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Neurodevelopmental Outcomes in Children After Fetoscopic Endoluminal Tracheal Occlusion for Severe Congenital Diaphragmatic Hernia: Results From a Multidisciplinary Clinic

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ABSTRACT

Background: We compared early neurodevelopmental morbidity in young children with severe CDH who underwent FETO to those without fetal therapy.
Methods: We conducted a prospective study of severe CDH patients undergoing FETO (n = 18) at a single North American center from 2015 to 2021 (NCT02710968). Outpatient survivors (n = 12) were evaluated by a multidisciplinary team and compared to expectantly managed CDH patients. Neurodevelopmental outcomes were assessed using the Capute Scales [Clinical Linguistic and Auditory Milestone Scales (CLAMS) and Cognitive Adaptive Test (CAT)], with a developmental quotient (DQ) < 85 indicative of at-risk for delay.
Results: At one year, 58% (n = 7) of FETO patients underwent evaluation, with notable concern for language delay (CLAMS median DQ, 80.1 [interquartile range, 67.6–86.7]). FETO scores improved by 24-months, whereas high severity/non-FETO scores declined [CLAMS median DQ (Difference in DQ), 92.3 (+12.2) vs. 77.1 (−13.4), respectively; p = 0.049]. On the initial CAT, FETO patients had concern for visual motor and problem-solving delays, with a median DQ of 81.3 (62.1–89.4). At 24-months, FETO patients had improving scores [Median CAT DQ, 90.8 (+9.5)], whereas high severity/non-FETO [87.5 (−3.0), p = 0.28] had declining scores.
Conclusion: These initial data suggest that FETO is associated with favorable neurodevelopmental outcomes at 24-months compared to severe CDH under expectant management.
Level of Evidence: III.

1. Introduction

Congenital diaphragmatic hernia (CDH) is a critical anatomic anomaly characterized by abdominal viscera intrathoracic herniation and varying degrees of pulmonary hypoplasia and pulmonary hypertension [1,2]. Despite the highly coordinated, multidisciplinary approach to care, the neonatal mortality rate remains high at 25–30% [1,2]. In fetuses with the most severe prenatal disease, as measured by an observed/expected lung-to-head ratio (O/E LHR) < 25%, fetoscopic endoluminal tracheal occlusion (FETO) has been shown to increase in-hospital survival rates based on a recent international, multicenter trial (Tracheal Occlusion to Accelerate Lung Growth, TOTAL) [3].

Among CDH survivors, there can be persistent cardiac, pulmonary, gastrointestinal, and neurologic morbidities that require lifelong monitoring [4–7]. Neurodevelopmental delays (NDD) are often pervasive in those at the more severe end of the clinical spectrum, with increased days of mechanical ventilation and extracorporeal life support (ECLS) being associated with language and motor delays as well as autism [8–20]. Studies suggest brain

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perfusion delay and neuroimaging changes in CDH, which are also associated with NDD [21–25]. While there are numerous studies pointing to the risk of NDD in CDH, there is a paucity of contemporary, long-term data specific to FETO patients managed in the United States [26,27]. Such data might be useful for pediatric surgeons involved in prenatal consultation with CDH families regarding the relative advantages and disadvantages of FETO on long-term outcomes.

The objective of our study was to report our initial neurodevelopmental outcomes data on CDH patients who underwent FETO at a comprehensive CDH referral center. We compared FETO outcomes with CDH patients treated along the same multidisciplinary care pathways, stratified by disease severity. We hypothesized that FETO patients would have similar neurodevelopmental outcomes when compared to a cohort of CDH children with high severity disease managed without FETO.

2. Methods

2.1. Study design

After obtaining institutional review board approval (IRB00127299), we reviewed prospectively collected data on all CDH patients managed at the Johns Hopkins Hospital and the Johns Hopkins Children's Center (JHCC) in Baltimore, Maryland from 2015 to 2022. As described previously, these patients are managed within an integrated healthcare delivery system involving: (1) fetal management by the Johns Hopkins Center for Fetal Therapy, (2) initial postnatal care by pediatric providers at JHCC, and (3) regular outpatient follow-up provided by a multidisciplinary team at the adjacent Kennedy Krieger Institute that includes surgery, pulmonary, cardiology, nutrition, developmental neurology and related services of physical therapy, occupational therapy, neuropsychology, and social work as needed [28]. Data collection included demographic variables, prenatal and postnatal markers of severity, hospital clinical course, and neurodevelopmental outcomes. Patients with prenatally identified major cardiac anomalies and/or chromosomal anomalies were excluded.

2.2. Treatment groups

The inclusion and exclusion criteria for FETO were based on a previously published non-randomized prospective trial (NCT02710968/IRB00054901) under a U.S. Food and Drug Administration (FDA) investigational device exemption [28,29]. The inclusion criteria for the FETO cohort included prenatal findings of severe CDH, namely left or right sided CDH with an O/E LHR<30% with intrathoracic liver herniation. Other criteria were normal karyotype, singleton pregnancy, absence of additional anatomic anomalies, maternal age>18 years, absence of any maternal contraindication to fetoscopic surgery, and maternal compliance to follow the FETO care pathway as detailed elsewhere [29].

The non-FETO group, which was deemed ineligible for FETO based on O/E LHR, underwent expectant fetal management with standard postnatal care, including ECLS when indicated. These patients were stratified by disease severity using a post-hoc classification system (Supplemental Table 1) [30]. The low severity cohort included patients with a Type A defect without intrathoracic liver herniation or ECLS. Medium severity patients were those with a Type B or C defect without liver herniation or ECLS. High severity/non-FETO patients were those with ECLS utilization or those with Type C/D defects and intrathoracic liver herniation.

2.3. Study outcomes

FETO and severe/non-FETO patient data on the early postnatal course as well as long-term pulmonary, cardiac, and gastrointestinal morbidity have been previously reported [28]. The primary neurodevelopmental outcomes were assessed utilizing the Capute Scales [Clinical Linguistic and Auditory Milestone Scales (CLAMS) and Cognitive Adaptive Test (CAT)] at the 3-, 12-, and 24-month appointments. These validated tests provide critical information regarding expressive and receptive language, and visual-motor integration (non-verbal problem-solving skills) in children <3 years [31,32]. A developmental quotient (DQ) < 85 is indicative of at-risk for language delay or visual motor and problem-solving delay on the CLAMS and CAT, respectively [33]. CLAMS and CAT DQ were calculated by a developmental neurologists (VJB) as described elsewhere [30–32]. For those patients who underwent telehealth visits, a Developmental Assessment of Young Children 2 (DAYC-2) was performed and age equivalents were converted to DQ.

2.4. Statistical analysis

FETO patients served as the reference comparison group for all analyses. Continuous and ordinal data were assessed with Wilcoxon rank sum and presented as median (interquartile range, IQR). Categorical data were evaluated by Chi^2 analysis or Fisher's exact test, as appropriate, and presented as n (%). Simple linear regression was utilized to compare trends in neurodevelopment DQ. Statistical analyses were performed with STATA 16.1. A p-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Prenatal and birth characteristics

There were 58 patients with CDH treated at JHCC during the study period, of which 18 (31%) were FETO, 19 (33%) were high severity/non-FETO, 13 (22%) were medium severity, and 8 (14%) were low severity. FETO patients were comparable to non-FETO patients based on demographic data (Table 1). As expected, FETO patients had a significantly lower O/E LHR (median (IQR), 23%) [18–25] compared to high severity/non-FETO (36%, [28–47] $p = 0.04$), medium severity (45%, [43–45] $p < 0.001$), and low severity (63%, [59–82] $p = 0.008$) patients. Despite similar gestational age, FETO patients weighed less than low severity patients (2889 [2300–3100] grams vs. 3665 [3025–3905] grams, $p = 0.02$), but were comparable to medium and high severity/non-FETO patients. The median Apgar scores at 5-min was 7 (5–8) and were similar in all cohorts. The rate of cardiac anomalies that were diagnosed postnatally and required intervention was low at 5% and was similar between FETO and non-FETO cohorts.

3.2. In-hospital clinical course

On initial echocardiogram, there was pulmonary hypertension in all cohorts, with 73% of FETO patients, 74% of high severity/non-FETO patients ($p = 0.24$), 77% of medium severity patients ($p = 0.84$), and 76% of low severity patients ($p = 0.83$) having two-thirds systemic to suprasystemic right ventricular (RV) pressure (Table 2). This increased RV pressure decreased to 23%, 28% ($p = 0.73$), 0% ($p = 0.23$), and 38% ($p = 0.30$), respectively, at discharge. FETO patients had significantly lower rates of ECLS than high severity/non-FETO patients [10 (56%) vs. 17 (89%), $p = 0.02$], but significantly higher rates than medium severity [0 (0%), $p = 0.001$] and low severity [0 (0%), $p = 0.007$] patients. FETO

Table 1
Baseline characteristics of FETO patients compared to non-FETO patients with diaphragmatic hernia, stratified by disease severity.

	Overall (n = 58)	FETO n = 18 (Reference)	High/non- FETO n = 19	*p-value*	Medium n = 13	*p-value*	Low n = 8	*p-value*
Male sex, n (%)	33 (57)	10 (56)	12 (63)	0.64	8 (62)	0.74	3 (38)	0.40
Race, n (%)				0.20		0.54		0.58
White	34 (59)	11 (61)	6 (32)		11 (85)		6 (75)	
Black	4 (7)	0 (0)	4 (21)		0 (0)		0 (0)	
Hispanic	4 (7)	2 (11)	2 (11)		0 (0)		0 (0)	
Asian	6 (10)	2 (11)	3 (16)		1 (8)		0 (0)	
Unknown	10 (17)	3 (17)	4 (21)		1 (8)		2 (26)	
O/E LHR, % (IQR)	40 (27–50)	23 (18–25)	36 (28–47)	0.04	45 (43–45)	<0.001	63 (59–82)	0.008
Birthweight, grams (IQR)	3080 (2700–3530)	2889 (2300–3100)	3030 (2730–3370)	0.17	3170 (2820–3410)	0.06	3665 (3025–3905)	0.02
GA, weeks (IQR)	39 (37–39)	38 (35–39)	39 (37–39)	0.27	39 (38–39)	0.15	39 (36–39)	0.29
Apgar, 5-min (IQR)	7 (5–8)	7 (5–8)	6 (4–8)	0.14	8 (6–9)	0.44	8 (6–9)	0.46
Cardiac intervention, n (%)	3 (5)	3 (17)	0 (0)	0.06	0 (0)	0.12	0 (0)	0.22
Chromosomal anomalies, n (%)	11 (19)	1 (6)	4 (21)	0.17	5 (38)	0.02	1 (13)	0.54

Abbreviations: FETO = fetoscopic endoluminal tracheal occlusion, GA = Gestational Age, O/E LHR = Observed/expected lung-to-head ratio.

Table 2
Initial hospital course of FETO patients compared to non-FETO patients with diaphragmatic hernia, by disease severity.

	Overall (n = 58)	FETO n = 18 (Reference)	High/non- FETO n = 19	*p-value*	Medium n = 13	*p-value*	Low n = 8	*p-value*
PHTN at birth, n (%)				0.24		0.84		0.83
None	2 (3)	1 (6)	0 (0)		0 (0)		1 (13)	
<2/3 systemic	4 (7)	1 (6)	2 (11)		1 (8)		0 (0)	
2/3 systemic-systemic	29 (50)	10 (56)	6 (32)		8 (62)		5 (63)	
Suprasystemic	14 (24)	3 (17)	8 (42)		2 (15)		1 (13)	
Unknown	9 (16)	3 (17)	3 (16)		2 (15)		1 (13)	
ECLS, n (%)	27 (47)	10 (56)	17 (89)	0.02	0 (0)	0.001	0 (0)	0.007
Days on ECLS, median (IQR)	9 (5–20)	6 (5–13)	10 (9–20)	0.47	–	–	–	–
Days intubated, median (IQR)	16 (7–36)	49 (23–55)	29 (18–36)	0.18	8 (6–29)	0.006	6 (4–12)	0.006
DOL at repair, median (IQR)	5 (3–10)	4 (3–7)	9 (3–1)	0.19	6 (3–12)	0.28	4 (2–7)	0.93
Laterality, n (%)				0.13		0.73		0.33
Left	48 (83)	16 (89)	13 (68)		11 (85)		8 (100)	
Right	10 (17)	2 (11)	6 (32)		2 (15)		0 (0)	
Defect Size[a], n (%)				0.58		0.01		<0.001
A	10 (18)	0 (0)	2 (11)		0 (0)		8 (100)	
B	8 (14)	0 (0)	1 (6)		7 (54)		0 (0)	
C	26 (46)	12 (67)	8 (44)		6 (46)		0 (0)	
D	13 (23)	6 (33)	7 (39)		0 (0)		0 (0)	
Patch repair[a], n (%)	43 (75)	18 (100)	15 (83)	0.07	10 (77)	0.10	0 (0)	<0.001
Intrathoracic liver[a], n (%)	31 (54)	17 (94)	14 (78)	0.15	0 (0)	<0.001	0 (0)	<0.001
PHTN prior to discharge[a], n (%)				0.73		0.23		0.30
None	17 (30)	4 (22)	4 (22)		6 (46)		3 (38)	
<2/3 systemic	18 (32)	8 (44)	4 (22)		5 (38)		1 (13)	
2/3 systemic-systemic	9 (16)	3 (17)	3 (17)		0 (0)		3 (38)	
Suprasystemic	3 (5)	1 (6)	2 (11)		0 (0)		0 (0)	
Unknown	10 (18)	2 (11)	5 (28)		2 (15)		1 (13)	

Abbreviations: FETO = fetoscopic endoluminal tracheal occlusion, PHTN = Pulmonary hypertension, ECLS = extracorporeal life support, DOL = day of life.
[a] 1/19 patients in high severity cohort with mortality prior to surgical repair; denominator n = 18 for intraoperative variables and PHTN prior to discharge.

patients were on ECLS for a similar amount of time compared to high severity/non-FETO patients (6 [5–13] days vs. 10 [9–20] days, p = 0.47). FETO patients were mechanically ventilated for significantly longer than medium (49 [23–55] days vs. 8 [6–29] days, p = 0.006) and low severity patients (vs. 6 [4–12] days, p = 0.006), but were comparable to high severity/non-FETO patients (vs. 29 [18–36] days, p = 0.18).

FETO patients had either Type C/D defects with intrathoracic liver herniation confirmed at CDH repair [17 (94%)]. This was comparable to high severity/non-FETO patients, who had 83% Type C/D defects (p = 0.58), with 78% of patients having intrathoracic liver herniation (p = 0.15). FETO patients had comparable patch repair rates to high severity/non-FETO patients [18 (100%) vs. 15 (83%), p = 0.07] and medium severity patients [10 (77%)], but higher rates than low severity patients [0 (0%), p < 0.001]. There were 47 patients who survived to discharge, including 14 (78%) FETO patients, 12 (63%) high severity/non-FETO, 13 (100%) medium severity, and 8 (100%) low severity.

3.3. Neurodevelopmental outcomes

There was variable follow-up in multidisciplinary clinic due to relocation, transfer of care, and inconsistent attendance at multidisciplinary clinic. Fifty eight percent of FETO patients, 73% of high severity/non-FETO, 31–77% of medium severity, and 25–38% of low severity patients followed at each visit. The CLAMS scores are presented in Fig. 1 and Table 3. At a median of 12.5 months, 75% of FETO patients had concern for language delay (CLAMS median DQ, 80.1 [67.6–86.7]), in contrast to scores from low (93.5 [92–95]), medium (92 [87.6–93.3]), and high severity/non-FETO patients (90.5 [87.6–93.3]). However, at a median of 24.2 months, FETO scores improved to scores comparable to

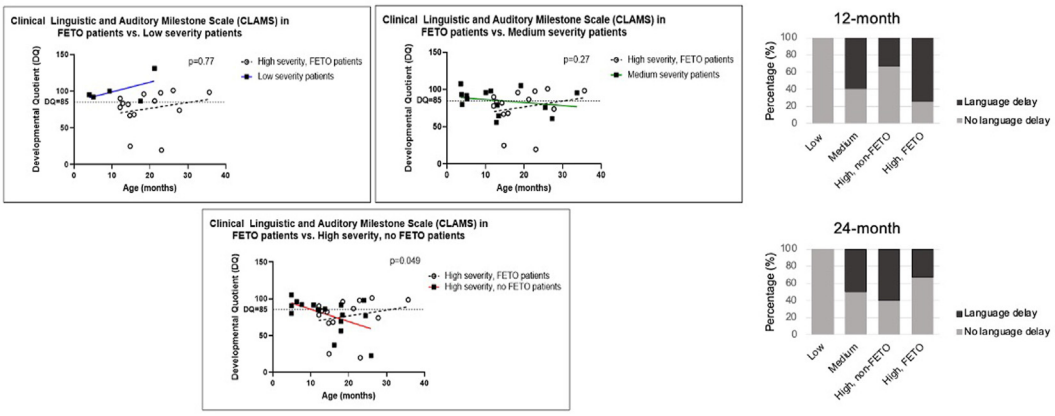

Fig. 1. Clinical Linguistic and Auditory Milestone Scale (CLAMS) Developmental Quotients (DQ) in fetoscopic endoluminal tracheal occlusion (FETO) patients. **(A)** Scatterplot trends in DQ scores in FETO (white circles) compared to low, medium, and high severity without FETO, respectively. **(B)** Bar graphs illustrating percentage with language delay (black) compared to those without language delay (gray) at 12- and 24- month follow up.

Table 3
Median developmental quotient (DQ) for Clinical Linguistic and Auditory Milestone Scale (CLAMS) and Cognitive Adaptive Test (CAT) in fetoscopic endoluminal tracheal occlusion (FETO) compared to low, medium, and high severity without FETO.

	FETO (n = 18)	High, non-FETO (n = 19)	*p*-value	Medium (n = 13)	*p*-value	Low (n = 8)	*p*-value
CLAMS			0.049		0.27		0.77
12 months	80.1 (67.6–86.7	85.1 (77.8–91.4)		79.2 (64.9–96)		100 (100–100)	
>24 months	92.3 (74–98.6)	77.1 (69.4–91.4)		85.8 (68.5–100.4)		108.8 (86.5–131)	
CAT DQ			0.28		0.38		0.83
12-months	81.3 (62.1–89.4)	95.2 (85.1–103.1)		97.3 (94.9–110)		116.3 (116.3–116.3)	
>24 months	90.8 (80–101.4)	87.5 (75.6–95.2)		95.8 (72.8–106.6)		112.2 (100.5–123.8)	

medium severity patients, whereas high severity/non-FETO patients had the worst DQ scores secondary to declining scores over time [median DQ (Difference in DQ), 92.3 (+12.2) vs. 77.1 (−13.4), p = 0.049].

The CAT scores are shown in Fig. 2 and Table 3. From 12- to 24-months, FETO patients had an increase in their median CAT scores from at risk 81.3 [62.1–89.4] to 90.8 [80.0–101.4]. This change over time was comparable to that seen in high severity/non-FETO patients (Difference in slopes: 0.85 vs. −0.93, p = 0.28), medium severity patients (vs. −0.42, p = 0.38), and low severity patients (vs. 1.38, p = 0.83). All FETO and non-FETO cohorts had a CAT DQ > 85 at the 24-month appointment (FETO vs. high severity/non FETO: 90.8 [80.0–101.4] vs. 87.5 [75.6–95.2], p = 0.72) (medium severity: vs. 95.8 [72.8–106.6], p = 0.75) (low severity: vs. 112.2 [100.5–123.8], p = 0.32).

4. Discussion

Our group recently published data showing that FETO was associated with a 78% survival rate to discharge and a long-term survival rate of 67% at a median follow-up of more than five years [28]. These results compare quite favorably to the 40% 6-month survival rates reported in the severe TOTAL trial [3]. We speculate that our increased long-term survival after FETO may be related to avoidance of preterm deliveries, enhanced integration of prenatal and postnatal care, greater standardization and multidisciplinary input in postnatal

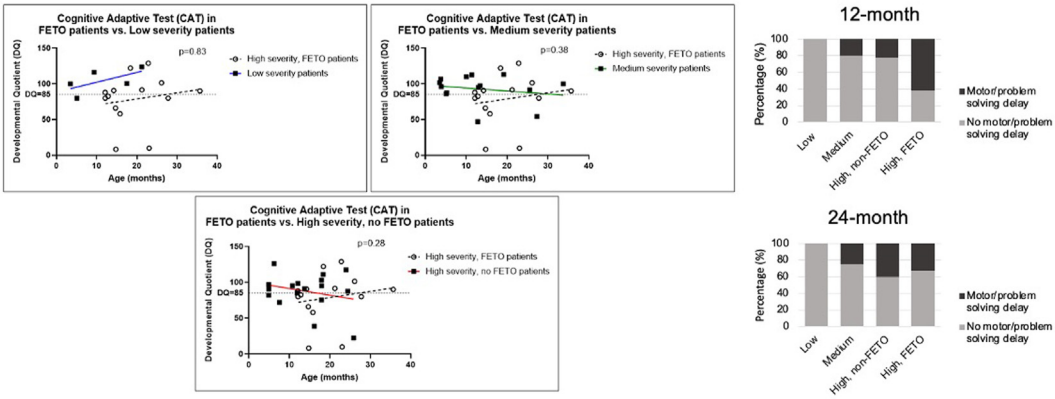

Fig. 2. Cognitive Adaptive Test (CAT) Developmental Quotients (DQ) in fetoscopic endoluminal tracheal occlusion (FETO) patients. **(A)** Scatterplot trends in DQ scores in FETO (white circles) compared to low, medium, and high severity without FETO, respectively. **(B)** Bar graphs illustrating percentage with motor/problem solving delay (black) compared to those without motor/problem solving delay (gray) at 12- and 24- month follow up.

critical care, and more liberal use of ECLS. Cardiopulmonary morbidity in our FETO patients consistently improved over the course of five years, but a large majority continued to face gastroesophageal reflux and other oral feeding challenges [28]. While our morbidity and mortality data compared favorably to a cohort of severe/non-FETO patients, neurodevelopmental outcomes were not assessed. In this study, we provide additional data from an experienced North American center on NDD, a critical long-term measure of functional outcomes when evaluating the utility of FETO as a viable treatment option for severe CDH.

Our results showed that FETO was associated with favorable markers of language and motor function at 24 months when compared to a cohort of severe/non-FETO patients that had higher prenatal lung volumes. Although the majority of FETO patients were at-risk for NDD at the 12-month visit, FETO patients progressed rapidly, with only a third of patients showing persistent signs of language or motor delay at the 24-month assessment. The majority of children in this group were walking, speaking in at least 2-words sentences, and had over 50 single words. They were demonstrating appropriate problem-solving skills as demonstrated by completing simple puzzles and block constructions. Language development scores after FETO were similar to those with medium disease severity. Our data are comparable to the existing literature reporting a 22–29% rate of NDD after FETO [26,27]. These findings are particularly noteworthy given our relatively high survival rates and an ECLS cannulation rate (56%) that was higher compared to the 6–15% ECLS rates reported in prior studies [26,27].

We also found that the trajectory of patients in our most relevant comparison group, those with severe CDH who were not managed with FETO, suggested worsening NDD from 12 to 24-months, with 60% of patients having language delay and 40% of patients having motor delay at 24 months. Despite having significantly higher O/E LHR values when compared to those undergoing FETO, the high rate of NDD may be secondary to the neurologic effects associated with high ECLS utilization (89%), which has been shown to be a major determinant of NDD [11,13,14,18,34,35]. In additional to delayed brain maturation observed in severe CDH patients, the proposed neural connectivity changes that occur during ECLS, may account for some of the cognitive changes seen after cannulation [24,25,36]. Should the lung growth induced by FETO lead to reduced ECLS use in a larger group of CDH patients, we speculate that improved neurodevelopmental outcomes might be a compelling long-term benefit of fetal therapy among survivors.

The study results after FETO are encouraging but should be interpreted in the context of its limitations [28]. First, this is a relatively small single institution study of an emerging technology, which inherently limits statistical power and increases the potential for bias. Second, we were unable to correlate our findings with neuroimaging results since such studies were not routinely obtained and are of unclear utility. Third, we have little quantitative data on what early developmental interventions and services were utilized among our CDH patients. Fourth, our non-FETO comparison group was generated in a post hoc manner based on both established prenatal and postnatal predictors of disease severity. This was meant to serve as a reference group to better contextualize our neurodevelopmental outcomes. The ideal comparison group would have been composed solely of fetuses who were eligible for FETO but declined the procedure through an informed consent process. Unfortunately, this was not possible since nearly all mothers referred to our institution with an eligible fetus desired FETO. Finally, due to our fetal surgical expertise and multidisciplinary care model leading to a relatively low incidence of preterm delivery, the external validity of this study may not be relevant to centers without expertise in FETO or without a comprehensive approach to CDH management in the outpatient setting. Larger, multi-institutional studies with longer follow up on neurocognitive outcomes are clearly needed to determine the impact of FETO on reducing CDH morbidity.

5. Conclusions

This study addresses the neurodevelopmental outcomes in severe CDH survivors undergoing FETO. Using a combinatorial treatment strategy consisting of FETO, aggressive postnatal resuscitation with adjunctive therapies, and long-term multidisciplinary care, our results revealed improved rates of language and motor delay over a follow-up period of two years. Taken together, these early data should be useful for pediatric surgeons in prenatal discussions with families regarding the long-term developmental outcomes of FETO in appropriately selected patients with severe CDH.

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Conflicts of interest

There are no competing interests to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2024.03.041.

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