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Retrospective analysis of neurological findings in esophageal atresia: Allostatic load of disease complexity, cumulative sedation, and anesthesia exposure

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Abstract

Background: There is limited knowledge regarding the impact of perioperative critical care on frequency of neurological imaging findings following esophageal atresia (EA) repair.

Methods: This is a retrospective study of infants ($n = 70$) following EA repair at a single institution (2009–2020). Sex, gestational age at birth, type of surgical repair, underlying disease severity, and frequency of neurologic imaging findings were obtained. We quantified the length of postoperative pain/sedation treatment and anesthesia exposure in the first year of life. Data were presented as numerical sums and percentages, while associations were measured using Spearman's Rho.

Results: Vertebral/spinal cord imaging was performed in all infants revealing abnormalities in 44% (31/70). Cranial/brain imaging findings were identified in 67% (22/33) of infants in the context of clinically indicated imaging (47%; 33/70). *Long-gap* EA patients ($n = 16$) received 10 times longer postoperative pain/sedation treatment and twice the anesthesia exposure compared with *short-gap* EA patients ($n = 54$). The frequency of neurologic imaging findings did not correlate with underlying disease severity scores, length of pain/sedation treatment, or cumulative anesthesia exposure. Lack of associations between clinical measures and imaging findings should be interpreted with caution given possible underestimation of cranial/brain findings.

Conclusions: We propose that all infants with EA undergo brain imaging in addition to routine spinal imaging given the high burden of abnormal brain/cranial findings in our cohort. Quantification of pain/sedation and anesthesia exposure in *long-gap* EA patients could be used as indirect markers in future studies assessing the risk of neurological sequelae as evidenced by early abnormalities on brain imaging.

Abbreviations: ASA, American Society of Anesthesiologist; EA, esophageal atresia; EGD, esophagogastroduodenoscopy; MAC, minimal alveolar concentration; PRAm, pediatric risk assessment; *r*, Spearman's Rho; VACTERL, vertebral, anorectal, cardiac, tracheo-esophageal fistula and/or esophageal atresia, renal, and limb defects/malformations.

KEYWORDS

anesthetic exposure, brain, central nervous system, EA, LGEA, neurologic, opioids, peripheral nervous system

1 | INTRODUCTION

Although esophageal atresia (EA) is a rare congenital anomaly with a worldwide prevalence of 1 in 2500 to 1 in 4500 births (Badran et al., 2020; Baldwin & Yadav, 2023), it is one of the most common gastrointestinal birth defects (Aspirot et al., 2013). Traditionally, EA has been classified into types A-D according to anatomical characteristics in relation to airway structures (Gross, 1962). In addition, EA can also be described and categorized by the length of esophageal gap into *short-gap* and *long-gap* EA, which reflects the complexity of underlying disease and perioperative critical care (Rassiwala et al., 2016). Specifically, infants born with *short-gap* EA undergo repair by primary anastomosis, requiring only one major surgery (Hunt et al., 2016) and shorter postoperative sedation and pain management course. In contrast, infants born with *long-gap* EA (>3 cm or >2 vertebral bodies in length) (Castilloux et al., 2010) undergo more complex perioperative care. At our institution, *long-gap* EA is repaired by the revolutionary Foker process (Bairdain et al., 2015; Foker et al., 1997; Foker et al., 2009; Kunisaki & Foker, 2012) that allows for lengthening of infant's existing esophageal pouches. However, this process requires at least two thoracotomies/thoracoscopies and subsequent prolonged postoperative mechanical ventilation (Hodkinson et al., 2019; Mongerson et al., 2019; Rudisill et al., 2019). As such, infants undergoing the Foker process with external traction almost invariably develop a physical dependence to drugs of sedation and pain management (Hodkinson et al., 2019; Solodiuk et al., 2019).

EA has previously been thought to have no neurological component, except when associated with syndromes (Cassina et al., 2016). However, recent reports have indicated that infants with gastrointestinal anomalies, including those born with EA, are at risk of long-term neurodevelopmental sequalae (Stolwijk et al., 2016). Furthermore, our recent case series reported incidental brain findings at birth in infants born with *long-gap* EA that worsen over the course of complex perioperative critical care with the Foker process (Rudisill et al., 2019). Our recent pilot MRI study of infants born with *long-gap* EA reported clinically significant incidental brain findings (Mongerson et al., 2019) and implicated risk of brain atrophy (Bajic et al., 2021; Lee Mongerson et al., 2019; Mongerson et al., 2019) following complex perioperative critical care with the Foker process. While the Foker process (Bairdain et al., 2015; Foker et al., 1997; Foker et al., 2009; Kunisaki & Foker, 2012) is a necessary and life-saving surgical intervention for children that otherwise would not survive, it is important to understand the long-term neurological implications of such complex care, especially now in the setting of prolonged survival of infants born with EA (Evanovich et al., 2022). The need for our better understanding of neurological risk can help better prepare families to address and seek early intervention for any neurologic sequelae that might arise.

In this novel retrospective analysis, we quantified the frequency of neurologic findings in infants born with EA in a previously described EA patient cohort (Evanovich et al., 2022) that underwent primary EA repair at our institution. Specifically, we quantified documented (a) vertebral/spinal cord and (b) cranial/brain findings in the context of (i) gestational age (term-born vs. premature), (ii) the type of surgical repair (e.g., primary anastomosis vs. the Foker process with prolonged sedation), and (iii) disease severity scores (American Society of Anesthesiologists [ASA] classification and Pediatric Risk Assessment [PRAm] score). Our secondary objective was to quantify postoperative sedation exposure following EA repair and cumulative anesthesia exposure in the first year of life as possible early indirect markers of underlying disease complexity in relation to the number of neurological imaging findings. Preliminary results were, in part, previously reported as an abstract (McMahon et al., 2022) and thesis (McMahon, 2022).

2 | METHODS

2.1 | Study design and study subjects

The current study is an extension of our previous retrospective study (Evanovich et al., 2022) of infants born with esophageal atresia (EA) that underwent repair at our institution over the period of 11 years (2009–2020). Data were obtained from a prospectively maintained *Esophageal and Airway Treatment Center* REDCap database established in 2009. The research study was approved by Institutional Review Board (IRB-P0000 07855) and was classified as a no greater than minimal risk study. The study conformed to the standards set by the Declaration of Helsinki and Good Clinical Practice

guidelines. Eligibility criteria included: (1) term-born (37–42 weeks of gestation at birth) and early-to-late premature infants (28 to <37 weeks of gestation) born with EA of any type and (2) patients that received all their surgical treatment at our institution. All infant patients in this retrospective cohort underwent surgery in the first month of life except for two patients that were born outside of the state and underwent primary surgical repair at our institution at 2 and 3 months of age. Exclusion criteria included history of: (1) surgical repair at other institutions (including but not limited to EA repair) and (2) extreme prematurity (<28 weeks of gestation). As we are interested in elucidating frequency of neurological findings in infants born with EA, we also excluded infants with a history of (3) chromosomal and genetic abnormalities (e.g., Trisomy 21, Trisomy 18, 4p duplication) known to be associated with either abnormal neurological imaging or abnormal neurodevelopmental outcomes ($n = 14$) (Evanovich et al., 2022). Due to the retrospective study design, identifications of associated genetic and congenital anomalies were obtained from the medical records as part of the clinical diagnostics and treatment. Therefore, our current retrospective study included a total of 70 patients ($n = 44$ term-born; $n = 26$ premature). Cohort characteristics with respect to other associated anomalies are summarized in Table 1.

TABLE 1 Esophageal atresia in context of other congenital anomalies.

	Number	Percentage (%)
(a) EA as part of complex congenital syndrome (cohort $n = 70$)		
VACTERL	24	34
CHARGE	0	0
Other	0	0
None	46	66
(b) EA with other co-anomalies apart from syndrome ($n = 46$)		
None	6	13
Isolated co-anomaly	3	7
2 co-anomalies	15	33
>2 co-anomalies	22	48
(c) Distribution of co-anomalies apart from syndrome ($n = 46$)		
Anorectal	0	0
Vertebral	9	20
Cardiac	36	78
Laryngeal cleft	8	17
Tracheo(broncho)malacia	23	50
Limb	2	4
Renal or kidney	12	26

Note: Esophageal Atresia (EA) in the Context of Other Congenital Anomalies. This table summarizes the frequency of EA with or without other congenital anomalies. "(a)" shows that 37% (26/70) of EA was a part of VACTERL association. "(b)" shows that of those EA infants with no complex congenital diagnosis (46/70; 66%), a majority had either 2 (15/46; 33%) or >2 (22/46; 48%) co-occurring congenital anomalies not associated with the syndrome. Frequency of specific co-existing anomalies is listed in "(c)". Interestingly, most patients had a cardiac anomaly (36/46; 78%) and no patients had a documented anorectal anomaly occurring outside of a syndrome. Acronyms: CHARGE, Coloboma, Heart defects, choanal Atresia, growth Retardation, Genital abnormalities, and Ear abnormalities; VACTERL, Vertebral, Anorectal, Cardiac, Tracheo-esophageal fistula and/or Esophageal atresia, Renal, and Limb defects/malformations.

2.2 | Chart review

As previously described in detail in our recent report (Evanovich et al., 2022), demographic and clinical characteristics were collected using the electronic medical record, Powerchart (Cerner, London, UK). Collected data included: (1) sex, (2) gestational age at birth (weeks), and (3) corrected post-natal age at first EA surgery (weeks). The latter represents the sum of gestational age at birth and chronological age. Furthermore, clinical data encompassed the following:

2.2.1 | Esophageal atresia types

Surgical type of EA was categorized based on the length of esophageal gap into *short-gap* EA and *long-gap* EA. At our institution, *short-gap* EA patients underwent primary anastomosis repair, while patients with *long-gap* EA underwent complex perioperative care as part of the Foker Process (Bairdain et al., 2015; Foker et al., 1997; Foker et al., 2009; Kunisaki & Foker, 2012). The Foker Process involves several stages (Liszewski et al., 2014): (1) Foker I thoracotomy to place traction sutures with continuous traction onto blind esophageal ends; (2) Prolonged postoperative mechanical ventilation with sedation to provide time for esophageal lengthening; (3) Foker II thoracotomy to approximate esophageal ends and perform esophageal anastomosis; and (4) post-Foker healing of the anastomosis with sedation and subsequent weaning of sedation while transitioning from total parenteral nutrition to enteral feeds (Rudisill et al., 2019). The time course for complex perioperative critical care spanning a period of weeks for the Foker process was illustrated previously (figure 1 in Mongerson et al. (2019) and figure 1 in Hodkinson et al. (2019)). Thus, the unique aspect of complex perioperative care in cases of *long-gap* EA repair relates to prolonged sedation requiring a slow and thoughtful weaning process to prevent symptoms of withdrawal (Anand et al., 1999; Dewey, 1984; Solodiuk et al., 2019). Furthermore, irrespective of the type of EA

repair, infants also undergo serial follow up esophagogastroduodenoscopies (EGD) (van Hoorn et al., 2021) requiring repeated anesthesia exposures in the first year of life to assess surgical healing and to allow for esophageal dilations to prevent anastomosis stricture formation.

2.2.2 | Neurological diagnostics and findings

We quantified the number of neurologic diagnostic studies obtained during the first year of life (e.g., spinal and/or cranial ultrasound and MRI). Subsequently, we classified neurologic findings into two categories: vertebral/spinal cord and cranial/brain findings (Table 2). Vertebral findings (e.g., fused, malformed, segmented vertebrae) were noted if present at birth. Vertebral findings not involving neurological tissue were also counted with spinal cord findings considering their potential impact on long-term spinal cord and peripheral nerve health and function. Spinal cord findings were categorized as the presence of a fatty filum terminale and/or a low laying conus medullaris, which together were counted as one spinal cord finding due to their coexistence in tethered cord syndrome (Apaydin, 2020). Cranial findings included the presence of abnormal head shape (viz. plagiocephaly, brachycephaly, etc.), and/or signs of traumatic perinatal injury (viz. cephalohematoma). Such cranial findings outside of the central nervous system (CNS) were counted with CNS findings considering their potential negative impact on long-term neurodevelopmental outcomes (Balan et al., 2002; Hussein et al., 2018; Vigo et al., 2017). Additionally, brain findings ranged from likely benign (e.g., a simple cyst) to more serious findings (e.g., cerebral ventriculomegaly, brain atrophy, intracranial hemorrhage).

2.2.3 | Disease severity

We documented underlying disease severity assessed at first EA surgery using two different disease severity scores: American Society of Anesthesiologists (ASA) classification (Abouleish et al., 2015) and Pediatric Risk Assessment (PRAm) scoring (Nasr et al., 2017; Nasr et al., 2020; Valencia et al., 2019), as it was recorded in the electronic medical record. The ASA classification was used to assess a patient's co-morbidities and scoring ranges from ASA I (a normal healthy patient) to ASA VI (a declared brain-dead patient) (Abouleish et al., 2015). The novel pediatric scoring system, PRAm (Nasr et al., 2017; Nasr et al., 2020; Valencia et al., 2019), was designed as a more objective assessment score of disease severity for specific use in infant and pediatric populations. PRAm scores range from

TABLE 2 Esophageal atresia and co-existing neurological findings.

	Number of patients		
	Term-born	Premature	Total
(a) Frequency of neurological findings (40/70; 57%)			($n = 70$)
Vertebral/spinal cord—only	11	7	18 (26%)
Cranial/brain—only	5	4	9 (13%)
Co-occurring vertebral/spinal cord and cranial/brain	7	6	13 (19%)
None	21	9	30 (43%)
(b) Vertebral/spinal cord findings (31/70; 44%)			($n = 70$)
Sacral dimple	13	8	21 (30%)
Spinal diagnostics	44	26	70 (100%)
Spine ultrasound	44	26	70 (100%)
Clinically indicated spine MRI	16	12	28 (40%)
Findings	17	12	29 (41%)
Vertebral anomalies	16	7	23 (33%)
Tethered cord	12	9	21 (30%)
Tethered cord release surgery	11	8	19 (27%)
None	26	13	39 (56%)
(c) Cranial/brain findings (22/70; 31%)			(n = 70)
Neurological symptoms	8	7	15 (21%)
Cranial findings	9	5	14 (20%)
Plagiocephaly	6	4	10 (14%)
Brachycephaly	2	0	2 (3%)
Cephalohematoma	2	1	3 (4%)
Brain diagnostics	20	13	33 (47%)
Head ultrasound	11	13	24 (34%)
Clinically indicated brain MRI	8	5	13 (18.5%)
Research brain MRI	5	0	5 (7%)
Brain findings	7	8	15 (21%)
Intraventricular cyst (viz., caudothalamic and choroid plexus)	1	4	5 (7%)

(Continues)

TABLE 2 (Continued)

	Number of patients		
	Term-born	Premature	Total
Increased CSF volume (e.g., subarachnoid spaces)	4	3	7 (10%)
Thinned corpus callosum	2	0	2 (3%)
Agenesis of the corpus callosum	0	1	1 (1%)
Absent septum pellucidum	0	1	1 (1%)
White matter injury	1	1	2 (3%)
Germinal matric hemorrhage (IVH grade I)	1	2	3 (4%)
IVH grade > I	0	1	1 (1%)
Subdural hematoma	1	0	1 (1%)
Brain surgery	0	0	0 (0%)
None	32	16	48 (79%)

Note: Co-existing neurological findings in infants born with esophageal atresia (EA). Table summarizes the frequency of neurological findings in a retrospective cohort of infants that underwent primary repair of esophageal atresia (EA) at a single institution ($n = 70$). Frequency of neurological findings in the cohort was 57% (a). All infant patients underwent spinal diagnostics (b), whereas brain diagnostics was performed only when clinically indicated (c). Thus, it is possible that cranial/brain findings have been underestimated. "c" also lists identified cranial/brain findings in selected cohort of infants that range from simple (e.g., plagiocephaly, brain cyst), to more significant findings (e.g., white matter injury, hemorrhage). Abbreviations: IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging.

0 to 13 and include the following scoring points: urgency of surgical procedure (+1), presence of at least one comorbidity (+2), presence of at least one indication of critical illness (+3), age < 12 months at surgery (+3), and co-existing malignancy (+4) (Nasr et al., 2017; Nasr et al., 2020; Valencia et al., 2019). Since all patients in our retrospective cohort received surgery within the first year of life and no patients had a co-existing malignancy, PRAm scores ranged from 3 to 9.

2.2.4 | Cumulative sedation exposure

Considering infants born with EA undergo complex thoracic non-cardiac perioperative critical care, we identified the classes of medications used for postoperative pain and/or sedation management for all infant patients in the cohort ($n = 70$): (i) opioids (viz. fentanyl, morphine), (ii) benzodiazepines (viz. midazolam, diazepam), and (iii) alpha 2-adrenergic agonists (viz. clonidine, dexmedetomidine). We also quantified the length of postoperative pain/sedation treatment (in days) following primary EA repair at our institution. Our postoperative pain/sedation end-point measures included: (1) postoperative mechanical ventilation as a proxy for postoperative sedation and (2) post-extubation weaning drugs of sedation. The latter was defined as the period following extubation that required withdrawal management to prevent signs of physical dependence. Weaning of medications following extubation is not to be confused with patterns of sedation weaning (i.e., "lifting the sedation") of critically ill children prior to extubation (Solodiuk et al., 2019). We did not measure or evaluate withdrawal; instead, data was obtained from patient charts as per primary team reports. Finally, we quantified (3) the length of total postoperative exposure to pain/sedation drug treatment (in days) stratified by weaning status, gestational age, and surgical group to illustrate for the first time the time-differences in postoperative care management. To avoid diversion of data in this analysis, we excluded one outlier with a history of extended postoperative mechanical ventilation that resulted in tracheostomy ($n = 69$).

2.2.5 | Anesthesia exposure in the first year of life

Considering that patients undergo repeated follow up EGDs (van Hoorn et al., 2021) to assess healing and to identify possible complications following primary repair, we quantified anesthesia exposure in the first year of life. Our end-point measures included: (1) the number of anesthesia events as defined by any procedure that required administration of either intravenous or inhalational anesthetics and (2) cumulative exposure to minimum alveolar concentration (MAC) equivalent hours of inhalational anesthetic agents in the first year of life. Since no infant in our cohort received an anesthesia procedure outside of our institution, we were able to obtain the number of procedural events requiring anesthesia administration from the medical record. Cumulative MAC equivalent hours of exposure to anesthesia for each patient was obtained from the anesthesia records (AIMS Charts, 2019 Citrix Receiver Application, v. 19.3.0.21). Specifically, the latter was calculated as the sum of MAC equivalent exposure to anesthesia for each surgery in the first year of life.

2.3 | Statistical analysis

2.3.1 | Overall statistics

Data were presented as numerical sums and percentages for (1) sex and surgical classification of EA (*short-gap* vs. *long-gap* EA), (2) frequency and distribution of neurological findings (vertebral/spinal cord vs. cranial/brain), (3) disease severity scores (ASA and PRAm), and (4) postoperative pain/sedation drug exposure. In addition, boxplot distributions indicating median scores, first and third quartile ranges, and absolute minimum and maximum values were used to present (1) gestational age at birth, (2) corrected post-natal age at first EA surgery (weeks), (3) sedation exposure (viz. length of postoperative mechanical ventilation, post-extubation weaning of sedation, and total postoperative pain/sedation drug treatment [days]), and (4) anesthesia exposure (e.g., number of anesthesia events and cumulative MAC equivalent hours of anesthesia in the first year of life).

2.3.2 | Correlation analysis

The following variables were assessed for normality using the Shapiro–Wilk test: (1) number of anesthesia events in the first year of life, (2) cumulative MAC equivalent hours of anesthetic agents in the first year of life, (3) postoperative mechanical ventilation (days), and (4) total postoperative pain/sedation drug treatment (days). The associations between the individual number of cranial/brain findings and listed variables were assessed by nonparametric Spearman correlations. Spearman was selected due to its resistance to the effects of outliers (Schober et al., 2018). Strength of correlation was described as weak (Spearman's Rho [r] < 0.4), moderate ($r \geq 0.4$ to <0.7), or strong ($r \geq 0.7$) according to published guidelines (Schober et al., 2018). We also used more stringent Bonferroni criteria of $p < .01$ as statistically significant to protect against false positive results due to repeated testing.

3 | RESULTS

This retrospective study quantified neurological findings in patients that underwent primary EA repair over a period of 11 years (2009–2020) at the *Esophageal and Airway Treatment Center* at Boston Children's Hospital (Evanovich et al., 2022). Patients born with co-existing chromosomal abnormalities (Evanovich et al., 2022) known to be associated with abnormal neurologic imaging findings or neurological outcomes were excluded, as well as extremely premature patients (born <28 weeks of gestation), as this population is at high risk for both abnormal neurologic imaging findings and abnormal neurological outcomes (Allin et al., 2006; Ritz et al., 2020).

3.1 | Demographic information and esophageal atresia types

3.1.1 | Esophageal atresia types and sex distribution

In this retrospective cohort of infants that underwent primary EA repair at a single institution ($n = 70$), we distinguished between *short-gap* ($n = 54/70$) and *long-gap* EA ($n = 16/70$; see Section 2). We report approximately equal distribution of sex with 53% (37/70) female and 47% (33/70) male patients and nearly equal sex distribution per surgical type of EA: 52% (28/54) female for *short-gap* EA and 56% (9/16) female for *long-gap* EA (Figure 1a).

3.1.2 | Gestational age at birth and corrected gestational age at first EA surgery

With exclusion of extreme prematurity (<28 weeks of gestation; see Section 2), we report more term-born (44/70, 63%) than premature patients (26/70; 37%) in this EA cohort. As illustrated in Figure 1b, *short-gap* EA patients were more likely to be classified as term-born (average gestational age (GA) of 37.53 weeks), while there were more premature *long-gap* EA patients (average GA of 35.59 weeks). Additional analysis showed that irrespective of the gestational age at birth, both *short-gap* and *long-gap* EA patients underwent their first EA surgery approximately at term-equivalent age (average 37.97 weeks GA for *short-gap* and average 40.59 weeks GA for *long-gap* EA; Figure 1c).

3.2 | Quantification of neurological findings

3.2.1 | Classification of neurological findings

Table 2 summarizes the frequency of neurological findings per gestational age group. Less than half of the cohort (43%; $n = 30/70$) had no neurological imaging findings (Table 2a). The remaining infants had either (1) vertebral/spinal cord findings (26%, 18/70), (2) cranial/brain findings (13%, 9/70), or (3) both vertebral/spinal cord and cranial/brain findings (19%, 13/70). For graphical illustration per gestational age at birth, see Figure 2.

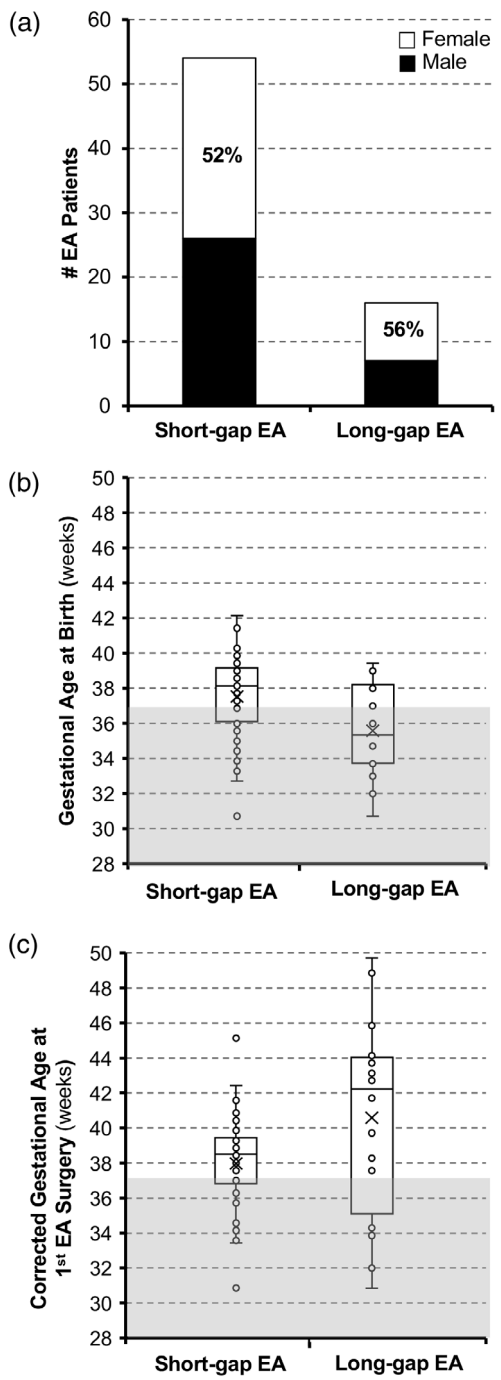


FIGURE 1 Frequency of esophageal atresia (EA) classified by sex, gestational age at birth, and corrected gestational age at first EA surgery. Data was retrospectively collected at a single institution ($n = 70$). (a) The number of EA patients per surgical group (viz. *short-gap* EA; $n = 54$ vs. *long-gap* EA; $n = 16$) and sex (viz. female; white bars vs. male; black bars). Gestational age at birth (weeks; b) and corrected gestational age at first EA repair surgery (weeks; c) were stratified by surgical group (*short-gap* vs. *long-gap* EA) while the gray area schematically marks prematurity (<37 weeks of gestation). Individual values are represented as dots, boxes span the interquartile range (first and third quartile), median score is shown as a thick horizontal line, mean is shown as an X, while whiskers represent maximum and minimum values. EA, esophageal atresia.

3.2.2 | Vertebral/spinal cord findings

All patients (100%, 70/70) underwent spinal ultrasound to rule out vertebral/spinal cord anomalies as part of clinical workup for VACTERL association (Vertebral, Anorectal, Cardiac, Tracheo-esophageal fistula and/or Esophageal atresia, Renal, and Limb defects/malformations), a constellation of malformations (Adam et al., 2020; Shaw-Smith, 2006). Additionally, 40% (28/70) of patients underwent a clinically indicated spine MRI. As a result, 44% (31/70) of EA patients were found to have vertebral/spinal cord findings, with 33% (23/70) having vertebral anomalies and 30% (21/70) having tethered cord syndrome (Table 2b). Additional information regarding the frequency of vertebral/spinal diagnostics and findings per gestational age groups are summarized in Table 2b.

3.2.3 | Cranial/brain findings

Unlike spinal imaging, cranial imaging is not standard of care in patients with EA. As such, cranial imaging was done in approximately half of the infants (47%, 33/70) for a range of clinical indications. Brain diagnostic evaluation included head ultrasound (34%, 24/70), clinically indicated brain MRI (18.5%, 13/70), and research brain MRI (7%, 5/70) (Table 2c). Cranial/brain findings were identified in 67% (22/33) of those that were evaluated, but just in 31% (22/70) of the cohort. Table 1c also lists identified cranial and brain findings in the selected cohort of infants. Brain findings ranged from likely benign (e.g., simple cysts) to major findings (e.g., intracranial hemorrhage). Increased cerebrospinal fluid volume in the subarachnoid spaces was the most frequent brain finding (10%, 7/70). However, for all infants that underwent brain imaging, including those that underwent research brain MRI scans, there was a high number of clinically significant brain findings (45%, 15/33). Considering not all infants underwent evaluation of potential brain findings, the reported frequency is a possible underestimation.

3.3 | Stratification of underlying disease severity

3.3.1 | American Society of Anesthesiologists (ASA) physical status classification

As previously reported, all patients of this cohort with neurological findings were classified as either ASA Physical Status III or IV (Evanovich et al., 2022). We report that neurological findings are identified irrespective of the physical status classification, gestational age at birth, or surgical groups (Figure 3). The majority of premature patients with

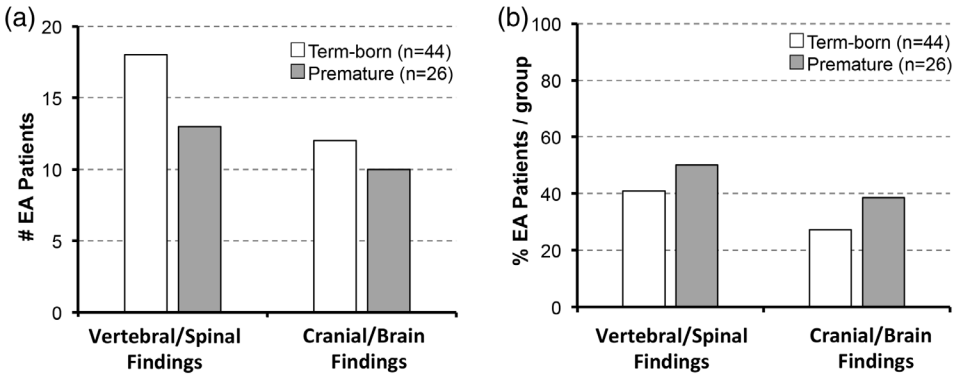


FIGURE 2 Frequency of neurological findings in infants born with esophageal atresia (EA). Graphs summarize the frequency of neurologic findings in a retrospective cohort of infants that underwent primary repair of EA at a single institution. Neurological data were presented for vertebral/spinal cord and cranial/brain findings for two groups: term-born ($n = 44$; white bars) and preterm patients ($n = 26$; gray bars) as absolute numbers (a) and percent (%; b) per gestational age group. A single patient could have had either or both categories' findings. Note that 100% (70/70) of patients underwent spinal ultrasound diagnostics while only 47% (33/70) of patients had brain diagnostics (see Table 1). EA, esophageal atresia.

neurological findings had a physical status classification of ASA IV irrespective of surgical group (viz. primary anastomosis for *short-gap* EA vs. the Foker process for *long-gap* EA). Specifically, 77% (10/13) of premature patients with vertebral/spinal cord findings and 80% (8/10) of premature patients with cranial/brain findings had ASA IV physical status classification regardless of surgical group (Figure 3a, b, respectively). As expected, most patients undergoing the Foker process (viz., *long-gap* EA repair) with cranial/brain findings had ASA IV physical status classification (83%, 5/6) regardless of the gestational age at birth.

3.3.2 | Pediatric risk assessment (PRAm) scores

The PRAm scores in this cohort ranged from 3 to 9 across gestational age groups (Evanovich et al., 2022) (Figure 4a) and surgical groups (primary anastomosis for *short-gap* EA and the Foker process for *long-gap* EA; Figure 4b). Despite this wide range (3–9), PRAm scores were evenly distributed making PRAm scoring less useful in assessing underlying disease severity in patients with EA. This data show that most patients with neurological findings had PRAm score of 5. For a detailed graphical illustration see Figure 4.

3.4 | Quantification of postoperative pain and sedation management

3.4.1 | Postoperative pain and/or sedation management

We identified the following classes of medications used in EA infants for postoperative pain and sedation management: (i) opioids (e.g., morphine, fentanyl, methadone), (ii) benzodiazepines (e.g., midazolam, lorazepam), and (iii) alpha-2 adrenergic receptor agonists (e.g., clonidine, dexmedetomidine). Data indicate that opioids were most frequently used across all surgical and gestational groups, while *long-gap* EA patients were additionally exposed to sedating agents. Specifically, nearly all patients in the cohort (99%, 69/70) received opioids for postoperative pain/sedation management following primary repair of EA regardless of gestational or surgical groups (Figure 5). For *long-gap* EA patients, benzodiazepines were used for sedation in 100% (7/7) term-born and 78% (7/9) premature infants. In contrast, only 24% (9/37) of term-born and 18% (3/17) of premature *short-gap* EA patients were exposed to benzodiazepines postoperatively. Data show a similar trend in the postoperative use of alpha-2 adrenergic receptor agonists: 14% (5/37) of term-born and 6% (1/17) of premature *short-gap* EA patients. Alternatively, alpha-2 adrenergic receptor agonists were used for postoperative sedation in 43% (3/7) of term-born *long-gap* EA infants and 67% (6/9) of premature *long-gap* EA infants. Although we report that benzodiazepines were used more frequently than alpha-2 adrenergic receptor agonists for sedation management of *long-gap* EA patients, this might not reflect current practice protocols since our cohort included period of 11 years (Section 2).

3.4.2 | Length of postoperative mechanical ventilation

Only one term-born patient with *short-gap* EA was extubated at the end of EA surgical repair just prior to transport to intensive care unit. The rest of infants (99%, 68/69) remained intubated following primary surgical repair of

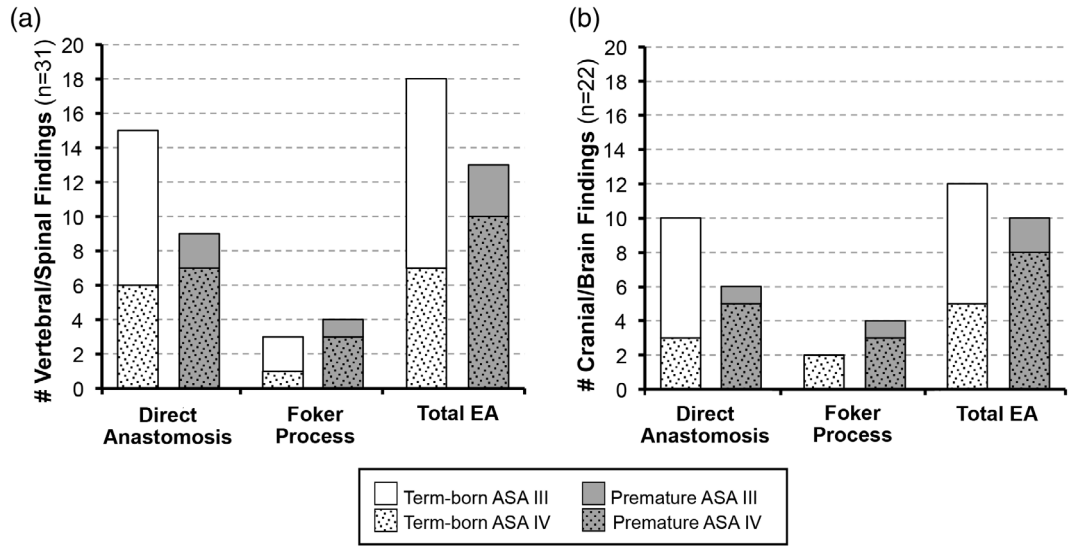
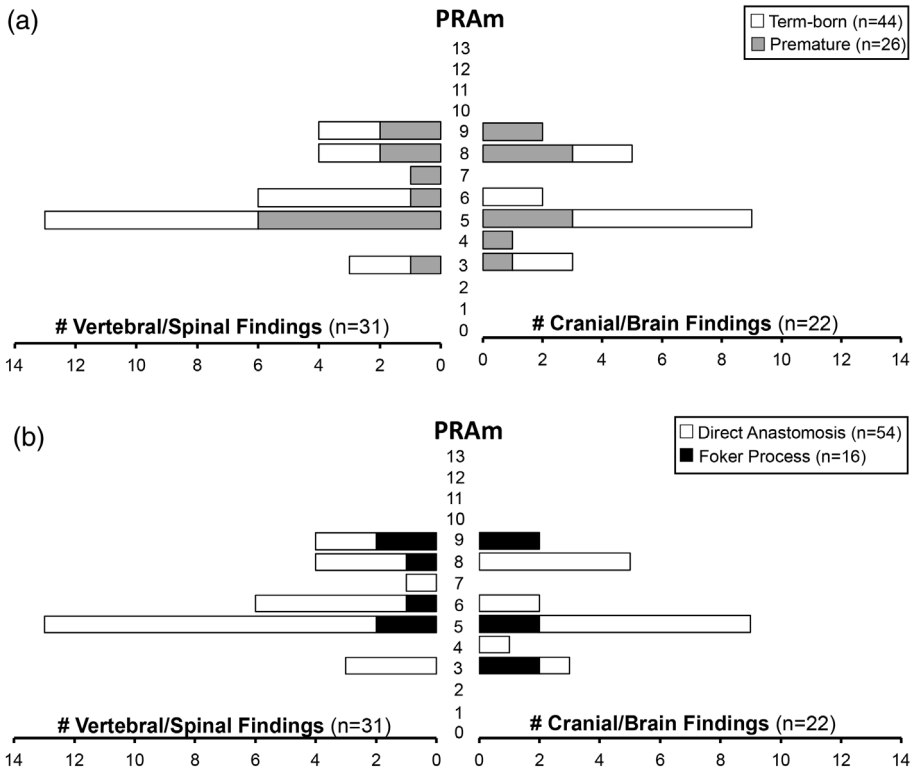


FIGURE 3 Frequency of neurological findings in relation to American Society of Anesthesiologist (ASA) Physical Status Classification. This cohort includes infants that underwent primary esophageal atresia (EA) repair of at a single institution. Neurological data were classified as vertebral/spinal findings ($n = 31$; a) and cranial/brain findings ($n = 22$; b). A single patient could have had either or both categories' findings. Data are presented for two groups: term-born ($n = 44$; white bars) and premature patients ($n = 26$; gray bars) that were classified as ASA III (open bars) or ASA IV (dotted bars), as well as per surgical group (viz. primary anastomosis for *short-gap* EA vs. Foker process for *long-gap* EA; Section 2). Neurologic findings are found irrespective of the gestational age or surgical group. Most premature patients and patients undergoing the Foker process with neurological findings had a score of ASA IV. ASA, American Society of Anesthesiologists; EA, esophageal atresia.

FIGURE 4 Frequency of Neurological Findings in Relation to Pediatric Risk Assessment (PRAm) Scores. Cohort includes infants that underwent primary esophageal atresia (EA) repair of at a single institution. Neurological data were classified as vertebral/spinal and cranial/brain findings. (a) Data distributed between two groups: term-born ($n = 44$; white bars) and premature patients ($n = 26$; gray bars). (b) Stratification according to the type of surgical group: primary anastomosis for *short-gap* EA (white bars) vs. Foker process for *long-gap* EA (black bars). Although PRAm scores spanned a wide score range (scores 3–9), scores were evenly distributed among gestational age and surgical type groups. PRAm, pediatric risk assessment.



EA across all gestational age and surgical groups (Figure 6a, a'). Of those that underwent postoperative mechanical ventilation (68/69), the group of patients with *long-gap* EA underwent a longer average period of postoperative mechanical ventilation (term-born: 21.86 days, premature: 20.13 days) in comparison to *short-gap* EA patients (term-born: 2.78 days, premature: 3.35 days), irrespective of gestational age group (Figure 6b).

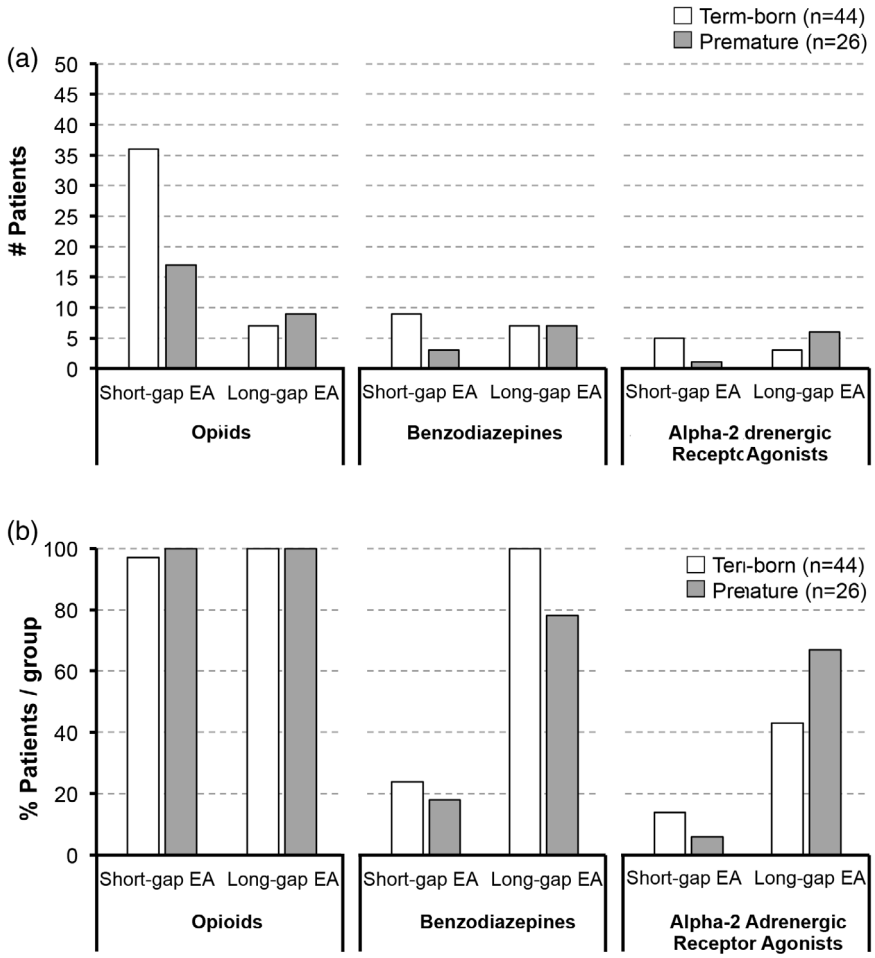


FIGURE 5 Quantification of postoperative pain/sedation management per pharmacological groups in esophageal atresia (EA) at a single institution. Graph shows the number (a) and percentage (%) (b) of patients with *short-gap* EA ($n = 54$) and *long-gap* EA ($n = 16$) that received selected pharmacological treatment. Data were also presented by gestational age (white bars for term-born, gray bars for premature patients). Pharmacological type was classified as follows: (i) opioids (viz. fentanyl, morphine, methadone); (ii) benzodiazepines (viz. midazolam, lorazepam); and (iii) alpha-2 adrenergic receptor agonists (viz. clonidine, dexmedetomidine). Individuals were counted multiple times if the patient was on multiple classes of medications. Benzodiazepines appear to be instituted more frequently that alpha-2 adrenergic receptor agonists for pain/sedation treatment in *long-gap* EA patients. EA, esophageal atresia.

3.4.3 | Length of post-extubation weaning

All *long-gap* EA patients (15/15) required weaning following extubation regardless of gestational age group, while only 15% (8/54) of *short-gap* EA patients required any weaning from drugs of sedation (16% (6/37) term-born; 12% (2/17) premature; Figure 6c, c'). *Long-gap* EA patients also required much longer weaning period from drugs of sedation than *short-gap* EA patients, with premature patients requiring more weaning than term-born patients. Specifically, *short-gap* EA patients only underwent an average of 2.67 days of weaning for term-born and 3.0 days of weaning for premature patients, while term-born and premature *long-gap* EA infants underwent an average of 17.86 and 36.22 days of weaning, respectively (Figure 6d).

3.4.4 | Length of Total postoperative pain/sedation drug treatment

Predictably, *short-gap* EA patients who required weaning underwent slightly longer periods of total postoperative pain/sedation drug treatment (term-born: 8.67 days; premature: 8.00 days) than *short-gap* EA infants who did not require weaning (term-born: 2.90 days; premature: 4.20 days; Figure 7a). However, patients with *long-gap* EA received about 10 times longer total pain/sedation treatment (term-born: 39.71; premature: 50.25 days) than those with *short-gap* EA, regardless of weaning (term-born: 3.84; premature: 4.65 days; Figure 7b).

3.5 | Quantification of anesthesia in the first year of life

Patients with *long-gap* EA underwent approximately double the number of anesthesia events in the first year of life when compared with *short-gap* EA patients, regardless of gestational age. Term-born and early-to-late premature *long-gap* EA patients underwent an average of 13 and 14 events, respectively, while *short-gap* EA patients underwent an average of six events (term-born and premature) in their first year of life (Figure 8a). Additionally, infants with *long-gap* EA were exposed, on

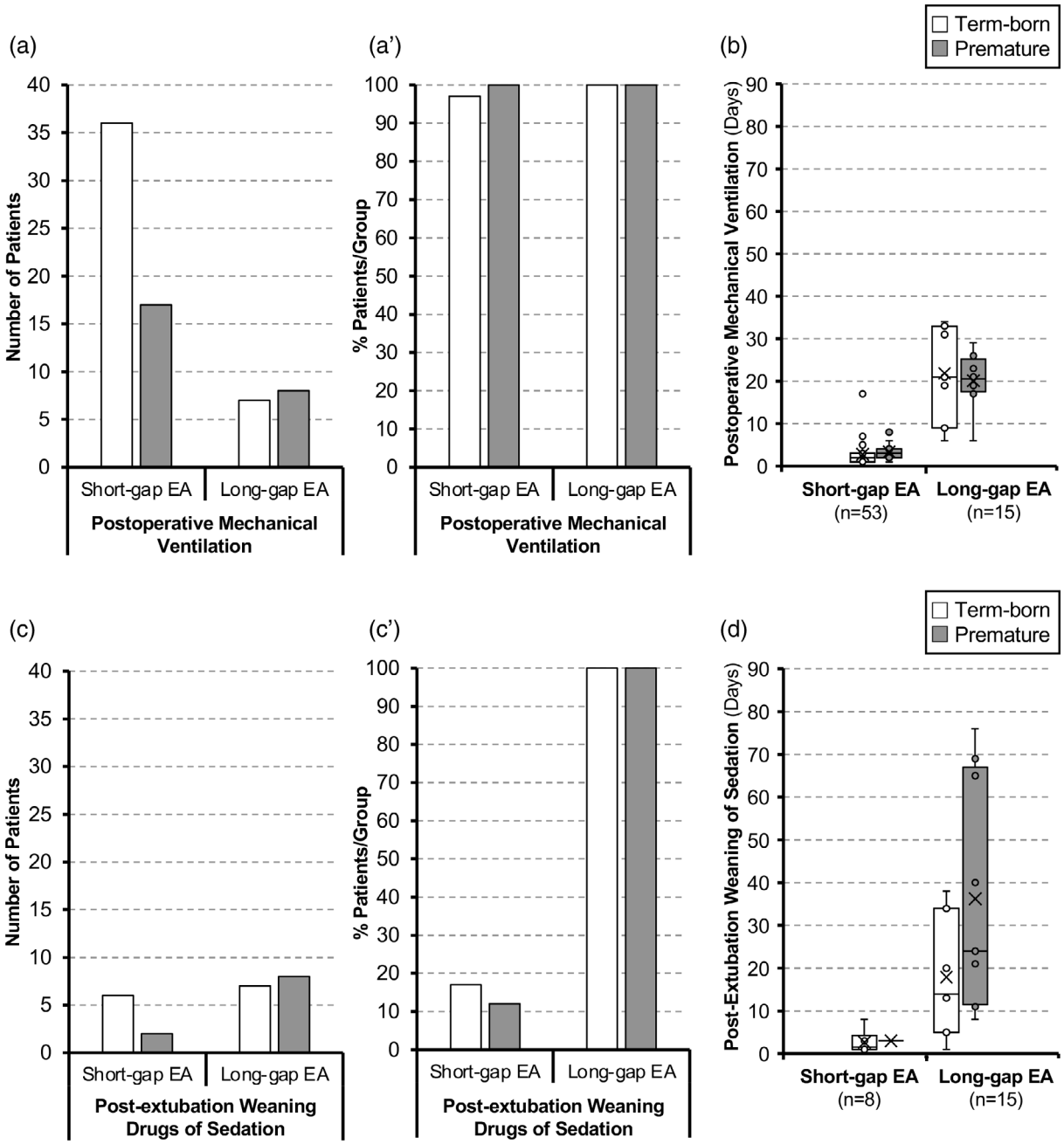


FIGURE 6 Length of pain/sedation treatment following primary repair of esophageal atresia (EA) at a single institution. Pain/sedation data were shown for *short-gap* EA ($n = 54$) and *long-gap* EA ($n = 15$) patients, stratified by gestational age: term-born ($n = 44$; white bars) and premature ($n = 25$; gray bars). Analysis excluded one *long-gap* EA outlier ($n = 69$; Section 2). Graphs summarize the number (a, c) and percentage (%; a', c') of EA patients that underwent postoperative mechanical ventilation and post-extubation weaning treatment, respectively. Quantification included the length (days) of: (1) postoperative mechanical ventilation ($n = 68$; b) and (2) post-extubation weaning of drugs of sedation ($n = 23$; d). Retrospective data confirm that all infants with *long-gap* EA develop tolerance and physical dependence to drugs of pain/sedation management. In box plot graphs (b, d), individual values are represented as dots, boxes span the interquartile range (first and third quartile), median score is shown as a thick horizontal line, mean is shown as an X, while whiskers represent maximum and minimum values. EA, esophageal atresia.

average, to more than twice as many cumulative MAC equivalent hours of anesthesia (term-born: 41.90 h; premature: 45.41 h) than *short-gap* EA patients (term-born: 17.47 h; premature: 17.40 h; Figure 8b) in the first year of life. Both measures indicate that regardless of gestational age at birth, *long-gap* EA patients underwent twice as much anesthetic exposure compared with *short-gap* EA patients.

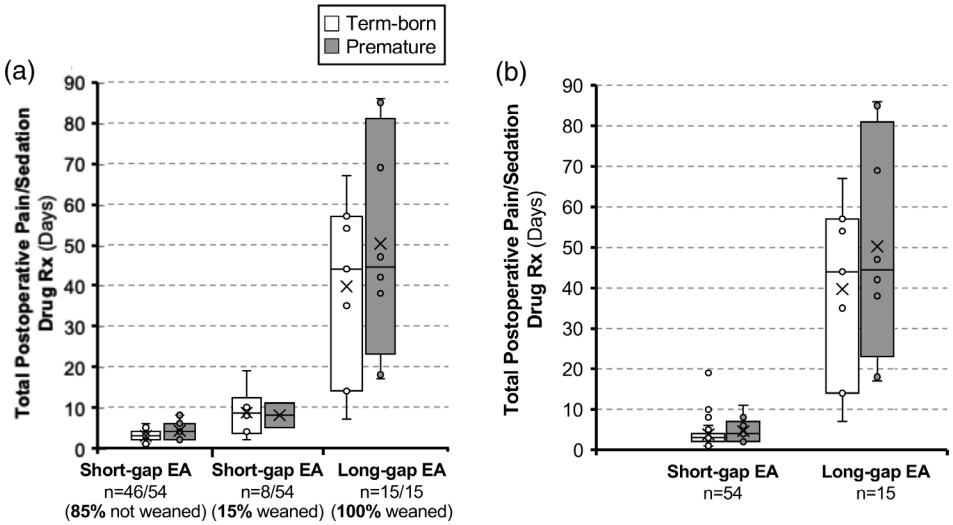


FIGURE 7 Length of total postoperative pain/sedation treatment following primary repair of esophageal atresia (EA) at a Single Institution. Total drug treatment data were measured for *short-gap* EA ($n = 54$) and *long-gap* EA ($n = 15$) patients, stratified by gestational age: term-born ($n = 44$; white bars) and premature ($n = 25$; gray bars). Analysis excluded one *long-gap* EA outlier ($n = 69$; Section 2). (a) Summarization of the length of total postoperative pain/sedation treatment (days) for: (i) infants with *short-gap* EA who were not weaned ($n = 46$), (ii) infants with *short-gap* EA who were weaned ($n = 8$); and (iii) infants with *long-gap* EA ($n = 15$). (b) Illustration of the total length of postoperative pain/sedation treatment per EA surgical groups irrespective of weaning. Individual values are represented as dots, boxes span the interquartile range (first and third quartile), median score is shown as a thick horizontal line, mean is shown as an X, while whiskers represent maximum and minimum values. EA, esophageal atresia.

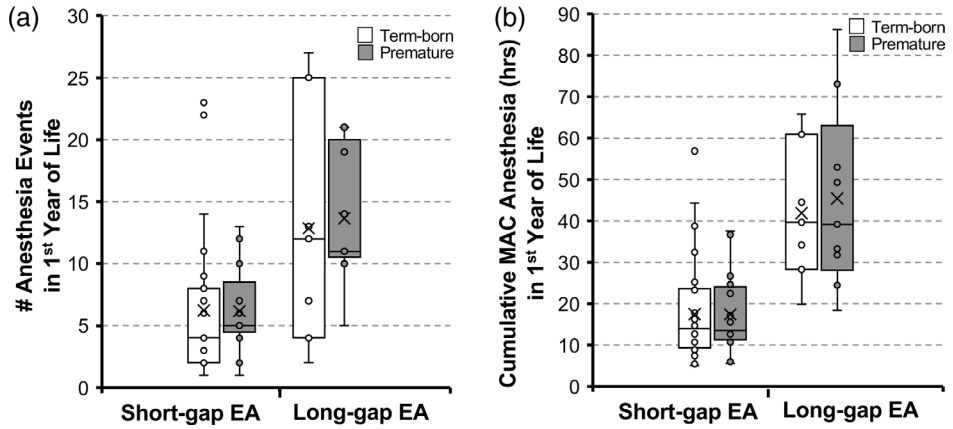


FIGURE 8 Quantification of cumulative anesthesia exposure in infancy of patients that underwent primary esophageal atresia (EA) repair at a single institution. Graphs show the number of anesthesia events/patient (a), and cumulative minimum alveolar concentration (MAC) equivalent hours of anesthetic exposure/patient (b) in the first year of life. Patients were categorized based on (1) gestational age at birth: term-born ($n = 44$; white bars) and premature ($n = 26$; gray bars); and surgical groups (primary anastomosis for *short-gap* EA; $n = 54$ and Foker process for *long-gap* EA; $n = 16$). Patients with *long-gap* EA underwent approximately twice as much anesthesia exposure compared with *short-gap* EA patients over the course of the first year of life. Individual values are represented as dots, boxes span the interquartile range (first and third quartile), median score is shown as a thick horizontal line, mean is shown as an X, while whiskers represent maximum and minimum values. EA, esophageal atresia; MAC, minimum alveolar concentration.

3.6 | Association analysis between clinical measures and number of cranial/brain findings

We failed to detect any significant associations between clinical end-point measures of postoperative sedation following primary EA repair or measures of anesthesia exposure in the first year of life with number of cranial/brain imaging findings. Interestingly, moderately strong, but not statistically significant positive associations were found in term-born *long-gap* EA patients between the number of cranial/brain findings and (1) length of

postoperative mechanical ventilation ($r = 0.445$, $p = .317$; Figure 9a'), (2) length of total postoperative pain/sedation treatment (term-born: $r = 0.401$, $p = .373$, Figure 9b'), and (3) number of anesthesia events in the first year of life ($r = 0.401$, $p = .373$; Figure 9c'). No definitive conclusions should be drawn from this analysis given the possible underestimation of cranial/brain findings (Table 2c) and low power in *long-gap* EA group ($n = 16$). For full statistical details see Figure 9.

4 | DISCUSSION

Our novel results quantified neurological imaging findings in a previously described retrospective cohort (Evanovich et al., 2022) and suggest that the frequency of cranial/brain findings in infants born with EA are most likely underestimated. The ASA physical status classification remains the gold standard in assessing underlying disease severity in infants born with EA (Evanovich et al., 2022), *as it pertains* to the frequency of neurological findings in comparison to recently described PRAm scoring system (Nasr et al., 2017; Nasr et al., 2020; Valencia et al., 2019). Furthermore, our retrospective quantitative analyses show that 15% patients with *short-gap* EA and 100% of patients with *long-gap* EA are at risk of developing tolerance and physical dependence to drugs of pain/sedation treatment. Importantly, we present that infants born with *long-gap* EA undergo more than 10 times the total postoperative pain/sedation treatment and double the anesthesia exposure in infancy compared with patients born with *short-gap* EA.

4.1 | Limitations of the retrospective chart review

In keeping with the retrospective study design (Gearing et al., 2006), data collected were not originally intended for research purposes (Hess, 2004; Jansen et al., 2005). The study depends on information stored for clinical use and our retrospective analysis may represent incomplete or missing documentation (e.g., attainment of PRAm scores (Nasr et al., 2017) for EA repair prior to 2017). However, since all infants underwent primary repair and follow up at our institution (see Section 2), our end-point measures did not include patient data that was difficult to identify, and patient chart information was generally well reported and appropriate for the medical standards at the time. Despite our exclusion criteria, this study retained a moderate sample size with enough power to quantify neurologic imaging findings and to evaluate sedation and anesthesia exposure. The sample size $n = 16$ for the *long-gap* EA group is considered sufficient by literature to obtain results that are both accurate and clinically relevant (Findley & Daum, 1989; Harrell Jr. et al., 1985; Haynes, 2012). Despite exclusion of extreme prematurity (see Section 2), the frequency of prematurity in our cohort remained within the originally reported 25%–40% of prematurity in EA (Deboer & Potts, 1957). Possible underestimation of cranial/brain findings in this study warrants future prospective analysis of cranial/brain findings in infants born with EA.

4.2 | Frequency of neurologic findings

4.2.1 | Vertebral/spinal cord findings

As shown in this study, all infants underwent spinal diagnostics to rule out associations (e.g., VACTERL), according to the standard of care for patients born with EA (Chetcuti et al., 1989; Sistonen et al., 2009; Solomon et al., 2014). Vertebral anomalies and tethered spinal cord are often present in patients with EA with VACTERL association (Chetcuti et al., 1989; O'Neill et al., 2010; Sistonen et al., 2009). Literature estimates the frequency of VACTERL association in EA patients at around 10% (Stoll et al., 2009), while frequency of VACTERL in our cohort was previously reported at 37% (Evanovich et al., 2022). Higher rate at our institution possibly reflects *The Esophageal and Airway Center's* international reputation as a referral center for patients born with EA (Evanovich et al., 2022), or possibly the recognized differences in VACTERL diagnostics (Brosens et al., 2014). In the current study, we report vertebral/spinal cord findings in 44% of patients, which could be due to our use of a more broadened definition of vertebral/spinal cord findings, that did not require VACTERL diagnosis specifically. Given that every patient underwent spinal diagnostics, our report serves as an accurate estimation of vertebral/spinal cord imaging findings in this retrospective cohort of infants with EA.

4.2.2 | Cranial/brain findings

In contrast to vertebral/spinal diagnostics, which are considered standard of care for all infants born with EA (Chetcuti et al., 1989; Sistonen et al., 2009; Solomon et al., 2014), evaluation of possible cranial/brain findings in EA patients were performed only when clinically indicated—as described in this study. In our cohort, just under half of infants underwent brain imaging (47%; 33/70), and of those imaged, 67% (22/33) showed at least one structural abnormality. A recent study (Stolwijk

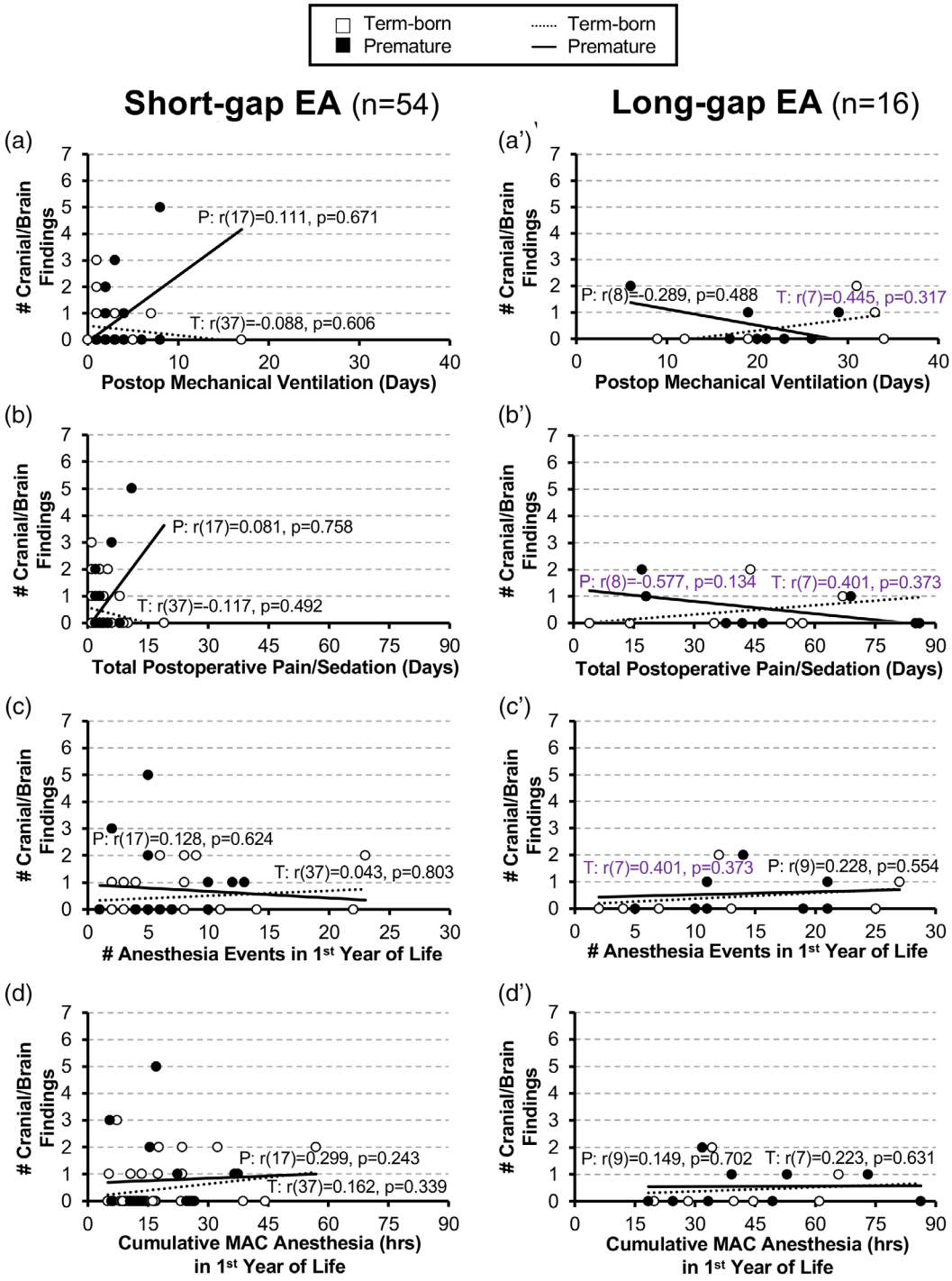


FIGURE 9 Associations between number of cranial/brain findings and clinical end-point measures in infants that underwent primary repair of esophageal atresia (EA) at a Single Institution. Our retrospective data cohort was classified per gestational groups: term-born (white circles) and premature (black circles) patients with *short-gap* (a–d) and *long-gap* EA (a'–d'). Graphs failed to show any significant associations between the number of cranial/brain findings and (1) length of postoperative mechanical ventilation (days; a, a'), and (2) length of total postoperative pain/sedation treatment (days; b, b') following initial EA repair, as well as (3) number of anesthesia events (c, c'), and (4) cumulative minimal alveolar concentration (MAC) equivalent hours of anesthesia in the first year of life (d and d'). Strength of correlation is described as weak ($r < 0.4$; black), moderate ($r \geq 0.4$ to <0.7; purple), or strong ($r \geq 0.7$; red) with $p < .01$ considered significant (Section 2). Future studies with full evaluation of cranial/brain findings and higher power for *long-gap* EA group are needed to confirm presented data results. EA, esophageal atresia; MAC, minimum alveolar concentration.

et al., 2017) reported that infants undergoing neonatal surgery for noncardiac congenital anomalies are at risk of postoperative brain injury (e.g., extra-parenchymal abnormalities, including intraventricular and subdural hemorrhage), potentially contributing to the higher rate of neurological sequelae observed in this population (Stolwijk et al., 2016). In our recent case series, we showed that pre-existing clinically significant brain imaging findings (either exacerbated and/or new findings) were reported following the complex postoperative course for *long-gap* EA (Rudisill et al., 2019), implicating a double-hit hypothesis regarding etiology of brain findings. In addition, our previous pilot brain MRI research findings (Hodkinson et al., 2019;Mongerson et al., 2019; Rudisill et al., 2019) also support likely underestimation of cranial/brain findings in this population. This is important because clinically significant qualitative and quantitative brain findings were detected in infants without any previous neurological concerns and may affect long term morbidity. While some of the brain imaging findings were of little clinical significance (e.g., benign cysts), a striking cranium-to-brain size discrepancy was noted in a pilot cohort of infants following *long-gap* EA repair. This report suggested that head circumference—as a previously established indirect measure of head size/growth—does not provide a reliable indirect assessment of brain size in the context of critical illness and perioperative care in selected group of infants undergoing Foker process for *long-gap* EA repair (Bajic et al., 2021). Therefore, our results call for future studies that would evaluate the intrinsic brain status of infants born with EA. Further research is warranted to better understand the potential (mal)adaptations during early brain development or brain injury in this population. As with vertebral/spinal evaluations, we propose that baseline brain imaging should be considered the standard of care for all infants born with EA.

We also report that increased cerebral spinal fluid volume was the most frequent brain finding in presented cohort (Table 1) in both term-born and premature infants. The latter findings are in accordance with our recent pilot MRI study of infants following *long-gap* EA repair (Mongerson et al., 2019; Rudisill et al., 2019). Presence of enlarged cerebrospinal fluid spaces on MRI was associated with poor short-term developmental outcomes in neonates treated with cardiopulmonary bypass (Lago et al., 1995). Whether resulting from prematurity, reduction in adjacent brain tissue volume, or an increase in cerebrospinal fluid itself (Alvarez et al., 1986; Iwata et al., 2016; Ment et al., 1981), an increased volume of cerebrospinal fluid spaces has been linked to moderate-to-severe disability (Inder et al., 2005; Shen et al., 2017) and long-term neurodevelopmental impairment (Cheong et al., 2016; Keunen et al., 2016). The impact of increased cerebrospinal fluid in infants with *long-gap* EA warrants future longitudinal neurobehavioral follow up.

4.3 | Severity stratification of underlying disease (ASA and PRAm)

The advantage of ASA in comparison to PRAm in assessing underlying disease severity was initially described in our previous study which described the cohort based on anatomical types of EA (type A–D) (Evanovich et al., 2022). In this study, ASA physical status classification was more useful in assessing the number of neurologic findings. Specifically, higher ASA scores (e.g., ASA IV; Figure 3) were noted for those with cranial/brain imaging findings that were born premature or underwent the Foker process repair (viz. *long-gap* EA), while no trends were observed across PRAm scores (Figure 4). Thus, despite a wider range of PRAm scores (3–9), ASA physical status remains the gold standard for evaluation of underlying disease severity in infants born with EA. Future work should analyze unique risk factors related to type of surgical repair (viz. primary anastomosis vs. the Foker process; open vs. laparoscopic approach) to expand on current risk stratification of patients born with EA. With that, future morbidity risk assessment should also include assessment of the neurological imaging findings.

4.4 | Easily quantifiable clinical endpoint measures

4.4.1 | Postoperative pain/sedation treatment

We report, for the first time, quantified postoperative pain/sedation length following EA repair (Figure 7). Specifically, we report over 10 times the length of total postoperative pain/sedation treatment following primary EA repair in *long-gap* EA patients (average 45 days) compared with those with *short-gap* EA (average 4 days). All *long-gap* EA patients and 15% of patients born with *short-gap* EA underwent postoperative mechanical ventilation requiring sedation ≥5 days, which is the length of sedation previously reported to lead to physical dependence (Solodiuk et al., 2019). Our findings suggest that infants undergoing the Foker process for *long-gap* EA repair are uniquely vulnerable to development of tolerance and dependence to drugs of sedation due to their necessary exposure to postoperative mechanical ventilation during the repair process (Bairdain et al., 2015; Foker

et al., 1997; Foker et al., 2009; Kunisaki & Foker, 2012). We hypothesized that longer exposure to pain and sedation medications could serve as an early marker of the increased risk for neurological imaging abnormalities, but this was not found in our study. Reported lack of associations for *long-term* EA group (Figure 9a′, b′) should be interpreted with caution considering low power in the current cohort ($n = 16$), and possible underestimation of cranial/brain findings (Table 2). However, both clinical end-point measures of exposure to drugs of sedation are easily quantifiable and can be used as early markers in future studies of neurobehavioral outcomes. Indeed, the length of mechanical ventilation in pediatric patients has previously been used in a prospective clinical trial as a proxy for sedation when assessing sedation protocols and long-term neurodevelopmental outcomes (Curley et al., 2015).

4.4.2 | Quantification of anesthesia exposure in the first year of life

This is the first report of retrospectively assessing exposure to anesthesia in infants born with EA over the course of the first year of life. We report that *long-gap* EA patients undergo nearly double exposure to anesthesia in comparison to infants born with *short-gap* EA (Figure 8). This reflects the greater complexity of follow-up care of infants after *long-gap* EA repair (e.g., EGDs to assess healing and prevent strictures [Shah et al., 2015]). Thus, like previously proposed quantification of sedation, easily quantifiable number of anesthesia events and cumulative MAC equivalent hours of anesthesia exposure in the first year of life could also serve as an (1) indirect measure of perioperative complexity of care and (2) an early marker in future studies of neurobehavioral outcomes.

4.5 | Long-term neurodevelopmental sequalae in infants born with EA

Infant patients with congenital gastrointestinal anomalies experience multiple stressors while hospitalized in early life (Pierro & Eaton, 2008). Recent studies also showed that infants who underwent neonatal surgery are at risk of neurodevelopmental delay, which suggests possible long-term adverse sequelae in the setting of critical illness and surgery (Laing et al., 2011; Stolwijk et al., 2016; Walker et al., 2011; Wilder et al., 2009). More specifically, a study by Stolwijk et al. (2016) implicated that neonates undergoing surgery for gastrointestinal congenital anomalies are at risk of brain injury. There is growing evidence in the literature to support the notion these multiple early life stressors (Pierro & Eaton, 2008) may affect brain growth patterns (de Cunto et al., 2015; Schwarzenberg et al., 2018) and increase risk for adverse neurodevelopmental outcomes (Prado & Dewey, 2014; Ramel et al., 2016; Stolwijk et al., 2016). With increase in survival rates of infants born with EA over the last decade (Evanovich et al., 2022), follow up studies are needed to comprehensively examine the co-existing cranial/brain imaging findings as well as to evaluate the impact of complex perioperative critical care on long-term neurodevelopmental outcomes in this unique cohort of infants born with both *short-gap* and *long-gap* EA.

5 | CONCLUSIONS

This original retrospective analysis reports the frequency of neurological imaging findings in infants born with EA. Given that cranial/brain imaging in infants born with EA was evaluated only when clinically indicated, presented data might be underestimated at 31% in this cohort. We suggest that all infants born with EA undergo baseline brain imaging as a new standard of care. Infants born with *long-gap* EA undergo 10 times longer pain/sedation management following primary EA repair, as well as double anesthesia exposure in the first year of life. Whether this exposure puts them at increased risk for adverse neurological outcome requires further prospective study. We also propose that quantification of sedation and anesthesia exposure could be used as an indirect measures of underlying disease severity and early indirect markers in future long-term neurodevelopmental outcomes.

AUTHOR CONTRIBUTIONS

Authorship credit was based on substantial contribution to (1) the conception and manuscript design (Maggie Jean McMahon, Devon Michael Evanovich, Jue Teresa Wang, Dusica Bajic); (2) acquisition (Maggie Jean McMahon, Devon Michael Evanovich, Jue Teresa Wang, Russell William Jennings, and Dusica Bajic), analysis (Maggie Jean McMahon, Devon Michael Evanovich, Mackenzie Shea Kagan, Dusica Bajic), or interpretation of data (all authors); drafting the article (Maggie Jean McMahon, Devon Michael Evanovich, Mackenzie Shea Kagan, Dusica Bajic) or critical revision for important intellectual content (all authors); (4) final approval of the version to be published (all authors); and (5) are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (all authors)

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CONFLICT OF INTEREST STATEMENT

Authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article. Requests for any specific data format are available from the corresponding author [Dusica Bajic], upon reasonable request.

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