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## Predictors of Mortality and Morbidity in Infants with CDH

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### 1. Introduction

Congenital diaphragmatic hernia (CDH) accounts for 8% of all major congenital anomalies with an incidence of 1 in 2000 to 4000 births (Doyle & K.P. Lally 2004). It is associated with significant mortality and morbidity (Abdullah et al., 2009). Survival data for CDH are conflicting; a few centers reported 82% to 93% survival rate (Javid et al., 2004; Grushka et al., 2009; Mettauer et al., 2009) while others had significantly less figures (54%-56%) (Colvin et al., 2005; Levison et al., 2006). This divergence in survival data has been attributed to case selection bias at single tertiary care institutions because as many as 35% of live-born infants with CDH do not survive to transport resulting in a hidden mortality for this condition (Harrison et al., 1978; Colvin et al.; 2005, V.K. Mah et al., 2009). Hidden mortality is referred to patients who die before surgery, either during gestation or shortly after birth, and thus are not reported by individual institutions (Harrison et al., 1994).

Neurodevelopmental impairment is the most important morbidity among CDH survivors, apart from respiratory complications (D'Agostino et al., 1995; Nobuhara et al., 1996; McGahren et al., 1997; Danzer et al., 2010). At 8-12 years of age, mean IQ is 85 (1 SD below age expectations) (Bouman et al. (2000), 45% have poor academic achievement, 50% are rated as having emotional and/or behavioral problems; by adolescent age, they have problems with sustained attention (39%) (Peetsold et al., 2009). Between 23-46% of CDH survivors demonstrate academic difficulties on standardized achievement measures, and more than half receive a formal diagnosis of specific learning disability, attention deficit hyperactivity disorder, or developmental disability. In almost one third of cases, difficulties are severe enough to require placement in a special education class (Frisk et al., 2011). Cognitive delay in this population could be attributed to perinatal and postnatal hypoxia and acidosis. Perioperative hypocapnia, related to aggressive ventilation, is also linked to executive dysfunction, behavioral problems, lowered intelligence, and poor intellectual achievement especially in mathematics (Frisk et al., 2011).

In this chapter we plan to provide a review on specific predictors for outcomes of CDH infants. These predictors include basic laboratory findings, prenatal and postnatal characteristics, type of medical support, and timing of surgical repair.

## 2. Prenatal identification and imaging (Table 1)

### 2.1 Prenatal identification

Prenatal identification of CDH does not necessarily improve the chance for postnatal survival. In fact, studies demonstrated a two to four fold increase in mortality among prenatally diagnosed CDH patients when compared with postnatally diagnosed patients (Skari et al., 2000). Although the reason behind this association is not clear, prenatal diagnosis of CDH may infer that the defect is larger with more displaced bowel and worse pulmonary hypoplasia (Laudy et al., 2003; Heling et al., 2005). Also, prenatal diagnosis has been associated with higher frequency of associated abnormalities, which may contribute to decreased survival of CDH children (Skari et al., 2002).

### 2.2 Lung to head ratio

The most commonly used method to assess fetal lung volume, and subsequent outcomes, is the measurement of lung area to head circumference ratio (LHR) with the use of 2-dimensional ultrasound (US) (Metkus et al., 1996; Sbragia et al., 2000; Laudy et al., 2003; Heling et al., 2005; Jani et al., 2006a; Hedrick et al., 2007; S.H. Yang et al., 2007; Sinha et al., 2009). Sonographic assessment of LHR usually takes place at 24–26 weeks gestation wherein lung is measured at the level of the four-chamber view of the heart. Minimum LHR measurements had a high inter- and intraobserver correlation (coefficients of 0.7 and 0.8, respectively) making it attractive (Ba'ath et al., 2007; Jani et al., 2007), and also proved to be related to survival (an inverse relation), independent of therapy. LHR <1.0 is usually not compatible with life, whereas LHR >1.4 is associated with virtually no mortality; LHR of 1 may be the survival 'threshold' (Jani et al., 2006a). A more frequently used indicator is the LHR of the contralateral lung (Metkus et al., 1996; Laudy et al., 2003), although some recent studies questioned its prognostic value (Heling et al., 2005; Arkovitz et al., 2007; Ba'ath et al., 2007).

Predictor	Factors associated with unfavorable outcomes
<b>Ultrasound findings</b>	Small lung to head ratio (LHR) at 24 weeks of gestation
	Discrepancy of observed to expected LHR for different gestational ages
	Abnormal Liver position
<b>MRI findings</b>	Small total fetal lung volume
	Dense lung fields, the ratio of the lung signal intensity to the spinal fluid signal intensity
<b>Pulmonary vascular assessment</b>	Small diameters of pulmonary artery and its branches
	Small flow volume and velocity
	Absent or shallow reactivity to maternal oxygen

Table 1. Fetal parameters used to predict CDH outcomes

Of note, LHR normally changes with advancing gestational age; therefore, a fixed cutoff, as initially proposed, can be misleading (Peralta et al., 2005; Ba'ath et al., 2007; Jani et al., 2007; Usui et al., 2007). Therefore, an observed-to-expected (O/E) LHR could be used regardless of the gestational age at which the study was done (Peralta et al., 2005; Jani et al., 2006b, Kilian et al., 2009). It is worth mentioning that the presence of abdominal viscera in the pleural space and contralateral displacement of the heart and mediastinum seem to play no role in the prognosis of CDH (Kalache et al., 2007).

### **2.3 Liver position**

Liver position is the most significant and reproducible independent prenatal determinant of survival with liver herniation predictive of poor outcome (Albanese et al., 1998; Jani et al., 2006a; Hedrick et al., 2007). In a recent CDH series, newborns with the liver up had a mortality of approximately 55%, and 80% of CDH children born with intrathoracic liver position required extracorporeal membrane oxygenation (ECMO) (Hedrick et al., 2007). Intact discharge rates when the liver is down was shown to be 87%, while when the liver is up it ranged from 10%-47% (Kitano et al., 2011). As liver position is a predictor of severity, it is not surprising that liver herniation is not only predictive of survival but also predicts impaired neurodevelopmental outcome. Nearly 80% of CDH children with prenatally diagnosed liver herniation demonstrated borderline or delayed neurodevelopmental, neurocognitive, and/or psychomotor outcome (Danzer et al., 2010).

### **2.4 Total lung volume and signal intensity by MRI**

Total fetal lung volume (TFLV) measured by magnetic resonance imaging (MRI) have also been reported to be useful in the prediction of pulmonary hypoplasia. Some studies report a significantly higher likelihood of death if the O/E TFLV were < 30-35% (Büsing et al., 2008; Cannie et al., 2008; Bonfils et al., 2006). This measurement is considered, to date, as the most accurate prognostic factor for survival of both left-sided and right-sided CDH (Gerards et al., 2008).

Studies using MRI signal intensity for fetuses with CDH showed both positive (Matsushita et al., 2008) and negative (Nishie et al., 2009; Balassy et al., 2010) data for prediction of survival prognosis. The ratio of the lung signal intensity to the spinal fluid signal intensity (L/SF) were significantly larger in survivors compared with deaths (0.82 vs 0.61,  $P < 0.05$ ). This ratio correlated with duration of tracheal intubation ( $P < 0.01$ ) (Terui et al., 2011).

### **2.5 Pulmonary vascular assessment**

In addition to the severity of lung hypoplasia, the degree of pulmonary hypertension is equally important. Thus, in-utero assessment of lung vasculature seems another logical approach for predicting outcome. The branches, vessel diameters, flow velocimetry or flow volume can be measured using 2D or 3D ultrasound techniques (Suda et al., 2000; Sokol et al., 2006; Ruano et al., 2007). Vascular indicators are more accurate as negative predictors, so that the absence of vascular abnormalities is a good sign but not vice versa (Fuke et al., 2003; Okazaki et al., 2008). There are limited preliminary data on the utility of testing the reactivity of fetal pulmonary vessels to maternal hyperoxygenation (Broth et al., 2002). Unfortunately, this test can only be done in late gestation.

### 3. Delivery hospital and need for transport

#### 3.1 Location of delivery and neonatal transport

The quality of preoperative medical management can significantly impact outcomes of infants with CDH. This management includes resuscitation in the delivery room, medical stabilization in the early stages after birth, and the use of gentle ventilation to sustain adequate oxygenation while minimizing lung damage before surgery. Because these interventions require certain experiences and some technological resources such as extracorporeal membrane oxygenation (ECMO) that are not necessarily available in every birthing centers, it has been widely accepted to always deliver prenatally diagnosed CDH infants at high-risk perinatal centers. Maternal transfer is always safer than transfer of an unstable infant (Keshen et al., 1997; Sreenan et al., 2001; Boloker et al., 2002; Nasr et al., 2011). Location of delivery is a significant independent predictor for mortality, with an odds ratio (OR) of dying when outborn of 2.8 (Nasr et al., 2011). The thermal and hemodynamic instabilities that routinely occur during transport can be compromising to neonates; especially in the setting of CDH patients who have hypoplastic lungs and pulmonary hypertension. As up to one-third of infants with CDH may require ECMO therapy, some authors advocate delivery of infants with CDH in an ECMO center whenever possible (Sreenan et al., 2001). A recent study of a large database (Aly et al., 2010) demonstrated increased mortality and use of ECMO in CDH infants who utilized transport. Transported infants used more ECMO than non-transported ones (25% vs 15%; OR = 1.46) and had higher mortality after surgery (16% vs 13%; OR= 1.46). (Figure 1)

#### 3.2 Hospital volume

A controversial area which has been highlighted is the difference in survival between infants treated in “high volume” and “low volume” centers. Recently studies showed high volume centers (treating more than five cases per year) to perform significantly better. These data support the paradigm of regionalized perinatal centers (Javid et al., 2004; Skari et al., 2004; Bucher et al., 2010).

Javid et al (2004) from the Canadian Pediatric Surgery Network identified 88 children treated at 14 children’s hospitals over a period of 22 months; hospitals were grouped into low volume (<12 cases/yr) or high volume (>12 cases/yr). Low-volume hospitals had a significantly higher mortality compared with high volume hospitals (23% vs. 10%). A survey involving 13 pediatric surgical centers in Scandinavia have demonstrated a tendency towards better survival in the higher-volume centers (>5 cases/yr) (72.4%) than in the centers with lower volume ( $\leq 5$  cases/yr) (58.7%),  $p = 0.065$  (Skari et al., 2004). Another study including 2203 infants from 37 children’s hospitals categorized institutions into low-volume (< 6 cases/yr), medium-volume (6 -10 cases/yr), and high-volume (>10 cases/yr); compared with low-volume hospitals, medium-volume (aOR: 0.56, 95% CI: 0.32- 0.97,  $P = 0.05$ ) and high-volume (aOR: 0.44, 95% CI: 0.23- 0.80,  $P < 0.01$ ) hospitals had a significantly lower mortality (Bucher et al., 2010).

#### 3.3 Mode of delivery

There is still some doubt about the preferred mode of delivery and the timing of delivery in case of a CDH pregnancy. Recent studies reported no significant differences in overall

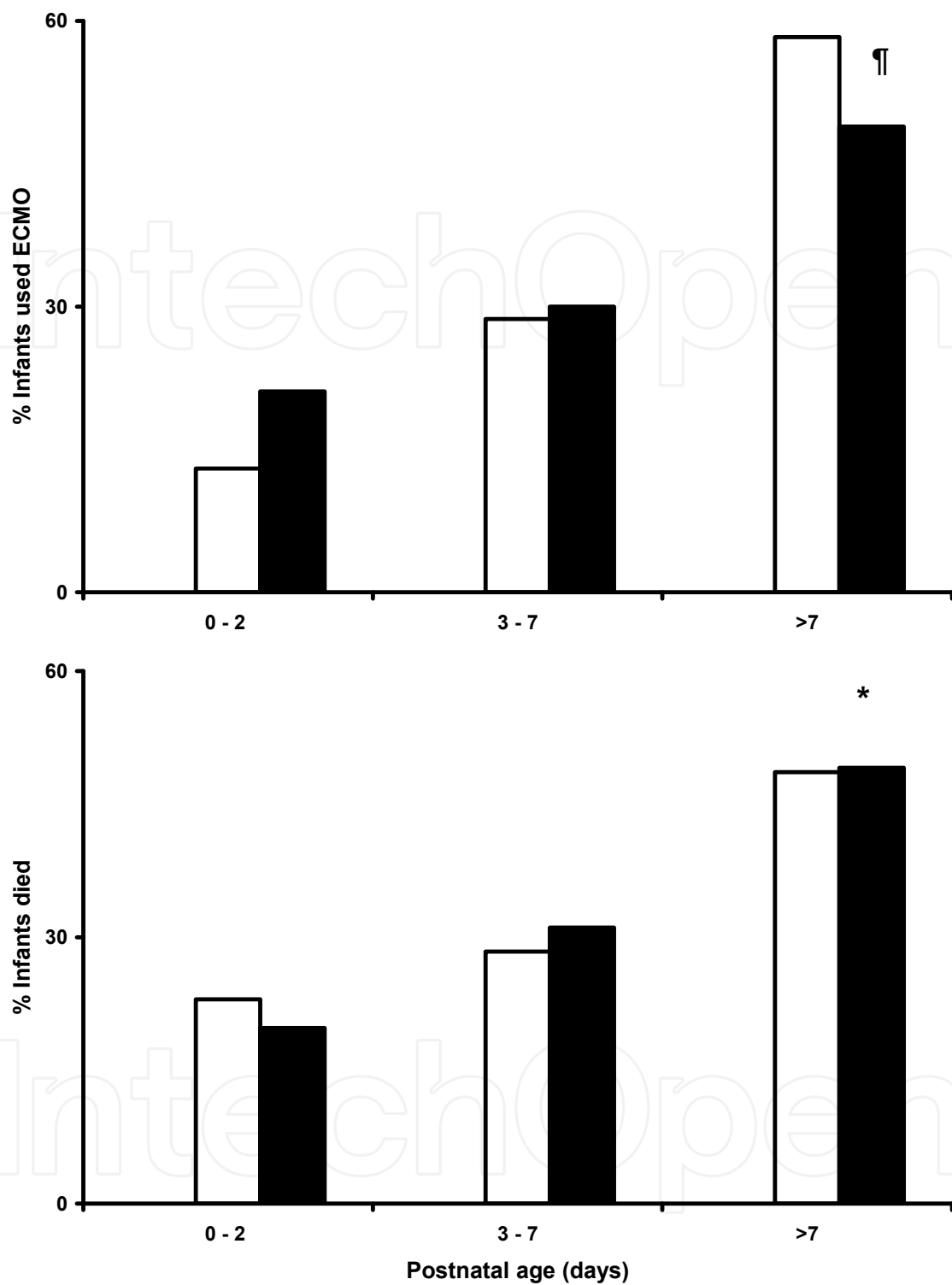


Fig. 1. Rates of mortality and use of ECMO in the study population stratified by date of surgery (Aly et al 2010)

The upper panel represents % of infants who used ECMO in the transported (■) and inborn (□) groups at the 3 different categories for age of operation. The lower panel represents % of infants who died in the transported (■) and inborn (□) groups at the 3 different categories for age of operation. ¶ \* Risks for mortality and use of ECMO are increased when CDH repair was delayed > 7days (P <0.001)

survival between patients born by spontaneous vaginal delivery, induced vaginal delivery and elective cesarean section (Frenckner et al., 2007; Stevens et al., 2009). Survival without the use of ECMO, however, was greater for patients born by elective cesarean section according to two studies (Bétrémieux et al., 2002; Frenckner et al., 2007).

#### 4. Gestational age, birth weight, race and others (Table 2)

##### 4.1 Gestational age and birth weight

Although outcomes for preterm infants are clearly worse than in the term infant, more than 50% of preterm infants still survived. Preterm infants with CDH remain a high-risk group. ECMO is of limited value in the extremely premature infant with CDH, however most preterm infants that live to undergo repair will survive. Survival decreases with decreasing gestational age. Prematurity should not be an independent factor in the treatment strategies of infants with CDH (Tsao et al., 2010).

A single study (Stevens et al., 2009) reported better outcomes in CDH infants when born at 37–38 weeks as compared to those born at 39–41 weeks gestation. There is no clear biological plausibility for such findings. Earlier data reported the opposite; that is better survival rates and a shorter duration of ECMO treatment in infants born at 40–42 weeks when compared to those born at 38–39 weeks gestation (Stevens et al., 2002). Therefore, the length of gestation should be determined based on an individualized approach.

Low birth weight has been identified as independent risk factors for poor outcomes (Keshen et al., 1997; Congenital Diaphragmatic Hernia Study Group, 2001; Stevens et al., 2002; Skarsgard et al., 2005; Haricharan et al., 2009; Bucher et al., 2010).

Predictor	Factors associated with unfavorable outcomes
Delivery location	Low hospital volume and inexperience with CDH Need for neonatal transport
Apgar score	Lower score at 5 minutes
Initial blood gases	Acidemia and hypoxemia
Gestational age	Prematurity
Birth weight	Lower birth weight

Table 2. Delivery location and perinatal predictors for CDH outcomes

##### 4.2 Race and other factors

African Americans diagnosed with CDH have lower survival compared to Whites (W. Yang et al., 2006; Frencker et al., 2007; Stevens et al., 2009). Multivariate analysis confirmed that race was an independent predictor of mortality with African Americans and other race (not Hispanics) experiencing a greater than 50% excess mortality compared to Whites (Sola et al., 2010).

Environmental factors play an equal pivotal role in neurodevelopmental outcome of CDH. In fact, a low socio-economical status has been associated with a worse outcome. Stolar et al. (1995) found that low-level maternal education, as a potential surrogate for socio-economic status, significantly correlated with the incidence of abnormal neurocognitive outcome in

CDH children. It is obvious that advantaged environments can reduce the impact of medical risk factors, while poor environment and the lack of social support can amplify biological risk factors (Sameroff, 1998).

In infants with CDH, a prolonged neonatal hospitalization and the use of supplemental oxygen at the time of discharge are associated with a poorer neurological outcome (Nield et al., 2000; Cortes et al., 2005). These two conditions could reflect the role of the severity of the primary disease.

## **5. Apgar scores and early blood gases**

### **5.1 Apgar scores**

Poor Apgar score is an early marker for maladaptation to cardiopulmonary resuscitation. Poor Apgar scores at 1 and 5 minutes were associated with mortality (Chao et al., 2010). The CDH study group analyzed 2524 neonates undergoing repair and reported that the use of neonatal transport, gestational age less than 37 weeks, low birth weight (< 2 kg), prenatal diagnosis, associated major cardiac anomaly or chromosome anomaly, low 5-minute Apgar score, right-sided hernia, and agenesis of diaphragm or defects needing patch repair were significantly unfavorable factors for survival (Congenital Diaphragmatic Hernia Study Group et al., 2007). Another study identified three independent risk factors for mortality with CDH: low 5-minute Apgar score, prematurity, and air leak. Among these, 5-minute Apgar score was the strongest risk factor (Levison et al., 2006)

### **5.2 Arterial blood gases**

Initial arterial blood gas (ABG) values have been linked to mortality since 1974 (Boix-Ochoa et al., 1974); since then ABG parameters have been used as indicators for the degree of pulmonary hypoplasia (Butt et al., 1992; Norden et al., 1994). Lower pH and lower PaO<sub>2</sub> in initial arterial blood gas (ABG) are associated with higher with mortality (Heiss & Clark, 1995; Chu et al., 2000; Chou et al., 2001; Haricharan et al., 2009; Chao et al., 2010).

Arterial PCO<sub>2</sub> is an accurate marker of the degree of lung hypoplasia and would explain the close association between severe hypercapnia (Pa CO<sub>2</sub> >60 mm Hg) and mortality (Bohn et al., 1984). However with the introduction of the concept for permissive hypercapnia to minimize ventilator-induced lung injury, tolerance to high PaCO<sub>2</sub> has become popular in neonates with CDH (Wung et al., 1985; Logan et al., 2007). Therefore, high PaCO<sub>2</sub> does not necessarily indicate lung hypoplasia but could rather indicate a more conservative ventilator management. Nowadays some centers are still reporting worse outcomes in CDH neonates if they had PaCO<sub>2</sub> values greater than 60 mm Hg before the initiation of ECMO (Haricharan et al., 2009).

## **6. Chest x-ray and echocardiographic findings**

### **6.1 Chest x-ray**

Currently it is believed that chest radiography serves to confirm the diagnosis of CDH, but does not predict outcome (Holt et al., 2004). Earlier attempts were made to correlate findings on plain-film chest radiography in CDH with rates of survival (Touloukian & Markowitz,



1984; Saifuddin & Arthur, 1993; Dimitriou et al., 2000). Positive predictors of survival included; ipsilateral lung aeration greater than 10%, contralateral lung aeration greater than 50%, mediastinum displaced by less than half the width (Donnelly et al., 1999). Poor signs included the presence of a contralateral pneumothorax, absence of contralateral aerated lung and an intrathoracic site for the stomach (Saifuddin & Arthur, 1993). Computer-assisted analysis of the lung area on the chest radiograph was thought to be a useful predictor postoperatively but not preoperatively (Dimitriou et al., 2000).

## 6.2 Echocardiography

A few studies focused on pulmonary artery size and pressure in CDH infants (Okazaki et al., 2008; Aggarwal et al., 2011a). When measured on the same day of birth, left and right pulmonary artery diameters and their ratios were significantly smaller among infants who died compared with those who survived (Aggarwal et al., 2011a). Persistent systemic or suprasystemic pulmonary artery pressure during the first 3 weeks of life was associated with decreased survival (Dillon et al., 2004). Calculating the ratio between the sum of the diameters of the 2 pulmonary arteries (measured at the hilus) and the diameter of the aorta (measured at the level of the diaphragm), could also be a good predictor of outcome in CDH (Suda et al., 2000).

The echocardiographic ratio of right ventricular systolic to diastolic duration was significantly higher in neonates with CDH, compared to term controls. Among infants with CDH, a ratio of 1.3 or greater was predictive of mortality (sensitivity= 93% and specificity= 62%) (Aggarwal et al., 2011b). Mortality was associated with the degree of impairment of global ventricular function and pulmonary hypertension (Aggarwal et al., 2011b).

The ratio of estimated pulmonary artery pressure to systemic pressure is helpful in assessing the severity of pulmonary hypertension. A ratio of 0.9 or greater preoperatively predicts mortality (sensitivity of 100% and specificity of 84%) (Al-Hathlol et al., 2011).

## 7. The diaphragmatic defect (Table 3)

### 7.1 Site of the diaphragmatic defect

Almost 20% of CDH is on the right-side and 1% is bilateral. Whether the site of the diaphragmatic defect is a significant factor in survival is controversial. Some studies reported higher mortality in right-sided CDH (Boix-Ochoa et al., 1974; Touloukian & Markowitz, 1984; Skari et al., 2000; Colvin et al., 2005; Jani et al., 2008; Chao et al., 2010; Schaible et al., 2012), others did not find statistical difference in mortality rate when compared with left-sided defects (Ontario Congenital Anomalies Study Group, 2004; J.E.Wright et al., 2010). Whether right-side CDH is associated with higher rates of malformations is also debatable (Skari, et al., 2000; Bedoyan et al., 2004; Hedrick et al., 2004). When the defect is bilateral, associated anomalies (Neville et al., 2003; Ninos et al., 2006) and mortality (Neville et al., 2003) are significantly increased.

### 7.2 Size of the diaphragmatic defect

Large hernia size—for which patch repair is a surrogate marker—strongly reduces overall survival as well as increases the risk of multiple adverse outcomes (D'Agostino et al., 1995;

McGahren et al., 1997; Cortes et al., 2005; Congenital Diaphragmatic Hernia Study Group et al., 2007; Danzer et al., 2010). Patch repair correlates with higher long-term morbidity, increased rate of gastroesophageal reflux and altered pulmonary function tests, especially in the first 6 months of life (Valfrè et al., 2011). A recent report from CDH Study Group found the size of the diaphragmatic defect to be the only independent risk factor associated with higher mortality rate (Congenital Diaphragmatic Hernia Study Group et al., 2007).

### 7.3 Associated malformations

The incidence of malformations in CDH infants is 33–50% (Fauza & J.M.Wilson, 1994; Colvin et al., 2005). Associated anomalies are very heterogeneous, but cardiovascular malformations are the most common (Zaiss et al., 2011). The presence of associated malformations increases mortality 4-6 folds (J.M.Wilson et al., 1997; Skari et al., 2000; Congenital Diaphragmatic Hernia Study Group, 2001; Stege et al., 2003; Colvin et al., 2005; Graziano & Congenital Diaphragmatic Hernia Study Group, 2005; W.Yang et al., 2006; J.E.Wright et al., 2010). Isolated CDH cases are more likely to survive and have lower morbidity than those occurring as part of a syndrome (Nobuhara et al., 1996; Doyle & K.P. Lally, 2004; Danzer et al., 2010).

Predictor	Factors associated with unfavorable outcomes
Diaphragmatic defect	Large size and need for patch
	Site of hernia (right vs. left) is controversial
	The presence of other associated anomalies
Medical management	Aggressive ventilation and hypocarbia are associated with morbidities
	Use of ECMO is associated with higher mortality and morbidities
	Prolonged hospitalization is a poor sign
	Oxygen supplementation at the time of hospital discharge is a poor sign

Table 3. Diaphragmatic defect and medical management as predictors of outcomes

## 8. Management strategy

### 8.1 Early, delayed, and very delayed surgical corrections

The timing of surgical repair has gradually shifted from emergent repair to delaying surgery until ventilatory and medical stabilization. The delay may range from several hours in stable patients up to several weeks in those subjected to ECMO therapy (Hosgor & Tibboel, 2004). However, surgery is generally performed at 24-96 hours (Nio et al., 1994), with the CDH study group noting a mean age at surgery of 73 hours for patients not treated with ECMO (Clark et al., 1998; Congenital Diaphragmatic Hernia Study Group, 2001).

It is important to note that surgical reduction of the hernia does not improve lung mechanics and may even temporarily decrease the compliance of the chest wall. This can be explained by increased abdominal pressure associated with reduction of the viscera into the small abdominal cavity (Sakai et al., 1987). Delayed surgery is theorized to provide additional time for remodeling of the pulmonary vasculature, leading to a more stable infant, who is better able to tolerate a postoperative decrease in compliance (Sakai et al., 1987; Boloker et al., 2002).

Although the evidence to support the delay in surgery is lacking (Skari et al., 2000; Moyer et al., 2002), logically it is safer not to operate on an infant during a transitional period of severe pulmonary hypertension and high oxygen demand. Two randomized trials showed no significant differences between early and late surgery, but risk stratification was difficult due to the small numbers (Nio et al., 1994; Frenckner et al., 1997). A recent study from United States National Database does not support a beneficiary effect for delaying surgical repair beyond 7 days. They have demonstrated no statistical difference in mortality, when comparing a group of babies operated before 3 days of life or between the ages of 3 to 7 days of life. However, when babies were operated after 7 days of life, their mortality and use of ECMO increased significantly. It is possible that infants who were not stabilized in the first 7 days of life before surgery had significant pulmonary hypertension and consequently had increased mortality. (Aly et al., 2010) (Figure 1)

We can reasonably conclude that the survival of infants with CDH is not affected by the duration of waiting but instead the rather specific physiologic parameters that need to be met before operating on CDH infants (Rozmiarek et al., 2004). These parameters include lower FiO<sub>2</sub> requirement, minimal ventilator setting and absence of discrepancy between pre- and post-ductal saturations. Therefore, the European task force for CDH (CDH EURO Consortium) recommends performing surgical repair after physiological stabilization, defined as: mean arterial blood pressure normal for gestational age; preductal saturation range of 85% to 95% on fractional inspired oxygen less than 50%; plasma lactate concentration less than 3 mmol/l; and urine output more than 2 ml/kg/h (Reiss et al., 2010).

## 8.2 Ventilatory management

The most important facet in managing CDH infants is careful manipulation of ventilatory support. Given that pulmonary hypertension is ubiquitous in infants with CDH, reports of amelioration of ductal shunting in infants with persistent pulmonary hypertension prompted an era of aggressive hyperventilation (Drummond et al., 1981). Unfortunately, this was probably responsible for more mortality and morbidity than pulmonary hypoplasia and pulmonary hypertension combined. In 1995, Wung et al. (1995), demonstrated increased survival and decreased use of ECMO with the use of 'gentle ventilation', namely permissive hypercapnea, spontaneous respiration, avoidance of hyperventilation, avoidance of paralytic agents and continuous sedation infusion. Most centers now advocate prevention of ventilator-induced lung injury by tolerating hypercapnea while using low to moderate ventilator settings to achieve adequate pre-ductal oxygenation. Virtually all centers with survival over 80% employ this technique. The experience from Boston demonstrated that abandoning hyperventilation in favor of permissive hypercapnea resulted in an immediate 25% increase in survival (J.M.Wilson et al., 1997).

## 8.3 The use of extracorporeal membrane oxygenation (ECMO)

Roughly 50% of infants with high risk CDH are treated with ECMO (Breux et al., 1991). Survival of CDH infants treated with ECMO is 40% (Aly et al., 2010). As an index of the degree of pulmonary hypoplasia, pre-ECMO pCO<sub>2</sub> is particularly predictive of survival in CDH infants requiring ECMO (Hoffman et al., 2011).

Infants who utilize ECMO are obviously those with a severe form of pulmonary hypertension, who would otherwise die if this technology was not available. These infants are shown to have greater use of diaphragmatic patches during repair and frequently undergo other procedures such as funduplications and gastrostomy tube insertion (McGahren et al., 1997). Use of ECMO is associated with poorer neurological outcomes including; hearing deficits (Y. Sakurai et al., 1999, Lund et al., 1994; Nobuhara et al., 1996), brain abnormalities (Davenport et al., 1992; Lund et al., 1994), and developmental delay (Davenport et al., 1992; Nobuhara et al., 1996). However, as CDH survivors move through their school-age years, neurodevelopmental weaknesses become more apparent.

Between 10%-30% of patients treated with ECMO, including CDH-survivors, have neurological deficits (Towne et al., 1985; Glass et al., 1989; Schumacher et al., 1991). Among ECMO survivors, the diagnosis of CDH does not independently contribute to neurological risk (Stolar et al. 1995) although CDH infants are more unstable and have more complications while on ECMO (Stolar et al., 1995). The rate of adverse neurologic sequelae is lower when ECMO used with venovenous cannulation (Dimmitt et al., 2001; Kugelman et al., 2003). Therefore, ECMO improved survival in infants with CDH without long-term benefit (Morini et al., 2006).

The duration of ECMO has a substantial impact on survival. Beyond two weeks of ECMO support, survival decreases significantly (Tiruvoipati et al., 2007; Seetharamaiah et al., 2009). This could be related to increased renal, hematological, and CNS complications (Stevens et al. 2002). However, even after controlling for complications, duration of ECMO independently affected survival (Haricharan et al., 2009). Prolonged ECMO is a marker for severe pulmonary hypoplasia with its associated ventilation and oxygenation issues. Also, prolonged ECMO causes amplification of inflammatory response that may lead to severe edema and progressive organ dysfunction (Radhakrishnan & Cox, 2005).

## 9. Conclusion

Despite advances in neonatal care and surgeries, mortality and morbidity of infants with CDH are significant. There are multiple predictors for adverse outcomes in this population. Fetal lung volume can be measured via ultrasound or MRI. Early postnatal indicators for the severity of the disease include Apgar score at 5 minutes and early blood gas parameters. Delivery at a regional perinatal center without subsequent need for transport is favorable. Gentle ventilation and delaying surgery until physiological stabilization are associated with better outcomes. The use of ECMO is indicative of severe pulmonary hypertension and hemodynamic instability that are associated with worse outcomes.

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