



Congenital lung abnormality quantification by computed tomography: The CLAQ method

Sergei M. Hermelijn MD¹ | Olivier V. Dragt BSc^{2,3} | Jochem J. Bosch MD^{2,3} |
Annelieke Hijkoop PhD¹ | Luis Riera MD⁴ | Pierluigi Ciet MD, PhD^{2,3} |
René M. H. Wijnen MD, PhD¹ | Johannes Marco Schnater MD, PhD¹ |
Harm A. W. M. Tiddens MD, PhD^{2,3}

¹Department of Paediatric Surgery, Erasmus University Medical Centre, Sophia Children's Hospital, Rotterdam, the Netherlands

²Department of Paediatric Pulmonology, Erasmus University Medical Centre, Sophia Children's Hospital, Rotterdam, the Netherlands

³Department of Radiology, Erasmus University Medical Centre, Rotterdam, the Netherlands

⁴Department of Radiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Correspondence

Harm A. W. M. Tiddens, MD, PhD, Department of Paediatric Pulmonology, Department of Radiology, Erasmus University Medical Centre, Sophia Children's Hospital, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
Email: h.tiddens@erasmusmc.nl

Abstract

Introduction: To date, no consensus has been reached on the optimal management of congenital lung abnormalities, and factors predicting postnatal outcome have not been identified. We developed an objective quantitative computed tomography (CT) scoring method, and assessed its value for clinical decision-making.

Methods: Volumetric CT-scans of all patients born with a congenital lung abnormality between January 1999 and 2018 were assessed. Lung disease was quantified using the newly-developed congenital lung abnormality quantification (CLAQ) scoring method. In 20 equidistant axial slices, cells of a square grid were scored according to the abnormality within. The scored CT parameters were used to predict development of symptoms, and SD scores for spirometry and exercise tolerance (Bruce treadmill test) at 8 years of age.

Results: CT-scans of 124 patients with a median age of 5 months were scored. Clinical diagnoses included congenital pulmonary airway malformation (49%), broncho-pulmonary sequestration (27%), congenital lobar overinflation (22%), and bronchogenic cyst (1%). Forty-four patients (35%) developed symptoms requiring surgery of whom 28 (22%) patients became symptomatic before a CT-scan was scheduled. Lesional hyperdensity was found as an important predictor of symptom development and decreased exercise tolerance. Using receiver operating characteristic analysis, an optimal cut-off value for developing symptoms was found at 18% total disease.

Conclusion: CT-quantification of congenital lung abnormalities using the CLAQ method is an objective and reproducible system to describe congenital lung abnormalities on chest CT. The risk for developing symptoms may increase when more than a single lung lobe is affected.

KEYWORDS

congenital, congenital lung malformations, congenital pulmonary airway malformation, cystic adenomatoid malformation of lung, high-resolution computed tomography

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1 | INTRODUCTION

Congenital lung abnormalities (CLA) are considered rare developmental disorders of the respiratory tract and pulmonary vascularization. In the past decades, an increase in the incidence of CLA has been observed, due to improved ultrasound technology and structured prenatal screening.¹ The most common abnormalities, in order of prevalence, are congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (BPS), congenital lobar overinflation (CLO)—previously known as congenital lobar emphysema and bronchogenic cyst (BC). Quantitative prenatal measurements, such as the CPAM-volume-ratio, have been found to predict fetal hydrops and neonatal respiratory distress.² Postnatal predictive factors have not yet been identified, and to date, no consensus has been reached on the optimal management of CLA.³ To close this gap, quantitative measurements may be of added value, to accurately describe disease extent.⁴

Surgical resection is warranted for symptomatic CLA patients presenting with recurrent infections and respiratory distress, but the optimal management of asymptomatic patients is still being debated.^{5,6} Some authors propose a “wait and see” policy, while others advocate an operative approach in the first year of life for all cases. Arguments for elective surgery include avoiding the onset of symptoms and reducing the risk for malignant transformation.⁷ In addition, the complication rate of elective surgery is believed to be lower than that of emergency surgery,⁸ and early surgical resection may allow for compensatory lung growth and reduce parental anxiety.⁹ Conversely, conservative management is supported by evidence that the risk associated with surgery exceeds the risk of symptom development, and prevents the perhaps unnecessary removal of functional lung tissue. Additionally, the possible regression with increasing age,¹⁰ and the weak association with malignancy do not outweigh the surgical risks.^{7,11,12} All aforementioned arguments are based on retrospective studies, “expert’s opinion,” or empiricism, but hard evidence is lacking.^{3,6}

To determine the optimal management of CLA patients, we need to identify an objective postnatal outcome predictor. With this in mind, we have developed the congenital lung abnormality

quantification (CLAQ) scoring method, to objectively characterize and quantify disease extent on chest computed tomography (CT) in CLA patients. The aim of this study was to evaluate the reproducibility of the CLAQ scoring method and assess its value as an outcome predictor.

2 | METHODS

2.1 | Development and procedure of scoring method

The CLAQ scoring method is based on morphometric principles for quantifying cystic fibrosis lung disease.^{4,13} A heterogeneous random sample of 86 CT-scans of pediatric patients with various CLAs was obtained from the electronic patient records of the Erasmus MC-Sophia Children’s Hospital to identify the scoring parameters for the CLAQ method. Blinded for clinical data, a trained observer (JB) with experience in quantitative lung image analysis, reviewed the scans, and noted all visible parenchymal abnormalities. All identified abnormalities were classified into objective radiological categories and assigned a scoring order according to the clinical relevance of the abnormality by consensus between a pediatric pulmonologist, radiologist, and surgeon. The feasibility and reproducibility of the CLAQ scoring method were initially tested on CT-scans from 31 CLA patients, obtained from the electronic patient records of the Vall d’Hebron hospital in Barcelona, Spain.

2.2 | Preparation for annotating

A square grid is overlaid on 20 equidistantly spaced CT-scan slices and each grid cell containing 50% lung tissue or more is scored according to the content within (Figure 1). To correct for lung size variability between patients, the size of the grid cell corresponds to the largest airway diameter and is calculated by dividing the lung width at the carina by 20, and rounded to the nearest millimeter.⁴

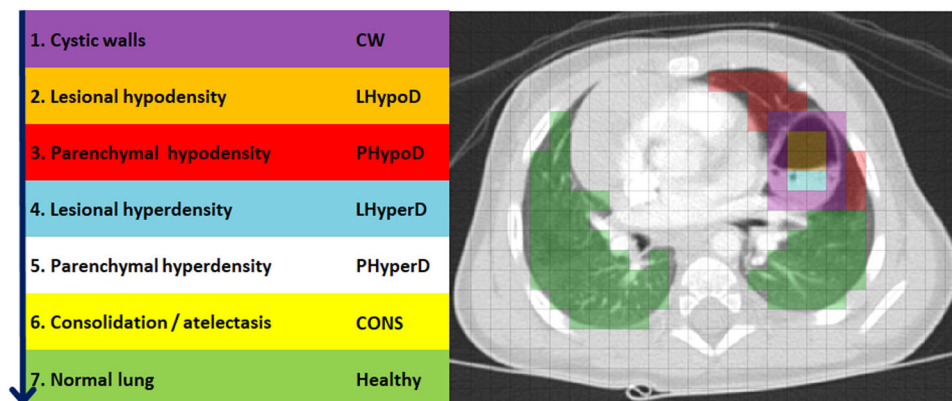


FIGURE 1 Example of congenital lung abnormality quantification scoring method including hierarchical components [Color figure can be viewed at wileyonlinelibrary.com]

2.3 | Slice annotation interval

To select which slices should be scored, a top and bottom slice are identified as the uppermost and lowermost slice in which a grid cell in each lung contains at least 50% lung tissue. Between these margins, 20 equidistant slices are scored. Approximately 15% to 20% of total lung tissue is scored, assuming volumetric scans with a 1 mm slice thickness, and a maximum lung length of 12 cm in 1-year old patients.^{14,15} Although only selected slices are annotated, observers are permitted to scroll through the entire lung.

2.4 | Selection of scoring parameters

Abnormalities that can be scored in a grid cell are divided into seven hierarchical categories (Figure 1). Highest priority is assigned to cystic walls (CW), as these characterize the cyst. The second priority is assigned to lesional hypodensity (LHypoD), and the third to parenchymal hypodensity (PHypoD), which were defined as low-attenuating areas of respectively the lesion or parenchyma. The fourth priority is assigned to lesional hyperdensity (LHyperD) and the fifth to parenchymal hyperdensity (PHyperD), defined as hyperdense tissue of the lesion and parenchymal ground-glass opacity, respectively. Hypodensity and hyperdensity are only scored if 50% or more of the grid cell contains the abnormality. Consolidation (CONS) is scored as sixth priority for hyperdense lung parenchyma with obscuration of pulmonary vessels. The lowest priority is assigned to grid cells that contain healthy lung tissue.

2.5 | Output

For scoring we used a software, developed with the MeVislab development environment for medical image processing (MeVis Medical Solutions AG and Fraunhofer MEVIS, Bremen, Germany). The volume of each grid cell is measured by the software and the cumulative volumes with relative percentages of each annotated abnormality are calculated. The total percentage of abnormal lung tissue was computed by subtracting the percentages of normal lung tissue and consolidation from 100%. Consolidation was subtracted as it could either be diseased lung or compressed healthy lung tissue.

2.6 | Training and reproducibility

Three observers (SH, OD, and MM) completed a CLAQ training module in which they scored four practice batches of five CT-scans each, including all CLA and guided by an instruction manual. After having scored each batch, the observer received feedback based on the annotations. After successful completion of the training module, the observers annotated the included CT-scans in random order, using the CLAQ scoring method. To determine intraobserver reliability, two observers (OD and MM) annotated a random sample of

20 CT-scans twice. To limit recall bias, this was done 4 weeks after completing annotation of all scans. To determine the interobserver reliability the annotations of all three observers were compared.

2.7 | Patient selection

Patients were selected from the electronic patient records of CLA patients enrolled in the surgical long-term follow-up program (CHIL) of the Erasmus MC-Sophia Children's Hospital Rotterdam. This structured follow-up program includes all CLA patients either born at or referred to Sophia Children's Hospital from January 1999 onward. The program is composed of structured hospital visits at set ages during which physical growth, developmental and lung function tests are obtained.¹⁶

We included all CLA patients born between January 1999 and January 2018 with CPAM, BPS, CLO, or BC located within the lung parenchyma, diagnosed using a volumetric inspiratory CT-scan. Exclusion criteria were CT-scans that would make annotation unreliable, such as sequential CT-scans, scans with a poor image quality, scans with a slice thickness exceeding 3 mm, and CT-scans with a large pneumothorax as these scans do not allow reliably scoring lung tissue. When multiple scans of a single patient were available, the first obtained CT-scan was annotated. Due to technical advancements and changes in hospital protocol over the span of 18 years, various CT protocols and scanners have been used in both sedated and conscious patients.

2.8 | Clinical parameters

Clinical data were obtained from the electronic patient records and included neonatal data and information on the surgical procedure, if applicable. Patients were divided into two groups symptomatic and asymptomatic patients. In our center, we adhere to a wait-and-see policy for all CLA patients unless they exhibit symptoms such as respiratory distress, recurrent infections or cardiac volume overload. Respiratory distress was defined as prolonged respiratory support (>24 hours) including oxygen supplementation and ventilation while recurrent infections were defined as more than or equal to 2 lower respiratory tract infections necessitating antibiotics within a year. Cardiac volume overload causing hemodynamic changes as assessed by a pediatric cardiologist was also a reason for resection. Symptomatic patients were defined as those undergoing a surgical resection due to aforementioned symptoms. In all patients who had undergone lobectomy or pneumonectomy, the estimated percentage lung tissue lost was determined according to previously published percentages.¹⁷ Lung height was calculated by subtracting the number of the top slice by the number of the bottom slice and multiplying this by the slice thickness. Spirometry and exercise tolerance had been performed according to previously described methods at 8 years of age. Exercise tolerance testing with the Bruce treadmill protocol was part of the follow-up program and time to the maximal effort was converted to standard deviation scores according to Dutch reference values.¹⁸

2.9 | Statistical analysis

Statistical analysis was performed using SPSS (version 25; IBM Corp, Armonk, NY) and RStudio (version 1.0.153; RStudio, Inc, Boston, MA). We used the “cutpointr,” “ROCR,” and “rpart” packages. Differences between the group asymptomatic, symptomatic before and after CT were assessed using the Kruskal-Wallis test. Spearman correlation was used to assess correlation between the total disease percentage and the percentage estimated loss of lung volume. The Wilcoxon signed-rank test was used to determine whether spirometry values and exercise tolerance were significantly below 0 SDS (standard deviation score). The intraobserver and interobserver reliability were assessed with intraclass correlation coefficient (ICC), using a two-way mixed-effects model with an absolute agreement. In general, an ICC score lower than 0.40 was considered poor, between 0.40 and 0.59 moderate, between 0.60 and 0.79 good, and above 0.80 excellent.¹⁹ CLO was analysed separately from the cystic CLAs (CPAM/BPS/BC) due to the difference in CT appearance and clinical presentation. The optimal cut-off value for total disease percentage was defined as the value yielding the maximal Youden index in the receiver operating characteristic curve.²⁰ To compare the cystic vs parenchymal scores as predictors in cystic abnormalities, a multivariable logistic regression was performed for these composite scores. Parenchymal scores included PHypoD, PHyperD, and CONS, while the other scores, apart from healthy lung tissue, were considered cystic.

We performed an exploratory decision tree regression to assess which parameters best predict symptoms requiring surgery and abnormal FVC/FEV₁/FEF₂₅₋₇₅ and Bruce SD-scores (<1.64 SD) in this cohort. Decision tree regression creates a flowchart in which data is repeatedly partitioned into smaller groups (nodes) on a yes or no basis. The best discriminative parameter is chosen as the first parameter (root node) after which the data is further partitioned until either less than 20 observations remain in a node or if any split does not increase the overall fit of the model by at least 0.01.²¹ The following parameters were used as predictors for growing the decision tree all scored components of the CLAQ method, the diagnosis, the location of the lesion, gestational age at birth, birthweight, and oxygen demand at birth. The purpose of using decision trees was mostly exploratory, thus no division between training and test data was made and assessment of accuracy was based on the original data using the area under the receiver operating characteristic (AUC). Interpretation of AUC followed Hosmer and Lemeshow in which an AUC of 0.5 was considered as no better than by chance, 0.6 to 0.69 considered to have poor discrimination, 0.7 to 0.79 acceptable discrimination, 0.8 to 0.89 good discrimination, and 0.9 to 1.0 excellent discrimination.²² The two-tailed statistical significance was set at a $P < .05$, unless Bonferroni's correction for multiple testing was applied.

3 | RESULTS

We identified 192 CLA patients participating in the CHIL follow-up program, of whom 124 remained after we applied the inclusion and

exclusion criteria. In 33 patients no CT-imaging was done and in 19 no abnormalities were seen on CT. Furthermore, eight patients had a mediastinal BC, seven did not have a volumetric CT-scan, and one had a large bilateral pneumothorax. Baseline patient characteristics are summarized in Table 1. Eighty (65%) patients remained asymptomatic and 44 (35%) became symptomatic and subsequently underwent surgery. Of these 44 patients, 28 (22%) patients became symptomatic before a CT-scan was scheduled and 16 (13%) thereafter. In order of prevalence, CPAM, BPS, CLO, hybrid lesions, and parenchymal BC had been diagnosed, and were similarly distributed in all three groups. Patients who became symptomatic before the CT-scan was scheduled required neonatal respiratory support more often, underwent surgery at a younger age—mostly due to respiratory insufficiency—and lesions were more often located in multiple lung lobes. Overall, abnormalities were most commonly found in the left (29%) or right (30%) lower lung lobe; a small number of patients (5%) showed bilateral lesions. Lesions were resected at a median age of 0.9 months for reason of respiratory insufficiency (96%) in those symptomatic before CT, and 28.7 months for reason of recurrent infections (50%) or cardiac volume overload (31%) in those symptomatic after CT. Overall, lobectomy (74%) was the most common type of surgery. In all symptomatic patients, the median estimated loss of lung volume was 24%. The scored total disease percentage was not correlated to the percentage estimated loss of lung volume in the cystic CLAs ($r_s = 0.22$, $P = .26$) and in CLO ($r_s = -0.33$, $P = .43$). Most scans had a slice thickness of 1.3 mm or less; a median of 20% of total lung volume was scored in each scan (Table 2).

3.1 | Outcome characteristics

Outcome characteristics are summarized in Table 2. Lung function and exercise tolerance were performed at the age of 8 years and have been reported previously.¹⁸ In the asymptomatic group, the median FEF₂₅₋₇₅ SDS was significantly below 0 ($P < .0001$), while the FVC SDS and FEV₁ SDS were not significantly different from reference values. In patients who became symptomatic before CT, the FVC ($P = .03$), FEV₁ ($P = .01$), and FEF₂₅₋₇₅ ($P = .02$) all had SDS significantly below 0, while these were all not significantly different from reference values in patients who became symptomatic after CT. The exercise tolerance at 8 years of age was significantly below 0 SDS in all three groups ($P < .02$). When comparing groups, only the FVC SDS was significantly lower in those symptomatic before CT ($P < .05$).

3.2 | Reproducibility CLAQ

The ICC scores for the intraobserver reliability were excellent for all categories of the CLAQ score (all >0.9, confidence interval [CI] lower limit > 0.9). Similarly, the scores for interobserver reliability were excellent for all categories (>0.8, CI lower limit > 0.7), except PHyperD (0.183, CI: -0.0440.395). See Table 1 in the online supporting information for details.

TABLE 1 Baseline characteristics

	Asymptomatic n = 80 (65%)	Symptomatic before CT n = 28 (22%)	Symptomatic after CT n = 16 (13%)
Male	41 (51)	19 (68)	10 (63)
Gestational age at birth, weeks	39.3 (36.0-41.6)	38.6 (31.7-41.3)	39.2 (36.7-41.1)
Birthweight, g	3383 (1825-4440)	3095 (1650-4505)	3240 (2480-3905)
Oxygen demand after birth*	12 (15)	23 (82)	1 (7)
Intubation and ventilation after birth*	1 (1)	17 (68)	...
ECMO during neonatal period*	1 (1)	3 (12)	...
Diagnosis			
CPAM	38 (48)	18 (64)	4 (25)
BPS	15 (19)	3 (11)	7 (44)
CLO	19 (24)	6 (21)	3 (19)
BC	1 (6)
Hybrid	6 (8)	1 (4)	1 (6)
CPAM + BPS	2 (3)
Location*			
RUL	8 (10)	2 (7)	...
RML	1 (1)	2 (7)	1 (6)
RLL	29 (36)	4 (14)	4 (25)
LUL	9 (11)	4 (14)	2 (13)
LLL	25 (31)	5 (18)	6 (38)
Multiple	8 (10)	11 (39)	3 (19)
Reason for resection*			\$
Respiratory insufficiency		27 (96)	2 (13)
(recurrent) Infections			8 (50)
Volume overload heart		1 (4)	5 (31)
Age at surgery (months)*		0.9 (0-3.6)	28.7 (3.1-196.8)
Thoracoscopy ^a		2 (7)	6 (40)
Extent of resection ^a			
Lobectomy		21 (75)	11 (73)
Segmentectomy		3 (11)	4 (27)
Pneumectomy		4 (14)	
Estimated % loss of lung volume		24 (10-55)	21 (10-36)

Note: Data are presented as N (%) or median (range).

Abbreviations: BC, bronchogenic cyst; BPS, bronchopulmonary sequestration; CLO, congenital lobar overinflation; CPAM, congenital pulmonary airway malformation; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

^a1 patient underwent coiling of a BPS under general anesthesia \$ 1 lesion was resected due to atypical CT appearance.

*Significant difference between groups ($P < .05$; the Kruskal-Wallis test).

3.3 | CLAQ method outcome

In Table 3, CLAQ percentages of all three groups are summarized separately for cystic and noncystic CLAs. All individual components, except PHyperD were significantly different between CLO and the cystic CLAs. Regarding the cystic CLAs, the total disease percentage was significantly

higher in those becoming symptomatic before the CT-scan compared with those after and asymptomatic patients. This was attributable to the significantly higher scores for CW, LHyperD, and PHyperD. In contrast, PHypoD was significantly higher within the asymptomatic group. Regarding CLO, the total disease percentage was significantly higher in patients symptomatic before CT-scan compared with those after and

	Asymptomatic n = 80 (65%)	Symptomatic before CT n = 28 (22%)	Symptomatic after CT n = 16 (13%)
Age at CT-scan, y*	0.5 (0-6.2)	0 (0-0.2)	0.5 (0.1-15.6)
Time between CT and Surgery, mo*	...	0 (0-1)	6 (0-73)
Slice thickness of CT-scan, mm	1.3 (0.5-2.5)	1.3 (0.6-3)	1.3 (1-3)
Percentage of lungs annotated	20 (0-50)	20 (10-40)	20 (10-50)
Lung length, mm	131.5 (80-333)	135.3 (72-351.3)	124 (77.5-264)
Lung width at the carina, mm*	95.5 (62-173)	75.5 (61-92)	103 (79-220)
Spirometry ^a			
FVC (SD)*	0.1 (-3.1-2)	-0.9 (-3.6-0.9)	0.3 (-0.8-1.3)
FEV1 (SD)	-0.6 (-4.4-1.4)	-1.6 (-4.6-1)	-1.7 (-2.5-1.7)
FEV1/VC (SD)	-0.8 (-2.9-0.8)	-1.1 (-3.1-0.7)	-1.9 (-3.3-1)
FEF25-75 (SD)	-1.2 (-5.2-0.5)	-1.3 (-4.1-0.8)	-2.5 (-3.2-1.2)
Bruce at 8 y (SD) ^b	-0.7 (-3.2-1.6)	-0.8 (-4.3-0.2)	-0.8 (-2.8-0.5)

Note: Data are presented as N (%) or median (range).

Abbreviations: Bruce, maximal exercise tolerance test according to bruce treadmill protocol; CT, computed tomography; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF25-75, forced expiratory flow at 25% to 75% of forced vital capacity.

^aAsymptomatic n = 31; symptomatic before CT n = 11; symptomatic after CT n = 7.

^bAsymptomatic n = 29; symptomatic before CT n = 11; symptomatic after CT n = 7.

*Significant difference between groups ($P < .05$; the Kruskal-Wallis test).

asymptomatic patients, which was attributable to the significantly more PHypoD, PHyperD, and consolidation.

3.4 | Cut-off

We determined optimal cut-off values for developing symptoms requiring surgical resection. For the total disease percentage we found a cut-off at 18% for cystic abnormalities (sensitivity 31%, specificity 98%, and accuracy 86%) and 17% for CLO (sensitivity 66%, specificity 89%, and accuracy 86%).

3.5 | Outcome prediction

Using decision tree regression, we found that the only determinant predicting the development of symptoms requiring a surgical intervention and exercise tolerance measured using the Bruce treadmill test, was lesional hyperdensity (LHyperD) with a cut-off at 4.4% (AUC = 0.73), and 6.4% (AUC = 0.66), respectively (Figure 2). The main determinant of an abnormal FEV₁ (Figure 3) was a lesion in the right middle lobe or multiple lobes, followed by a CLO or Hybrid BPS diagnosis (AUC = 0.83). The main determinant of abnormal FEF₂₅₋₇₅ (Figure 3) was a CPAM, CLO, or Hybrid BPS diagnosis, followed by a lesion in the left upper lobe or multiple lobes, and birthweight exceeding 3378 g (AUC = 0.89). Decision tree regression for predicting

abnormal FVC did not find any parameters which performed better than chance.

4 | DISCUSSION

To our knowledge, this is the first study to describe an objective scoring method to characterize and quantify disease extent on chest CT in CLA patients. Patients who underwent surgical resection due to symptoms had a significantly higher total disease percentage than asymptomatic patients managed by a wait-and-see policy. An increased risk for developing symptoms was found above the cut-off value of 18% total disease percentage. Lesional hyperdensity was found as an important predictor of symptom development and decreased exercise tolerance.

Our study cohort was comparable to that in previous studies in terms of distribution of CLA diagnoses,²³⁻²⁵ disease extent,^{26,27} development of symptoms, and reason for surgical resection. In our cohort, nearly two-thirds of patients remained asymptomatic, which proportion is comparable to that in previous studies ranging from 55% to 74%.²⁸⁻³⁰ However, this cohort consists of a selected group of patients who met our imaging inclusion criteria; conclusions regarding the total cohort of our center cannot be drawn. Similar to previous studies, the most common reasons for surgical resection were respiratory distress followed by recurrent infections.^{31,32}

We distinguished CLO from the cystic abnormalities because the clinical course as well as the radiological appearance of these

TABLE 2 CT and follow-up characteristics

TABLE 3 Congenital lung abnormality quantification (CLAQ) percentages

	CPAM/BPS/BC		CLO			
	Asymptomatic n = 63 (64%)	Symptomatic before CT n = 22 (22%)	Symptomatic after CT n = 14 (14%)	Asymptomatic n = 17 (68%)	Symptomatic before CT n = 6 (24%)	Symptomatic after CT n = 2 (8%)
<i>CLAQ score percentages</i>						
Cystic walls (CW)	1.9 (0-12.3)	17.8 (0-71.7)	0 (0-11.2)*	0 (0-0.1)	0 (0-0)	0 (0-0)
Lesional hypodensity (LHypoD)	0.1 (0-4.5)	0.5 (0-40.1)	0 (0-0.7)	0 (0-0)	0 (0-0)	0 (0-0)
Parenchymal hypodensity (PHypoD)	1.1 (0-12.6)	0 (0-28.6)	0 (0-12.1)*	7.8 (3.9-59.6)	47 (30.6-74)	23.6 (2.8-45)*
Lesional hyperdensity (LHyperD)	0 (0-7.5)	15.6 (0-41.4)	5.6 (0-31.6)*	0 (0-0)	0 (0-0)	0 (0-0)
Parenchymal hyperdensity (PHyperD)	0 (0-6.6)	0.4 (0-11.8)	0 (0-0.6)*	0 (0-2.8)	1 (0-7.4)	0 (0-0)*
Consolidation (CONS)	0 (0-5.3)	0 (0-29.5)	0.4 (0-17.2)	0.1 (0-7.4)	6.9 (1.2-14.1)	0.4 (0-0.7)*
<i>Composite CLAQ score percentages</i>						
Lesional abnormalities	3.2 (0-13.7)	41.6 (14.5-76.7)	5.6 (1.5-31.7)*	0 (0-0.1)	0 (0-0)	0 (0-0)
Parenchymal abnormalities	2.3 (0-12.6)	4.3 (0-30.6)	2.9 (0-17.2)	10.1 (3.9-61.7)	55.6 (46-80.4)	24.3 (3.2-45)*
Total disease (%Dis)	5.1 (0-19.1)	48.2 (15.6-84.9)	6 (1.5-36.6)*	7.8 (3.9-59.6)	51.4 (31.9-74.8)	23.6 (2.8-45)*

Note: Data are presented as N (%) or median (range).

Abbreviations: BC, bronchogenic cyst; BPS, bronchopulmonary sequestration; CLO, congenital lobar overinflation; CPAM, congenital pulmonary airway malformation.

*Significant difference between groups ($P < .05$; the Kruskal-Wallis test).

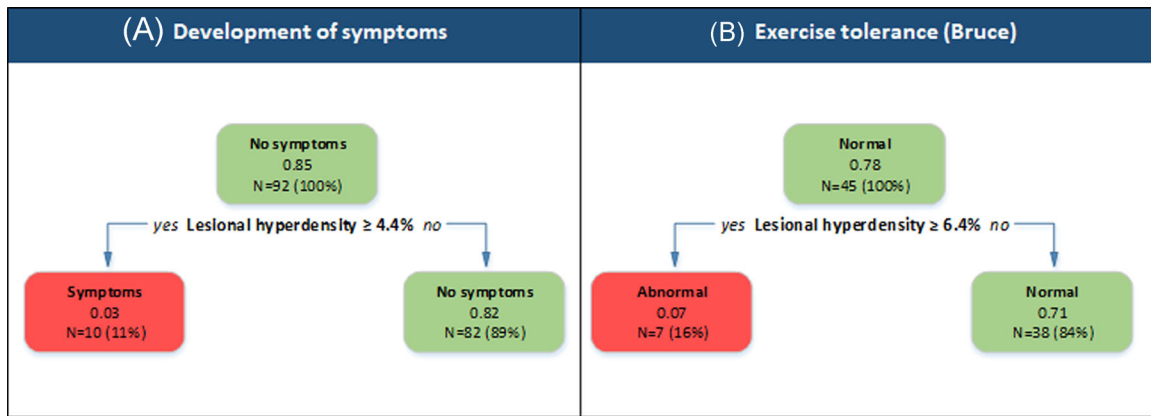


FIGURE 2 Decision tree models for predicting (A) development of symptoms and (B) exercise tolerance (Bruce treadmill test). Poor outcome is labeled red and good outcome green. Each node shows the predicted outcome, the probability of a good outcome, and the percentage of observations in that node. A, The probability of not developing symptoms is 0.85, which decreases to 0.03 if lesional hyperdensity is more than or equal to 4.4%. B, The probability of having a normal exercise tolerance (Bruce SD > -1.64) is 0.78, which decreases to 0.07 if lesional hyperdensity is more than or equal to 6.4% [Color figure can be viewed at wileyonlinelibrary.com]

abnormalities are quite different. While CLO presents as over-inflated, hypodense lung parenchyma on CT-imaging, which is not commonly seen in cystic abnormalities, none of the cyst-related abnormalities are seen in CLO.³³

Due to the current lack of consensus on the optimal management of asymptomatic CLA, studies identifying reliable and objective predictive factors are urgently needed. In our cohort, the CLAQ method was reproducible, as shown by the excellent interobserver and intraobserver reliability scores, similar to the Barcelona cohort which was used to develop the method. These scores were slightly better than the SALD and PRAGMA-CF scoring methods on which the

CLAQ method is based.^{4,13} A likely explanation is that CLA are focal and distinct abnormalities, which are easier to detect than a diffuse lung disease such as cystic fibrosis.

Quantitative imaging using the CLAQ method was shown to predict development of symptoms and exercise tolerance. The risk of developing symptoms was increased when more than 18% of the total lung volume was affected by the CLA. As a single lung lobe encompasses approximately 18% to 26% of total lung volume,¹⁷ lesions occupying or exceeding a whole lung lobe had a higher risk of becoming symptomatic, according to our cut-off value. A previous study suggested resection of lesions exceeding 25% of the ipsilateral lung, which amounts to 11% to

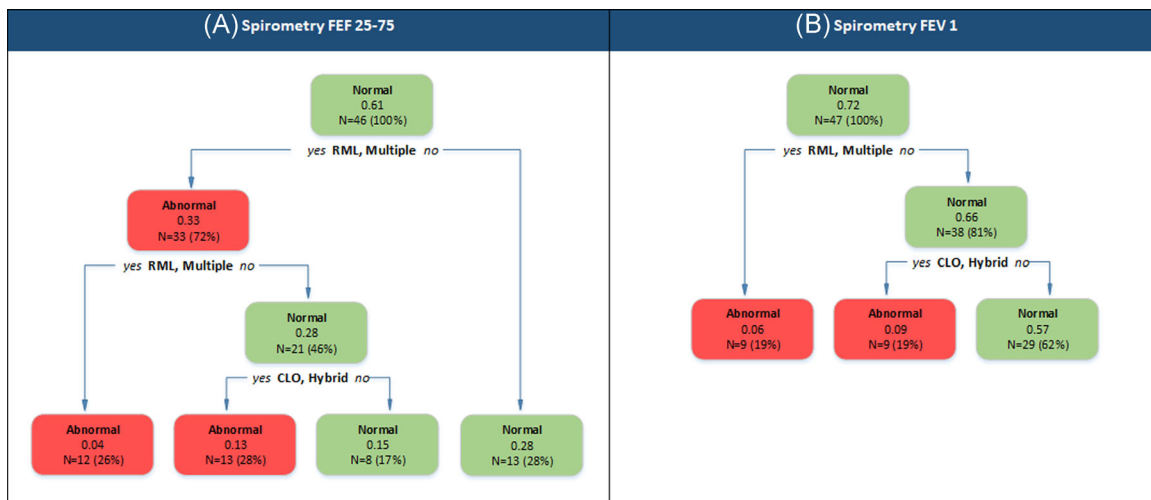


FIGURE 3 Decision tree models for predicting FEF₂₅₋₇₅ (A) and FEV₁ (B) measured at 8 years of age. Poor outcome is labeled red and good outcome green. Each node shows the predicted outcome, the probability of a normal SD score (> -1.64), and the percentage of observations within the node. A, The probability of having a normal FEF₂₅₋₇₅ (> -1.64) is 0.61, which decreases 0.33 if a CPAM, CLO, or Hybrid lesion is diagnosed. If the lesion is also located in the LUL or in multiple lobes the probability further decreases to 0.04. B, The probability of having a normal FEV₁ (> -1.64) is 0.72, which decreases to 0.06 if the lesion is located in the RML or in multiple lobes. CLO, congenital lobar overinflation, birthweight is in grams; CPAM, congenital pulmonary airway malformation; LUL, left upper lobe; RML, right middle lobe [Color figure can be viewed at wileyonlinelibrary.com]

14% of the total lung volume.³⁴ Although this percentage is lower than the cut-off we found, it was arbitrarily chosen.

Caution is warranted when using lesion size as an indication to operate asymptomatic patients, because the size of the lesion on imaging does not necessarily match the extent of the surgical resection. This is clear from the weak correlation between the total disease percentage on CT and the estimated percentage of resected lung tissue in the present study. This finding may be attributed to the frequent choice of lobectomy, which often requires healthy lung tissue to be resected as well, especially in small lesions.²⁶ A wedge resection is generally less preferable due to postoperative air leakage and residual disease in up to 15% of cases,⁸ in which malignant degeneration in the residual tissue remains a concern.³⁵ On the contrary, lesions may also appear larger on CT due to hyperinflation.²⁴

Identification of specific CT-features may be of value in predicting outcome for prospective studies. To this end, we assessed individual components of the CLAQ method and found that hyperdensity within lesions were associated with an increased probability of becoming symptomatic and having a lower exercise tolerance. Hyperdensity within lesions may be attributable to air-fluid levels which are seen within infected lesions.³⁶ Recurrent infection is a reason for resection and may lead to long-term respiratory sequelae.^{9,37}

In contrast, decreased long-term spirometry values of FEV₁ and FEF₂₅₋₇₅ were predicted by lesion location and diagnosis rather than individual components of the CLAQ method. We hypothesize that lesion location may influence maximum airflow measured by FEV₁ and airflow in the small airways measured by FEF₂₅₋₇₅. The type of lesion can have an influence on the amount of compression on the adjacent airways.

Our study is limited due to the retrospective study design and the use of different CT-imaging protocols over the years. Even though we used criteria to select CT-scans, the acquisition and image quality of CT-scans varied, which may have influenced the interpretation. Furthermore, a randomized stratified sample of approximately 20% of total lung tissue is scored with the CLAQ method. This is still considered a reliable sample of the lung, however, as we scored 20 CT-slices opposed to 10 slices in previously validated CT-quantification studies on diffuse lung diseases.^{15,38,39} The use of a hierarchical scoring system may have caused parameters which are lower in the hierarchy to be underreported. However, individual scoring of all abnormalities would be a time-intensive task that may be expedited by using machine learning methods in the future. Predictions in future studies may be improved by performing a prospective follow-up study, with a uniform imaging protocol and utilizing automatic whole lung segmentation, automated image analysis methods may be utilized in the future to expedite this process, although manual annotations will be needed for training the system.⁴⁰ Even though we analysed a decent-sized cohort, it concerned a heterogeneous group of diagnoses in a single-center, which may have introduced bias

In conclusion, the CLAQ method is a reproducible, objective scoring method to characterize and quantify disease extent in CLA

patients. Lesional hyperdensity was found as an important predictor of symptom development and decreased exercise tolerance. The risk for developing symptoms might be increased when more than 18% of the total lung volume, equal to a single lung lobe, is affected. The CLAQ method may be used to stratify patients into low- and high-risk groups which may need closer monitoring.

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CONFLICT OF INTERESTS

Prof Dr Tiddens is heading the Erasmus MC core laboratory Lung Analysis which is a non-profit core image analysis laboratory.

ORCID

Annelieke Hijkoop  <http://orcid.org/0000-0003-0833-8455>

REFERENCES

- Gajewska-Knapik K, Impey L. Congenital lung lesions: prenatal diagnosis and intervention. *Semin Pediatr Surg.* 2015;24(4):156-159.
- Crombleholme TM, Coleman B, Hedrick H, et al. Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. *J Pediatr Surg.* 2002; 37(3):331-338.
- Wong KKY, Flake AW, Tibboel D, Rottier RJ, Tam PKH. Congenital pulmonary airway malformation: advances and controversies. *Lancet Child Adolesc Health.* 2018;2(4):290-297.
- Rosenow T, Oudraad MC, Murray CP, et al. PRAGMA-CF. A quantitative structural lung disease computed tomography outcome in young children with cystic fibrosis. *Am J Respir Crit Care Med.* 2015; 191(10):1158-1165.
- Lo AY, Jones S. Lack of consensus among Canadian pediatric surgeons regarding the management of congenital cystic adenomatoid malformation of the lung. *J Pediatr Surg.* 2008;43(5):797-799.
- Morini F, Zani A, Conforti A, et al. Current management of congenital pulmonary airway malformations: a "European Pediatric Surgeons' Association" Survey. *Eur J Pediatr Surg.* 2018;28(1):1-5.
- Casagrande A, Pederiva F. Association between congenital lung malformations and lung tumors in children and adults: a systematic review. *J Thorac Oncol.* 2016;11(11):1837-1845.
- Stanton M, Njere I, Ade-Ajayi N, Patel S, Davenport M. Systematic review and meta-analysis of the postnatal management of congenital cystic lung lesions. *J Pediatr Surg.* 2009;44(5):1027-1033.
- Singh R, Davenport M. The argument for operative approach to asymptomatic lung lesions. *Semin Pediatr Surg.* 2015;24(4):187-195.
- Sauvat F, Michel JL, Benachi A, Emond S, Revillon Y. Management of asymptomatic neonatal cystic adenomatoid malformations. *J Pediatr Surg.* 2003;38(4):548-552.
- Stanton M. The argument for a non-operative approach to asymptomatic lung lesions. *Semin Pediatr Surg.* 2015;24(4):183-186.
- Priest JR, Williams GM, Hill DA, Dehner LP, Jaffe A. Pulmonary cysts in early childhood and the risk of malignancy. *Pediatr Pulmonol.* 2009; 44(1):14-30.
- Loeve M, van Hal PT, Robinson P, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. *Thorax.* 2009;64(10):876-882.

14. Dimeglio A, Canavese F. The growing spine: how spinal deformities influence normal spine and thoracic cage growth. *Eur Spine J.* 2012; 21(1):64-70.
15. Emans JB, Ciarlo M, Callahan M, Zurakowski D. Prediction of thoracic dimensions and spine length based on individual pelvic dimensions in children and adolescents: an age-independent, individualized standard for evaluation of outcome in early onset spinal deformity. *Spine (Phila Pa 1976).* 2005;30(24):2824-2829.
16. van Dijk M, Poley MJ, Gischler SJ, et al. Parental satisfaction with follow-up services for children with major anatomical congenital anomalies. *Child Care Health Dev.* 2010;36(1):101-109.
17. Seo H, Mori Y, Nakano S, et al. Quantitative evaluation of pulmonary ventilation dynamics using MR imaging: comparison of smokers and non-smokers. *Radiat Med.* 1999;17(2):131-135.
18. Hijkoop A, van Schoonhoven MM, van Rosmalen J, et al. Lung function, exercise tolerance, and physical growth of children with congenital lung malformations at 8 years of age. *Pediatr Pulmonol.* 2019; 54(8):1326-1334.
19. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33(1):159-174.
20. Youden WJ. Index for rating diagnostic tests. *Cancer.* 1950;3(1):32-35.
21. Breiman L, Friedman J, Stone CJ, Olshen RA. *Classification and Regression Trees.* Boca Raton, FL: CRC Press; 1984.
22. Hosmer DW Jr, Lemeshow S, Sturdivant RX. *Applied Logistic Regression.* Hoboken, NJ: John Wiley & Sons; 2013.
23. Burge D, Wheeler R. Increasing incidence of detection of congenital lung lesions. *Pediatr Pulmonol.* 2010;45(1):103.
24. Kunisaki SM, Saito JM, Fallat ME St, et al. Current operative management of congenital lobar emphysema in children: a report from the Midwest Pediatric Surgery Consortium. *J Pediatr Surg.* 2019;54(6): 1138-1142.
25. Stocker LJ, Wellesley DG, Stanton MP, Parasuraman R, Howe DT. The increasing incidence of foetal echogenic congenital lung malformations: an observational study. *Prenat Diagn.* 2015;35(2):148-153.
26. Andrade CF, Ferreira HP, Fischer GB. Congenital lung malformations. *J Bras Pneumol.* 2011;37(2):259-271.
27. Zylak CJ, Eyley WR, Spizarny DL, Stone CH. Developmental lung anomalies in the adult: radiologic-pathologic correlation. *Radiographics* 2002;22(suppl_1):S25-S43.
28. Calvert JK, Boyd PA, Chamberlain PC, Syed S, Lakhoo K. Outcome of antenatally suspected congenital cystic adenomatoid malformation of the lung: 10 years' experience 1991-2001. *Arch Dis Child Fetal Neonatal Ed.* 2006;91(1):F26-F28.
29. Hammond PJ, Devdas JM, Ray B, Ward-Platt M, Barrett AM, McKean M. The outcome of expectant management of congenital cystic adenomatoid malformations (CCAM) of the lung. *Eur J Pediatr Surg.* 2010;20(3):145-149.
30. Cook J, Chitty LS, De Coppi P, Ashworth M, Wallis C. The natural history of prenatally diagnosed congenital cystic lung lesions: long-term follow-up of 119 cases. *Arch Dis Child.* 2017;102(9):798-803.
31. Raychaudhuri P, Pasupati A, James A, Whitehead B, Kumar R. Prospective study of antenatally diagnosed congenital cystic adenomatoid malformations. *Pediatr Surg Int.* 2011;27(11):1159-1164.
32. Aziz D, Langer JC, Tuuha SE, Ryan G, Ein SH, Kim PC. Perinatally diagnosed asymptomatic congenital cystic adenomatoid malformation: to resect or not? *J Pediatr Surg.* 2004;39(3):329-334.
33. Chowdhury MM, Chakraborty S. Imaging of congenital lung malformations. *Semin Pediatr Surg.* 2015;24:168-175.
34. Davenport M, Warne SA, Cacciaguerra S, Patel S, Greenough A, Nicolaidis K. Current outcome of antenally diagnosed cystic lung disease. *J Pediatr Surg.* 2004;39(4):549-556.
35. Muller CO, Berrebi D, Kheniche A, Bonnard A. Is radical lobectomy required in congenital cystic adenomatoid malformation? *J Pediatr Surg.* 2012;47(4):642-645.
36. Ou J, Lei X, Fu Z, et al. Pulmonary sequestration in children: a clinical analysis of 48 cases. *Int J Clin Exp Med.* 2014;7(5):1355-1365.
37. Calzolari F, Braguglia A, Valfre L, Dotta A, Bagolan P, Morini F. Outcome of infants operated on for congenital pulmonary malformations. *Pediatr Pulmonol.* 2016;51(12):1367-1372.
38. Reske AW, Rau A, Reske AP, et al. Extrapolation in the analysis of lung aeration by computed tomography: a validation study. *Crit Care.* 2011; 15(6):R279.
39. Ball L, Braune A, Corradi F, et al. Ultra-low-dose sequential computed tomography for quantitative lung aeration assessment-a translational study. *Intensive Care Med Exp.* 2017;5(1):19.
40. Perez-Rovira A, Kuo W, Petersen J, Tiddens HA, de Bruijne M. Automatic airway-artery analysis on lung CT to quantify airway wall thickening and bronchiectasis. *Med Phys.* 2016;43(10):5736.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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