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*Original Article*

# Congenital Diaphragmatic Hernia, Survival Outcome Over the Years

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**Abstract** Congenital diaphragmatic hernia remains a challenge to physicians worldwide. Studies have shown that several antenatal and postnatal factors affect the survival outcome of congenital diaphragmatic hernia (CDH). We reviewed our patients with this condition from 2005 to 2016. The overall survival was 82.5%. High pre-operative oxygen index remains a significant risk factor for death. There was marked improvement in survival with the standard use of inhaled nitric oxide on patients with pulmonary hypertension since 2005. Patients with repair-operation performed within the first week of life also showed significantly higher survival. We also looked into the possible benefits of extracorporeal membrane oxygenation (ECMO) in CDH. Reviewing with the Extracorporeal Life Support Organization criteria, if ECMO is available, 2.5 more survivals may be anticipated compared with no ECMO. Technological advancement in management of CDH has shown promising survival results in the past years. While ECMO is more readily available nowadays, we may be able to save more babies with CDH.

**Key words** *Congenital diaphragmatic hernia; Outcome; Oxygen index*

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## Introduction

Congenital diaphragmatic hernia (CDH) is a condition characterised by a diaphragmatic defect leading to the protrusion of abdominal contents into the thoracic cavity interfering with normal development of the lungs. The pathophysiology is a combination of severity of lung hypoplasia and immaturity associated with persistent pulmonary hypertension of newborn and cardiac dysfunction. The main focus of management includes gentle ventilation, haemodynamic monitoring and treatment of pulmonary hypertension followed by surgery. Despite technological advancement in neonatal intensive care, the management of CDH remains a challenge to physicians worldwide. Previous studies have shown that the side of CDH, liver herniation into chest, associated anomalies, prenatal diagnosis and fetal lung volume on magnetic resonance imaging (MRI), gestational age, birth weight, oxygen index and the presence of major air leak

affect the survival outcome of CDH.[1-4] As one of the three paediatric surgical centres in Hong Kong, we reviewed our patients with this condition from 2005 to 2016 and study the factors that affect survival outcome. Data from 1988 to 2004 were extracted from previously published review by Lee et al[5] and from a review by Wong et al[6] to compare the performance in our unit during different eras.

## Patients and Methods

Forty patients with congenital diaphragmatic hernia treated at our institution from 2005 to 2016 were reviewed. The pre- and post-operative features of these patients were studied. These include documentation of a prenatal diagnosis, whether they were inborn or transferred from other institution, gestational age at birth, sex, birth weight, side of hernia, associated anomalies, intrathoracic localisation of liver, worst pre- and post-operative oxygen index, use of inhaled nitric oxide (iNO) and high frequency oscillatory ventilation (HFOV), and time from birth to repair-operation. We compared the characteristics of survivors and non-survivors using Fisher's exact test. Data from 1988 to 2004 were extracted from previously published review by Lee et al[5] and from a review by Wong et al6 to compare the performance in our unit during different eras. We have obtained approval from the institutional review board for this study.

## Results

Forty patients were identified. The results are shown in Table 1. There were 21 males (53%) and 19 females (48%). There were 27 inborns and 13 outborns. Gestational age at birth ranged from 31-41 weeks (mean 37.9 +/- SD 2.27 weeks). Six of them were preterm with gestational age at birth less than 37 weeks and 34 (85%) of them were term babies. Birth weight ranged from 1430-3785 g (mean 2761 +/- SD 526 g). Six (15%) of them were small for gestational age. Of these 40 patients, 25 (62.5%) of them were diagnosed antenatally, 14 (35%) of them were diagnosed postnatally and one of them was diagnosed on post-mortem examination. Thirty-seven had left-sided lesions and 3 had right-sided lesions. The rate of intrathoracic localisation of liver was 6/40 (15%). Pulmonary hypoplasia was documented in 16/40 (40%) and pulmonary hypertension was documented in 15/40 (37.5%). There were 14 patients with associated anomalies and syndromes. These included left undescended testes (n=2), cardiac anomalies with perimembranous ventricular septal defect, atrioventricular septal defect, multiple atrial septal defect (n=4), omphalocele (n=1), inguinal hernia (n=1), Dandy Walker syndrome (n=1), Patau syndrome (n=1), right paratracheal bronchogenic cyst (n=1) and right congenital ptosis (n=1). A number of complications were documented in 8 out of 40 of our patients. These include intestinal obstruction (n=1), gut ischaemia (n=1), liver derangement (n=1) and sepsis (n=5). None of these complications was associated with mortality. The oxygen index (OI=mean airway pressure x $FiO_2$ x 100/$PaO_2$) pre- and post-operatively were calculated. Twenty-three patients had their worst pre-operative OI of 20 or less. Nine patients had their worst pre-operative OI of more than 20. There were 8 pieces of missing data. Comparing the mortality of patients with worst pre-operative OI >20 and >30, the mortality was 5/9 (56%, p=0.003) and 4/5 (80%, p=0.002) respectively (Table 2). We cannot find any significant effect of post-operative OI on mortality. Concerning the treatment received, the use of high

**Table 1** Survival results and patient characteristics

| Characteristics | No. of patients (%) | P-value |
|---|---|---|
| Gender | | 0.226 |
| Male | 19/21 (90%) | |
| Female | 14/19 (74%) | |
| Prenatal diagnosis vs diagnosis after birth | | 0.224 |
| Prenatal | 19/25 (76%) | |
| Postnatal | 14/14 (100%) | |
| Postmortem | 0/1 (0%) | |
| Inborn | 21/27 (78%) | 0.393 |
| Gestational age | | 0.953 |
| Preterm (less than 37 weeks) | 5/6 (83%) | 1.0 |
| Full term (37 weeks or more) | 28/34 (82%) | |
| Small for gestational age | 3/6 (50%) | 0.055 |
| Site of hernia | | 1.0 |
| Left-sided | 30/37 (81%) | |
| Right-sided | 3/3 (100%) | |
| Associated anomalies | 10/14 (71%) | 0.214 |
| Intrathoracic localisation of liver | 3/6 (50%) | 0.055 |
| Definitive repair before vs on/after 7 days postpartum | | <0.001 |
| <7 days | 29/29 (100%) | |
| on/after 7 days | 4/11 (36%) | |

frequency oscillatory ventilation was documented in 13/40 (32.5%) and the use of inhaled nitric oxide was documented in 11/40 (27.5%). A total of 29 patients underwent repair-operation within the first week of life and 1 patient underwent operation on day 8 of life. Three cases with late diagnosis underwent operation at day 173, 150 and 60 of life. All of them survived. All 7 death cases were deceased before any operation done. Most patients who underwent operation were ventilated up to 5 days after operation (n=21, 53%). The overall survival was 82.5%, up to 13.1 years (Figure 1).

iNO was available in our unit since 1995 but was used in selected cases only. From 2005 onwards, it became the standard treatment in persistent pulmonary hypertension of newborn. Despite the fact that high pre-operative oxygen index remains a significant risk factor for death, there was marked improvement in the survival of patients with worst pre-operative oxygen index >20 over the years (0/4 during 1988-1996, 0/3 during 1997-2004, 4/9 [44%] during 2005-2016) (Table 3).[5,6] There was also one out of five patients with pre-operative OI >30 surviving during 2005-2016. Out of the eleven patients given inhaled nitric oxide, six survived (survival=55%, p=0.0108). We postulated that with the standard use of inhaled nitric oxide in CDH with pulmonary hypertension introduced since the year 2005, the survival of patients with high pre-op OI >20 has much improved and thus improve the overall survival. The use of HFOV is also shown to have a statistically significant positive correlation with survival (survival=62%, p= 0.0268) (Tables 4 and 5).

## Discussion

Researchers have been studying the determining factors which can help predict the outcome of CDH. Previous studies have shown that the side of CDH, liver

**Table 2** Survival rate and ventilatory parameters

| Ventilatory parameters | No. of patients (%) | P-value |
|---|---|---|
| Pre-operative | | |
| OI 20 or less | 22/23 (96%) | |
| OI >20 | 4/9 (44%) | 0.003 |
| OI 30 or less | 25/27 (93%) | |
| OI >30 | 1/5 (20%) | 0.002 |

OI: oxygen index

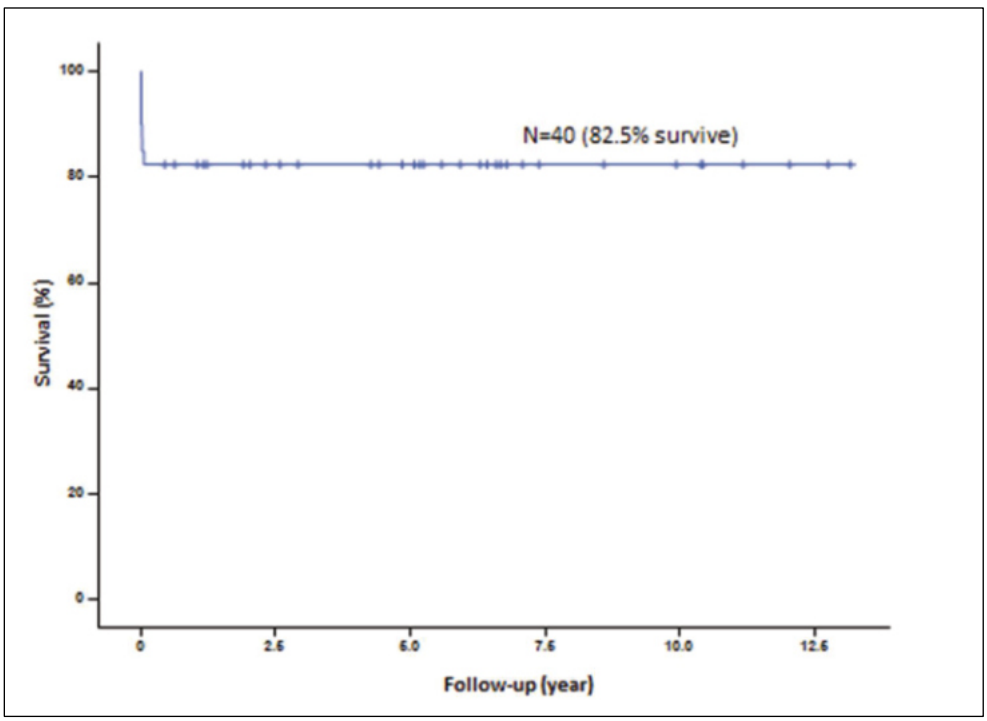


**Figure 1** Kaplan-Meier survival curve showing the overall survival of forty patients with congenital diaphragmatic hernia treated at our institution from 2005 to 2016 at 82.5%, up to 13.1 years.

herniation into chest, associated anomalies, prenatal diagnosis and fetal lung volume on MRI, gestational age, birth weight, oxygen index and the presence of major air leak affect the survival outcome of CDH. Reviewing our cases, high pre-operative oxygen index remains a significant risk factor for death. Patients with repair-operation performed within the first week of life showed significantly higher survival. No prenatal diagnosis was accompanied by a MRI finding with fetal lung volume. No major air leak was documented in our patients. While liver herniation into chest and small for gestational age seems to cause poorer survival, they do not reach a statistical significance (survival=50% in both factors, p value >0.05). The other factors mentioned above do not have a significant impact on the survival of our patients, probably due to a small sample size. In our review, we did not include deaths before arrival to the hospital, fetal deaths due to termination of pregnancy and in-utero deaths. Only postnatal mortality is studied. This may decrease the apparent overall mortality.

Nowadays, we use iNO as our initial treatment for pulmonary hypertension in congenital diaphragmatic hernia after excluding cyanotic congenital heart disease. In case of pre- and post-ductal saturation difference of 10% or more, oxygen index of 20 or more, and raised right ventricle pressure (estimated by the degree of tricuspid

**Table3** Survival rate and worst pre-op oxygen index throughout the years

| Worst pre-op oxygen index | 2005-2016 | 1997-2004 | 1988-1996 |
|---|---|---|---|
| 20 or less | 22/23 (96%) | 10/10 (100%) | 6/7 (86%) |
| >20 | 4/9 (44%) | 0/3 (0%) | 0/4 (0%) |
| >30 | 1/5 (20%) | -- | -- |

Use of inhaled nitric oxide (iNO):

iNO available since 1995

1988-1996: no use of iNO

1997-2004: use in selected cases

2005 onwards: standard use of iNO in persistent pulmonary hypertension of the newborn

Data from 1988 to 2004 adopted from Lee et al[5] and Wong et al[6]

**Table 4** Patient characteristics and survival

| | QMH HK (2005- 2016) | QMH HK (1997- 2004) | QMH HK (1988-1996) |
|---|---|---|---|
| No. of infants | 40 | 18 | 21 |
| Male to female ratio | 21:19 | 15:3 | 13:8 |
| Inborn | 67.5% | 61% | 38% |
| Term babies | 85% | 76% | 52% |
| Small for gestational age | 15% | -- | -- |
| Site of lesion | | | |
| Left | 92.5% | 82% | 84% |
| Right | 7.5% | 18% | 19% |
| Bilateral | 0% | 0% | 0% |
| Associated anomalies | 35% | 22% | 38% |
| Overall survival | 82.5% | 67% | 71% |

QMH HK: Queen Mary Hospital, Hong Kong

**Table 5** Treatment and survival (2005-2016)

| | No. of patients (%) | Survival | P-value |
|---|---|---|---|
| Inhaled nitric oxide | 11/40 (27.5%) | 6/11 (55%) | 0.0108 |
| High frequency oscillatory ventilation | 13/40 (32.5%) | 8/13 (62%) | 0.0268 |

regurgitation) demonstrating significant pulmonary hypertension on echocardiogram, we will initiate iNO therapy starting with 20 parts per million (ppm). iNO dosage can be titrated up to 40 ppm as required but its side effect of methaemoglobinaemia should be closely monitored. We begin weaning iNO when fraction of inspired oxygen ($FiO_2$) is less than 40-50%, by 5 ppm every 4-6 hours. Once iNO dose is 5 ppm, gradual weaning by 1 ppm per hour is performed. Regular echocardiogram assessment will be performed till all support is withdrawn. As inhaled nitric oxide improves ventilation-perfusion matching and overall oxygenation, partial pressure of oxygen ($PaO_2$) and $FiO_2$ requirement usually improve after its use and so the use of iNO usually improves oxygen index.

While the standard use of iNO in CDH with pulmonary hypertension and the use of high frequency oscillatory ventilation have statistically positive correlations with survival, we also looked into the possible benefits of extracorporeal membrane oxygenation (ECMO) in CDH. One of our survivors was put on ECMO post-operatively. The benefits of ECMO in CDH are still controversial, since there are only few randomised trials demonstrating the advantages of this therapeutic option. However, some centres and networks have demonstrated an increase in survival rates in CDH with the employment of ECMO by retrospective analysis in their series.[7] The overall survival of infants with CDH requiring ECMO is around 51%.[8] The use of ECMO in CDH varies according to location. Majority of patients was placed on ECMO before repair operation, with only 5% postoperative use. It is reserved for patients who are failing optimal medical management, including pressure-limited ventilation and pharmacological management with inotropic support and pulmonary vasodilatation with inhaled nitric oxide and sildenafil.[9] We studied the 13 death cases over the period 1997 to 2016 and identify cases that we could save with ECMO. After excluding patients with contraindications to ECMO by the ELSO criteria, we identified 5 cases which might be eligible for ECMO (Table 6). Stolar et al showed that 60% of infants who received ECMO enjoyed normal cognition[10] and McGahren et al showed that 67% of survivors exhibited neurological compromise.[11] In our review, if ECMO is available, 2.5 more survivals may be anticipated compared with no ECMO. 1.5 of them would have normal cognition.

In conclusion, technological advancement with standard use of iNO in CDH patients with PPHN has shown promising survival results in the past years. While ECMO is more readily available nowadays, we may be able to save more babies with CDH. Further literature review and prospective randomised trials are necessary to help with evaluating the efficacy of ECMO and refining the criteria for ECMO use in CDH.

## Ethics Approval

We have obtained approval from the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster for this study. The IRB reference number is UW 20-375.

## Conflicts of Interest

All authors have disclosed no conflicts of interest.

**Table 6** Extracorporeal membrane oxygenation criteria for congenital diaphragmatic hernia

| Indications | Contraindications |
|---|---|
| Hypoxia: | Significant congenital anomalies (major cardiac anomalies) |
| Preductal $SaO_2$ consistently <80-85% | Lethal chromosomal abnormalities (trisomy 13, 18) |
| oxygen index >40 for >=4 hours or $PaO_2$ | or other lethal malformations |
| <40 mmHg/5.3 kPa for 2 hours | Irreversible brain damage |
| Acidosis: | Uncontrolled bleeding |
| Metabolic (lactate >5 mmol/L or pH <7.20) or | Grade 3/4 intracranial haemorrhage |
| Respiratory (pH <7.20 due to hypercarbia) | Body weight <2 kg |
| Hypercarbia: | Gestational age <34 weeks |
| Persistent $PaCO_2$ >70 mmHg/9.3 kPa leading to pH <7.20 | Prolonged mechanical ventilation (>10-14 days) |
| Hypotension: | requiring prolonged high pressure |
| Poor tissue perfusion, urine output <0.5 mL/kg/hr (for 12-24 hours) | |
| unresponsive to IV fluid and inotropic support | |

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