The Congenital Diaphragmatic Hernia Study Group registry update

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**SUMMARY**

The Congenital Diaphragmatic Hernia Study Group (CDHSG) is an international consortium of centers that prospectively collect and voluntarily contribute data about live-born CDH patients they manage. These data are compiled to form a registry from which any participating center may utilize the dataset to answer specific clinical questions and monitor outcomes. Since its inception in 1995, 112 centers have participated (including 66 centers from 13 countries currently active), data on more than eight thousand total children have been collected, and 35 manuscripts have been generated using registry data. This review covers the formation and structure of the CDH study group and registry, including function, center involvement, and the evolution of data collection. We also review reports generated by the CDHSG, with particular focus on the work after 2008. International multicenter consortiums, such as the CDHSG, allow physicians that manage uncommon, complex, heterogeneous diseases to develop evidence-based hypotheses and conclusions for clinical questions.

**1. Introduction**

The Congenital Diaphragmatic Hernia Study Group (CDHSG) was established in 1995 with the purpose of uniting multiple centers/physicians who manage children with a congenital diaphragmatic hernia (CDH) to collect and collate data, and answer clinical questions that would otherwise be impossible to study. At that time, there was an emerging realization that no single institution had a sufficient number of children to develop meaningful, accurate evidence. Thus, there was general acknowledgement that a collective effort was imperative to gather data on as many patients as possible, in order to adequately address critical questions.

Sixty-nine centers participated in initial data collection. Any children born in or after 1995 were eligible to have information collected for the dataset. Institutional review board approval was obtained for waiver of written consent due to the collection of de-identified data. Both submitting center and individual patient information were (and remain) anonymous, ensuring Health Insurance Portability and Accountability Act (HIPAA) compliance. Additionally, waiver of consent optimized the opportunity to collect data on all patients with CDH. One of the initial goals was to intentionally limit or focus data collection to prevent expansive and onerous data collection. Hypothesis-driven data points are carefully considered to focus data collection.

The intent of CDHSG is to collect information on all infants born with CDH managed at a participating center. Center participation is voluntary, driven by the individual institutional desire to contribute to the formation of a meaningful data set.

The CDH registry performs a variety of functions. First, data submitted from individual institutions are entered into and maintained in a database. Additionally, each participating center receives an annual report summarizing its submitted data in comparison with other centers worldwide.

**2. Contributing centers**

Any center that manages/treats children with CDH is invited to participate in the CDHSG. Today, 66 centers are active participants. Thirty-six centers have been consistent contributors since the inception of the CDHSG. Centers from 14 countries have contributed patients (Argentina, Australia, Canada, Chile, Germany, Italy, Japan, Malaysia, Poland, Russia, Scotland, Sweden, The Netherlands, USA).

The range of center contribution is highly variable. Whereas 14 centers have contributed >10 patients per year over the last 5 years, other centers contribute one or two patients per year. Contributions from a wide variety of centers, which have highly varied practice...
patterns and see different volumes of patients, are important to understand the range of care CDH patients receive.

In total, 8,279 patients were in the database as of June 2014. The vast majority are neonates (7998; 96.6%), although 281 patients were late presenters. Overall mortality since 1995 is shown in Fig. 1.

3. Evolution of data collection

Since inception, there have been three versions of specific data collection. There is a continual evaluation of the data being collected, with a constant and intentional effort to focus data collection based on pertinent, timely clinical questions. The information captured included basic demographics, prenatal evaluation, associated anomalies, pharmacologic/critical care/surgical management, and clinical outcome. Version 1 (1995–2001) focused on defining the problem including medications being used, ventilator strategies, and use of extracorporeal membrane oxygenation (ECMO). Version 2 (2001–2006) focused on method of delivery, oxygen/carbon dioxide values, discharge oxygen/nutritional status, and elaboration of cardiac anomaly association. Version 3 (2006–2014) focused on classifying the size of the defect using a standardized classification scheme and its relation to outcome. This version also captured reasons for not repairing the diaphragm. Finally, severity of pulmonary hypertension was an additional area of focus, including descriptive and management data. Version 4 will be designed to capture increased information on prenatal diagnosis, including ultrasonographic and fetal magnetic resonance imaging parameters. There are also plans to create a follow-up registry that would include neurodevelopment, pulmonary function, and nutritional status.


During this period, 15 reports were generated using the data collected by the CDHSG. The publications fell into three broad categories: (1) those using specific data to predict outcome; (2) those describing associated anomalies or rare defects/clinical scenarios; and (3) those assessing the outcomes of specific therapies. An overview of the results from these publications was compiled in a review article published in 2008 [1].

One of the initial reports from the CDHSG defined the surgical management approach at that time [2]. Based on 2 years of data collection, including 461 patients, they reported that delayed surgical repair (mean age at surgery was 73 h) had become generally accepted, that 51% of repaired patients required a patch (polytetrafluoroethylene) was the most common material), and that overall survival was 63%. The overall survival of patients requiring ECMO was 54%. Interestingly, 15% of the patients went unrepaired, identifying a subset of challenging patients and highlighting the potentially subjective nature of center variation.

In 2001, data obtained at birth were used to stratify risk and predict outcome [3]. More than one thousand patients from 71 institutions were included to determine whether variables collected at birth could be used to assess potential mortality. A multivariate analysis of the first 322 patients identified that birth weight and 5 min Apgar score correlated most strongly with survival. This was used to create an equation, subsequently validated with 673 patients, and used to stratify patients into groups that correlated with mortality.

Early arterial blood gas analysis was also evaluated for the ability to accurately and easily predict survival [4]. The highest PaO2 minus the highest PCO2 (WHSRPF) was developed from institutional data and validated against CDHSG data. Despite a reasonable ability to predict outcome, an area under the curve of 0.79, and generally compelling data, the model did not have sufficient clinical accuracy and further evaluation was recommended.

One of the strengths of the multi-institutional collaborative contribution is the ability to identify the incidence and outcome of rare anomalies associated with CDH. Fryns syndrome was identified in 1.3% of infants with CDH [5]. The association was found to have a high mortality, with only 17% survival. Cardiac anomalies have long been associated with CDH. One study identified that 10.6% of patients with CDH have hemodynamically significant congenital cardiac disease [6]. Survival was lower for this subset of patients (41.1%) and those with specific cardiac lesions (uni-ventricular anatomy) had a particularly poor survival (5.1%). The incidence of bilateral CDH was identified as 0.9%, with a mortality of 65%, significantly worse than children with a unilateral CDH [7]. Finally, 2.6% of infants born with CDH present after 30 days of life [8]. These patients with a “late presentation” tended to present with gastrointestinal symptoms if they had a left-sided defect and respiratory symptoms with a right-sided defect. Survival among the late presenters was 100%.

The relationship between the size of the defect and outcome began to be identified in a study of 9 years of CDHSG data [9]. Among many variables analyzed, size of the defect was determined to have the greatest impact on survival. At this point in the data collection, size was defined as agenesis (based on operative description), non-agenesis requiring a patch, and primary closure. The odds ratio for mortality associated with diaphragm agenesis was 14.07 when compared with primary repair. This analysis solidified the concept that defect size and severity of disease were associated. Further, this prompted the generation of an objective grading system incorporated into version 3 (Fig. 2). The results of this data analysis are discussed below.

In 1999, the CDHSG published the first report demonstrating improved survival among high-risk CDH patients (defined as predictive mortality >80%) when ECMO was utilized [10]. Overall survival among patients requiring ECMO was 52.9%, significantly worse than those not requiring ECMO.

Surfactant was a promising therapy for infants with CDH, given preclinical data suggesting that CDH and surfactant deficiency were associated. The CDHSG published three analyses of the use of surfactant among infants with CDH. The first study evaluated 522 infants with CDH, including 122 treated with exogenous surfactant [11]. Those treated with surfactant were more likely to require ECMO and had a higher mortality. No evidence of benefit was identified. Two additional studies attempted to identify a subset of CDH patients that may benefit from surfactant therapy. Analyses of both preterm CDH infants [12] and those requiring ECMO [13] (presumably a subset with an expected higher morbidity and mortality) failed to identify any significant difference between treated and untreated patients.

Fig. 1. Congenital Diaphragmatic Hernia Study Group overall mortality by year.
A cohort of patients from the CDHSG was analyzed, along with a small group of CDH patients enrolled in a prospective trial, to determine whether prenatal corticosteroids held promise as a treatment strategy among prenatal infants with CDH [14]. No differences in survival, liberation from mechanical ventilation, inpatient length of stay, or oxygen requirement at 30 days were identified.

Mode of delivery was evaluated as a potentially significant management decision among patients with CDH [15]. Elective cesarean delivery, induced vaginal delivery, and spontaneous vaginal delivery were compared and no difference in survival was identified. Again, limitations of these data were acknowledged and further prospective studies recommended.

5. Reports from the CDHSG 2008–2014

Over the last 6 years, there have been 12 publications using the CDHSG data. These publications addressed questions about staging and standardized reporting, survival and long-term morbidity, associated defects and complications, specific patient populations, as well as interventions such as ECMO and minimally invasive repair.

The development of a standardized reporting system [16] for this heterogeneous disease allowed surgeons to objectively classify and stage an individual patient based on defect size (Fig. 2) and presence or absence of a major cardiac anomaly. As previously mentioned, version 3 of the data collection included the classification of the defect size into four types (A–D) where an “A” defect is a small defect able to be easily repaired primarily, and a “D” defect is diaphragmatic agenesis (Fig. 2). Nearly 2000 infants were evaluated and grouped into five stages (plus a group for non-repair) based upon the size of the diaphragmatic defect and the presence of a severe cardiac anomaly. These variables were the most significant and objectively captured risk factors affecting mortality in the model. The proposed staging system and survival based on stage are shown in Table 1. Patient survival is 99% for stage I, 96% stage II, 78% stage III, 58% stage IV, 39% stage V, and 0% for non-repair.

In a separate study, defect size alone was found to correlate with mortality and presence of associated anomalies. Over a 4-year period, 1350 patients entered into the registry had defect classification, including 173 A, 557 B, 438 C, and 182 D [17]. Mortality rate was 0.6% (A), 5.3% (B), 22.6% (C), and 45.6% (D). There was an increase in the prevalence of associated anomalies and number of abnormal systems as the defect size increased. Table 2 shows the significant differences identified between the four defect size groups.

The outcome of the premature infant with CDH was reported in 2010 [18]. More than 5000 infants (including 1127 preterm infants),

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\begin{array}{ccccccccc}
\text{Stage} & \text{Defect} & \text{Major cardiac anomaly} & n & \text{Died} & \text{Survived} & \text{Group survival} & \text{Stage survival} \\
\hline
1 & A & 164 & 0 & 164 & 100% & 99% & 99% \\
2 & A & + & 8 & 1 & 7 & 88% & 96% \\
2 & B & 572 & 21 & 551 & 96% \\
3 & B & + & 18 & 6 & 12 & 67% & 78% \\
3 & C & 372 & 21 & 351 & 96% \\
4 & C & + & 27 & 12 & 15 & 56% & 58% \\
4 & D & 144 & 60 & 84 & 58% \\
5 & D & + & 18 & 11 & 7 & 39% & 39% \\
\end{array}
\]

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Values are mean ± standard deviation or prevalence.

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compiled over 15 years, were evaluated to determine the impact of prematurity on survival among premature infants. Whereas overall survival of infants in the cohort was 68.7%, term infants had a significantly higher survival than preterm infants: 73.1% versus 53.5%, respectively. Mortality was inversely proportional to estimated gestational age (EGA) at birth (Fig. 3). The overall survival for the most premature infants, <28 weeks EGA, was 31.6%. Preterm infants were twice as likely as term infants to have chromosomal anomalies or cardiac defects. Whereas 86% of term infants underwent operative repair, 69% of preterm infants underwent repair. The percentage of infants who underwent operative repair decreased with decreasing gestational age.

Minimally invasive approaches for CDH have been controversial. Initial publications identified rates of recurrence that were concerning [19–22]. The CDHSG studied 151 infants who underwent minimally invasive CDH repair [23]. An early, in-hospital recurrence rate of 7.9% was identified, as opposed to a 2.6% recurrence rate for the open approach (P < 0.05). Specifically, the thoracoscopic approach had an 8.8% rate of recurrence, the highest rate of all approaches. The overall survival rate for the minimally invasive approach was nearly 99%, almost certainly a reflection of the selection bias.

Three studies evaluated challenging aspects of CDH patients that require ECMO support. The first one, published in 2009, identified factors associated with survival among patients with CDH [24]. Overall survival among patients requiring ECMO, when repair was attempted, was 61%. Of the patients treated with ECMO, greater survival was identified among those with a greater estimated gestational age, greater birth weight, those not prenatally diagnosed, and those requiring less time on ECMO.

Two studies attempted to identify a survival advantage based on timing of surgery among patients with CDH requiring ECMO. One institution compared their single center data to the CDHSG data and to the Extracorporeal Life Support Organization [25]. They evaluated 34 neonates who were cannulated to VA ECMO and were subsequently repaired (on ECMO) 55 ± 21 h into the support. Neonates at the authors’ institution were repaired earlier in the course compared with the CDHSG patients (2.4 versus 7 days, P < 0.0001). Survival among the single institution cohort was 71%, as compared to the CDHSG survival rate of 50.9%. Eleven (32%) of the 34 patients experienced some type of bleeding complication (most were clinically insignificant) and only three patients (8.8%) had a surgical site hemorrhage.

A second group used the CDHSG registry to investigate survival differences between those who underwent repair during ECMO and those who underwent repair after liberation from ECMO support [26]. This group identified 636 patients, over a 10-year period, which underwent repair and required ECMO therapy. Interestingly, they found that repair after ECMO was associated with increased survival relative to repair on ECMO. Though they attempted to control for factors associated with the severity of CDH, selection bias undoubtedly existed, given the fact that patients able to be weaned off ECMO were more likely to have the pulmonary development necessary to survive. Additionally, the authors hypothesized that some of the survival benefit may also have been due to the decreased rate of hemorrhagic complications when the diaphragm repair was performed off ECMO.

Even among infants with CDH who do not require ECMO support, the optimal timing of surgery remains unknown. The CDHSG evaluated 1385 infants without preoperative ECMO and stratified them by timing of repair [27]. Those repaired on day of life (DOL) 0–3 were group 1, DOL 4–7 were group 2, and DOL >8 were group 3. The effect of timing of surgery on mortality was determined and risk-adjusted for severity of illness. Forty percent of the patients were in group 1, 40% in group 2, and 20% in group 3. Using group 1 as a reference, unadjusted multivariate logistic regression analysis

**Table 2**

<table>
<thead>
<tr>
<th>Defect</th>
<th>A (173 points)</th>
<th>B (557 points)</th>
<th>C (438 points)</th>
<th>D (182 points)</th>
<th>P</th>
<th>P(trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (weeks)</td>
<td>38.10 ± 2.05</td>
<td>37.93 ± 1.89</td>
<td>37.55 ± 2.19</td>
<td>37.25 ± 2.47</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>3.15 ± 0.01</td>
<td>3.08 ± 0.54</td>
<td>2.97 ± 0.00</td>
<td>2.84 ± 0.61</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MLF (%)</td>
<td>24.9</td>
<td>23.7</td>
<td>33.6</td>
<td>41.6</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CVM (%)</td>
<td>10.4</td>
<td>13.6</td>
<td>24.2</td>
<td>22.0</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major CVM (%)</td>
<td>3.5</td>
<td>3.4</td>
<td>7.8</td>
<td>12.1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abn. systems</td>
<td>1.07 ± 0.35</td>
<td>1.26 ± 0.63</td>
<td>1.37 ± 0.84</td>
<td>1.46 ± 0.92</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>Chr. (%)</td>
<td>3.0</td>
<td>1.8</td>
<td>2.6</td>
<td>6.2</td>
<td>0.0719</td>
<td>0.0806</td>
</tr>
<tr>
<td>Hernia sac (%)</td>
<td>27.2</td>
<td>23.3</td>
<td>16.9</td>
<td>17.6</td>
<td>0.0014</td>
<td>0.0001</td>
</tr>
<tr>
<td>LU</td>
<td>10.3</td>
<td>20.5</td>
<td>49.8</td>
<td>32.2</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

GA, gestational age; BW, birth weight; MLF, associated anomalies; CVM, cardiovascular malformations; Abn. systems, abnormal systems considered: craniofacial, skeletal, muscular, cardiovascular, genitourinary, gastroenterological, and nervous; Chr., chromosomal anomalies; LU, liver-up in the chest (at surgery).

Values are mean ± standard deviation or prevalence.

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demonstrated a significant association of delayed repair with mortality for group 2 (1.73; 95% confidence interval: 1.00–2.98) and group 3 (3.42; 1.97–5.96). However, when risk-adjusted for associated anomalies, defect size, and birth weight (among others), timing of repair was not found to influence mortality.

Assessing the severity of disease and prognosis among patients with CDH remains challenging. Data from the registry were used to evaluate the predictive capability of the degree of pulmonary support on hospital day 30 [28]. Over a 4-year period, 862 CDH patients were identified who had a length of stay >30 days. At day 30, their pulmonary support was categorized as: (1) room air (n = 320); (2) non-invasive supplementation (n = 244); (3) mechanical ventilation (n = 279); and (4) ECMO (n = 19). Survival was found to be: (1) 99.7%; (2) 98.0%; (3) 74.9%; and (4) 26.3%, respectively (P < 0.001). Further, the level of support at 30 days also predicted need for supplemental oxygen at discharge and directly correlated with length of hospital stay.

The rate of development of bronchopulmonary dysplasia (BPD) among infants with CDH and the risk factors associated with this subset of CDH patients were unknown. In 2010, an analysis of 2078 patients from the CDHSG, collected between 2001 and 2008, was completed to address this chronic respiratory disorder [29]. Among infants who survived until day 30, the prevalence of BPD was 41%.

Multivariate logistic regression analysis identified several significant variables associated with BPD including gestational age, cardiac abnormality, inborn status, prenatal diagnosis, right-sided defect, 5 min Apgar score, and high frequency oscillatory ventilation. This was the first study to describe the development of chronic lung disease and the risk factors among a large cohort of patients with CDH.

Finally, the association between CDH and esophageal atresia (EA) [30], and the impact of chylothorax [31] among CDH patients were both reported. Over an 11-year period, 4888 patients with CDH were collected in the registry and 23 (0.5%) had an associated EA. These patients had a significantly lower survival than the registry mean (26.1% vs 70.3%, P < 0.001). These patients had a significantly lower birth weight, more cardiac abnormalities, and more chromosomal abnormalities. Survival among patients with CDH and EA is low, though it is not uniformly lethal, making intent of repair a viable approach. With regard to chylothorax, a cohort of 1383 patients, collected during a period of 3 years, identified 65 patients (4.7%) with a chylothorax, diagnosed by pleural fluid evaluation. Patch repair and ECMO were statistically significant risk factors for chylothorax. Most chylothoraces (83.1%) were successfully managed without surgical intervention. Although patients who developed a chylothorax experienced increased morbidity (increased length of stay and increased oxygen use), their morbidity was unchanged.

6. CDH prior to 1995

There have been significant advancements in our understanding and management of CDH, both medical and surgical, since the inception of the CDHSG in 1995. At that time, CDH was transitioning from a surgical emergency, requiring a rapid trip to the operating room to relieve the intrathoracic tension created by the abdominal contents, to an initial stabilization phase, followed by repair [32,33]. The utility (or lack thereof) of steroids, surfactant, nitric oxide, and sildenafil were unknown. Fetal surgery for CDH was in its translational transition from preclinical work to clinical application [34,35]. The correlation between defect size and outcome was largely unknown. In the late 1980s and early 1990s, overall survival was unclear, due to small, individual center reports, but was likely around 50%, depending upon many factors [36].

The CDHSG has been a part of the growth of the CDH field into the modern era. Initial stabilization, oscillatory ventilation, ECMO, and delayed repair are part of the current management armamentarium. Steroids and surfactant were found unlikely to be clinically efficacious [12–14]. Nitric oxide and sildenafil are commonly used, though their effect on mortality remains unproven. Fetal surgery has seen significant advances, though it continues to be critically evaluated [37]. Correlation between defect size and survival is known [17]. Overall survival is >70%.

7. Future directions

The CDHSG continues to evolve alongside advances in knowledge (basic science and clinical), clinical care, and technology. Version 4, as discussed above, will explore prenatal diagnosis and pulmonary hypertension. Advances in prenatal imaging have enhanced visualization of the anatomy of the fetus. The next version should help to answer questions about the prognostic value and accuracy of prenatal imaging.

Approximately 20 projects using the data set are at various stages in the production process. These include projects evaluating diagnostic/prognostic variables such as preductal oxygen saturation, defect size/anomaly association, and pulmonary hypertension. There are also projects examining various areas of management including timing of repair, treatment heterogeneity among centers, chest tube placement, the influence of multiple ECMO runs, and variability in management strategy between centers.

8. Conclusion

The CDHSG has been an important part of the increasing foundation of knowledge and evolution of management of CDH. For nearly 20 years, centers around the world have been voluntarily making valuable contributions that, collectively, have significantly advanced our ability to understand and manage CDH. Overall survival has slowly improved, increasing ~5%, since the inception of data collection. The focus of each version has changed, allowing new hypotheses and clinical questions to be addressed. Ongoing participation of current centers and the addition of new centers will continue to be the foundation of the CDHSG, allowing valuable contributions in the future.

Conflict of interest statement

None declared.

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References


