Journal of Pediatric Surgery 57 (2022) 501–509

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg.org

Review Article

Long term outcomes in CDH: Cardiopulmonary outcomes and health related quality of life

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ARTICLE INFO

Article history:
Received 21 December 2021
Revised 27 February 2022
Accepted 18 March 2022

Keywords:
Congenital diaphragmatic hernia: Outcomes
Cardiopulmonary
Health-related quality of life

ABSTRACT

Background: With improvements in clinical management and an increase in CDH survivorship there is a crucial need for better understanding of long-term health outcomes in CDH.
Aim: To investigate the prevalence of cardiopulmonary health morbidity and health related quality of life (HRQoL) in CDH survivors.
Methods: We included all studies (n = 65) investigating long-term cardiopulmonary outcomes in CDH patients more than 2 years published in the last 30 years. The Newcastle-Ottawa Scale and the CASP checklist for cohort studies were utilized to assess study quality. Results were reported descriptively and collated by age group where possible.
Results: The incidence of pulmonary hypertension was highly variable (4.5–38%), though rates (%) appeared to diminish after 5 years of age. Lung function indices and radiological outcomes were frequently abnormal, and Health Related Quality of Life (HRQoL) reduced also. Long term diseases notably emphysema and COPD are not yet fully described in the contemporary literature.
Conclusion: This study underscores cardiopulmonary health morbidity and a reduced HRQoL among CDH survivors. Where not already available dedicated multidisciplinary follow-up clinics should be established to support these vulnerable patients transition safely into adulthood. Future research is therefore needed to investigate the risk factors for cardiopulmonary ill health and morbidity in CDH survivors.
Type of study: Systematic review of case control and cohort studies.

1. Introduction

In congenital diaphragmatic hernia (CDH) failure of diaphragmatic closure in utero leads to herniation of abdominal contents into the thoracic cavity. This rare disease occurs in 1 in 3000 births [1], with a current mortality rate of 30%–50% [2–4]. Improvements in clinical management over the past two decades have led to an increase in the number of CDH survivors. Infants that do survive to hospital discharge may be left with complex problems affecting many aspects of Health-Related Quality of Life (HRQoL). These significant complications may affect the cardiopulmonary, neurological, or gastrointestinal systems. It is well reported that CDH is linked with developmental insults that induce lung hypoplasia and pulmonary hypertension [5,6], and is also associated with extrapulmonary cardiac anomalies [7–9]. There is, however, less research investigating long-term complications in childhood and adulthood caused by CDH. This is important to understand, so that families of CDH survivors may take appropriate measures to better recognise these and/or prevent adverse sequelae. Healthcare professionals should be increasingly mindful of CDH co-morbidities, and follow-up programmes in certain 'high volume' speciality centers do seek to incorporate elements of multispecialty care.

To the best of our knowledge, there are however currently no systematic reviews focusing specifically on long-term cardiopulmonary outcomes in CDH. We therefore aimed to study and comprehensively appraise the true prevalence of long-term cardiopulmonary outcomes in CDH survivors more than 2 years of age.

2. Aims

(1) To investigate the prevalence of adverse cardiopulmonary outcomes in survivors with CDH more than 2 years of age.
(2) To determine risk factors for cardiopulmonary morbidity and poor HRQoL in CDH survivors.

3. Methods

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors have no competing interests to declare. Data is available on request from the corresponding author.
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https://doi.org/10.1016/j.jpedsurg.2022.03.020
0022-3468/

Analyses (PRISMA) guidance [10]. A PROSPERO protocol (CRD42021254998) was developed and published which defined - (I) study objectives, (II) search strategy, (III) assessment of study quality, (IV) data extraction and (V) analysis.

3.1. Search strategy

We searched Pubmed and SCOPUS, a platform for searching multiple databases, using the search '(congenital diaphragmatic hernia OR CDH) AND (Outcome* OR Sequelae OR follow-up OR long-term OR survivors) AND (Cardio* OR Pulmonary OR Respiratory OR Exercise OR Quality of life)'. CENTRAL was also searched using the heading term 'congenital diaphragmatic hernia'. Databases were last searched on 14/05/2021.

We examined all potential studies based on title and abstract. The selected studies were then read in full to screen for eligibility.

Studies were included in the systematic review if they were published in the last 30 years and specifically investigated long term cardiopulmonary outcomes in CDH patients aged more than 2 years. We included all cohort studies of those patients with pulmonary hypertension (diagnosed clinically, or by electrocardiogram, or echocardiogram) or having extracorporeal membrane oxygenation (ECMO) where CDH patients were specifically herein evaluated as a distinct group.

We excluded studies of non-English language publications.

3.2. Data extraction, quality assessment and data synthesis

Data from the selected eligible studies were extracted by the study authors. Extracted data here included study characteristics and results.

From each study we scrutinized the following characteristics: (a) study design, (b) single or multi-center study, (c) country of origin, (d) number of patients, and (e) age of patients.

The study results were related to:

(a) Prevalence of adverse cardiopulmonary outcomes in CDH
(b) Risk factors for adverse cardiopulmonary outcomes and HRQoL in CDH

3.2.1. Adverse cardiopulmonary outcomes

(a) Indices of lung function

Basic spirometry is often used by clinicians, but more complex areas of physiologic lung function include plethysmography and exhaled nitric oxide. We extracted absolute measurements e.g. litres or % predicted values, and Z scores (which are a marker of results in comparison to the normal healthy population).

- **Forced Expiratory Volume in the first second (FEV1)** - this is considered a measure of the size of the airways
- **Forced vital capacity (FVC)** - this is a marker of overall lung capacity
- **FEV1/FVC ratio** - this is a marker of airway obstruction
- **Full body plethysmography** - this is a test only used in specialist tertiary centers as a way of evaluating alveolar volume and total lung volume
- **Exhaled nitric oxide** – a marker of airway inflammation

(b) Pulmonary hypertension (PHT)

There are various direct and indirect methods of establishing a diagnosis of PHT. This may be clinical by ECG monitoring (however this is non-specific), by echocardiography (which is non-invasive), and cardiac catheterization (an invasive technique undertaken in select patients under general anaesthesia). Right ventricular function gives a reproducible indication of the 'work over time' of the right ventricle distributing blood to the pulmonary vasculature.

- **Prevalence of PHT** - either by echocardiogram (Tricuspid Regurgitation > 2.8 m/s), direct catheter pressure (mean pulmonary artery pressure >25 mmHg), or ECG)

If PHT was present we then looked specifically at:

- **Severity of PHT** - mild/moderate/severe (by echocardiogram or catheter)
- **Right Ventricle function** – normal or mild/ moderate/ severe impairment
- **Use of PHT medications**
- **Death related to pulmonary hypertension**

(c) Risk of asthma, emphysema and chronic obstructive pulmonary disease (COPD)

(d) Functional outcomes

- **Exercise tolerance and breathlessness** – including a 6 min walk test or a cardiopulmonary exercise test
- **Health Related Quality of life (HRQoL)**

(e) Radiological outcomes

- **Chronic visible changes identified on Chest X-ray, CT scan or MRI**

3.3. Study quality

The authors assessed study quality based primarily on study design and whether the recruitment of the participants was considered adequate. The Newcastle-Ottawa Scale [11] was then used to quality assess case-control studies, evaluating studies on their selection, comparability, and exposure of the cases and controls. Cohort studies were quality assessed using the CASP checklist for cohort studies [12]. This well-known quality appraisal tool evaluates study quality based on the validity and applicability of their results. Checklist criteria are shown in Supplementary Table E1. Any studies with a high risk of bias were excluded.

3.4. Result analysis

Results are reported descriptively and where possible we made effort to collate results by different age groups (2–4, 5–12, 13–18, more than 18 years).

4. Results

4.1. Study search and selection

The search of PubMed yielded 838 results, Scopus yielded 928, CENTRAL yielded 168 papers, and 7 were found from additional sources, totaling 1941 papers. After removal of 507 duplicates, 1434 papers were further screened. Titles and abstracts were assessed in full for eligibility, excluding 1332 papers. The remaining 102 publications were independently read in full and a further 37 papers excluded, see **Supplementary Table E2** – 'reasons for exclusion'.

65 papers were finally included, 22 case control studies in the main analysis, as the best levels of evidence currently available. A further 43 cohort studies were included in the additional analysis. **Fig. 1** shows the PRISMA flowchart for the study.

4.2. Study characteristics

There were 65 studies, which overall included 3061 CDH patients. The mean number of CDH patients were 47 per publication (range 7–251). All studies were observational (22 case control and 43 cohort). 54 were single-center studies and 11 were multi-center. Studies were conducted in various countries including those in the UK, Europe, USA, Canada, Asia, Africa, and Australia. CDH patient age ranged from 0 to 42 years, though the mean or median age in each selected study was above 2 years.

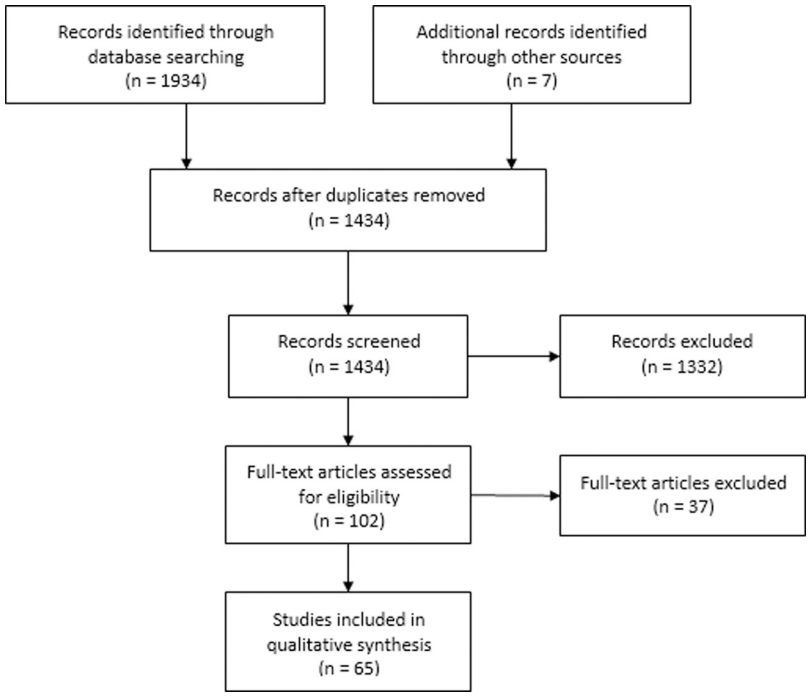

Fig. 1. PRISMA flowchart.

4.3. Study quality

Case control study quality (assessed using the Newcastle Ottawa Scale [11]) is shown in **Supplementary Table E3**. Cohort study quality (assessed using the CASP checklist for cohort studies [12]) is available in **Supplementary Table E4**.

Study quality was considered adequate. Outcomes were often measured accurately, papers investigating spirometry data almost always followed the American Thoracic Society (ATS) or European Respiratory Society (ERS) guidelines, and the majority of papers investigating pulmonary hypertension deployed echocardiography as sole means of determining PHT. However, very few papers here reported results with corresponding confidence intervals. 20/64 (31%) studies were retrospective rather than prospective. Retrospective studies are notably less likely to have predetermined objectives and standardized outcomes and are therefore more susceptible to having confounding variables. Not all relevant confounding factors were considered in these papers. Many papers identified gestational age as a confounding factor, but not for example the exposure of CDH patients to 'second-hand smoke', family history of cardiorespiratory disease, or socioeconomic/deprivation factors.

4.4. Study results

4.4.1. Indices of lung function

Spirometry results - FEV1, FVC, and FEV1/FVC ratio: Spirometry results are shown in **Table 1**. Outcomes were reported in various different ways, as raw values, % predicted, Z score, and standard deviation score. Heterogeneity observed here limited the comparisons we could make between the spirometry results.

Spirometry results in CDH cases vs healthy controls: Seven papers compared spirometry results between CDH patients and healthy controls [13–19].

5 studies had a mean participant age of between 5 and 12 years (children) and found FEV1 to be reduced in CDH vs controls in 4/5 studies [13,14,16,18], FVC in 3/5 studies 264) [14,18] and FEV1/FVC in 2/3 studies [16,18] ($p < 0.05$).

A single paper [15] had a mean participant age range of 13–18 years (adolescents) and found FVC, FEV1, and FEV1/FVC to be all significantly reduced in CDH vs controls ($p < 0.05$).

A further paper [19] noted FEV1/FVC to be statistically significantly reduced ($p < 0.05$) in adults with CDH vs controls (mean standard deviation score [SDS] (mean) −0.8 (1.2) vs 0.0 (1.0) $p = 0.008$). FEV1 (mean SDS (SD) −1.2 (1.4) vs −0.2 (1.5) $p = 0.071$) and FVC (mean SDS (SD) −0.7 (1.1) vs −0.3 (1.3) $p = 0.243$) were not statistically significantly different between CDH survivors and controls.

Full body plethysmography: Ijsselstijn et al. [20] reported CDH patients to have significantly higher residual volumes and residual volume/total lung capacity vs. control patients ($p = 0.001$ and 0.006) at a mean age of 11.7 (range 7–18) years.

Laviola et al. [21] found tidal volume was significantly lower in CDH patients compared to healthy controls ($p < 0.05$) both in those with prosthetic patch and native primary diaphragm repair. This was however not the case when tidal volume was then normalized to body weight. Air trapping was not significantly different between CDH vs. controls.

Spoel et al. [19] found that TLC, Residual Volume (RV), and Functional Residual Capacity (FRC) were not significantly different in CDH vs controls ($p = 0.977$, $p = 0.071$ and $p = 0.960$, respectively). Spoel et al. [22] reported mean standard deviation (SD) scores for total lung capacity (TLC) to be 0.21 (1.61), and RV%TLC - 25.3 (4.48). This was not compared to any control group(s).

Spoel et al. [17] showed that 12/14 (86%) CDH patients had a significant volume of air trapping (FRC plethysmography / spirometry >1.10) on body plethysmography at age(s) 8 and 12 years.

Exhaled nitric oxide: Gischler et al. [23] reported the median fraction of exhaled Nitric Oxide (FENO) in CDH patients to be in the low range of normative values (median 5.2 (range, 2.8–10.0)).

Risk factors for reduced indices of lung function:

Factors associated with reduced PFTs included:

(i) Diaphragm defect size - CDH International Study Group Grading – notably here 'severe' Grades C and D [24]

Table 1
Spirometry results in CDH patients before bronchodilator therapy.

Study	Age of Patients (years) mean (median) ± SD (range)	Spirometric values /mean ± SD (range)			% predicted /mean ± SD (range)			Z score /mean ± SD (range)			SD score /mean ± SD (range)		
		FEV1	FVC	FEV1/FVC	FEV1	FVC	FEV1/FVC	FEV1	FVC	FEV1/FVC	FEV1	FVC	FEV1/FVC
Children (5–12 years)													
Spoel et al. [17]	5										−0.71 ± 0.40	−0.69 ± 0.43	0.11 ± 0.35
Gischler et al. [23]	5				91 (72–122)								
Koh et al. [13]	6.2 ± 0.2	1.1 ± 0.05	1.2 ± 0.1		90.7 ± 2.7	91.2 ± 2.6	91.1 ± 1.3						
Turchetta et al. [94]	6.6 ± 2.6				78.7 ± 19.3	75.5 ± 15							
Spoel et al. [17]	8										−2.27 ± 0.36	−1.48 ± 0.35	−1.47 ± 0.39
Majaesic et al. [95]	8				63 ± 18	72 ± 18	80 ± 14						
Stefanutti et al. [26]	8.15 ± 2.80				89.77 ± 16.33	88.23 ± 16.11	91.10 ± 6.44						
Bojanic et al. 2016 [27]	8.2 ± 5.7	2.33 ± 1.05	2.66 ± 1.19	0.89 ± 0.09	91.6 ± 20.1	91.2 ± 19.4							
Moawd et al. [96]	(9–11)				72.3 ± 8.5	78.5 ± 9.8							
Tan et al. [16]	10 (4–22)							−1.49 ± 1.99	0.26 ± 1.81	−1.92 ± 0.87			
Zaccara et al.	11.25 (6–19)				86 ± 13	90 ± 15							
Haliburton et al. [25]	11.3 ± 3.4							−2.21 ± 1.68	−1.32 ± 1.39	−1.78 ± 0.73			
Marven et al. [14]	11.5 (7.3–16.9)				78.7 (72.5–84.8)	84.7 (78.8–90.6)							
Ijsselstijn et al. [20]	(11.7) (7–18)				89 ± 3		77 ± 2						
Peetsold et al. [18]	11.9 ± 3.5							−1.63 ± 1.78 (−7.14–1.45)	−1.28 ± 1.62 (−6.33–1.93)	−0.84 ± 1.27 (−4.03–1.07)			
Spoel et al. [17]	12										−2.73 ± 0.61	−1.28 ± 0.98	−2.16 ± 0.30
Spoel et al. [19]	11.8 ± 2.6										−0.8 ± 1.2	−0.4 ± 1.0	−0.6 ± 1.2
Adolescents (13–17 years)													
Trachsel et al. [15]	13.2 (10.2–16.9)				79 ± 16	85 ± 14	78 ± 10						
Adults (>18 years)													
Peetsold et al. [57]	24.3 ± 4.1							−1.30 ± 1.37	−0.84 ± 1.52	−0.80 ± 1.34			
Spoel et al. [19]	26.8 ± 2.9										−1.3 ± 1.4	−0.7 ± 1.2	−0.9 ± 1.2
Spoel et al. [22]	28.4 (18.1–31.0)										−1.47 ± 0.96		

(ii) Smaller patient head size or abdominal circumference at birth [13]
(iii) A lower BMI [25]
(iv) Gastro-oesophageal reflux disease [18]
(v) Duration of ventilation [18,20,26]
(vi) Oxygen use at hospital discharge [24]
(vii) Lower total lung volume(s) [13]
(viii) Ventilated volume of the ipsilateral lung to the diaphragmatic defect [22]

Factors not proven to be significantly associated with reduced PFTs:

(a) Patients with a sedentary vs active lifestyle [27,28]
(b) Gestational age [20]
(c) Birth weight [20]
(d) Parental smoking [20]
(e) Neonatal factors including highest peak inspiratory pressure(s), highest partial pressure of carbon dioxide (paCo2), APGAR score(s) at 5 mins [15] and maximum fraction inspired oxygen (FiO2) [20]
(f) ECMO use [24]
(g) Left-sided CDH defect [24]
(h) Respiratory muscle training [29]
(i) Primary vs patch diaphragm repair [30]

4.4.2. Pulmonary hypertension

Thirteen studies [16,26,27,31–40] investigated pulmonary hypertension in CDH survivors. Five of which were case control studies [16,27,31–33], six retrospective cohort studies [34–37,39,40], and two prospective cohort studies [26,38]. Patient age ranged from 4 months - 26 years.

Prevalence of pulmonary hypertension: Eleven studies investigated the prevalence of pulmonary hypertension in CDH. Five studies had a mean or median participant age of between 2 and 5 years (pre-school), five papers had a mean or median participant age range of between 5 and 13 years (children), one paper reported on PHT in both pre-schoolers and children. No papers focused exclusively on adolescents or adult survivors with PHT. No publications focused on the natural history of pulmonary vascular pressures over time in patients with CDH.

Pulmonary hypertension in pre-schoolers with CDH: Six papers reported prevalence of PHT in participants with CDH where the average age was between 2 and 5 years (preschool). All six papers used echocardiography to diagnose PHT. Rates of pulmonary hypertension ranged here from 4.5% to 38% [33,34,36–38,40].

Pulmonary hypertension in children with CDH: Six papers investigated prevalence of PHT in children with CDH. Four studies again used exclusively echocardiography for diagnosis [16,26,27,32], one study used both echocardiogram and ECG [31], and a single study did not specify their exact mode of diagnosis for PHT [36]. No studies with an average participant age group of more than 5 years reported any incidence (%) of PHT, despite a single study recording 33% of CDH newborns having PHT [27] and another study reporting that some 5.1% of preschool aged children had PHT [36].

Pulmonary hypertension in adolescents and adults with CDH: Strikingly, there were no reports evident of PHT recorded in adolescents or adults with CDH.

Severity of pulmonary hypertension: A single manuscript documented PHT as 'severe' in two preschool aged children with CDH, though the study authors did not provide a clear definition with regard to severity [37].

Right ventricle function: Pulmonary hypertension can result in varying severity and degrees of right ventricle dysfunction. Five studies here sought to investigate right ventricle function.

From Doppler imaging Egan et al. [32] showed a significant reduction in systolic (s') and early diastolic wave (e') velocities in children with CDH, indicating a degree of right ventricle impairment, compared to matched controls ($p < 0.01$ and $p = 0.02$, respectively) . Right ventricle strain values were however not significantly different between CDH survivors and controls ($p > 0.05$).

Schwartz et al. [33] and Van Meurs et al. [38] reported right ventricular hypertrophy and right axis deviation from ECG studies conducted in preschool aged patients. Schwartz et al. showed that 6/21 (29%) of patients had either right axis deviation or right ventricular hypertrophy, 2 of whom also had PHT. Van Meurs et al. reported 6/18 (33%) CDH patients having evidence of right ventricular hypertrophy, four here (4/18 22%) also had right axis deviation.

Stefanutti et al. [26] estimated right ventricle systolic pressure (RVsp) in children with CDH (mean age ± SD, 8.15 years ± 2.80), and found these values to be apparently normal.

Values ranged from 20 to 30 mmHg (mean SD 24.43 ± 3.57 mm Hg). These were not compared to systolic blood pressure, but an RVsp of less than 30 mmHg was considered normal.

Wong et al. [39] also deployed echocardiography to monitor right ventricular systolic pressure(s) (RVsp) in preschool aged patients.

Mean RVsp was between 25 and 30 mmHg (read from graph) though again this was not compared to mean systolic blood pressure or left ventricular pressure.

Use of pulmonary hypertension agent medication(s): Three papers reported pharmacologic use of PHT medications. All three papers here reported that all the CDH study participants with PHT required pulmonary vasodilator therapies, such as sildenafil [34,37,40].

Reports of late death: A single paper [35] reported a late death from pulmonary hypertension in a 9-year-old CDH survivor.

Risk factors for PHT: The only associated factor(s) linked with presence of pulmonary hypertension (defined as raised RVsp) were in those CDH infants defined as 'high risk' index cases. High risk patients were notably those with an Observed/Expected lung to head ratio (O/E LHR) ≤ 45%. High risk CDH survivors had persistently higher right ventricular systolic pressures on serial echocardiography at 2–5 years old compared to 'low risk' CDH survivors ($p < 0.05$) [39].

Garcia et al. [34], however by contrast, found LHR not to be associated with presence of PHT ($p = 0.54$).

A further study by Shieh et al. [40] showed that CDH patients who had underwent ex utero intrapartum treatment (EXIT) then onto ECMO support to have higher rates of PHT requiring sildenafil, though this was not statistically significant (0/8 vs 2/9 $p = 0.16$).

4.4.3. Asthma, emphysema, chronic obstructive pulmonary disease (COPD)

Asthma: Eight case control papers [14,16,19,32,41–43] investigated asthma diagnosis, symptoms, or medication use in CDH survivors. Results were very mixed - publications found rates of asthma, symptoms, or medication use to be both significant [16,19,42,43] and not significant [16,19,20,43] when compared to aged matched controls. Often the amount of scattered data reported here was too small to draw firm conclusions [14,32,41].

14/15 cohort studies that investigated rates of asthma reported asthma (%) or asthma agent medication use in CDH survivors [23,30,36,40,44–54]. This was found to be closely associated with pulmonary support on day 30 of life, low birthweight, and lower gestational age [43,46].

Emphysema and COPD: There were no documented reports of emphysema or COPD in CDH survivors or controls though it is likely that patients here were too young at the point of publication of these studies to fully accurately reflect these factors.

4.4.4. Cardiopulmonary exercise testing (CPET)

Eight studies described using CPET with CDH survivorship follow-up. All four case control studies found CPET to be reduced in CDH survivors compared to controls ($p < 0.05$) [14,27,55,56]. A further four cohort studies noted abnormal CPET parameters in CDH patients [23,28,57,58].

There were significant differences recorded in CPET between CDH survivors who were considered 'athletic' vs. those who had a 'sedentary' lifestyle ($p < 0.05$) [27,28,56]. Of interest here CDH survivors often perceived their own levels of fitness to be worse than their healthy counterparts [14].

Risk factors for reduced CPET results: Predictors for worse CPET results were (i) a reduced FEV1 [55], (ii) a higher residual volume/total lung capacity value [55], (iii) diffusion capacity corrected for alveolar volume (Kco) [58], (iv) ECMO use [58] (v) duration of hospital stay [58], (vi) parent's estimation of their child's exercise capacity [58], and (vii) those CDH index cases who were considered sedentary rather than athletic [14,27,56]. Duration of neonatal ventilation support was not found to be significantly associated with CPET results [27].

4.5. Radiological outcomes

4.5.1. Diaphragm radiology

Diaphragm growth [59] and markers of diaphragmatic strength were reduced in CDH survivors compared to controls [60] ($p < 0.05$). Another study found diaphragm mechanical dysfunction to be present in CDH survivors [61].

4.5.2. Chest CT imaging

Three studies examined and reported Chest CT imaging in CDH survivors, two of which showed abnormalities. These imaging findings included 'subpleural triangular opacities, architectural lung distortion, and linear lung opacities' [16] as well as 'flat costophrenic angles, peripheral opaque spikes of parenchymal consolidation, lung hyperlucency, and mediastinal shift' [26].

4.5.3. Lung perfusion

Three studies described measurement of lung perfusion [39,53,62] and found this to be reduced in the ipsilateral lungs of CDH patients. A single study found ipsilateral mean lung density to be reduced also compared to controls ($p = 0.0005$) [63]. Ventilation/perfusion (V/Q) mismatch or ventilation abnormalities were present in all three CDH studies where fully investigated [22,51,63–66].

4.5.4. Risk factors for abnormal radiology

Markers of abnormal radiology evident in CDH survivors included: (i) those who had a diaphragm patch repair [51,53,64] (ii) ECMO or high flow oscillatory ventilation (HFOV) use [51,64,66], (iii) individuals with frequent respiratory tract infections [51], (iv) index cases with right sided CDH defects [51], and (v) those on pulmonary support at day 30 of life [46]. Kamata et al., however, found patch repair not to be correlated with abnormal radiology findings [59]. Wong et al. *reported that* lung perfusion did not significantly differ between high and low risk patients [39].

4.5.5. Health related quality of life

Four case control studies reported HRQoL of which, all here found HRQoL to be reduced in CDH survivors compared to healthy matched controls [16,41,67,68]. Ten cohort studies also examined HRQoL. Six out of ten publications found health related quality of life [52,69–73] to be considerably reduced in the CDH survivors.

Risk factors for reduced HRQoL: Risk factors significantly associated with reduced HRQoL included (i) oxygen dependence on day 30 of life [74], (ii) hospital length of stay [73], (iii) lack of prenatal diagnosis (%) [75], (iv) those with ongoing medical morbidities [68,70] particularly respiratory symptoms [41,67], (v) primary diaphragm defect repair, [69] (vi) supplemental GI feeds [69] and (vii) neonatal ECMO use [72].

Thoracoscopic CDH repair was found to be associated with a higher median HRQoL score [52]. Patient age was notably associated with both a better and a worse HRQoL [52,72].

Risk factors found not to be significantly associated with a reduced HRQoL included (a) prematurity [76], (b) prolonged hospital stay [76], (c) Oxygen requirement at primary hospital discharge [76], (d) use of neonatal ECMO [70,74], (e) cardiac problems [70], (f) genetic abnormalities [70], (g) disease severity [74], and (h) prenatal imaging characteristic values [74].

5. Discussion

The primary outcome of this current study was to investigate the prevalence of cardiopulmonary health outcomes and HRQoL in CDH survivors.

We show that indices of lung function are clearly abnormal in CDH survivors. There was varied quality of reporting here regarding spirometry data. This meant an in-depth analysis into the precise extent of lung function morbidity and its severity was hampered. Nevertheless, there is evidence that reduced indices of lung function are associated with poorer health outcomes [77,78].

The incidence of pulmonary hypertension in CDH survivors was further markedly highly variable because of the non-standardized diagnostic criteria utilized for establishing PHT between individual cohort studies and variances in diagnostic modalities i.e. ECG/Echocardiogram. Rates (%) of PHT appeared appreciably much higher in preschool aged children than in those CDH survivors more than 5 years old indicating the speculative possibility that PHT may diminish in incidence with age. The reduced rates of PHT noted with age could also be because of 'late unrecorded deaths' from PHT, or the fact that reports of late PHT may be more likely to appear in case reports or case series, rather than case control or cohort studies, particularly for example those involving lung transplantation [79]. We found eight recorded cases of late death in those patients <2 years of age, five of which were attributed and linked to respiratory causes [35,48,49], one of which was because of persistent pulmonary hypertension [35].

Radiological outcomes in CDH survivors were often very abnormal with CPET including HRQoL frequently diminished. Findings regarding asthma diagnosis or medication use showed mixed and varied results from many case-controlled studies, though were well reported by the cohort studies. There were no definitive reports detailing the diagnosis of emphysema or COPD.

Our secondary outcome was to investigate then risk factors for cardiopulmonary morbidity in CDH survivors. Unfortunately, there was limited data available here. Most notably was the lack of robust data surrounding CDH defect size and poor long-term outcomes, despite some reports detailing a linkage between CDH defect size and its severity [80]. It is clear therefore that further prospective multicentre studies on risk factors for cardiopulmonary health morbidity in CDH survivors are needed. Additional research into other notable long-term health sequelae namely neurological morbidity and failure to thrive in CDH survivors are also required.

At the time of writing this report we do not have enough robust data to show if varying surgical techniques, notably open vs thoracoscopic and primary vs patch repair, have significant differences on long term health outcomes other than diaphragm recurrence or HRQoL. Detailed research into surgical technique and its consequences on hernia recurrence should be a major focus of future ongoing collaborative network studies.

Reduced oxygenation index (OI) has been shown to indicate poor neonatal outcomes and mortality [81]. We did not include OI as a pre-specified outcome in this systematic review study, however again further research work into the usefulness of oxygenation index (OI) as a long-term prognostic marker is needed.

In context of the overall findings of this current study it is clear CDH survivors should be followed up in specialist clinics / health care programmes that can readily identify complications. In the multidisciplinary CDH clinic held in Liverpool we regularly monitor children up to adulthood. We are cognizant that there is a crucial window of 'optimal airway growth and lung development' with our CDH patients, during which we routinely test pulmonary function at our lung laboratory. Spirometry is commenced from age 5 years, when children can be better engaged and cooperative with invasive testing [82,83]. Gas transfer studies and body plethysmography to test for lung volumes are commenced around age 11 years and are undertaken on an individual basis up to adulthood depending on the needs of the child. One limitation we acknowledged from the current study is the small sample (n) size of CDH patients in all the eligible publications we scrutinized, although because of the rare nature of the birth defect itself this is perhaps to be expected. Another limitation, open to debate, is perhaps the inclusion of studies spanning a time period of 30 years. This time period covers an era during which new and emerging care strategies have evolved yielding a wide spectrum of CDH disease morbidity whilst also bringing into sharp focus the ongoing challenges of CDH to all clinicians as an 'unsolved problem' in 2022.

To the best of our knowledge this is the first systematic review study to comprehensively analyse long term cardiopulmonary health outcomes in CDH survivors. Various narrative reviews have made effort to tackle outcomes including asthma, respiratory tract infections, bronchopulmonary dysplasia, pulmonary function testing, chest X-ray radiology, health related quality of life (HRQoL) and exercise endurance in CDH.

A single yet crucially important paper has also focused additionally on the impact of CDH to the wider family [84]. These varied and useful published reports share some ideological themes [6,84–92].

The requirement for long term after care CDH follow-up has been arguably emphasized before [5,93]. The current study, however, crucially shows an underscored prevalence of chronic health morbidity in CDH and strikingly what we consider are the real 'unmet needs' of vulnerable at-risk patients and families. There is compelling evidence now for CDH multidisciplinary clinics to be made more widely available in all world healthcare systems.

6. Conclusion

In summary we show that cardiopulmonary morbidity and a reduced HRQoL are widely prevalent and underscored among CDH survivors. Multidisciplinary follow-up should be a 'standard of care' established by clinical teams to support CDH patients and their families transition health needs smoothly into adulthood. Future well designed prospective studies into the risk factors for cardiopulmonary complications, as well as research work addressing other long-term outcomes are vitally needed.

Level of evidence

Level III.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jpedsurg.2022.03.020.

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