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WILEY PEDIATRIC PULMONOLOGY

Lung function, exercise tolerance, and physical growth of children with congenital lung malformations at 8 years of age

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Abstract

Objective: To improve counseling on congenital lung malformations (CLM) by describing long-term outcomes of children either operated on or managed by observation.

Study design: We analyzed lung function (spirometry), exercise tolerance (Bruce treadmill), and physical growth of 8-year-old children with CLM who participated in our longitudinal prospective follow-up program. The data are shown as median standard deviation scores (SDS) with IQR, or estimated marginal means (95% CI) on the basis of general linear models.

Results: Twenty-nine (48%) of the 61 children had required surgery at a median age of 108 (IQR: 8-828) days, and 32 (52%) were managed by observation. In the surgery group, all lung function measurements (except for forced vital capacity [FVC]) were significantly below 0 SDS, with median FEV_1 −1.07 (IQR: −1.70 to −0.56), FEV_1/FVC −1.49 (−2.62 to −0.33), and $FEF_{25\%-75\%}$ −1.95 (−2.57 to −0.63) (all $P < 0.001$). Children in the observation group had normal FEV_1 and FVC, whereas FEV_1/FVC (−0.8_1 (−1.65 to −0.14)) and $FEF_{25\%-75\%}$ (−1.14 (−1.71 to −0.22)) were significantly below 0 SDS (both $P < 0.001$). Mean exercise tolerance was significantly below 0 SDS in both groups (observation: −0.85 (95% CI: −1.30 to −0.41); surgery: −1.25 (−1.69 to −0.80)); eight (28%) children in the observation group and ten (40%) in the surgery group scored <−1 SDS. Physical growth was normal in both groups.

Conclusion: Children with CLM may be at risk for reduced lung function and exercise tolerance, especially those who required surgery. As little pulmonary morbidity was found in children with asymptomatic CLM, this study supports a watchful waiting approach in this group.

KEYWORDS

Bruce Treadmill Protocol, Congenital Pulmonary Airway Malformation, Long-Term Follow-Up Spirometry

1 | INTRODUCTION

Congenital lung malformations (CLM) are a heterogeneous group of malformations, including cystic pulmonary airway malformation (CPAM), bronchopulmonary sequestration, congenital lobar emphysema, bronchogenic cysts, and hybrid forms of these lesions.[1] CLM are increasingly detected prenatally as a result of routine fetal anomaly scanning and improved ultrasound technology. The current estimated incidence is 4.15 per 10 000 births.[2] Children with CLM who develop symptoms, either directly after birth or later in life, undergo surgery. However, the majority of children with CLM remain asymptomatic. The best management strategy—ie elective surgical resection or watchful waiting—in these children remains controversial, because of uncertainty about the risk of postoperative complications, the most accurate timing of surgical resection, and the risks of infection and malignancy related with watchful waiting.[3,4] A previous study at our center showed airflow obstruction in approximately one-third of children with CLM at the ages of 6 and 12 months, both in those who had required surgery and in those who remained asymptomatic.[5] The data on the long-term outcome are scarce, especially in children with asymptomatic CLM.[6–8]

To optimize follow-up and to improve counseling, we primarily aimed to describe pulmonary outcomes (ie lung function, exercise tolerance and lower respiratory tract infections [LRTIs]) and physical growth in 8-year-old children with CLM; both in those operated on and those managed by observation. We hypothesized that children with asymptomatic CLM have normal growth and no pulmonary morbidity and that children who needed surgery have a more complicated clinical course with growth failure and pulmonary morbidity. Secondarily, physical growth, exercise tolerance, and LRTIs were evaluated longitudinally in all children.

2 | MATERIALS AND METHODS

2.1 | Study population

We analyzed prospectively collected data of live-born children born with CLM between January 1999 and March 2010, and followed in the Erasmus Medical Center-Sophia Children's Hospital Rotterdam. These children had been diagnosed either prenatally or after birth, because of symptoms or coincidentally. The postnatal diagnosis had been made using computed tomography (CT) and/or histology. In our hospital, we advocate a wait-and-see policy in children with asymptomatic CLM; this group is scheduled for CT-imaging approximately 6 months after birth. Those who develop symptoms—such as respiratory distress after birth or recurrent LRTIs—undergo surgical resection, usually after a CT-scan is made. Parents of all surviving children with CLM are invited to enter their child in our longitudinal prospective follow-up program. Since 1999, this program is the standard of care for children with anatomical congenital malformations treated in our center.[9] Follow-up visits are planned at the ages of 1, 2, 5 and 8 years. The Medical Ethical Review Board waived approval because data obtained during routine care were retrospectively analyzed (MEC-2018-1086).

2.2 | Variables and definitions

Neonates born <37 weeks' gestation were considered preterm. Those with a birth weight below the 10th centile of Dutch reference curves were considered small for gestational age.[10] Multiple congenital anomalies (MCA) were only documented if they required surgery or multiple follow-up visits. We registered the need for hospitalization within 28 days after birth, including the length of stay and the need for and duration of respiratory support (ie supplemental oxygen only, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]). Children who had required supplemental oxygen for at least 28 days were diagnosed with chronic lung disease.[11] Spinal and thoracic deformities were assessed during a physical examination at 8 years of age.

2.3 | Pulmonary outcomes

2.3.1 | Lung function

Dynamic lung volumes were measured using spirometry at the age of 8 years. We documented the forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and the forced expiratory flow (FEF) at 25%-75% of FVC ($FEF_{25\%-75\%}$). Standard deviation scores (SDS) were calculated according to the Global Lung Initiative 2012, with −1.64 to +1.64 SDS considered as normal range.[12] In addition, bronchodilator reversibility was reported. Significant reversibility was defined as an increase in FEV1 of >12% compared with the pre-bronchodilator test. Static lung volumes were measured by body plethysmography and expressed in residual volume (RV), total lung capacity (TLC), and RV/TLC. Diffusion capacity was assessed with carbon monoxide diffusion (DLCO) and DLCO corrected for alveolar volume (DLCO/VA). SDS for static lung volumes and diffusion capacity were calculated according to the Utrecht data set.[13]

2.3.2 | Exercise tolerance

Exercise tolerance was determined with the Bruce treadmill protocol.[14] Time to the maximal effort was assessed at 5 and 8 years, and converted to SDS according to Dutch reference values.[15,16]

2.3.3 | Occurrence of LRTIs

At each follow-up visit (1, 2, 5, and 8 years), parents reported whether or not their child had suffered from an LRTI in the past year. Only LRTIs treated with antibiotics were documented.

2.3.4 | Additional imaging

The program does not include routine imaging at 8 years of age yet. Children were, however, referred to the pediatric pulmonologist in a low-threshold setting.

2.4 | Physical growth

Height and weight were measured at 1, 2, 5, and 8 years of age. We calculated height-for-age (HFA) and weight-for-height (WFH) SDS according to Dutch reference norms; −2 to +2 SDS was considered normal range.[17,18] Target height SDS was calculated from parental heights.[19] To correct HFA for target height, distance-to-target-height (DTH) SDS was calculated as follows: DTH SDS = HFA SDS − target height SDS.

2.5 | Statistical analysis

The data are summarized as number (%) or median (interquartile range [IQR]), as appropriate. Differences in characteristics between the observation group and the surgery group were evaluated with chi-square or Fisher's exact tests for categorical data, and with Mann-Whitney tests for continuous data. We assessed with Wilcoxon signed-rank tests whether median lung function parameters were below 0 SDS. The courses of exercise tolerance and physical growth over time were evaluated with general linear models. These models included the following independent variables: need for surgery (coded as a time-dependent dichotomous variable: negative before and positive after surgery), the time point (5 and 8 years in case of exercise tolerance; 1, 2, 5 and 8 years in case of physical growth), the interaction effect of the need for surgery and time point, and presence of MCA. To account for within-subject correlations, we used an unstructured error covariance matrix. The results are summarized as estimated marginal means (ie the predicted values of the dependent variable, adjusted for covariates in the model) with their 95% confidence intervals (95% CIs). Statistical analyses were performed using IBM SPSS Statistics 24, with a two-sided significance level of 0.05.

3 | RESULTS

Of 79 infants born with CLM between January 1999 and March 2010, 76 (96%) had survived. The three others, who had been diagnosed prenatally, had died within 2 weeks after birth. Two of them had a pneumonectomy because of CPAM in the entire lung, and required ECMO for 5 and 13 days, respectively. Both died because of therapy-resistant pulmonary hypertension. The other infant was diagnosed with bronchopulmonary sequestration and died of cecum perforation complicated by septic shock and intracerebral hemorrhage.

Sixty-one (80%) children underwent follow-up examination at 8 years of age, of whom 43 (70%) had been seen at all four-time points (Figure 1). Characteristics of children examined at 8 years and those not examined did not differ significantly, except for the proportion of children not subjected to CT or histology, which was higher in those not examined (E-Table 1). E-Figure 1 provides an overview of the number of children per follow-up time point, categorized according to the type of management (ie observation or surgery).

Twenty-nine of the 61 (48%) children had undergone surgery at a median age of 108 (IQR: 8-828) days. The indications for surgery were respiratory insufficiency (14/29, 48%), recurrent infections (7/29, 24%), increasing size (3/29, 7%), and miscellaneous (5/29, 17%).

One child with an extralobar bronchopulmonary sequestration had undergone embolization of the aberrant artery at 3 years of age because of cardiac insufficiency. This child was included in the surgery group. No features of malignancy were found in any of the resected specimens. The children in the surgery group had less often been diagnosed prenatally; they had a slightly shorter median gestational age at birth, and they had more often required mechanical ventilation than those in the observation group (Table 1).

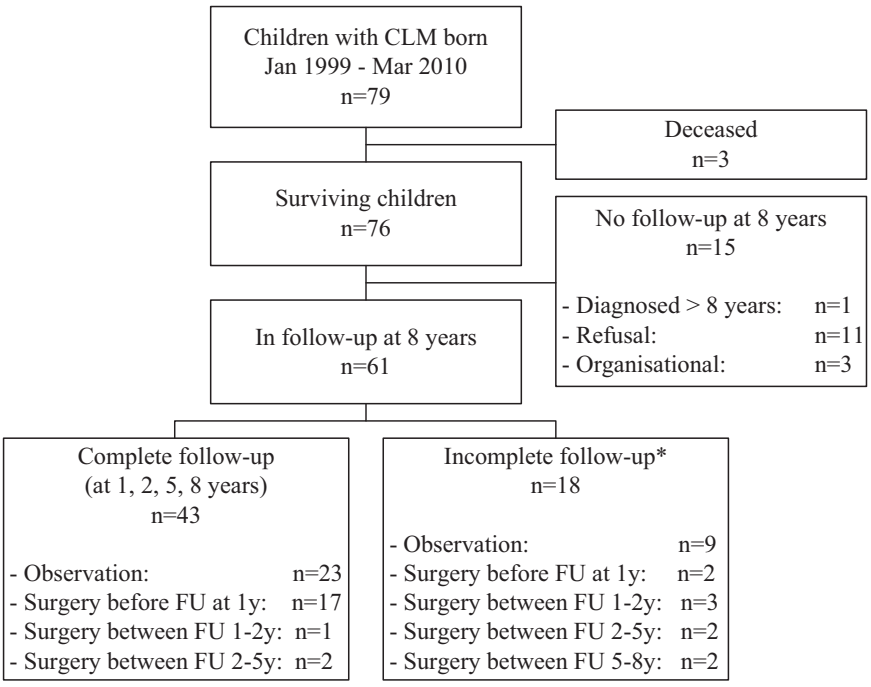

FIGURE 1 Inclusion flowchart CLM, congenital lung malformations, FU, follow-up, y: years. %"* Reasons for incomplete follow-up: organisational (n = 10; seen at 1, 5, and 8 y: n = 1; seen at 2, 5 and 8 y: n = 4; seen at 5 and 8 y: n = 4; seen at 8 y: n = 1), refusal (n = 6; seen at 1, 2, and 8 y: n = 3; seen at 1, 5, and 8 y: n = 3), diagnosed >1 year (n = 1, seen at 2, 5, and 8 y), diagnosed >2 y (n = 1, seen at 5 and 8 y).%"

TABLE 1 Prenatal, perinatal, and postnatal characteristics of children examined at 8 y (n = 61)

	n	Observation group (n = 32; 52%)	n	Surgery group[a] (n = 29; 48%)	*P* value
Maternal age, y	31	30.7 (29.0-35.1)	22	29.6 (26.9-35.1)	0.43
Male sex	32	16 (50%)	29	20 (69%)	0.13
Multiple pregnancy	32	-	29	2 (7%)	0.22
Prenatal characteristics					
Prenatal diagnosis	32	29 (91%)	29	18 (62%)	0.01
Gestational age, wk at diagnosis	29	20.4 (19.9-21.7)	15	20.9 (20.1-29.0)	0.15
Perinatal characteristics					
Cesarean section	32	8 (25%)	23	2 (9%)	0.17
Gestational age at birth, wk	32	39.6 (28.9-41.0)	25	38.7 (36.5-40.1)	0.02
Preterm birth	32	3 (9%)	29	7 (24%)	0.17
Birth weight, gm	32	3503 (2878-3879)	26	3070 (2838-3648)	0.13
Small for gestational age	32	3 (9%)	22	1 (5%)	0.64
Apgar score at 5 min	32	9 (9-10)	23	9 (8-10)	0.64
Apgar score <7 at 5 min	32	2 (6%)	24	2 (8%)	1.00
Umbilical cord pH	29	7.28 (7.26-7.34)	16	7.30 (7.26-7.36)	0.64
Postnatal characteristics					
Type of CLM	32		29		
CPAM		15 (47%)		13 (45%)	0.87
Bronchopulmonary sequestration		5 (16%)		8 (28%)	0.26
Congenital lobar emphysema		4 (13%)		4 (14%)	1.00
Bronchogenic cyst		-		2 (7%)	0.22
Hybrid or inconclusive[b]		4 (13%)		2 (7%)	0.67
CLM in regression		3 (9%)		-	0.24
Insufficient diagnostics (no CT or histology)		1 (3%)		-	1.00
CT imaging available	32	31 (97%)	29	25 (86%)	0.18
Age at CT, mo	31	3.0 (0.1-4.5)	25	1.3 (0.1-6.3)	0.84
Localization of CLM	32		29		
Left upper lobe		5 (16%)		3 (10%)	0.71
Left lower lobe		7 (22%)		8 (28%)	0.61
Right upper lobe		4 (13%)		-	0.11
Right middle lobe		1 (3%)		1 (3%)	1.00
Right lower lobe		13 (41%)		8 (28%)	0.28
Multilobar		2 (6%)		4 (14%)	0.41
Mediastinal		-		3 (10%)	0.10
Extralobar		-		2 (7%)	0.22
Multiple congenital anomalies[c]	32	6 (19%)	27	5 (17%)	0.88
Hospitalized ≤28 d after birth	32	32 (100%)	27	24 (89%)	0.09
Duration, d	32	4 (2-8)	23	14 (3-29)	0.003
Respiratory support during hospitalization	32		24		
None		21 (66%)		7 (29%)	0.01
Supplemental oxygen only		8 (25%)		4 (17%)	0.45
Mechanical ventilation		3 (9%)		10 (42%)	0.01

(Continues)

TABLE 1 (Continued)

	n	Observation group (n = 32; 52%)	n	Surgery group[a] (n = 29; 48%)	*P* value
ECMO		-		3 (13%)	0.07
Chronic lung disease	32	-	27	3 (11%)	0.09

Abbreviations: CLM, congenital lung malformation; CPAM, congenital pulmonary airway malformation; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; n/a, not applicable.
The data presented as median (interquartile range) or n (%).
[a]Thoracotomy (n = 20); thoracoscopy (n = 6); laparotomy (n = 1); embolization (n = 1); unknown (n = 1).
[b]CPAM and/or congenital lobar emphysema (n = 3); CPAM and/or bronchogenic cyst (n = 3).
[c]Ventricular septal defect (n = 2); atrial septal defect (n = 2); tetralogy of Fallot (n = 1); patent ductus arteriosus and duplicated renal collecting system (n = 1); laryngeal cyst (n = 1); Filamin A deficiency (n = 1); congenital diaphragmatic hernia (n = 1); bladder exstrophy and anal atresia and duplicated renal collecting system (n = 1); bilateral ovarian cysts (n = 1).

Spinal and thoracic deformities were assessed in 56 (92%) children at 8 years of age. None of them had scoliosis. One child in the observation group had pectus excavatum (1/28; 4%) vs three children in the surgery group (3/28; 11%). These three children had all undergone thoracotomy.

3.1 | Pulmonary outcomes

3.1.1 | Lung function

Reliable spirometry tests at 8 years of age were obtained in 57/61 (93%) children. Spirometry results per diagnosis are shown in Figure 2. Overall, children in the observation group (n = 31) had median FEV_1 SDS (−0.37 (IQR: −0.94 to 0.49)), and FVC SDS (0.10 (−0.59 to 0.74)) comparable to reference norms, whereas median FEV_1/FVC SDS (−0.81 (− 1.65 to −0.14)) and $FEF_{25\%-75\%}$ SDS (−1.14 (−1.71 to −0.22)) were significantly below 0 (both $P < 0.001$). Four (13%) children scored $FEV_1 < -1.64$ SDS, two (6%) scored FVC < −1.64 SDS, and FEV_1/FVC and $FEF_{25\%-75\%}$ were <−1.64 SDS in eight (26%) children.

In the surgery group (n = 26), median FVC SDS was comparable to reference norms (−0.39 (IQR: −1.16 to 0.68)). The other lung function parameters were significantly below 0 SDS, with median FEV_1 −1.07

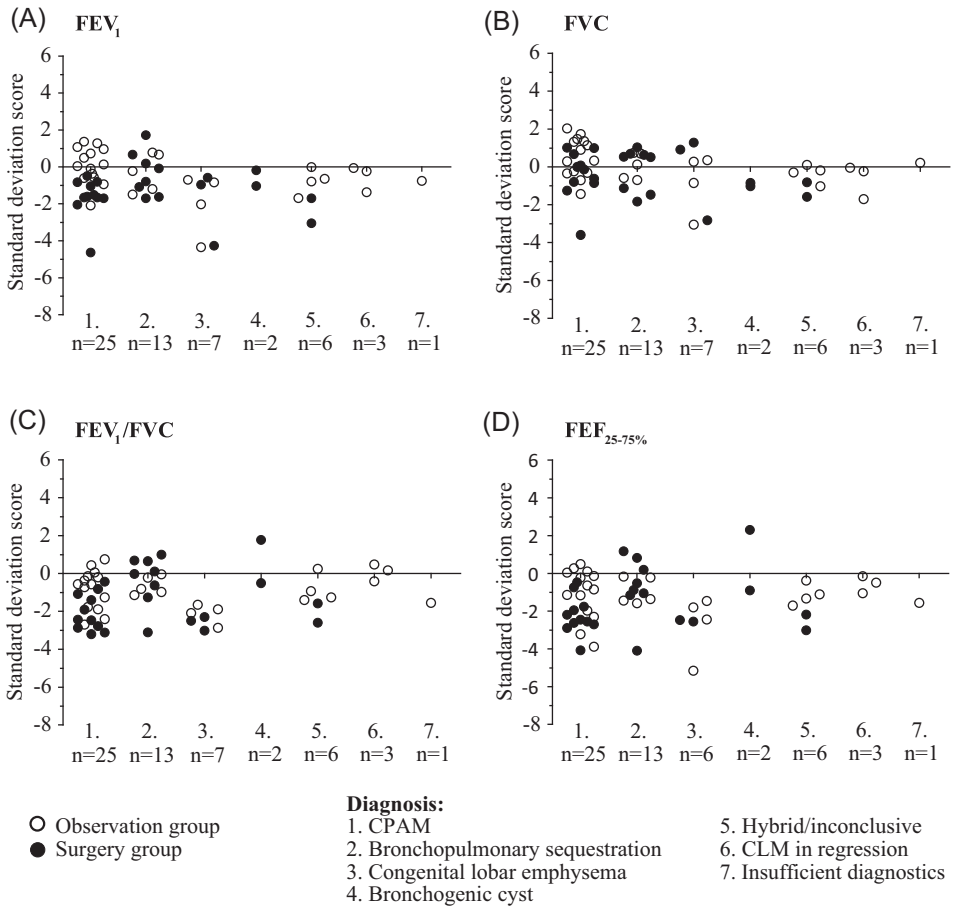

FIGURE 2 Scatter plots showing lung functions at 8 years of age in the observation group and in the surgery group, per diagnosis. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF25-75%: forced expiratory flow at 25%-75% of FVC; CPAM, congenital pulmonary airway malformation; CLM, congenital lung malformation

(−1.70 to −0.56), FEV_1/FVC −1.49 (−2.62 to −0.33) and $FEF_{25\%-75\%}$ −1.95 (−2.57 to −0.63) (all $P < 0.001$). Nine (35%) children scored $FEV_1 < -1.64$ SDS, three (12%) scored FVC < −1.64 SD, FEV_1/FVC was <−1.64 SDS in 12 (46%) children, and 14 (56%) scored $FEF_{25\%-75\%} < -1.64$ SDS. Compared with children in the observation group, those in the surgery group had lower median FEV_1 SDS ($P = 0.007$), and a higher proportion scored $FEF_{25\%-75\%} < -1.64$ SDS ($P = 0.02$); the other parameters did not differ significantly.

Bronchodilator reversibility was tested in 38 children. Two of 19 (11%) children in the observation group and 2/19 (11%) in the surgery group showed significant reversibility. One of these four children had been prescribed inhaled corticosteroids; the others were asymptomatic.

Body plethysmography was performed in 41/61 (67%) children. In the observation group (n = 20), median static lung volumes (SDS) were comparable to reference norms (RV 0.15 (IQR: −0.33 to 0.40); TLC 0.13 (−1.12 to 0.58); RV/TLC 0.17 (−0.34 to 0.78)). In the surgery group (n = 21), median RV (−0.23 (−1.34 to 0.13)), and RV/TLC (−0.20 (−1.21 to 1.01)) were comparable to reference norms, whereas median TLC was significantly below 0 (−0.44 (−1.35 to 0.19), $P = 0.047$). Body plethysmography parameters did not differ significantly between both groups.

Diffusion capacity was assessed in 37/61 (61%) children. In both groups, median DLCO and DLCO/VA SDS were comparable to reference norms (observation group (n = 20): 0.05 (IQR: −1.03 to 0.54) and 0.07 (−0.50 to 0.54), respectively; surgery group (n = 17): 0.05 (−0.41 to 0.52) and −0.16 (−0.69 to 0.35), respectively). Diffusion capacity did not differ significantly between the observation group and the surgery group.

3.1.2 | Exercise tolerance

Exercise tolerance had been assessed in 44/57 (77%) children at 5 years and in 54/61 (89%) at 8 years of age. Forty-three children were seen at both time points. At 5 years, the estimated marginal mean exercise tolerance SDS of children in the observation group (n = 25; −0.13 (95% CI: −0.56 to 0.30)) did not differ significantly from 0 SDS. Those in the surgery group (n = 19) scored significantly below 0 SDS (−0.56 (−1.05 to −0.07)). At 8 years, both groups scored significantly below 0 SDS (observation group (n = 29): −0.85 (−1.30 to −0.41); surgery group (n = 25): −1.25 (−1.69 to −0.80)). Eight (28%) children in the observation group and 10 (40%) in the surgery group scored <−1 SDS, of whom two children in the observation group and three in the surgery group scored <−2 SDS.

Overall, the general linear model analysis showed a significant decrease in exercise tolerance SDS from 5 to 8 years of age of −0.70 (95% CI: −1.01 to −0.40). Children in the surgery group had significantly lower exercise tolerance SDS than those in the observation group (mean difference: 0.49 (0.03 to 0.95)).

3.1.3 | Occurrence of LRTIs

LRTIs during the past year had been reported for 2/50 (4%) children at 1 year follow-up, in 4/51 (8%) at 2 years, for 7/57 (12%) at 5 years, and for 3/61 (5%) children at 8 years. Of 61 children in follow-up, 14 (23%) had suffered at least one LRTI (E-Figure 2). Three of them had an LRTI after surgical resection, four underwent surgical resection because of the infection, and seven had been managed by observation despite having had an LRTI.

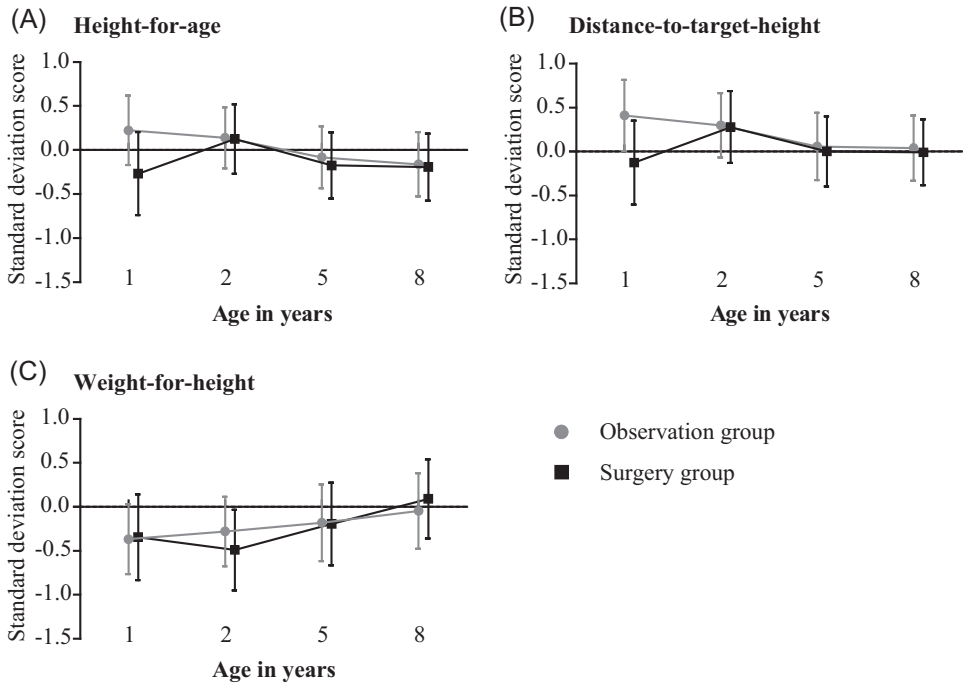

FIGURE 3 Line charts showing physical growth parameters measured at ages 1, 2, 5, and 8 years. Symbols represent estimated marginal means with 95% confidence intervals, on the basis of a general linear model that includes age, need for surgery (coded as a time-dependent dichotomous variable), the interaction effect of need for surgery and time point, and the presence of multiple congenital anomalies as explanatory variables

3.1.4 | Additional imaging

In 37 of 61 (61%) children in follow-up at 8 years, additional imaging had been performed after the initial diagnostic CT-scan, at a median age of 8.4 years (range, 1.2-15.4 years). Additional imaging had been performed mostly because of respiratory symptoms (n = 19, 51%), including coughing, fatigue, or deteriorating lung function, or because previous imaging had been inconclusive with respect to the type of CLM (n = 5, 14%). Eighteen of them were managed by watchful waiting (observation group), 18 had undergone surgery before the imaging, and one child underwent surgical resection after additional imaging.

Of the 37 children who underwent imaging, CT-imaging was performed in 21 (57%) children, 14 (38%) children were subjected to X-ray, and two (5%) children underwent magnetic resonance imaging. Of the 23 children who had undergone CT or magnetic resonance imaging, gas trapping was reported in 10 (43%).

3.2 | Physical growth

Physical growth data of all children in follow-up at 8 years are shown in Figure 3. Estimated marginal mean HFA, DTH, and WFH SDS were within reference norms at 1, 2, 5, and 8 years in both the observation group and the surgery group. Only WFH SDS in the surgery group at 2 years (−0.49 (95% CI: −0.95 to −0.03)) was significantly below 0 SDS.

Overall, the general linear model analysis showed a significant decrease of HFA SDS (−0.26 (−0.46 to −0.07)) and DTH SDS (−0.26 (−0.46 to −0.06)) between 2 and 5 years, and a significant increase of WFH SDS (0.41 (0.10 to 0.71)) between 2 and 8 years. Neither the presence of MCA nor the need for surgery affected any physical growth parameter.

4 | DISCUSSION

To our knowledge, this is the first study to evaluate lung function, exercise tolerance, and physical growth in 8-year-old children with either observationally or surgically managed CLM. As we hypothesized, most children with asymptomatic CLM had normal lung function parameters, exercise tolerance, and physical growth. Those who had required surgery had worse lung function and exercise tolerance than healthy children, but, in contrast to what we expected, showed normal physical growth.

The optimal management strategy in asymptomatic CLM remains debatable.[4] In this study, more than half of the children with CLM did not require surgical resection, which is consistent with a previous study that advocated a watchful waiting approach.[6] When only looking at the infants who had been diagnosed prenatally, it appears that approximately two-thirds (ie 29/47, 62%) could be managed observationally. Children in the observation group showed normal physical growth, and most of them had normal lung function parameters and exercise tolerance at 8 years of age, which supports a watchful waiting approach in asymptomatic CLM. About a quarter of children in this group did show reduced lung function parameters and/or exercise tolerance, however, and clinicians and parents should be aware of this. Several factors could have negatively influenced pulmonary outcomes, such as parental smoking and the presence of asthma. Parents should be carefully counseled and encouraged to stimulate physical activity and sport participation of their children.

Approximately half of the children in the surgery group had abnormal lung function parameters (except for FVC, which was abnormal in only 12%), and mean exercise tolerance fell below −1 SD at 8 years of age. In contrast, a previous study showed that over 75% of 21 children who had undergone lobectomy for CLM had normal lung function at a median age of 6 years (range 3-16).[20] Most of these children, however, had been diagnosed prenatally and underwent surgical resection regardless of having symptoms. In our study, the majority of these children would have been included in the observation group. We, therefore, assume that the pulmonary morbidity we found in our surgery group was caused by the severity of the CLM, rather than by the surgery itself. In other words, these malformations may not be just isolated or localized defects, and weaknesses might occur in adjacent lung sections. In addition, while we included children who underwent surgery in the first decade of this century, the 21 children in the previous study underwent surgery between 2005 and 2016, when medical technologies—including surgical techniques, ventilation methods, and use of ECMO—had advanced.

At each follow-up time point, 4%-12% of parents reported that their child had suffered from an LRTI during the past year. This is higher than the incidence reported in healthy European children (ie 14.5 per 10 000 children per year).[21] Two recent studies evaluated the data of children with CLM who had been diagnosed prenatally; in both studies, 9% of children required surgery because of respiratory infections.[6,22] In our study, LRTIs in the observation group did not always lead to surgical resection, for example, because children recovered well from a single LRTI or because no imaging data were available to confirm that the LRTI had been located in the same lobe as the CLM. LRTIs have also been reported in children with CLM in regression or after surgery. Hence, resection does not necessarily eliminate LRTIs; previous research even reported a paradoxical increase of pulmonary infections after resection of CLM,[7] and a high prevalence of recurrent LRTIs (ie 19%) in 7-year-olds who had undergone early surgery regardless of having symptoms.[23]

Strengths of our study include the data collection from a longitudinal prospective follow-up program, the high proportion (80%) of children that entered this program, the length of follow-up of both observationally and surgically managed children, and the standardized assessments during follow-up. Several limitations need to be addressed. First, we included children born from 1999 onwards, whereas the 20-week fetal anomaly scan was introduced in the Netherlands only in 2007. This has probably led to an underestimation of the number of children in the observation group. Second, there was a selection bias of children in the surgery group: as only symptomatic children underwent surgery, it is no surprise that

this group showed more morbidity. In some children, symptoms even led to the diagnosis of CLM. Third, our study does not answer the question whether early surgery in all children with CLM, including asymptomatic ones, would have resulted in everyone having a normal lung function and exercise tolerance or whether it would have worsened pulmonary outcomes. To find out whether surgical treatment could be superior to observation management in children with asymptomatic CLM, a randomized controlled trial or case-control study could be carried out to evaluate long-term outcomes in asymptomatic children who either do or do not undergo surgery. Fourth, LRTIs were parent-reported and we were unable to include the data on specific pathogens or on the location of the LRTI. To limit recall bias, we asked parents to report LRTIs that had occurred during the 12 months preceding the follow-up visit; hence, we have no data on LRTIs for ages 2 to 4 years and 5 to 7 years. Last, the patient samples were too small and the follow-up period was not long enough to evaluate the risk of malignancy in CLM, particularly CPAM.

In conclusion, children with CLM may be at risk for reduced lung function and exercise tolerance, especially those who required surgery. This study does not give a clear answer regarding the optimal management strategy in children with asymptomatic CLM. Still, as little pulmonary morbidity was found in these children, this study supports a watchful waiting approach in this group. Continued follow-up until adulthood is recommended to evaluate the risk of malignancy in both symptomatic and asymptomatic CLM.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

PRIOR PRESENTATION OF STUDY DATA

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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