Congenital Diaphragmatic Hernia Guidelines

Initial Development June 2013, Updated Oct 2020
v.10-28-20

Prenatal:

1. Consult with perinatology, cardiology for fetal echo, pediatric surgery and neonatology (jointly if possible after initial antenatal US/MRI screenings) and discuss infant at perinatal conference—we should not have unannounced CDH cases followed by obstetricians.
   The prediction of pulmonary hypoplasia aids in antenatal counseling.
   a. Fetal Ultrasound: Determine observed-to-expected lung-head ratio (o/e LHR) using the manual tracing method as early as possible in second trimester between 22-32 weeks gestation. O/E LHR may be calculated www.totaltrial.eu. Time is critical as mother may be candidate for fetal therapy prior to 29 weeks.
   b. Fetal MRI: For the assessment of fetal lung volume and liver position (up/down and percent herniation). Obtain first MRI during second trimester to determine possible need for fetal intervention (FETO). If first MRI suggests need for fetal intervention, then refer family to FETO center. If not, obtain second fetal MRI at 32 weeks to determine potential need for ECMO. See #2 below.
   c. There is some variation between MRI and US and we do not have ECMO at SLCH. MRI and o/e LHR combined help improve prediction characteristics. (CMAJ 2018).
2. Optimal timing of fetal MRI is not clear. Ideally, a second trimester MRI to assess TFLV, o/e TFLV, liver position, and percent of liver herniation is obtained. For late presentations, a third trimester MRI likely still has utility in predicting need for ECMO and pulmonary hypertension. Second trimester MRI to assess o/e TFLV independently predicts survival by logistic regression. Second or third trimester fetal lung volumes predict need for ECMO and persistent pulmonary hypertension. In individualized cases where a second trimester MRI has been obtained, there may be utility in obtaining a third trimester MRI to assess interval fetal lung growth to predict severe versus mild/no PAH after birth. (Olotoye OO, Lee TC, et al, Fetal Diagnosis and Therapy 2020; 47:205-213).
3. Several publications contain reference tables to predict survival, need for ECMO, persistence of pulmonary hypertension, but significant overlap exists. See Appendix 1 for additional references.

Observed-to-Expected Lung to Head Ratio by Ultrasound

Left CDH, Liver Up	**o/e LHR (ultrasound)**	**Survival**
Very Severe	<15%	<5%
Severe	16-25%	20-30%
Moderate	26-45%	40-60%
Mild	>45%	95%

Total Observed-to-Expected Fetal Lung Volume by MRI and Liver Position

	o/e TFLV (MRI)	Survival with Liver UP	Survival with Liver Down
Very Severe	<15%	12%	40%
Severe	16-25%	40%	85%
Moderate	26-45%	65%	85%
Mild	>45%	75%	85%

(Cordier AG, Russo FM, et al. Prenatal diagnosis, imaging, and prognosis in Congenital Diaphragmatic Hernia. Seminars Perinatol 2020: 44;1-7)

4. Severe cases may be a candidate for fetal endoscopic tracheal occlusion (FETO), which requires balloon placement in fetal trachea usually at 27 to 29 weeks and balloon removal by about 34 weeks. University of Texas (Texas Children's Hospital) is only US site participating in the TOTAL Trial (Tracheal Occlusion to Accelerate Lung Growth).
5. Indications for fetal surgery per UCSF (see https://fetus.ucsf.edu/cdh for full inclusion/exclusion criteria).
    a. Mother must be 18 years or older
    b. Singleton pregnancy
    c. Normal fetal karyotype and/or microarray (FISH ok if > 26 weeks)
    d. Isolated Left CDH with liver up (may do right CDH on compassionate basis)
    e. LHR O/E < 25% (measured 18^0 to 29^5 weeks)
    f. Evaluation and enrollment prior to 29 weeks gestation
    g. Family meets psychosocial criteria and has the ability to reside in or near San Francisco
    h. re-authorization from third-party payor for fetal intervention OR the ability to self-pay
6. Parents must be aware and understand the lack of ECMO at SLCH. If parents desire possible ECMO, delivery should be planned at an ECMO center.
7. Referral center is at discretion of family (Seattle, Portland, Salt Lake, etc.), but Primary Children's in Salt Lake has active protocol with published high survival (Yang, M.J., Fenton, S., Russell, K. *et al.* Left-sided congenital diaphragmatic hernia: can we improve survival while decreasing ECMO?. *J Perinatol* **40,** 935–942 (2020).)
8. Antenatal betamethasone should be given to improve neonatal lung function.
9. Obtain antenatal genetic evaluation (karyotype/microarray).

On Maternal Admission:

1. Notification of neonatologists.
2. Notification of pediatric surgeon by neonatologist with review of expected DR management.

Delivery Management (neonatologist and pediatric surgeon to be present):

1. No data regarding delayed cord clamping.
2. Avoid PPV using bag/mask directly to face to minimize entrainment of air into stomach/intestines.
3. Intubate immediately (most qualified person) and confirm with end tidal CO2. Secure ETT with NeoBar.
4. No clear evidence for ideal initial FIO2. High levels of O2 may cause pulmonary oxidative damage. Centers use 50-100% (no studies guide this). Likely start around 50%, then adjust supplemental oxygen to achieve pre ductal goal of > 70% initially, then goal of 85-95%. Can adjust FIO2 by 10% (up or down) every 90 seconds (Per Johns Hopkins protocol).
5. Use NeoT to provide ventilation. PEEP about 4 to 5, PIP up to 25, but generally start lower (Johns Hopkins uses initial total PIP 20 in DR).
6. Appropriately dry infant after securing airway (avoid cold stress).
7. Attach to CR monitor and pulse ox on right hand per standard NRP.
8. Place 8 to 10 French Replogle and manually aspirate frequently with 30 ml syringe.

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Stabilization Phase (first 2 to 3 hours):

1. Admit infant to low-stimulation room. Do not bathe infant. Maintain normothermia.
2. Use conventional vent [shown to decrease duration of ventilation, decrease ECMO need, decrease use of iNO and sildenafil, decreased vasopressor use (VICI trial, Annals of Surgery, 2016)].
3. Begin conventional vent at extubatable settings with total PIP around 16, PEEP 4 to 5, rate of 30 to 40, light sedation. If PIP > 25 (Texas Children's will go to 28) and rate > 50 with persistent hypercarbia (> 65) consider HFOV.
4. Place infant on radiant warmer in NICU—radiant warmer should:
    a. have x-ray film tray drawer to minimize handling of infant
    b. have a bed scale to minimize handling of infant
5. Place PIV to maintain glucose and give sedation if needed while umbilical lines are attempted.
6. There is no rationale for routine surfactant administration in the CDH term or preterm infant (d/t varying lung sizes) and it has been associated with worsened outcomes in term infants (increased mortality rate, greater use of ECMO, and more CLD) and lower survival in premature infants. However, in a significantly premature infant (32 wk or less) it may be considered in joint discussion with neonatology and pediatric surgery. If given, it must be given slowly by drip with close monitoring to prevent destabilization.
7. Attempt UAC and UVC. If UAC unsuccessful, consider right radial PAL for BP management and assessment of preductal PaO2. If UVC unsuccessful, place PICC line to provide stable access, but may defer until infant is more stable provided a low UVC is working.
8. Place Replogle (8 to 10 Fr) to low-intermittent (20 cm H2O) wall suction.
9. CXR/AXR for line placement, anatomic survey for other malformations. Goal contralateral lung inflation on CXR is 8 to 9 ribs. Avoid flattened diaphragms and more than 9 rib expansion to avoid overdistension of hypoplastic lungs.
10. Initial Labs: CBC, blood gas, lactate, type and screen, +/- blood culture
11. Subsequent labs:
    a. ABG q30 min x 2, then hourly x 2, then q2h x 2, then q4h.
    b. Lactate q6h
    c. CBC q12h
    d. Ionized calcium q12h
    e. BMP and CMP alternating q12h
12. Sedation should be provided as needed. Deep sedation and paralytics should be provided selectively (impairs resp function and lung compliance). Overall goal is to have a comfortable, spontaneously breathing patient.
13. Begin D10 SPN with total fluids of about 60 ml/kg/day (some centers use as low as 40 ml/kg initially).
14. During first 2 hours, preductal saturations as low as 70% are acceptable provided O2 saturations are slowly improving, PCO2 goal is < 65, pH at least 7.2 with acceptable lactate.
15. Thereafter, goal preductal O2 saturation > 85-95% by 2 hours. Postductal saturations should be > 70%.
16. Goal PCO2 up to 65 by 2 hours.
17. Goal pH 7.2-7.4 by 2 hours
18. Goal lactate level < 3 mmol/L

19. Treat hypotension: poor perfusion (CRT >3), elevated lactate (>3) and low UOP (< 1 ml/kg/hr.). Treat metabolic acidosis if present.
    a. Use NS (10-20 ml/kg up to twice in first 2 hours) but monitor for s/s of pulm edema due to small/dysfunctional LV.
    b. Dopamine (first line agent in 75% of protocols—Jancelewicz T, Brindle ME, et al, Toward Standardized Management of Congenital Diaphragmatic Hernia: An analysis of Practice Guidelines. Journal of Surgical Research 2019;243:229-235). Recognize that there is no clear guideline for use of dopamine and it may begin to elevate pulmonary vascular resistance at moderate levels (>8 mcg/kg/min per Neonatal Heart Society webinar: Controverses in Congenital Diaphragmatic Hernia conference August 6, 2020.)
    c. Epinephrine 0.05 mcg/kg/min initially to max of 0.5 to 1 mcg/kg/min
    d. Milrinone (PPHN and ventricular dysfunction—Phase 2 trial ongoing, estimated completion in 2021)—improves ventricular contractility, lusitropy, and decreases afterload. May cause hypotension. Initial dose 0.25 mcg/kg/min titrated upwards to 0.5 mcg/kg/min by 6 hours. Treat hypotension with NS bolus or stop infusion. Very little data thus far on milrinone in CDH despite widespread use. Yoder et al. did not find it provided any improvement in retrospective of mild to moderate CDH compared to matched patients who did not receive it (Mears M, Yang M, Yoder B, Is Milrinone Effective for Infants with Mild to Moderate Congenital Diaphragmatic Hernia? Am J Perinatol. 2020; Vol 37(3), 258-63.)
    e. If poor perfusion persists after NS boluses and pressor, obtain echocardiogram to assess pulmonary hypertension and ventricular function.
    f. Hydrocortisone may also be used, but randomized clinical trials are lacking. Dose unclear: 1-2 mg/kg/dose IV q8h. Obtain cortisol level prior to initial dose.
    g. PGE (may reduce right ventricular afterload associated with PPHN and RV failure, especially with a closing duct). Keep fluid status even if possible.
    h. For refractory shock with inability to transfer (weather, transport team unavailable, etc.) and impending collapse, Vasopressin may be attempted (no RCT data). Animal models show pulmonary vasodilation with systemic constriction. Dose 0.0001 to 0.007 units/kg/min. (See Acker SN, Kinsella JP, et al. Vasopressin Improves Hemodynamic Status in Infants with Congenital Diaphragmatic Hernia. J Pediatr. 2014; 165(1):53-58.) Significant hyponatremia due to natriuresis may require 3% saline or fluid restriction (see Kinsella's article if this is needed). This is likely a "last ditch" effort for a baby who would otherwise be transferred for ECMO, but cannot be due to weather or other circumstances.
20. Treatment of pulmonary hypertension.
    a. Ensure appropriate lung inflation (about 8 ribs expansion of contralateral lung on CXR)
    b. iNO 20 ppm may be started for suprasystemic pulmonary arterial pressure without left ventricular dysfunction, but this would likely be in preparation for transport ("bridge to ECMO"). If no response to iNO by 24h, it should be stopped as it was previously associated with higher EMCO need.
        1) iNO has not been shown to improve outcomes and has been associated with increased need for ECMO (see NINOS trial). This may be due to adverse effect of pulmonary vasodilation causing worsened pulmonary edema in presence of LV

dysfunction. If LV is not functioning well, echo may show left to right shunting at atrial level due to "back up" of blood into left atrium. iNO would likely not improve hemodynamics in this case and could worsen pulmonary edema.

c. Milrinone may be beneficial with ventricular dysfunction.
d. Sildenafil may be considered as adjunctive therapy or when weaning iNO.
e. Prostaglandin E may be used to open a closing PDA in presence of PPHN with RV failure.

Failure of stabilization phase:

1. Persistent preductal sat < 70% w/PIP up to 25 (?28) on CMV.
2. Persistent PO2 < 20 to 30 and persistent metabolic acidosis/hypotension despite maximum therapy.
3. Persistent PCO2 > 75 or pH < 7.15 at PIP up to 25 (?28) and rate = 60.
4. Failure of stabilization phase → Escalation phase.

Escalation Phase, consider ECMO center if approaching these criteria:

1. Keep in touch with ECMO referral center if escalating care.
2. iNO at 20 ppm if no LV dysfunction with signs of suprasystemic RV pressures (do not use if atrial shunt is left to right).
3. High frequency with MAP up to 15-17.
4. Inability to consistently maintain preductal sat > 85%, postductal sat > 70, or persistent lactic acidosis suggesting inadequate tissue oxygenation. Short drops in saturations are OK provided general trend is stable or improving.
5. Increased CO2 > 75 and respiratory acidosis with pH <7.15 and lactate > 5.
6. Systemic hypotension resistant to fluid and inotropic therapy.
7. Oxygenation Index (IO) > 40 x 3 hrs.
8. Obtain head US if considering transfer to ECMO center.

Maintenance Phase:

1. Goal pre-ductal O2 sat > 85% up to 95%.
2. Oxygen may be weaned to keep preductal saturations 90 to 95%. Salt Lake will not wean beyond 30 to 40% oxygen prior to surgery.
3. Goal pH > 7.2, PCO2 < 65, PaO2 25-35 on assist control with PIP usually < 25
4. Light or no sedation to allow for spontaneous breathing but treat pain
5. Limited volume expansion. Keep fluid status as even as possible
6. Treat metabolic acidosis
7. Failure of Maintenance Phase
    a. Persistent hypotension or metabolic acidosis
    b. Persistent pH < 7.2 or PCO2 > 65
    c. Persistent pre-ductal O2 sat < 85%
    d. Evidence of tissue hypoxemia (NIRS), rising lactate.
8. Obtain Echocardiogram within 48 hrs, most sites will complete in first several hours of life and/or before starting iNO and another at 2 weeks of life.

Surgical Repair:
No studies provide criteria for "ready for surgery". Must be physiologically stable prior to surgery (UOP > 1 ml/kg/hr., FiO2 < 50% and pre ductal sat between 85-95%, BP normal for gestational age, lactate < 3 and pulm artery pressure less than systemic pressure). Surgery is recommended within 2 weeks of life if "ready" with the above criteria. If not, attempted repair or palliative care approach should be considered.

Long Term Follow Up:
1. Multidisciplinary care for CDH is needed to provide screening and surveillance.
2. Refer to pediatric care coordinator
3. Follow up with pediatric cardiology, pulmonology, GI. Assess for musculoskeletal issues and poor neurodevelopmental outcomes. Growth and hearing follow up is especially important

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Nuts and Bolts Version of CDH Protocol:

Prenatally

1. Meet w/surgery, neonatology, antenatal echo.
2. Assess severity of defect, preferably early during second trimester using both observed to expected Lung to Head Ratio (o/e LHR) and fetal MRI, to enable realistic counseling re: survival, potential for fetal surgery, potential need for ECMO, parental desires re: ECMO.
3. Parents must know we do not have ECMO and that transport of such a critically ill infant is difficult.
4. Severe defects must be referred early (preferably well before 29 wk) for consideration of fetal surgery.

DR:

1. Intubate immediately: most experienced person—confirm with end tidal CO2 and secure ETT.
2. Use T-piece (NeoT) to control maximum pressure with PEEP around 4 to 5, total PIP initially 15 to 20 (lower than usual level to minimize barotrauma). Avoid PIP > 25.
3. Initial FiO2 varies depending on site. Some centers (Johns Hopkins and CHOP) are starting with 50% rather than 100% to avoid hyperoxic injury to lung. Goal preductal sats > 70 in DR and in first 2 hours after birth, then 85-95 with stabilization
4. Place Replogle (8 to 10 F) and manually aspirate using 30 ml syringe to decompress intestines/stomach
5. CR monitor and pre/post ductal saturations.

Stabilization Phase:

1. On arrival in NICU, place on radiant warmer with scale and slide for x-ray.
2. CXR/AXR for ETT and Replogle placement.
3. Replogle to LIS (20 cm H2O). If excessive gas in intestines/stomach, can try continuous suction (20 cm H2O).
4. Place PIV to maintain glucose while placing umbilical lines.
5. Initially use Conventional Ventilator: use assist control, start low at extubatable settings, avoid volume-based ventilation.
    a. Total PIP initially around 16. Try not to exceed Total PIP > 28.
    b. PEEP 4 to 5 cm H2O.
    c. Rate around 40 initially.
    d. Do not use volume-based ventilation—lungs are hypoplastic.
6. Light sedation to allow spontaneous breathing.
    a. Midazolam prn initially (0.05-0.1 mg/kg/dose).
    b. May need Midazolam drip. Consider Precedex (term infant). May need opioids for pain (Morphine or Fentanyl). Avoid paralytics if possible and remain cognizant of hypotensive effects of sedatives.
7. Goal preductal sat > 70% in first 2 hours (provided adequate perfusion) and then 85-95% at 2 to 3 hr, tolerate relative post ductal desaturation due to shunting—follow lactate to assess adequacy of oxygenation.
8. Goal PCO2 45-65
9. Goal pH 7.25-7.4

10. Goal Mean BP at least equal to EGA. CRT 3 sec or less, UOP > 1 ml/kg/hr. Use NS 10-20 ml/kg up to 2x and inotropes (dopamine then epi) to support. Consider Milrinone (if ventricular dysfunction), sildenafil, and PGE if needed.
11. Hydrocortisone is often given for presumed adrenal insufficiency in presence of pressor-resistant hypotension regardless of cortisol level (1 mg/kg test dose). Infants with cortisol levels < 15 usually run more severe course. See Kinsella JP, et al. Adrenal Insufficiency in Newborns with Congenital Diaphragmatic Hernia, J Pediatr 2010: 156(3); 495-7.
12. Echo when stable or needed for medical management (usually obtain by 48 hours). If normal antenatal echo, less urgency immediately after delivery unless concerned about severity of PPHN or LV function. Usually give some time to stabilize during first few hours after placing lines. Second echo due at 2 weeks. Repeat echo due to refractory hypotension.
13. In presence of PPHN (suprasystemic) without LV dysfunction, start iNO at 20 ppm as a holdover for transfer. Has not shown to be helpful overall and may increase need for ECMO (NINOS trial), and may be harmful in presence of left ventricular dysfunction. Discontinue iNO within 24 hr if not clinically improving and not transferred.

Escalation Phase—if unable to stabilize to enter Maintenance Phase

1. HFOV w/MAP to 15 cm H2O.
2. Likely would begin iNO if no LV dysfunction is evident (assess for L to R shunting at atrial level) and transfer if unable to stabilize.
3. Dexamethasone (no clear dose and no trial data to date).

Maintenance Phase

1. Continue conventional ventilation—try to minimize PIP provided oxygenation and ventilation are acceptable. PEEP 4 to 5
2. Light sedation (or no sedation if possible).
3. Goal preductal sat > 85-95%. Tolerate R→L ductal shunting, causing lower post ductal sats, as long as not compromising tissue metabolism (check lactates).
4. Goal pH > 7.2-7.4. Goal lactate < 3. Goal CO 2 45-65.
5. Normal BP, perfusion, UOP and lactates.
6. Wean O2 as able to minimize oxygen toxicity **(? upper limit sat 97%).** Goal high sat is 95%. Consider not weaning beyond 30% oxygen prior to surgery.

Appendix A: Reference Tables for Antenatal Counseling based on Fetal MRI and Ultrasound.

1. Style CC, Mehollin-Ray AR, et al. Timing of Prenatal Magnetic Resonance Imaging in the Assessment of Congenital Diaphragmatic Hernia. Fetal Diagn Ther. 2020; 47:205-213. See Table 2, page 209 re: o/e TFLV ranges for persistent PAH, need for ECMO, and survival.

Table 2. Predictor variables of PAH, ECMO, and survival

Predictor variables	Severe PAH (68%, *n* = 39)	Mild/no PAH (*n* = 18)	*p* value
O/e TFLV 2nd trimester, %	32±11.7	39.4±14	0.060
O/e TFLV 3rd trimester, %	30±9.9	35±13.2	0.118
ΔO/e TFLV	6.63±6.3	10.3±8.2	0.115
ΔTFLV: growth rate/week, mL	1.23±0.6	1.87±1.1	**0.009**
%LH 2nd trimester, %	20.3±12.5	25±11	0.238
%LH 3rd trimester, %	25±15.9	24.3±14	0.904
	Persistent PAH (*n* = 15)	Resolution of PAH (*n* = 35)	*p* value
O/e TFLV 2nd trimester, %	25.7±9.1	38.3±13.1	**0.002**
O/e TFLV 3rd trimester, %	25.6±13.1	34.4±10.7	**0.031**
ΔO/e TFLV	9.4±8.8	6.91±6.21	0.275
ΔTFLV: growth rate/week, mL	1.33±1.2	1.46±0.77	0.667
%LH 2nd trimester, %	27.9±12.5	12.6±12.1	**0.001**
%LH 3rd trimester, %	25.4±18.2	14.9±13.8	0.099
	ECMO (*n* = 23)	No ECMO (*n* = 34)	*p* value
O/e TFLV 2nd trimester, %	25.9±10	39.17±11.9	**<0.001**
O/e TFLV 3rd trimester, %	24.6±9.2	36±9.4	**<0.001**
ΔO/e TFLV	7.92±8.0	7.84±6.56	0.414
ΔTFLV: growth rate/week, mL	1.08±0.93	1.65±0.76	**0.021**
%LH 2nd trimester, %	23.9±11.4	20.9±12.6	0.462
%LH 3rd trimester, %	27.9±12.1	23.1±16.1	0.351
	Non-survival (*n* = 12)	Survival (*n* = 45)	*p* value
O/e TFLV 2nd trimester, %	24.6±6.3	36.1±13.1	**<0.001**
O/e TFLV 3rd trimester, %	26±12.2	32.4±11.2	0.12
ΔO/e TFLV	7.75±7.79	7.8±6.92	0.98
ΔTFLV: growth rate/week, mL	1.5±1.4	1.34±0.77	0.73
%LH 2nd trimester, %	24.3±13.5	21.6±12.1	0.719
%LH 3rd trimester, %	26.7±14.5	24.3±15.2	0.732

Analysis with independent *t* test. *p* value <0.05 considered significant. Bold values indicate statistical significance between groups. Values expressed as mean ± SD. O/e TFLV, observed to expected total fetal lung volume; TFLV, total fetal lung volume; %LH, liver herniation; PAH, pulmonary hypertension; ECMO, extracorporeal membrane oxygenation.

2. Kilian AK, Busing KA, et al. Fetal MR Lung Volumetry in Congenital Diaphragmatic Hernia (CHD): Prediction of Clinical Outcome and the Need for Extracorporeal Membrane Oxygenation (ECMO). Klin Padiatr 2009;221:295-301. Examines survival and ECMO need based on fetal lung volume (FLV) at 33-36 wk gestation. See table 1, p 297.

Table 1 Patients' characteristics.

	Study population (n=36)	Survivors (n=27)	Non-Survivors (n=9)	p	ECMO (n=17)	Non-ECMO (n=19)	p
maternal age*	30.9±5.1	30.7±5.2	31.4±5.1	n.s.	30.3±5.5	31.4±5.4	n.s.
gestational age at birth+	37.6±1.1	37.6±1.2	37.4±0.5	n.s.	37.7±1.1	37.5±1.0	n.s.
gestational age at MRI+	34.6±1.4	34.5±1.3	34.8±1.6	n.s.	34.6±1.2	35.5±1.5	n.s.
left-sided CDH	83% (30/36)	93% (25/27)	56% (5/9)	n.s.	82% (14/17)	84% (16/19)	n.s.
birth weigth§	2991.3±405.7	3042.5±437.6	2818.8±209.9	n.s.	3017.1±320.6	2967.1±480.7	n.s.
FLV§	20.6±11.5 (3.1–41.6)	25.0±9.7 (8.1 –41.6)	7.6±4.4 (3.1–15.6)	<0.0001	18.2±10.1 (3.1–36.9)	27.2±10.2& (11.8–41.6)	0.003
ECMO therapy	47% (17/36)	44% (12/27)	56%& (5/9)	n.s.	–	–	–
survival	75% (27/36)	–	–	–	71% (12/17)	79% (15/19)	n.s.

*years, +weeks, ‡g, §ml (range), n.s. = non significant, &exclusion of 4 patients who died after birth before ECMO therapy was started based on extreme lung hypoplasia (see text). The 2-sample-t-test was used to compare two mean values; Fisher's exact test was used to compare two relative frequencies

3. Jani J, Nicolaides KJ, Keller RL, et al. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. Ultrasound Obstet Gynecol 2007; 30:67-71.
   See Figure 3 relating o/e LHR (perpendicular method) to survival for isolated left (with/without liver herniation) and right CDH. Does not include ECMO analysis.

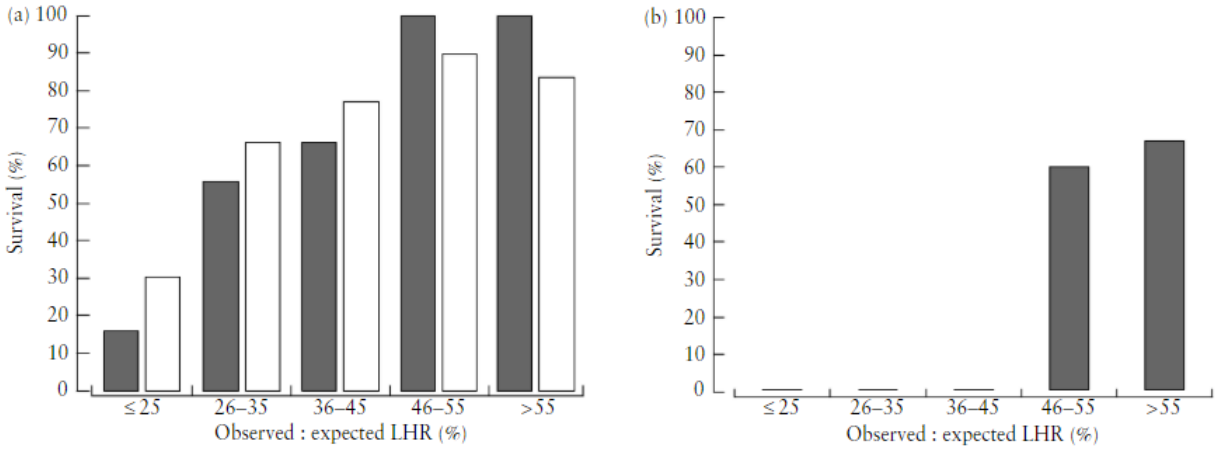

Figure 3 Survival rate according to the fetal observed to expected lung area to head circumference ratio (LHR) in fetuses with isolated left-sided (a) and right-sided (b) diaphragmatic hernia. The filled bars represent fetuses with intrathoracic herniation of the liver and the open bars represent those without herniation.

4. Akinkuotu AC, Cruz SM, Abbas PI, et al. Risk-stratification of severity for infants with CDH: Prenatal versus Postnatal predictors of Outcome. Journal Of Pediatric Surgery 2016;51:44-48.

   See Table 1 and 2 assessing survival based on o/e TFLV, LHR, o/e LHR, percent liver herniation.

Table 1

Comparison of CDH survivors and nonsurvivors at 6 months of life.

	Survivor (n = 131)	Nonsurvivor (n = 45)	p-value
Right CDH, n (%)	26 (19)	10 (22)	0.83
GA at diagnosis, weeks	23.8 ± 6.0	22.4 ± 6.0	0.30
O/E-TFLV, %	36.6 ± 14.4	25.9 ± 7.7	**< 0.001**
LHR	1.8 ± 0.70	1.3 ± 0.47	**< 0.001**
O/E- LHR, %	54.2 ± 20.5	40.0 ± 15.7	**0.003**
%LH	10.7 ± 15.4	23.6 ± 14.0	**< 0.001**
GA at birth, weeks	37.9 ± 1.9	36.3 ± 3.2	**0.004**
Birth weight, grams	2960 ± 570	2610 ± 847	**0.02**
5-minute Apgar score, median (range)	8 (2–9)	6 (1–9)	**< 0.001**
Postnatal-based CDH study group score, median (range)	1 (0–6)	3 (0–8)	**< 0.001**

Abbreviations: GA, gestational age; O/E-TFLV, observed to expected total fetal lung volume; LHR, lung-to-head ratio; O/E-LHR, observed to expected lung-to-head ratio; %LH, % liver herniation.

Table 2

Comparison of prenatal and postnatal predictors of 6-month mortality between CDH survivors and nonsurvivors.

Variable	CDH survivor (n = 131)	CDH nonsurvivor (n = 45)	% Survival	p-value
GA at birth				
> 37 weeks	98	27	79%	0.05
< 37 weeks	29	17	63%	
LHR				
> 1.4	57	9	86% [a]	**0.003**
1–1.4	18	13	58%	
< 1	10	7	59%	
O/E-TFLV				
≥ 35%	44	3	94% [b]	**< 0.001**
< 35%	35	27	56%	
Liver herniation				
0%	53	4	93%	**0.001**
1–20%	26	3	90%	
> 20%	26	15	64% [c]	
Postnatal-based CDH mortality risk group				
Low	46	2	96% [d]	**< 0.001**
Intermediate	60	17	78%	
High	25	26	49%	

Abbreviations: O/E-TFLV, observed to expected total fetal lung volume; LHR, lung-to-head ratio.

a $p < 0.05$ comparing to LHR 1–1.4 and LHR < 1.

b $p < 0.05$ in comparison to other O/E-TFLV groups.

c $p < 0.05$ in comparison to other %LH groups.

d $p < 0.05$ in comparison between all risk groups.

See Table 5 assessing ECMO need based on LHR, o/e LHR, o/e TFLV, percent liver herniation.

Table 5

Univariate and multivariate analyses for ECMO use based on prenatal and postnatal risk factors.

	Univariate analysis				Multivariate analysis
Variable	ECMO (n = 55)	No ECMO (n = 121)	% ECMO use	p-value	Adjusted OR (95% CI)
GA at birth					
> 37 weeks	44	81	35%		
< 37 weeks	11	35	24%	0.198	0.404 (0.082–2.00)
LHR					
> 1.4 [a]	18	48	27%	0.108	
1–1.4	15	16	48%		n/a
< 1	7	10	41%		
O/E-LHR, % (mean ± SD)	45.8 ± 17.2	53.2 ± 21.4	n/a	0.094	0.20 (0.008–5.09)
O/E-TFLV					
> 35%	5	42	11%	**< 0.001**	
< 35%	30	32	48%		**7.86 (1.89–32.8)**
Liver herniation					
0% [a]	7	50	12%	**< 0.001**	
1–20%	6	23	21%		**0.45 (.073–2.75)**
> 20%	21	15	58%		**2.65 (0.54–12.9)**
Postnatal-based CDH mortality risk group					
Low [a]	8	40	17%	**0.037**	
Intermediate	29	48	38%		1.31 (0.29–5.97)
High	18	33	35%		0.969 (0.15–6.22)

a Indicates reference group.

5. Jani J, Cannie M, et al. Value of prenatal magnetic resonance imaging in the prediction of postnatal outcome in fetuses with diaphragmatic hernia. Ultrasound Obstet Gynecol 2008; 32: 792-799.

Figure 3: assess survival based on o/e TFLV and position of liver (up/down).

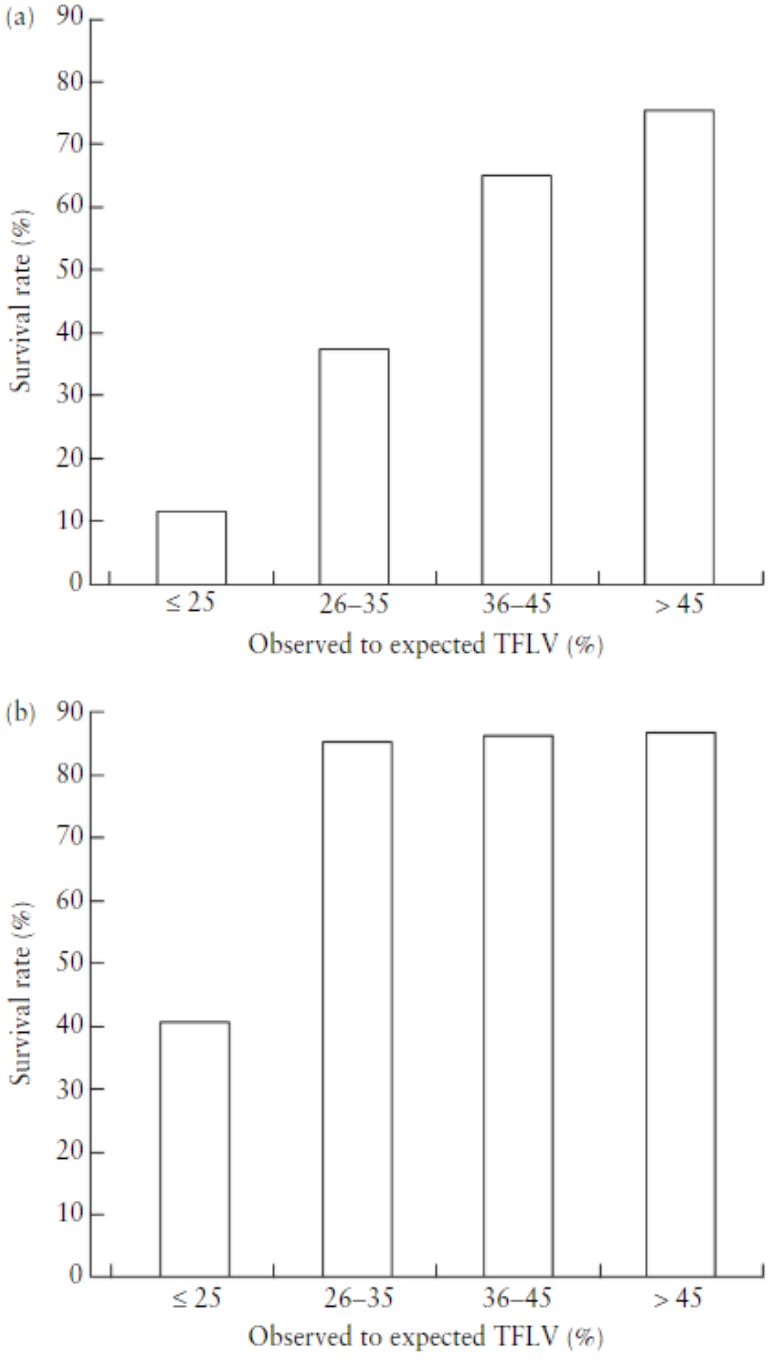

Figure 3 Survival rate according to the fetal observed to expected total fetal lung volume (TFLV) in fetuses with isolated diaphragmatic hernia with (a) and without (b) intrathoracic herniation of the liver.

6. Walleyo A, Debus A, et al. Periodic MRI Lung Volume Assessment in Fetuses with Congenital Diaphragmatic Hernia: Prediction of Survival, Need for ECMO, and Development of Chronic Lung Disease. AJNR 2013;201:419-426.

Assess survival (Table 2), ECMO need (Table 4) based on o/e FLV by gestational age ranges.

TABLE 2: Prognostic Value of Observed-to-Expected MRI Fetal Lung Volume Ratio for Prediction of Neonatal Survival

Parameter	Survivor	Nonsurvivor	*p*	Area Under the Curve
< 28 weeks' gestation				
Overall	37.1 ± 12.8 (*n* = 44)	23.2 ± 7.6 (*n* = 12)	0.0029	0.828
Left-sided hernia, liver up	37.8 ± 14.1 (*n* = 24)	22.6 ± 6.7 (*n* = 10)	0.0101	0.875
Left-sided hernia, liver down	36.3 ± 11.1 (*n* = 15)	36.8 (*n* = 1)	—	—
Right-sided hernia	36.5 ± 13.8 (*n* = 5)	15.7 (*n* = 1)	—	—
28–32 weeks' gestation				
Overall	31.2 ± 8.6 (*n* = 37)	20.9 ± 4.6 (*n* = 13)	0.0025	0.888
Left-sided hernia, liver up	30.5 ± 8.1 (*n* = 16)	20.5 ± 5.2 (*n* = 10)	0.0139	0.891
Left-sided hernia, liver down	35.0 ± 9.2 (*n* = 14)	23.7 (*n* = 1)	—	—
Right-sided hernia	25.2 ± 4.2 (*n* = 7)	21.5 ± 0.4 (*n* = 2)	—	—
> 32 weeks' gestation				
Overall	28.8 ± 12.1 (*n* = 97)	16.0 ± 8.6 (*n* = 23)	< 0.0001	0.819
Left-sided hernia, liver up	25.3 ± 11.3 (*n* = 39)	16.8 ± 9.4 (*n* = 17)	0.0145	0.779
Left-sided hernia, liver down	32.2 ± 12.3 (*n* = 44)	17.8 ± 3.6 (*n* = 2)	—	—
Right-sided hernia	27.5 ± 11.2 (*n* = 14)	11.5 ± 6.4 (*n* = 4)	0.0776	0.946
All				
Overall	31.3 ± 12.1 (*n* = 178)	19.1 ± 8.0 (*n* = 48)	< 0.0001	0.806
Left-sided hernia, liver up	30.2 ± 12.8 (*n* = 79)	19.4 ± 8.0 (*n* = 37)	< 0.0001	0.763
Left-sided hernia, liver down	33.6 ± 11.5 (*n* = 73)	24.0 ± 9.2 (*n* = 4)	0.1199	0.772
Right-sided hernia	28.6 ± 10.8 (*n* = 26)	15.0 ± 6.5 (*n* = 7)	0.0195	0.885

Note—All parameter values are percentages. Dash (—) indicates dataset not evaluable owing to small number of cases.

TABLE 4: Prognostic Value of MRI Relative Fetal Lung Volume for Prediction of Neonatal Need for Extracorporeal Membrane Oxygenation (ECMO) Therapy

Parameter	ECMO	No ECMO	*p*	Area Under the Curve
< 28 weeks' gestation				
Overall	25.9 ± 9.9 (*n* = 17)	37.7 ± 12.9 (*n* = 39)	0.0044	0.736
Left-sided hernia, liver up	25.6 ± 10.1 (*n* = 12)	37.6 ± 14.4 (*n* = 22)	0.0312	0.720
Left-sided hernia, liver down	30.0 (*n* = 1)	36.7 ± 11.0 (*n* = 15)	—	—
Right-sided hernia	25.9 ± 12.2 (*n* = 4)	47.3 ± 7.7 (*n* = 2)	—	—
28–32 weeks' gestation				
Overall	24.4 ± 6.1 (*n* = 19)	31.0 ± 9.5 (*n* = 31)	0.0195	0.746
Left-sided hernia, liver up	24.7 ± 6.7 (*n* = 13)	28.7 ± 10.0 (*n* = 13)	0.2416	0.663
Left-sided hernia, liver down	34.1 (*n* = 1)	34.2 ± 9.7 (*n* = 14)	—	—
Right-sided hernia	21.9 ± 1.4 (*n* = 5)	27.4 ± 4.2 (*n* = 4)	0.1087	0.900
> 32 weeks' gestation				
Overall	20.1 ± 8.7 (*n* = 45)	30.0 ± 13.1 (*n* = 75)	< 0.0001	0.743
Left-sided hernia, liver up	18.4 ± 7.6 (*n* = 28)	27.1 ± 12.9 (*n* = 28)	0.0077	0.727
Left-sided hernia, liver down	24.8 ± 7.9 (*n* = 11)	33.7 ± 12.9 (*n* = 35)	0.0467	0.717
Right-sided hernia	19.5 ± 12.4 (*n* = 6)	26.2 ± 12.1 (*n* = 12)	0.2837	0.646
All				
Overall	22.3 ± 8.7 (*n* = 81)	32.3 ± 12.7 (*n* = 145)	< 0.0001	0.742
Left-sided hernia, liver up	21.5 ± 8.6 (*n* = 53)	31.1 ± 13.6 (*n* = 63)	0.0002	0.728
Left-sided hernia, liver down	25.9 ± 7.8 (*n* = 13)	34.5 ± 11.7 (*n* = 64)	0.0192	0.718
Right-sided hernia	22.0 ± 9.7 (*n* = 15)	28.8 ± 12.1 (*n* = 18)	0.1051	0.659

Note—All parameter values are percentages. Dash (—) indicates dataset not evaluable owing to small number of cases.

Table 3 assesses o/e TLV giving 100% mortality/100%survival and 100% ECMO/0% ECMO by gestational age.

TABLE 3: Percentage Limits of Observed-to-Expected MRI Fetal Lung Volume Ratio for Neonatal Survival and Death, Requirement for Extracorporeal Membrane Oxygenation Therapy, and Development of Chronic Lung Disease

Weeks' Gestation	Survival		Extracorporeal Membrane Oxygenation		Chronic Lung Disease	
	0%	100%	0%	100%	0%	100%
< 28	< 10.1	> 36.8	> 42.1	< 16.5	> 52.8	< 25.4
28–32	< 18.0	> 28.1	> 40.7	< 10.8	> 40.7	< 26.0
> 32	< 8.9	> 38.4	> 43.5	< 6.6	> 58.6	< 12.9
Overall	< 8.9	> 38.4	> 43.5	< 6.6	> 58.6	< 12.9

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