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Fetal Congenital Pulmonary Airway Malformation: The Role of an Objective Measurement of Cardiomediastinal Shift

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Abstract

Objective—To examine the relationship between cardiomediastinal shift angle (CMSA) and adverse perinatal outcomes and hydrops in cases of congenital pulmonary airway malformation (CPAM).

Study Design—This retrospective study evaluated CPAM cases referred to our institution from 2008 to 2015. The primary outcome was a composite score for adverse perinatal outcome. CMSA was measured for each case and evaluated for its association with the primary outcome. The prediction accuracy of CMSA for adverse perinatal outcome was assessed using receiver operator characteristic (ROC) curves.

Results—Eighteen (21.2%) of the 85 cases experienced an adverse perinatal outcome. Increases in CMSA were associated with adverse perinatal outcomes and hydrops in bivariate analyses. Adjusted analyses found each 10-degree increase in CMSA to be associated with increased odds of an adverse perinatal outcome (adjusted odds ratio [aOR] 2.2, 95% confidence interval [CI]: 1.4–3.3) and hydrops (aOR 3.0, 95% CI: 1.5–6.1). CMSA performed well and was comparable to CPAM volume ratio in predicting adverse perinatal outcomes (area under the curve 0.81 and 0.84, respectively).

Conclusion—We describe a novel measurement of mediastinal shift in cases of CPAM and its relationship with adverse perinatal outcomes and hydrops. These findings may shape the evaluation and management of CPAMs, improve our understanding of their prognosis, and influence patient counseling.

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Note

Conflict of Interest

None.

Keywords

cardiomediastinal shift; congenital pulmonary airway malformation; fetal lung lesion; hydrops; mediastinal shift; perinatal outcomes

Congenital pulmonary airway malformations (CPAM) comprise the majority (95%) of congenital lung lesions.[1] The reported incidence is now 1 in 7,200 to 12,000 live births, which is higher than previously reported, presumably due to improvements in ultrasound technology.[2,3] CPAMs exhibit variability in their natural history. Prior studies have found that 15 to 55% of lesions have significant regression by the end of pregnancy and have little or no effect on fetal development,[4–6] while 5 to 10% of affected fetuses will develop hydrops.[2,7,8] Administration of maternal corticosteroids has been advocated in cases when hydrops is present, or when the lesion is determined to be at high risk for developing hydrops. In these cases, steroid administration has been associated with resolution or improvement of hydrops and decrease in CPAM size.[9,10]

The presence of hydrops is known to portend a high risk for fetal or neonatal death,[1,4,11] and few risk factors for the development of hydrops aside from CPAM volume to head ratio (CVR) have been confirmed.[6,7,11,12] Conflicting evidence exists about the pathophysiology of hydrops in the setting of CPAM,[13–16] and some evidence suggests a contribution from mediastinal compression.[17] Prior studies have largely found no association between subjective severity of cardiomediastinal shift and adverse perinatal outcomes;[13,15,18] though one did report extreme shifting to be associated with worse outcomes.[16] An objective measurement of cardiomediastinal shift has not been evaluated and doing so may improve our ability to anticipate prognosis, counsel patients, and improve detection of which cases warrant intervention, the administration of prenatal corticosteroids, or referral to a fetal treatment center.

The primary objective of this study was to examine a novel measurement of cardiomediastinal shift and describe its association with adverse perinatal outcomes in cases of CPAM. We hypothesized that an increasing degree of cardiomediastinal shift would correlate with greater risk for having an adverse outcome.

Materials and Methods

This was a retrospective study of prenatally diagnosed CPAM cases. Eligible patients included all singleton gestations with a confirmed CPAM evaluated in the Fetal Treatment Center at the University of California, San Francisco (UCSF) between January 2008 and December 2015. Exclusion criteria included multifetal gestation, coexisting congenital diaphragmatic hernia, and other types of pulmonary lesions including pulmonary sequestrations (solid-appearing lesions, where a feeding systemic artery could be identified) and hybrid lung lesions (lesions with cystic and solid components and a feeding systemic artery identified). Institutional review board approval was obtained for the study (Institutional Review Board No. 10–04093, approval 11/15/2010).

Data were primarily extracted from the Fetal Treatment Center database, with supplemental data collected from the electronic medical record by R.S. and from ultrasound images and reports by R.S. and R.B.G. Some cases received all obstetric and neonatal care at UCSF, and pregnancy and neonatal outcomes were directly extracted from the medical record. Others were co-managed with an outside institution and were delivered either at UCSF or at the outside institution. For these cases, data collection was limited to that available within the database, as well as the information collected by K.G., who personally called the family, the delivering institution, or both to obtain as many details of the delivery and neonatal course as possible.

The primary outcome was a composite score for adverse perinatal outcome, which was defined as the presence of one or more of the following: intrauterine fetal demise, neonatal demise, or admission to the neonatal intensive care unit (NICU). Those who underwent pregnancy termination were excluded from analysis of the primary outcome. The secondary outcome was the presence of fetal hydrops at the time of referral to our institution. Hydrops was defined as the presence of abnormal fluid accumulation in at least two fetal body cavities, and was confirmed through review of the initial ultrasound performed at our institution.

For each participant, cardiomediastinal shift angle (CMSA) was measured retrospectively from stored images obtained at the time of the initial ultrasound at our institution. The protractor tool within the picture archiving and communication system was utilized to measure each angle. The CMSA was measured from a transverse image of the fetal chest where the classic four-chamber view of the heart is seen. Primarily, a reference line (solid line in ►Fig. 1) was drawn from the fetal sternum to the center of the vertebral body, as is typically done when assessing cardiac axis. With normal fetal anatomy (►Fig. 1A), this line lies at a 45-degree angle to the interventricular septum, and intersects the atrial septum, crossing just superior to the crux of the heart through approximately two thirds of the right atrium and a small portion of the right ventricle. In affected cases, the reference line was again drawn from the fetal sternum to the center of the vertebral body (solid line in ►Fig. 1B), but when mediastinal shift is present it does not intersect the heart in the same manner as described for normal fetal anatomy. Therefore, a second line (dashed line in ►Fig. 1B and 1C) was drawn to cross through the displaced heart in the same manner that the reference line had in ►Fig. 1A. The angle between the reference (solid) and index (dashed) lines (►Figs. 1B and 1C) was measured as the CMSA. For each participant, the CMSA was measured up to five times by the senior author, who is an experienced radiologist (R.B. G.), and the average of these measurements was used for the final CMSA value.

Maternal demographics, including gestational age at the time of referral to our institution, maternal age, parity, other pregnancy complications, and maternal comorbidities were collected. Gestational age was determined by last menstrual period and first ultrasound as described and endorsed by the American College of Obstetrics and Gynecology.[19] Characteristics of the CPAM lesion were recorded including CVR, laterality (right or left-sided), the subjective presence of mediastinal shift as noted in the ultrasound reports reviewed by R.S., and lesion subtype (microcystic, macrocystic, or mixed microcystic and macrocystic). CPAM lesion characteristics were verified by reviewing the ultrasound reports

for each case. The CVR was calculated as the CPAM lesion length × width × height × 0.52/head circumference[11] in cm^2. The presence and types of any coexisting fetal anomalies were also recorded. Intrauterine therapies for CPAM were collected, including steroid administration (gestational age at administration and number of courses given) and invasive procedures (shunt placement, amnioreduction, thoracocentesis).

Both CVR and CMSA were analyzed as continuous variables, and also categorized by severity. The lowest CVR category (0–1.5) was chosen based on the established association between CVR greater than or equal to 1.6 and hydrops. The middle category (1.6–2.5) was chosen to encompass a 1-unit increase in CVR. The final CVR category included those with CVR 2.6. CMSA categories were defined by calculating 3 quantiles of this value amongst the study cohort. As such, the lowest quantile (0–11.5 degrees) was categorized as mild, the middle quantile (11.54–28.75 degrees) was categorized as moderate, and the highest quantile (28.8–69.7 degrees) was categorized as severe.

The sample size for this study was predetermined by the dataset. However, the fixed sample size of 85 will provide 80% power to detect a statistically significant effect of CMSA, on having an adverse perinatal outcome (with 2-sided α error set at 0.05), if the true effect size is at least 13.9 degrees. Categorical variables and nonparametric continuous variables were compared using Fisher's exact test and Wilcoxon's rank-sum, respectively. Multivariate logistic regression was used to generate odds ratios, adjusting for potential confounding variables. Spearman correlation coefficient was used to evaluate the relationship between CVR and CMSA. Receiver operator characteristic (ROC) curves were generated to evaluate the prediction accuracy of CMSA for adverse perinatal outcome and compare CMSA accuracy to that of CVR. All statistical analyses were performed using STATA software (Version 14, College Station, TX) and SAS software (Version 9.4, Cary, NC).

Results

A total of 89 eligible CPAM cases were identified during the study period, 4 of which underwent pregnancy termination leaving 85 cases for our analysis. One case did not have a CVR documented nor adequate ultrasound images or measurements, from which to calculate CVR. No cases had structural cardiac abnormalities on fetal echocardiogram. Three cases had coexisting anomalies (central nervous system variant, hypospadias, clubfoot), and the frequency of anomalies did not differ between the groups. Of the cases that underwent invasive prenatal diagnostic genetic testing, no abnormalities were detected. Five participants had an invasive fetal treatment for their CPAM after the time of their referral and CMSA determination (two shunt placements, two amnior-eductions, one thoracocentesis), and all of these cases had hydrops.

CMSA was not correlated with lesion laterality or gestational age. CMSA did differ by lesion subtype ($p = 0.03$). Median CMSA was 13.8, 26.5, and 30.2 degrees for microcystic, macrocystic, and mixed microcystic and macrocystic lesions, respectively. This is similar to how CVR differed between lesion subtypes. Median CVR was 0.6, 1.1, and 1.55 for microcystic, macrocystic, and mixed microcystic and macrocystic lesions, respectively ($p =$

0.004). Evaluating the relationship between these variables, CVR and CMSA were found to have a strong, positive correlation with one another (►Fig. 2, $r = 0.86$).

Regarding the primary outcome, 18 (21.2%) of the 85 participants included in the analysis had an adverse perinatal outcome. Maternal demographics and baseline CPAM characteristics (►Table 1) were similar between those with and without an adverse perinatal outcome except in regards to lesion laterality, subjective mediastinal shift, and gestational age at delivery. On average, those with an adverse perinatal outcome delivered 1 week earlier than those without an adverse outcome (38.1 vs. 39.1 weeks, $p = 0.007$). Cases with an adverse perinatal outcome were more likely to have a right-sided lesion (88.9 vs. 11.1%, $p = 0.006$) or mediastinal shift (88.9 vs. 64.2%, $p = 0.048$). Hydrops at referral was present in 7 of the 18 cases (38.9%) with an adverse perinatal outcome and in only 1 of the 67 cases (1.5%) without an adverse outcome ($p < 0.001$). ►Table 2 displays bivariate analyses indicating that increases in CMSA and CVR are associated with adverse perinatal outcome.

In multivariable analyses of the primary outcome, controlling for gestational age at the time of evaluation and lesion laterality, each 10-degree increase in CMSA was associated with having over a 2-fold increase in the odds of an adverse perinatal outcome (adjusted odds ratio [aOR] 2.2, 95% CI: 1.4–3.3, $p < 0.001$), and each 1-unit increase in CVR was associated with over a 4-fold increased odds of an adverse perinatal outcome (aOR 4.6, 95% CI: 2.0–10.3, $p < 0.001$). Adjusting for the same confounders, being in the highest category of CMSA and CVR were each associated with a significant increase in the odds of an adverse perinatal outcome (aOR 39.5, 95% CI: 5.0–314.8, $p = 0.001$; aOR 47.2, 95% CI: 5.6–400.4, $p < 0.001$).

For the secondary analysis, eight (9.4%) had hydrops at the time of referral. Maternal demographics and baseline CPAM characteristics were similar between those with and without hydrops except in regards to parity and lesion laterality. The median gestational age at delivery was earlier in those with hydrops than those without (32.6 vs. 39.1 weeks, $p < 0.001$). Bivariate analyses found increasing CMSA and CVR to be correlated with the presence of hydrops (►Table 3).

In multivariable analyses, controlling for gestational age at the time of evaluation and lesion laterality, we found CVR and CMSA to have a similar association with hydrops. Each 10-degree increase in CMSA increased the odds of hydrops significantly (aOR 3.0, 95% CI: 1.5–6.1, $p = 0.002$), and each 1-unit increase in CVR increased the odds of hydrops as well (aOR 8.3, 95% CI: 1.7–40.1, $p = 0.009$).

ROC curves for CMSA and CVR (►Fig. 3) illustrate the high performance of these measurements in predicting adverse perinatal events (area under the curve 0.81 and 0.84, respectively). CMSA and CVR did not differ significantly from one another in their ability to predict adverse perinatal outcomes ($p = 0.53$). The ability of CMSA to predict adverse perinatal outcome is optimized at a cutoff of 34.3 degrees with a sensitivity of 72% and specificity of 85%.

Discussion

In this study, we describe a novel objective measurement of mediastinal shift (CMSA) in cases of fetal CPAMs. Amongst a cohort of CPAM lesions referred to a high volume Fetal Treatment Center, we found CMSA to correlate strongly with CVR and to be independently associated with increased odds of adverse perinatal outcomes and hydrops. In our cohort only 1 of the 30 cases with mild CMSA had an adverse perinatal outcome, and none of the 60 cases with mild or moderate CMSA had hydrops at the time of their referral ultrasound, which demonstrates the utility of CMSA to identify cases that are likely to do well. Additionally, our findings reaffirm those of prior studies correlating CVR with increased odds of adverse perinatal outcomes and hydrops.

Regarding our primary outcome, prior studies have failed to find an association between cardiomediastinal shift and adverse perinatal outcome.[13,15,18] In contrast to our methodology, these studies utilized a subjective measurement of cardiomediastinal shift, whereas we used an objective measurement, CMSA. Objectively measuring mediastinal shift has advantages over subjectively assessing this shift. Measuring the CMSA allowed us to numerically quantify cardiomediastinal shift, objectively characterize the severity of the shift, and evaluate each case in an exact and procedural fashion. This difference is likely accountable for the deviation in our findings from that of prior studies. One prior study; however, did report an association between severe cardio-mediastinal shift and neonatal death, when using criteria for cardiomediastinal shift as being complete deviation of the fetal heart into the contralateral thorax.[16] Their use of an extreme definition of cardiomediastinal shift likely led them to find this positive association.

It has been proposed that mediastinal compression leads to increased central venous pressure and decreased venous vascular return, ultimately causing nonimmune hydrops in cases of CPAMs.[17] In our findings, increasing CMSA is associated with hydrops, which is consistent with such a proposed pathophysiology. Several other authors have failed to find a relationship between cardiomediastinal shift and hydrops, including a prior study from our own institution.[13–15,18] Again, we suspect that the subjective assessment of cardiomediastinal shift in prior studies explains this negative association, while we report a positive association when examining an objective measurement of cardiomediastinal shift in relationship to hydrops.

The association we report between increasing CVR and adverse perinatal outcome has been observed previously.[20] Our results support prior studies establishing a CVR greater than 1.6 to be associated with hydrops.[6,7,11,12] We found the odds of hydrops to be significantly increased when CVR is greater than or equal to 2.6. This suggests that a second threshold may exist, above which the risk of hydrops is higher than that when CVR is between 1.6 and 2.6.

The data obtained from the ROC curves suggest that CMSA performs well in predicting adverse perinatal outcomes. Comparing the ROC curve for CMSA to that of CVR, the current gold standard measurement in assessment of CPAMs, suggests that CMSA performs en par with CVR. CMSA may offer an alternative means for evaluating CPAM lesions, and

predicting which cases will have poor perinatal outcomes when the CVR is difficult to assess or equivocal. Larger sample sizes and ideally prospective data would need to be evaluated to determine an optimal cutoff value for CMSA that could be used clinically.

Our study represents a relatively large cohort of CPAM cases, which occur rarely in the general population. Additionally, the availability of extensive ultrasound data for each participant allowed us to characterize a novel measurement of cardiomediastinal shift that may have important implications for counseling and prediction of prognosis in the prenatal setting. However, our study is not without limitations. Limitations include those intrinsic to retrospective study design. We were unable to analyze data that were not originally captured. Some details of perinatal outcomes were not available for those who delivered at outside institutions. Additionally, practice patterns across institutions may have impacted our primary outcome. For example, while some institutions may admit all neonates with anomalies to the NICU for observations, others (such as our own) do not. Limited access to postnatal records did not allow us to determine the indication for NICU admission or gestational age at delivery in all cases. We did not assess long-term outcomes of infants or details regarding definitive postnatal treatment of their CPAM, limiting the longterm applicability of our data. Postnatal imaging and pathology reports were not available to us, and therefore, we were unable to confirm a postnatal diagnosis for these cases. It is possible that our sample does not reflect the population at large, as reflected by our relatively high rate of hydrops. This may be attributed to our institution being a referral center with the capability to perform fetal intervention. It was beyond the scope of the current study to assess reproducibility and reliability of this newly described measurement, CMSA, but future studies will focus on such evaluations. Large confidence intervals were observed with our multivariable analyses, reflecting the size of our cohort. However, CMSA and CVR clearly demonstrated positive associations with adverse perinatal outcomes. The secondary outcome of hydrops was determined at the time of participants' referral to our institution and only two cases without hydrops at the time of referral later developed hydrops. Therefore, the current study did not evaluate CMSA as a predictor of hydrops and can only comment on the association between CMSA and hydrops.

CMSA is a novel measurement of cardiomediastinal shift that is associated with adverse perinatal outcomes and hydrops. In our cohort, CVR was also associated with the primary and secondary outcomes. In cases such as CPAM, where outcomes are widely variable, identifying additional objective data to guide evaluation, counseling, and management have important clinical utility. While our results are favorable, they should be confirmed in other populations and in a prospective fashion. These studies will also focus on the feasibility, ease, and reproducibility of measuring CMSA. These technical features of measuring CMSA should be compared with that of determining CVR. Subsequent studies may also focus on comparison of CMSA to the cardiac axis in cases of CPAM and determining how fetal interventions affect CMSA and perinatal outcomes. Utilizing CMSA in addition to CVR or in cases where CVR is technically difficult to obtain has the potential to improve how we counsel patients regarding prognosis, make clinical decisions surrounding fetal therapy or steroid-administration, and anticipate neonatal needs at delivery.

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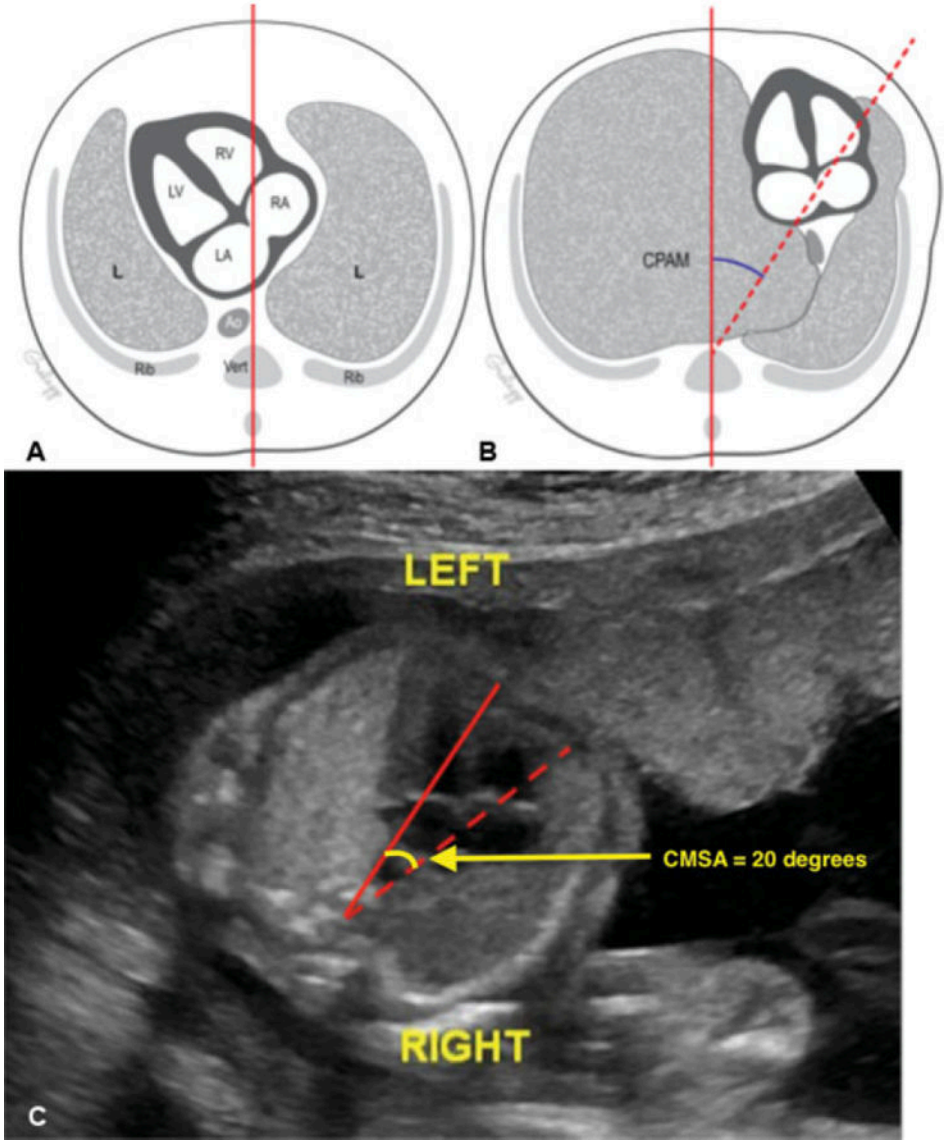

Fig. 1.

Illustration and ultrasound depiction of measuring cardiomediastinal shift angle (CMSA). (A) Illustration of the normal positioning of the fetal heart with the reference line drawn (solid). (B) Illustration of a large left-sided lesion, leading to severe cardiomediastinal shift with CMSA drawn, as the angle between the reference (solid) and index lines (dashed). (C) Depiction of how CMSA was measured to be 20 degrees in a case of a large left-sided congenital pulmonary airway malformation with the reference (solid) and index (dashed) lines imposed.

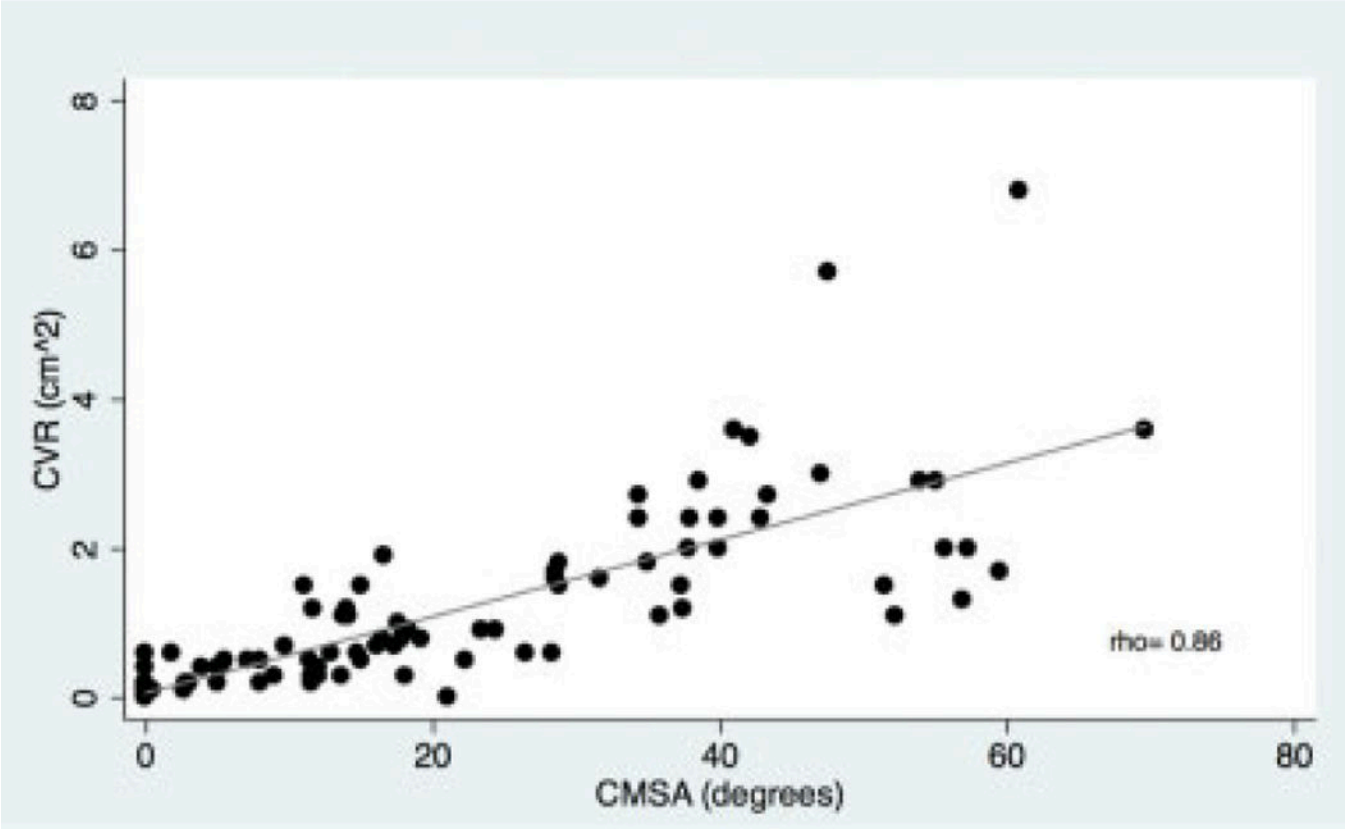

Fig. 2.

Correlation between CPAM volume ratio (CVR) and cardio-mediastinal shift angle (CMSA). It illustrates the strong positive correlation between CVR and CMSA with $r = 0.86$ ($p < 0.001$).

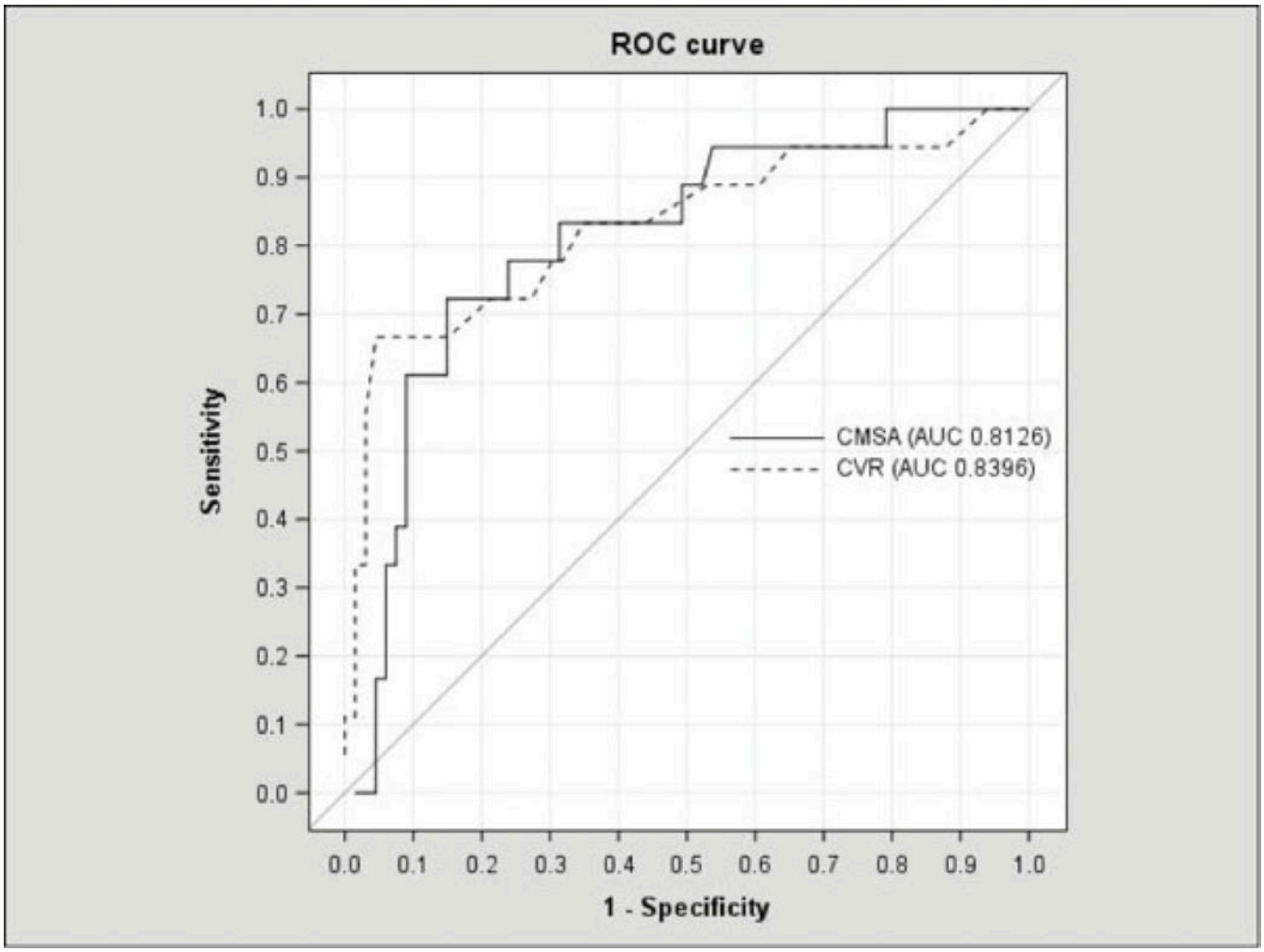

Fig. 3.

Receiver operator characteristic (ROC) curves assessing the performance of cardiomediastinal shift angle (CMSA) and CPAM volume ratio (CVR) in their ability to predict adverse perinatal outcomes. It illustrates that CMSA and CVR similarly predict adverse perinatal outcomes (area under the curve 0.81 and 0.84, respectively, $p = 0.53$).

Table 1

Comparison of select demographics and CPAM characteristics in those with and without adverse perinatal outcome

	All (*n* = 85)	**Adverse perinatal outcome (*n* = 18)**	**No adverse perinatal outcome (*n* = 67)**	***p*-Value[a]**
Median maternal age, y (IQR)	31 (26–35)	31 (24–36)	31 (26–35)	0.96
Nulliparous (*n* %)	33 (38.8)	9 (50)	24 (35.8)	0.20
Median GA at referral, wk (IQR)	21.3 (20.1–22.9)	22.2 (20.1–23.0)	21.3 (20.1–22.9)	0.53
Median GA at delivery, wk (IQR)	39.1 (38.4–39.9)	38.1 (32.1–39.4)	39.1 (38.7–40.0)	0.007
Lesion subtype (*n* %)				0.15
Microcystic	49 (57.7)	7 (38.9)	42 (62.7)	
Macrocystic	19 (22.4)	5 (27.8)	14 (20.9)	
Mixed	17 (20.0)	6 (33.3)	11 (16.4)	
Lesion laterality (*n* %)				0.006
Right	51 (60.0)	16 (88.9)	45 (52.2)	
Left	34 (40.0)	2 (11.1)	32 (47.8)	
Mediastinal shift (*n* %)	59 (69.4)	16 (88.9)	43 (64.2)	0.048
Steroids given prior to referral (*n* %)	8 (9.4)	4 (22.2)	4 (6.0)	0.06

Abbreviations: CPAM, congenital pulmonary airway malformation; GA, gestational age; IQR, interquartile range.

[a]Wilcoxon's rank-sum was used for nonparametric continuous variables and Fisher's exact test was used for categorical variables.

Table 2

Comparison of CMSA and CVR amongst cases of CPAM with and without adverse perinatal outcome

	All (n = 85)	Adverse perinatal outcome (n = 18)	No adverse perinatal outcome (n = 67)	p-Value[c]
Median CMSA, degrees (IQR)	16.1 (5.5–34.4)	38.3 (26.5–47.5)	13.57 (3.8–24.4)	<0.001
CMSA category[a]				<0.001
Mild	30 (33.7%)	1 (5.6%)	29 (43.3%)	
Moderate	30 (33.7%)	4 (22.2%)	26 (38.8%)	
Severe	25 (29.4%)	13 (72.2%)	12 (17.9%)	
Median CVR[b] at referral, cm^2 (IQR)	0.8 (0.3–1.6)	2.4 (1.1–2.9)	0.6 (0.3–1.2)	<0.001
CVR[b] category				<0.001
0–1.5 cm^2	62 (73.8%)	6 (33.3%)	56 (84.9%)	
1.6–2.5 cm^2	13 (15.5%)	5 (27.8%)	8 (12.1%)	
2.6 cm^2	9 (10.7%)	7 (38.9%)	2 (3.0%)	

Abbreviations: CMSA, cardiomediastinal shift angle; CPAM, congenital pulmonary airway malformation; CVR, CPAM volume ratio; IQR, interquartile range.

[a] CMSA categories defined as: Mild: 0–11.5 degrees; Moderate: 11.54–28.75 degrees; Severe: 28.8–69.7 degrees.

[b] For variables containing CVR, n = 84.

[c] Wilcoxon's rank-sum was used for nonparametric continuous variables and Fisher's exact test was used for categorical variables.

Table 3

Comparison of CMSA and CVR amongst cases of CPAM with and without hydrops

	All (*n* = 85)	**Hydrops (*n* = 8)**	**No hydrops (*n* = 77)**	***p*-Value[c]**
Median CMSA, degrees (IQR)	16.1 (5.5–34.4)	42.5 (39.5–49.5)	14.2 (5.0–28.5)	<0.001
CMSA category[a]				<0.001
Mild	30 (35.3%)	0 (0.0%)	30 (39.0%)	
Moderate	30 (35.3%)	0 (0.0%)	30 (39.0%)	
Severe	25 (29.4%)	8 (100%)	17 (22.1%)	
Median CVR[b] at referral, cm^2 (IQR)	0.8 (0.3–1.6)	2.6 (2.2–3.6)	0.6 (0.3–1.4)	<0.001
CVR[b] category				<0.001
0.0–1.5 cm^2	62 (73.8%)	1 (12.5%)	61 (80.3%)	
1.6–2.5 cm^2	13 (15.5%)	3 (37.5%)	10 (13.2%)	
> 2.6 cm^2	9 (10.7%)	4 (50.0%)	5 (6.6%)	

Abbreviations: CMSA, cardiomediastinal shift angle; CPAM, congenital pulmonary airway malformation; CVR, CPAM volume ratio; IQR, interquartile range.

[a]CMSA categories defined as: Mild: 0–11.5 degrees; Moderate: 11.54–28.75 degrees; Severe: 28.8–69.7 degrees.

[b]For variables containing CVR, $n = 84$.

[c]Wilcoxon's rank-sum was used for nonparametric continuous variables and Fisher's exact test was used for categorical variables.