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Calculating Observed-to-Expected Total Fetal Lung Volume in CDH Fetuses in Twin Gestation: Is There a Better Way?

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Keywords
Fetal magnetic resonance imaging · Total fetal lung volume · Congenital diaphragmatic hernia · Twin gestation

Abstract
Background: Congenital diaphragmatic hernia (CDH) is a potentially lethal birth defect, and identifying prenatal predictors of outcome is important. Observed-to-expected total fetal lung volume (o/e TFLV) has been shown to be a predictor of severity and useful in risk stratification but is variable due to different TFLV formulas. ***Objectives:*** To calculate o/e TFLV for CDH patients part of a twin gestation using the unaffected sibling as an internal control and comparing these values to those calculated using published formulas for TFLV. ***Methods:*** Seven twin gestations with one fetus affected by CDH were identified between 2006 and 2017. The lung volume for each twin was calculated using magnetic resonance imaging (MRI), and o/e TFLV was calculated using the unaffected twin's TFLV. This percentage was then compared to the o/e TFLV calculated using published formulas. ***Results:*** Lung volumes in the unaffected twins were within normal ranges at the lower end of the spectrum. No single TFLV formula was found to correlate perfectly. Intraclass correlation coefficient estimate was most consistent for o/e TFLV calculated with the Meyers formula and supported by Bland-Altman plots. ***Conclusions:*** O/e TFLV measured in CDH/non-CDH twin gestations using the unaffected sibling demonstrated agreement with o/e TFLV calculated using the Meyers formula. We urge the fetal community to standardize the method, use, and interpretation of fetal MRI in the prenatal evaluation of CDH.

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Introduction

Despite significant progress, congenital diaphragmatic hernia (CDH) continues to be a potentially lethal birth defect with significant short- and long-term morbidity [1]. Abdominal contents herniate into the thoracic cavity resulting in detrimental sequelae to pulmonary and vascular development with a spectrum of severity and outcomes [2]. Advancements in prenatal imaging allow more cases of CDH to be identified antenatally – up to 68% [3, 4] – and these cases are associated with poorer outcomes compared to those diagnosed postnatally [4, 5]. Judicious application of prognostic tests is critical for prenatal counseling, selection for fetal therapy, and perinatal management planning.

Data obtained from ultrasound and magnetic resonance imaging (MRI) have been studied to predict outcomes. Lung-to-head ratio (LHR) and observed-to-expected LHR (o/e LHR) are the most commonly utilized and best validated ultrasound measures, favored by some for easy accessibility and low cost [6, 7]. With MRI, total fetal lung volume (TFLV), observed-to-expected TFLV (o/e TFLV), and similar measures (relative fetal lung volume and percent predicted lung volume) have been validated as important adjuncts for prenatal diagnosis and prognosis [8, 9]. However, not only do methods vary in the measurement of the "observed" TFLV, but at least 5 formulas exist to calculate TFLV based on gestational age, and additional formulas use other image-based parameters [10, 11]. A 2010 literature review identified 10 papers that reported on MRI-based normal lung volumes: the authors concluded that high variability in reporting of normal lung values makes reliable prediction of pulmonary hypoplasia difficult and calls for universally accepted standardized values [12]. A review of fetal imaging techniques for CDH described several studies that reach conflicting conclusions with regard to which imaging modality and calculation best correlate with clinical outcomes [13].

Fetuses affected with CDH that are part of a twin gestation present a unique opportunity to compare volumetric data using the unaffected twin as an internal control for a directly measured TFLV. In this study, we compare o/e TFLV based on the "observed" TFLV in a healthy unaffected gestational age- and size-matched twin against o/e TFLV based on the TFLV as calculated by 5 different published formulas.

Table 1. Formulas for calculating TFLV

Study	Formula
Rypens et al. [14]	$V = 0.0033\ g^{2.86}$
Osada et al. [15]	$V = (2.41 \times g) – 37.6$
Duncan et al. [16]	$V = 0.8375e^{0.1249\ g}$
Mahieu-Caputo et al. [17]	$V = \exp\ (1.24722 + 0.08939 \times g)$
Meyers et al. [18]	$V = 0.000865\ g^{3.254}$

V, fetal lung volume; g, gestational age (weeks); TFLV, total fetal lung volume.

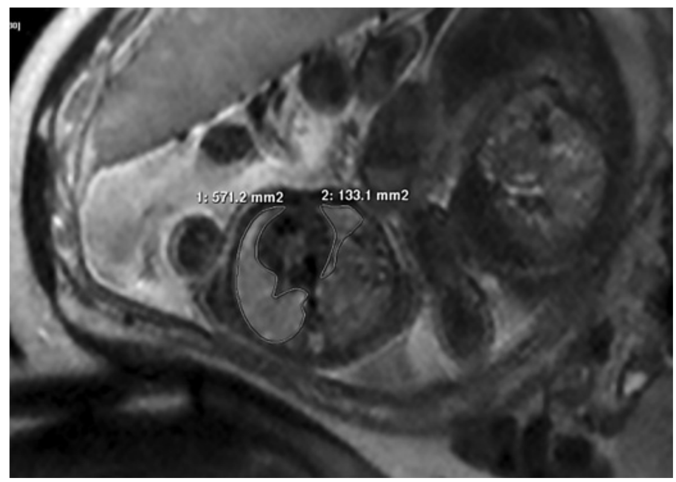

Fig. 1. Fetal MR image, axial SSFSE T2-weighted image. Twins at 29 weeks' gestation. Twin A with a left congenital diaphragmatic hernia. TFLVs were calculated for each twin from consecutive sections in 2 out of 3 imaging planes. Lung area measured by manually outlining the lung boundary, excluding pulmonary hila.

Materials and Methods

The study was approved by the University of Michigan Institutional Review Board (HUM00031524). Twin gestations with one fetus affected by CDH were identified from 2006 to 2017 at a single institution. Medical charts were retrospectively reviewed to abstract prenatal radiographic studies as well as demographic data and clinical outcomes including need for extracorporeal membrane oxygenation (ECMO) and survival to discharge.

Fetal MRI was performed on a 1.5-Tesla Philips Achieva MRIscanner (Philips Healthcare) using a SENSE XL 16-element phased-array torso coil or on a 1.5-Tesla Philips Ingenia MRIscanner (Philips Healthcare) using a 32-channel phased-array torso coil with the mother in the left lateral decubitus position. Axial, coronal, and sagittal SSFSE T2-weighted images relative to the fetal body were obtained. All sequences were performed with fast acquisition imaging technique minimizing the likelihood of capturing fetal motion. Fetal MRI total lung volumes were calculated for each twin from consecutive sections in 2 out of 3 imaging planes. In each consecutive slice, the lung area was measured by manually

Table 2. Patient characteristics

Twin ID	Diagnosis	Defect side	Liver position	GA at ultrasound	Percent difference in EFW*	GA at birth
1	CDH non-CDH	Right –	Up –	28 weeks 1 day	–16	33 weeks 3 days
2	CDH non-CDH	Left –	Up –	23 weeks 3 days	–8	38 weeks 0 day
3	CDH non-CDH	Left –	Down –	20 weeks 3 days	+5	33 weeks 1 day
4	CDH non-CDH	Left –	Down –	26 weeks 3 days	+4	37 weeks 3 days
5	CDH non-CDH	Left –	Down –	22 weeks 4 days	–8	38 weeks 3 days
6	CDH non-CDH	Left –	Down –	32 weeks 4 days	+9	37 weeks 3 days
7	CDH non-CDH	Left –	Down –	28 weeks 0 days	–13	31 weeks 5 days

* Percent difference in EFW compared to unaffected twin. GA, gestational age; EFW, estimated fetal weight; CDH, congenital diaphragmatic hernia.

outlining the lung boundary, excluding pulmonary hila. To calculate lung volume, the sum of all areas was multiplied by the slice thickness (3 mm; Fig. 1). The fetal MRI was read and/or reviewed by a single Pediatric Radiologist with 10 years' experience with fetal imaging to confirm the observed TFLV measurement. O/e TFLV was calculated using the affected twin's lung volume as the observed TFLV and the unaffected twin's lung volume as the expected TFLV and the following formula:

O/e TFLV = (measured TFLV of CDH Twin/measured TFLV of unaffected twin) ×100

This percentage was then compared to the o/e TFLV calculated using the TFLV formulas published by Rypens et al. [14], Osada et al. [15], Duncan et al. [16], Mahieu-Caputo et al. [17], and Meyers et al. [18] (Table 1). These studies were selected for having published gestational age-based equations to calculate fetal lung volume based on measurements from normal singleton fetuses in cohorts ranging from $n = 56$ to 665. Each study utilized MRI planimetry to measure TFLV, though there were differences in specific methodology amongst them (e.g., sequence, plane, region of interest) [12]. In our study, each dyad had 1 fetal MRI, except for 1 patient that had 2 fetal MRIs performed 8 weeks apart for evaluation of a suspected bronchopulmonary sequestration (BPS). Functional lung volume was measured for the TFLV in this case, excluding the volume of the BPS. Measurements, calculations, and analyses were applied to both studies.

Interrater reliability and the agreement between the different measures were assessed using intraclass correlation coefficient (ICC 2,1) defining the TFLV as the "target" and each method of calculation (or formula) as the "judge" [19]. The ICC 2,1 was derived using a 2-way mixed-effects ANOVA where the rating method and the twins were regarded as random effects. Each of the established methods (o/e TFLV calculated using Rypens', Osada's, Duncan's, Maheuio-Capitu's, and Meyers' TFLV formulas) was compared against the twin-based method to derive the absolute agreement between the techniques. Additionally, Bland–Altman plots were used to compare each of the formulas to the twin-based method. All analyses were performed using Microsoft Excel and STATA version 15 (College Station, TX, USA). Statistical significance was interpreted at $p < 0.05$.

Results

Patient Characteristics

Seven twin gestations in which 1 twin had a diagnosis of CDH were identified. All dyads were dichorionic diamniotic gestations. Aside from the CDH and a BPS identified on prenatal ultrasound of one CDH twin, no other structural abnormalities were identified in any fetus (Table 2). On ultrasound examination performed between 20 and 32 weeks of gestation, all except for one of which were performed on the same day as the MRI, each dyad exhibited similar expected fetal weights, with <20% difference between the 2 (mean difference of –3.9%, range: –16 to 4%). O/e LHRs ranged from 28 to 66% in the 6 cases in which they were available. Six of 7 patients had left-sided defects and 2 of 7 exhibited evidence of liver herniation.

Table 3. Measured TFLV and derived o/e TFLV for CDH twin based on MRI planimetry of unaffected

Twin ID	GA at MRI	CDH twin TFLV, mL	Unaffected twin TFLV, mL	o/e TFLV based on twin, %
1	28 weeks 1 day	6.4	38.3	17
2	23 weeks 3 days	5.1	18.0	28
3	22 weeks 4 days	7.0	19.0	37
4	26 weeks 3 days	16.1	33.8	48
5a	22 weeks 4 days	8.1	15.4	53
5b	30 weeks 4 days	19.9	38.0	52
6	32 weeks 4 days	32.6	61.3	53
7	28 weeks 0 days	36.9	51.7	71

GA, gestational age; TFLV, total lung volume; o/e TFLV, observed-to-expected TFLV; CDH, congenital diaphragmatic hernia; MRI, magnetic resonance imaging.

Three of 7 had prenatal genetic testing and had normal karyotypes; the remaining 4 lacked genetic testing. Median gestational age at birth was 37 weeks' gestation (interquartile range 33–38 weeks), and both twins in each dyad were delivered on the same day via cesarean.

MRI Results and Clinical Outcomes

MRIs were performed between 22 and 32 weeks' gestation. One dyad had a second MRI performed 10 weeks after the initial. Lung volumes were measured from all MRIs performed and o/e TFLV calculated as described in the Methods section (Table 2). Lung volumes in the CDH fetuses measured 5.1–36.9 mLs and in the unaffected fetuses measured 18.0–51.7 mLs; the latter were consistent with published normal ranges for gestational age but generally less than the published median/mean values [18]. O/e TFLV percentages based on the unaffected twin TFLV and the 5 published TFLV formulas were calculated and plotted (Table 3, Fig. 2).

Three of 7 CDH fetuses required ECMO (43%). Two were repaired after decannulation; one underwent early repair while on ECMO and was never able to be decannulated. The 3 patients who required ECMO exhibited larger defect sizes and the lowest o/e TFLV percentages in the series across all methods of calculation (Table 4).

Four of 7 CDH fetuses survived to discharge (57%) with a median hospital length of stay of 30 days (interquartile range 21–82 days). Two deaths were secondary to complications of severe pulmonary hypoplasia and pulmonary hypertension despite ECMO. These 2 also exhibited larger defect sizes and lower o/e TFLV percentages. The third patient underwent successful CDH repair, but subsequently developed fulminant necrotizing enterocolitis totalis and died on postoperative day 10.

ICC 2,1 estimates with 95% CIs were calculated for the o/e TFLV derived from each of the 5 different TFLV formulas: o/e TFLV based on the Meyers formula demonstrated the best agreement with an ICC 2,1 value of 0.850 (95% CI 0.405–0.968; Table 5). The Bland-Altman plots corroborated the results from the ICC (Fig. 3). The o/e TFLV based on the Meyer's formula had the least bias when compared with the twin-based with the narrowest limits of agreement (mean difference: 6.174; 95% limits of agreement: –12.006 to 24.354), showing the strongest agreement compared to the other formulas.

Discussion/Conclusion

Application of antenatal ultrasound and MRI in patients with CDH provides critical prognostic information to guide prenatal counseling and plan perinatal management. Currently, significant variability exists among institutions in the methods used to derive observed and expected total lung volumes. This not only confounds the ability to deliver consistent and accurate information to patients but also limits comparison of management strategies and outcomes. In this study, we identified a cohort of twin gestations in which one fetus is affected with CDH and compared it to the healthy unaffected sibling. We utilized MRI planimetry to directly measure the TFLV in each sibling and calculated the CDH twin's o/e TFLV utilizing the observed TFLV of the healthy unaffected sibling as the "expected" TFLV denominator. We compared these values to o/e TFLV derived from 5 published gestational age-based lung volume formulas. The 3 patients with the lowest o/e TFLV values (regardless of formula) had the poorest outcomes: all required ECMO, all demonstrated Type C or D defects, 2 had liver herniation (1 with a right-sided defect), and 2 did not survive to discharge. In ICC estimate analysis, o/e TFLV using the Meyers formula correlated best with the twin-based o/e TFLV. This was further corroborated by the Bland-Altman plots that showed the lowest bias with the narrowest limits of agreement for the Meyers formula.

CDH presents on a spectrum of disease severity. The twin cohort, despite being a limited sample, also spanned all severity categories, regardless of which formula or method was used to calculate the o/e TFLV, with the majority in the mild category. The rate of ECMO utilization in this small cohort was 43%, consistent with a

Table 4. Comparison of o/e TFLV based on unaffected twin TFLV versus GA-based formula TFLV

	o/e TFLV based on twin, %	Rypens, %	Osada, %	Duncan, %	Mahieu-Caputo, %	Meyer, %	Defect type	ECMO	Survival
1	17	14	21	23	15	14	D	Yes	No
2	28	19	27	33	18	21	C	Yes	Yes
3	37	29	42	50	27	32	C	Yes	No
4	48	42	62	72	44	44	B	No	Yes
5a	53	33	48	58	31	37	B	No	Yes
5b	52	34	55	52	37	34	–	–	–
6	53	47	81	68	52	45	B	No	Yes
7	71	81	123	133	87	83	B	No	No

o/e TFLV, observe-to-expected total fetal lung volume; GA, gestational age; ECMO, extracorporeal membrane oxygenation.

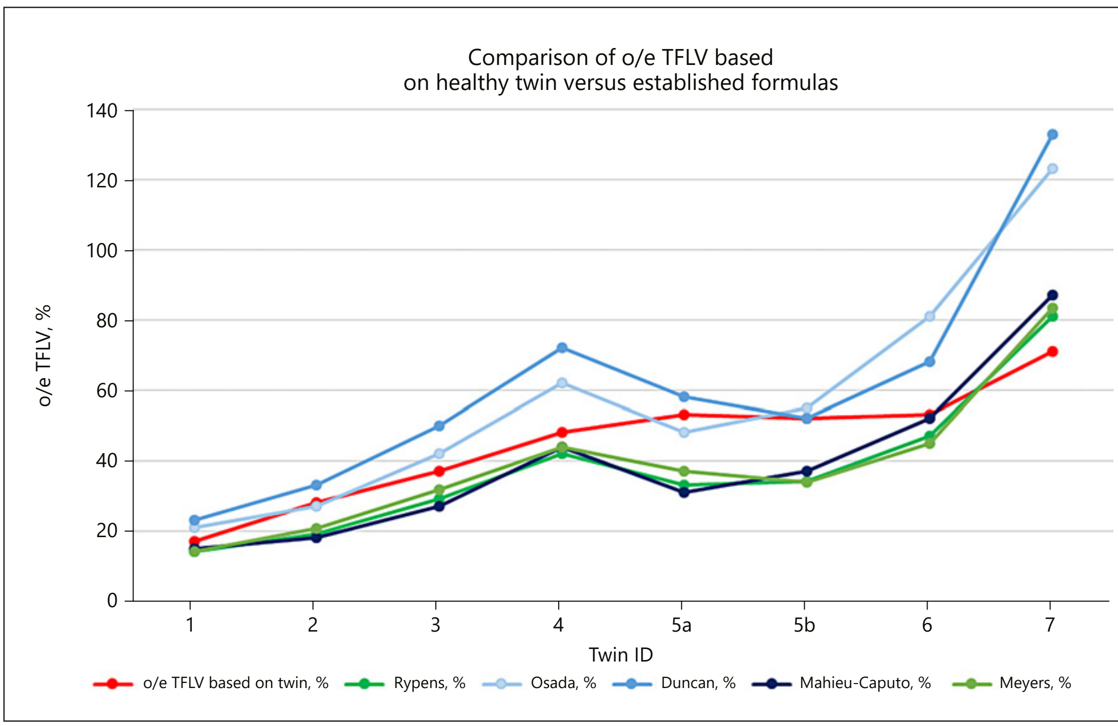

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Fig. 2. Plot of o/e TFLV percentages based on unaffected twin TFLV (in red) compared against o/e TFLV calculated from published formulas: Rypens, Osada, Duncan, Mahieu-Caputo, and Meyers. o/e TFLV, observed-to-expected total fetal lung volume.

larger institutional cohort rate of 38% [unpublished data, manuscript under review]. This is higher than in other larger published studies reporting an ECMO utilization rate of ~32% [5, 20, 21], though our institutional cohort was a significantly smaller sample and with dissimilar inclusion criteria. The twin cohort is too small for statistical analysis; however, those patients with lower o/e TFLV exhibited outcomes consistent with more severe disease (higher mortality, use of ECMO, larger defect type).

The o/e LHR values in the cohort similarly described a spectrum of disease, with 3 of 7 studies depicting CDH

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Table 5. ICC 2,1

	ICC	95% CI
Rypens et al. [14]	0.827	0.271–0.964
Osada et al. [15]	0.679	0.083–0.924
Duncan et al. [16]	0.620	–0.020–0.908
Mahieu-Caputo et al. [17]	0.823	0.385–0.961
Meyers et al. [18]	0.850	0.405–0.968

ICC, intraclass correlation coefficient.

of moderate severity based on the categories laid out by Deprest et al. [22] and the remaining 4 studies describing cases of mild severity. Of note, in the case of the patient who underwent 2 MRIs, the o/e LHR doubled from 31 to 66%, with a resultant change in the prognostic category from moderate to mild; however, the twin-based o/e TFLV remained essentially unchanged (53–52%) in the mild category. Almost a third of studies yielded discordant prognoses between the o/e LHR and the twin-based o/e TFLV, reflective of the fact that the 2 measures are not equal or interchangeable.

Where ultrasound reaches its limits, MRI may provide critical details. The ability to assess finer anatomic detail on MRI allows for accurate volumetric measurements of TFLV (including both the affected and the unaffected sides) as well as measurement of lung signal intensity, which may correlate with pulmonary hypoplasia [15, 23]. To maximize the potential of fetal MRI, however, its method, use, and interpretation should be standardized across the fetal community as prenatal US has been standardized. This will serve to provide not only consistent and accurate information for prenatal counseling, risk stratification, and potential selection for fetal therapy but also optimize the sharing and comparison of data across institutions for research.

Use of the unaffected twin's measured TFLV as the basis to calculate the CDH twin's o/e TFLV is a novel approach with applicability for other multiple gestations in which one fetus exhibits space-occupying intrathoracic pathology, whether CDH, congenital pulmonary airway malformation, or other conditions. Although this approach will not be helpful in most pregnancies, the higher incidence of multiple gestation pregnancies related to assisted reproduction allows a unique opportunity to better refine our methods [24]. In this study, we addressed just the one variable in the denominator, the TFLV formula, by measuring the lung volume of the healthy unaffected twin and using this as the "expected TFLV." Our measured TFLV values were less than both the median and the mean published TFLV values for gestational age in 6 of 7 fetuses [18]. This may represent the slowed growth rate seen later in gestation in twin compared to singleton gestations [25]. Also, fetuses with CDH exhibit pulmonary hypoplasia with smaller lung areas, greater lung lengths, and smaller volumes than those in equivalent-gestation normal fetuses [26]. Purely gestational age-based formulas may overestimate "expected" TFLV in CDH, and consequently underestimate o/e TFLV, especially in cases of a multiple gestation. In these special cases, utilizing the TFLV of an age- and size-matched healthy in utero sibling may yield a more accurate o/e TFLV. Additional biometric parameters and variables, such as signal intensity [15] and fetal body volume [27], have been studied as adjuncts to MRI planimetry to assess fetal lung volume, but these methods have not yet been validated. Despite its limitations, gestational age is accessible, convenient, and objective, and a formula allows for reproducible data in serial intra- and interpatient comparison.

Our twin-based o/e TFLV values were most consistent with o/e TFLV calculated using the Meyers formula on ICC analysis, and these results were corroborated by Bland-Altman plots. The Meyers formula was derived from measured fetal lung volumes from the largest sample size to date (665 patients), more than half of which were evaluated in the second trimester [18]. The Rypens formula was based on measurements from the second largest population (336 patients) and also exhibited good correlation with the twin-based o/e TFLV. When the 2 formulas were compared by Meyers et al. [18], values were very similar for most gestational ages, but the Meyers' group found that their mean measured TFLV was significantly lower in the 19–22 weeks' gestational age group. This is likely because the Rypens formula is based on only a few patients at 21 and 22 weeks' gestation and no patients <21 weeks' gestation; the Meyers cohort had 167 patients from 18 to 22 weeks' gestation. Considering 2 of 7 cases in our twin cohort had MRIs at 22 weeks' gestation, this may explain why the Meyers formula outperformed the Rypens formula in our study. Using the Meyers formula to calculate a more accurate expected TFLV and o/e TFLV as early as mid-second trimester may be critical when prenatal counseling includes consideration of termination or fetal intervention in those singleton cases meeting clinical criteria.

There are several limitations to this study. First, this is a retrospective study of a small number of patients that limits strong conclusions with regard to clin-

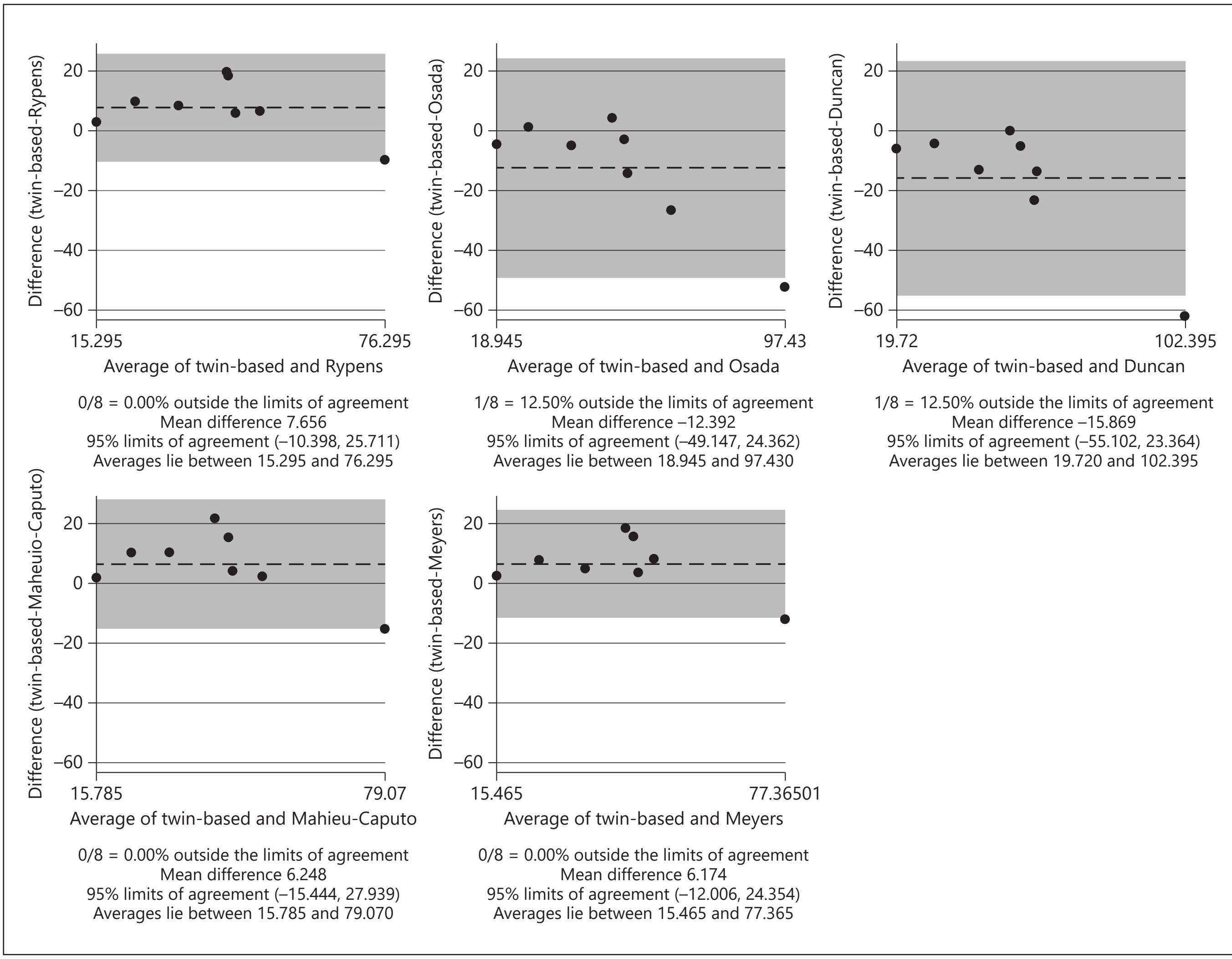

Fig. 3. Bland-Altman plots comparing the o/e TFLV derived from the twin-based method to each of the published formulas. The Meyers formula demonstrates the least bias with the narrowest limits of agreement.

ical outcomes or generalizability. A multi-institutional study of twin gestations with one fetus affected with CDH may improve understanding and lead to stronger support for one formula or method. There has been evidence to suggest that fetal lung development may not be identical in approximately 10% of twin gestations [28]; however, without significant growth difference or other confounding anomalies, the TFLV of a healthy unaffected twin offers a comparable size- and age-matched data-point. Second, we only address one variable of the o/e TFLV calculation in a select cohort. For true standardization, the fetal community needs to reach consensus on the method not only for estimating the expected TFLV (determining MRI sequence, planes, and the measured region of interest) but also for measuring the observed TFLV. Data from our small cohort support using the Meyers formula for calculating o/e TFLV across a broad range of gestational ages in order to maintain consistent values.

Conclusion

The unaffected twin's measured TFLV was useful to obtain a more realistic o/e TFLV in the CDH sibling, although its broader applicability is limited due to the small sample size. Comparison of the twin-based o/e TFLV with those calculated using published formulas maintained a relationship between low o/e TFLV and poorer outcomes (specifically the need for ECMO), and the o/e

TFLV based on the Meyers formula correlated best with our results. The fetal community should agree upon a standardized approach in fetal MRI to define, measure, and calculate lung volumes as an important adjunctive diagnostic modality for prenatal counseling, clinical decision-making, and research.

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Statement of Ethics

The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E.E.P., J.K., M.L.-T., M.C.T., and G.B.M.: study conception and design. A.G.K., R.A.M., J.K., and M.L.-T.: data acquisition. E.E.P., M.K., A.G.K., R.A.M.: analysis and data interpretation. A.G.K., M.K., E.E.P.: drafting of manuscript. R.A.M., J.K., M.L.-T., M.C.T., G.B.M.: critical revision of manuscript.

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