Fetal Risk Stratification and Outcomes in Children with Prenatally Diagnosed Lung Malformations

Results from a Multi-Institutional Research Collaborative

Shaun M. Kunisaki, MD, MSc,✉ Jacqueline M. Saito, MD, MSCI,†*
Mary E. Fallat, MD,‡ Shawn D. St. Peter, MD,§ Dave R. Lal, MD, MPH,‖
Monita Karmakar, PhD,¶ Katherine J. Deans, MD, MHSc,#
Samir K. Gadepalli, MD, MBA,¶ Ronald B. Hirschl, MD,¶
*Peter C. Minneci, MD, MHSc,# and Michael A. Helmrath, MD,***
for the Midwest Pediatric Surgery Consortium

Objective: The aim of this study was to assess current clinical outcomes in children with prenatally diagnosed congenital lung malformations (CLMs) and to identify prenatal characteristics associated with adverse outcomes.

Summary Background Data: Despite a wide spectrum of clinical disease, the identification of fetal CLM subgroups at increased risk for hydrops and respiratory compromise at delivery has not been well defined.

Methods: A retrospective cohort study was conducted using an operative database of prenatally diagnosed CLMs managed at 11 children's hospitals from 2009 to 2016. Statistical analyses were performed using nonparametric bivariate or multivariable logistic regression.

Results: Three hundred forty-four children were analyzed. Fifteen (5.5%) fetuses were managed with maternal steroids in the setting of hydrops, and prenatal surgical intervention was uncommon (1.7%). Seventy-five (21.8%) had respiratory symptoms at birth, and 34 (10.0%) required neonatal lung resection. Congenital pulmonary airway malformation volume ratio (CVR) measurements were recorded in 169 (49.1%) cases and were significantly associated with perinatal outcome, including hydrops, respiratory distress at birth, need for supplemental oxygen, neonatal ventilator use, and neonatal resection ($P < 0.001$). An initial CVR ≤1.4 was significantly correlated with a reduced risk for hydrops [area under the curve (AUC), 0.93; 95% confidence interval (CI), 0.87–1.00]. A maximum CVR <0.9 (AUC, 0.72; 95% CI, 0.67–0.85) was associated with a low risk for respiratory symptoms at birth.

Conclusions: In this large, multi-institutional study, an initial CVR ≤ 1.4 identifies fetuses at very low risk for hydrops, and a maximum CVR < 0.9 is associated with asymptomatic disease at birth. These findings represent an opportunity for standardization and quality improvement for prenatal counseling and delivery planning.

Keywords: congenital lung malformations, congenital pulmonary airway malformations, fetal lung lesions

(*Ann Surg* 2022;276:e622–e630)

Fetal congenital lung malformations (CLMs) represent a broad range of pulmonary anomalies, including congenital pulmonary airway malformations (CPAMs), bronchogenic cysts, bronchial atresia, bronchopulmonary sequestrations (BPS), and congenital lobar emphysema (CLE).[1–3] Historically, the rate of hydrops and in utero demise in fetal CLMs were reported to be as high as 40%,[4] and termination of pregnancy of fetuses with a CLM diagnosis occurred in up to 33% of cases.[5,6]

Over the past 20 years, the incidence of CLMs has been increasing, with more recent studies suggesting a frequency that may be as high as 1 in 2000 pregnancies.[7,8] This rise is likely secondary to the detection of smaller lesions in an era of more widespread prenatal screening and improvements in ultrasound image quality.[7–9] In parallel with the increased incidence,

From the *Fetal Program, Division of General Pediatric Surgery, Department of Surgery, Johns Hopkins University School of Medicine, Johns Hopkins Children's Center, Baltimore, MD; †Division of Pediatric Surgery, Department of Surgery,Washington University School of Medicine, St. Louis, MO; ‡Division of Pediatric Surgery, Hiram C. Polk, Jr., MD Department of Surgery, University of Louisville, Norton Children's Hospital, Louisville, KY; §Division of Pediatric Surgery, Department of Surgery, Children's Mercy Hospital, Kansas City, MO; ‖Division of Pediatric Surgery, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI; ¶Section of Pediatric Surgery, Department of Surgery, University of Michigan and Michigan Medicine, C.S. Mott Children's Hospital, Ann Arbor, MI; #Center for Surgical Outcomes Research, the Research Institute and Department of Surgery, Nationwide Children's Hospital, Ohio State University College of Medicine, Columbus, OH; and **Division of Pediatric Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

✉skunisa1@jhmi.edu.

Author contributions: S.M.K.: conception and design, acquisition of data, analysis and interpretation, manuscript drafting, critical revision, final approval; J.M S.: conception and design, acquisition of data, critical revision, final approval; M.E.F.: conception and design, acquisition of data, critical revision, final approval; S.D.S: conception and design, acquisition of data, critical revision, final approval; D.R.L.: conception and design, acquisition of data, critical revision, final approval; M.K.: analysis and interpretation, critical revision, final approval; K.J.D: acquisition of data, critical revision, final approval; S.K.G.: acquisition of data, critical revision, final approval; R.B.H.: analysis and interpretation, critical revision, final approval; P.C.M.: acquisition of data, critical revision, final approval; M.A.H.: acquisition of data, analysis and interpretation, critical revision, final approval.

Disclosure Statement: This project was supported by intramural funding from each institution within the Midwest Pediatric Surgery Consortium (www.mwpsc.org). No competing financial interests exist, and all authors have nothing to disclose.

The authors report no conflicts of interest.

Note: Some of the data from this manuscript were previously presented in abstract form at the American Academy of Pediatrics 2019 Annual Meeting, Section on Surgery, October 25–27, 2019 (New Orleans, LA).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.

ISSN: 0003-4932/22/27605-e622
DOI: 10.1097/SLA.0000000000004566

contemporary experience suggests that the majority of affected neonates are asymptomatic at birth.[10–12] As a result, there has been a shift in focus toward developing risk stratification tools to better counsel families on timing of surgery and the potential for adverse postnatal outcomes in affected infants.[13–20] Despite these efforts, recent studies have been limited by low patient numbers, and the majority of prenatal predictors of outcome have not been well validated in a multicenter fashion.[21]

Using a multi-institutional database, our primary objective was to correlate prenatal imaging characteristics with clinical outcomes in CLM patients. Our group hypothesized that the congenital pulmonary airway malformation volume ratio (CVR),[4] a volumetric relative index of CLM size obtained by ultrasound, would be significantly associated with hydrops, respiratory morbidity, and need for early surgical resection.

MATERIALS AND METHODS

A central reliance agreement (#96707) was approved by the institutional review boards at each of the eleven major children's hospitals associated with the Midwest Pediatric Surgery Consortium (www.mwpsc.org) to perform a retrospective cohort study based on an operative registry of lung lesions (n = 506) from 2009 to 2016 as described elsewhere.[22] Those with pleuropulmonary blastoma (PPB) were also included. All CVR values were calculated by 2-D ultrasonography based on the formula for an ellipsoid (ie, product of the 3D mass dimensions multiplied by a 0.52 correction factor) divided by the head circumference to normalize for gestational age, as described elsewhere.[4] Data from prenatally diagnosed patients were extracted from REDCap (Research Electronic Data Capture, 8.1.20, Vanderbilt University, Nashville, TN).

Statistical analyses were performed using nonparametric bivariate or multivariable logistic regression, controlling for variables including mediastinal shift and hydrops, as appropriate with STATA (StataCorp, College Station, TX). For each disease outcome measure, receiver-operating characteristic (ROC) curves were generated to define optimal cutoff values (Youden's index) based on the CVR.[23] Significance was defined as $P < 0.05$.

RESULTS

From 506 patients in the consortium, 344 cases (68.0%) were prenatally diagnosed. The median number of cases contributed per center was 22 (range, 8–58; Supplemental Table 1, http://links.lww.com/SLA/C681). There were 160 (47.1%) right-sided and 179 (52.6%) left-sided lesions. One (0.3%) had bilateral disease. The most common anatomic locations were left lower lobe (n = 116, 34.0%) and right lower lobe (n = 112, 32.8%). Based on pathology data, the most common CLM was CPAM without a feeding vessel (formerly referred to as congenital cystic adenomatoid malformation) in 175 (51.8%) followed by BPS in 136 (40.2%). Eighty (58.8%) of the BPS lesions were intralobar. There were 44 (13.0%) mixed CPAMs in association with a systemic feeding vessel, 13 (3.8%) CLEs, and no specimen with a malignancy.

Prenatal Diagnosis

Table 1 summarizes the prenatal data. The median age at fetal diagnosis was 22.0 weeks gestation [interquartile range (IQR), 20.0–25.0]. A specific description of lesion cystic appearance (eg, based on the Stocker classification) was given in 164 (47.7%) cases. The presence or absence of mediastinal shift was documented in 229 (69.2%) patients. Due to a marked variability in the reporting of CVR measurements across member hospitals (Supplemental Table 1, http://links.lww.com/SLA/C681), CVR data were recorded in only 169 (49.1%) fetuses. Two (18.2%) institutions did not obtain any CVR measurements for any fetus. The mean maximum CVR in those with mediastinal shift was 1.60 ± 1.04 compared a mean maximum CVR of 0.67 ± 0.49 in those without mediastinal shift ($P < 0.0001$, Table 1). Magnetic resonance imaging (MRI) as part of the prenatal evaluation was performed in 39.2% of cases at a median gestational age of 25.3 weeks (IQR, 22.7–29.4). The MRI utilization rate by institution ranged from 7.7% to 82.5% cases, and there was a significant increase in MRI use in cases in which a CVR was already recorded ($P = 0.0328$).

Fifteen (4.4%) fetuses developed signs of hydrops. The most common finding consistent with hydrops was ascites (n = 13, 86.7%) followed by skin edema (n = 8, 53.3%) and pleural effusion (n = 4, 26.7%). Although all hydropic fetuses had sonographic evidence of mediastinal shift, this was nonspecific given that 49.8% of fetuses without hydrops also had mediastinal shift ($P < 0.0001$). Fifty-eight percent of the hydropic fetuses had macrocystic disease, but this was not statistically significant when compared to those with microcystic disease (30.3%, $P = 0.0576$). Five (33%) hydropic fetuses had pathologically confirmed BPS.

Initial CVR data were available in 11 (73.3%) hydropic fetuses and showed a mean initial CVR of 3.0 ± 1.7 (median: 2.65; IQR, 1.5–4.4) at a median gestational age of 21.2 weeks (IQR, 20.0–23.6; Supplemental Digital Content Fig 1A, http://

TABLE 1. Prenatal Characteristics of 344 Lung Malformations

Variable	All Lesions (n = 344)	CVR Data (n = 169)	No CVR Data (n = 175)	*P*
Gestational age at initial scan, median (IQR)	22.0 wk (20.0–25.0)	22.0 wk (20.1–25.0)	22.0 wks (20.0–23.6)	0.1832
Concomitant major anomalies, n (%)	34 (10)	15(9)	19(11)	0.5901
Left sided lesion, n (%)	179 (53)	96 (57)	83 (47)	0.1290
Systemic feeder vessel, n (%)	52 (17)	34 (20)	18 (10)	0.0490*
Macrocystic (Stocker type I), n (%)	53 (32)	33 (35)	20 (21)	0.2666
Mediastinal shift, n (%)	121 (53)	90 (55)	31 (48)	0.3789
Hydrops, n (%)	15 (4)	11 (7)	4 (2)	0.0691
Initial CVR, mean ± stdev		0.89 ± 0.90		
Maximum CVR, mean ± stdev†		1.21 ± 0.97		
Initial CVR >1.6‡, n (%)		24 (14)		
MRI performed, n (%)	118 (39)	75 (45)	43 (32)	0.0328*

*$P < 0.05$ between lung malformations with recorded CVR data and those without CVR data (Mann-Whitney *U* test or Fisher exact test).
†Interclass correlation coefficient (7.52e–20) suggests lack of clustering of CVR values by center.
‡Initial CVR >1.6 cutoff chosen based on Crombleholme et al.[4]

link-s.lww.com/SLA/C681). The initial CVR in hydropic fetuses was significantly increased compared to that in fetuses without hydrops (mean: 0.7 ± 0.6, $P < 0.0001$). Hydropic fetuses had a mean maximum CVR of 3.4 ± 1.3 (median: 2.9; IQR, 2.6–4.0), which was significantly increased compared to the maximum CVR in those without hydrops (mean: 1.1 ± 0.8, $P < 0.0001$; Supplemental Digital Content Fig 1B, http://links.lww.com/SLA/C681). The significant differences in the CVR between hydropic and nonhydropic fetuses remained in subgroup analyses based on pathology (Supplemental Digital Content, Fig 2, http://links.lww.com/SLA/C681).

Based on ROC curve analyses, the optimal cutoff point for the initial CVR was 1.36 for predicting hydrops [area under curve (AUC), 0.93; 95% confidence interval (CI), 0.87–1.0]. The sensitivity and specificity for hydrops for an initial CVR >1.36 was 90% and 86%, respectively. The positive predictive value (PPV) was 31%. The negative predictive value (NPV) was 99%, suggesting that hydrops is very unlikely below this cut-off. The optimal cutoff point associated with hydrops was a maximum CVR of 2.25 (AUC, 0.96; 95% CI, 0.95–1.0), yielding a sensitivity and specificity for developing hydrops of 100% and 92%, respectively. The PPV and NPV were 46% and 100%, respectively. There were no significant differences between the 2 ROC curves ($P = 0.3164$, Supplemental Digital Content Fig. 3A, http://links.lww.com/SLA/C681).

Fetal Management

Serial observation without any active pharmacologic agent, percutaneous intervention, or surgical therapy occurred in 302 (87.8%) cases. Maternal steroids, given as betamethasone 12.5 mg intramuscularly daily for 2 days, were the most common therapy. Forty-one (11.9%) fetuses received steroids at a median gestational age of 23.0 weeks (IQR, 21.8–27.5) at 8 (72.7%) different institutions. Fifteen (36.6%) fetuses managed with steroids had macro-cystic lesions. The indications for steroids included increasing size and/or CVR (n = 34, 85.0%) and hydrops (n = 13, 32.5%). The mean initial CVR and mean maximum CVR in those receiving steroids were 1.8 ± 1.3 and 2.49 ± 1.1, respectively.

Invasive prenatal procedures were infrequent (n = 6, 1.7%), ranging from thoracentesis (n = 2, median 27.3 weeks' gestation), thoracoamniotic shunt placement (n = 1, 26.3 weeks' gestation), and ex utero intrapartum treatment (EXIT; n = 3, median 37.0 weeks' gestation). Although there were no fetal surgical resections performed, 2 lung resections and 2 extracorporeal membrane oxygenation (ECMO) cannulations were conducted as part of an EXIT procedure. Among the 15 hydropic fetuses, only 3 (20%) received an invasive therapeutic intervention before delivery.

Neonatal Course

The neonatal clinical course of these children is shown in Table 2. Excluding those undergoing an EXIT procedure, 72 (21.1%) had neonatal respiratory symptoms, defined as documentation of tachypnea, oxygen saturation < 90%, and/or placement on supplemental oxygen or need for more intensive respiratory support within 24 hours of life. Eighty-six percent (n = 12) with a history of hydrops had respiratory distress at birth. Fifty-two (69.3%) symptomatic newborns were delivered at an inborn facility, whereas 23 (30.7%) symptomatic newborns were outborn ($P = 0.0014$). Among symptomatic outborn patients, 14 (60.9%) did not have any recorded CVR data. Lesions with fetal mediastinal shift were more likely to be inborn, but this did not meet statistical significance ($P = 0.07$). The maximum CVR significantly correlated with inborn status (inborn mean: 1.3 ± 1.1 vs outborn mean: 0.9 ± 0.5; $P < 0.01$).

Sixty-six neonates (19.2%) received supplemental oxygen at delivery, and 27 (7.8%) were mechanically ventilated preoperatively via endotracheal tube (Table 2). The median total time on ventilator support in this latter cohort of patients was 7.0 days (IQR, 3.0–12.5). Thirty-one (9.1%) children underwent lung resection during the newborn period due to severe or persistent respiratory symptoms.

Forty-two (12.2%) patients had concomitant anomalies. The most common organ systems involved were cardiac (n = 17, 4.9%), neurologic (n = 8, 2.3%), and renal (n = 4, 1.2%). There was 1 (0.3%) child with a chromosomal abnormality. Sixteen (39.0%) of these anomalies were detected prenatally. There was no significant association between fetal cyst description based on Stocker classification and the incidence of concomitant anomalies (type I, 7.5%; type II, 17.6%; type III, 11.7%; $P = 0.1457$; Supplemental Digital Content Fig1C, http://links.lww.com/SLA/C681).

Predictors of Neonatal Outcome

Predictors of neonatal outcome using bivariate statistical methods are presented in Tables 3 and 4. Although the majority (64.3%) with fetal mediastinal shift were asymptomatic at birth, the presence of mediastinal shift was significantly associated with an increased risk of respiratory symptoms ($P = 0.0005$), need for supplemental oxygen ($P = 0.0003$), and preoperative neonatal ventilator use ($P = 0.0012$). There was no association between neonates with macrocystic lesions and either likelihood of respiratory symptoms at birth or need for supplemental oxygen compared to those with microcystic disease ($P = 0.3624$ and

TABLE 2. Clinical Course of Neonates With Prenatally Diagnosed Lung Malformations

Outcome Measure	All Neonates (n = 344)	Inborn Neonates (n = 168)	Outborn Neonates (n = 167)	*P*
Maximum CVR, mean ± stdev	1.21 ± 0.97	1.33 ± 1.07	0.89 ± 0.51	0.0095*
Gestational age at birth, median (IQR)	39.0 wk (37.3–39.1)	39.0 wk (38.0–39.2)	38.7 wk (37.0–39.0)	0.0642
Birthweight, median (IQR)	3.2 kg (2.8–3.6)	3.3 kg (2.9–3.7)	3.2kg (2.7–3.5)	0.2791
Apgar score at 1-min, mean ± stdev	7.6 ± 1.9	7.5 ± 1.9	7.6 ± 1.9	0.8746
Apgar score at 5-min, mean ± stdev	8.6 ± 1.1	8.6 ± 1.1	8.6 ± 1.3	0.9162
Mass on chest radiograph, n (%)	187 (76)	118 (79)	68 (72)	0.2223
Respiratory symptoms at birth, n (%)	75 (22)	52 (31)	23 (14)	0.0002*
Received supplemental oxygen, n (%)	66 (19)	45 (27)	21 (13)	0.0015*
Required endotracheal tube intubation, n (%)	27 (8)	18(11)	9 (5)	0.1069
Lung resection within 28 days after delivery, n (%)	31 (9)	27 (16)	4 (2)	< 0.0001*

*$P < 0.05$ between newborns with lung malformations delivered at inborn facilities compared to those delivered at outborn facilities (Mann-Whitney *U* test or Fisher exact test).

TABLE 3. Bivariate Analysis of Neonatal Respiratory Distress and Oxygen Requirement in Children With Prenatally Diagnosed Lung Malformations

A. Respiratory Symptoms

Variable	Present	Absent	*p* value
Gestational age at birth, median (IQR)	38.0 wk (34.9–39.0)	39.0 wk (38.0–39.7)	<0.0001*
Birthweight, median (IQR)	3.1 kg (1.5–3.6)	3.3 kg (3.0–3.7)	0.0080*
Concomitant major anomalies, n (%)	19 (25)	19 (8)	0.0002*
Macrocystic (Stocker type I), n (%)	19 (39)	34 (30)	0.3624
Fetal mediastinal shift, n (%)	44 (73)	77 (47)	0.0005*
Hydrops, n (%)	13 (20)	2 (1)	<0.0001*
Initial CVR, mean ± stdev	1.46 ± 1.35	0.68 ± 0.53	<0.0001*
Maximum CVR, mean ± stdev	1.91 ± 1.28	0.96 ± 0.67	<0.0001*

B. Supplemental Oxygen

Variable	Present	Absent	p value
Gestational age at birth, median (IQR)	37.0 wk (34.2–39.0)	39.0 wk (38.0–39.6)	<0.0001*
Birthweight, median (IQR)	3.0 kg (2.2–3.6)	3.3 kg (3.0–3.7)	0.0021*
Concomitant major anomalies, n (%)	18 (27)	24 (9)	0.0002*
Macrocystic (Stocker type I), n (%)	19 (43)	34 (30)	0.0900
Fetal mediastinal shift, n (%)	40 (74)	81 (46)	0.0003*
Hydrops, n (%)	13 (22)	2 (1)	<0.0001*
Initial CVR, mean ± stdev	1.51 ± 1.40	0.69 ± 0.55	<0.0001*
Maximum CVR, mean ± stdev	1.96 ± 1.31	0.98 ± 0.69	<0.0001*

$P = 0.0900$, respectively; Supplement eFig 1D, http://links.lww.com/SLA/C681). Both the initial and maximum CVR were found to be significantly associated with respiratory symptoms at birth, need for supplemental oxygen, preoperative neonatal ventilator use, and neonatal lung resection ($P < 0.0001$, Tables 3 and 4).

To establish the optimal cutoff point associated with respiratory symptoms at birth, ROC curve analyses were performed (Table 5). A maximum CVR cut-off of 0.93 had a significantly higher AUC value while maintaining equivalent diagnostic accuracy when compared to those calculated for the initial CVR ($P = 0.0348$, Supplemental Digital Content Fig 3B, http://links.lww.com/SLA/C681). Table 5 reveals ROC curve analyses of the CVR and more severe indicators of respiratory morbidity, namely need for supplemental oxygen and use of invasive ventilator support (optimal cutoff points, 1.18 and 1.98, respectively). Both the initial CVR and the maximum CVR were significantly correlated with an increased likelihood of neonatal surgical resection (optimal cutoff point, 1.73; $P < 0.0001$; Table 5).

Multivariable logistic regression analyses, which included CVR, mediastinal shift, hydrops, and macrocystic subtype as independent variables, showed that the CVR was the only prenatal ultrasound finding that was significantly associated with respiratory symptoms at birth [odds ratio for initial CVR: 2.42 (95% CI, 1.234.75), $P = 0.010$; odds ratio for maximum CVR: 3.03 (95%CI, 1.695.43), $P < 0.0001$; Table 6]. When analyzing

TABLE 4. Bivariate Analysis of Neonatal Preoperative Intubation and Lung Resection in Children With Prenatally Diagnosed Lung Malformations

Preoperative Endotracheal Intubation

Variable	Present	Absent	*P*
Gestational age at birth, median (IQR)	35.0 wks (31.2–38.5)	39.0 wks (38.0–39.4)	<0.0001*
Birthweight, median (IQR)	2.5 kg (1.7–3.3)	3.3 kg (2.0–3.7)	0.0001*
Concomitant major anomalies, n (%)	10 (37)	32 (10)	0.0005*
Macrocystic (Stocker type I), n (%)	19 (61)	42 (29)	0.0137*
Fetal mediastinal shift, n (%)	19 (86)	77 (49)	0.0012*
Hydrops, n (%)	13 (32)	7 (3)	<0.0001*
Initial CVR, mean ± stdev	2.17 ± 1.39	0.77 ± 0.74	<0.0001*
Maximum CVR, mean ± stdev	2.43 ± 1.27	1.11 ± 0.86	<0.0001*

Neonatal Lung Resection

Variable	Present	Absent	*P*
Gestational age at birth, median (IQR)	38.0 wk (35.2–39.0)	39.0 wk (37.7–39.2)	0.0069*
Birthweight, median (IQR)	3.0 kg (2.5–3.6)	3.3 kg (2.9–3.6)	0.0766
Concomitant major anomalies, n (%)	11 (34)	31 (10)	0.0006*
Macrocystic (Stocker type I), n (%)	12 (44)	39 (29)	0.1187
Fetal mediastinal shift, n (%)	26 (93)	92 (47)	<0.0001*
Hydrops, n (%)	8 (28)	6 (3)	<0.0001*
Initial CVR, mean ± stdev	1.98 ± 1.59	0.71 ± 0.55	<0.0001*
Maximum CVR, mean ± stdev	2.54 ± 1.38	1.01 ± 0.71	<0.0001*

stdev indicates standard deviation.*$P < 0.05$ (Mann-Whitney U test or Fisher exact test).

TABLE 5. Predictive Value for Neonatal Respiratory Morbidity in Prenatally Diagnosed Lung Malformations at Optimal CVR Cutoff Values

A. Respiratory Distress						
	AUC (95% CI)	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
Initial CVR >0.65	0.66 (0.60–0.79)	63	68	42	84	67
Maximum CVR >0.93	0.72 (0.67–0.85)*	83	60	43	91	66
B. Supplemental Oxygen						
	AUC (95% CI)	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
Initial CVR >0.65	0.65 (0.59–0.80)	69	61	34	87	63
Maximum CVR >1.18	0.71 (0.66–0.86)*	74	67	40	90	69
C. Endotracheal Intubation						
	AUC (95% CI)	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
Initial CVR >1.29	0.77 (0.69–0.92)	75	80	24	97	80
Maximum CVR >1.98	0.81 (0.76–0.95)	75	87	33	98	86
D. Neonatal Lung Resection						
	AUC (95% CI)	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
Initial CVR >0.85	0.75 (0.65–0.85)	81	69	29	96	71
Maximum CVR >1.73	0.81 (0.69–0.93)	76	87	48	96	86

*$P < 0.05$ compared to initial CVR AUC.

TABLE 6. Multivariable Logistic Regression Analyses of Prenatal Variables on Respiratory Morbidity in Children With Lung Malformations

A. Respiratory Symptoms at Birth, Model 1 (Initial CVR)				
Variable	**Odds Ratio**	**SE**	**95% CI**	***P***
Initial CVR	2.42	0.83	1.23–4.75	0.010*
Hydrops	2.86	2.69	0.45–18.08	0.265
Macrocystic disease	1.19	0.24	0.81–1.76	0.370
Mediastinal shift	0.58	0.25	0.25–1.36	0.214
B. Respiratory Symptoms at Birth, Model 2 (Maximum CVR)				
Variable	**Odds Ratio**	**SE**	**95% CI**	**P**
Maximum CVR	3.03	0.90	1.69–5.43	<0.001*
Hydrops	1.45	1.41	0.22–9.72	0.703
Macrocystic disease	1.14	0.23	0.76–1.70	0.531
Mediastinal shift	0.66	0.29	0.28–1.55	0.344
C. Composite Ordinal Outcome Measure of Respiratory Morbidity, Model 1 (Initial CVR)				
Variable	**Odds Ratio**	**SE**	**95% CI**	**P**
Initial CVR	1.93	0.53	1.13–3.30	0.016*
Hydrops	2.86	2.26	0.61–13.43	0.184
Macrocystic disease	1.04	0.19	0.73–1.48	0.831
Mediastinal shift	0.49	0.20	0.22–1.09	0.079
D. Composite Ordinal Outcome Measure of Respiratory Morbidity, Model 2 (Maximum CVR)				
Variable	**Odds Ratio**	**SE**	**95% CI**	**P**
Maximum CVR	1.94	0.39	1.31–2.87	0.001*
Hydrops	1.07	0.62	0.35–3.33	0.903
Macrocystic disease	1.10	0.16	0.83–1.46	0.518
Mediastinal shift	0.64	0.23	0.31–1.30	0.218

SE indicates standard error.*$P < 0.05$.

the same independent variables in relationship to a composite ordinal outcome measure of neonatal respiratory morbidity (scale 0–4, based on respiratory distress, supplemental oxygen, preoperative ventilation, and/or neonatal resection), the CVR was the only prenatal ultrasound finding that remained significant in multivariable logistic regression analyses [odds ratio for initial CVR: 1.93 (95% CI, 1.13–3.30), $P = 0.016$; odds ratio for maximum CVR: 2.64 (95% CI, 1.60–4.33), $P < 0.0001$].

Perioperative Outcomes

There were 164 (48.1%) open, 150 (44.0%) thoracoscopic, and 27 (7.9%) thoracoscopic converted to open resections. Operations included 258 (75.7%) lobectomies, 63 (18.5%) simple excisions, 22 (6.5%) wedge resections, and 14 (4.1%) segmentectomies. The median patient weight at surgical resection was 7.3 kg (IQR, 6.1–8.8), and the median age at resection was 6.1 months (IQR, 3.8–9.1, Supplement Fig 4, http://links.lww.com/SLA/C681). The most common indication for surgery was to prevent future complications in an otherwise asymptomatic child (n = 276, 80.5%). Forty (11.7%) resections were performed due to ongoing respiratory symptoms. Eleven (3.2%) patients had an operation (median age of 9.8 months, IQR, 7.5–31.5) due to a previous episode of pneumonia.

The length of stay was significantly longer amongst neonates when compared to older children [median: 18.5 days (IQR, 11.8– 40.3) vs 3.0 days (IQR, 2.0–4.0), respectively; $P < 0.0001$]. Three (0.9%) neonates were managed with ECMO postoperatively. All 344 (100%) patients survived both to hospital discharge and for >30 days after resection. Postoperative 30-day complications occurred in 51 (15.2%) patients, the most common being pneumothorax necessitating a pleural drain procedure (8.3%).

DISCUSSION

In this report, we utilized a regional operative database of 344 children with a prenatally diagnosed lung malformation to evaluate clinical outcomes and predictors of morbidity. This multi-institutional analysis had several interesting findings. First, maternal betamethasone was given as treatment to 41 (12%) cases at a mean of 23 weeks' gestation, thereby confirming the increasing use of steroids as the empiric first line of therapy for larger fetal lung malformations, regardless of cyst characteristics and whether hydrops is present.[24] Despite having several centers within the consortium that were capable of performing invasive in utero operations, fetal procedures were strikingly uncommon, accounting for <2% of fetal CLMs managed in our study.[25–27] Although our results may seem unusually low compared to those reported in prior studies,[28] we believe that our multi-institutional data are less susceptible to referral bias and therefore are likely to be more reflective of the clinical disease spectrum of fetal CLMs managed nationwide.

Our results also highlight the tremendous heterogeneity in the clinical management and disease spectrum of children with prenatally diagnosed CLMs. Half were delivered at outborn facilities, many of which likely had minimal critical care support and pediatric surgical coverage. In contrast to another prenatally diagnosed surgical disease of the lung, congenital diaphragmatic hernia, our data showed that approximately 4 of 5 neonates with a CLM had no respiratory symptoms at birth and that only 1 in 10 underwent neonatal surgery. There were no deaths, and the utilization of ECMO, a technology that was available at all participating centers, was <1%. Among those undergoing resections for asymptomatic disease after the neonatal period, the age at resection was 6 months, and the median hospital length of stay was 3 days. These excellent postoperative outcomes compare quite favorably to single surgeon and single institution reports described elsewhere.[29–32] Since all of the lesions in our study were resected, the absence of any malignancy within 344 evaluated specimens should alleviate concerns that families and providers may have regarding a high risk for an occult PPB or other cancer within prenatally diagnosed lung masses.[33,34]

The frequency of concomitant anomalies in our study was approximately 10%, a rate similar to that reported elsewhere.[35] Cardiac defects were the most common, occurring in 5% of children. Our data confirm the negative prognostic implications of a concurrent anomaly in fetal CLM patients. However, in contrast to Stocker et al's[36] work on the association between cystic features in CPAM and concomitant anomalies, we did not find any correlation between type II cystic lesions and other birth defects.

Given the broad range of disease severity amongst fetuses with CLMs, perhaps the most important finding from our study is the predictive value of the CVR in determining perinatal outcomes. In the seminal descriptive report on the CVR from a single center,[4] a threshold value of 1.6 was established to identify a subgroup of fetuses who might need fetal lung resection. However, the validity of this metric was immediately challenged by some investigators,[37] and there has always been lack of clarity as to whether the 1.6 cutoff applies to the initial CVR or the maximum CVR.[38] The issue of timing of CVR measurements is not trivial given the known increase in mass size that can occur in the CVR between 20 and 26 weeks' gestation in one-third of fetuses.[39,40] Based on initial CVR data at a median of 21 weeks, we propose that an initial CVR ≥ 1.4 more accurately identifies the subgroup at an elevated risk of hydrops (~31%) with a negative predictive value of 99%. Although our study did not specifically gather data on CPAMs with a single dominant cyst, our data do not support the belief that ultrasound-based cystic characteristics, whether defined by macrocystic/microcystic subtype (Adzick) or by Stocker classification, have additional predictive value for determining hydrops risk.[4,36,41] Moreover, since prenatal imaging is often not accurate in determining the pathologic diagnosis when compared to postnatal imaging or pathologic examination,[42] our data give some reassurance that pathologically confirmed BPS behave similarly to confirmed CPAMs with respect to CVR and outcome.[43,44]

Five prenatal variables, namely mediastinal shift, hydrops, concomitant anomalies, macrocystic disease, and CVR, were associated with at least one outcome measure of respiratory morbidity in bivariate analysis. We also observed a significant, stepwise association between increasing CVR values and the severity of pulmonary symptoms. Critically, only the CVR remained as a significant independent variable of respiratory morbidity in multivariable regression. These results are congruent with findings recently reported by others.[15–17,45–48] Unfortunately, nearly all of these previous studies were hampered by low patient numbers and a single center study design, while others did not fully endorsed the utility of CVR as a reliable predictor of outcome.[18,35,49]

Four symptomatic fetuses with a maximum CVR > 0.9 were not delivered at affiliated birth centers, and CVR measurements were missing from reports in half of all cases. Given our prenatal risk stratification data and the maternal-fetal medicine practice variation that currently exists in routinely measuring the CVR, there is an opportunity for standardization and quality improvement in ultrasound evaluations performed

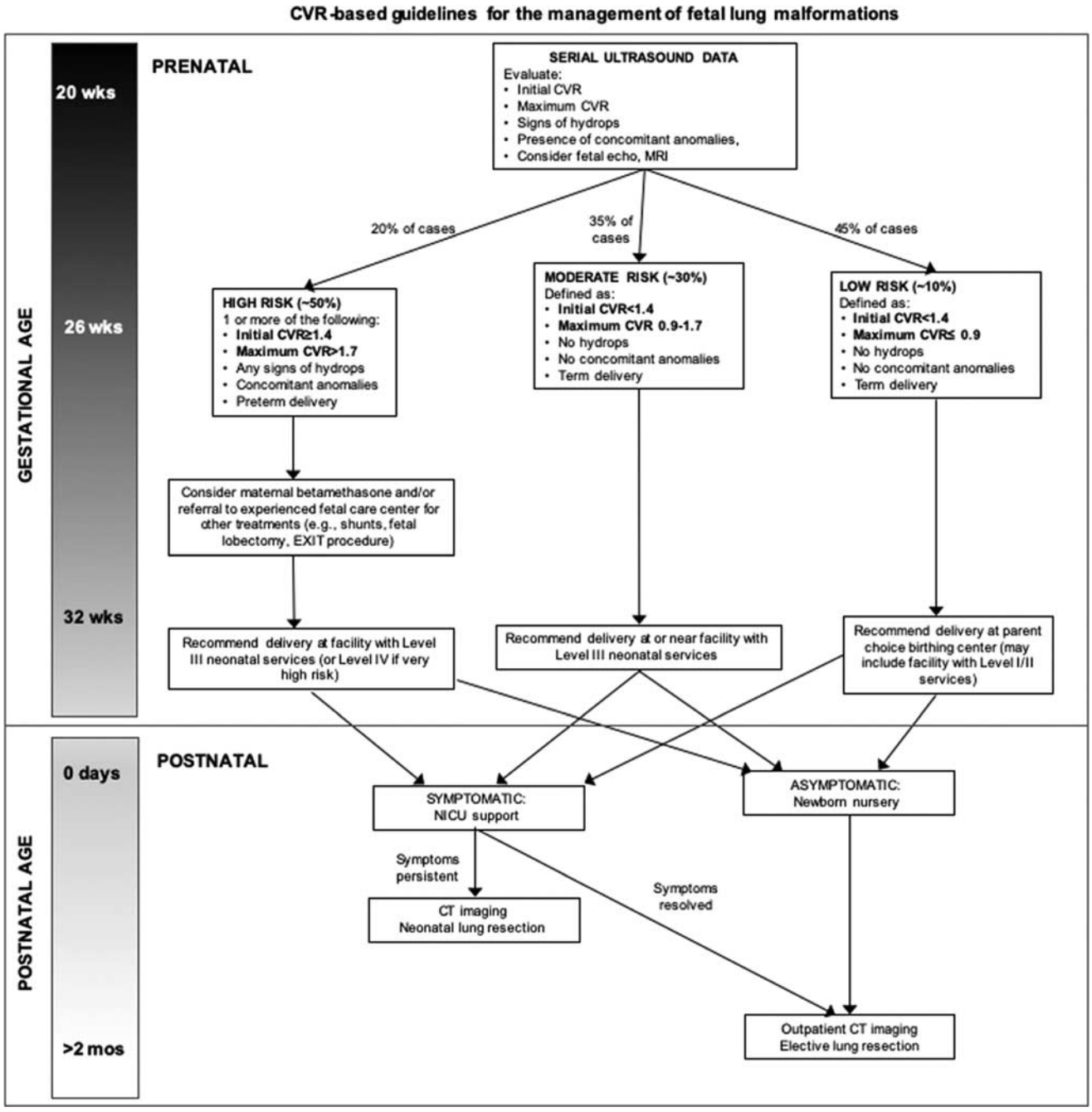

FIGURE 1. Proposed congenital pulmonary airway malformation (CVR)-based guidelines for the management of fetal lung malformations based on likelihood of hydrops and degree of respiratory morbidity at birth. Signs of hydrops include ascites, pleural fluid, pericardial fluid, skin thickening, and placentomegaly.

for this condition. The reasons for the lack of CVR data remain unclear, but we speculate that the paucity of CVR measurements during sonographic evaluation are secondary to multiple factors, including the additional time required to measure each lesion and calculate the value, the belief that the CVR is not a good surrogate to quantify mass effect, and the perception that the CVR is only relevant for the small subset of large lesions at risk for hydrops.[21,50,51] Although the interclass correlation coefficient (Table 1) did not suggest clustering of CVR values by center, the inter- and intra-observer variability of CVR measurements for a given fetus is largely unknown.

Based on our multicenter results, we propose updated clinical guidelines for the risk stratification for prenatal lung lesions based on low-, intermediate-, and high-risk groups (Fig. 1). An initial CVR should be calculated in all new fetal CLM cases. Since the positive predictive value for hydrops with an initial CVR ≥1.4 is approximately one-third, this CVR cutoff identifies nearly all fetuses with CLMs that would warrant closer

ultrasound surveillance. These fetuses should also be considered for maternal betamethasone therapy and referral to an experienced fetal care center capable of invasive therapeutic interventions. The frequency of these scans should be individualized based on mass size rather than by cyst characteristics or the presence of mediastinal shift.

By the beginning of the third trimester, most lesions will have reached their maximum CVR,[39,40] which can be used to guide providers and families on the appropriate facility for delivery of these children. Based on our data suggesting that fetuses with a maximum CVR ≤0.9 are at low risk (~10%) for respiratory symptoms at birth, expectant mothers can be given the option to deliver at term at a local birthing center without Level III/IV support. In contrast, those fetuses with a maximum CVR between 0.9 and 1.7 should be placed into an intermediate risk category for having respiratory symptoms and needing supplemental oxygen (~30%), and the ideal site of delivery in this cohort would be at or in close proximity to a Level 3 neonatal facility. Finally, for all high-risk lesions (ie, a maximum CVR ≥ 1.7), these cases should be delivered at an institution with a minimum of Level III neonatal services, given that most of these patients will have respiratory distress and a ~50% chance of requiring neonatal lung resection.

To our knowledge, this is first contemporary and truly multicenter study validating the CVR as a risk prognosticator of a variety of measures associated with clinical disease severity in fetal lung malformations. Despite its aforementioned strengths, several limitations should be acknowledged. First, all data including CVR measurements were extracted in a retrospective manner, and some variables were limited by missing data points in the electronic medical record. We did not have fetal echocardiography data to support the diagnosis of hydrops, and we did not collect more specific gestational age data at later time points, as suggested by others.[52] A large, prospective cohort study, perhaps with comparative cost/benefit data using other imaging modalities such as fetal MRI,[53,54] would be helpful in validating the accuracy of our proposed risk stratification algorithm. Because our analysis was obtained using an operative database, a small fraction of CLM patients were likely excluded, such as those who never had surgery due to nonoperative management and those fetuses who were terminated or died either in utero or in the neonatal period before resection.[55] Finally, although less susceptible to referral bias than single-institution studies from major quaternary care centers,[29,30] our results and proposed cutoff values may still not be generalizable to some hospitals, particularly in places that rarely evaluate these lesions or do not have similar ultrasound technology and clinical support.

CONCLUSIONS

This multicenter study of 344 patients showed that the majority of children with prenatally diagnosed CLMs required no perinatal intervention and are asymptomatic at birth. The CVR obtained by fetal ultrasound was significantly associated with prenatal and postnatal outcome. Given that over half of all prenatal evaluations in our consortium did not include any CVR measurements, these findings represent a "call to action" for improved standardization and quality improvement in the evaluation of these patients. An initial CVR ≤1.4 identifies fetuses at very low risk for hydrops, and a maximum CVR < 0.9 portends a low likelihood for neonatal respiratory morbidity. These data on fetal risk stratification of CLMs should be highly useful for maternal-fetal medicine specialists, neonatologists, and pediatric surgeons during prenatal counseling discussions with families and in triaging deliveries to the appropriate birthing facility.[56,57]

ACKNOWLEDGMENTS

The authors acknowledge Kevin Johnson, Rodrigo Mon, and Sarah Fox from the University of Michigan for their expert data collection and all of the founding members and research residents associated the Midwest Pediatric Surgery Consortium for their assistance with this project: Cheryl Adams (Cincinnati), Bola Ala-degbami (Washington University), Christina Bence (Milwaukee), R. Cartland Burns (Indiana), Kristine Corkum (Lurie), Cynthia Down-ard (Louisville), Jason Fraser (Kansas City), Rashmi Kabre (Lurie), Matthew Landman (Indiana), Charles Leys (Wisconsin), Allison Linden (Comer), Joseph Lopez (Columbus), Grace Mak (Comer), Brooks Rademacher (Wisconsin), Aimen Shaaban (Cincinnati), Sarah Walker (Milwaukee), Tiffany Wright (Louisville), Thomas Sato (Milwaukee), Daniel von Allmen (Cincinnati), Jonathan Kohler (Indiana), and Daniel Ostlie (Kansas City).

REFERENCES

1. Langston C. New concepts in the pathology of congenital lung malformations. *Semin Pediatr Surg*. 2003;12:17–37.
2. Adzick NS. Management of fetal lung lesions. *Clin Perinatol*. 2009;36:363–376x.
3. Stocker JT. Cystic lung disease in infants and children. *Fetal Pediatr Pathol*. 2009;28:155–184.
4. Crombleholme TM, Coleman B, Hedrick H, et al. Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. *J Pediatr Surg*. 2002;37:331–338.
5. Adzick NS, Harrison MR, Crombleholme TM, et al. Fetal lung lesions: management and outcome. *Am J Obstet Gynecol*. 1998;179:884–889.
6. Thorpe-Beeston JG, Nicolaides KH. Cystic adenomatoid malformation of the lung: prenatal diagnosis and outcome. *Prenat Diagn*. 1994;14:677–688.
7. Lau CT, Kan A, Shek N, et al. Is congenital pulmonary airway malformation really a rare disease? Result of a prospective registry with universal antenatal screening program. *Pediatr Surg Int*. 2017;33:105–108.
8. Lima JS, Camargos PA, Aguiar RA, et al. Pre and perinatal aspects of congenital cystic adenomatoid malformation of the lung. *J Matern Fetal Neonatal Med*. 2014;27:228–232.
9. Burge D, Wheeler R. Increasing incidence of detection of congenital lung lesions. *Pediatr Pulmonol*. 2010;45:103. author reply 104.
10. Miller JA, Corteville JE, Langer JC. Congenital cystic adenomatoid malformation in the fetus: natural history and predictors of outcome. *J Pediatr Surg*. 1996;31:805–808.
11. Pumberger W, Hormann M, Deutinger J, et al. Longitudinal observation of antenatally detected congenital lung malformations (CLM): natural history, clinical outcome and long-term follow-up. *Eur J Cardiothorac Surg*. 2003;24:703–711.
12. Davenport M, Warne SA, Cacciaguerra S, et al. Current outcome of antenally diagnosed cystic lung disease. *J Pediatr Surg*. 2004;39:549–556.
13. Usui N, Kamata S, Sawai T, et al. Outcome predictors for infants with cystic lung disease. *J Pediatr Surg*. 2004;39:603–606.
14. Vu L, Tsao K, Lee H, et al. Characteristics of congenital cystic adenomatoid malformations associated with nonimmune hydrops and outcome. *J Pediatr Surg*. 2007;42:1351–1356.
15. Yong PJ, Von Dadelszen P, Carpara D, et al. Prediction of pediatric outcome after prenatal diagnosis and expectant antenatal management of congenital cystic adenomatoid malformation. *Fetal Diagn Ther*. 2012;31:94–102.
16. Ehrenberg-Buchner S, Stapf AM, Berman DR, et al. Fetal lung lesions: can we start to breathe easier? *Am J Obstet Gynecol*. 2013; 208:151 e151–151 e157.
17. Ruchonnet-Metrailler I, Leroy-Terquem E, Stirnemann J, et al. Neonatal outcomes of prenatally diagnosed congenital pulmonary malformations. *Pediatrics*. 2014;133:e1285–e1291.

18. Tuzovic L, Copel JA, Stitelman DH, et al. Utility of fetal cardiac axis and cardiac position assessment in predicting neonatal respiratory morbidity in fetal congenital lung lesions. *J Ultrasound Med*. 2019;38:2361–2372.
19. Kane SC, Da Silva Costa F, Crameri JA, et al. Antenatal assessment and postnatal outcome of fetal echogenic lung lesions: a decade's experience at a tertiary referral hospital. *J Matern Fetal Neonatal Med*. 2019;32:703–709.
20. King A, Lee TC, Steen E, et al. Prenatal imaging to predict need for urgent perinatal surgery in congenital lung lesions. *J Surg Res*. 2020;255:463–468.
21. Kane SC, Ancona E, Reidy KL, et al. The utility of the congenital pulmonary airway malformation-volume ratio in the assessment of fetal echogenic lung lesions: a systematic review. *Fetal Diagn Ther*. 2019;1–11.
22. Kunisaki SM, Saito JM, Fallat ME, et al. Development of a multi-institutional registry for children with operative congenital lung malformations. *J Pediatr Surg*. 2020;55:1313–1318.
23. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. *Biom J*. 2005;47:458–472.
24. Peranteau WH, Wilson RD, Liechty KW, et al. Effect of maternal betamethasone administration on prenatal congenital cystic adenomatoid malformation growth and fetal survival. *Fetal Diagn Ther*. 2007;22:365–371.
25. Wilson RD, Baxter JK, Johnson MP, et al. Thoracoamniotic shunts: fetal treatment of pleural effusions and congenital cystic adenomatoid malformations. *Fetal Diagn Ther*. 2004;19:413–420.
26. Hedrick HL, Flake AW, Crombleholme TM, et al. The ex utero intrapartum therapy procedure for high-risk fetal lung lesions. *J Pediatr Surg*. 2005;40:1038–1043. discussion 1044.
27. Grethel EJ, Wagner AJ, Clifton MS, et al. Fetal intervention for mass lesions and hydrops improves outcome: a 15-year experience. *J Pediatr Surg*. 2007;42:117–123.
28. Loh KC, Jelin E, Hirose S, et al. Microcystic congenital pulmonary airway malformation with hydrops fetalis: steroids vs open fetal resection. *J Pediatr Surg*. 2012;47:36–39.
29. Rothenberg SS. First decade's experience with thoracoscopic lobectomy in infants and children. *J Pediatr Surg*. 2008;43:40–44. discussion 45.
30. Tsai AY, Liechty KW, Hedrick HL, et al. Outcomes after postnatal resection of prenatally diagnosed asymptomatic cystic lung lesions. *J Pediatr Surg*. 2008;43:513–517.
31. Kunisaki SM, Powelson IA, Haydar B, et al. Thoracoscopic vs openlobectomy in infants and young children with congenital lung malformations. *J Am Coll Surg*. 2014;218:261–270.
32. Laje P, Pearson EG, Simpao AF, et al. The first 100 infant thoracoscopic lobectomies: observations through the learning curve and comparison to open lobectomy. *J Pediatr Surg*. 2015;50:1811–1816.
33. Miniati DN, Chintagumpala M, Langston C, et al. Prenatal presentation and outcome of children with pleuropulmonary blastoma. *J Pediatr Surg*. 2006;41:66–71.
34. Nasr A, Himidan S, Pastor AC, et al. Is congenital cystic adenomatoid malformation a premalignant lesion for pleuropulmonary blastoma? *J Pediatr Surg*. 2010;45:1086–1089.
35. Japanese Study Group of Pediatric Chest Surgery, Kuroda T, Nishijima E, Maeda K, et al. Perinatal features of congenital cystic lung diseases: results of a nationwide multicentric study in Japan. *Pediatr Surg Int*. 2016;32:827–831.
36. Stocker JT, Madewell JE, Drake RM. Congenital cystic adenomatoid malformation of the lung. Classification and morphologic spectrum. *Hum Pathol*. 1977;8:155–171.
37. Davenport M. Prognosis of antenatally diagnosed cystic adenomatoid malformation. *J Pediatr Surg*. 2002;37:1784. author reply 1784–1785.
38. Cass DL, Olutoye OO, Cassady CI, et al. Prenatal diagnosis and outcome of fetal lung masses. *J Pediatr Surg*. 2011;46:292–298.
39. Macardle CA, Ehrenberg-Buchner S, Smith EA, et al. Surveillance of fetal lung lesions using the congenital pulmonary airway malformation volume ratio: natural history and outcomes. *Prenat Diagn*. 2016;36:282–289.
40. Eyerly-Webb S, Nicolas CT, Watson D, et al. Dynamic discriminant model for predicting respiratory distress at birth based on mass volume ratio in fetuses with congenital lung malformation. *Ultrasound Obstet Gynecol*. 2019;54:759–766.
41. Adzick NS, Harrison MR, Glick PL, et al. Fetal cystic adenomatoid malformation: prenatal diagnosis and natural history. *J Pediatr Surg*. 1985;20:483–488.
42. Mon RA, Johnson KN, Ladino-Torres M, et al. Diagnostic accuracy of imaging studies in congenital lung malformations. *Arch Dis Child Fetal Neonatal Ed*. 2019;104:F372–F377.
43. Riley JS, Urwin JW, Oliver ER, et al. Prenatal growth characteristics and pre/ postnatal management of bronchopulmonary sequestrations. *J Pediatr Surg*. 2018;53:265–269.
44. Zhang H, Tian J, Chen Z, et al. Retrospective study of prenatal diagnosed pulmonary sequestration. *Pediatr Surg Int*. 2014;30:47–53.
45. Hellmund A, Berg C, Geipel A, et al. Prenatal diagnosis and evaluation of sonographic predictors for intervention and adverse outcome in congenital pulmonary airway malformation. *PLoS One*. 2016;11: e0150474.
46. Girsen AI, Hintz SR, Sammour R, et al. Prediction of neonatal respiratory distress in pregnancies complicated by fetal lung masses. *Prenat Diagn*. 2017;37:266–272.
47. Fuchimoto Y, Watanabe T, Fujino A, et al. Predictors of early lobectomy after birth in prenatally diagnosed congenital pulmonary airway malformation. *J Pediatr Surg*. 2018;53:2386–2389.
48. Feghali M, Jean KM, Emery SP. Ultrasound assessment of congenital fetal lung masses and neonatal respiratory outcomes. *Prenat Diagn*. 2015;35:1208–1212.
49. Jeong BD, An SA, Lee MY, et al. Comparison of the prognostic factors of fetuses with congenital pulmonary airway malformations according to type. *J Ultrasound Med*. 2020;39:2243–2252.
50. Downard CD, Calkins CM, Williams RF, et al. Treatment of congenital pulmonary airway malformations: a systematic review from the APSA outcomes and evidence based practice committee. *Pediatr Surg Int*. 2017;33:939–953.
51. Zobel M, Gologorsky R, Lee H, et al. Congenital lung lesions. *Semin Pediatr Surg*. 2019;28:150821.
52. Cass DL, Olutoye OO, Ayres NA, et al. Defining hydrops and indications for open fetal surgery for fetuses with lung masses and vascular tumors. *J Pediatr Surg*. 2012;47:40–45.
53. Zamora IJ, Sheikh F, Cassady CI, et al. Fetal MRI lung volumes are predictive of perinatal outcomes in fetuses with congenital lung masses. *J Pediatr Surg*. 2014;49:853–858. discussion 858.
54. Euser AG, Meyers ML, Zaretsky MV, et al. Comparison of congenital pulmonary airway malformation volume ratios calculated by ultrasound and magnetic resonance imaging. *J Matern Fetal Neonatal Med*. 2016;29:3172–3177.
55. Criss CN, Musili N, Matusko N, et al. Asymptomatic congenital lung malformations: Is nonoperative management a viable alternative? *J Pediatr Surg*. 2018;53:1092–1097.
56. Aite L, Zaccara A, Trucchi A, et al. Is counselling for CCAM that difficult? Learning from parental experience. *J Prenat Med*. 2011;5:65–68.
57. Baird R, Puligandla PS, Laberge JM. Congenital lung malformations: informing best practice. *Semin Pediatr Surg*. 2014;23:270–277.