## Introduction

With an incidence of 1 in 2,500-5,000 live births, congenital diaphragmatic hernia (CDH) remains one of the most common and challenging conditions for neonatologists and neonatal surgeons.[1,2] Despite significant advances in antenatal detection, antenatal therapy, neonatal intensive care and neonatal surgery, the morbidity and mortality rates of infants with CDH remain high due to the combination of pulmonary hypoplasia, cardiac dysfunction and pulmonary hypertension.[3]

In an effort to improve the outcome of infants with CDH, multicenter studies and collaborative registries have been established over the years.[3,4] Recently, some studies have focused on short-term outcomes of infants with CDH to identify prognostic factors associated with early mortality.[5-9] Similarly, to analyze the perioperative risk factors for mortality and short-term outcomes, the American College of Surgeons has developed a registry, the National Quality Improvement Program Pediatric (NSQIP-P).[10] Developed in partnership with the American Pediatric Surgical Association, the NSQIP-P is the first and only risk-adjusted, clinical, outcomes-based program to measure and improve pediatric surgical care.[10] In the present study, we aimed to analyze for the first time the short-term outcomes of infants who underwent CDH repair by identifying predictive factors for adverse outcome of CDH patients registered on this large North American database.

## Methods

### *Data Source*

Due to the de-identified and public nature of the data herein collected and analyzed, the present study was exempt from review by the Hospital for Sick Children Research Ethics Boards. Data from the 2015 and 2016 NSQIP-P participant use data file was used. As previously described, the NSQIP-P samples and collects data in 8 day cycles with 35 procedures per cycle by dedicated clinical abstractors using a defined methodology.[10] During 2015, 80 participating centers uploaded a total of 84,056 cases, and during 2016, 101 participating sites submitted 101,887 cases with 95 perioperative data points on the NSQIP-P database. The data files were available in a SAS file, which was converted to an Excel spreadsheet. We searched the participant use data file for the current procedural terminology code 39503 indicating "Repair, neonatal diaphragmatic hernia, with or without chest tube insertion and with or without creation of ventral hernia" and a postoperative ICD-9-CM code confirming a diagnosis of diaphragmatic hernia (553.3). Patients that had their CDH repaired later than 90 days of life were excluded from the study.

### *Variables*

Demographic variables included gestational age at birth, birth weight (kg), ethnic background (White, Black, Asian, Hispanic, Other), prematurity (<37 weeks of gestation), delivery mode (vaginal delivery, caesarian section), as well as Apgar scores at 1 and 5 minutes. Preoperative variables included major cardiac risk factors (as already classified by NSQIP-P), ECMO use, and age at surgery (corrected gestational age in weeks). Operative variables included anesthesia time (min), surgery time (min), surgical approach (open or minimally invasive), use of inotropes during

surgery, and the need for blood transfusion either intraoperatively or within 72 hours after surgery.

***Outcome Variables***

Outcomes included 30-day postoperative complications, reoperations and mortality. The postoperative complications included diaphragmatic hernia recurrence, surgical site infections (SSI – classified as superficial, deep or organ space), wound dehiscence, unplanned reintubation, pneumonia, acute renal failure, seizures, systemic sepsis, septic shock, central line associated blood stream infections, cerebrovascular accidents and cardiac arrest that required cardio-pulmonary resuscitation.

***Statistical Analysis***

Patient demographics, preoperative and operative variables were tabulated using descriptive statistics with continuous variables presented as medians and interquartile ranges (IQR) and categorical variables as frequencies and percentages. A comparison between 30-day survivors and non-survivors was performed using Chi-squared test, Chi-squared test for trend or Fisher's exact test for categorical variables and Wilcoxon rank sum tests for continuous variables.

Binary logistic regression was performed to test associations between risk factors and mortality. The following variables were tested in a backwards conditional model: sex, race, ethnicity, age at repair, gestational age, birth weight, ventilation (y/n), cardiac risk factor (none/minor/major), 1 minute APGAR, delivery mode (vaginal, scheduled section, emergency section), operation time (minutes), ECMO 7 days prior to surgery (y/n), inotropes during surgery (y/n), transfusion (y/n). A p value $<0.05$ was considered significant.

**Results**

A total of 432 infants underwent CDH surgical repair during the study period (**Table 1**). The median birth weight was 3.1 kg (IQR 2.8 – 3.5). The majority of patients were male (61%) and white (66%). Prematurity was present in 17% of infants. Most of the patients (62%) were born via vaginal delivery. The median Apgar score was 5 (IQR 3-7) at 1 minute and 8 (IQR 6-8) at 5 minutes. The majority of infants (82%) had cardiac risk factors identified (72% were reported as major). Extra-corporeal membrane oxygenation (ECMO) was employed in 13% of patients prior to surgery. The majority of infants (83%) were ventilated preoperatively. Median age at surgery was 5 days (IQR 3-10) and the median gestational age was 39 weeks (IQR 38– 40). The median anesthesia time was 200 minutes (IQR 149 – 250), median operative time 120 minutes (IQR 89 – 162). Thoracoscopic/laparoscopic approach was attempted in 18% of infants, out of which 41% were converted to open. Intraoperative use of inotropes was recorded for 34% of patients. More than a third of patients (32%) received a blood transfusion peri-operatively. The post-operative 30-day mortality rate was 9%. In this cohort of patients, the 30-day postoperative complication rate was 27% (**Table 2**).

**Table 1** also shows unadjusted risk factors for 30-day mortality. Factors associated with an increase in risk of mortality include birth weight ($p=0.01$), gestational age at birth ($p=0.04$), Apgar score at 1 minute ($p<0.0001$) and at 5 minutes ($p<0.0001$), and anesthesia time ($p=0.04$).

At binary logistic regression for testing associations between risk factors and mortality, out of all variables only major cardiac risk factors (OR 1.7 [0.9-3.2] $p=0.095$), Apgar at 1 minute (OR 0.7 per unit [0.5-0.8] $p<0.005$), and birth weight (OR 0.5 per kg [0.2-1.0] $p<0.05$) were retained in the final model as significantly associated with mortality (**Table 3**).

**Discussion**

This multi-institutional cohort based study on infants with CDH shows that risk factors predictive for 30-day mortality for CDH are low birth weight, low gestational age, low Apgar scores and the presence of major cardiac risk factors. This is the first study conducted using the NSQIP-P database, an initiative of the American College of Surgeons to guide quality improvement in the participating hospitals. One of the advantages of using such a database is the large scale of patients, whose data are systematically collected every year.[10] The NSQIP-P database collects reliable clinical data including 30-day outcomes and it is designed with benchmarking purposes. For this, it differs from other registries whose purpose is instead to capture longitudinal data, to provide long-term follow-up information on patients.

Given the poor prognosis of some CDH babies, efforts have been made to identify patients at high mortality risk.[11] Some studies have focused on the identification of prenatal predictors of outcome to be used for parental counselling or for risk stratification of fetal interventions.[12-15] Other studies have created clinical prediction rules using regression models to calculate postnatal outcomes, such as mortality.[11] Using the NSQIP-P database, we were able to detect variables that could predict 30-day outcomes in a population of infants who underwent CDH repair. Our study is different from others which have focused on outcome measures relative to fetuses or neonates that have not necessarily undergone a surgical intervention. For this reason, our population of CDH infants was relatively healthier than that of other studies, as these infants have survived and have been stable as much as to be operated on. Interestingly, we have noticed that important predictors of mortality in our CDH population are birth weight, gestational age, and Apgar scores.

The same variables were identified in a seminal analysis from the CDH Study Group (CDHSG), where a probability of survival equation was developed based on birth weight and Apgar score.[16] A more recent study from the same registry has proposed a prediction model equation using binary baseline predictors generated from very low birth weight, absent or low 5-minute Apgar score, presence of chromosomal or major cardiac anomaly, and suprasystemic pulmonary hypertension.[17] Although some of the variables included in the latter study were not available in the NSQIP database, most predictive factors of mortality for CDH were the same extracted in our analysis. Other prediction models using SNAP-II (Score for Neonatal Acute Physiology, Version II) and its recently modified version SNAPPE II (Score for Neonatal Acute Physiology with Perinatal Extension-II) focused on similar variables to the ones that we have identified in our study.[18,19]

In our analysis, the presence of a major cardiac risk factor in infants with CDH was associated with short-term mortality. Overall, more than two thirds of infants in our cohort had major risk factors, that included congenital heart defects (CHD), severe pulmonary hypertension, or a combination of the two. The association between CDH and CHD is well described and it has been recognized to add further morbidity and mortality risk to these babies. A report on 4,268 infants with CDH registered on the CDHSG showed that survival was significantly lower in babies with CDH and CHD compared with patients with minor or no heart defect.[20] Moreover, in our study, 41% of infants with CDH had severe pulmonary hypertension classified as a major cardiac risk factor. Pulmonary hypertension is a constant finding in CDH babies, as it develops postnatally following the vascular remodelling that occurs before birth.[21]

In the present study, 13% of infants with CDH received ECMO. The proportion of patients could be considered relatively low in comparison with other case series. The most recent study from the CDHSG on 3,746 cases of CDH managed between 2007 and 2015 has shown that the need for ECMO in this cohort of patients was 29%.[22] The low use of ECMO in our study could be explained by different factors. As the NSQIP database records the use of ECMO only in the 7 days prior to surgery, a proportion of patients may have not been captured. Moreover, as we previously mentioned, the infants recorded on the NSQIP database have all undergone surgical repair and can be considered the healthier cohort of all babies with CDH. Interestingly, in a study on 2,173 infants who underwent surgical repair for CDH, the use of ECMO was 17.8%.[23] This percentage is close to the one found in our analysis, possibly because both studies focus on a population of surgical babies.

The majority of babies with CDH in the NSQIP database underwent preoperative ventilation. This is in line with the clinical practice guidelines of the American Heart Association and the American Academy of Pediatrics, the EURO Consortium and the Canadian Congenital Diaphragmatic Hernia Collaborative.[24-26] These guidelines support immediate postnatal endotracheal intubation for neonates with a known diagnosis of CDH. The small proportion of babies captured in the NSQIP database who did not receive preoperative ventilation may be due to a late diagnosis of CDH.

In our study, the proportion of infants (18%) that underwent minimally invasive surgery (MIS) for CDH was very similar to that reported in an international survey on the management of CDH (~20%),[27] and in a large cohort study of 3,067 CDH patients (~16%) reported by the CDHSG and

the Pediatric Surgery Research Collaborative.[28] The conversion rate from MIS to open approach was 41% in our study. This cannot be compared to the CDHSG report as the conversion rate was not captured in their dataset as acknowledged by the authors.[28] Nonetheless, the conversion rate to open repair of CDH has been reported in single institution studies and varies from 3% to 75%.[29]

In our cohort of patients, we detected a postoperative complication rate comparable to the one reported in the literature. We observed an "in hospital" hernia recurrence rate similar to that reported by the CDHSG[30] and by the Japanese CDH study group.[31] Moreover, in our cohort we found a rate of central line associated blood stream infections of 4%, that is similar to the 9% reported in a study from the Children's Hospital Neonatal Database on 572 infants with CDH.[6] This latter study also documented a rate of brain injury documented on imaging studies of 1.6%, which is similar to the one detected in our cohort of patients as 0.5%.

We acknowledge the limitations of our study, which are similar to those of large-volume databases.[32] As in any database, there could be coding variability and errors. However, whilst for most registries the onus of data accuracy falls onto the responsible physician, NSQIP is managed by the American College of Surgeons with dedicated professionals that ensure a high quality of data collection and minimize the risk of biases and errors. As the database is not disease or procedure specific, on the one hand many variables collected are not relevant for a CDH population, and on the other hand some data that could be important for a comprehensive view of the patient population are not collected. Moreover, the data captured in the NSQIP-P database include a narrow perioperative interval and outcome is limited to the 30 postoperative days,

making it challenging to evaluate the long-term effects of the studied variables. Nonetheless, this database has the advantage of providing clinical details that are not usually collected in other registries and instead could be important for benchmarking purposes. An example could be the accuracy with which surgical site infections are captured.

In conclusion, this is the first report on CDH outcomes from the NSQIP-P database. In this study, we found that the risk factors predictive for 30-day mortality were the low birth weight, low gestational age, low Apgar scores and the presence of major cardiac risk factors. Utilization of ECMO was low compared with single-center studies from North America. Conversely, other parameters such as the use of preoperative ventilation, the MIS approach, and the postoperative complication rates were comparable to other international studies. The early post-operative mortality rate of babies with CDH considered suitable for surgery was found to be 9%.

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**Table 1.** Demographic, preoperative, and operative variables for CDH infants captured in the 2015-2016 NSQIP-P database. Comparisons between survivors and non-survivors are considered significant when the P value was <0.05.

| | **Total** (n=432) | **Survivors** (n=394, 91%) | **Non-survivors** (n=38, 9%) | **P value** |
|---|---|---|---|---|
| **Demographic variables** | | | | |
| Birth weight (kg) | 3.1 (2.8 – 3.5) | 3.09 (2.8 – 3.5) | 2.9 (2.5-3.3) | 0.0122 |
| GA at birth | 38 (37 – 39) | 38 (37-39) | 37 (35-39) | 0.04 |
| Gender (male) | 61% | 61% | 58% | 0.7 |
| Ethnic background | | | | |
| White | 53% | 54% | 50% | |
| Black | 10% | 9% | 13% | |
| Asian | 4% | 4% | 8% | 0.3 |
| Hispanic | 17% | 18% | 8% | |
| Other | 16% | 15% | 21% | |
| Prematurity | 17% | 17% | 13% | 0.7 |
| Mode of delivery (c-section) | 38% | 38% | 40% | 0.9 |
| Apgar at 1 minute | 5 (3-7) | 5 (3-8) | 3 (1-5) | <0.0001 |
| Apgar at 5 minutes | 8 (6-8) | 8 (6-8) | 5 (3-7) | <0.0001 |
| **Preoperative variables** | | | | |
| Cardiac risk factors | | | | |
| Major | 72% | 69% | 84% | 0.1 |
| Minor | 10% | 11% | 5% | |
| Ventilation | 83% | 82% | 89% | 0.4 |
| ECMO | 13% | 13% | 13% | 1 |
| **Operative variables** | | | | |
| GA at surgery (weeks) | 39 (38 – 40) | 39 (38-40) | 39 (37-41) | 0.8 |
| Age at surgery (days) | 5 (3-10) | 5 (3 – 9) | 6 (3-11) | 0.4 |
| Anesthesia duration | 200 (149 – 250) | 202 (150-250) | 178 (130-255) | 0.04 |
| ASA | 4 (3 – 4) | 4 (3 - 4) | 4 (4 - 4) | 0.003 |
| Surgery duration | 120 (89 – 162) | 119 (88-158) | 128 (99-186) | 0.07 |
| MIS | 18% | 19% | 11% | 0.3 |
| MIS to open | 41% | 25% | 41% | 0.6 |
| Inotropes during OR | 34% | 34% | 34% | 1 |
| Blood transfusion | 32 % | 32% | 26% | 0.6 |

**Table 2.** Short-term (30-day) complications following CDH repair

| | **Total** (n=432) |
|---|---|
| Diaphragmatic hernia recurrence | 2 (0.5%) |
| Surgical site infection | 14 (3%) |
| superficial | 11 |
| deep | 1 |
| organ space | 1 |
| Wound dehiscence | 10 (2%) |
| Unplanned reintubation | 41 (9%) |
| Pneumonia | 13 (3%) |
| Acute renal failure | 5 (1%) |
| Seizure | 3 (0.7%) |
| Cerebrovascular accident | 2 (0.5%) |
| Sepsis | 14 (3%) |
| CLABSI | 4 (0.9%) |
| Cardiac arrest | 11 (3%) |

CLABSI: Central line associated blood stream infections

**Table 3.** Binary logistic regression for testing associations between risk factors and mortality in infants with CDH captured in the 2015-2016 NSQIP-P database.

| **Variable** | **Odds ratio (95% CI)** | **P value** |
|---|---|---|
| Cardiac malformation | 1.7 (0.9-3.2) | 0.095 |
| Apgar at 1 minute | 0.7 per unit (0.5-0.8) | <0.005 |
| Birth weight | 0.5 per kg (0.2-1.0) | <0.05 |