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Predictors of the need for extracorporeal membrane oxygenation and survival in congenital diaphragmatic hernia: a center's 10-year experience

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Objective To determine the prenatal factors associated with the need for extracorporeal membrane oxygenation (ECMO) and neonatal survival in congenital diaphragmatic hernia (CDH).

Study design A retrospective cohort study of all cases of CDH seen in our center between 1998 and 2008. Prenatal ultrasound and neonatal records were reviewed. Both univariable and logistic regression analyses were performed to determine the significant factors associated with the use of ECMO and survival.

Results Among 107 cases of CDH seen during the study period, 62 were evaluated prenatally in our center and 49 had information on all variables evaluated. The overall rate of ECMO use was 27/107 (25%) and survival rate was 53/107 (49.5%). The lung area to head circumference ratio (LHR) and gestational age (GA) at delivery were the only significant factors associated with ECMO use, and the LHR and absence of liver herniation were significantly associated with survival. LHR values under 1.0 were associated with 57% need for ECMO and 100% neonatal death. Although, overall, the observed : expected LHR (O : E LHR) was not significantly associated with ECMO use or survival, levels below 65% were associated with 58% need for ECMO ($p = 0.004$) and 100% neonatal death ($p = 0.002$).

Conclusion The study confirms the LHR, GA at delivery and liver herniation as significant prenatal predictors of the need for ECMO or survival in cases with CDH. This information is helpful for counseling women with fetuses complicated by CDH. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: diaphragmatic hernia; lung head ratio; survival; ECMO

INTRODUCTION

Congenital diaphragmatic hernia (CDH) affects approximately 1 in 5000 live births and a neonatal mortality rate that may be as high as 60% (Skari *et al*., 2000; Witters *et al*., 2001; Stege *et al*., 2003). The main mechanism resulting in neonatal demise is the development of pulmonary hypoplasia secondary to lung compression from the CDH.

In cases with respiratory difficulties that make immediate postnatal surgery inadvisable, extracorporeal membrane oxygenation (ECMO) is employed. The use of ECMO has been associated with a higher incidence of chronic lung disease in infants with CDH (Jaillard *et al*., 2003).

Given the high mortality and morbidity rates in cases of CDH, attempts at predicting fetuses at risk for adverse neonatal outcomes have been made over the last decade. The most common methods used to indirectly predict postnatal lung volume in the prenatal period include measurement of the lung area to head circumference ratio (LHR) and documentation of liver herniation (Metkus *et al*., 1996; Lipshutz *et al*., 1997; Jani *et al*., 2006; Coakley *et al*., 2000; Rypens *et al*., 2001). The use of the LHR after 26 weeks of gestation has been inconsistent in many centers including ours, due to suggestions that it is unreliable after this gestational age. Recent studies report that the observed to expected LHR (O : E LHR) for gestational age is a better predictor of postnatal survival as it corrects for the gestational age limitation of LHR mentioned above (Jani *et al*., 2007a, 2009). Most of these reports are yet to be validated from other centers.

Our objective is to evaluate the prenatal factors associated with the need for ECMO and neonatal survival in CDH and to determine how the LHR and the O : E LHR perform in our center.

METHODS

This is a retrospective cohort study of all cases of CDH seen in our center between 1998 and 2008. Prenatal ultrasound and neonatal records were reviewed.

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We included only cases with isolated CDH in the models predicting survival and ECMO use. We excluded those with chromosomal abnormalities from all analyses.

The prenatal records were examined to identify those with documented LHR, liver herniation, location of CDH (left or right sided), gestational age at diagnosis. The lung area was measured as described by Metkus *et al.* (1996). Briefly, from a transverse section of the fetal chest showing the four-chamber view of the heart, the LHR is calculated by multiplying the two longest perpendicular diameters of the contralateral lung. To derive the O : E LHR, the observed LHR for each fetus was divided by the mean LHR for the gestational age and multiplied by 100 as described by Jani *et al.* (2007b). In the later calculation, the expected LHR for the gestational age was derived from the chart reported by Jani *et al.* (2007b). The study was approved by the institutional review board of Washington University School of Medicine.

The primary outcome measures for the study were the prediction of the need for ECMO or neonatal survival. We also compared the screening efficiency of the LHR versus O : E LHR by comparing their sensitivity and specificity in predicting the need for ECMO and neonatal survival. The discriminating ability of the LHR and O : E LHR were compared using the area under the ROC curves (AUC).

Statistical analysis included the use of chi-square test for categorical variables and t-test for continuous variables. Logistic regression analyses were performed to determine the significant factors associated with the use of ECMO and survival. A p-value <0.05 was considered statistically significant. All analyses were performed using STATA 10 SE (STATA Corp. College Station, TX, USA).

RESULTS

Among the 107 cases of CDH observed during the study period, 62 were evaluated prenatally in our center and 49 had information on all variables evaluated. The overall rate of ECMO use was 27/107 (25%) and survival rate was 53/107 (49.5%). The general characteristics of cases seen in the prenatal period in our center are shown in Table 1.

Of the 50 cases with isolated CDH, 15 (30%) required ECMO and 22 (44%) survived.

Significant factors associated with ECMO use and survivals are shown in Table 2. The LHR and gestational age (GA) at delivery were the only significant factors associated with ECMO use, and the LHR and absence of liver herniation were significantly associated with survival. LHR values under 1.0 were associated with 57% need for ECMO and 100% neonatal death. Although, overall, the O : E LHR was not significantly associated with ECMO use or survival, levels below 65% were associated with 58% need for ECMO ($p = 0.004$) and 100% neonatal death ($p = 0.002$).

The AUC for predicting survival using the LHR and the O : E LHR are 0.74 (95% CI, 0.60–0.88) and 0.65 (95% CI, 0.49–0.80), respectively (Figure 1). The difference between the AUC using the two methods of assessment was not statistically significant ($p = 0.21$). Using a cut-off threshold for the LHR >1.2, the sensitivity and specificity for survival are 84 and 43%, respectively. If the cut-off is an LHR >1.0, the sensitivity and specificity for survival are 100 and

Table 1—General characteristics of all cases with diaphragmatic hernia seen prenatally

	$N = 62$ (%)
Mean gestational age at ultrasound ± SD (weeks)	25.7 ± 6.3
Isolated CDH	50 (80.6)
Liver herniation	23 (21.5)
Left sided defect	54 (87.1)
Mean LHR	1.6 ± 0.8
Mean O : E LHR	87.6 ± 32.9
Mean gestational age at delivery ± SD (weeks)	37.4 ± 2.7
Mean birth weight ± (g)	2931.9 ± 746
ECMO	17 (27.4)
Survival	27 (43.5)

ECMO, extracorporeal membrane oxygenation; LHR, lung area to head circumference ratio; O : E LHR, observed : expected LHR.

Table 2—Predictors of the need for ECMO and neonatal survival in cases with congenital diaphragmatic hernia

	ECMO (OR, 95% CI)	Survival (OR, 95% CI)
LHR	0.25 (0.07–0.95)*	2.5 (1.1–6.1)*
O : E LHR	0.98 (0.95–1.00)	1.01 (0.9–1.04)
Right sided defect	0.33 (0.04–2.99)	1.3 (0.3–6.0)
No liver herniation	1.71 (0.4–6.8)	5.1 (1.2–22)*
Isolated CDH	1.3 (0.2–8.4)	1.1 (0.2–6.7)
GA at diagnosis	0.9 (0.88–1.1)	1.1 (0.9–1.2)
GA at delivery	1.3 (1.0–1.6)*	0.8 (0.6–1.2)

ECMO, extracorporeal membrane oxygenation; LHR, lung area to head circumference ratio; CDH, congenital diaphragmatic hernia; O : E LHR, observed : expected LHR.
* Significant at $p < 0.05$.

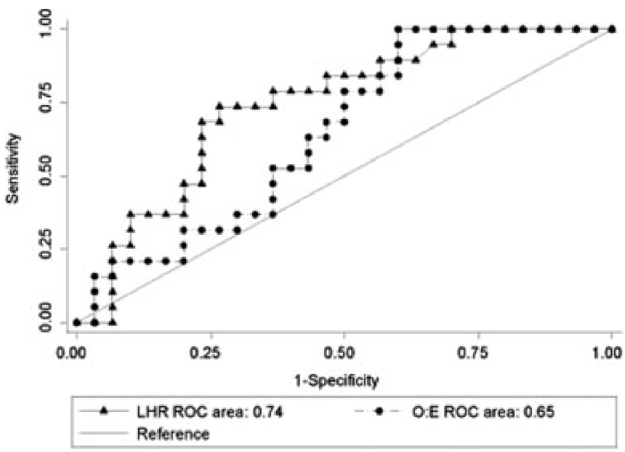

Figure 1—ROC curves for survival comparing LHR and O : E LHR

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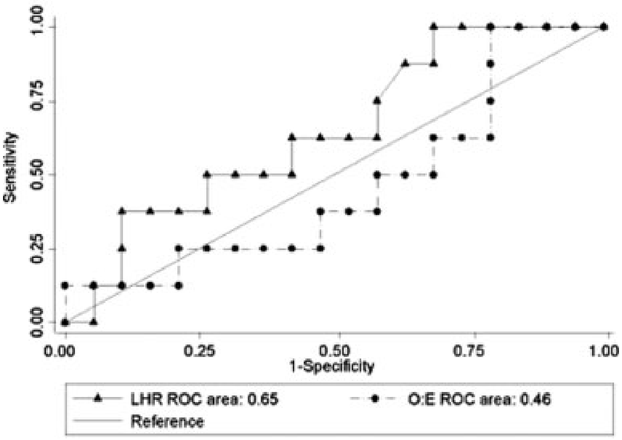

Figure 2—ROC comparing LHR versus O : E LHR for cases of CDH diagnosed under 26 weeks

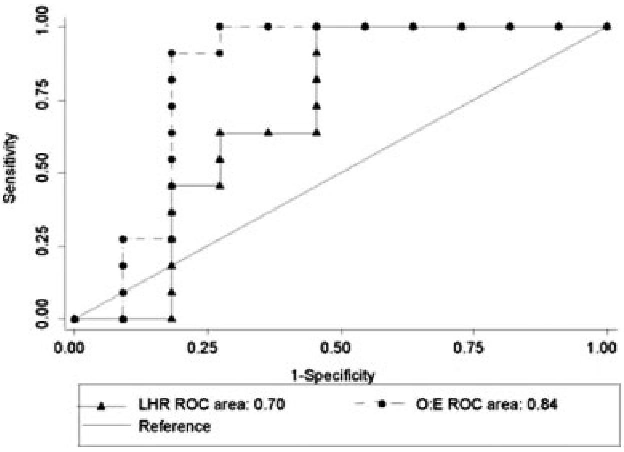

Figure 3—Comparing LHR versus O : E LHR for cases of CDH diagnosed after 26 weeks

30%, respectively. An O : E LHR >65% has a 100% sensitivity for survival but a specificity of 36.7%.

To determine the impact of the gestational age at diagnosis on the performance of the LHR versus O : E LHR in predicting neonatal survival, we performed a stratified analysis with data dichotomized by cases diagnosed prior to 26 weeks and those detected at or after 26 weeks. The AUC for those seen prior to 26 weeks ($n = 27$) were 0.65 (95% CI, 0.42–0.87) and 0.46 (95% CI, 0.21–0.71), using the LHR and O : E LHR, respectively (Figure 3). The difference in AUC for this sub-analysis was statistically significant ($p = 0.03$). For those diagnosed at or after 26 weeks ($n = 22$), the AUC were 0.70 (95% CI, 0.45–0.95) and 0.84 (95% CI, 0.62–1.00), respectively (Figures 2 and 3). The difference in the AUC for the later comparison was barely statistically significant ($p = 0.048$).

Both the LHR and O : E LHR are poor predictors of ECMO use with an AUC of 0.31 (95% CI, 0.14–0.48) and 0.35 (95% CI, 0.15–0.55), respectively (Figure 4).

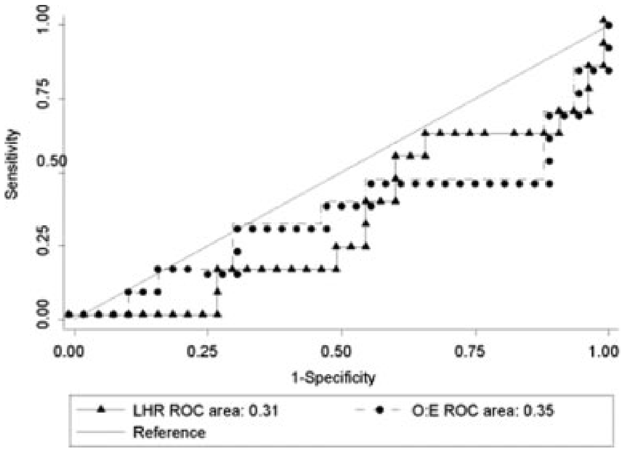

Figure 4—ROC curve for the need for ECMO comparing LHR and O : E LHR

DISCUSSION

This study found the LHR and absence of liver herniation to be the best predictors of fetal survival while the LHR and the gestational age at delivery were the best predictors of the need for ECMO. However, the efficacy of the LHR is predicting the need for ECMO was poor. The side of the hernia and the presence of other anomalies were not significant predictors of survival.

When compared with the LHR, the O : E LHR was not as efficient in predicting neonatal survival in the overall analysis. The difference in the AUC for this comparison was, however, not statistically significant. When the comparison is stratified by the GA at diagnosis, the LHR appears to perform better prior to 26 weeks, whereas the O : E LHR performed better after this gestational age. The reason for using the GA of 26 weeks as the threshold for this analysis is due to previous publications suggesting that the LHR is not a reliable predictor of survival when used after 26 weeks (Yang *et al.*, 2007). Our finding suggests that the performance of each method of assessment is dependent on the GA of evaluation. This is contrary to that reported by Jani *et al.* suggesting that the use O : E LHR as a predictor of neonatal survival is independent of gestational age (Jani *et al.*, 2008). Furthermore, our finding is different from the report by Yang *et al.* suggesting that the LHR is more reliable after 24 weeks (Yang *et al.*, 2007). The conflicting conclusions from these reports calls for a prospective multicenter study comparing the LHR with the O : E LHR.

The clinical implications of our findings suggest a two-tiered approach to the use of LHR and the O : E LHR in counseling expectant mothers with fetuses with CDH. Under 26 weeks, we suggest using the LHR as most centers (at least in the USA) currently do and beyond 26 weeks to use the O : E LHR. Our study also suggests that another variable to be used for counseling is the absence or presence of liver herniation.

Although the LHR is inversely related to the need for ECMO, the ROC curves suggests that neither the LHR nor the O : E LHR is a reliable predictor of a need

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for ECMO in the neonatal period. The gestational age at delivery was the only other significant predictor of the need for ECMO. The finding is not surprising as the indications/triggers for the use of ECMO vary widely by centers and even within the same center. Some centers use ECMO as rescue mode, others much earlier in the course of CDH, and others more routinely. Until these indications are standardized, efforts at predicting those infants needing ECMO will continue to have a low yield.

The strength of our study is that it reflects our center's long-term experience and therefore would be useful for counseling our patients. The study however, has some limitations that must be considered in interpreting our results. These include the retrospective study design and the relatively small sample size. We calculated the LHR using the longitudinal method of measuring the LHR and not the trace method, which has been suggested to be more reliable for predicting survival in a previous study (Jani *et al*., 2007b).

However, as the longitudinal method is the one currently used in our center, the conclusions of the study is relevant to our situation and other centers using that method. Similar to most studies in the prenatal period, we were unable to determine the size of the defect prenatally and the potential impact of this on survival. Future studies should investigate surrogate markers for the size of the defect because a recent multicenter study suggests that this may be the major factor influencing outcome in infants with CDH (The Congenital Diaphragmatic Hernia Study Group, 2007). The rate of intrathoracic liver herniation of 21.5% reported in this study is relatively lower than in previous series. The possibility of ascertainment bias cannot be ruled out as in the early periods of this series, not all fetuses with CDH had a fetal MRI to confirm the presence of liver herniation. However, our rate is similar to the 24% rate of intrathoracic herniation reported by Jani *et al*. among survivors with congenital diaphragmatic hernia (Jani *et al*., 2009).

In conclusion, the study confirms the LHR, GA at delivery and liver herniation as significant prenatal predictors of the need for ECMO or survival in cases with CDH. We also confirm that the efficiency of the LHR and the O : E LHR is dependent on the gestational age of evaluation. This information is helpful for counseling women with fetuses complicated by CDH.

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