**Introduction**

Congenital Diaphragmatic Hernia (CDH), characterised by a range of developmental defects in the thoracic diaphragm, the muscular tendinous partition between the thorax and abdomen, affects 1 in 3000 pregnancies [1–4]. Bochdalek, Morgagni, anterior and central defects are recognised anatomical variants with distinct embryological origins. Alternatively CDH can be classified as being ‘isolated’ or ‘complex’ associated with other structural anomalies, chromosomal aberrations or syndromes [3].

Antenatal diagnosis in ~50 - 70% of CDH permits parental prenatal counselling, planning of fetal interventions, timing of delivery and planned intubation at delivery to avoid gaseous distension of herniated bowel loops [3,5,6]. The innovation, clinical implementation and adoption of antenatal strategies such as fetal endoscopic occlusion of the trachea (FETO) may favourably adjust risk of mortality in selected cases [7,8]. Careful case selection is imperative here since fetal interventions can inadvertently increase mortality through associated adverse outcomes such as premature onset of labour.

Prenatal risk stratification allows targeting of antenatal interventions to populations with favourable benefit to risk ratios. Recognised risk adjusters include observed to expected lung to head ratios (O:E LHR), gestational age an easily assessed surrogate measure of lung/airway maturity, co-existing cardiac anomalies, liver herniation and chromosomal anomalies or syndromic fetuses [3,9–11].

Additional features may allow improved accuracy in risk quantification and allow further optimisation of target population selection. Presence or absence of a hernia sac in CDH fetuses can be assessed by fetal MRI scanning and may be an indicator of improved survival [12–18].

Though prenatal risk assessment is important, identifying a CDH hernia sac at the time of surgery may also usefully further guide likelihood of survival and benefit post-operative parental counselling. In this study we therefore aimed to quantify the survival benefit(s) of hernia sac identification at operation in newborns with Bochdalek type CDH by reviewing our single centre experience.

**Material and methods**

Case identification and hospital chart review was undertaken as previously described [19]. Newborns admitted with CDH from 1 February 1990 to 31 December 2017 were identified, case records retrospectively retrieved and new data were combined with that collected [19].

Records were retrieved, data extracted and recorded in an electronic database. Duplicates were removed. Newborns with Morgagni, other anterior or central diaphragm tendon defects were excluded. Additional exclusion parameters included diagnosis of CDH beyond the neonatal period.

Data collection included demographics, gestational age, timing of diagnosis, side/type of defect, birth weight, age at operation, co-morbidities, need for patch repair, patch material, presence of hernia sac, requirement for high-frequency oscillatory ventilation, inhaled nitric oxide (iNO) or extracorporeal membrane oxygenation (ECMO), hernia recurrence, adhesive intestinal obstruction and requirement for reoperation [19]. CDH with hernia sac was defined as the presence of a peritoneal covering associated with the defect overlying the herniated intrathoracic viscera / solid organs (liver and spleen). Hernia sacs were not routinely sent for histology.

Operative repairs were performed as previously described [19]. Briefly all patients underwent open surgical repair through a subcostal incision after stabilisation of labile physiology. Herniated abdominal viscera including bowel, liver and spleen were reduced, hernia sac if present excised, diaphragm edges mobilised and the defect closed either primarily with non absorbable sutures or in large defects with a prosthetic patch [19]. Postoperatively patients were transferred to the intensive care unit.

Survivors were routinely followed-up in a CDH multi-disciplinary clinic, which included a surgeon and a respiratory physician.

Binomial tests and two sided Fisher’s exact test was used for comparing contingencies and p < 0.05 was considered significant. Power analysis was performed assuming 20% of patients with CDH will have a sac, survival in the CDH with no sac cohort is 65% and survival in the CDH with sac cohort is 95%. This suggested a sample size of 95 neonates would give a power of 81% to detect a difference at p < 0.05.

Survival analysis was performed using a Kaplan-Meier plot and survival times were compared using the Log-rank test. Statistical significance was defined as p < 0.05.

**Results**

192 case records were retrieved from which 29 were ‘late diagnosis’ beyond the neonatal period, 9 Morgagni lesions and 1 anterior CDH defect associated with Pentalogy of Cantrell. 153 newborns with Bochdalek type diaphragmatic defect were identified.

100 (65%) CDH neonates were male giving a significant male preponderance of approximately 1.8:1 (p value = 9e-5, binomial test). There were 125 (82%) left sided defects confirming the well known left sided predominance (p value = 3.9e-16, binomial test). 66 CDH newborns (43%) were antenatally detected and 146 (95%) survived to undergo operation. At operation, 22 (15%) had a hernia sac identified, Fig. 1.

Median time to surgery was 3 days (IQR 2 – 5 days) and overall survival after surgery was 128 (88%). There was no difference in age at operation, specifically in the cohort of CDH infants with sac the median age at operation was 3 (IQR 2 - 4.75) days and in the cohort of CDH neonates without sac the median age at operation was 3 (IQR 2 - 5) days (p = 0.96, Wilcoxon rank sum test). There was no significant difference in the proportion of newborns with an antenatal CDH diagnosis between the sac and no sac groups, 40% in sac and 55% without sac (p = 0.25, Fisher’s exact test).

ECMO data was available on 100 patients. 4 out of 80 neonates with CDH and no hernia sac and none of 16 neonates with CDH and hernia sac required ECMO support. The median number of ventilatory support days was no different in the two groups, 9.5 (IQR 5.25 - 17) days in neonates without hernia sac and 10.5 (IQR 4.5 – 15.5) days in neonates with hernia sac (p = 0.88, Wilcoxon rank sum test).

Data on HFOV utilisation was available in 101 cases. There was no significant difference in HFOV utilisation between CDH newborns without sac 21/85 and CDH newborns with sac 1/16 (p = 0.18, Fisher’s exact test).

Survival in CDH newborns with a hernia sac was 21/22 (95%) compared to 107/124 (86%) in those without sac showing no significant survival benefit (p = 0.2, log-rank test) after a median follow-up of 13.7 years (IQR 7 - 19), Fig. 2. This trend towards a ‘non-significant survival advantage’ in newborns with sac was consistent in both sexes. The one non-survivor in the sac cohort was a male infant with a chromosomal anomaly and was discharged home at 1 month. This patient suffered a cardiac arrest at home at the age of 2 months and the cause of death was unclear. Given the better survival outcomes in the no sac group in our series than other reported cohort studies an extensive power analysis was performed to assess the power of any such study given a sample size and survival in the no sac group assuming a 95% survival in the sac cohort. To have 80% power to establish a difference at p < 0.05 between 95% survival in sac compared to 85% survival in no sac with 15% of infants having a sac would require a sample size of 1010 patients, Fig. 3.

In the 22 CDH neonates with a hernia sac, 9 (41%) defects were right sided lesions. In contrast for the 124 CDH newborns without hernia sac only 16 (12%) had a right-sided defect (p value = 3.5e-3, Fisher’s exact test). Male predominance in newborns with CDH was no different in neonates with a hernia sac 1.5:1 as compared to those without sac 1.8:1 (p value = 0.8, Fisher’s exact test). Diaphragmatic patch utilisation was similar with 39/121 (32%) CDH newborns without a sac and 9/22 (41%) CDH newborns with a sac having patch repair (p value = 0.5, Fisher’s exact test). There were two CDH recurrences, one in a patient who had CDH sac and one who had CDH with no sac. Both recurrences occurred in newborns undergoing CDH patch repair with the bioprosthesis Surgisis (Cook Medical Inc., USA). Similarly abdominal patch utilisation was no different 14/121 (12%) in CDH newborns with sac vs. 3/22 (14%) in those without a sac, (p = 0.7, Fisher’s exact test). The presence or absence of a hernia sac made no difference to the proportion of CDH newborns diagnosed on antenatal screening. 50/124 (40%) CDH newborns without sac and 12/22 (55%) CDH newborns with sac (p value = 0.25, Fisher’s exact test) were detected with antenatal imaging.

**Discussion**

Spaggiari and colleagues [12] from Necker Hospital in Paris, France were the first group to propose a potential link between hernia sac and improved outcomes in CDH neonates. Additionally by retrospectively reviewing prenatal imaging they reported a significant difference in observed to expected pulmonary volume on prenatal MRI but not in observed to expected lung to head ratios. Since then several other publications have reported the association of hernia sac in CDH with either improved survival or other surrogate measures associated with better outcomes [13–18].

It has been proposed that the distinction between CDH with sac and diaphragm eventration is not clear and there does appear to be some confusion in the literature likely originating from an incomplete understanding of the embryology and the urge to classify and discretise a continuum. The aetiology of a Bochdalek diaphragmatic hernia is widely believed to be due, in part, to the embryological failure of fusion of the pleuro-peritoneal membranes or when a sac is present, consisting solely of a pleuro-peritoneal membrane with complete failure of muscularisation. In contrast an eventration is believed to be due to inadequate muscularisation.

CDH cases with a hernia sac may be a separate entity from CDH without hernia sac and despite the difficulties in classification, taking a pragmatic approach patients identified to have CDH with a sac at operation in this current study showed a trend towards a ‘non-significant’ survival advantage in what is a comparatively large UK single centre cohort population with the longest reported follow-up to date. This is in keeping with the findings of Levesque et al. showing in their population of 71 patients no association between presence of a hernia sac and either mortality or oxygen dependence [20].

We found no difference(s) in sex ratios between CDH with sac and CDH without a sac, both showing 2:1 male predilection. Interestingly the side of the defect in CDH patients with a sac in our series is significantly more symmetric with 41% right-sided defects compared to only 16% right-sided defects in CDH without a sac. These findings may lend further support to the conjecture that the two entities (‘CDH sac vs. no CDH sac’) may have distinct embryological origins and subsequent pathophysiology [12,17,21].

Ultrasound remains the main screening modality during the fetal period with selective use of MRI, which is expensive and time consuming. The utility of ultrasound in identifying neonates with a CDH sac based on three criteria has been recently published showing limited positive predictive values [17]. Unfortunately authors of this latter study do not report exact patient numbers rather percentages so precluding analyses of a composite score. Furthermore it remains evident that only some 50% of CDH neonates are identified on antenatal imaging.

In this current study there was no difference in either diaphragmatic or abdominal patch utilisation between CDH newborns with or without hernia sac in contrast to Bouchgoul et al. [17] who reported significantly lower rates of diaphragmatic patch repair in CDH newborns with a hernia sac.

Some limitations of this study may include that the hernia sacs were not routinely sent for histological analysis and that ‘hidden mortality’ from early pregnancy loss and terminations is incompletely captured. A particular strength of our work and its findings reported here is the comparatively longer duration of patient follow-up compared to other published studies [12–18].

The effect size or survival difference(s) in CDH neonates identified to have a sac at operation compared to no sac at our UK centre is not significant in contrast to previous studies examining this issue with shorter patient follow-up. This is despite our series being the largest reported and thus having the greatest statistical power to detect a potential difference. These findings are predominantly due to the better overall survival outcomes in our cohort of CDH babies managed at this single specialist centre with no hernia sac (86%) compared to those reported in other series. It is notable that Levesque et al. in one of the few series with no significant difference between CDH newborns with or without sac also reported excellent survival in the no sac cohort (95%) [20].

Ours is not the first such report to highlight the difficulty in defining the survival rate for infants with CDH with challenges arising due to geographic and institutional variations in clinical practice [21]. This highlights the potential problems with external validity and thus the generalizability of findings particularly ‘effect size’ from one institution or geographic location to another. The direction of the effect herein observed with improved survival in CDH newborns with sac compared to CDH newborns without sac though remains consistent with the contemporaneous literature at present. Future multicentre studies and registry(s) may provide additional ‘*big data*’ to fully answer this intriguing hypothesis.

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Legends

Figure 1: Case identification and selection

Figure 2: Kaplan Meier plot of survival in CDH with and without sac.

Figure 3: Heatmap showing power analysis for sudies by cohort size and survival rate in CDH with no sac.