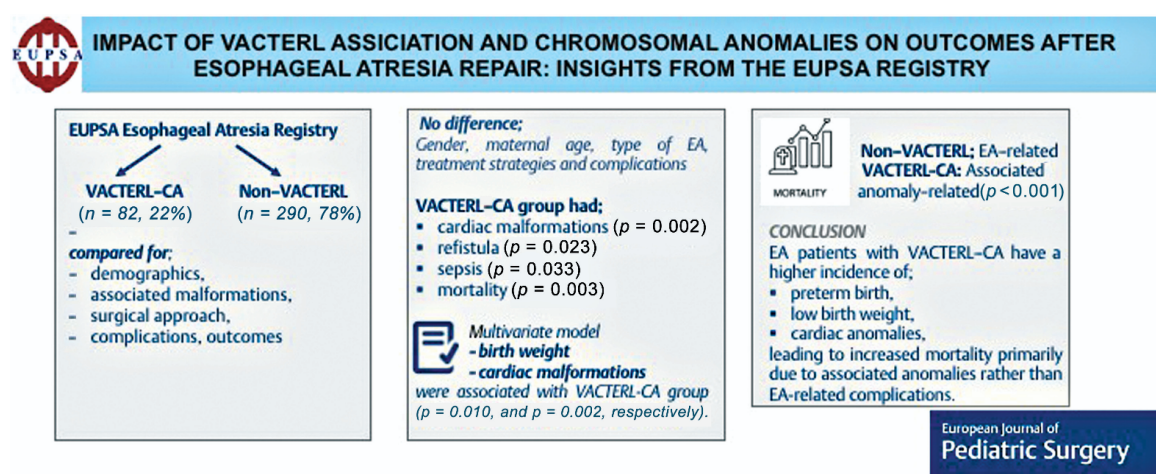
Original Article

Impact of VACTERL Association and Chromosomal Anomalies on Outcomes After Esophageal Atresia Repair: Insights from the EUPSA Registry

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GRAPHICAL ABSTRACT



ABSTRACT

Objective Although VACTERL association is a recognized entity in patients with esophageal atresia (EA), its impact on surgical outcomes remains unclear. This study aimed to evaluate the influence of VACTERL association and chromosomal anomalies (VACTERL-CA) on the surgical outcomes of EA patients, offering novel insights into risk stratification.

Methods All patients enrolled in the European Pediatric Surgeons' Association (EUPSA) Esophageal Atresia Registry (EAR) between July 2014 and December 2017 were included. Patients were classified into two groups: those with VACTERL-CA and those without these anomalies (non-VACTERL). Groups were compared for demographics, associated malformations, surgical approach, complications, and outcomes.

Results Among 372 patients, 22% ($n = 82$) were classified as VACTERL-CA. This group had significantly lower gestational age (35.9 weeks vs. 37.1 weeks, $p = 0.004$), birth weight (2,312 g vs. 2,663 g, $p < 0.001$), and APGAR scores at 5 and 10 minutes ($p = 0.005$). Surgical strategies, including rates of primary anastomosis (88% in both groups), did not differ. Anastomotic leak and stricture rates were similar; however, recurrent fistula was more common in VACTERL-CA (4.9% vs. 1.0%, $p = 0.023$). Overall mortality was higher in VACTERL-CA (14.6% vs. 5.2%, $p = 0.003$), largely due to associated anomalies such as cardiac or neurologic conditions, whereas EA-related mortality was more frequent in non-VACTERL (1% vs. 0%). Sepsis was also more frequent in VACTERL-CA (10.9% vs. 4.5%, $p = 0.033$). In multivariate analysis, low birth weight (adjusted odds ratios [aOR]: 0.95 per 100 g, $p = 0.010$) and cardiac malformations (aOR: 2.33, $p = 0.002$) were independently associated with VACTERL-CA.

Conclusion EA patients with VACTERL-CA represent a high-risk subgroup characterized by prematurity, major cardiac defects, and increased sepsis risk. These findings highlight the need for early cardiac screening, standardized infection-prevention bundles, and tailored multidisciplinary care to improve survival and reduce preventable complications.

Keywords esophageal atresia, VACTERL, chromosomal anomalies, outcome, tracheoesophageal fistula

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‡ The details of the Esophageal Atresia Registry participants are mentioned in [►Supplementary Appendix](#) (available in the online version).

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Introduction

Esophageal atresia (EA) is the most common congenital anomaly of the esophagus and one of the major components of the VACTERL association. Associated anomalies can be seen in 50% of EA patients and most commonly correspond to features of the VACTERL spectrum. The VACTERL association was first described by Quan and Smith in 1973, following an earlier definition known as VATER, which did not include cardiac and limb anomalies. Since then, its diagnostic criteria have been refined.¹ The current definition requires the presence of at least three of the following anomalies, in the absence of a specific genetic diagnosis: vertebral, anal, cardiac, tracheoesophageal fistula, renal, or limb anomalies.²

Previous studies have reported that among EA patients, 14% fulfill criteria for VATER, 19% for VACTERL association, and 12% have anomalies attributable to a single-gene disorder or syndrome.³ In addition to VATER/VACTERL association, several chromosomal and single-gene syndromes, such as trisomy 21, trisomy 18, and CHARGE syndrome, are known to be associated with EA.⁴ The etiology of nonsyndromic EA remains unclear, with various genetic and environmental factors proposed.

Recent genomic studies underscore that VACTERL is genetically heterogeneous with a relatively low yield of single, unifying diagnoses on standard testing: contemporary series using exome/genome approaches report diagnostic findings in a minority of VACTERL cases, and suggest involvement of multiple developmental pathways (including cilia-related signaling), while many patients lack a discrete, known syndrome despite trio exome sequencing.^{5–7} These observations support a model in which VACTERL represents a convergent phenotype from diverse genetic/epigenetic and environmental perturbations rather than a single disease entity.

Outcomes and prognosis may differ significantly between syndromic and nonsyndromic EA. In a contemporary, registry-based study, syndromic EA, both VACTERL and non-VACTERL syndromes, was associated with a higher risk of death than nonsyndromic EA, and this excess risk was independent of syndrome lethality, birth weight, and cardiac disease, emphasizing the importance of stratifying EA by genetic/chromosomal status in outcome analyses.⁸ The presence of chromosomal anomalies (CA) is now incorporated into the EA risk stratification framework. In addition to classic systems (Waterston/Spitz), recent work has revisited and expanded disease-severity and perioperative risk models for EA, reflecting modern outcomes and adjuncts to care.^{9,10}

However, while the co-occurrence of syndromes and chromosomal abnormalities is well documented in EA patients, limited information exists regarding outcomes specifically in patients with VACTERL association and/or CA.¹¹ Some studies have reported no significant relationship between VACTERL and specific complications such as anastomotic stricture or gastroesophageal reflux,¹² while others have found prematurity and VACTERL to be risk factors for long-term gastrointestinal and respiratory morbidity.¹³ Never-

theless, large-scale studies directly comparing the surgical outcomes of EA patients with and without VACTERL association and chromosomal anomalies remain scarce. It is still unclear whether adverse outcomes in these patients result from the VACTERL association itself or from the higher prevalence of additional risk factors in this subgroup.

The European Pediatric Surgeons' Association (EUPSA) Esophageal Atresia Registry (EAR) is a patient-based registry that collects standardized data on EA patients. Using this resource, we aimed to define the clinical features and surgical outcomes of EA patients with VACTERL association and/or CA, and to compare them with those of patients without these associations.

Methods and Patients

All EA patients enrolled in the EUPSA EAR database between July 2014 and December 2017 were included in the study. The EUPSA EAR is an international collaboration of 23 European and non-European pediatric surgical centers, collecting standardized data on infants with EA who were born at or transferred to a participating center before any major esophageal surgery.¹⁴ Data were submitted anonymously via a standardized online form, verified for consistency, and stored in a central database. The dataset included prenatal information, demographic characteristics, perioperative and postoperative management, and outcomes until death or hospital discharge. Participating centers contributed cases voluntarily. Informed consent was obtained from parents or guardians, and ethical approval was obtained according to the local regulations. Additional ethical approval was not required for this study, as only anonymized registry data were analyzed.

Patients were classified into two groups:

- VACTERL-CA group: patients with at least three anomalies from the VACTERL spectrum or those with a diagnosed CA. CA included microdeletions, trisomies, and syndromic conditions confirmed by genetic testing and counseling.
- Non-VACTERL group: patients without VACTERL association or CA, including those with one or two associated anomalies not meeting VACTERL criteria.

Associated anomalies:

- Cardiac anomalies were classified as major if they were hemodynamically significant lesions requiring surgical or catheter-based intervention or intensive perioperative monitoring (e.g., ventricular septal defect > 3 mm, tetralogy of fallot, and hypoplastic left heart syndrome), and as minor if they were clinically insignificant lesions not requiring intervention (e.g., small patent ductus arteriosus or patent foramen ovale).
- Renal anomalies were defined as structural defects confirmed on ultrasound (agenesis, dysplasia, and obstructive uropathy).
- Vertebral anomalies required radiographic confirmation.

- Limb anomalies included radial dysplasia, polydactyly, or limb-length discrepancies.

Mortality was categorized as:

- EA-related mortality: death attributable to surgical complications directly related to EA repair (e.g., anastomotic leak and mediastinitis).
- Comorbidity-related mortality: death due to associated anomalies or medical complications (e.g., congenital heart disease, renal failure, and sepsis unrelated to EA surgery).

Statistical Analysis

Categorical data were presented as frequencies and percentages. Continuous data were summarized as means with standard deviation (SD) or medians according to distribution.

Univariate and multivariate logistic regression analyses were performed to evaluate the associations between the VACTERL spectrum and/or CA as the dependent variable, and the independent variables birth weight, in vitro fertilization, cardiac malformations, anastomotic leak, stricture requiring therapy, recurrent fistula, sepsis, and the final outcome (discharge/death).

Additionally, univariate and multivariate logistic regression analyses were performed to assess the associations between anastomotic complications (including anastomotic leak, stricture, and recurrent fistula) with independent variables such as the presence of VACTERL spectrum and/or CA, birth weight, presence of cardiac malformations, sepsis, and the final outcome (discharge/death).

For the multivariate analysis, only variables without missing values were included. Missing data were limited to maternal age (three cases in the VACTERL-CA group and 10 in the non-VACTERL group) and APGAR scores (1 at 5 minutes and 4 at 10 minutes in the VACTERL-CA group; 5 at 5 minutes and 16 at 10 minutes in the non-VACTERL group).

Although similar data were collected and analyzed from all centers, it was not possible to identify all center-related confounding factors and include them in multivariate analysis.

Demographic and clinical characteristics of patients in the two groups were compared, considering the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. All the tests were two-tailed.

Odds ratios (OR) and adjusted odds ratios (aOR) with 95% confidence intervals (CI) and *p*-values of significance were calculated and presented for each independent variable. A *p*-value of < 0.05 was taken as statistically significant. Statistical analyses were performed using R version 4.3.1 (2023, R core team, Vienna, Austria).

Results

Among 372 patients included in the EUPSA EAR database, 82 (22.0%) were classified into the VACTERL-CA group and 290 (78.0%) into the non-VACTERL group. The demographic and clinical characteristics are summarized in **Table 1**. Compared with the non-VACTERL group, patients in the VACTERL-CA group had significantly lower mean gestational age ($p = 0.004$), birth weight ($p < 0.001$), and APGAR scores at both 5 minutes ($p = 0.005$) and 10 minutes ($p = 0.005$). No significant differences

were observed between the groups in terms of EA type, maternal age, type of conception, or mode of delivery (**Table 1**).

Associated Anomalies

The distribution of associated anomalies in the EUPSA EAR database is summarized in **Table 2**. After grouping the patients according to VACTERL-CA status, the incidence and types of associated anomalies are shown in **Fig. 1**. Within the VACTERL spectrum, after EA (99%) and TEF (98%), the most common anomalies were cardiac ($n = 52$, 63%) and vertebral ($n = 44$, 54%). CA were identified in 23% ($n = 19$) of cases. Six VACTERL components were present in five patients (6%), five components in 15 patients (18%), four components in 33 patients (40%), and three components in 18 patients (22%). In the non-VACTERL group, 41% of cases ($n = 116$) had major or minor cardiac anomalies as the sole associated anomaly. Of these, 35% were minor cardiac anomalies (such as patent ductus arteriosus or foramen ovale), while 6% were major cardiac anomalies requiring surgery. In comparison, 11% of patients in the VACTERL-CA group had major cardiac anomalies. Although other associated anomalies were observed in the non-VACTERL group, these cases did not meet the VACTERL criteria, which require at least three defining anomalies.

The most common genetic or CA included microdeletion and structural chromosomal defects ($n = 9$), followed by trisomy 18 ($n = 3$), CHARGE syndrome ($n = 2$), trisomy 21 ($n = 1$), trisomy 16 ($n = 1$), trisomy 13 ($n = 1$), DiGeorge syndrome ($n = 1$), and Feingold syndrome ($n = 1$).

Surgical Procedures and Complications

Management strategies in both groups are shown in **Fig. 2**. Thoracoscopy was performed in 3% ($n = 2$) of VACTERL-CA patients and 6% ($n = 16$) of non-VACTERL patients. Primary anastomosis was achieved in 88% of cases in both the VACTERL-CA ($n = 72$) and non-VACTERL ($n = 255$) groups. There was no significant difference between the two groups in terms of surgical approach.

Rates of anastomotic leak (9.7% vs. 9.3%, $p = 0.902$) and stricture (14.6% vs. 14.8%, $p = 0.965$) did not differ significantly between groups. However, recurrent fistula was more common in the VACTERL-CA group (4.9% vs. 1.0%, $p = 0.023$; **Table 3**).

Mortality

Overall mortality was significantly higher in the VACTERL-CA group compared with the non-VACTERL group (14.6% vs. 5.2%, $p = 0.003$). EA-related mortality occurred only in the non-VACTERL group ($n = 3$, 1%) and was absent in the VACTERL-CA group (0%). Comorbidity-related mortality due to associated anomalies or medical complications was significantly more frequent in the VACTERL-CA group ($n = 12$, 14.6%) than in the non-VACTERL group ($n = 12$, 4.1%; $p < 0.001$).

Across the entire EAR database, the mean interval between repair and death was 54.5 days (total range: 2–328). Two-thirds of deaths ($n = 18$, 66%) occurred within the first 30 postoperative days. The timing of death did not differ according to surgical strategy (primary vs. delayed repair, $p = 0.83$).

Table 1 Demographic and clinical characteristics of patients in the VACTERL-CA and non-VACTERL groups

Parameters	VACTERL-CA (n = 82)	Non-VACTERL (n = 290)	p-Value
Gross type of EA (n, %)			
Type-C	75 (91%)	253 (87%)	0.295
Type-B	2 (2%)	3 (1%)	0.329
Type-A	3 (4%)	27 (9%)	0.097
Type-D	1 (1%)	3 (1%)	0.885
Type-E	1 (1%)	4 (1%)	0.911
Gestational age at birth (wk, mean ± SD)	35.9 ± 3.3	37.1 ± 3.08	0.004 ^a
Birth weight (g, mean ± SD)	2,312 ± 710.5	2,663 ± 738.5	<0.001 ^a
Maternal age (y, mean ± SD)	31.1 ± 6.5	30.6 ± 6.7	0.412
Gender (n, M/F)	44/38	168/122	–
In vitro fertilization (n, %)	7 (8.5%)	20 (6.9%)	0.613
Type of delivery (n, %)			
–Vaginal	42 (51.2%)	168 (57.9%)	0.279
–C/S	40 (48.8%)	120 (41.4%)	0.231
APGAR 5 min (median, range)	8 (6–9)	9 (8–9)	0.005 ^a
APGAR 10 min (median, range)	9 (8–10)	9 (9–10)	0.005 ^a
Overall mortality (n, %)	12 (14.6%)	15 (5.2%)	0.003 ^a
–EA-related mortality	0	3 (1%)	–
–Comorbidity-related mortality (associated anomaly or medical complications)	12 (14.6%)	12 (4.1%)	<0.001 ^a
–Cardiac causes	5 (6%)	9 (3%)	0.208
–Renal failure	2 (2%)	5 (2%)	0.674
–Cerebral causes/chromosomal	6 (7%)	3 (1%)	0.001 ^a
–Other causes	8 (10%)	9 (3%)	0.010 ^a

Note: Comparisons were performed using the chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. Some patients had more than one reported cause of mortality. “Cerebral/chromosomal” mortality refers to deaths due to neurologic disorders with or without associated chromosomal anomalies.

^arefers to the p-value less than 0.05 is considered as significant

Sepsis was more frequent in the VACTERL-CA group (10.9% vs. 4.5%, $p = 0.033$). Line infections occurred in 5% versus 2% of patients, respectively, although this difference was not statistically significant ($p = 0.340$). The EAR database did not provide further information regarding the underlying source of sepsis.

Multivariate Regression Analysis

When considering all variables jointly in a multivariate model with VACTERL-CA as the dependent variable (**Fig. 3**), birth weight (per 100 g) was significantly associated with reduced odds of belonging to the VACTERL-CA group (aOR: 0.95, 95% CI: 0.92–0.99, $p = 0.010$). Cardiac malformations were also significantly associated with the VACTERL-CA group (aOR: 2.33, 95% CI: 1.37–4.00, $p = 0.002$). Other variables, including in vitro fertilization, anastomotic leak, stricture, refistula, sepsis, and final outcome (death), were not significantly associated.

When assessing anastomotic complications as the dependent variable, sepsis was the only independent variable significantly associated with increased risk (aOR: 6.41, 95% CI: 2.49–17.36, $p < 0.001$). Birth weight (per gram), presence of cardiac malformations, VACTERL-CA, and outcome (death) were not significantly associated with anastomotic complications in the multivariate model (**Fig. 4**).

Discussion

In this multicenter registry analysis, VACTERL-CA marked a distinct clinical phenotype among infants with EA: earlier gestation, lower birth weight, and a heavier burden of major cardiac defects. These baseline differences, not the VACTERL label per se, appear to drive risk. In adjusted models, lower birth weight and cardiac

Table 2 The distribution of associated anomalies in EUPSA EAR

Associated anomalies	n, %
Cardiac malformations	166 (44.6%)
–Major requiring operation	22 (5.9%)
–Minor	144 (38.7%)
–PDA ligation	6 (1.6%)
–Right aortic arc	16 (4.3%)
Gastrointestinal malformations	62 (16.6%)
–Duodenal atresia	12 (3.2%)
–Intestinal atresia	1 (0.2%)
–Anorectal malformation	44 (11.8%)
CDH	8 (2.1%)
Renal malformations	55 (14.7%)
Musculoskeletal malformations	80 (21.5%)
–Vertebral	55 (14.7%)
–Ribs	25 (6.7%)
–Other skeletal parts	29 (7.7%)

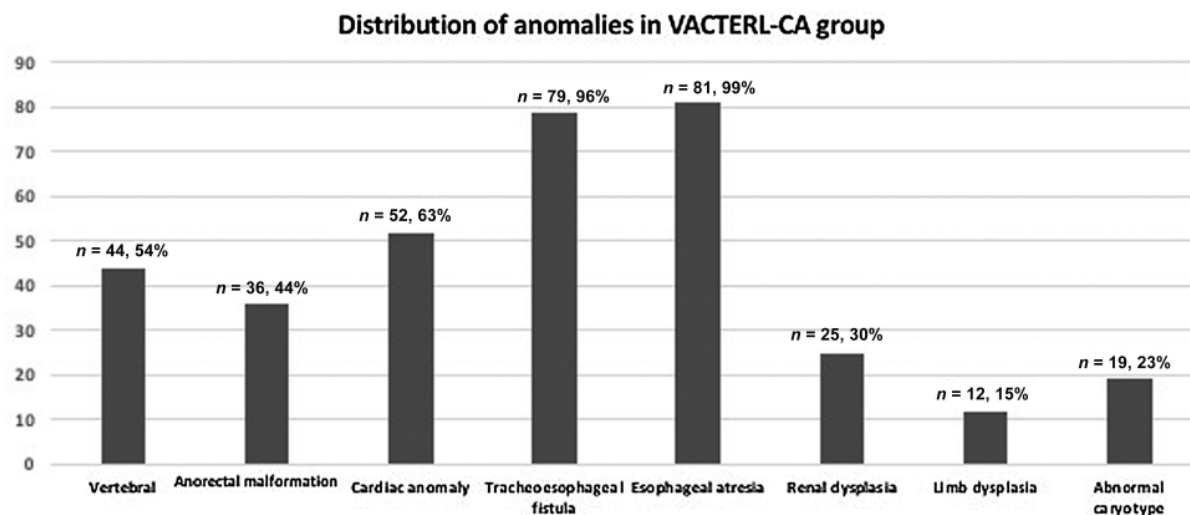


Fig. 1 Distribution of associated anomalies in the VACTERL-CA group.

malformations were independently associated with VACTERL-CA status, whereas VACTERL-CA itself did not predict anastomotic complications. This aligns with contemporary risk-stratification frameworks in EA emphasizing birth weight and major cardiac disease (e.g., the revised Spitz classification).^{8,10,15}

Compared with prior studies, Hew et al reported a higher rate of anastomotic complications in syndromic EA, implying a potential direct effect of syndromic status.¹² In contrast, Rayyan et al showed that complication rates were largely driven by comorbidity load, specifically low birth weight and major cardiac anomalies,

rather than syndromic classification per se.¹³ Our findings align with Rayyan et al, reinforcing that the apparent increased risk in VACTERL-CA is mediated by baseline patient factors rather than the label itself, clarifying prior discrepancies.^{12,13}

Our mortality signal mirrors population-level data showing poorer survival in syndromic EA, including VACTERL. In a national cohort, syndromic cases, particularly VACTERL, had higher hazards of death after adjustment for case-mix, underscoring that the excess risk resides largely in comorbidity load rather than in the esophageal anomaly alone.⁸ In our series, EA-related deaths were

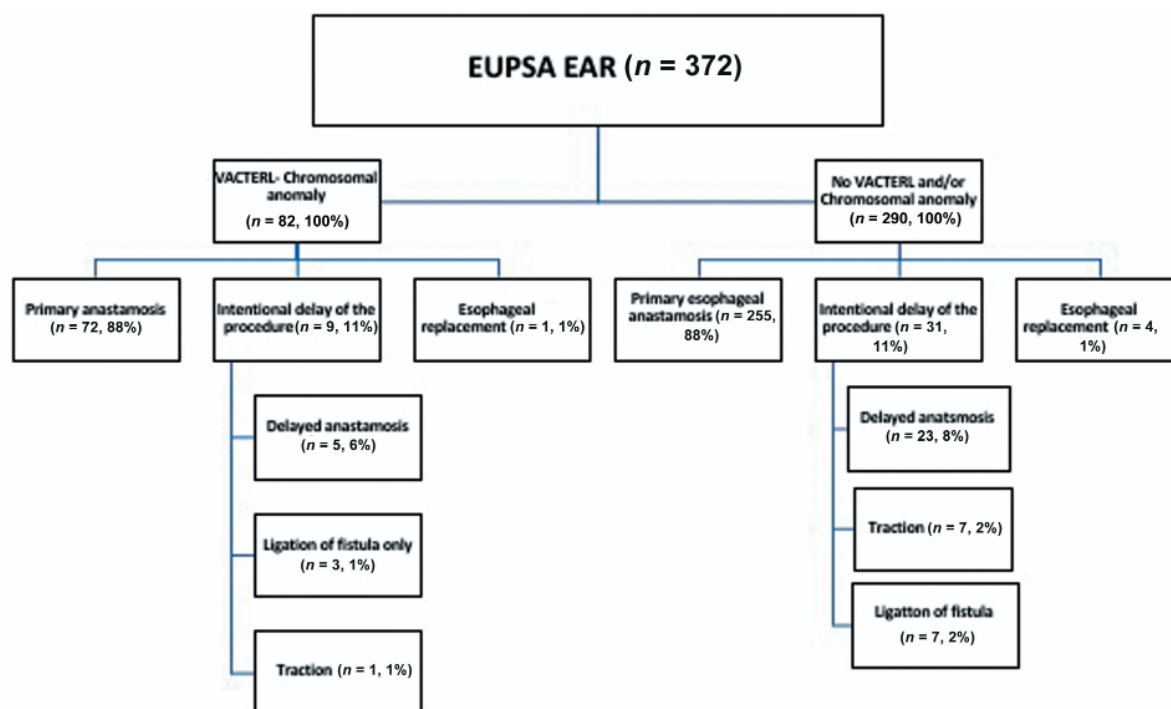


Fig. 2 Surgical treatment of VACTERL-CA and non-VACTERL groups.

Table 3 Comparison of surgical complication rates between VACTERL-CA and non-VACTERL groups

	VACTERL-CA (n = 82)	Non-VACTERL (n = 290)	p-Value
Anastomotic leak (% , count)	9.7 8/82	9.3 27/290	0.902
Stricture (% , count)	14.6 12/82	14.8 43/290	0.965
Recurrent fistula (% , count)	4.9 4/82	1.0 3/290	0.023 ^a

^ap-Value < 0.05 was considered statistically significant.

uncommon in VACTERL-CA; instead, deaths clustered around associated anomalies (notably cardiac) and intercurrent illness, consistent with prior observations that survival in EA increasingly depends on extra-esophageal factors.^{16,17}

Several pathways plausibly link the VACTERL-CA profile to adverse outcomes: first, hemodynamic fragility from congenital heart disease can impair tissue perfusion and oxygen delivery, increasing susceptibility to postoperative complications and sepsis. Second, low birth weight/prematurity compromises immune function and wound healing, elevating risk of infection and anastomotic problems. Third, care complexity (multiple procedures, prolonged lines/ventilation) expands exposure to nosocomial pathogens. Literature outside VACTERL confirms sepsis as a

potent driver of postoperative morbidity in EA, and anastomotic disruptions further perpetuate local inflammation and stricture formation.^{18–20}

We acknowledge that while prior studies have suggested that refistula formation is associated with poor outcomes, our analysis did not independently assess this.¹⁹ Importantly, we found sepsis to be the only independent predictor of anastomotic complications. While causality cannot be inferred, this bidirectional relationship is biologically plausible: systemic infection may impair anastomotic healing, and conversely, occult leak can seed infection. Prior studies also connect leak and subsequent stricture, supporting vigilant surveillance and early treatment when infection or leak is suspected.^{18,19} The correlation between sepsis and complications is striking, as it was the only independent predictor in our cohort, underscoring the need for early detection and aggressive management.

Our findings also fit within a broader genetic context. Although most VACTERL cases lack a single unifying mutation, emerging population-based data demonstrate that syndromic EA and VACTERL confer higher mortality and complex trajectories, reinforcing the need to integrate phenotype and genotype into risk models.⁸ Neurodevelopmental comorbidity has been reported more frequently in VACTERL survivors, highlighting the importance of longitudinal, multidisciplinary follow-up.²¹

In this context, the high rate of sepsis in VACTERL-CA patients underscores the need for standardized infection-prevention bundles, including perioperative antibiotic prophylaxis, strict central line stewardship, early removal of invasive devices,

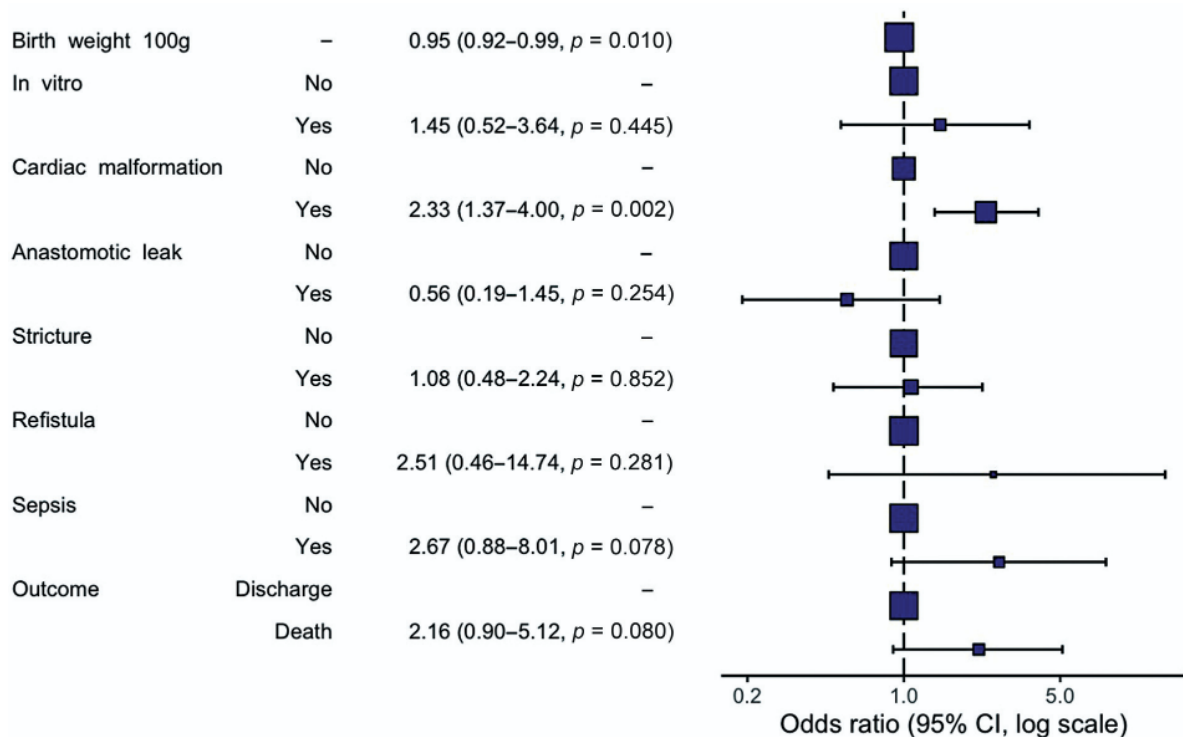


Fig. 3 Multivariate logistic regression analysis assessing factors associated with belonging to the VACTERL-CA group (dependent variable: VACTERL-CA vs. non-VACTERL). Independent variables: birth weight (per 100 g), in vitro fertilization, cardiac malformations, anastomotic leak, stricture requiring therapy, recurrent fistula, sepsis, and final outcome (discharge vs. death).

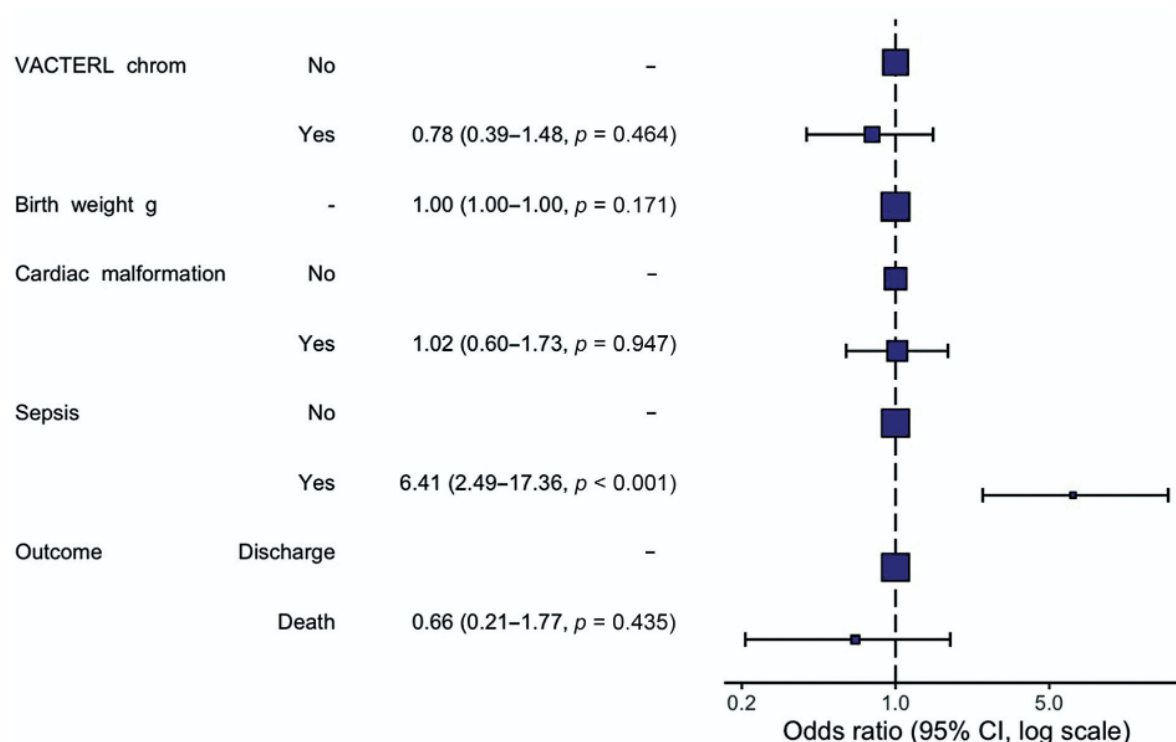


Fig. 4 Multivariate logistic regression analysis assessing factors associated with anastomotic complications (dependent variable: presence vs. absence of leak, stricture, or refistula). Independent variables: presence of VACTERL-CA, birth weight (per gram), presence of cardiac malformations, sepsis, and final outcome (discharge vs. death).

and multidisciplinary sepsis rounds. Moreover, given the high prevalence of cardiac anomalies, all neonates with EA and suspected VACTERL should undergo early echocardiography and cardiology consultation. Early identification of cardiac lesions can inform surgical timing, anesthetic strategy, and postoperative monitoring, thereby reducing preventable complications.

The first clinical implication is to recommend immediate, protocolized cardiac evaluation and incorporation of cardiac severity and birth weight into perioperative risk discussions, consistent with modern EA stratification.^{10,15} Second, given the strong association between sepsis and anastomotic morbidity, units should intensify infection-prevention bundles (vascular access, ventilation, and perioperative antibiotics stewardship) and adopt low thresholds for investigating leaks in clinically unstable infants.¹⁵ Third, because VACTERL-CA signals a multisystem care pathway, standardized postdischarge surveillance (cardiology, nephrology/urology, orthopedics, and gastroenterology/airway) is warranted.

It is important to distinguish VACTERL association from CA, as they are biologically and clinically distinct entities. Chromosomal syndromes (e.g., trisomy 18, trisomy 21, and trisomy 13) confer independent mortality and morbidity risks beyond EA, while VACTERL represents a phenotypic constellation without a unifying genetic lesion. Our dataset was underpowered for formal subgroup analyses, but future studies should stratify patients into isolated VACTERL, isolated CA, and combined phenotypes.

We acknowledge that VACTERL and CA are heterogeneous. Our cohort of isolated CA was too small for powered subgroup or sensitivity analyses; future multicenter collaborations should pre-specify VACTERL versus chromosomal strata and incorporate time-to-event endpoints to disentangle pathways to mortality and morbidity. Harmonized genetic testing and standardized definitions (e.g., major vs. minor cardiac anomalies) will further refine risk estimates.⁸ Despite its strengths, our study has several limitations. Not all patients in the EUPSA EAR database underwent genetic testing, raising the possibility that some non-VACTERL patients had undiagnosed CA. Missing data were minimal, and variables with missingness (maternal age and APGAR) were excluded from multivariable models; practice variation across centers may also influence outcomes, though such heterogeneity enhances generalizability. Although similar data were collected and analyzed from all centers, it was not possible to identify all center-related confounding factors and include them in multivariate analysis.

In EA, the risk phenotype commonly attributed to “VACTERL” is largely explained by low birth weight, major cardiac malformations, and sepsis. Targeting modifiable or monitorable factors such as cardiac comorbidities and sepsis may help improve outcomes, although the optimal impact of these strategies remains to be confirmed. While our findings support early cardiac evaluation and implementation of infection-prevention bundles in high-risk infants, these recommendations require prospective validation, and our conclusions are tempered by the retrospective design, limited sample size, and underpowered subgroup analyses.

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Statements and Additional Information

Conflict of Interest The authors declare that they have no conflict of interest.

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