


# Ex utero intrapartum therapy in infants with congenital diaphragmatic hernia: a propensity score matching analysis

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## ABSTRACT

**Objective** Previous studies have shown that ex utero intrapartum therapy (EXIT) is safe and feasible for newborns with congenital diaphragmatic hernia (CDH). This study reports our experience with EXIT in fetuses with CDH in an attempt to explore the efficacy of EXIT on the survival rate of this population.

**Methods** A retrospective analysis of the clinical data of 116 children with CDH was conducted. The children were assigned to EXIT and non-EXIT groups. Propensity score matching (PSM) toward clinical data was performed, and the clinical characteristics and outcomes were compared. Taking survival at discharge as the main outcome, logistic regression analysis was carried out to explore the efficacy of EXIT on survival.

**Results** During the study period, 30 of 116 children received EXIT. After PSM, the survival rates of the EXIT group and the non-EXIT group were 82.76% (24/29) and 48.28% (14/29), respectively ( $p=0.006$ ). EXIT (OR=0.083, 95% CI=0.013 to 0.525,  $p=0.008$ ), liver herniation (OR=16.955, 95% CI=2.342 to 122.767,  $p=0.005$ ), and gestational age at diagnosis (OR=0.662, 95% CI=0.497 to 0.881,  $p=0.005$ ) were independent mortality-related risk factors of all children with CDH. Ninety-nine of 116 children underwent surgery. After PSM, the postoperative survival rates of the EXIT group and non-EXIT group were 84.6% (22/26) and 76.9% (20/26), respectively ( $p=0.754$ ). Liver herniation (OR=10.451, 95% CI=1.641 to 66.544,  $p=0.013$ ) and gestational age at diagnosis (OR=0.736, 95% CI=0.577 to 0.938,  $p=0.013$ ) were independent mortality-related risk factors of children after surgery.

**Conclusion** EXIT can be performed safely for selected prenatally diagnosed CDH neonates with potentially better survival and does not cause more maternal complications compared with traditional cesarean section.

## INTRODUCTION

Congenital diaphragmatic hernia (CDH) is caused by a congenital defect in the diaphragm that allows abdominal organs herniating into the thoracic cavity, leading to neonatal pulmonary hypoplasia and pulmonary hypertension. CDH occurs in approximately 2.6 of 10 000 live births.<sup>1</sup> Although neonatal surgical techniques and neonatal

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Infants with congenital diaphragmatic hernia (CDH) often experience cardiorespiratory instability immediately after birth.
- ⇒ Resuscitation with an intact cord is feasible, is without adverse events for mothers and infants with CDH, and may result in short-term physiological benefit.
- ⇒ Ex utero intrapartum therapy (EXIT) may improve the outcome for infants born with airway compromise.

## WHAT THIS STUDY ADDS

- ⇒ EXIT can be performed safely for selected prenatally diagnosed CDH neonates with potentially better survival, and EXIT does not cause more maternal complications compared with traditional cesarean section.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

- ⇒ EXIT is a safe and reliable option for infants born with CDH.
- ⇒ The effect of EXIT in infants with CDH needs to be addressed in a large multicenter trial.

intensive care have made significant progress in the past few decades, the mortality rate of children with severe CDH has still been high, reaching 70%<sup>2</sup> without significant improvement.<sup>3</sup> Patients with the most severe CDH often suffer from severe hypoxemia and acidosis and even require emergency intubation and extracorporeal membrane oxygenation (ECMO) for support. Ex utero intrapartum therapy (EXIT) was initially developed to establish an airway in fetuses that had undergone in utero tracheal occlusion. Then the indications for the EXIT procedure have expanded, and any fetus with a prenatal diagnosis that is consistent with potential airway compromise or cardiorespiratory instability at birth are potential candidates for EXIT.<sup>4,5</sup>

The hemodynamic transition from fetal to neonatal in healthy neonates is different



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from that in CDH neonates. When the umbilical cord is clamped, the loss of umbilical venous return reduces left ventricular preload, and due to the placental vascular bed with low resistance is removed from the systemic circulation, the systemic vascular resistance increases, resulting in reduced cardiac output and lower stroke volume and heart rate. Lung aeration decreased pulmonary vascular resistance and increased pulmonary blood flow trigger the transition from fetal circulation to neonatal circulation.<sup>6,7</sup> In healthy newborns, lung aeration is established rapidly after birth thereby avoiding severe hypoxia.<sup>8</sup> CDH neonates have delayed lung aeration after birth due to poor lung development and low compliance. As a result, after clamping the umbilical cord, there is a prolonged period of reduced cardiac output, leading to fetal hypoxia and fluctuating blood pressure. For this reason, delayed clamping of the umbilical cord—the practice of resuscitation followed by clamping the umbilical cord through EXIT—has been used by some centers to treat children with CDH.<sup>9</sup> Previous research supports the opinion that application of intact cord resuscitation for treatment of children with CDH is safe and feasible.<sup>10</sup> Foglia *et al*<sup>11</sup> demonstrated that first measured hemoglobin and mean blood pressure values at 1 hour of life were higher in infants treated with intubation and ventilation prior to umbilical cord clamping (UCC). There has been no randomized controlled trial (RCT) reporting the role

of intubation prior to UCC or EXIT in the survival of neonates with a prenatal diagnosis of CDH.

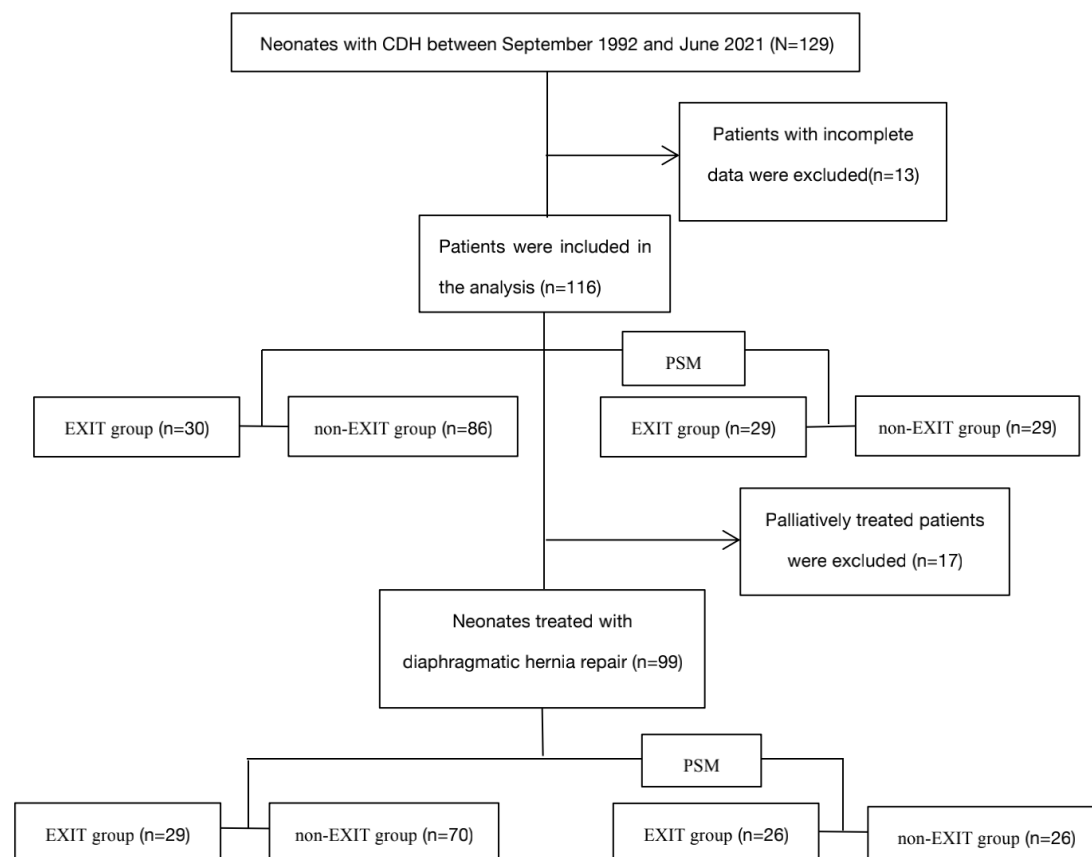
Because selection bias might exist due to the significant difference in disease severity, we applied propensity score matching (PSM) to minimize the effect of other confounding factors for prognosis and to simulate the research conditions of an RCT. The purposes of this study were to: (1) explore the efficacy of EXIT on the survival rate of children with CDH and (2) analyze the mortality-related risk factors of infants with CDH.

## MATERIALS AND METHODS

### Study design and setting

This study was carried out at the Children's Hospital of Capital Institute of Pediatrics in Beijing, China. Inclusion criteria are as follows: (1) definite diagnosis of CDH through imaging examination from September 1992 to June 2021; (2) treated at our hospital after birth; (3) complete medical records and follow-up data; and (4) prenatal diagnosis of CDH (EXIT group, from January 2018 to June 2021). Exclusion criteria are as follows: (1) not being treated for the first time in our hospital after birth; (2) incomplete medical records; (3) chromosomal abnormalities; (4) non-CDH death ([figure 1](#)).

Our hospital cooperated with Peking Union Medical College Hospital (PUMCH) to treat selected children



**Figure 1** Study flow diagram. CDH, congenital diaphragmatic hernia; EXIT, ex utero intrapartum therapy; PSM, propensity score matching.

with CDH by EXIT since 2019. All the children born through EXIT in the study group were from PUMCH. There is no absolute contraindication for EXIT at present. In this study, the criteria for the inclusion of the child in the EXIT group were prenatal diagnosis of CDH, and EXIT was considered feasible for the puerpera after multidisciplinary discussion. EXIT was not considered if the mother had severe pregnancy complications, such as severe gestational hypertension, which would increase the risk of anesthesia and surgery for the mother and child. Choice of delivery methods was informed by discussions with parents of patients in our multidisciplinary clinic. For the non-EXIT group, there were children who were transferred to our center after birth through traditional delivery approach in PUMCH and other hospitals.

### Intervention

EXIT was performed in the operating theatre by a team consisting of obstetricians, neonatal surgeons, neonatal physicians, and anesthetists. For fetuses with EXIT, when the head and neck were exposed and the rest of the body remained within the uterine cavity (cesarean deliveries) or immediately after delivery (vaginal deliveries), the fetus was intubated with the support of placental blood circulation and ventilated (initial settings: peak inspiratory pressure/positive end expiratory pressure (PIP/PEEP) 20–25/5 cm H<sub>2</sub>O, fractional inspired oxygen 0.4). When the SpO<sub>2</sub> of the child was measured ( $\geq 85\%$ , monitored by a pulse oximeter that was placed on the upper limb of the fetus), the umbilical cord was clamped and cut. The child was transported to the neonatal intensive care unit (NICU) under mechanical ventilation. According to the protocol, if intubation could not be completed successfully within 5 min from birth, umbilical cord avulsion, hemorrhage, or any obstetrician or neonatologist concerns, the umbilical cord should be clamped before tracheal intubation. In our hospital, it is a protocol to perform immediate endotracheal intubation for infants with a known diagnosis of CDH, avoiding the use of bag-valve mask ventilation for these patients. Later, the ventilator can be removed if blood oxygen can be maintained under very low ventilator conditions. Before surgery, the following physiological criteria must be met: urine output  $>1$  mL/kg/hour; FiO<sub>2</sub>  $<0.5$ ; preductal oxygen saturation between 85% and 95%; normal mean arterial pressure for gestational age; lactate  $<3$  mmol/L; estimated pulmonary artery pressures less than systemic pressure.

### Data collection

We assigned survival at discharge as the main outcome. The patients' information included: gestational age at birth; gestational age at diagnosis (when CDH was found on the first ultrasound screening or MRI examination); gender; birth weight; heart structural abnormalities; chromosomal abnormalities; liver position; and whether a patch was used during the operation. We also recorded the affected side (left/right) and the classification

(A–D) based on the size of the diaphragmatic defect by the criteria by Lally *et al.*<sup>12</sup> We used the postpartum risk prediction model developed by Brindle *et al.*<sup>13</sup> to divide patients into low, medium and high risk based on scores of 0, 1–2, and  $\geq 3$ .

### Propensity score matching

Currently, it is believed that the lesion site, liver herniation, gestational age at prenatal diagnosis, gestational age at birth, and birth weight have an impact on survival of CDH neonates.<sup>14–16</sup> Here, a 1:1 matching was undertaken to overcome potential selection bias by the PSM method between the two groups. Using multiple logistic regression analysis, a propensity score was estimated for all patients. Variables used in the model included gender, lesion site, diaphragmatic defects, liver herniation, surgical approach, gestational age at diagnosis, gestational age at birth, and birth weight. We performed calliper matching on the propensity score (nearest available matching). Pairs on the propensity score logit were matched within a range of 0.05 SD. Matching was performed by the minimal adjacent method of 1:1 pairing.

### Follow-up

Patients were evaluated in the outpatient clinics at 1 week, 2 weeks, 1 month, 3 months, 6 months and 1 year, 2–5 years, and 10 years after discharge. The follow-up included examinations of the heart and lungs, gastrointestinal function, nutrition, neurodevelopment and musculoskeletal system.

### Statistical analysis

Data processing was conducted using SPSS V.25.0. Continuous data were compared between the EXIT and non-EXIT groups using a t-test for normally distributed variables and a Wilcoxon rank sum test for non-parametric variables. Dichotomous variables were assessed with  $\chi^2$  test or Fisher's exact test, and the variables between the two groups after PSM were assessed with McNemar test. The mortality-related risk factors were calculated by logistic regression (LR) (step forward: LR). The following confounding factors were adjusted in the multivariable analysis of overall mortality: the side of the defect, presence of liver herniation, gestational age at prenatal diagnosis, gestational age at birth, birth weight, EXIT, Brindle. Whether a patch was used and defect size also were adjusted in the multivariable analysis of post-operative mortality. The models were tested by receiver operating characteristic (ROC) curve. A p value  $<0.05$  was considered statistically significant.

### RESULTS

A total of 129 cases were reviewed, and 13 were excluded due to incomplete data. The remaining 116 children were included in the analysis. Thirty with CDH were intubated under EXIT at birth. Among the 86 children in the non-EXIT group, 62 children diagnosed prenatally

**Table 1** Demographic characteristics of all patients and PSM patients stratified by EXIT

	Before PSM			After PSM		
	EXIT (n=30)	Non-EXIT (n=86)	P value	EXIT (n=29)	Non-EXIT (n=29)	P value
Outcome						
Survival	24 (80%)	51 (59.3%)	0.041	24 (82.8%)	14 (48.3%)	0.006
Death	6 (20%)	35 (40.7%)		5 (17.2%)	15 (51.7%)	
Gender						
Male	18 (60%)	50 (58.1%)	0.859	17 (58.6%)	14 (48.3%)	0.629
Female	12 (40%)	36 (41.9%)		12 (41.4%)	15 (51.7%)	
Gestational age at diagnosis (week)	24.0 (23.75–30.0)	28.0 (23.0–36.0)	0.098	24.0 (23.5–30.0)	24.0 (22.0–30.5)	0.899
Birth weight (kg)	3.05 (2.60–3.31)	2.96 (2.58–3.32)	0.588	3.09 (2.59–3.31)	3.04 (2.50–3.34)	0.948
Gestational age at birth (week)	37.3 (37.0–37.6)	38.0 (36.0–39.0)	0.066	37.3 (37.0–37.6)	38.0 (35.7–39.0)	0.699
Length of hospital stay (days)	28.5 (18.75–38.25)	11.5 (1.0–19.5)	<0.001*	30.0 (19.00–38.5)	6.00 (1.0–18.5)	<0.001*
Method of delivery (cesarean section)	28 (93.3%)	60 (69.8%)	0.012	27 (93.1%)	20 (69.0%)	0.039
Site						
Left	22 (73.3%)	74 (86.0%)	0.112	21 (72.4%)	22 (75.9%)	1
Right	8 (26.7%)	12 (14.0%)		8 (27.6%)	7 (24.1%)	
Any portion of liver in chest n=97						
Yes	11 (37.9%)	17 (25%)	0.198	11 (37.9%)	11 (37.9%)	1
No	18 (62.1%)	51 (75%)		18 (62.1%)	18 (62.1%)	
Surgical repair						
Yes	29 (96.7%)	70 (81.4%)	0.082	29 (100%)	25 (86.2%)	0.125
Brindle						
Low	9 (30%)	38 (44.2%)	0.151	9 (31.0%)	11 (37.9%)	0.674
Medium	19 (63.3%)	45 (52.3%)		18 (62.1%)	16 (55.2%)	
High	2 (6.7%)	3 (3.5%)		2 (6.9%)	2 (6.9%)	
Recurrence						
Yes	2 (6.7%)	2 (2.3%)	0.275	2 (6.9%)	0 (0%)	0.491

Dichotomous data are presented as number (percentage), continuous data are presented as median (IQR).

\*P<0.05 was considered statistically significant.

EXIT, ex utero intrapartum therapy; PSM, propensity score matching.

received immediate endotracheal intubation after birth. Among the other 24 children diagnosed postnatally, 4 were intubated immediately due to respiratory distress at birth. The remaining 20 were intubated after the occurrence of respiratory distress. No child was taken off the ventilator before surgery.

All 116 children were matched by PSM, and 29 children in the EXIT group and 29 in the non-EXIT group were matched. Before PSM, the two groups had significant differences in survival rate, length of hospitalization, and delivery methods ( $p<0.05$ ). After PSM, the differences in survival rate, length of hospitalization, and delivery methods of the two groups were significant ( $p<0.05$ ), but there was no difference in other characteristics ( $p>0.05$ ) (table 1 and online supplemental figure 1). Taking survival at discharge as the outcome, multivariable LR analysis showed that EXIT, liver herniation, and gestational age at diagnosis were independent

mortality-related risk factors of all children before and after PSM (table 2). The models were tested by ROC analysis: area under the curve (AUC)=0.865;  $p<0.001$ /AUC=0.924;  $p<0.001$ , respectively (online supplemental figures 2 and 3).

According to whether EXIT was performed, 99 children who underwent surgical treatment were divided into two groups: the EXIT group and the non-EXIT group. Twenty-six cases of EXIT children and 26 cases of non-EXIT children were matched by PSM. Before PSM, the two groups had significant differences in gestational age at diagnosis, length of hospitalization, delivery methods, surgical approach, and presence of hernia sacs ( $p<0.05$ ). After PSM, the two groups showed only a significant difference in the length of hospitalization ( $p<0.05$ ) (table 3, and online supplemental figure 4). Analysis showed that liver herniation and gestational age at diagnosis were independent mortality-related risk factors



**Table 2** Logistic multivariable regression of risk factors of overall mortality

Variable	Multivariable analysis (before PSM )		Multivariable analysis (after PSM )	
	OR (95% CI)	P value	OR (95% CI)	P value
EXIT (ref. non-EXIT )	0.234 (0.062 to 0.883 )	0.032*	0.083 (0.013 to 0.525 )	0.008*
Any portion of liver in chest: (ref.: no)	5.609 (1.626 to 19.348)	0.006*	16.955 (2.342 to 122.767)	0.005*
Gestational week at diagnosis (per week)	0.782 (0.686 to 0.89)	<0.001*	0.662 (0.497 to 0.881)	0.005*

\*P<0.05 was considered statistically significant.

EXIT, ex utero intrapartum therapy; PSM, propensity score matching.

of neonates after surgery before and after PSM, respectively (table 4 and online supplemental figures 5 and 6). The models were tested by ROC analysis: AUC=0.831; p<0.001/AUC=0.881; p<0.001 (online supplemental figures 5 and 6).

During birth in the EXIT group, all 30 fetuses were successfully intubated before UCC, and none of them required chest compression. The intubations were completed within 30s to 2 min from birth, and neonates were transferred to the NICU with mechanical ventilation. There were no maternal complications, such as postpartum hemorrhage (blood loss  $\geq$ 500mL) and placental abruption. No women needed intraoperative blood transfusion, and no wound infections occurred in the EXIT group.

We followed up the patients in the outpatient clinic and found no dyskinesia or language retardation in the surviving children after the operation.

## DISCUSSION

EXIT was initially used for children who had undergone fetoscopic tracheal occlusion to remove the obstructive balloon or clip during delivery. Later, it was gradually used to deal with cases of suspected neonatal airway malformations, such as congenital high airway obstruction syndrome, neck mass, micrognathia, etc.<sup>4 17-21</sup>

According to Bence and Wagner,<sup>22</sup> EXIT is mainly classified into the following categories: EXIT-airway establishment (EXIT-to-airway), EXIT-tumor resection (EXIT-to-resection), EXIT-intubation ECMO treatment (EXIT-to-ECMO), and EXIT-conjoined fetus separation (EXIT-to-separation). The main focus of the present study was the EXIT-to-airway procedure, which comprised maintaining placental circulation to support laryngoscopy, endotracheal intubation, and even tracheotomy before UCC. The advantage of EXIT is that it can extend the placental transfusion time so that doctors have more time to perform some life-saving operations, such as bronchoscopy, endotracheal intubation, and tracheotomy. Studies have reported that the placental transfusion can be maintained for 60 min, and in the best case up to 150 min.<sup>23 24</sup> The risk of the EXIT procedure is that the mother needs to maintain uterine relaxation during the EXIT process, which may lead to placental abruption or excessive blood loss. Moreover, the incision is longer

than traditional cesarean section and it is more likely to cause wound infection.<sup>4 25 26</sup>

Previously, the application of EXIT in CDH was mainly for ECMO treatment (EXIT-to-ECMO). Shieh *et al*<sup>27</sup> showed that EXIT-to-ECMO did not significantly increase the survival rate of children with severe CDH, but the author believed it was because the patients in the EXIT-to-ECMO group might have been more severely ill and the patients were not randomized. However, the study showed that children in the EXIT-to-ECMO group had an overall shorter initial hospital stay, shorter ECMO duration, and lower stroke rates. The author believed that this might be related to the use of EXIT by avoiding harsh ventilation during initial resuscitation and ECMO cannulation. Previous studies have shown that intubation before clamping the umbilical cord did not increase the risk of the infants or their mothers.<sup>28</sup> And it was safe and feasible to cut the umbilical cord after 5 min after birth.<sup>29</sup> Two studies have confirmed the safety and feasibility of intubation and ventilation for children with CDH before UCC.<sup>10 11</sup> The present study is the first to explore the efficacy of EXIT-to-airway for neonatal CDH on the survival rate of children. The main considerations were as follows: (1) intubation before spontaneous breathing is established in children with severe CDH during delivery, which can minimize lung barotrauma; (2) smooth transition in the terms of the physiological process from fetus to newborn infant may help reduce the occurrence of hypoxemia, hypercapnia, hypotension, acidosis, and ischemic brain injury<sup>30</sup>; (3) EXIT-to-airway is relatively easy to complete in an experienced medical centre. Our expected time to complete the operation was within 5 min, and almost all intubations were completed within 2 min, which did not increase the risk to pregnant women and fetuses; (4) compared with EXIT-to-ECMO, the respiratory and circulatory support provided by ECMO is at the cost of patient's physiological balance and is more traumatic. EXIT-to-airway can also optimize the perioperative comprehensive treatment, and its application range is wider.

In our study, the survival rate of children in the EXIT group was higher than that in the non-EXIT group in all children before and after PSM, and the multivariable logistic analysis before and after PSM showed that EXIT was a protective factor for survival of children with

**Table 3** Demographic characteristics of postoperative patients and PSM postoperative patients stratified by EXIT

	Before PSM			After PSM		
	EXIT (n=29)	Non-EXIT (n=70)	P value	EXIT (n=26)	Non-EXIT (n=26)	P value
Outcome						
Survival	24 (82.8%)	51 (72.9%)	0.295	22 (84.6%)	20 (76.9%)	0.754
Death	5 (17.2%)	19 (27.1%)		4 (15.4%)	6 (23.1%)	
Gender						
Male	17 (58.6%)	40 (57.1%)	0.892	14 (53.8%)	15 (57.7%)	1
Female	12 (41.4%)	30 (42.9%)		12 (46.2%)	11 (42.3%)	
Gestational week at diagnosis (week)	24.0 (23.5–30.0)	30.0 (23.0–36.0)	0.061	25.0 (23.75–30.0)	25.0 (22.75–36.25)	0.38
Birth weight (kg)	3.09 (2.59–3.31)	2.96 (2.6–3.33)	0.672	3.095 (2.595–3.305)	3.0 (2.6–3.5)	0.829
Gestational age at birth (week)	37.3 (37.0–37.6)	38.0 (36.9–39.0)	0.021*	37.35 (37.0–37.6)	38.0 (36.75–39.15)	0.191
Length of hospital stay (days)	30.0 (19.0–38.5)	15.0 (4.0–24.0)	<0.001*	28.50 (19.0–38.0)	17.5 (7.0–28.0)	0.03*
Method of delivery (cesarean section)	27 (93.1%)	48 (68.6%)	0.012*	24 (92.3%)	17 (65.4%)	0.065
Site						
Left	21 (72.4%)	61 (87.1%)	0.14	20 (76.9%)	19 (73.1%)	1
Right	8 (27.6%)	9 (12.9%)		6 (23.1%)	7 (26.9%)	
Any portion of liver in chest n=92						
Yes	11 (37.9%)	14 (22.2%)	0.116	9 (34.6%)	10 (38.5%)	1
No	18 (62.1%)	49 (77.8%)		17 (65.4%)	16 (61.5%)	
Surgery approach						
MIS	22 (75.9%)	35 (50%)	0.018*	19 (73.1%)	18 (69.2%)	1
Other	7 (24.1%)	35 (50%)		7 (26.9%)	8 (30.8%)	
Brindle						
Low	9 (31.0%)	30 (42.9%)	0.182	8 (30.8%)	10 (38.5%)	0.439
Medium	18 (62.1%)	39 (55.7%)		17 (65.4%)	16 (61.5%)	
High	2 (6.9%)	1 (1.4%)		1 (3.8%)	0 (0%)	
Defect Size (n=82)						
A	0	0	0.726	0	0	1
B	2 (7.1%)	7 (13.0%)		2 (8%)	4 (16%)	
C	16 (57.1%)	28 (51.9%)		15 (60%)	10 (40%)	
D	10 (35.7%)	19 (35.1%)		8 (32%)	11 (44%)	
Hernial sac (n=75)						
Yes	10 (34.5%)	7 (15.2%)	0.052*	9 (34.6%)	2 (10.5%)	0.453
No	19 (65.5%)	39 (84.8%)		17 (65.4%)	17 (89.5%)	
Patch (n=98)						
Yes	8 (27.6%)	19 (27.5%)	0.996	19 (73.1%)	17 (65.4%)	0.774
No	21 (72.4%)	50 (72.5%)		7 (26.9%)	9 (34.6%)	
Recurrence						
Yes	2 (6.9%)	2 (2.9%)	0.578	2 (7.7%)	1 (3.8%)	1

Dichotomous data are presented as number (percentage), continuous data are presented as median (IQR).

\*P<0.05 was considered statistically significant.

EXIT, ex utero intrapartum therapy; PSM, propensity score matching.

CDH, which might improve the overall survival rate. However, before and after PSM in children who underwent surgical repair, there was no significant difference in postoperative survival rates between the two groups. Multivariable logistic analysis did not show that EXIT was an independent mortality-related risk factors of patients after surgery. Therefore, we hypothesize that the way that

EXIT improves the survival rate of children with CDH may be to reduce lung barotrauma and hypoxic insult, thereby giving the opportunity for surgery, and saving some patients who might have died. It was found that the surgical treatment rate of all children in the EXIT group before and after PSM was higher than that in the non-EXIT group (table 1 and online supplemental figure 7),

**Table 4** Logistic multivariable regression of independent risk factors of postoperative mortality

Variable	Multivariable analysis (before PSM)		Multivariable analysis (after PSM)	
	OR (95% CI)	P value	OR (95% CI)	P value
Any portion of liver in chest: (ref.: no)	5.473 (1.483 to 20.207)	0.011	10.451 (1.641 to 66.544)	0.013*
Gestational week at diagnosis (per week)	0.763 (0.647 to 0.899)	0.001*	0.736 (0.577 to 0.938)	0.013*

\*P<0.05 was considered statistically significant. PSM, propensity score matching.

but the differences were not significant. We consider that it was because of insufficient sample size.

The results of this study showed that for children with CDH and patients undergoing surgical repair, the gestational age at diagnosis and liver herniation were mortality-related risk factors. It was consistent with other researches.<sup>14-16</sup> The dual-hit theory<sup>31</sup> proposes that pulmonary hypoplasia in CDH is caused by two insults, one impacting both lungs before diaphragm formation and the other affecting the ipsilateral lung by mechanical forces after incomplete diaphragm development. Although this hypothesis has not been validated, it follows that the earlier lung development is affected, the more disrupted the development of lung parenchyma and vascularization is, and the more likely they are to have severe pulmonary dysplasia and pulmonary hypertension after birth. Pulmonary hypoplasia and pulmonary hypertension are two important factors affecting the survival rate of patients with CDH.<sup>2</sup> In addition, an earlier gestational age at diagnosis, according to some research, is an independent predictor of CDH mortality and morbidity.<sup>16 32</sup> And it could potentially reflect the size of the defect.<sup>33</sup> The larger the defect, the earlier the gestational age at which it was discovered. Because the larger the defect, the more abdominal organs that have herniated into the thorax, making it easier to identify. The size of the defect is associated with mortality rate and appears to be an important factor determining outcomes in CDH newborns.<sup>34 35</sup> That may explain why gestational age at the time of the diagnosis is important.

The limitations of this study included the small sample size and the inherent limitations of a single-center retrospective study. Although this study represents a large EXIT-to-airway cohort of children with CDH, the sample size was still small. If an event had not happened in this sample, then it does not mean it never will. Although PSM has the advantage of reducing selection bias, it was limited by the available data, and it is not yet possible to rule out the influence of some confounding factors that could not be effectively measured. Because the patients in our study were from different regions of China, the lung-to-head ratio (LHR) data of some patients were unavailable. Therefore, LHR was not included in this study. Therefore, this conclusion still needs to be verified by a large-sample, multicenter RCT, and more researches are needed to verify the advantages of this delivery strategy, the benefits to patients, and the risks.

In conclusion, EXIT is safe and feasible, our data indicate that EXIT is a reliable option for prenatally diagnosed CDH in selected neonates, with potential benefit of lower mortality.

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