Received: 1 April 2019 | Revised: 21 June 2019 | Accepted: 21 July 2019

DOI: 10.1002/pd.5546

ORIGINAL ARTICLE

WILEY PRENATAL DIAGNOSIS

The validity of the viscero-abdominal disproportion ratio for type of surgical closure in all fetuses with an omphalocele

Nina C.J. Peters[1] | Annelieke Hijkoop[2] | Rosan L. Lechner[2] | Alex J. Eggink[1] | Joost van Rosmalen[3] | Dick Tibboel[2] | René M.H. Wijnen[2] | Hanneke IJsselstijn[2] | Titia E. Cohen-Overbeek[1]

[1] Department of Obstetrics and Gynaecology, Division of Obstetrics and Fetal Medicine, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

[2] Department of Paediatric Surgery and Paediatric Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

[3] Department of Biostatistics, Erasmus MC, Rotterdam, The Netherlands

Correspondence
Nina C. J. Peters, Department of Obstetrics and Gynaecology, Division of Obstetrics and Fetal Medicine, Erasmus MC-Sophia Children's Hospital, University Medical Centre Rotterdam, Room Na-16, PO box 2060, NL-3000 CA. Rotterdam, The Netherlands.
Email: n.peters@erasmusmc.nl

Abstract

Objective: To determine the predictive value of the fetal omphalocele circumference/abdominal circumference (OC/AC) ratio for type of surgical closure and survival and to describe the trajectory of OC/AC ratio throughout gestation.

Methods: This cohort study included all live-born infants prenatally diagnosed with an omphalocele in our tertiary centre (2000–2017) with an intention to treat. The OC/AC ratio and liver position were determined using 2D ultrasound at three periods during gestation (11–16, 17–26, and/or 30–38 weeks). Primary outcome was type of closure; secondary outcome was survival. In the secondary analyses, the predictive value of the OC/AC-ratio trend for type of closure and survival was assessed.

Results: Primary closure was performed in 37/63 (59%) infants, and 54/63 (86%) survived. The OC/AC ratio was predictive for type of closure and survival in all periods. Optimal cut-off values for predicting closure decreased throughout gestation from 0.69 (11–16 weeks) to 0.63 (30–38 weeks). Repeated OC/AC-ratio measurements were available in 33 (73%) fetuses. The trend of the OC/AC ratio throughout gestation was not significantly associated with type of closure. All infants without liver herniation underwent primary closure.

Conclusion: Type of omphalocele surgical closure and survival can be predicted prenatally on the basis of the OC/AC ratio and liver herniation independent of associated anomalies.

Learning objective: The reader will be able to use the OC/AC ratio throughout gestation in all omphalocele cases for prediction of type of closure and survival and thus patient counselling.

1 | INTRODUCTION

An omphalocele is a congenital anomaly characterized by herniation of the abdominal viscera through the abdominal wall at the umbilicus covered by a membrane.[1] It is reported to occur in 1 to 2 per 10 000 live births.[2] Multiple congenital anomalies (MCAs) are observed in 30% to 70% of fetuses with an omphalocele, and chromosomal abnormalities are present in 10% to 30%.[1,3,4] Infants with MCA or chromosomal abnormalities carry a significantly higher risk of comorbidity than those with an isolated omphalocele.[1,3-6] In the Netherlands, in up to 74% of cases, depending on the presence of associated anomalies and gestational age at diagnosis, the pregnancy is terminated.[7]

A small (or minor) omphalocele can be closed primarily, ie, within 48 hours after birth. If the postnatal defect size equals or is larger than 5 cm, with liver (partly) protruding,[8] closure is usually delayed in view of the viscero-abdominal disproportion.[9] These infants with a "giant" omphalocele are at risk for chronic lung disease (CLD), feeding problems, prolonged hospital stay, and a lower chance of survival, besides the difficulty of closure of the abdominal wall defect.[10-13]

Today, around 90% of omphaloceles and most of the additional anomalies are detected by prenatal ultrasound from 11 week gestation onwards.[2,14] Previous studies have shown that ultrasound parameters can predict postnatal outcome in fetuses with an omphalocele.[15-19] More recent studies showed that the ratio between the omphalocele circumference (OC) and the abdominal circumference (AC)—the OC/AC ratio—predicts the method of postnatal surgical closure.[17,20] These studies were mostly limited to single measurements and infants whose omphalocele was assumed to be isolated at prenatal ultrasound. Still, in approximately one-third of such cases, additional anomalies are detected after birth.[4,21] These additional anomalies may influence postnatal outcome, including type of closure.

The primary aim of this study was to evaluate the predictive value of the OC/AC ratio as either cross-sectional or a repeated measurement in all fetuses with an omphalocele (isolated and non-isolated) and a postnatal intention to treat. Secondarily, we examined the predictive value of the OC/AC ratio for survival before and after birth.

What's already known about this topic?

- In fetuses with an isolated omphalocele, the OC/AC ratio is less than 24 weeks; gestation is of predictive value for postnatal type of closure.

What does this study add?

- The OC/AC ratio is predictive for type of surgical closure and survival in all fetuses with an omphalocele.
- This report is the first concerning the trend of the OC/AC ratio throughout gestation.
- The OC/AC ratio best predicts type of closure and survival in the third trimester of pregnancy.

2 | METHODS

2.1 | Study population

We analysed prospectively stored data of live-born infants, who were prenatally diagnosed with an omphalocele in our tertiary referral centre from January 2000 up to and including December 2017. On a postnatal intention-to-treat basis, those infants were included for whom at least one prenatal ultrasound image was available. Fetuses with a rare abdominal wall defect (eg, body stalk anomaly, pentalogy of Cantrell, or amniotic band syndrome) and infants lost to follow-up were excluded. Data of pregnancies resulting in intrauterine fetal death (IUFD) or neonatal death (NND; defined as death during the first 28 days) were stored in a separate database. Fourteen of the included isolated cases have previously been studied to validate the OC/AC ratio measured prior to 24-week gestation.[4,17] The Medical Ethical Review Board waived approval because data obtained during routine care were retrospectively analysed (MEC-2015-308).

2.2 | Prenatal measurements and parameters

The OC and AC were measured, if possible, at three time periods during gestation: at the beginning of the second trimester (11- to 16-week gestation; US1), mid-second trimester (17- to 26-week gestation; US2), and in the third trimester (30- to 38-week gestation; US3). Based on availability of data, the OC/AC ratios were calculated according to a previously described method.[17] We included three examples of third trimester measurements of the OC/AC ratio as Figure S1. All measurements were performed in retrospect by two experienced physicians (TECO and NCJP), who were unaware of postnatal outcome. We retrieved data on content of the omphalocele, presence of fetal growth restriction, polyhydramnios (defined as an amniotic fluid index [AFI] of >24 cm), presence of chromosomal abnormalities, and MCA. Those MCAs that required surgery or multiple follow-up visits were regarded as major.

2.3 | Postnatal parameters

We retrieved data on delivery mode, gestational age (GA) at delivery, birth weight, and Apgar score at 5 minutes. Preterm birth was defined as delivery prior to 37-week gestation. The method of closure was recorded as either primary or delayed. Delayed treatment included both initial epithelization and later surgical closure.[9,10] Additional data retrieved were the durations of parenteral feeding, length of hospital stay (LOS), and supplemental oxygen dependency during the initial hospital stay after birth as well as the presence of CLD, defined as oxygen supplementation for at least 28 days.[10,22] A giant omphalocele was defined as a postnatal defect size of at least 5 cm, with liver (partly) protruding. Survival was defined as survival until at least 1 year of age. Infant death is defined as a death greater than 28 days after birth.

2.4 | Statistical analysis

Patient characteristics are described as number (%) for categorical data and median (interquartile range, IQR) for continuous data.

Prenatal and postnatal parameters were compared between neonates with primary and delayed closure and between survivors and nonsurvivors using the chi-square or Fisher exact tests (nominal or ordinal variables) or Mann–Whitney tests (continuous variables). The mean OC/AC ratios at the three time periods were compared using a general linear model that accounts for the within-subject correlations. The association between OC/AC ratio at these three time periods and type of closure, survival, or presence of CLD was evaluated using univariable logistic regression analysis. The association between OC/AC ratio at these three time periods and LOS was evaluated using Spearman's rank correlation coefficient.

The intraclass correlation coefficient (ICC) was used to quantify the interobserver agreement. TECO and NCJP both measured the OC/AC ratio in 20 randomly selected cases, where they were blinded to each other's result. For good agreement, the ICC has to be .75, and for excellent agreement, the ICC has to be higher than .90. The ICC was calculated in a two-way mixed model with absolute agreement and reported as single measures.

To calculate the predictive value of the OC/AC ratio for type of postnatal closure and for survival, a receiver-operating characteristic (ROC) curve was made for each time period separately. Data are presented as area under the curve (AUC) with a 95% confidence interval (95% CI). The cut-off with the highest value of the Youden index (sensitivity plus specificity minus 1) was regarded as the most suitable.

To examine the trend in the OC/AC ratio throughout gestation, we performed a linear regression of the OC/AC ratio at the three time periods for each patient separately, with GA (coded as a continuous variable) as the only independent variable. To summarize the longitudinal data of the OC/AC ratio, we used an estimated level (intercept in the linear regression) and time trend (slope in the linear regression). This analysis concerned only fetuses for whom two or three OC/AC ratios were available. The resulting estimates of the intercept and slope in the linear regressions served as independent variables in logistic regressions for type of closure. The slope is calculated per 1-day difference in gestation.

Logistic regressions were performed to predict type of closure and survival rate only in fetuses with liver herniation with the OC/AC ratio as independent variable, for the time periods US2 and US3 separately.

For the purpose of the secondary aim, ie, to examine the predictive value of the OC/AC ratio for survival before birth, we included data of fetuses with an IUFD or NND—referred to as "fetuses without intention to treat." Those who were live-born and survived past 1 month (ie, not an IUFD or NND) are referred to as "fetuses with an intention to treat" for this analysis.

All odd ratios are related to the occurrence of either a delayed closure when the outcome is type of postnatal surgical closure or mortality when the outcome is survival. All calculations were performed using SPSS version 21.0 for Windows and Windows Excel 2010. A two-sided p value of less than .05 was considered statistically significant.

3 | RESULTS

3.1 | Study population

Sixty-three live-born infants with an intention to treat were eligible for analyses (Figure 1). Primary closure had been performed in 37 (59%) infants. Fifty-four (86%) infants survived. The OC/AC ratio could be calculated for 22 fetuses at US1, for 50 at US2, and for 58 at US3. Two or three OC/AC ratios were available for 48 (76%) fetuses. The required image for measurement of the OC/AC ratio was not available for two fetuses at US1 and two fetuses at US3. There were no differences between the assessments of liver location (extra abdominal vs intra-abdominal) at the different time periods per fetus. Interobserver agreement calculations resulted in an ICC of .966 (95% CI, 0.917–0.986), representing excellent agreement. Patient characteristics are summarized in Table 1.

Additional anomalies were diagnosed in 19/63 (30%) of fetuses in the prenatal period. In nine out of 44 (20%) cases where the omphalocele was assumed isolated, additional anomalies were detected after birth. In six of these cases, the anomalies were major (Table 2). Eleven fetuses were diagnosed with a clinically significant syndrome and/or chromosomal abnormality; nine of them had Beckwidth-Wiedemann syndrome (BWS). The OC/AC ratio in these fetuses ranged from 0.20 to 0.63 at US2 or US3. In 10 (91%) cases, there was no herniation of the liver through the defect (p = .006 compared with fetuses without a syndrome or chromosomal abnormality). In the case with liver herniation, only a very small slip of liver was present in the omphalocele. In all cases with a syndrome or chromosomal abnormality, a primary closure was performed (p = .002, compared with fetuses without a syndrome or chromosomal abnormality). Three (33%) of the nine fetuses with BWS had shown polyhydramnios.

3.2 | Type of surgical closure

At all three time periods, the OC/AC ratio was significantly positively associated with the probability of requiring a delayed closure (Figure 2 , Table S1 for logistic regression). Based on ROC curve analysis, the type of closure was predicted correctly by the OC/AC ratio with optimal cut-off values of 0.69 at US1 (sensitivity 0.93 and specificity 0.90; AUC 0.96, 0.88–1.00; p < .001), 0.66 at US2 (sensitivity 0.88 and specificity 0.93; AUC 0.98, 0.95–1.00; p < .001), and 0.63 at US3 (sensitivity 0.95 and specificity 0.94; AUC 0.98, 0.95–1.00; p < .001) (Figure 3).

The mean OC/AC ratio differed significantly between the three time periods (p = .002), showing a decreasing trend throughout gestation. On the basis of the different optimal cut-offs per time period, the prediction of the type of closure at the first time period did not change for 43/48 (90%) fetuses for whom multiple OC/AC ratios were

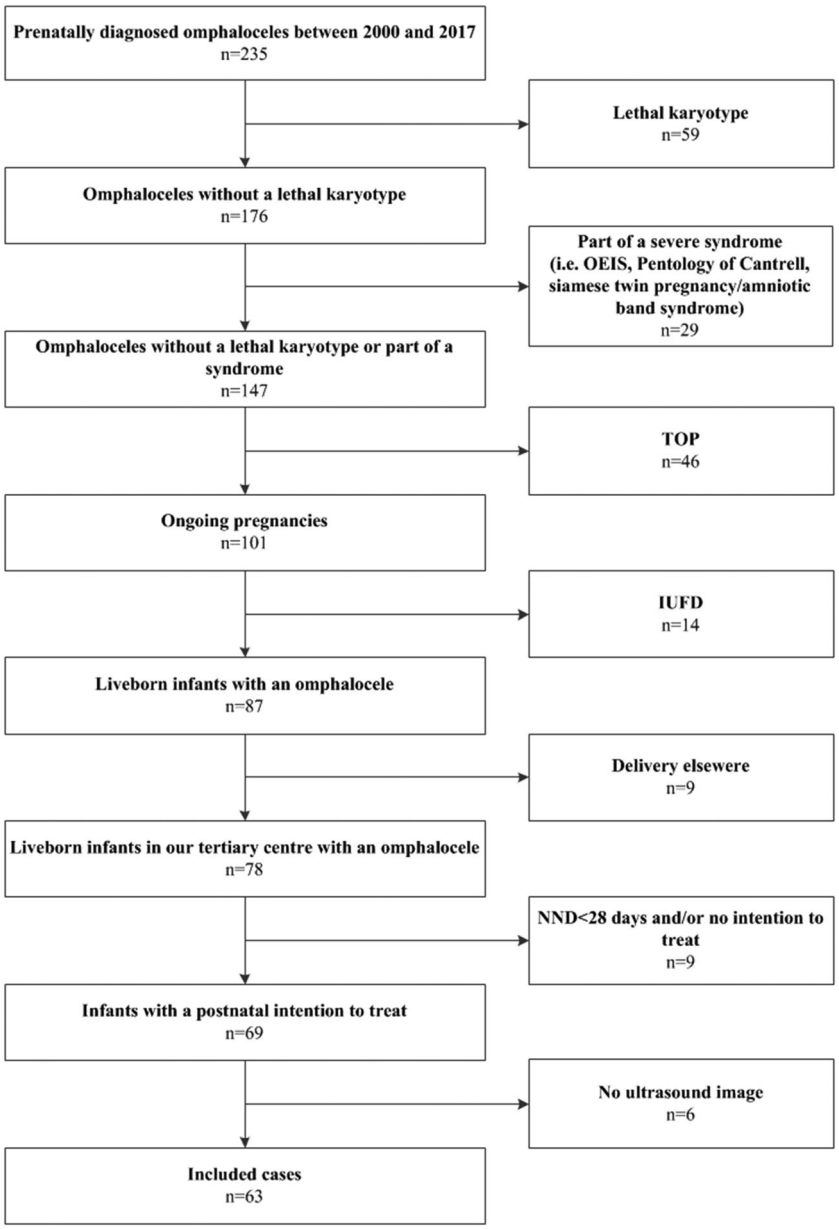

FIGURE 1 Flowchart of inclusion

available. The type of closure would have been predicted correctly at all time periods for 42/48 (88%) fetuses but incorrectly for one fetus (primary closure predicted; delayed closure performed). In the remaining five fetuses, the predicted method of closure differed between the time periods; in four out of five, a primary closure was performed.

With the use of multivariable logistic regression analyses, we found a significant association between the intercept of the OC/AC ratio and type of closure (OR 1.31; p = .006) but not for the slope (OR 0.82; p = .79), ie, no association was found between the trend in OC/AC ratio throughout gestation and type of postnatal closure (Figure S2).

The presence of MCA prenatally was found predictive of type of surgical closure (p = .02), and the presence of MCA postnatally was not significantly predictive of type of surgical closure (p = .18). In the group of infants with delayed closure, we found a significantly lower median Apgar score at 5 minutes, longer LOS, more frequent CLD, more often a giant omphalocele, and worse survival rates compared with infants who underwent primary closure (Table 1). With the use of logistic regression analysis, we found a significant association between the OC/AC ratio at US2 and US3 and presence of CLD (p = .01 and p = .003, respectively). With the use of Spearman's rank correlation, we also found a significant correlation between the OC/AC ratio at US2 and US3 and LOS (p < .001 and p < .001, respectively).

3.3 | Liver herniation

The omphalocele was closed primarily in all 32 infants without liver herniation, and 31 infants survived. Not having liver herniation, independent of the OC/AC ratio, was a perfect predictor for primary closure. We selected only fetuses with liver herniation (n = 31) for the logistic regression analysis. The OC/AC ratio was available for 15 fetuses at US1, for 27 at US2, and for 27 at US3. Two or three

TABLE 1 Patient characteristics

	Primary Closure (n = 37)	Delayed Closure (n = 26)	p value
Prenatal parameters			
US 11–16 weeks			
GA (w^{+d})	13^{+1} (12^{+4}–15^{+4})	16^{+1} (13^{+5}–16^{+6})	**.02**
OC/AC ratio (n = 22; P = 9/D = 13)	0.51 (0.44–0.68)	0.94 (0.79–1.00)	**<.001**
Liver herniation (n = 21; P = 8/D = 13)	2 (25)	13 (100)	**.001**
US 18–26 weeks			
GA (w^{+d})	20^{+4} (20^{+0}–21^{+5})	20^{+5} (19^{+5}–21^{+2})	.63
OC/AC ratio (n = 50, P = 28/D = 22)	0.46 (0.30–0.56)	0.84 (0.76–0.92)	**<.001**
Liver herniation (n = 51, P = 28/D = 23)	5 (18)	23 (100)	**<.001**
US 30–38 weeks			
GA (w^{+d})	31^{+4} (30^{+4}–32^{+1})	31^{+1} (30^{+1}–32^{+0})	.58
OC/AC ratio (n = 58, P = 36/D = 22)	0.40 (0.32–0.46)	0.77 (0.72–0.88)	**<.001**
Liver herniation (n = 58, P = 35/D = 23)	5 (14)	23 (100)	**<.001**
Liver herniation	5 (14)	26 (100)	**<.001**
Isolated	23 (62)	23 (89)	**.02**
Postnatal parameters			
GA at delivery (w^{+d})	38^{+1} (36^{+3}–38^{+6})	38^{+3} (35^{+6}–38^{+6})	.93
Delivery <32-week GA	3 (8)	3 (12)	.65
Spontaneous vaginal delivery	25 (68)	15 (58)	.42
Apgar score at 5 min	9 (8–10)	8 (6–9)	**.002**
Birthweight (g)	2960 (2433–3330)	2815 (1994–3378)	.40
Gender: female	21 (57)	12 (46)	.41
Isolated	19 (51)	17 (66)	.19
Giant omphalocele	2 (5)	24 (92)	**<.001**
Survival	36 (97)	18 (69)	**.002**
CLD	7 (19)	15 (58)	**.002**
LOS (d)	10 (7–35)	52 (19–107)	**<.001**

Note. Data are presented as median (interquartile range) or numbers (%). Statistical significance was tested via the chi-square/Fisher exact test (nominal or ordinal variables) or Mann–Whitney U test (continuous variables). Per US period, the number of cases (n) are described per analysis for the total group and per type of closure, where the P represents primary closure and the D represents delayed closure. A giant omphalocele is defined as a postnatal defect size of at least 5 cm, with liver included. Survival was defined as survival until at least 1 year of age.

The statistically significant results (p-value <0.05) are printed in bold.

Abbreviations: CLD, chronic lung disease defined as need for supplemental oxygen for greater than or equal to 28 days; d, days; GA, gestational age; g, grams; LOS, length of initial hospital stay; OC/AC ratio, omphalocele circumference/abdominal circumference ratio; US, ultrasound; w^{+d}, weeks + days.

measurements were available for 26/31. We found a statistically significant difference between the OC/AC ratio and type of surgical closure at both US2 (p = .001) and US3 (p = .04). The number of cases at US1 was too small for a meaningful statistical analysis. Since the parental counselling period coincides with US2, we designed a flowchart for prediction of type of closure and survival based on OC/AC ratio at US2 (n = 59). In 5/27 (21%) infants with an available OC/AC ratio at US2 and herniated liver, the defect was closed primarily; they all survived. All of these infants had an OC/AC ratio < 0.76 at US2 and a relatively large defect diameter, which enabled an uncomplicated return of the abdominal organs back into the abdominal cavity. The other 22 all required delayed closure, and 17 (77%) survived (Figure 4).

3.4 | Survival

Separate ROC analyses (data not shown) for each of the three-measurement time periods revealed a statistically significant negative association between the OC/AC ratio and survival at US2 and US3.

TABLE 2 Omphalocele cases with additional anomalies detected prenatally and postnatally

OC/AC Ratio US1	OC/AC Ratio US2	OC/AC Ratio US3	Survival	Prenatal Liver	Type of Closure	Prenatal Anomalies	Postnatal Anomalies
	0.31	0.4	Yes	No	Primary	Suspicion of BWS	BWS
	0.53	0.44	Yes	No	Primary	Suspicion of BWS	BWS
		0.46	Yes	No	Primary	Suspicion of BWS	BWS, naevues flammeus glabella eyelid
	0.56	0.61	Yes	No	Primary	Suspicion of BWS	BWS
	0.63	0.61	Yes	No	Primary	Suspicion of BWS	BWS
0.51	0.2	0.22	Yes	No	Primary	mVSD, suspicion of CoAo, X-linked ALAS2 mutatie[c]	Bicuspid aorticvalve, X-linked ALAS2 mutatie
		0.29	Yes	No	Primary	Multicystic left kidney	BWS, unilateral kidney agenesis/ urethrocystocele, mPVS
0.33	0.49	0.4	Yes	No	Primary	Bilateral schisis, ToF, Blake's pouch, SUA	Bilateral schisis, ToF, Blake's pouch[d]
	0.52	0.65	No	No	Primary	AVSD, ToF, suspicion of small intestine atresia	AVSD, ToF, TAPVR, hiatus hernia, asplenia, UPJ stenosis
	0.56		Yes	No	Primary	SUA, Paternal microdeletion 16p13.11	Paternal microdeletion
	0.72	0.42	Yes	No	Primary	Turner syndrome[e]	Turner syndrome[e]
		0.78	No	Yes	Delayed	Dilated right atrium (cardiomegalie)	Dilated right atrium and ventricle
0.8	0.66	0.85	No	Yes	Delayed	Postaxial polydactyly[a]	Postaxial polydactyly
	0.37	0.35	Yes	Yes	Primary	Femurlength <p5	BWS, soft palate schisis
		0.39	Yes	No	Primary	Suspicion of small intestine atresia	Small intestine atresia, bilateral polydactyly
		0.5	Yes	No	Primary	Suspicion of BWS	BWS, bowel volvulus
	0.74	0.65	Yes	Yes	Delayed	Thoracic situs inversus, ascites	Dextrocardia, ASD, VSD, ODB, desmoid torticollis
0.96	0.81		Yes	Yes	Delayed	SUA with umbilical cord cyst	Hydro-urether and hydronephrosis, ASD
	0.9	0.75	Yes	Yes	Delayed	Narrow thorax, dilated stomach	Bicuspid aorticvalve with stenosis/ insufficience
0.46	0.3	0.32	Yes	No	Primary	-	Pierre Robin, sliding hernia
	0.37	0.31	Yes	No	Primary	-	BWS[f]
		0.4	Yes	No	Primary	-	Clasped thumb
0.52	0.56	0.42	Yes	No	Primary	-	BWS, two mVSDs[f]
	0.66	0.74	Yes	Yes	Primary	-	Mild pelvic dysplasia[b]
0.89	0.81	0.78	Yes	Yes	Delayed	-	Aplasia cutis congenita, Morgagni hernia, ASD type 2[f]

(Continues)

TABLE 2 (Continued)

OC/AC Ratio US1	OC/AC Ratio US2	OC/AC Ratio US3	Survival	Prenatal Liver	Type of Closure	Prenatal Anomalies	Postnatal Anomalies
0.76	0.91	0.73	No	Yes	Delayed	-	Large pVSD with overriding aorta, ODB[f]
1	1.05		No	Yes	Delayed	-	Small ASD and VSD (clinically not relevant), CCA[f]
		1.11	No	Yes	Delayed	-	ToF, oesophageal atresia with fistula[f]

Note. Cases are ranked by concordance between prenatal and postnatal associated anomalies, severity of the anomalies, and OC/AC-ratio.

Abbreviations: ASD, atrial septal defect; AVSD, atrial ventricular septal defect; BWS, Beckwith-Wiedemann syndrome; CCA, corpus callosum agenesis; CoAo, Coarctation Aortae; LV and RV, left ventricle and right ventricle; MCA, multipel congenital anomalies; mPVS, mild pulmonary valve stenosis; mVSD, musculous ventricular septal defect; NT, nuchal translucency; ODB, open Ductus Botalli; pVSD, perimembranous ventricular septal defect; sIUGR, selective intra uterine growth restriction; SUA, single umbilical artery; TAPVR, total anomalous pulmonary venous return; ToF, Tetralogy of Fallot; UPJ, uteropelvic junction; VSD, ventricular septal defect.

[a]DiTri triplet.

[b]Monochorionic twin pregnancy, sIUGR.

[c]Mutation causing congenital sideroblastic anemia.

[d]CHARGE-syndrome.

[e]Prenatal with MCA: enlarged NT 4.1 mm, suspicion of CoAo with LV < RV, dilated bowel, IUGR, and postnatal with MCA: CoAo, bicuspid aortic valve, bilateral dilated renal pelvis, dysplastic ears.

[f]Fetus prenatally assumed isolated with postnatally major associated congenital anomalies.

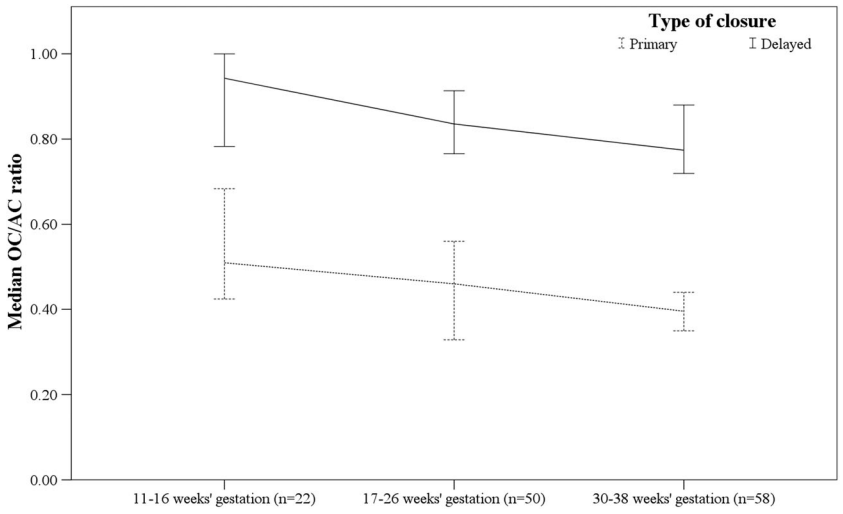

FIGURE 2 The omphalocele circumference/abdominal circumference (OC/AC) ratio throughout gestation per type of postnatal closure

The ROC at US1 had an AUC of 0.72 (with a 95% CI of 0.48–0.96; $p = .15$), at US2 an AUC of 0.81 (with a 95% CI of 0.61–1.00; $p = .01$), and at US3 an AUC of 0.89 (with a 95% CI of 0.79–0.98; $p = .001$).

Thirty-six (97%) of the 37 infants who underwent primary closure of the defect survived. One infant who did not survive had MCA, including a congenital heart defect with a total abnormal pulmonary venous return and severe insufficiencies over the atrioventricular valves. All nonsurvivors ($n = 9$) had CLD, and eight (89%) of them showed herniation of the liver.

In univariable logistic regression analyses, we found a significant association between the slope (OR 13.9 with a 95% CI of 2.13–91.18; $p = .006$) of the OC/AC ratio for survival and for the intercept (OR 1.07 with a 95% CI of 1.01–1.13; $p = .015$). Patient numbers were insufficient for multivariable analysis. In fetuses who survived, the decline in OC/AC ratio throughout gestation was steeper than in fetuses who did not survive, especially between US1 and US2 (Figure S3).

3.5 | IUFD and NND

In a secondary analysis of data of 11 fetuses, we evaluated whether the OC/AC ratio of IUFD (n = 9) or NND ($n = 2$) differed from that of live-born fetuses who survived at least 28 days, ie, fetuses with an intention to treat (Figure S4). For four out of nine IUFD cases, no

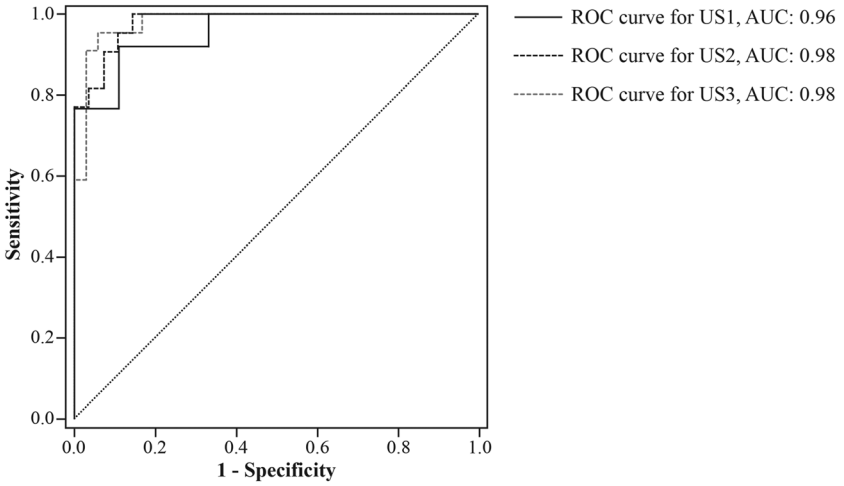

FIGURE 3 Receiver-operating characteristic (ROC) analysis of the omphalocele circumference/abdominal circumference (OC/AC) ratio at the different time periods for type of closure

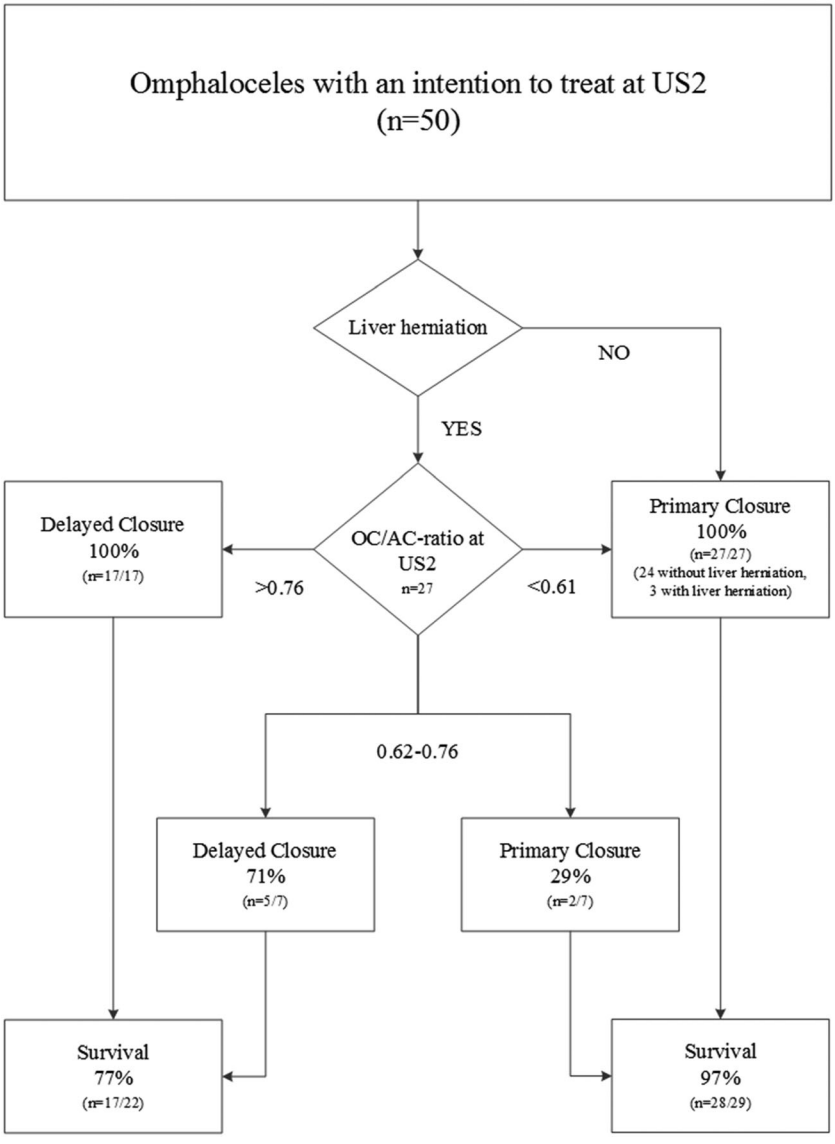

FIGURE 4 Counselling flowchart for type of surgical closure and survival rate according to prenatal liver position and the omphalocele circumference/abdominal circumference (OC/AC) ratio in fetuses with an omphalocele and an intention to treat

cause for the intrauterine demise was found other than the presence of an omphalocele. For the remaining five cases, other factors next to the omphalocele contributed to the cause of death (Table S2). The median (IQR) OC/AC ratio at US1 was 0.74 (0.50–0.91) and at US2 0.55 (0.48–0.73). Five of 11 (46%) fetuses had liver herniation. The two NND cases were born at 27- and 28-week GA. The median

OC/AC ratios of the IUFD or NND cases at US1 or US2 were not statistically different from those of fetuses with an intention to treat, $p = .76$ and $p = .75$, respectively.

4 | DISCUSSION

In this cohort of fetuses with an omphalocele, the OC/AC ratio throughout the second and third trimesters of pregnancy proved an important determining factor for the prediction of both type of postnatal surgical closure and survival. The OC/AC ratio decreased significantly throughout gestation, resulting in different cut-offs during gestation for prediction of type of surgical closure. The most reliable period for this prediction was the third trimester. The OC/AC-ratio time trend was not significantly associated with type of surgical closure. Fetuses without liver herniation underwent primary closure. In infants with a syndrome or chromosomal abnormality, more often a small omphalocele was present, and primary closure was possible.

In previous studies, a number of ratios have been investigated,[15,16,18-20] including the OC/AC ratio.[17,20] Differing outcome parameters and study population inclusion criteria hamper comparison. The cut-offs we found in the current study are lower than previously reported[17] in a group of 24 isolated omphalocele cases but comparable with those reported by Kleinrouweler et al.[20] In the latter cross-sectional study, the predictive value of the OC/AC ratio for type of closure was examined in all (isolated and non-isolated) omphalocele cases. Since the cut-offs are comparable in these two separate patient populations, we expect a good clinical applicability. In line with our finding, Kleinrouweler et al also found a decreasing OC/AC ratio with increasing GA, which resulted in different cut-offs per GA.[20] Kiyora et al[18] and Montero et al,[15] however, found no difference in ratios per GA. The latter study[15] used fetal growth parameters (AC, femur length, and head circumference), which remained relatively constant throughout gestation. The suggested ratios resulted in a lower predictive value for the prediction of postnatal closure (AUC 0.67–0.72) than the OC/AC ratio in our study (AUC 0.96–0.98), as did all ratios including omphalocele diameter instead of circumference.[16,18,19] Additional research should make clear whether correction for GA could result in a constant cut-off throughout gestation, without negatively affecting the predictive value.

An omphalocele is usually diagnosed prior to 24-week GA, and parents prefer counselling shortly thereafter.[23-25] At US1, the result of the invasive prenatal testing is not immediately available, which influences prenatal counselling of future parents. In addition, we found that type of closure and survival can be more accurately predicted by the OC/AC measurements in the late second (US2) and third trimester (US3). The latter especially in cases where around 24-week gestation, the OC/AC ratio is measured between 0.62 and 0.76, and the liver is herniated. Parents should be informed about this early in pregnancy. Although the predictive value of the OC/AC ratio at US3 is limited for counselling purposes as referred to in the previous article,[17] it is beneficial for both perinatal planning and preparing parents for the period after birth. When a case predicts delayed closure, both physicians and patients can prepare for a higher mortality and neonatal morbidity (eg, longer hospital stay, increased risk of feeding problems, increased risk of respiratory problems). To our knowledge, there are no previous studies evaluating the value of repeated measurements throughout gestation per case. Although we did not find a significant association between the trend of the OC/AC ratio and type of surgical closure, we did find an association between the intercept of the OC/AC ratio and type of closure. Since the intercept describes the average OC/AC ratio throughout gestation, it is more precise than a single measurement. Therefore, we do advise repeated measurements to improve prenatal counselling.

The occurrence of an omphalocele is not seldomly (80%) associated with additional anatomical and/or chromosomal abnormalities that may influence the postnatal outcome.[1,3-7,21,26,27] We also know from previous studies[4,17] that in approximately 20% of prenatally assumed isolated cases, postnatally associated anomalies are detected. Although we found a statistically significant association between type of surgical closure and MCA prenatally, this was not confirmed postnatally. The presence of associated anomalies in a neonate may therefore not influence type of surgery, which should be considered when counselling future parents. In our study, based on the OC/AC ratio and liver position, delayed closure and a lower chance of survival would have been predicted for all but one fetus with major MCA, thus irrespective of the presence of these additional anomalies. This is in contrast to fetuses with a syndrome or chromosomal abnormality, who showed a relatively small OC/AC ratio, less liver herniation, and primary closure.

Like Kleinrouweler et al, we were unable to identify prenatal parameters predictive for the occurrence of IUFD or NND.[20] It is highly likely that the sample sizes were too small (13 and 11 cases, respectively), especially since in only four out of 11 cases in our study, there was no apparent cause found for the occurrence of an IUFD and/or NND. Further multicentre studies in larger cohorts are needed to verify this outcome.

In all cases without liver herniation, the defect was closed primarily, irrespective of the OC/AC ratio. Previous studies[17,20,27,28] confirm our findings of lower survival and a higher occurrence of delayed closure in fetuses with liver herniation. Still, our findings show that predicting type of closure and survival in fetuses with liver herniation and an OC/AC ratio between 0.62 and 0.76 around 24-week gestation remains challenging; in our study, 29% of these neonates underwent a primary closure. The group of patients with an OC/AC ratio between 0.62 and 0.76 around 24-week gestation warrants further investigation.

5 | CONCLUSION

In fetuses with an omphalocele, the OC/AC ratio determined from ultrasound measurements in the late second and third trimesters, combined with position of the liver, predicts the type of postnatal surgical closure and survival. The predictive value increases with increasing GA and can be used throughout pregnancy with different cut-offs for different time periods in pregnancy. The OC/AC ratio can be a valuable predictive tool in the counselling of parents.

ACKNOWLEDGEMENT

Ko Hagoort provided editorial advice.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Nina C.J. Peters https://orcid.org/0000-0003-2427-7269
Annelieke Hijkoop https://orcid.org/0000-0003-0833-8455
Joost van Rosmalen https://orcid.org/0000-0002-9187-244X

REFERENCES

1. Barisic I, Clementi M, Hausler M, et al. Evaluation of prenatal ultrasound diagnosis of fetal abdominal wall defects by 19 European registries. *Ultrasound Obstet Gynecol*. 2001;18(4):309-316.
2. European Surveillance of congenital anomalies (EUROCAT) Guide 1.4 Section 3.3 2014. Available from: www.eurocat-network.eu.
3. Khalil A, Arnaoutoglou C, Pacilli M, Szabo A, David AL, Pandya P. Outcome of fetal exomphalos diagnosed at 11-14 weeks of gestation. *Ultrasound Obstet Gynecol*. 2012;39(4):401-406.
4. Cohen-Overbeek TE, Tong WH, Hatzmann TR, et al. Omphalocele: comparison of outcome following prenatal or postnatal diagnosis. *Ultrasound Obstet Gynecol*. 2010;36(6):687-692.
5. Brantberg A, Blaas HG, Haugen SE, Eik-Nes SH. Characteristics and outcome of 90 cases of fetal omphalocele. *Ultrasound Obstet Gynecol*. 2005;26(5):527-537.
6. Lakasing L, Cicero S, Davenport M, Patel S, Nicolaides KH. Current outcome of antenatally diagnosed exomphalos: an 11 year review. *J Pediatr Surg*. 2006;41(8):1403-1406.
7. Fleurke-Rozema H, van de Kamp K, Bakker M, Pajkrt E, Bilardo C, Snijders R. Prevalence, timing of diagnosis and pregnancy outcome of abdominal wall defects after the introduction of a national prenatal screening program. *Prenat Diagn*. 2017;37(4):383-388.
8. Bauman B, Stephens D, Gershone H, et al. Management of giant omphaloceles: A systematic review of methods of staged surgical vs. nonoperative delayed closure. *J Pediatr Surg*. 2016;51(10):1725-1730.
9. van Eijck FC, de Blaauw I, Bleichrodt RP, et al. Closure of giant omphaloceles by the abdominal wall component separation technique in infants. *J Pediatr Surg*. 2008;43(1):246-250.
10. van Eijck FC, Aronson DA, Hoogeveen YL, Wijnen RMH. Past and current surgical treatment of giant omphalocele: outcome of a questionnaire sent to authors. *J Pediatr Surg*. 2011;46(3):482-488.
11. Rijhwani A, Davenport M, Dawrant M, et al. Definitive surgical management of antenatally diagnosed exomphalos. *J Pediatr Surg*. 2005;40(3):516-522.
12. Hijkoop A, Peters NCJ, Lechner RL, et al. Omphalocele: from diagnosis to growth and development at 2 years of age. *Arch Dis Child Fetal Neonatal Ed*. 2019;104(1):F18-F23.
13. Partridge EA, Hanna BD, Panitch HB, et al. Pulmonary hypertension in giant omphalocele infants. *J Pediatr Surg*. 2014;49(12):1767-1770.
14. Kelly KB, Ponsky TA. Pediatric abdominal wall defects. *Surg Clin North Am*. 2013;93(5):1255-1267.
15. Montero FJ, Simpson LL, Brady PC, Miller RS. Fetal omphalocele ratios predict outcomes in prenatally diagnosed omphalocele. *Am J Obstet Gynecol*. 2011;205(3):284.e1-284.e7.
16. Tassin M, Descriaud C, Elie C, et al. Omphalocele in the first trimester: prediction of perinatal outcome. *Prenat Diagn*. 2013;33(5):497-501.
17. Peters NC, Hooft ME, Ursem NT, et al. The relation between viscero-abdominal disproportion and type of omphalocele closure. *Eur J Obstet Gynecol Reprod Biol*. 2014;181:294-299.
18. Kiyohara MY, Brizot ML, Liao AW, et al. Should we measure fetal omphalocele diameter for prediction of perinatal outcome? *Fetal Diagn Ther*. 2014;35(1):44-50.
19. Diemon N, Funke K, Mollers M, et al. Thorax-to-head ratio and defect diameter-to-head ratio in giant omphaloceles as predictor for fetal outcome. *Arch Gynecol Obstet*. 2017;295(2):325-330.
20. Kleinrouweler CE, Kuijper CF, van Zalen-Sprock MM, Mathijssen IB, Bilardo CM, Pajkrt E. Characteristics and outcome and the omphalocele circumference/abdominal circumference ratio in prenatally diagnosed fetal omphalocele. *Fetal Diagn Ther*. 2011;30(1):60-69.
21. Heider AL, Strauss RA, Kuller JA. Omphalocele: clinical outcomes in cases with normal karyotypes. *Am J Obstet Gynecol*. 2004;190(1):135-141.
22. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723-1729.
23. Asplin N, Wessel H, Marions L, Georgsson Öhman S. Pregnant women's experiences, needs, and preferences regarding information about malformations detected by ultrasound scan. *Sex Reprod Healthc*. 2012;3(2):73-78.
24. Kuppermann M, Feeny D, Gates E, Posner SF, Blumberg B, Washington AE. Preferences of women facing a prenatal diagnostic choice: long-term outcomes matter most. *Prenat Diagn*. 1999;19(8):711-716.
25. Lalor JG, Devane D, Begley CM. Unexpected diagnosis of fetal abnormality: women's encounters with caregivers. *Birth*. 2007;34(1):80-88.
26. Conner P, Vejde JH, Burgos CM. Accuracy and impact of prenatal diagnosis in infants with omphalocele. *Pediatr Surg Int*. 2018;34(6):629-633.
27. Nicholas SS, Stamilio DM, Dicke JM, Gray DL, Macones GA, Odibo AO. Predicting adverse neonatal outcomes in fetuses with abdominal wall defects using prenatal risk factors. *Am J Obstet Gynecol*. 2009;201(4):383.e1-383.e6.
28. Hidaka N, Tsukimori K, Hojo S, et al. Correlation between the presence of liver herniation and perinatal outcome in prenatally diagnosed fetal omphalocele. *J Perinat Med*. 2009;37(1):66-71.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Peters NCJ, Hijkoop A, Lechner RL, et al. The validity of the viscero-abdominal disproportion ratio for type of surgical closure in all fetuses with an omphalocele. *Prenatal Diagnosis*. 2019;39:1070–1079. https://doi.org/10.1002/pd.5546