Improved Survival in Left Liver-Up Congenital Diaphragmatic Hernia by Early Repair Before Extracorporeal Membrane Oxygenation: Optimization of Patient Selection by Multivariate Risk Modeling

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BACKGROUND: Delayed repair of congenital diaphragmatic hernia (CDH) for days or longer has become standard, allowing improved stabilization for many, but potentially complicating treatment in severely affected infants who require extracorporeal membrane oxygenation (ECMO) and arrive unrepaired. Survival in left liver-up CDH, the most severe anatomic subset, averages 45% in published studies, with deaths often occurring in patients who failed to improve on ECMO and are repaired late, or not at all. Reliable early prediction of ECMO risk in these patients could identify the best candidates for repair before ECMO. We sought to predict ECMO risk in left liver-up CDH, and to further evaluate survival stratified by surgical timing in these patients.

STUDY DESIGN: We reviewed 298 single-center, consecutive CDH patients, focusing on 87 inborn left liver-up patients without associated lethal anomalies. Multivariate analysis using anatomic and physiologic markers of severity was performed to define associations with need for ECMO.

RESULTS: Sixty of 87 ECMO-eligible inborn left liver-up CDH patients required ECMO (69%). Of these, 20 of 21 (95%) repaired in the first 60 hours and before ECMO survived; whereas 13 of 20 (65%) who had repair delayed and arrived to ECMO unrepaired survived ($p = 0.018$). Lung-to-head ratio, Apgar scores, Congenital Diaphragmatic Hernia Study Group-predicted survival, pH, PCO_2, and PO_2 at 1 hour of life all correlated strongly with risk for ECMO. Accurate multivariate models to predict ECMO (area under the receiver operating characteristic curve [AUC] 0.91 and 0.91) were successfully developed.

CONCLUSIONS: Early repair of left liver-up CDH before ECMO results in improved survival. Multivariate models can accurately assess risk for ECMO at 1 hour of life, permitting stratification of CDH surgical timing to maximize survival potential while minimizing risk. (J Am Coll Surg 2016;222:459–470. © 2016 Published by Elsevier Inc. on behalf of the American College of Surgeons.)

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The surgical history of congenital diaphragmatic hernia (CDH) has evolved from one of emergency repair for all patients as soon after delivery as possible, a practice common for decades or more, to one of delayed repair, again for all patients, an evolutionary change that began in the 1990s.[1,2]

Although the literature fails to define exactly what delayed repair is, time to repair currently commonly ranges from several days to sometimes weeks, depending on the center. Regardless, the therapeutic pendulum has swung far in the direction of delayed repair, as defined

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Abbreviations and Acronyms

AUC = area under the receiver operating characteristic curve
CDH = congenital diaphragmatic hernia
CDHSG = Congenital Diaphragmatic Hernia Study Group
ECMO = extracorporeal membrane oxygenation
LHR = lung-to-head ratio
o/e = observed-to-expected ratio

by efforts to "stabilize" the patient, or to wait until resolution of pulmonary hypertension.[2-4] No convincing evidence exists, however, to define any survival benefit from delayed or early repair, as the limited prospective evidence shows no benefit to either strategy.[5] Regardless, the question of repair timing is usually posed for the full spectrum of disease severity.

The "all or none" application of treatment strategy occurs despite the common knowledge that congenital diaphragmatic hernia represents a wide spectrum of disease. Severity can be defined by a variety of anatomic and physiologic metrics that correlate with outcomes. These include side of defect, amount and type of visceral herniation into the chest, defect size defined at the time of repair, and by measurements of lung size and/or volume.[6-9] Physiologic measurements at birth and soon thereafter also correlate strongly with survival, risk of extracorporeal membrane oxygenation (ECMO), risk of second ECMO, and other disease severity-related outcomes measures.[10]

It is plausible and even probable that the physiologic benefits and stresses that accrue from surgical repair of CDH are differentially expressed across the spectrum of pulmonary hypoplasia and pulmonary hypertension that define CDH.[11,12] In 2013, we published a large retrospective review showing that patients with left liver-down CDH, a less severe anatomic form of CDH, benefit from delay of repair for at least 48 hours.[12] Repair before 48 hours resulted in an increased need for ECMO in that anatomic subset, but without any offsetting increase in survival. Conversely, data from that same report suggested that patients with more severe left liver-up CDH may enjoy a survival advantage when repaired before ECMO, but without any statistical evidence of increased risk of ECMO.

Left liver-up CDH is the most severe anatomic subset, and the sub-population upon whom refinement of strategies will have the largest potential impact. Survival to discharge in a recent meta-analysis of left liver-up CDH was only 45%, a rate confirmed in a contemporary publication from a large US children's hospital.[13,14] Within left liver-up CDH, however, there is still a spectrum of severity, and the challenge is to define a treatment strategy that will optimize survival while minimizing risk. As we demonstrated in left liver-down CDH, the potential exists for inadvertently increasing the risk for ECMO by performing early repair in less severe forms of left liver-up CDH. Although this postulated risk of early repair increasing ECMO is unproven, it is a natural extension of concepts previously demonstrated, and it fits our overall theory of CDH physiology and recovery. It would be beneficial then, to be able to reliably define an individual's specific risk for ECMO, so that informed treatment strategies could be implemented.

In this study, we collected a full range of anatomic and physiologic risk stratifiers, and asked how soon after birth and how accurately can we define the risk of ECMO in left liver-up CDH patients. Our goal was to identify the more severe end of the left liver-up spectrum—those patients who will likely need ECMO regardless of the potential effects of surgical repair timing. We sought to compare outcomes in those we chose to repair early before ECMO vs those for whom we chose to delay repair and who then arrived to ECMO unrepaired. If evidence of improved outcomes exists, then prediction of ECMO risk can be used to ask prospectively who may benefit from early surgical intervention vs who may benefit from delaying repair. We chose to exclusively study inborn left liver-up CDH patients from our center, as inborns most accurately represent the full spectrum of disease severity. Further, the vast majority of inborns were prenatally diagnosed and underwent planned births with highly consistent resuscitation, optimizing the potential that measured differences in physiologic variables reflect differences in disease severity rather than differences in resuscitation. This should increase the potential to develop accurate predictive models that can help evaluate and serve the hypothesis that optimal timing of CDH repair varies across the spectrum of CDH physiology.

METHODS

This was a retrospective, IRB-approved review of all Bochdalek type CDH patients, symptomatic in the first 6 hours of life, who were cared for at the University of Florida Health, Shands Children's Hospital between September 1, 1992 and June 30, 2014. Two hundred ninety-eight patients were identified and all were included, regardless of associated anomalies, degree of pulmonary hypoplasia, and medical condition on arrival. Two separate hospital medical record queries were cross-referenced with operative records, autopsy records, a pediatric surgery database, and 2 prenatal evaluation databases to assure that no patients were missed. Patients with Morgagni CDH, diaphragmatic eventration, and patients

in whom the diagnosis of diaphragmatic hernia was delayed more than 48 hours after delivery were not included. Overall results for the 298 patients are reported.

This study focuses on 87 consecutive, inborn, left liver-up CDH patients who were without highly severe or lethal associated anomalies, and who were considered ECMO eligible, as defined by gestational age of 33 weeks or higher, and birth weight of 1,800 g or higher. All had significant amounts of liver in the chest, as defined by surgical repair, imaging, or post-mortem exam. Patients with trivial amounts of liver in the chest (roughly estimated as 5% or less) were not defined as liver-up. Liver-up size was also estimated at "20% or less" and "more than 20%."

In order to accurately compare the results for early vs delayed repair in patients requiring ECMO, newborns who were too unstable for early repair and went to ECMO in the first 12 hours were considered to not have "opportunity" for early repair. These patients are not included in the comparison of results for early vs delayed repair, but are included in the analysis of risk for ECMO.

Data collected and used for this analysis include prenatal lung-to-head ratio (LHR), calculated observed-to-expected LHR (LHR o/e) (perinatology.com), gestational age, birth weight, Apgar scores at 1 and 5 minutes, calculation of CDH Study Group-predicted survival (nicutools.com), post-ductal blood gas values measured as close to 1 hour of life as possible, side of defect, position of liver, and presence of associated anomalies. Time from birth to repair was calculated, as was time from birth to ECMO. The anatomic definition of liver position and estimate of percent herniated were defined from direct observation at repair, at post-mortem examination, or from noninvasive imaging if neither was available.

Clinical care

This study focuses on inborn patients. More than 90% were prenatally diagnosed and counseled. Terminations for CDH in the absence of severe associated anomalies did not occur. Delivery was generally performed between 38 and 39 weeks by induction or Caesarean section. The pediatric surgeon attended all deliveries of prenatally diagnosed CDH patients. Newborns were intubated in the first minutes of life, and Apgar scores were assigned by the neonatal staff present at delivery.

Clinical care has been previously described. Ventilation specifics and ECMO care have changed little over the nearly 22 years of the study, and have not changed appreciably from those in previous publications.[12,15]

Decisions on surgical timing in patients with left liver-up CDH have evolved, but with defined periods in which delay of repair was actively practiced. Over the last 5 years, however, and especially since our publication in 2013, we have moved toward earlier repair of severe left liver-up CDH, usually in the first 24 hours of life, and including repair as early as 6 hours of life in highly severe cases that would certainly need ECMO. As experience has increased, we've gained confidence in our ability to safely perform repair, even in these severely affected newborns. Early repair is performed at the bedside in the neonatal ICU, with operating room and anesthesia teams in attendance. Anesthetic techniques and goals are protocolled. Nitric oxide is held in reserve for rescue should critical instability occur, and ECMO is also available as stand-by. When CDH repair is performed in left liver-up CDH before ECMO, exacting hemostasis is achieved. If ECMO seems imminent, the goal is to achieve a minimum of 4 hours from surgical closure before ECMO (heparin) to minimize risks of bleeding on ECMO. Amicar is not used.

ECMO support is never initiated prophylactically, and the indication to start ECMO is declining stability with life- or brain-threatening hypoxemia, generally defined as the inability to maintain pre-ductal saturations above 80% to 85%, despite what we consider to be optimal ventilatory support, including the use of nitric oxide, volume support, vasopressors, pulmonary vasodilators, and steroids.

The ECMO support is usually veno-arterial for left liver-up CDH, the ECMO strategy and support are highly consistent, and are marked by the conceptual goal of supporting rather than controlling the patient's native physiology. Modest pressure limited ventilator settings and rate are maintained during ECMO support to allow lung accommodation to moderate workload. Neither "lung rest" nor "recruitment maneuvers" are performed. Nitric oxide is weaned off within 24 hours of commencing ECMO, diuretics are usually begun after 72 hours of ECMO support, and renal replacement therapy of all types is actively avoided. As the patient's physiology improves post-operatively, ECMO is weaned slowly and deliberately to allow the child's cardiovascular and pulmonary systems to adapt to the increasing workload. Weaning off ECMO is based on satisfactory hemodynamics and improving lung function, as evidenced by improving post-ductal blood gases. ECMO weaning is never based on echocardiographic estimates of pulmonary hypertension.

Analysis

Independent variables of physiologic severity were analyzed independently and in multivariate logistic regression assessing effects on the outcome variables of survival and need for ECMO. We used the R statistical software package (V3.0.2). Fisher's exact test was used to compare groups on categorical variables and Mann-Whitney tests to compare them on continuous variables.

We used best-fit multivariate techniques to model survival, risk for ECMO, and probability of survival without ECMO. Logistic regression using stepwise variable elimination based on the Akaike Information Criterion informed model development, and a model's predictive ability was assessed using the area under the receiver operating characteristic curve (AUC). The potential effect of covariates was considered in constructing the predictive models.

RESULTS

We identified 298 consecutively treated CDH patients, and overall results are shown in Table 1. Of these, 87 were inborn, left liver-up CDH, without associated highly severe or lethal anomalies, were considered ECMO eligible, and represent the study subjects. The full dataset of postnatal markers of severity was complete for all 87, while prenatal measures of lung size, LHR and LHR observed/expected were missing in 12 (75 of 87, 86%) due to the random effects of incomplete prenatal testing in those 12.

Of the 87 patients, 71 survived to discharge (82%), 60 of 87 required ECMO, and 44 of those survived (73%). Of the 60 who required ECMO, 15 were too unstable and did not have an "opportunity" for repair before ECMO. These 15 went onto ECMO less than 12 hours after birth (mean 4.6 ± 3.4 hours), and 8 of these 15 survived (53%).

Table 1. Congenital Diaphragmatic Hernia Survival to Discharge Results: 298 Consecutive Patients

		Survived	
Characteristic	**n**	**n**	**%**
Overall	298	234	79
Left liver-down	111	107	96
Left liver-up	118	85	72
Right	55	42	76
Bilateral (included in lethal anomalies)	7	0	0
Lethal/major anomalies	32	1	
Minus lethal/major anomalies	266	233	88
Left liver-down	108	107	99
Left liver-up	111	85	77
Right	45	41	91

Of the remaining 45 who ultimately required ECMO and had the "opportunity" for early repair, 25 had repair before ECMO and 23 survived (92%), while 20 had repair delayed and arrived to ECMO unrepaired. Of these 20, 13 survived (65%, $p = 0.0567$). Of the 25 repaired before ECMO, 22 underwent "early" repair (<60 hours, mean time to repair 20.8 hours ± 10.6 hours), while the mean time to repair of the remaining 3 approached 5 days (112.8 ± 35.4 hours). Of the 22 who underwent early repair before ECMO, 21 survived (95%).

Left liver-up CDH patients who underwent "early" repair and subsequently required ECMO survived at a significantly higher rate (21 of 22, 95%) compared with those who were treated with delayed repair and arrived at ECMO unrepaired (13 of 20, 65%, $p = 0.018$). Those repaired early and subsequently requiring ECMO were not statistically different across all anatomic and physiologic severity metrics tested from those who had repair delayed and arrived to ECMO unrepaired, nor were they different in highly correlated multivariate survival and ECMO-risk modeling (Table 2).

Analysis of cause of deaths in ECMO patients with "opportunity"

Repair before ECMO

Of 25 patients repaired before ECMO, 2 died. The first was repaired at 5 days (122 hours of life), but suffered late onset fungal sepsis. He declined rapidly and was placed on ECMO at 15 days of life, but did not recover. The second was repaired at 27 hours, successfully treated with ECMO, decannulated, and later extubated. She was doing well on nasal cannula oxygen, but died acutely from an unfortunate and unrelated complication.

Delay of repair

In contrast, of 20 patients who had surgery delayed and arrived to ECMO unrepaired, 7 patients died. Three developed organ failure on ECMO and died without repair. The other 4 failed to improve after more than 2 weeks on ECMO and were repaired at a mean of 20 days of life while either still on ECMO or during a minimal hiatus between a first and second ECMO run. One succumbed to bleeding and 3 had surgical complications related to loss of abdominal domain.

Multivariate predictive modeling (inborn left liver-up congenital diaphragmatic hernia)

Modeling of survival

In these 87 patients, pH at 1 hour ($p = 0.0009$) and first LHR ($p = 0.008$) correlated most strongly with survival. The best predictive model for survival in this group

Table 2. Statistical Comparison of Risk Stratifiers for 22 Left Liver-Up Congenital Diaphragmatic Hernia (CDH) Patients Who Underwent Early CDH Repair before Extracorporeal Membrane Oxygenation (ECMO), Compared with 20 Patients Treated with Delayed Repair and Who Arrived to ECMO Unrepaired

Variable	ECMO first (n = 20)	Surgery before 60 h and before ECMO (n = 22)	p Value (Mann-Whitney test)
Survived, n (%)	13 (65.0)	21 (95.5)	0.018 (Fisher's exact test)
Apgar 1			0.251
Mean (SD)	2.75 (2.1)	3.6 (2.0)	
Median [IQR] (range)	2 [1, 5] (0, 6)	4 [1, 5] (1, 7)	
Apgar-5			0.610
Mean (SD)	5.85 (1.8)	6.0 (2.1)	
Median [IQR] (range)	6 [4.8, 6.5] (3, 9)	6.5 [5, 7] (1, 9)	
CDHSG			0.364
Mean (SD)	52.4 (19.6)	58.2 (22.9)	
Median [IQR] (range)	49.5 [40, 63] (16, 84)	64.5 [41, 76] (9, 88)	
First LHR			0.791
Mean (SD)	1.1 (.45)	1.1 (.40)	
Median [IQR] (range)	1 [0.88, 1.3] (0.5, 2.4)	0.96 [0.83, 1.4] (0.6, 1.9)	
LHR observed/expected			0.868
Mean (SD)	30.6 (13.1)	28.5 (7.9)	
Median [IQR] (range)	28 [23.5, 35] (16, 76)	27.5 [22, 33] (17, 43)	
pH 1 h			0.319
Mean (SD)	7.1 (.14)	7.1 (.08)	
Median [IQR] (range)	7.1 [7.0, 7.2] (6.8, 7.2)	7.1 [7.1, 7.2] (6.9, 7.2)	
PO_2 1 h, mmHg			0.705
Mean (SD)	46.1 (8.9)	46.9 (17.3)	
Median [IQR] (range)	45 [41.8, 54.3] (29, 62)	46 [36, 51] (21, 99)	
PCO_2 1 h, mmHg			0.307
Mean (SD)	85.8 (21.6)	77.1 (14.9)	
Median [IQR] (range)	78 [70, 100] (62, 130)	79 [65, 83] (54, 111)	
Birthweight, g			0.188
Mean (SD)	2,724 (340)	2,910 (478)	
Median [IQR] (range)	2,778 [2,510, 3,049] (2,099, 3,247)	2,870 [2,680, 3,220] (1,880, 3,740)	
Gestational age, wk			0.199
Mean (SD)	37.2 (1.5)	37.7 (1.2)	
Median [IQR] (range)	37.5 [36, 38] (34, 40)	38 [37, 38] (35, 39)	
Survival equation:1(predicted survival rate)			0.537
Mean (SD)	0.79 (0.13)	0.77 (.14)	
Median [IQR] (range)	0.81 [0.75, 0.89] (0.42, 0.93)	0.77 [0.72, 0.88] (0.38, 0.95)	
ECMO risk equation:1 (AUC = 0.91)			0.734
Mean (SD)	0.77 (0.18)	0.80 (0.13)	
Median [IQR] (range)	0.82 [0.70, 0.90] (0.21, 0.96)	0.84 [0.69, 0.90] (0.50, 0.99)	
ECMO risk equation: 2 (AUC = 0.87)			0.325
Mean (SD)	0.82 (0.08)	0.77 (0.15)	
Median [IQR] (range)	0.83 [0.76, 0.88] (0.64, 0.95)	0.81 [0.75, 0.85] (0.29, 0.95)	
Probability of survival w/o ECMO (AUC = 0.91)			0.801
Mean (SD)	0.20 (0.18)	0.16 (0.12)	
Median [IQR] (range)	0.16 [0.07, 0.28] (0.03, 0.77)	0.13 [0.07, 0.22] (0, 0.44)	

AUC, area under receiver operating characteristic curve; CDH, congenital diaphragmatic hernia; CDHSG, Congenital Diaphragmatic Hernia Study Group; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; LHR, lung-to-head ratio.

combined a best (prenatal) anatomic variable and a best (postnatal) physiologic variable.

$$\text{Probability of survival} = \exp(A + B + C)/(1 + \exp(A + B + C))$$

Where A = −32.44, B = 4.61*pH1, and C = 1.24*LHR. (AUC = 0.78)

Risk of ECMO

Physiologic variables at birth, Apgar-1 (p = 0.004) Apgar-5 (p = 0.010), and CDH Study Group-predicted survival (p = 0.016) all correlated with risk for ECMO. The anatomic variable "First LHR" (p = 0.0002) correlated better with risk for ECMO than birth physiology, but LHR observed/expected (p < 0.0001) correlated even more strongly than LHR. Physiologic (post-ductal) blood gas variables (pH at 1 hour, PCO_2 at 1 hour, and PO_2 at 1 hour) all correlated exceptionally strongly (p < 0.0001) with risk for ECMO (Table 3).

Receiver operator curves for the 4 most correlated individual variables are shown in Figure 1. The resultant multivariate model equation predicting ECMO is:

$$\text{Probability of ECMO Eq. 1} = \exp(A + B + C + D)/(1 + \exp(A + B + C + D))$$

Where A = 40.18, B = −4.919*pH1, C = −0.0567*LHR O/E, and D = −0.0444*PO_2. (AUC = 0.91) (Fig. 2A)

For those patients for whom anatomic data may not be available, the best model equation predicting ECMO, based on these data, is:

$$\text{Probability of ECMO Eq.2} = \exp(A + B + C)/(1 + \exp(A + B + C))$$

Where A = 35.94, B = −4.654*pH1, and C = −0.0320*PO_2. (AUC = 0.87).

Table 3. Correlation of Severity Variables with Need for Extracorporeal Membrane Oxygenation in Left Liver-Up Congenital Diaphragmatic Hernia

Variable	No ECMO (n = 27, 31.0%)	ECMO (n = 60, 69.0%)	p Value (Mann-Whitney test)
Apgar 1			0.0004
Mean (SD)	4.9 (2.1)	3.0 (2.0)	
Median [IQR] (range)	5 [3, 6.5] (1, 8)	3 [1, 5] (0, 7)	
Apgar-5			0.010
Mean (SD)	6.8 (1.5)	5.6 (2.1)	
Median [IQR] (range)	7 [6, 8] (3, 9)	6 [4, 7] (1, 9)	
CDHSG			0.016
Mean (SD)	63.9 (22.4)	51.9 (22.1)	
Median [IQR] (range)	69 [49.5, 81] (12, 94)	52 [39, 70.5] (6, 88)	
First LHR			0.0002
Mean (SD)	1.6 (.67)	1.1 (.40)	
Median [IQR] (range)	1.5 [1.2, 2] (0.6, 3)	0.97 [0.8, 1.2] (0.5, 2.4)	
LHR observed/expected			<0.0001
Mean (SD)	42.9 (18.3)	28.2 (10.8)	
Median [IQR] (range)	39 [29.5, 49] (17, 100)	26.5 [22, 34] (14, 76)	
pH 1 h			
Mean (SD)	7.2 (0.15)	7.0 (0.17)	<0.0001
Median [IQR] (range)	7.2 [7.2, 7.3] (6.85, 7.61)	7.1 [6.9, 7.2] (6.6, 7.4)	
PO_2 1 h, mmHg			<0.0001
Mean (SD)	136.0 (117)	46.3 (16.2)	
Median [IQR] (range)	74 [52, 212] (37, 393)	45 [37, 53] (15, 108)	
PCO_2 1 h, mmHg			
Mean (SD)	58.6 (18.6)	87.5 (23.9)	<0.0001
Median [IQR] (range)	61 [44, 71] (17, 101)	82.5 [69, 100] (34, 145)	

CDHSG, Congenital Diaphragmatic Hernia Study Group; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; LHR, lung-to-head ratio.

We modeled the combined endpoint of "likelihood of survival without ECMO." Because all patients who died also received ECMO, this is a mathematical variation of "probability of ECMO," but uses the log(n) of PO_2 to increase the linearity of the association.

$$\text{Prob(survival without ECMO)} \quad \text{Eq.3}$$
$$= \exp(A + B + C + D)/(1 + \exp(A + B + C + D))$$

Where $A = -49.69$, $B = 0.0587$*LHR O/E, $C = 5.151$*pH1, and $D = 2.584$*log(PO_2). (AUC = 0.91) (Fig. 2B)

Retrospective application of equations to the dataset

We retrospectively applied the 4 equations to each of the 87 patients in this dataset. Missing LHR data in 12 patients limited full expression of those models, but in each case the equations added valuable information that could be used to define those left liver-up patients most likely to need ECMO, and conversely, those most likely to succeed in avoiding ECMO by delaying repair.

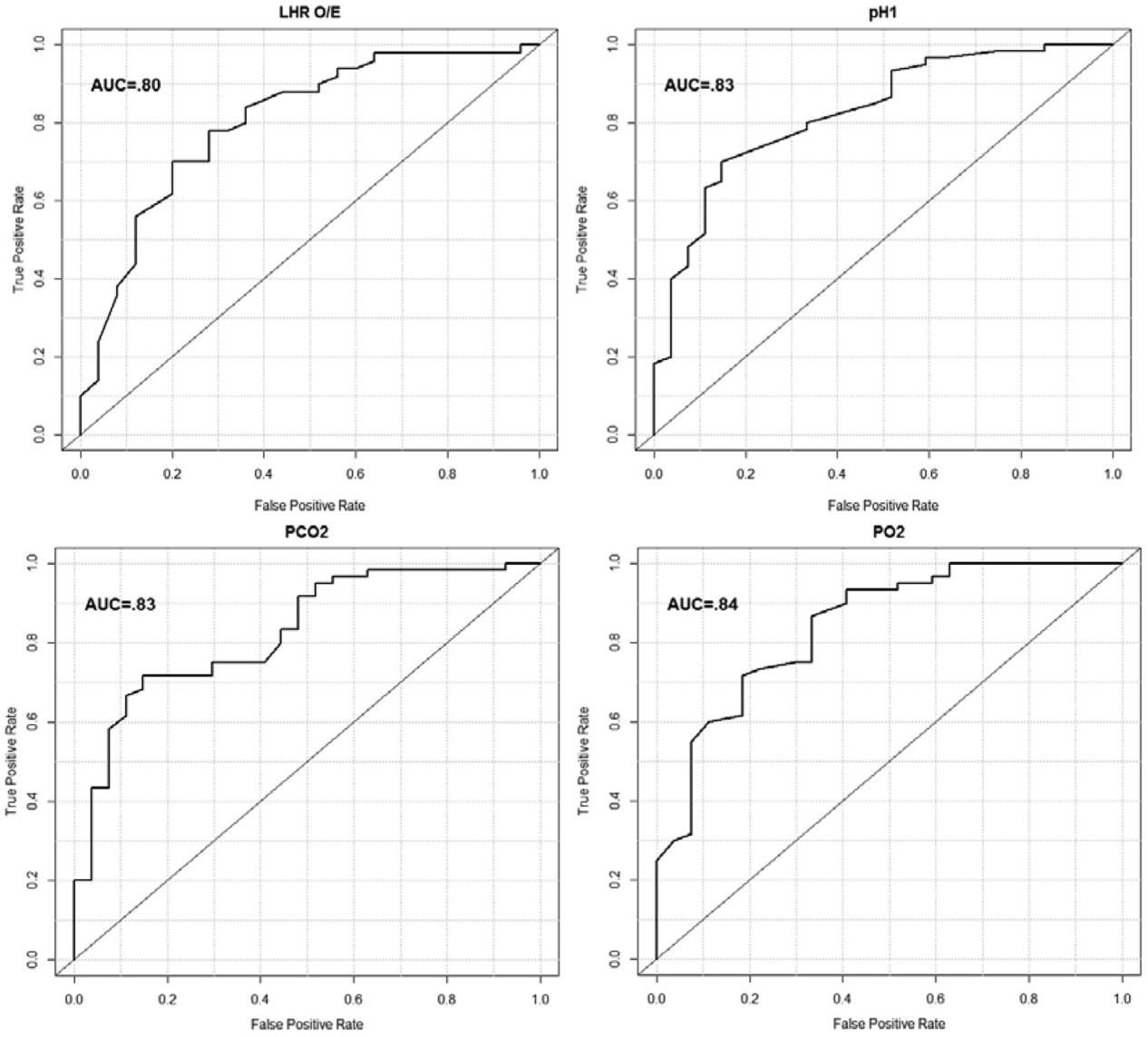

Figure 1. Receiver operating characteristic/area under the curve for individual severity markers that correlate significantly with need for extracorporeal membrane oxygenation in left liver-up congenital diaphragmatic hernia. AUC, area under the curve; LHR O/E, lung-to-head ratio, observed/expected.

We tested the utility of the models by color-coding cells of interest (need for ECMO and survival) in a flat-file (Excel) spreadsheet. We assigned red cells for patients who had a delayed repair strategy and died either without repair or after prolonged delay of repair, and green for those who had delayed repair strategy and avoided ECMO. We then sorted the data based on calculated values of the equation in question. Redistribution of the color-coded spreadsheet cells allowed visualization of the resulting effect of assigning an ECMO risk cut point to our retrospective experience. In each case, the predictive modeling showed visually the improved accuracy of decision-making regarding which patients to choose for early repair. For example, using 0.37 and lower as the defining value for choosing early repair using the "Probability of survival without ECMO" calculation would have correctly identified 6 of 7 patients with poor outcomes from repair delay, who could have potentially benefitted from early repair, while also correctly identifying 3 of 6 who had successfully avoided ECMO using delayed repair (Fig. 3). Variations in set-point for defining early repair result in higher or lower capture of patients who might have benefitted from early repair, but set points that increase capture also increase assignment to early repair of patients who avoided ECMO with delayed repair.

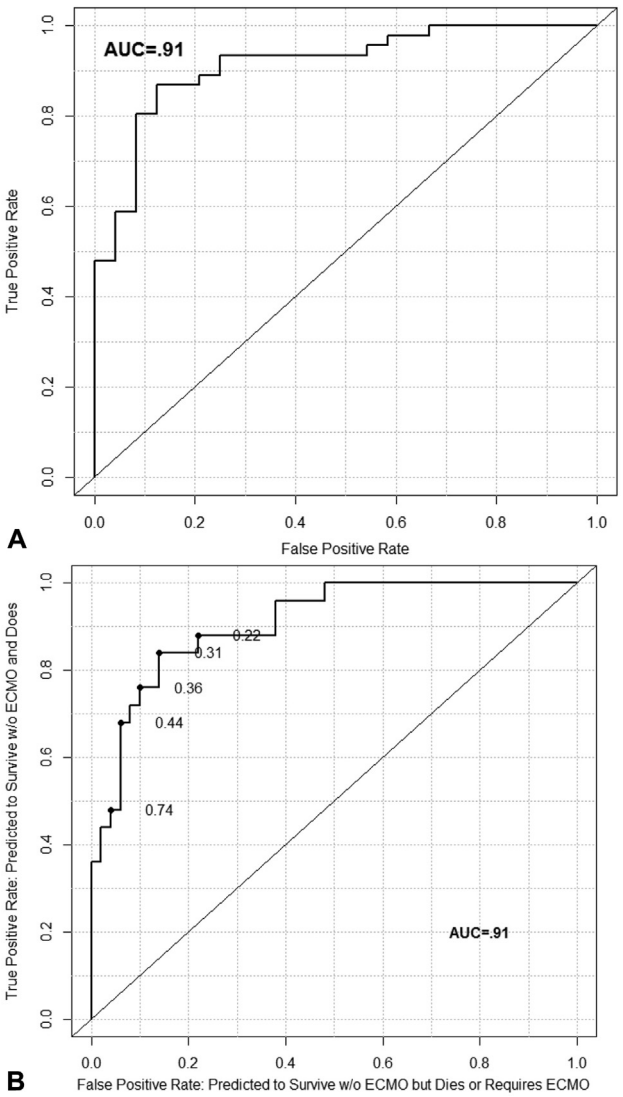

Figure 2. (A) Extracorporeal membrane oxygenation (ECMO) risk equation: 1. Risk of ECMO using pH-1, LHR o/e, and PO_2-1. (B) Probability of survival without ECMO: using pH-1, LHR o/e, and logPO_2-1. AUC, area under the curve; LHR o/e, lung-to-head ratio, observed/expected.

DISCUSSION

Congenital diaphragmatic hernia represents a wide spectrum of disease, and patients with left liver-up CDH represent the more severe end of that spectrum. Because published survival averages 45%,[13,14] this report of 72% overall survival in left liver-up CDH, and 82% survival in a consecutive series of inborn patients who were ECMO-eligible and without other severe anomalies, is notable.

These data support the concept that CDH repair before ECMO in left liver-up patients who ultimately need ECMO is a viable approach for improving survival in this difficult group, as equivalent patients repaired before ECMO survived at significantly higher rates than those who arrived to ECMO unrepaired. This difference did not occur because of a higher than expected rate of death in the delayed repair group because the 65% survival rate achieved in that group is still higher than published standards. Rather, the very high survival rate in left liver-up CDH patients who were repaired early and before ECMO accounts for the difference.

Early repair before ECMO, however, is decidedly uncommon. The majority of CDH patients nationally and internationally are treated with delay of repair, and those who require ECMO arrive unrepaired. For those patients, a decision about repair on ECMO vs trying to get off ECMO unrepaired is required. In a report on CDH Study Group patients that ended up on ECMO unrepaired, repair after ECMO was associated with higher survival compared with repair on ECMO,[16] but it is important to note that patients repaired after ECMO had complete ECMO runs that averaged 8.4 ± 4.9 days. That report was not focused on left liver-up CDH patients, and CDH patients who successfully wean off ECMO unrepaired in that time frame have defined their survivability. In this report, focused solely on left liver-up patients, delay of repair on ECMO resulted in

Opportunity	Survived	ECMO	What Actually Happened	Prob Surv w/o ECMO LHR o/e, ph-1, log PC
No	Yes	Yes	ECMO First, Surgery on ECMO	0.00
Yes	Yes	Yes	Surgery First, ECMO Second	0.00
No	Yes	Yes	ECMO First, Surgery on ECMO	0.00
No	Yes	Yes	ECMO First, Surgery on ECMO	0.00
No	No	Yes	Treated with ECMO, not repa	0.01
No	No	Yes	Treated with ECMO, not repa	0.01
No	Yes	Yes	ECMO First, Surgery Second (	0.01
No	Yes	Yes	ECMO First, Surgery on ECMO	0.01
Yes	Yes	Yes	ECMO First, Surgery Second (	0.03
Yes	No	Yes	Surgery First, ECMO Second	0.03
No	Yes	Yes	ECMO First, Surgery on ECMO	0.03
No	Yes	Yes	ECMO First, Surgery on ECMO	0.03
Yes	No	Yes	Surgery First, ECMO Second	0.03
No	No	Yes	ECMO First, Surgery on ECMO	0.04
No	No	Yes	ECMO First, Surgery on ECMO	0.04
Yes	Yes	Yes	Surgery First, ECMO Second	0.04
Yes	Yes	Yes	ECMO First, Surgery Second (	0.04
No	No	Yes	ECMO First, Surgery on ECMO	0.04
No	No	Yes	ECMO First, Surgery on ECMO	0.05
Yes	Yes	Yes	Surgery First, ECMO Second	0.05
No	Yes	Yes	ECMO First, Surgery on ECMO	0.05
Yes	No	Yes	ECMO First, Surgery on ECMO	0.05
Yes	Yes	Yes	ECMO First, Surgery Second (	0.06
Yes	No	Yes	ECMO First, Surgery on ECMO	0.06
Yes	Yes	Yes	Surgery First, ECMO Second	0.06
Yes	Yes	Yes	ECMO First, Surgery Second (	0.07
Yes	Yes	Yes	Surgery First, ECMO Second	0.07
Yes	Yes	Yes	Surgery First, ECMO Second	0.08
Yes	Yes	Yes	ECMO First, Surgery Second (	0.09
Yes	Yes	Yes	Surgery First, ECMO Second	0.09
Yes	Yes	Yes	ECMO First, Surgery Second (	0.10
No	No	Yes	ECMO First, Surgery on ECMO	0.10
Yes	Yes	Yes	Surgery First, ECMO Second	0.11
Yes	Yes	Yes	Surgery First, ECMO Second	0.12
Yes	Yes	No	Surgery only, No ECMO	0.12
Yes	No	Yes	ECMO First, Surgery Second (	0.12
Yes	Yes	Yes	Surgery First, ECMO Second	0.12
Yes	Yes	Yes	Surgery First, ECMO Second	0.13
Yes	Yes	Yes	Surgery First, ECMO Second	0.14
Yes	Yes	Yes	ECMO First, Surgery Second (	0.15
Yes	Yes	No	Surgery only, No ECMO	0.15
Yes	Yes	No	Surgery only, No ECMO	0.17
Yes	Yes	Yes	ECMO First, Surgery Second (	0.17
Yes	Yes	Yes	ECMO First, Surgery Second (	0.17
Yes	No	Yes	Treated with ECMO, not repa	0.19
Yes	Yes	Yes	ECMO First, Surgery on ECMO	0.19
Yes	Yes	Yes	Surgery First, ECMO Second	0.20
Yes	Yes	Yes	Surgery First, ECMO Second	0.20
Yes	Yes	Yes	Surgery First, ECMO Second	0.20
Yes	Yes	Yes	Surgery First, ECMO Second	0.23
Yes	Yes	No	Surgery only, No ECMO	0.23
Yes	Yes	Yes	Surgery First, ECMO Second	0.26
Yes	Yes	Yes	ECMO First, Surgery Second (	0.27
Yes	Yes	Yes	ECMO First, Surgery Second (	0.30
Yes	No	Yes	Treated with ECMO, not repa	0.31
Yes	Yes	Yes	Surgery First, ECMO Second	0.31
Yes	Yes	No	Surgery only, No ECMO	0.32
Yes	Yes	No	Surgery only, No ECMO	0.33
Yes	Yes	Yes	Surgery First, ECMO Second	0.35
Yes	No	Yes	Treated with ECMO, not repa	0.37
Yes	Yes	Yes	Surgery First, ECMO Second	0.37
Yes	Yes	No	Surgery only, No ECMO	0.38
Yes	Yes	Yes	ECMO First, Surgery Second (	0.39
Yes	Yes	No	Surgery only, No ECMO	0.39
Yes	Yes	Yes	Surgery First, ECMO Second	0.44
Yes	Yes	No	Surgery only, No ECMO	0.44
Yes	Yes	No	Surgery only, No ECMO	0.47
Yes	Yes	No	Surgery only, No ECMO	0.60
Yes	Yes	No	Surgery only, No ECMO	0.72
Yes	Yes	No	Surgery only, No ECMO	0.74
Yes	Yes	Yes	Surgery First, ECMO Second	0.74
Yes	Yes	No	Surgery only, No ECMO	0.76
Yes	No	Yes	ECMO First, Surgery Second (	0.77
Yes	Yes	No	Surgery only, No ECMO	0.81

Figure 3. Favorable distribution after sorting by predictive modeling of color-coded cells of patients who died without having repair.

a significant subgroup of unrepaired CDH patients who had improved little, even after more than 2 weeks on ECMO. These unrepaired patients who failed to improve even after weeks on ECMO illustrate the risk of waiting to successfully wean from ECMO before repair.

We interpret the deaths that occurred in the current delayed repair subgroup as directly related to the failure of timely repair in those patients. Many patients will improve enough on ECMO to be weaned off unrepaired, and robust risk stratification may help to prospectively identify those patients, but to also save those who don't recover on ECMO unrepaired requires a strategy that provides earlier repair while still minimizing risk. Early repair before ECMO offers this, and timely repair is likely the critical factor affecting the improved survival seen in this series. That a significant proportion of left liver-up patients fail to improve on ECMO unrepaired, but equivalent patients survive with a strategy of early repair before ECMO, attests to the importance of timely repair in those patients. These data suggest that for patients on the more severe end of the CDH spectrum, repair rather than nonoperative stabilization is the critical therapeutic intervention, and that failure to provide repair in a timely fashion contributes to poor outcomes.

Historical prospective randomized studies of repair timing showed no survival difference in early vs delayed repair, but they lacked risk stratification.[5] Defining optimal CDH repair timing requires an understanding of the risks and potential benefits associated with differing repair timing options, and accumulating data suggests these issues vary along the CDH spectrum. For patients who ultimately don't need ECMO, Hollinger and colleagues[11] showed that timing of repair likely isn't important. Our previous report showed excellent survival for left liver-down patients repaired in the first 48 hours, but suggested an increased need for ECMO in those less-severe patients when repaired in that early time frame.[12]

To assure their patients on ECMO received the benefits of repair, Dassinger and associates[17] performed CDH repair of all CDH/ECMO patients within days of ECMO initiation. Thirty-four of 34 CDH patients requiring ECMO were successfully repaired at an average of 2.3 days after cannulation, with a 9% rate of surgical bleeding and a 71% survival rate.[17]

This strategy of early repair on ECMO ensures that repair is performed, but repair on ECMO is associated with significant risk of bleeding compared with repair off of ECMO. Although not specifically addressed in this study, the risk of postoperative bleeding was very low (less than 4%) when we repaired the CDH before

ECMO, and minimum of 4 hours elapsed between closure and ECMO. An additional advantage of early repair before ECMO is the absence of edema of the liver or abdominal wall, which eliminated the risk of loss of abdominal domain. Finally, early repair before ECMO avoids the decision tree of deciding whether to repair early, late, or after ECMO when arriving to ECMO unrepaired.

Early repair before ECMO in left liver-up CDH is not without risks, and these include critical decompensation during repair, an elevated risk of bleeding with early transition to ECMO, and the potential concern for increasing need for ECMO.

The potential for added risk of ECMO from early repair is not clear. We saw no demonstrable difference in CDH severity in those patients who arrived to ECMO after early repair compared with those who underwent delay and arrived to ECMO unrepaired, suggesting that early repair added little risk of ECMO in these more severe left liver-up patients. We believe this difference compared with patients with less severe CDH relates to more severe pulmonary hypoplasia in left liver-up patients compared with left liver-down patients. Smaller lungs have smaller pulmonary vascular beds, and the resultant pulmonary hypertension is increasingly composed of a fixed component based on vascular bed size,[18] and decreasingly composed of a reactive component that could be negatively affected by surgical stress.

Defining the point on the CDH spectrum where the benefits of delay give way to the need for earlier repair requires increasingly granular knowledge of an infant's CDH severity. Akinkuotu and coworkers[6] compared the predictive strength of prenatal vs postnatal variables in CDH risk-stratification. Our data presented here combine prenatally defined anatomic and postnatal physiologic variables to maximize predictive accuracy. The first level of stratification is anatomic, limited to left sided, liver-up CDH. Lung size (LHR observed/expected) used alone provided good predictive modeling (AUC = 0.80). Of physiologic stratifiers, post-ductal blood gas values at 1 hour were highly predictive of eventual need for ECMO, with an AUC for individual variables of 0.83 to 0.84. The anatomic and physiologic risk variables, LHR observed/expected, pH, and PO_2 at 1 hour combined in a comprehensive model to predict ECMO reached an AUC of 0.91, a very high level of correlation for a biologic system. Park and coauthors[19] and Coleman and colleagues[20] also used severity variables, predictive equations, and SNAP-II score to predict mortality and ECMO, but not to this level of predictive accuracy, nor to define varying treatment strategies. Khmour and associates[21] also referenced early blood gas values in CDH, successfully correlating admission blood gas values with outcome.

The equations defined here to predict ECMO are likely center-specific, as they are based on our style of resuscitation and treatment. These models and results represent proof of concept that risk stratification can facilitate better informed treatment decisions across the spectrum of CDH. These equations may have limited value at other centers, and should be evaluated retrospectively to assess predictive value. Because each equation is slightly different, we intend to use the models side-by-side to define as granular a picture of ECMO risk as possible, and to present this information to parents as we shape our strategy for a given newborn with left liver-up CDH. Patients with high predicted risk of ECMO (greater than 80%) will be counseled and offered early repair, while parents with newborns with increased but lesser risk (65% to 80%) will be counseled similarly but more cautiously about the risks and potential benefits of early repair. Those with estimated risk below 65% will be treated with delayed repair attempting to minimize risk of ECMO.

We note that the survivals achieved here, 95% in a cadre of left liver-up CDH patients who were repaired early and subsequently required ECMO, and 82% in the total 87 left liver-up CDH patients who were ECMO eligible and without lethal associated anomalies, suggest a survival potential in these patients that is largely unrecognized. These data show that high survival in left liver-up CDH is achievable. It is important to note, however, that these results were achieved in a high volume, dedicated CDH program with consistent and experienced oversight. As not all centers will have these attributes, referral of prenatally diagnosed CDH patients to the best centers should be encouraged.

This report has important strengths. The series is large and continuous, allowing analysis of reasonable sized sub-populations, such as the inborn left liver-up patients studied here. Second, the series is inclusive and therefore reflects the full spectrum of CDH disease. Terminations for isolated CDH have not been chosen by families of prenatally diagnosed patients seen in our program, and patients come from long distances with severe CDH specifically to avoid termination. Further, the CDH care strategy and treatment specifics at our center are highly consistent, including birth resuscitation, the application of ventilatory support, and ECMO support. Measured physiologic variables in this environment will more accurately reflect differences in disease state than in centers with less resuscitation consistency. This consistency is likely reflected in the high statistical correlation of the individual variables to the measured endpoint, their

relatively high AUC even as individual variables, and in the strength of the combined predictive equations as expressed as area under the curve (AUC).

The major weakness of this series is the retrospective nature of the review, with risk of bias in data collection and analysis. We collected these data in standardized web-based forms, and statistically evaluated the study population in a variety of ways, attempting to minimize and eliminate the potential for bias. Another weakness is that although the concepts defined here are likely universal, the equations are likely center-specific, and should be evaluated cautiously and retrospectively by other centers. It is also important to note that this study is limited to left liver-up CDH patients, and the conclusions from this study apply to this anatomic sub-group only.

CONCLUSIONS

Left liver-up CDH represents the severe end of the CDH spectrum. Patients of equivalent severity repaired early and before ECMO survive at higher rates compared with those who arrive to ECMO unrepaired, highlighting the benefits of repair in this high-severity anatomic subset, balanced with concern that early repair could increase risk of ECMO in those with only moderate ECMO risk. Sophisticated predictive modeling can define future risk of ECMO with a high degree of accuracy at 1 hour of life, allowing individualized risk-stratified decisions regarding surgical repair timing in left liver-up CDH, to improve survival potential while minimizing risk of ECMO. Successful application of these concepts has resulted in survival rates exceeding 80% in left liver-up CDH, with the potential to go even higher by using multivariate risk stratification to better inform critical surgical decisions in these high-risk patients.

Author Contributions

Study conception and design: Kays, Talbert, Islam
Acquisition of data: Kays, Talbert, Islam, Larson, Taylor, Perkins
Analysis and interpretation of data: Kays, Talbert, Islam
Drafting of manuscript: Kays, Talbert, Islam, Larson, Taylor, Perkins
Critical revision: Kays, Talbert, Islam, Larson, Taylor, Perkins

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Discussion

DR EUGENE MCGAHREN (Charlottesville, VA): I am old enough to remember the days when we were rushing to the operating room when these babies with diaphragmatic hernias were born and then seeing this wonderful little "golden period" of recovery. However, the babies tended to have significant difficulties very soon after that. We realized, through our own experience and the experience of others, that we did not have to rush things quite so fast. So, ultimately, a belief in a "delayed repair" came to be. We at least understood that by not rushing repair emergently, we were not hurting the babies.

When extracorporeal membrane oxygenation (ECMO) was introduced, the timing of all this started getting a little bit more difficult to discern. We were trying to understand how best to determine the timing of repair, not only in and of itself, but also how it related to the use of ECMO. In 1995, we published a paper of our earlier experience with diaphragmatic hernia at the University of Virginia, and at least suggested that we ought to be trying to repair babies relatively early so as to have the repair done before they would need ECMO. We really did not base this suggestion on much more than the concerns about what complications might come from ECMO and just a general sense of what we thought was right at the time.

I will say that over time, many practices, including ours, have evolved to adopt a more prolonged stabilization period for these babies. This has resulted in allowing some babies to go on ECMO before repair, and, in many cases (and even in some of the references in the manuscript) trying to wean the babies off of ECMO before a repair is undertaken, or at least time the repair for when the weaning and decannulation will occur. I would say that our practice has tended a bit toward the latter practice.

What it really gets down to now is figuring out what the best time for repair really is. Also, what do we really mean by "early" and "delayed"? It may be, in fact, that as Dr Kays suggested in the paper, there is physiology involved in some of these babies that really defines at what point we should be repairing these hernias to help enhance recovery and progress of these babies. The left upper lung is, in my view, being used as the window to this question.

From 1992 to 2014, there have been many changes in our management of diaphragmatic hernia with regard to pharmaceutical agents, nitric oxide for example, ventilator capabilities, and even our strategies, such as permissive hypercapnia, which we have both written on and which we discussed here 4 years ago at the Southern Surgical Association meeting. How have these affected the need for ECMO in the study population over that period of time?

The second question relates to Dr Kays' discussion about "the opportunity for repair" before ECMO. Of course, being a retrospective study, this was described in retrospect. In the series of babies in this manuscript, there were some babies repaired sooner and some later. In particular, for the delayed repairs, what propagated the delay in repair in those particular babies? Were there active decisions about delay? Was the description in the manuscript really more just an interpretation of what was being observed retrospectively?

The third question is, is there any way to stratify the left liver-up group? I am incredibly impressed by the survival that Dr Kays reports. On the other hand, I do not know what the overall stratification of the left liver-up group is. In the manuscript, he does describes left liver up as being 5% or more of the liver, and it is also based on observations either made in the operating room, prenatal imaging, or postnatal imaging. There is the possibility that if there is a very small amount of left liver-up, this might not have the physiologic ramifications of more of the liver being up.

I say that because there are emerging data showing that the spectrum of diaphragmatic hernia is really reflected by development of the lungs and development of the diaphragm as being an all in 1 process. We know that the size of the diaphragm defect does fall out in stratification to survival based on data from the Congenital Diaphragmatic Hernia Registry. But we do not know the size of that defect until we actually operate on a baby. It may be, in fact, that stratifying the left liver-up may be our "canary in the coal mine" in terms of better understanding that process.

Finally, is there the opportunity to use the modeling equation described in the manuscript across the board for diaphragmatic hernia babies so that we may learn more about managing these babies in general?

DR MAX LANGHAM (Memphis, TN): Dr Kays also summarized the previous work that he has presented at the American Surgical, showing that a delay of 48 hours or more in the repair of babies with lower risk left-sided diaphragmatic hernia is associated with a decreased need for ECMO, while maintaining outstanding survival rates. Here he presents work suggesting that early repair for high-risk, left-sided diaphragmatic hernia is associated with improved survival compared with placing these children on ECMO and repairing them later. A multivariable logistic regression model is presented as a potential clinical decision support tool to