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ARTICLE

Prenatally diagnosed omphalocele: characteristics associated with adverse neonatal outcomes

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Abstract

Objective To characterize factors associated with adverse neonatal outcomes in prenatally diagnosed omphalocele cases.

Study design Prenatally diagnosed omphalocele cases at a single referral center from 1 January 2009 to 31 December 2017 were retrospectively reviewed. Clinical variables and antenatal imaging measurements were collected. Associations between prenatal and neonatal characteristics and the adverse outcome of death or prolonged length of stay (LOS) were analyzed.

Results Out of 63 fetal cases, 33 were live-born, >50% had other anomalies, and neonatal mortality was 12%. Adverse outcomes were associated with neonatal variables, including lower median 1-min Apgar score, initial mechanical ventilation, and late-onset sepsis, but not approach to omphalocele closure. With multivariate analysis, death or prolonged LOS was associated only with low lung volumes by fetal MRI (OR 34 (3–422), $p = 0.006$).

Conclusion Low lung volumes by fetal MRI were associated with death or prolonged LOS in neonates with prenatally diagnosed omphalocele and may guide clinicians with counseling families.

Introduction

Omphalocele is an anterior abdominal wall defect usually detected in the prenatal period. This condition has an estimated incidence of 1 in 4000 live births and may be associated with genetic and structural anomalies, including trisomy 13, 18, and 21; Beckwith–Wiedemann syndrome; and cardiac, renal, gastrointestinal, limb, or central nervous system defects [1, 2]. Outcomes vary depending on definitions of findings (ruptured, small, or giant omphaloceles), pre- or postnatal identification, and diagnostic testing and imaging offered. While advances in surgical and neonatal care have improved survival of neonates with omphalocele, challenges with respiratory failure, prolonged intensive care stay, poor feeding and growth, and neurodevelopmental delay remain significant risks [3, 4].

It is critical to identify factors associated with adverse neonatal outcomes to improve counseling and optimize care of infants with prenatally diagnosed omphalocele. While earlier studies have focused on mortality, few have described predictors of early hospital outcomes of infants with omphalocele, particularly with the increased availability of

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fetal MRI and newer surgical approach with delayed closure, especially for larger defects [5]. The aim of this study was to evaluate prenatal characteristics and imaging, as well as neonatal factors associated with short-term adverse neonatal outcomes in a contemporary cohort of fetuses diagnosed with omphalocele at a single, referral center.

Methods

A retrospective review was conducted from a convenience sample of all cases of prenatally diagnosed omphalocele referred to the Fetal and Pregnancy Health Program at Lucile Packard Children's Hospital Stanford from 1 January 2009 to 31 December 2017 and entered into the Stanford University Institutional Review Board (IRB)-approved mother–fetus–baby-linked database. Subjects were excluded if diagnosis was revised to gastroschisis, hernia of the umbilical cord, or diagnosis other than omphalocele after additional prenatal imaging. From this cohort, we reviewed (i) maternal and fetal characteristics; (ii) antenatal imaging characteristics from ultrasound and fetal MRI studies; and (iii) neonatal outcome data.

Maternal, fetal, and neonatal clinical variables were collected from the electronic medical record. The prenatal diagnosis of suspected omphalocele was confirmed by a maternal–fetal medicine specialist (YB) reviewing stored ultrasound images and cine clips of the latest ultrasound exams. Ultrasound measurements, including abdominal wall defect to abdominal circumference ratio (AWD/AC) and abdominal wall defect to head circumference ratio (AWD/HC), were calculated by a maternal–fetal medicine specialist (YB) blinded to clinical outcomes. Using pre-defined thresholds [6], cases with AWD/AC ≥ 0.24 or AWD/HC ≥ 0.21 were determined. Giant omphalocele was defined by abdominal wall defect larger than 5-cm diameter and/or defect containing >75% of liver [7, 8]. Fetal MRI was offered, and when obtained, a pediatric radiologist (ER or RJ) measured lung volumes and calculated observed-to-expected fetal lung volume ratios (O/E FLV) based on published criteria for gestational age [9]. Cases with O/E FLV <50% were also identified based on previously reported thresholds [10].

Expectant mothers were also offered fetal echocardiography and genetic counseling for prenatal genetic testing, including karyotype and microarray by amniocentesis or limited information by non-invasive prenatal testing (NIPT), although not all elected to have these studies done. Information regarding genetic abnormalities and other congenital anomalies was collected; lung hypoplasia by fetal imaging or scoliosis associated with omphalocele were not included as congenital anomalies for the purposes of this analysis. Prenatal consultations with Neonatology and Pediatric General Surgery teams were offered along with planning for relocation for delivery at a tertiary care center. Cesarean section delivery at term gestation was planned if giant omphalocele or if the liver was found to be extracorporeal by antenatal imaging. The typical approach to omphalocele closure in the immediate neonatal period included compression dressings and facilitating epithelialization with silver sulfadiazine treatment, unless surgical closure was deemed necessary by the Pediatric Surgery team, such as for smaller-sized defects.

The primary adverse neonatal outcome was prospectively defined as death before discharge or prolonged length of stay (LOS), defined as highest quartile LOS by post-menstrual age. This LOS definition was utilized to best account for preterm births. Additional neonatal outcomes included approach to omphalocele closure, total duration of positive pressure respiratory support, time to reaching full enteral feeds, discharge on home oxygen, discharge on nasogastric or gastric-tube feeds, and suspected or blood culture-proven late sepsis (defined as treatment with antibiotics for at least 5 days from 7 days of age through discharge). Univariate analysis with Fisher's exact test or Welch two-sample *t*-test was conducted to detect associations between prenatal or early postnatal characteristics and the primary adverse neonatal outcome. Multivariate analyses of all significant characteristics ($p < 0.05$ on univariate analysis) were then conducted. All *p*-values were two-sided. Statistical analyses were performed using R software, version 3.4.4. This study was approved by the Stanford University IRB with waiver of consent.

Results

Of 63 cases of prenatally diagnosed omphalocele, 15 resulted in termination, 8 resulted in fetal demise, 7 were lost to follow-up before delivery, and 33 were live-born (Fig. 1). Median gestational age at time of fetal referral was 20 weeks (IQR 16–25 weeks). Twelve of 52 total cases with prenatal genetic testing done (23%) had abnormal results. Ten cases were diagnosed with trisomy 18 after amniocentesis or chorionic villus sampling (10/52 or 19%), but none were known to survive the fetal period (7 with termination of pregnancy, 2 with intrauterine fetal demise, and 1 lost to follow-up). One case had trisomy 13 with termination of pregnancy. Of live-born infants, all had detailed serial antenatal ultrasounds, 17 (52%) had a fetal MRI, and 29 (88%) consented to prenatal genetic testing. One live-born infant was diagnosed with Beckwith–Wiedemann syndrome (BWS) by prenatal genetic testing. An additional live-born infant had positive genetic testing for BWS sent postnatally. Both infants with BWS had isolated, non-giant omphaloceles.

Four (12%) of the 33 live-born infants died prior to discharge home. Further details about cause and age of

death are in Table 1. An additional nine surviving infants (27%) were in the highest quartile of length of hospital stay by post-menstrual age for a total of 13 (39%) with the primary adverse outcome (Table 1). For all live-born infants surviving to discharge, median length of stay was 21 days (IQR 8–71 days), with median post-menstrual age at discharge of 41 + 1/7 weeks (IQR 39 + 3/7–46 + 1/7 weeks). Two infants died after discharge at 127 and 559 days of age. These infants both had prolonged LOS and a neonatal course notable for acute and chronic respiratory failure and multiple episodes of sepsis. Both infants also had fetal MRI findings of small, narrow chest and observed to expected fetal lung volumes of <50%.

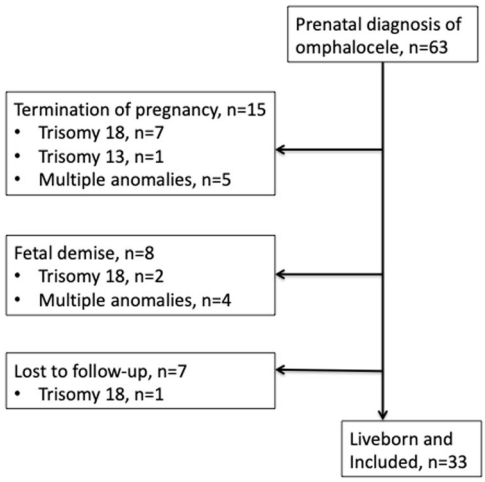

Fig. 1 Flow diagram of cohort with prenatally diagnosed omphalocele

Demographic and prenatal variables of live-born infants are shown in Table 2 along with fetal imaging characteristics. Infants with adverse outcome were more likely to be born of younger mothers (27 ± 6 vs. 33 ± 7 years, $p = 0.03$), but there was no difference in maternal conditions such as pre-eclampsia, diabetes, or chronic hypertension. The mean age at fetal MRI evaluation was 28 ± 5 weeks gestation (range 21–37 weeks). The last antenatal ultrasound examination was done at 33 ± 6 weeks gestation (range 19–39 weeks). From the last antenatal ultrasound, AWD/AC was associated with adverse outcome (0.20 ± 0.07 vs. 0.16 ± 0.04, $p = 0.05$). Using predetermined thresholds [6], cases with adverse outcome were more likely to have AWD/AC ratio ≥ 0.24 ($p = 0.02$) as well as AWD/HC ratio ≥ 0.21 ($p = 0.02$). Of those with normal outcomes, 19/20 (95%) had both ultrasound ratios below threshold, while of those with adverse outcome, 6/13 (46%) had either AWD/AC or AWD/HC over threshold. AWD/AC had sensitivity of 38% and specificity of 95%, while AWD/HC had sensitivity of 31% and specificity of 100%. Notably, the presence of an extracorporeal liver was not associated with adverse outcome ($p = 0.25$), nor was classification as a giant omphalocele ($p = 0.16$).

Fetal MRI characteristics demonstrated that observed to expected fetal lung volumes of < 50% were associated with adverse outcome (47% vs. 6%, $p = 0.02$). A subjective description of a small, narrow chest on fetal MRI was also more likely in infants with adverse outcome (47% vs. 18%, $p = 0.05$) (Fig. 2). Nine infants (53%) had O/E FLV < 50%, of which five ultimately died compared with no deaths in the group of infants with O/E FLV > 50%. Cases with low fetal lung volumes (O/E FLV < 50%) were more likely to

Table 1 Neonatal outcomes

Outcome	*n* (%) of live born ($N = 33$) or median (IQR)		
Death before discharge home		4 (12)	
Gestational age (weeks)	*Age at death (days)*	*Characteristics*	*Cause of death*
33	7	Giant omphalocele, small for gestational age, absent cavum septum pellucidum	Respiratory failure
34	26	Giant omphalocele, pulmonary hypoplasia, sepsis	Respiratory failure
38	1	Pentalogy of Cantrell, pulmonary hypoplasia	Respiratory failure after palliative care (< 2 h)
39	68	Cleft palate, dysmorphic facies, multiple brain anomalies (small vermis and brainstem, partial agenesis of corpus callosum, asymmetric ventricles)	Aspiration pneumonia, respiratory failure, central apnea after transition to palliative care
Median PMA at discharge, (IQR) (weeks)		41 + 1/7 (39 + 3/7–46 + 1/7)	
Median LOS, (IQR) (days)		21 (8–71)	
Death or prolonged LOS		13 (39%)	
Total days on positive pressure ventilation (median, IQR)		3 (0–26)	
Age at full enteral feeds (days) (median, IQR)		12 (5–18)	
Discharged on nasogastric or G-tube feeds		10 (30%)	
Discharged on oxygen		7 (21%)	

PMA post-menstrual age, *LOS* length of stay, *IQR* interquartile range

Patients who died before discharge were excluded in the calculation of median PMA at discharge and median LOS

Table 2 Factors associated with death or prolonged length of stay ($N = 33$)

Variable	Adverse outcome ($n = 13$)	Normal outcome ($n = 20$)	p-value
DEMOGRAPHICS/PRENATAL VARIABLES			
Maternal age (years)	**27.2 ± 6**	**32.8 ± 7**	**0.03**
Maternal race			
White	3 (9.1)	10 (30.3)	0.16
Hispanic	5 (15.2)	6 (18.2)	0.71
Asian	3 (9.1)	3 (9.1)	0.66
Other[a]	2 (6.1)	1 (3.0)	0.55
Other fetal anomalies	9 (27.3)	10 (30.3)	0.31
Cardiac anomaly	2 (15)	2 (10)	1
SGA (<10%ile)	3 (9.1)	0 (0)	0.05
Cesarean section delivery	11 (33.3)	17 (51.5)	1
FETAL IMAGING VARIABLES			
Antenatal ultrasound ($N = 33$)			
AWD/HC	0.17 ± 0.05	0.14 ± 0.03	0.1
AWD/AC	0.20 ± 0.07	0.16 ± 0.04	0.05
AWD/HC ≥ 0.21	**4 (12)**	**0 (0)**	**0.02**
AWD/AC ≥ 0.24	**5 (15)**	**1 (3)**	**0.02**
Extracorporeal liver	11 (33.3)	12 (36.4)	0.25
Giant omphalocele	9 (27.3)	8 (24.2)	0.16
Fetal MRI ($N = 17$)	9 (27.3)	8 (24.2)	0.16
O/E FLV < 50% on fetal MRI	**8 (47.1)**	**1 (5.9)**	**0.02**
Scoliosis	2 (11.8)	0 (0)	0.47
Small chest	8 (47.1)	3 (17.6)	0.05
Total lung volume (ml)	18.5 ± 9.5	32.0 ± 29.6	0.25
Right lung volume (ml)	8.7 ± 4.2	16.4 ± 16.0	0.23
Left lung volume (ml)	9.5 ± 6.2	16.9 ± 17.0	0.28
NEONATAL VARIABLES			
Male	9 (27.3)	9 (27.3)	0.28
<34 weeks gestational age	3 (9.1)	3 (9.1)	0.66
Mean gestational age (weeks)	36.2 ± 3.2	36.2 ± 3.8	1
Mean birth weight (g)	2646 ± 788	2779 ± 892	0.66
Median Apgar 1 min (IQR)	**4 (2–8)**	**8 (6–8)**	**0.04**
Median Apgar 5 min (IQR)	8 (5–9)	8 (8–9)	0.12
Need for initial mechanical ventilation	**11 (33.3)**	**8 (24.2)**	**0.02**
Primary surgical closure	4 (12.1)	7 (21.2)	1
Suspected or culture positive late sepsis	**9 (27.3)**	**3 (9.1)**	**0.003**

Results are mean ± SD or n (%)

AWD abdominal wall defect size, *AC* abdominal circumference, *HC* head circumference, *O/E FLV* observed/expected fetal lung volumes

[a]Other: includes African American, Native Hawaiian

Bold values are variables with $p < 0.05$ significance

require mechanical ventilation after birth (OR 8.9, 95% CI 0.9–449.9, $p = 0.05$). Moreover, 3/9 infants with O/E FLV < 50% required high frequency oscillatory ventilation or inhaled nitric oxide during their hospital course, and 3/6 that survived until discharge required tracheotomy or supplemental home oxygen use.

Additional neonatal characteristics associated with the primary adverse outcome are shown in Table 2. Median Apgar score at 1 min of age was lower in infants with adverse outcome compared with those with normal outcome (4 vs. 8, $p = 0.04$). Other neonatal characteristics associated with adverse outcome included initial need for mechanical ventilation for respiratory distress (33% vs. 24%, $p = 0.02$) and suspected or culture positive sepsis after 7 days of age (27% vs. 9%, $p = 0.003$). No cases of maternal chorioamnionitis were reported.

Other relevant patient variables were not found to be associated with the primary adverse outcome. The presence of other anomalies was detected in 19/33 (58%) of liveborns and included cardiac, renal, neurologic and skeletal anomalies, single umbilical artery, and OEIS complex. In eight cases, anomalies were diagnosed only in the postnatal period; these were skeletal anomalies, central nervous system abnormalities, facial dysmorphic features, dystrophic epidermolysis bullosa, two with aortic coarctation, and two with Beckwith–Wiedemann syndrome findings of macroglossia and renal abnormalities. Six infants were born preterm (ranging from 25 to 33 weeks gestational age) and 11 had primary surgical closure in the first week of life instead of delayed closure. Adverse outcome was not associated with approach to omphalocele closure or prematurity (< 34 weeks gestation). Thirteen infants had additional surgeries during their initial hospital course; four for inguinal hernia repair, one for broviac placement, and the remainder for surgeries related to other congenital anomalies. None required additional surgeries related to their omphalocele. Although all three small for gestational age (SGA) infants had an adverse outcome, SGA was not statistically significant ($p = 0.05$). Mode of delivery was not significant, and none of the omphaloceles ruptured at delivery. However, there were four emergent Cesarean section deliveries (31%) in the adverse outcome group compared with 2 (10%) in the normal outcome group.

When considering other neonatal outcomes, those with the primary adverse outcome also had more total days on positive pressure ventilation (median 26 days vs. 1 day, $p = 0.006$), older age at reaching full enteral feeds (median 15 days vs. 10 days, $p = 0.1$), and a greater likelihood of being discharged home on nasogastric or gastric-tube feeding if they survived to discharge (70% vs. 30%, $p = 0.01$).

Multivariate analysis of significant fetal and neonatal characteristics associated with death or prolonged LOS is shown in Table 3. If solely considering characteristics

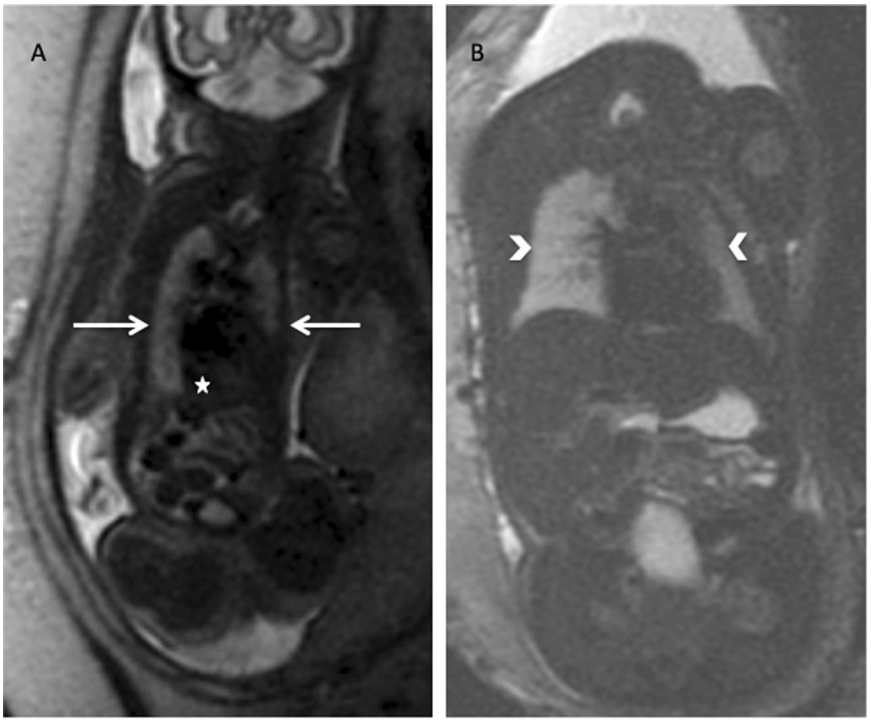

Fig. 2 **a** Fetal MRI done at 28 weeks gestation. Single shot T2 weighted sequence in the coronal plane demonstrates a narrow and elongated chest (arrows) and flattened diaphragm (star) due to traction from the giant omphalocele. The observed/expected fetal lung volume ratio measured by MRI was 30%. **b** Fetal MRI at similar gestational age demonstrating normal chest and lung volumes (arrowheads) with appropriately domed diaphragm

Table 3 Multivariate analysis of factors associated with adverse outcomes

	Odds ratio	95% Confidence interval	*p*-value
Prenatal variables (N = 33)			
O/E FLV < 50% on fetal MRI	34.4	2.8–422.4	0.006
Ultrasound ratio AWD/AC ≥ 0.24	1.67	0.05–61.2	0.78
Ultrasound ratio AWD/HC ≥ 0.21	>100	0-infinity	0.99
Prenatal and postnatal variables (N = 33)			
O/E FLV < 50% on fetal MRI	19.5	0.6–622.7	0.09
Ultrasound ratio AWD/AC ≥ 0.24	2.8	0.01–520	0.70
Ultrasound ratio AWD/HC ≥ 0.21	>100	0-infinity	1
Initial need for mechanical ventilation	7.3	0.3–161.2	0.21
Late sepsis (suspected or culture positive)	1.5	0.1–28.3	0.78
1-min APGAR	0.97	0.6–1.6	0.91

AWD abdominal wall defect size, *AC* abdominal circumference, *HC* head circumference, *O/E FLV* observed/expected fetal lung volumes

available prenatally, only low fetal lung volumes by MRI (O/E FLV < 50%) were significant for adverse outcome (OR 34, 95% CI 3–422, $p = 0.006$). When considering both significant prenatal and early postnatal factors, cases with low fetal lung volumes had a greater odds of adverse outcome, although no longer statistically significant (OR 20, 95% CI 0.6–623, $p = 0.09$).

Discussion

In our cohort of prenatally diagnosed cases of omphalocele, no cases with aneuploidy survived the fetal period. For live-born infants, over half (58%) had other congenital anomalies, but neonatal mortality was low (12%). The primary outcome of death or prolonged length of hospital stay was significantly associated with low fetal lung volumes determined by prenatal MRI, while no differences were found by traditional prenatal imaging parameters such as size of the defect and liver herniation (aka a "giant omphalocele"). Our findings are similar to other published contemporary omphalocele cohorts. A large multicenter neonatal database found a 35% rate of additional anomalies and 18% mortality rate prior to hospital discharge for infants with omphalocele [1], whereas other single center studies similar to ours have found lower mortality rates of 9–12% [11]. Discrepancies among studies may be due to increased proportion of giant omphaloceles or cases with additional anomalies contributing to mortality.

While the presence of other congenital anomalies was not found to be associated with the primary adverse outcome in our study, other investigators have described associated major anomalies as being the strongest predictor of mortality [12, 13] and morbidity, including length of intubation and hospital stay [14]. Differences are likely attributed to heterogeneous definitions of a congenital anomaly. Other studies have classified an anomaly as a defect requiring immediate medical or surgical management, may or may not have included chromosomal anomalies, and may have varied approaches to which defects are considered a consequence of the omphalocele itself (e.g., pulmonary hypoplasia, kyphosis, or intestinal malrotation) [12, 14, 15]. Further analysis of our data after exclusion of minor anomalies such as single umbilical artery, pelviectasis, and facial dysmorphic features still did not yield a statistically significant association between anomalies and adverse outcome. Notably, however, other congenital anomalies were not diagnosed in the prenatal period in 8/19 (42%) of cases despite serial antenatal ultrasound imaging, highlighting the necessity of postnatal surveillance for additional anomalies, which may affect prognosis [11, 15].

The presence of early neonatal risk factors may further stratify infants into higher risk groups for mortality and prolonged length of stay. The need for mechanical ventilation after birth was a significant neonatal risk for adverse outcome and is associated with low fetal lung volumes by MRI. Respiratory insufficiency at birth has previously been described as a predictor of mortality independent of gestational age, presence of other anomalies, or size of omphalocele [16, 17] and possibly related to pulmonary hypoplasia and/or pulmonary hypertension. Our study also found that suspected or culture positive sepsis after 7 days of age was a significant neonatal risk for adverse outcome. In several other small cohorts of patients with giant omphalocele, sepsis has been reported as a frequent complication and was associated with mortality [18, 19]. Targeting sepsis reduction in the omphalocele population may lead to improved outcomes. Our study also found a lack of association between prematurity or approach to omphalocele closure and adverse outcomes. Other investigators have suggested that prematurity may be a predictor of mortality [19], however, our study did not demonstrate this effect, and we also adjusted for prematurity for length of stay by considering post-menstrual age at the time of discharge. Others have also shown that delayed closure of omphalocele does not lead to an increase in morbidity or mortality [14, 20] and permits time for thoracic and abdominal growth. Our study supports this concept, as there was no difference in outcomes despite the majority of early closure cases being infants with small or isolated defects.

Pulmonary hypertension predicts mortality in the omphalocele population [17] and associated pulmonary hypoplasia may be best predicted on fetal MRI. Similar to fetuses with congenital diaphragmatic hernia [21], decreased lung volumes as measured on fetal MRI were found to be associated with adverse outcome. Danzer et al. [10] also reported that the fetal MRI characteristic of observed to expected total lung volumes <50% were predictive of increased postnatal morbidity in a cohort of 17 infants with giant omphalocele. Small and narrow thoracic chest width may additionally contribute to respiratory dysfunction in the postnatal period, with borderline significance from our study. These skeletal measurements were not consistently reported on fetal MRI and were often described subjectively, but could provide additional prognostic information. Others have described antenatal ultrasound parameters of AWD/AC or AWD/HC as predictive of poor outcome with thresholds of 0.24 and 0.21, respectively, and independent of gestational age at time of measurement [6, 22, 23]. We also found both ultrasound ratios to be associated with adverse outcomes using these previously defined thresholds, although in a multivariate model, fetal MRI was a better predictive characteristic and the only statistically significant prenatal variable. As ultrasound is more readily accessible than fetal MRI in some centers, the AWD/AC ratio and AWD/HC ratio may be useful alternatives to predicting outcomes from imaging.

This study was limited based on its smaller sample size and retrospective design at a single, subspecialty referral center with the potential for selection bias and confounding. The study was also not powered for multivariate analysis. Our focus on live births is biased toward cases that are less severe compared with those resulting in termination or pregnancy loss. Not all subjects received a fetal MRI, limiting conclusions about the predictive ability of MRI measures on outcomes. However, our findings align with what has been reported in the fetal MRI literature about the utility of calculated total lung volumes in similar-sized studies [10]. Further sub-analyses by size of omphalocele and presence of anomalies was not feasible due to smaller numbers. Echocardiographic measurements to establish pulmonary hypertension as a related complication will be analyzed in a future study. Longer-term survival and complications beyond hospital discharge also were not investigated.

Conclusions

In conclusion, this single center study, including patients from the current era demonstrated that prenatally diagnosed neonates with omphalocele generally had a low overall mortality rate, but a greater likelihood of associated congenital anomalies. Live-born infants were more likely to have an adverse outcome defined as death or prolonged length of hospital stay if they were prenatally identified with low fetal lung volumes. Determining fetal lung volumes may assist with prenatal counseling and better inform

families of the risk for adverse outcomes. In an era of increasing interventions, lung hypoplasia may be more limiting than the presence of other congenital anomalies, and future investigation should focus on the optimal timing and ideal assessment of lung volumes or thoracic size for prenatally diagnosed omphalocele.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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