Long-term outcomes for resected congenital lobar emphysema: Follow-up recommendations for primary care providers

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1. Abstract

Congenital lobar emphysema (CLE) is a rare lung anomaly characterized by hyperinflation of one or more pulmonary lobes. It most often presents within the first six months-of-life with respiratory failure. Treatment depends on disease severity, with resection of the affected lobe(s) necessary for children with severe respiratory compromise. Children with resected CLE may be followed by their surgeon, but more commonly, the long-term care of these patients falls to primary care providers, including physician assistants. As CLE is rare, primary care providers may not have the experience to assess and treat long-term outcomes as these patients grow up. The purpose of this study was to summarize the existing literature about the long-term outcomes of children with resected CLE and create a best practice guideline for the follow-up of patients after CLE resection. A literature search was performed, which revealed the 31 eligible references included in this review. The outcomes described in the references were grouped into five themes: survival, respiratory, musculoskeletal, anthropometric, and general well-being. Overall, the literature suggested that these children do well in terms of survival, growth and development, and general well-being. However, there are areas that primary care providers should screen for complications. Musculoskeletal complications such as pectus excavatum and scoliosis are more prevalent in children with resected CLE than in the general population. Additionally, children with resected CLE may be at increased risk of small airway obstruction and diminished, but not significant, pulmonary function.

2. Introduction

2.1 Congenital lung lesions and congenital lobar emphysema

Congenital lung lesions encompass a group of pulmonary disorders that includes congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (BPS), hybrid lesions (which contain elements of CPAM and BPS), bronchial atresia, and congenital lobar emphysema (CLE)(1). Also known as congenital lobar overinflation, CLE is a rare lung anomaly characterized by hyperinflation of one or more pulmonary lobes (Figure 1). It is believed to be caused by 'air trapping' distal to a partial obstruction of the associated bronchus. Usually, only one lobe is involved, most often the left upper lobe or the right middle lobe are affected. However, some patients have more than one emphysematous lobe; all three lobes on one side may be affected, or one or more lobes on either side may be affected(2).

The incidence of CLE is 1 in 20,000-30,000 live births, with a male to female ratio of 3:1. Approximately one-third of cases are symptomatic at birth, and the majority are diagnosed within the first six months-of-life. Those who are symptomatic present with progressive respiratory failure (chest wall retractions, wheeze, cyanosis) and/or feeding difficulties. Children with CLE often have additional congenital anomalies; cardiac malformations are the most common, occurring in 14-20% of CLE patients. Other systems that may be affected are the renal, musculoskeletal, and gastrointestinal systems(2).

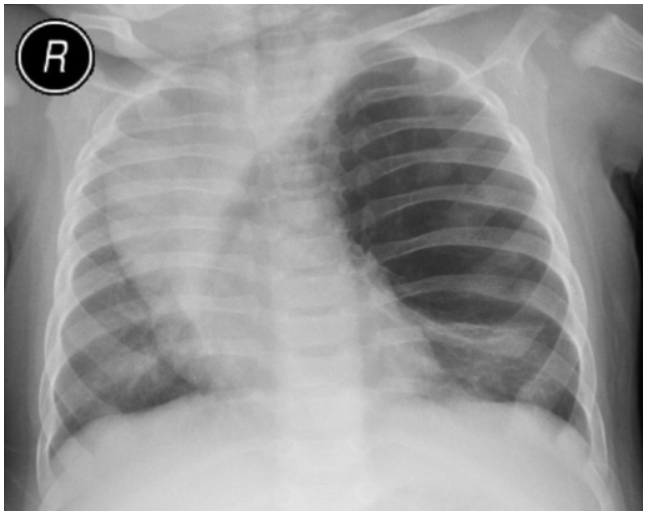

Figure 1. Chest x-ray of a 3-month-old male with congenital lobar emphysema, demonstrating hyperinflation of the left upper lobe with mediastinal shift towards the right (image from Radiopaedia, case contributed by Dr. Fakhry Mahmoud Ebouda).

2.2 Diagnosis

CLE can be diagnosed prenatally or postnatally. In the prenatal period, routine ultrasound may reveal hyperechogenic lung segments without aberrant arteries, mediastinal shift and/or polyhydramnios, in which cases CPAM or BPS should be considered. Prenatal magnetic resonance imaging (MRI) is superior to ultrasound for narrowing the differential diagnosis. Postnatally, in patients with respiratory distress, chest x-ray is the mainstay for evaluation. Chest

x-ray will show over-inflation and hyperlucency of the affected lobe(s). Mediastinal shift and herniation of the affected lobe to the opposite side may be present if over-inflation is extensive. The gold standard for diagnosis of CLE in the postnatal period is computed tomography (CT), as it can assess the anatomy of the emphysematous lobe and evaluate the adjacent lobes to determine if the other lung tissue is hypoplastic(2).

2.3 Treatment

The treatment for patients with CLE depends on the severity of the respiratory compromise. In cases where symptoms are mild, patients can be treated conservatively and monitored for the progression of symptoms. Asymptomatic CLE are electively resected by some surgeons due to small risks of future infection or pneumothorax, and a theoretical risk of malignancy. For patients in whom respiratory distress is severe, resection of the affected lobe(s) is necessary by lobectomy. Lobectomy can be done by open thoracotomy or by video-assisted thoracoscopy(2).

2.4 Role of physician assistants and the purpose of this study

Previous studies have reported the short- and long-term outcomes of children with CLE; however, a systematic review and narrative summary of the long-term outcomes has not been done. Therefore, there is a need to summarize the existing literature to determine what outcomes should be anticipated and screened for in the long-term care of these patients. Children with resected CLE may be followed by their surgeon, but more commonly, the long-term care of these patients falls to their primary care providers. Because congenital lung lesions, including CLE, are rare, primary care providers may not have the experience to know what expect as these patients grow up. By summarizing the long-term outcomes reported in the existing literature, a best practice guideline can be created to help guide primary care providers in the care of these

patients. According to the Canadian Association of Physician Assistants (CAPA) 2015 census, 46.95% of Canadian physician assistants work in primary care, making physician assistants a crucial part of the long-term care of complex patients such as those with resected CLE(3).

The purpose of this study was to comprehensively document and summarize the existing literature about the long-term outcomes of children with resected CLE as part of a series of systematic reviews on all congenital lung lesions. A secondary goal was to identify areas that will benefit from further research. Ultimately, the goal of this study is to help direct the creation of best practice guidelines for the follow-up of patients with CLE. With such a guideline, all primary care clinicians, including physician assistants, will have an evidence-based tool to investigate and manage the long-term outcomes of these patients.

3. Methods

A literature search was performed of the databases Medline (Ovid), EMBASE, PSYCHINFO, CNAHL, and SCOPUS using the keywords ‘congenital lung lesion(s)’, ‘cystic adenomatoid malformation of lung, congenital/’, ‘bronchopulmonary sequestration/’, ‘bronchogenic cyst/’, and ‘emphysema and congenital’. This search uncovered 3069 unique abstracts or papers which were uploaded into Rayyan, an online systematic review application. Within Rayyan, the titles and abstracts were independently screened by two reviewers to determine which articles might meet the inclusion criteria. Included papers needed to report post-discharge outcomes for patients who had a resection of a pathologically or radiographically confirmed CLE before 12 years-of-age. If a conflict arose regarding inclusion or exclusion, the title or abstract was screened by a third reviewer.

Potentially eligible papers were then independently reviewed by two reviewers to confirm inclusion or exclusion. The references of these papers were also reviewed to identify additional papers that met the inclusion criteria. The data abstracted included the description of the patients, the type of surgery the patients had, the age of follow-up, the description of the control group and how the control group was generated (where applicable), the outcomes measured, and the results of those outcomes. Each paper was critically appraised to identify limitations that may have affected results. To include all potentially important studies, abstracts were used for data abstraction when full papers could not be accessed. Google Translate® was used to interpret papers in languages other than English. Papers were excluded if the results did not include long-term outcomes. Long-term was defined as 'after discharge for resection of the lung lesion'. Studies were also excluded if they included multiple types of congenital lung lesions but did not separate the outcomes by type, thus making it impossible to determine which outcomes applied specifically to patients with CLE. A flow diagram of how papers were chosen for inclusion or exclusion is shown in Figure 2.

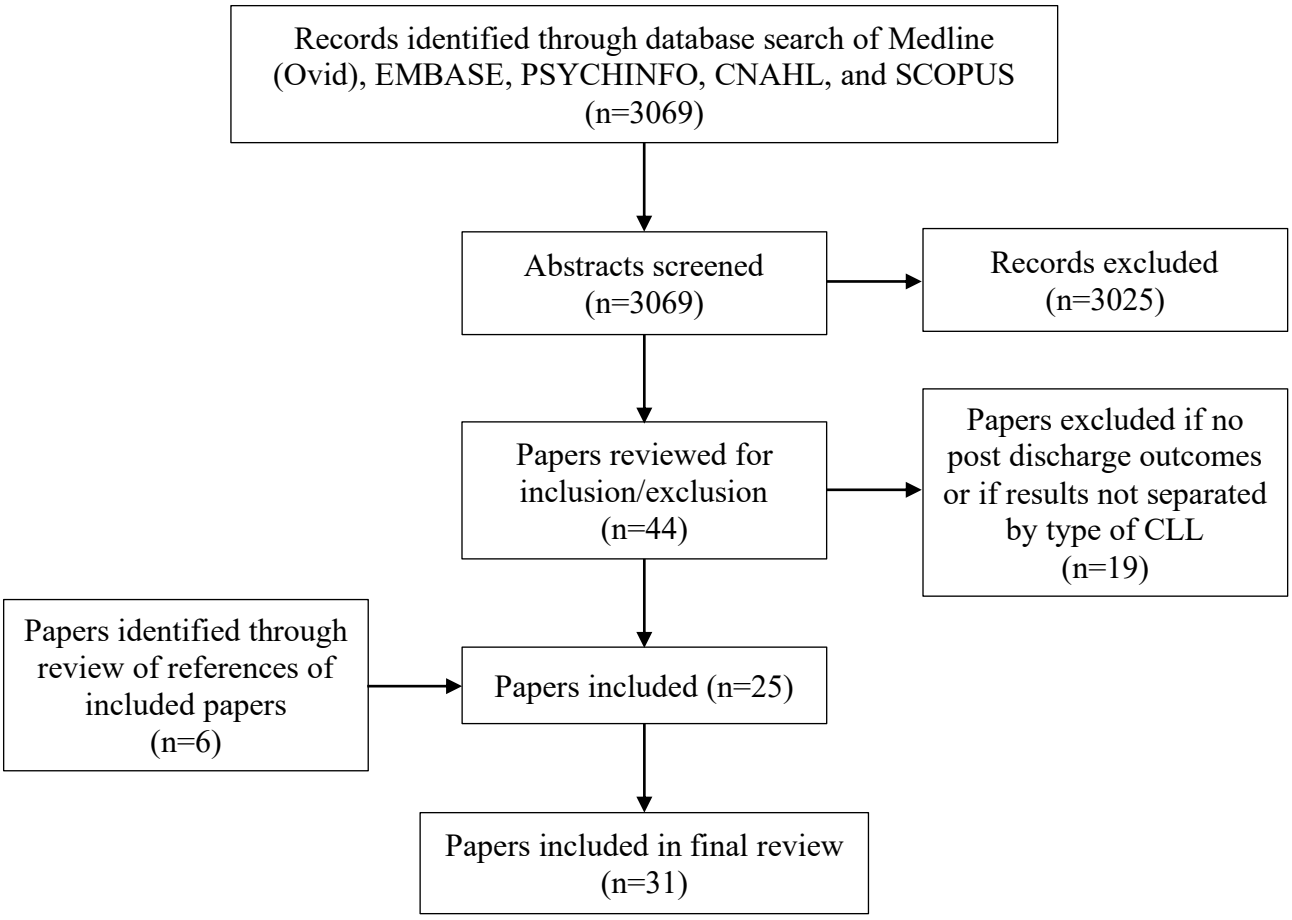

Figure 2. Flow diagram for inclusion and exclusion of papers retrieved through database search on long-term outcomes of children with resected CLE.

The results of the included papers were grouped by category of outcome: survival, respiratory, musculoskeletal, anthropometric, and general well-being. The outcomes of patients with bilateral CLE or CLE resected by pneumonectomy were considered separately from patients treated with unilateral lobectomy. We did this because we hypothesized that the more extensive surgery would result in worse outcomes. In addition to data abstraction, a MINORS score (methodological index for non-randomized studies) was calculated for each paper by two reviewers to quantify the quality of each included paper. Figure 3 shows the revised and validated version of MINORS by Slim *et al.* used in this systematic review(4).

Methodological items for non-randomized studies	Score†
1. **A clearly stated aim:** the question addressed should be precise and relevant in the light of available literature 2. **Inclusion of consecutive patients**: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion) 3. **Prospective collection of data**: data were collected according to a protocol established before the beginning of the study 4. **Endpoints appropriate to the aim of the study**: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis. 5. **Unbiased assessment of the study endpoint**: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated 6. **Follow-up period appropriate to the aim of the study**: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events 7. **Loss to follow up less than 5%**: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint 8. **Prospective calculation of the study size**: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes *Additional criteria in the case of comparative study* 9. **An adequate control group**: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data 10. **Contemporary groups**: control and studied group should be managed during the same time period (no historical comparison) 11. **Baseline equivalence of groups**: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results 12. **Adequate statistical analyses**: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk	

†The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Figure 3. The revised and validated version of MINORS by Slim *et al(4).*

4. Results

Long-term outcomes of patients with resected CLE were reported by 28 papers and 3 abstracts which were included in this review. The outcomes of these 31 references were grouped into five themes: survival, respiratory, musculoskeletal, anthropometric, and general well-being. Table 1 summarizes the papers included, the type of study, the years in which the study took place, the number of CLE patients followed, the range of follow-up, the categories of outcomes that were reported, and the MINORS score determined by the two reviewers.

Table 1. Summary of the papers included, the study type, the years that the studies took place, the number of patients, the range of follow-up, the outcomes measured, and the MINORS score.

Author	Study type	Years	# of patients	Time of f/u	Outcomes measured	MINORS
Barrena, S 2010	Retrospective cohort	1969-2009	1	0.6-23yr	Respiratory General well-being	8/16
Bogers, A 1993	Retrospective cohort	1987-1992	4	1-26mo	Survival Respiratory General well-being	5/16
Cataneo, D 2013	Retrospective cohort	1979-2009	20	Mean 60mo	General well-being	8/16
Coran, A 1994	Retrospective cohort	1974-1993	7	2mo-19yr	Survival Anthropometric General well-being	6/16
DeMuth, G 1966	Retrospective cohort	Not specified	6	5-14yr	Respiratory Anthropometric	5/16
Dewan, R 2012	Retrospective cohort	1995-2010	3	8mo-14yr	Survival General well-being	7/16
Dzakovic, A 2011	Retrospective cohort	2003-2010	37 (total CLL)	Mean 8.7mo	Musculoskeletal General well-being	8/16
Eigen, H 1976	Retrospective case control	Not specified	6	7.9-16.8yr	Respiratory Anthropometric Musculoskeletal General well-being	10/16
Ekkelkamp, S 1987	Case report	Not specified	1	1.5yr	General well-being	6/16
Fatureto, M 2008	Case report	Not specified	1	Not specified	General well-being	4/16
Floyd, F 1963	Case report	1958	1	Not specified	Respiratory General well-being	6/16
Frenckner, B 1982	Retrospective cohort	1970-1978	8	3-11yr	Survival Respiratory General well-being	10/16
Karunasumetta, C 2014	Retrospective cohort	2001-2011	4	1-8yr	Respiratory General well-being	6/16
Khemiri, M 2009	Retrospective cohort	1994-2004	17	4mo-7yr	Respiratory General well-being	6/16
Kissin, L 1977	Retrospective cohort	Not specified	5	1-12yr	General well-being	4/16
Krivchenya, D 2013	Retrospective cohort	1982-2012	42	6mo-10yr	Respiratory Anthropometric Musculoskeletal	7/16
Li, X 2007	Retrospective cohort	1993-2006	6	Not specified	General well-being	4/16
Maiya, S	Case report	Not	1	5yr	Respiratory	8/16

2005		specified			General well-being	
McBride, J 1980	Prospective cohort	1947-1970	15	8-32yr	Respiratory Anthropometric	9/16
Mhiri, R 2003	Retrospective cohort	1989-1999	8	1-8yr	Respiratory Musculoskeletal	6/16
Mullassery, D 2008	Retrospective cohort	1997-2004	14	2-88mo	Survival General well-being	9/16
Naumeri, F 2019	Retrospective cohort	2014-2017	2	Not specified	General well-being	3/16
Nazem, M 2010	Prospective cohort	1996-2008	26	1yr	Respiratory Anthropometric	6/16
Ozcelik, U 2003	Prospective cohort	1972-1999	21	3.5mo-16.9yr	Survival Respiratory Musculoskeletal General well-being	5/16
Perea, L 2017	Retrospective cohort	2014-2015	4	1yr	Respiratory Anthropometric	7/16
Salles, M 2005	Retrospective cohort	1997-2001	4	1mo-7yr	Survival	9/16
Shanmugam, G 2005	Retrospective cohort	1993-2003	9	1mo-10yr	Survival Respiratory	6/16
Szots, I 1977	Prospective cohort	1952-1965	10	10-23yr	Anthropometric General well-being	6/16
Takeda, S 1999	Retrospective cohort	1962-1996	2	2-30yr	General well-being	6/16
Tarrado, X 2010	Retrospective cohort	2008-2009	1	2-12mo	Respiratory General well-being	6/16
Ulku, R 2008	Retrospective cohort	1993-2004	8	1-89mo	General well-being	6/16

4.1 Survival

Of the papers reviewed, eight reported long-term survival. Five of these papers collectively followed 37 patients with CLE, all resected by lobectomy(5-9). The age at follow-up ranged from 1 month to 19 years. There were no deaths.

Three additional papers reported mortality of CLE patients at long-term follow-up. Bogers *et al.* followed 4 patients for 1 to 26 months(10). The resected lung from 1 patient harboured a rhabdomyosarcoma and the patient died at 3.5 years. Frenckner *et al.* followed 8 patients for 3 to 11 years after lobectomy for CLE(11). One of these patients had a cardiac

malformation and died at 11 months-of-age from cardiac failure and respiratory insufficiency. Özçelik *et al.* followed 21 patients after resection of CLE for 3.5 months to 16.9 years(12). Five patients had associated anomalies, including patent ductus arteriosus, ventral septal defect, atrial septal defect, pulmonary hypertension, cystinosis, pulmonary atresia, and omphalocele. One of these patients with a cardiac anomaly died during cardiac surgery 9 months after lobectomy for CLE.

4.2 Respiratory

Respiratory outcomes at long-term follow-up were reported in 17 of the papers reviewed. These outcomes included respiratory symptoms, asthma, respiratory infections, chest X-rays, ventilation perfusion (VQ) scans, and pulmonary function tests (PFT).

4.2.1 Unilateral CLE resected by lobectomy

General comments about the presence or absence of respiratory symptoms were reported by six papers. Three of these papers, which collectively followed 50 patients with CLE for 1 month to 10 years, reported no respiratory symptoms at long-term follow-up(10, 13, 14). In contrast, the presence of respiratory symptoms at follow-up was reported by the three other papers reviewed. Eigen *et al.* and Khemiri *et al.* collectively followed 23 patients with CLE for 4 months to 16.8 years(15, 16). Within this cohort, 4 patients had episodic wheeze. Exercise-induced dyspnea was reported by Mhiri *et al.* in 1 of their 8 patients(17).

Asthma was assessed in three of the papers reviewed. Two of these papers, by McBride *et al.* and Özçelik *et al.,* reported asthma diagnosed by PFT in children older than 6 years of age. In both papers combined, 5 of 20 patients had reversible small airway obstruction due to asthma(12, 18). Asthma was also reported by Shanmugam *et al.,* who stated that 2 of their 9

patients had bronchial asthma with mild wheeze at follow-up 1 month to 10 years after resection(9). However, they did not describe how asthma was diagnosed.

Respiratory infections were mentioned by two papers. DeMuth *et al.* reported that their 6 patients, who were followed for 5 to 14 years, had frequent respiratory infections that diminished with age(19). In contrast, Frenckner *et al.* followed 8 patients for 3 to 11 years and reported no over-representation of respiratory infections(11).

Oxygen requirements after resection of unilateral CLE was reported by one paper. Nazem *et al.* followed 26 patients for 1-year post-operative and reported that 2 patients were oxygen-dependent(20). Oxygen saturation was reported by Özçelik *et al*.; they recorded oxygen saturation at follow-up using pulse oximetry in 11 patients. Oxygen saturation was normal in 10 patients but showed hypoxia in 1 patient with cyanotic heart disease(12).

Chest x-ray results at long-term follow-up were reported in five of the papers reviewed. In three of these papers, which collectively followed 46 patients, chest x-rays were described as normal(14, 17, 21). In contrast, Eigen *et al.* reported over-inflation of both lungs with mediastinal shift toward the lobectomy side in 6 patients(15). Özçelik *et al.* performed chest x-rays in 17 patients at follow-up; 11 were normal and 6 showed hyperlucency(12).

Ventilation-perfusion (VQ) scans and radiospirometry are used to assess air and blood flow within the lungs; results of these tests were described in three papers. According to Mhiri *et al.,* 1 of their 8 patients showed hypoperfusion and hypoventilation of the remaining lung on the operated side(17). McBride *et al.* and Frenckner *et al.* collectively performed radiospirometry on 16 patients and found that ventilation and perfusion were not statistically different between the operated and non-operated lung(11, 18).

Pulmonary function tests (PFT) are used to assess lung volumes and lung function compared to normal values. PFT results of patients with resected CLE were described in six of the papers reviewed. According to Demuth *et al*. vital capacity, the maximum volume of air expellable after maximum inspiration, decreased after resection, but residual volume, the volume of air remaining in the lungs after maximum expiration, remined normal. Eigen *et al.* reported that vital capacity and total lung capacity decreased in proportion to the amount of lung resected; however, total lung capacity was normal, suggestive of trapped gas(15). Frenckner *et al.* reported decreased vital capacity and total lung capacity in 1 patient but the volumes were reduced less than expected for the amount of lung resected(11). Finally, McBride *et al.* reported vital capacity and total lung capacity as normal in 13 and 14 out of 15 patients, respectively, but conceded the mean values were less than expected(18).

Flow volume loops are a graphical representation of inspiration and expiration plotted against lung volume, used to assess if airflow of the lungs is normal for a particular lung volume. McBride *et al.* found forced expiratory volume in 1 second (FEV1) and FEV1 over forced vital capacity (FVC), FEV1/FVC, below normal in 14 of 15 patients, with 4 patients having a component of reversible airway obstruction with inhaled isoproterenol(18). Mhiri *et al.* had 1 patient with a restrictive pattern on PFT, and Özçelik *et al.* found small airway obstruction in 2 of their 5 patients, 1 of which being reversible with bronchodilators(12, 17).

4.2.2 CLE resected by bilateral lobectomies or pneumonectomy

Among the 17 papers that reported respiratory outcomes, two described post-pneumonectomy results, and three reported outcomes for patients after bilateral lobectomies. Barrena *et al.* followed children undergoing pneumonectomy for 0.6 to 23 years, including 1 case of CLE. PFT results were “encouraging” with average FVC 40-70% predicted, average

FEV_1 47-87% predicted, and average FEV_1/FVC 87-98% predicted(22). Karunasumetta *et al.* followed 4 children with CLE for 1 to 8 years, 2 of whom underwent pneumonectomy and were well at follow-up with good quality of life(13). Floyd *et al.* reported that a chest x-ray performed 3 years after bilateral lobectomies for CLE was normal with equal aeration bilaterally(23). Maiya *et al.* also presented a case of bilateral CLE treated with bilateral lobectomies followed 5 years post-op. Like Floyd *et al.,* they reported normal chest x-rays and VQ scans at follow-up. However, they reported that their patient had recurrent episodes of cough and wheeze exacerbated by respiratory tract infections, as well as left main bronchial malacia on bronchoscopy performed 6 months post-operative(24). Perea *et al.* followed 4 patients with bilateral CLE 1-year post-operative, 3 underwent unilateral lobectomy and 1 underwent bilateral lobectomies. At follow-up, all patients were on room air without oxygen requirements(25).

4.3 Musculoskeletal

Pectus excavatum was described in three papers. Two of these papers, by Eigen *et al.* and Krivchenya *et al.,* collectively followed 48 children with resected CLE for 6 months to 16.8 years(14, 15). Of these 48 patients, 4 had mild pectus excavatum. The third paper followed 21 patients with resected CLE for 3.5 months to 16.9 years(12). They reported that 5 patients had associated anomalies, including pectus excavatum. However, they did not report the exact number of patients who had pectus excavatum.

Scoliosis was reported in two papers. Mhiri *et al.* found that 1 of 8 patients had scoliosis at 8 years-of-age(17). Dzakovic *et al.* followed 37 patients with congenital lung lesions, including congenital pulmonary airway malformations, CLE, and sequestrations, for a mean of 8.7 months. There was no evidence of scoliosis at follow-up(26).

4.4 Anthropometric

Anthropometric outcomes were reported by nine papers and were reported in terms of height and weight or growth and development.

Outcomes of height and weight were mentioned by three papers. In two papers height and weight were reported as normal-for-age for the 21 patients followed(15, 18). The third paper included 26 patients with resected CLE followed 1-year post-operatively(20). At 6 months follow-up, 5 males and 4 females had delayed weight gain based on growth charts. Additionally, 3 males and 2 females were shorter than normal.

General comments about growth and development were included in six papers. In these papers, 71 children with CLE were followed for 2 months to 23 years, with no deficits in growth or development identified(5, 14, 19, 23, 25, 27).

4.5 General well-being

Comments about the general well-being of patients with resected CLE at long-term follow-up were included in 22 of the papers reviewed. These outcomes were all subjective, including quality of life, symptoms and complaints, physical limitations, and general comments about well-being.

Quality of life was mentioned in only one paper by Barrena *et al.,* who followed children after pneumonectomy for 0.6 to 23 years, including 1 case of CLE(22). They reported that at long-term follow-up there were no impairments in quality of life, however, they did not use an objective assessment tool.

Three of the papers reviewed reported no late complications at long-term follow-up(7, 10, 28). Collectively, these three papers followed 38 patients with CLE from 1 month to 7.3 years.

Seven papers reported that patients with resected CLE were asymptomatic with no complaints at long-term follow-up(6, 11, 21, 27, 29-31). These papers followed a total of 29 patients with CLE for 2 months to 23 years.

Physical limitations were mentioned in seven papers. Eigen *et al.* followed 6 patients with resected CLE for 7.9 to16.8 years and stated that 2 patients reportedly fatigued easily during play(15). However, they did not use an objective instrument for exercise tolerance. The remaining six papers reported that no limitations in physical performance and no restrictions in daily activities(6, 11, 13, 26, 32, 33).

Finally, ten papers simply reported that 81 patients with resected CLE were "well" at long-term follow-up ranging from 1 month to 30 years(5, 7, 12, 13, 16, 24, 29, 33-35).

5. Discussion

Children with CLE who undergo surgical resection of the affected lobe(s) may be followed by their surgeon in the post-operative period, but often the long-term follow-up into adulthood falls to primary care providers, including physician assistants. The objective of this review was to summarize the existing literature on long-term outcomes of children with resected CLE and propose follow-up and screening recommendations for primary care providers who may have these complex children in their care. A secondary objective was to identify areas that will benefit from further research. The themes identified in the literature as long-term outcomes were survival, respiratory, musculoskeletal, anthropometric, and general well-being. Overall, the literature suggested that long-term outcomes are good, but respiratory and musculoskeletal status should be routinely assessed in the primary care setting.

5.1 Survival

Overall, the literature reviewed suggested that long-term survival of patients with resected CLE is excellent. Although 2 peri-operative deaths were reported, long-term mortality was uncommon(16, 35). In five of the eight papers that reported long-term survival, no mortality was seen. In three papers that reported mortalities, the deaths were due to additional anomalies and not due to the CLE or its surgical management. For instance, one death occurred in a patient with rhabdomyosarcoma in the resected lung tissue; the death was due to recurrence of the malignancy(10). Two additional deaths were due to cardiac anomalies. Therefore, based on the evidence in the literature, primary care providers can reassure parents of children with successfully resected CLE and without significant comorbidities that long-term survival can be expected.

5.2 Respiratory

The literature reviewed suggested that most patients with resected CLE do not have respiratory complaints at long-term follow-up, but some experience mild wheeze or exercise dyspnea(10, 13-15). Therefore, primary care providers should inquire about respiratory symptoms to determine if further workup should be done for respiratory issues such as asthma.

In the three papers that assessed asthma, the prevalence of asthma was approximately 24%, compared to 8.4% of children less than 18 years-of-age from the general population(36). Because the prevalence of asthma in children with resected CLE may be higher than the general population, it should be screened for in the primary care setting. If asthma is suspected, the diagnosis can be confirmed by spirometry in children greater than 5 years-of-age as spirometry cannot be reliably performed in younger children(37).

The literature reviewed was equivocal with respect to the relative risk of respiratory tract infections in resected CLE survivors. Demuth *et al.* reported an increased frequency of respiratory infections but Frenckner *et al.* did not. Although only the abstract was available for Demuth *et al.*, both studies had small sample sizes, neither study included controls, and the method (i.e., x-ray, swabs, cultures, etc.) used to confirm the infections were not defined for either study. Therefore, there is not enough evidence to predict if children are at increased risk of respiratory infections after resection of CLE. This is an important area for future research because the benefits of resection are unproven in asymptomatic CLE patients; if resection incurs an increased risk of subsequent respiratory tract infections, fewer asymptomatic patients may request resection.

The literature showed that most children with resected CLE do not require long-term supplemental oxygen. Two papers reported hypoxia or oxygen dependency at follow-up. However, in both papers, hypoxia was secondary to cardiac anomalies(12, 20). Therefore, long-term oxygen dependency or hypoxia is more likely associated with cardiac anomalies and not to the CLE resection.

Post-operative chest x-rays, VQ scans, and radiospirometry were described in the literature reviewed. The weight of the evidence suggested that most chest x-rays were normal, however, some mediastinal shift or over-inflation was observed. Based on VQ scans and radiospirometry, Mhiri *et al.* suggested hypoperfusion and hypoventilation of the operated lung, while McBride *et al.* and Frenckner *et al.* reported near normal ventilation and perfusion of the operated lung compared to the contralateral lung. The authors of the two latter papers suggested that their results may represent compensatory growth of the unresected lung parenchyma and vasculature. These papers had longer follow-up and higher MINORS scores than Mhiri *et al.*

Therefore, while the evidence does not strongly lean one way or the other, compensatory growth of the affected lung may occur leading to improvements in ventilation and perfusion. Compensatory lung growth, broadly described as a return of alveolar number toward normal, is poorly understood. In children, alveolar multiplication is rapid before 2 years-of-age, slows after 4 years-of-age and is believed to stop at 8 years-of-age(38). Future research into the physiology of compensatory lung growth and interventions for its optimization are needed.

The six papers that reported PFT results reported lung volumes and flow volume loops. Vital capacity and total lung capacity were reportedly reduced but within normal limits after resection(11, 15, 18, 19). Demuth *et al.* and Eigen *et al.* concluded that these findings were more consistent with overdistention of the remaining lung rather than compensatory lung growth(15, 19). In contrast, Frenckner *et al.* believed compensatory lung growth did occur as they observed a 10% decrease in vital capacity and total lung capacity despite resection of 20% of the lung tissue(11). McBride *et al.* reported normal vital capacity and total lung capacity in most of their patients. They too attributed their findings to compensatory growth of the remaining lung(18). The broad range of normal PTF values (FVC 80-120%, FEV_1 80-120%, and FEV_1/FVC within 5% of the predicted ratio) will have affected the post-resection pulmonary status(39).

Obstructive patterns were commonly seen on flow volume loop studies but were not always attributed to asthma. McBride *et al.* thought the obstructive pattern may be due to slower airway growth compared to lung parenchyma growth(18). Özçelik *et al.* suggested the obstruction may be due to abnormal elastic recoil of the peripheral airways. Only Mhiri *et al.* reported a restrictive pattern in one patient suggesting that restrictive lung disease is uncommon after CLE resection.

Similar functional results have been described in children with a history of lobectomy for other congenital lung lesions or infectious diseases. These studies reported lung volumes close to normal, like CLE, and suggested that compensatory lung growth occurred when children were operated on early in life(38, 40-42). Although the etiology of CLE is still unknown, respiratory outcomes can be expected to be similar to children undergoing lobectomy for other reasons. Overall, primary care providers may expect slightly decreased lung volumes and possibly small airway obstruction in their patients with resected CLE. Therefore, it would be wise to perform baseline PFT on these patients at about 5 years-of-age to monitor for changes in respiratory function. Primary care providers should assess responsiveness to bronchodilators when an obstructive pattern is documented on PFT as it may not be secondary to asthma. Furthermore, primary care providers should endorse healthy respiratory habits (no exposure to second-hand smoke, avoidance of proven allergens) for patients and their families.

The outcomes of patients treated with bilateral lobectomies or pneumonectomy were reviewed separately from patients who had unilateral lobectomy. Overall, the outcomes of children with CLE managed with bilateral lobectomies did not differ from those undergoing a single lung surgery in terms of general well-being, chest x-rays, PFT, and oxygen requirements, as the majority of these results were reported as normal(13, 22-25). Only one paper reported cough or wheeze exacerbated by respiratory infections, as well as left main bronchus malacia in one of their patients(24). PFT volumes were lower than normal after pneumonectomy but did not affect quality of life(22). Therefore, despite having more lung resected and/or bilateral thoracotomies, the reported long-term respiratory outcomes did not differ from those with unilateral CLE.

Resection of a second emphysematous lobe may not be routinely necessary. Symptomatic patients with two emphysematous lobes have been rendered asymptomatic after resection of one CLE lobe leaving the second CLE lobe in situ(25). There is not, however, enough quantitative data in the literature to predict if double lobectomy is necessary and/or the functional outcomes for these uncommon cases.

5.3 Musculoskeletal

In the articles reviewed, the prevalence of pectus excavatum was approximately 1 in 12 while the prevalence in the general population is 1 in 400 to 1000 live births(43). Primary care providers should perform physical exams to screen for pectus excavatum in patients with resected CLE. Because severe pectus excavatum can compress the heart and lungs, primary care providers should monitor children with pectus excavatum for poor exercise tolerance, chest pain, and shortness of breath(43). In cases where cardiac or respiratory compromise is present, surgical correction may be considered(43).

The two papers that included scoliosis in their long-term outcomes had differing results. Mhiri *et al.* reported a prevalence of scoliosis of 1 in 8 in their study but Dzakovic et al. found no scoliosis in 37 patients. In the general population the prevalence of idiopathic scoliosis is approximately 1 in 30 and congenital scoliosis is 1 in 10,000 for(44). Dzakovic *et al.* only followed their patients for a mean of 8.7 months and did not explain how scoliosis was ruled out. While infantile scoliosis can occur prior to the age of 3 years it comprises only 1% of scoliosis in children(45). Therefore, if Dzakovic *et al.* had followed patients longer, they may have detected scoliosis. Since scoliosis can be diagnosed relatively easily through physical exam, it should be screened for in children with resected CLE in the primary care setting(46).

Similar musculoskeletal outcomes have been reported for children who had lobectomies for reasons other than CLE. This suggests that thoracotomy, rather than CLE, increases the risk of chest wall deformities(47, 48). Although direct comparison studies have not been done, children with resected CLE probably have a similarly increased risk of musculoskeletal abnormalities as all children undergoing lobectomy via thoracotomy. Although not studied specifically in CLE patients, pediatric thoracotomy patients have been found to subsequently develop winged scapula, shoulder, breast and nipple asymmetry, and pectoralis major, latissimus dorsi and serratus anterior atrophy(48). Screening for these conditions in CLE patients will identify deficits for which physiotherapy or surgery may be helpful. Because chest wall deformities have been observed within months of resection, CLE musculoskeletal screening should start after resection and continue to maturity(47). Minimally invasive thoracic procedures are increasingly common and have been shown to decreased, but not eliminate, chest wall anomalies after lobectomy(47).

5.4 Anthropometric

Children with resected CLE have normal growth and physical development. Only one of nine papers reported deficits in height and weight. Nazem *et al.* reported delayed weight gain in 35% and delayed height in 19% of their patients(20). However, these delays were reported after only 6 months of follow-up, and there was no mention of whether these deficits persisted into childhood or adulthood. Therefore, there is no evidence to suggest that children with resected CLE should be expected to have lower than predicted height and weight when they grow up.

5.5 General well-being

The literature suggested that children who underwent resection of CLE are generally well at long-term follow-up. The only limitations in general well-being mentioned in the literature

were exercise intolerance and fatigue during play(15). Exercise tolerance should be monitored by primary care providers; however, primary care providers should feel confident reassuring parents that their children can be expected to have no significant long-term impairments in daily activities or quality of life.

Table 2 summarizes our recommendations for screening in patients with resected CLE.

Table 2. Summary of screening recommendations for primary care providers for the 5 themes of outcomes found in the literature: survival, respiratory, musculoskeletal, anthropometric, and general well-being.

Outcome	Recommendations for screening
Survival	None. Long-term survival can be expected in children with resected CLE. Mortality in these patients is secondary to additional comorbidities.
Respiratory	Perform baseline PFT when patients are able and monitor for changes in respiratory status. Children with resected CLE are at increased risk of asthma and reduced lung volumes.
Musculoskeletal	Children with resected CLE are at increased risk of chest wall deformities and scoliosis which should be routinely screened for through physical exam. When severe, these children should be referred to a specialist for consideration of intervention.
Anthropometric	None. Children with resected CLE have normal growth and development.
General well-being	Children with resected CLE have no significant long-term impairments in general well-being. Primary care providers should monitor for exercise intolerance.

6. Limitations

One limitation of this literature review is the quality of the studies reviewed. Most of the studies were retrospective cohort studies without controls. Two reviewers independently

assigned each paper a MINORS score. As shown in Table 1, the MINORS scores ranged from 3 to 10 out of 16, with a mean of 6.5. This suggested that the quality of the studies reviewed was low by today's standards. We acknowledge, however, the importance of the work done by all of the authors whose work is include here; CLE is a rare condition and efforts to understand and better manage it are invaluable to affected children and their families. A second limitation of this study is the rarity of CLE, as demonstrated by the small sample sizes of the literature reviewed. A third limitation of this study is that standardized protocols for follow-up were uncommon among the papers reviewed. This report was also limited to outcomes which the included authors choose to report. The effect of CLE resection on many unexplored outcomes such as breast symmetry, socioeconomic status, and neurodevelopment, could not be included herein. Finally, the duration of follow-up ranged greatly between the 31 papers, making them difficult to compare.

This review was intentionally limited to outcomes that occurred after patients were discharged post-resection of their CLE. Therefore, post-operative complications were not reported. Because our intended audience was primary care providers responsible for the long-term care of CLE survivors, these short-term outcomes were excluded.

7. Conclusion

Children with CLE treated with surgery are rarely encountered in primary care and can be medically complex. Primary care providers may have little exposure to these patients and limited experience anticipating potential long-term complications. This systematic review has attempted to summarize the literature and propose evidence-based guidelines to aid in the comprehensive long-term care of CLE patients.

Overall, the literature suggested that these children do well in terms of survival, growth and development, and general well-being, but there are areas that primary care providers should screen for complications. Musculoskeletal complications such as pectus excavatum and scoliosis are more prevalent in children with resected CLE compared to the general population. Screening with physical examination should start in infancy. Severe deformities should be referred to a specialist for consideration of intervention. Children with resected CLE may be at increased risk of small airway obstruction and diminished lung volumes. Pulmonary function and lung volume assessments in school-age children will identify potentially reversible disorders, such as asthma, but will also prevent unnecessary exposure to bronchodilators in irreversible obstructive patterns.

Until we understand what causes CLE and can prevent or repair it in utero, children born with CLE will continue to require urgent resection to relieve respiratory distress. Children born with CLE will benefit from research directed at the physiology of compensatory lung growth, the effects of resection on respiratory tract infections, and the risks and benefits of minimally invasive thoracoscopic surgery for resection.

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