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A Validated Model for the Imaging Diagnosis of Cystic Lung Disease

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Abstract

Rationale and Objectives: Cystic lung disease may be accurately diagnosed by imaging interpretation of specialist radiologists, without other information. We hypothesized that with minimal training non-specialists could perform similarly to specialist physicians in the diagnosis of cystic lung disease. **Methods:** 72 cystic lung disease cases and 25 cystic lung disease mimics were obtained from three sources: 1) a prospective acquired diffuse lung disease registry, 2) a retrospective search of medical records and 3) teaching files. Cases were anonymized, randomized and interpreted by 7 diffuse lung disease specialists and 15 non-specialist radiologists and pulmonologists. Clinical information other than age and sex was not provided. Prior to interpretation, non-specialists viewed a short PDF training document explaining cystic lung disease interpretation. **Results:** Correct first choice diagnosis of 85% - 88% may be achieved by high-performing specialist readers and 71% - 80% by non-specialists and lower-performing specialists, with mean accuracies in the diagnosis of LAM (91%, $p < 0.0001$), BHD (93%, $p < 0.0001$), PLCH (89%, $p < 0.0001$) and LIP (92%, $p < 0.0001$). A strategy based on cyst appearance: simple cysts (LAM), peri-septal cysts (BHD), bizarre-shaped cysts (PLCH) and vascular indented cysts (LIP) gave non-specialists accuracies of 90% ($p < 0.0001$), 94% ($p < 0.0001$),

92% ($p < 0.0001$) and 88% ($p < 0.0001$), respectively, for these diagnoses. Cystic lung abnormalities caused by diseases other than LAM, BHD, PLCH and LIP are rarely accurately diagnosed by imaging alone. **Conclusion:** With specific but limited training, non-specialist physicians can diagnose cystic lung diseases from CT appearance alone with similar accuracy to specialists, correctly identifying approximately 75% of cases.

Keywords

Lymphangioleiomyomatosis, Histiocytosis, Langerhans-Cell, Idiopathic Interstitial Pneumonias, Birt-Hogg-Dube Syndrome, Lung Diseases, Interstitial, Diagnoses, Differential

1. Introduction

Widespread cystic lung disease is an uncommon imaging finding that may be clinically irrelevant or cause significant morbidity and mortality. Pulmonary cysts appear as low-attenuation regions with a surrounding wall and are often round or oval in shape, but other appearances may occur [1].

The most common causes of cystic lung disease are Lymphangioleiomyomatosis (LAM), Langerhans Cell Histiocytosis (PLCH), Birt-Hogg-Dube (BHD) syndrome and Lymphocytic Interstitial Pneumonia (LIP) [2] [3] [4] [5] [6]. Other causes include metastases, amyloidosis, neurofibromatosis, light-chain deposition disease, pneumocystis pneumonia, hypersensitivity pneumonitis, pulmonary interstitial glycogenosis and nonspecific interstitial pneumonia [2]-[12].

Most diffuse parenchymal lung diseases require clinical information to establish a diagnosis. However, the imaging appearance of cystic lung diseases is often diagnostic, even without clinical information [3] [13] [14]. Prior studies indicate that experts may be highly accurate in the diagnosis of cystic lung disease based on imaging appearance alone [2] [13]. Previous studies have suggested that pulmonologists and trainees perform less well than chest radiologists [2]. Our hypothesis was that limited training with a simple strategy based on cyst appearance would allow non-specialists to achieve similar accuracy to experts in the diagnosis of cystic lung disease.

2. Materials and Methods

The authors have no conflict of interest, the study is IRB-approved (IRB# 820774) and HIPA compliant. Informed consent was waived by the IRB. We acquired all cases of cystic lung disease available from a single medical center, from three sources: 1) our institution prospectively acquired diffuse lung disease registry, 2) a retrospective search of medical records, and 3) teaching files.

Our institution began a diffuse lung disease registry in January 2013. To be entered into the registry, cases were evaluated jointly by two pulmonologists, a thoracic radiologist and a pulmonary pathologist and classified by cause and confi-

dence in the diagnosis. Thirty-nine cases with moderate or high confidence diagnosis of cystic lung disease were included in this study (Figure 1).

Our radiology information system database was searched using a commercially available search engine (MONTAGE™ Search and Analytics, Nuance mPower Clinical Analytics, Nuance Communications, Inc.) from 2012-2018 for 5 thoracic CT exam codes and the following search terms: "lymphangioleiomyomatosis", "LAM", "Langerhans cell histiocytosis", "PLCH", "eosinophilic granuloma", "Birt-Hogg-Dube", "Birt Hogg Dube", "lymphocytic interstitial pneumonia", "LIP" and "cystic PCP". The time frame was chosen to match that of the ILD registry resulting in 270 cases.

CT reports and a limited evaluation of medical records separated cases into those likely or unlikely to meet criteria for a diagnosis of cystic lung disease. Causes for exclusion at this stage included, 1) no evaluation by a pulmonologist (n = 118), 2) duplicate cases (n = 27), 3) other lung disease diagnosed (n = 18), 4) a history of disease without imaging findings (n = 9), 5) superimposed lung disease (n = 6). Cases without a pulmonologist evaluation were excluded because analysis showed these cases were unlikely to have sufficient documentation to prove a diagnosis. Each "likely case" received an extensive review of medical records by two individuals independently, a chest radiologist and pulmonologist specializing in diffuse lung disease to determine if the case met criteria for a diagnosis of a cystic lung disease (LAM and LIP: American Thoracic Society guidelines [14] [15], PLCH: guidelines by Girschikofsky [16], BHD: guidelines by Menko [17]). Both reviewers had to agree on a diagnosis for study inclusion, adding 31 cases to the study. Teaching file case diagnoses were also confirmed by agreement following independent review of the medical record by both reviewers, adding 27 cases to the study (Figure 1).

The database was augmented with cases of emphysema, cystic bronchiectasis and honeycombing that might be confused with cystic lung disease. Proof of diagnosis followed the same protocol as the cystic lung diseases, but cases were selected for a high likelihood of confusion with cystic lung disease.

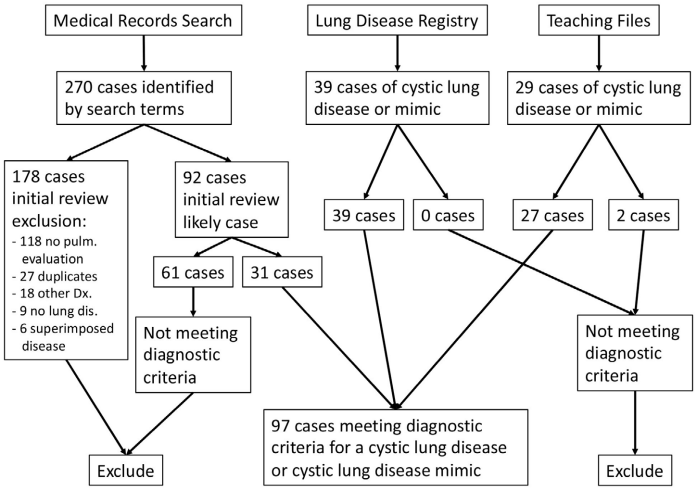


Figure 1. Source of cases for the cystic lung disease database.

Searches yielded a total of 72 cystic lung disease cases and 25 cystic mimics.

2.1. Reviewers

Cases were anonymized, randomized and blindly reviewed by 22 individuals of varying experience for the diagnosis of cystic lung disease. Reviewers were recruited from several medical centers in our metropolitan area. Seven reviewers were specialists in thoracic imaging or pulmonologists specializing in diffuse lung diseases. The remaining reviewers were non-specialist radiologists or pulmonologists. The reviewers had not previously been exposed to the any cases used in the study.

2.2. Training Algorithm

Two separate training documents were created and tested. A PDF document of 12 PowerPoint slides, which is a synopsis of the experience of the first author, a radiologist with 24 years of subspecialty experience, outlined a method with imaging examples, for distinguishing cystic lung diseases. The algorithm is similar to one independently proposed by another group [3] and is follows a pattern typically used by chest radiologists. The critical points of the document are as follows:

1) True cysts must be distinguished from honeycombing, emphysema, and cystic bronchiectasis.

2) Most common cystic lung diseases are: LAM, PLCH, BHD and LIP.

3) Simple cysts have round or oval shape and a thin wall.

4) Number of cysts may be helpful in the diagnosis. High profusion simple cysts (defined as ≥100) (**Figure 2**) is usually LAM. A low profusion of simple cysts (defined as <50) is usually BHD or LIP.

5) Appearance of BHD cysts may be peri-septal or peri-pleural and lenticular in shape (**Figure 3**).

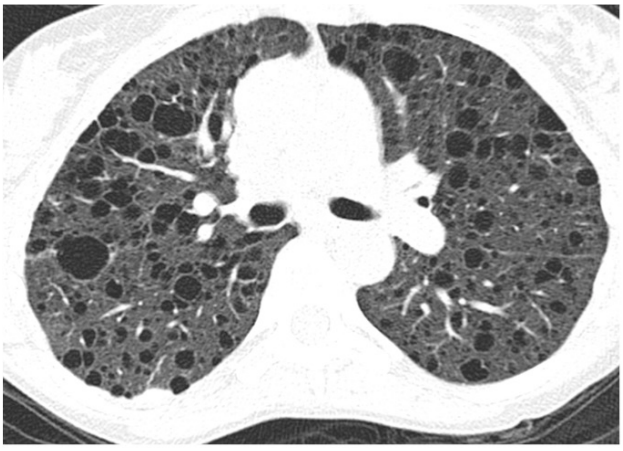


Figure 2. Simple cysts. This 29-year-old woman had a history of tuberous sclerosis and multiple spontaneous pneumothoraxes. The CT exam shows a high profusion of round or oval, thin walled (simple) cysts.

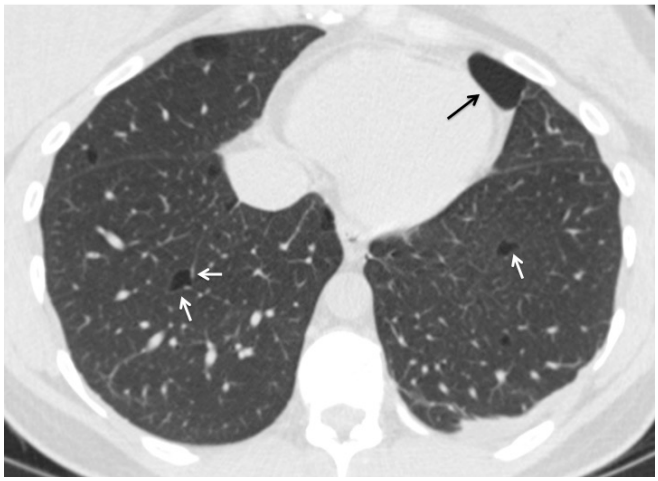


Figure 3. Birt-Hogg-Dube (BHD) type cysts. This 33-year-old woman presented with a spontaneous pneumothorax. Two lower lobe cysts have a vague lenticular shape. This is because sides of the cysts are created by borders of secondary pulmonary lobules (white arrows). These peri-septal cysts are typical of BHD. There is also a larger cyst adjacent to the pleura (peri-pleural) (black arrow). Evaluation of performance after Round 1, suggested that this feature introduced diagnostic error in the diagnosis of BHD and was excluded as a criterion in the second teaching document.

6) Appearance of PLCH cyst may be irregularly or bizarrely shaped and/or thick walled (**Figure 4**).

Analysis of results of the first round of cases showed deficiencies in the training document and a second training document was created, with five principal changes: 1) Cyst counting was discarded and LAM was recommended as first choice diagnosis of all simple cysts in women and PLCH as first diagnosis in men, 2) BHD-type cysts were defined as peri-septal (removing peri-pleural from the criteria), 3) PLCH-type cysts were defined as irregularly or bizarrely shaped (removing thick walled as a criterion), 4) cheerio-type cysts (small thick walled cysts) were explained to be caused by a variety of diseases, usually PLCH and metastasis in approximately equal frequency (**Figure 5**), 5) LIP-type cysts were defined as those containing vascular indentations or septations (**Figure 6**).

2.3. Image Review

Images were viewed using a DICOM imaging database (Horus, 2019 Horus project, https://horosproject.org/) on each reader's personal computer. Horus allows for scrollable images, window/level conversion and coronal and axial reconstructions. Reviewers were blinded to clinical information, except age and sex. Reviewers were aware that the database contained a variety of cystic lung diseases and cystic mimics but were unaware of the relative frequencies within the database.

Specialists reviewed the cases without other input. In Round 1, 8 non-specialist

reviewers were given the first training document prior to case interpretation. In Round 2, non-specialists numbers 2 and 5 reviewed the second training document and re-evaluated cases for the diagnosis of disease an average of 4 months after the previous interpretation session. An additional 7 new non-specialists were given the second training document prior to evaluation of cases.

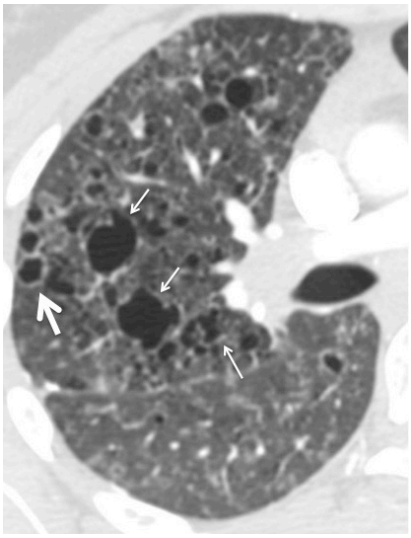
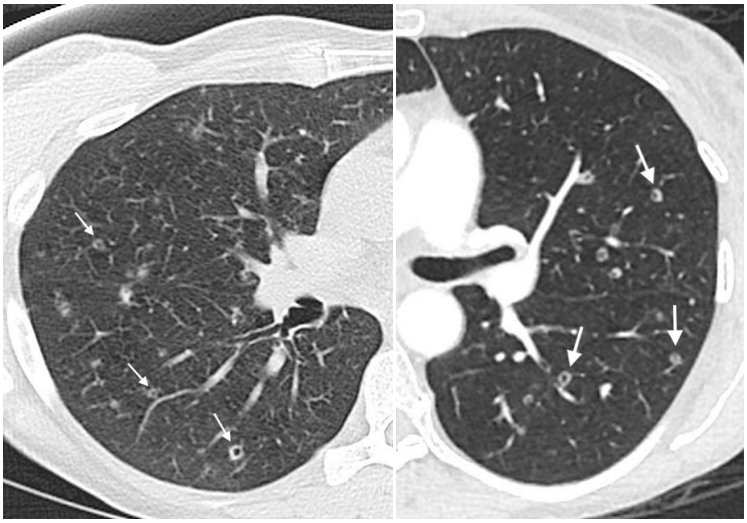


Figure 4. Langerhans Cell Histiocytosis (PLCH) type cysts. This 23-year-old woman had a 10-pack year smoking history. Small arrows demonstrate irregularly, bizarrely shaped cysts, these are characteristic of PLCH and usually indicate a diagnosis of PLCH. The large arrow shows a thick-walled cyst that can be seen in PLCH but is not specific.



(a) (b)

Figure 5. Cheerio type cysts in LCH and metastasis. (a) This 54-year-old woman had a chronic cough. The CT image shows several small thick-walled cysts proven to be due to LCH. (b) This 54-year-old woman had a history of colon cancer. The CT image shows several thick-walled cysts due to metastasis.

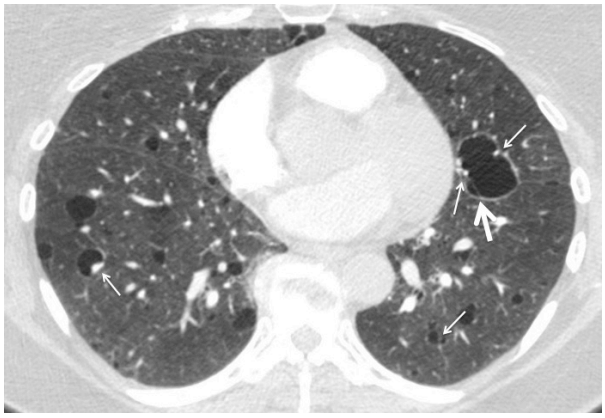


Figure 6. Lymphocytic Interstitial Pneumonia (LIP) type cysts. This 56-year-old woman had a history of Sjogren syndrome. There are three cysts where the wall is indented by blood vessels (small arrows). One also has a thin septation (large arrow). These features often indicate a diagnosis of LIP.

Reviewers were asked to provide the 1st, 2nd and 3rd most likely diagnoses for each case to simulate a typical differential diagnosis given in radiology reports. Answers were selected from a drop-down menu: LAM, PLCH, BHD, LIP, honeycombing, bronchiectasis, emphysema and other diagnosis. If "other diagnosis" was selected, an additional free text box was supplied. Non-specialist reviewers in Round 1 were asked to provide the cyst character and cyst number from specified lists. Cyst character choices were: 1) true cyst: thin wall round or oval, 2) true cyst: thick wall and/or bizarre shape, 3) true cyst: lenticular, subpleural and/or peri-septal, 4) true cyst: other, 5) honeycombing, 6) emphysema, 7) cystic bronchiectasis. Cyst number choices: 1) ≥100, 2) <50, 3) 51 - 99, 4) <5, and 5) Not applicable. Reviewers in Round 2 were asked to evaluate for cyst character with choices: 1) Simple-type, 2) BHD-type, 3) PLCH-type, 4) LIP type, 5) cheerio-type, 6) other.

2.4. Statistical Evaluation

Data were imported into the R statistical environment for analyses [18]. Basic statistical tabulations were made to count the number of correct diagnoses for each rater. Diagnostic performance was assessed for each rater by calculating sensitivity, specificity Positive Predictive Value (PPV), Negative Predictive Value (NPV), and accuracy for each diagnosis separately (*i.e.* LAM, LCH, LIP, BHD, Mimics). Total accuracy (*i.e.* irrespective of specific diagnoses) was also assessed. For each rater, Receiver Operating Characteristic (ROC) curves were generated for each diagnosis, and the Area under the Curve (AUC) was estimated. In addition to individual measures, group estimates (e.g. pulmonary specialists as a whole) were estimated based on group means. 95% confidence intervals for proportions were estimated based on the formula:

$$\hat{p} \pm z * \sqrt{\frac{\hat{p} * (1 - \hat{p})}{N}}$$

where $\hat{p}$ represents the proportion, N the sample size, and $z = 1.96$. Categorical variables were also evaluated for statistical significance with two-tailed Fisher's exact tests.

3. Results

3.1. Characteristics of the Database

The patients' age ranged from 20 to 86 years with both mean and median ages of 48 years. Women accounted for 71/97, 73% of patients. The causes, frequency and source of cases are listed in Table 1.

3.2. Reader Performance

Table 2 lists the clinical experience of the reviewers and the fraction of correct 1st choice and 1st and 2nd choice diagnoses. Rad-specialists 1 and 2 performed better than all other readers with 1st diagnosis true positive rates of 87% and 82%, respectively. Utilizing the first teaching tool, two non-specialist readers, a 3rd year radiology resident and a general pulmonologist were able to outperform rad-specialists 3 and 4 and the two pulmonary specialists. Four additional non-specialists: a body imaging fellow, interventional radiologist, body imaging radiologist and a 2nd year radiology resident performed similarly to rad-specialists 4 and 5 and the two pulmonary specialists.

Using the second teaching tool, two non-specialists (general pulmonologist, body imaging radiologist) outperformed rad-specialists 3 and 4 and the two pulmonary specialists. Five other non-specialists (two 4th year radiology residents, one 3rd year radiology resident, and two 2nd year radiology residents) performed similarly to rad-specialists 4 and 5 and the two pulmonary specialists.

Table 3 shows the performance of readers for the correct first choice diagnosis of LAM, BHD, LIP, LCH and non-cystic lung disease respectively. Rad-specialists 1 and 2 achieved accuracies of greater than 94% for each of the five specific diagnoses. The accuracy of diagnosis was high, usually >80% for all readers individually. Of the 115 diagnostic accuracies measured (23 readers × 5 categories), 86 (75%) were ≥90% among both specialists and non-specialists. In general, across both rounds, the lowest performance measures for all diseases were the sensitivity and PPV.

Figure 7 shows the mean and standard deviation of the area under the ROC curve for each of the reader groups for each of the diseases, showing overlap in the performance of all readers. However, two rad-specialists, 1 and 2, did generally better than all other readers for all diseases. The performance of rad-specialists 3 and 4, the pulmonary specialists and the non-specialists for each diagnosis is nearly indistinguishable. LIP was the most problematic diagnosis with the lowest average area under the ROC curve and the greatest variance among all readers. The training algorithms in Round 1 and Round 2 performed similarly, with the exception of the diagnosis of LIP, where the second algorithm resulted in substantial improvement in diagnosis.

Table 1. Causes of cystic lung disease and cystic mimics.

Cystic Disease	DLD Registry*	MR Search^	Teaching File	Total
LAM	19	1	10	30
PLCH	4	5	4	13
BHD	2	13	1	16
LIP	2	5	0	7
Cystic Metastasis	0	0	3	3
Amyloidosis	0	0	1	1
Neurofibromatosis	0	1	0	1
Sarcoidosis	1	0	0	1
IPF	0	1	0	1
Total Cystic Disease	**28**	**26**	**19**	**73**
Cystic Mimics				
Emphysema	1	4	4	9
Honeycombing				
IPF	2	0	0	2
CTD	3	0	0	3
HP	1	0	1	2
Sarcoidosis	4	1	0	5
Cystic Bronchiectasis	0	0	3	3
Total Mimics	**11**	**5**	**8**	**24**
Grand Total	**39**	**31**	**27**	**97**

*Diffuse lung disease registry; ^Medical records search.

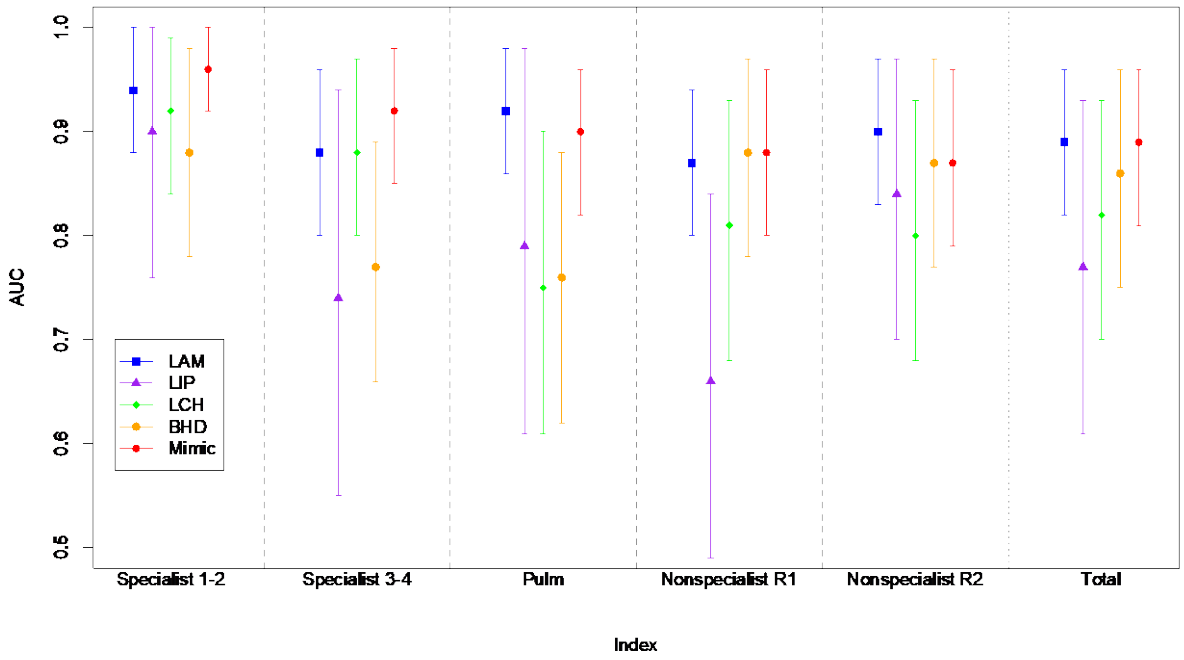


Figure 7. Areas under the ROC curve for reader type and clinical diagnosis. The figure shows the mean and standard deviation of the area under the ROC curve for each reader group and each diagnosis.

Table 2. Diagnostic accuracy of cystic lung disease diagnosis as a function of training.

Reader	Specialty	Years Practice	Pulm ILD+	Dx1 TP*	Dx1-2 TP^
Rad-specialist 1	Radiology (Thoracic)	5	5 yr	83 (86)	87 (91)
Rad-specialist 2	Radiology (Thoracic)	5	5 yr	79 (82)	81 (84)
Rad-specialist 3	Radiology (Thoracic)	8	4 yr	73 (75)	81 (84)
Rad-specialist 4	Radiology (Thoracic)	1	1 yr	67 (70)	78 (81)
Pulm-specialist 1	Pulmonology (DLD specialist)	7	7 yr	66 (69)	71 (74)
Pulm-specialist 2	Pulmonology (DLD specialist)	5	5 yr	68 (71)	74 (77)
Round 1					
Non-specialist 1	Radiology (3rd Year Resident)	3	2 mo	78 (81)	80 (83)
Non-specialist 2	Pulmonology (General)	14	6 mo	73(76)	76 (79)
Non-specialist 3	Radiology (Body Imaging Fellow)	6	6 mo	69 (72)	77 (80)
Non-specialist 4	Radiology (Interventional)	6	4 mo	71 (74)	77 (79)
Non-specialist 5	Radiology (Body Imaging)	13	4 mo	69 (72)	74 (77)
Non-specialist 6	Radiology (2nd Year Resident)	1.8	2 mo	67 (70)	75 (78)
Non-specialist 7	Radiology (1st Year Resident)	0.8	1 mo	55 (58)	69 (72)
Non-specialist 8	Radiology (2nd Year Resident)	1.8	3 mo	54 (57)	69 (72)
Round 2					
Non-specialist 2	Pulmonology (General)	14	6 mo	77 (80)	83 (87)
Non-specialist 5	Radiology (Body Imaging)	13	4 mo	79 (82)	86 (90)
Non-specialist 9	Radiology (4th Year Resident)	3.3	3 mo	75 (78)	87 (91)
Non-specialist 10	Radiology (4th Year Resident)	3.3	3 mo	72 (75)	76 (79)
Non-specialist 11	Radiology (3rd Year Resident)	2.3	3 mo	72 (75)	73 (76)
Non-specialist 12	Radiology (2nd Year Resident)	1.3	1 mo	73 (76)	87 (91)
Non-specialist 13	Radiology (2nd Year Resident)	1.3	2 mo	69 (72)	82 (86)
Non-specialist 14	Radiology (2nd Year Resident)	1.3	2 mo	64 (66)	75 (78)
Non-specialist 15	Radiology (1st Year Resident)	0.3	1 mo	64 (67)	71 (74)

+Years of specialization in thoracic radiology (radiologists) or pulmonary diffuse infiltrative lung disease (pulmonologists) or months of specific training in thoracic radiology or diffuse infiltrative lung disease. *Frequency of 1st choice correct diagnosis (% correct in parentheses). ^Frequency that correct diagnosis was in the top 2 diagnoses (% correct in parentheses).

3.3. Rare Causes of Cystic Lung Disease

There were 7 cases of cystic disease (9.6%) that were not one of the four common causes: 3 cases of cystic metastases and one each of amyloidosis, neurofibromatosis, sarcoidosis and idiopathic pulmonary fibrosis. None of these, except for cystic metastasis, were correctly diagnosed by any reader. Correct diagnosis of cystic metastasis was made in 2/12 (17%) instances by rad-specialists. Non-specialists correctly diagnosed cystic metastasis in 0/24 instances in Round 1 and in 15/27 (55%) instances in Round 2 after specific training regarding cheerio type cysts was given in the second training document.

Table 3. Reader performance in the diagnosis of LAM, BHD, PLCH, LIP and cystic mimics.

Reader	Sensitivity	Specificity	PPV	NPV	Accuracy
Lymphangioleiomyomatosis (N = 30)					
Rad-specialists 1-2	**90** (84 - 96)	**99** (96 - 99)	**97** (93 - 99)	**96** (92 - 99)	**96** (92 - 99)
Rad-specialists 3-4	**80** (72 - 88)	**96** (91 - 99)	**89** (83 - 95)	**91** (86 - 97)	**91** (85 - 96)
Pulmonary Specialists	**92** (86 - 97)	**92** (86 - 97)	**84** (77 - 91)	**96** (92 - 99)	**92** (86 - 97)
Round 1 Non-specialists	**81** (73 - 89)	**94** (89 - 99)	**86** (79 - 93)	**92** (86 - 97)	**90** (84 - 96)
Round 2 Non-specialists	**86** (79 - 93)	**94** (89 - 98)	**86** (79 - 93)	**94** (89 - 99)	**91** (86 - 97)
All Readers	**84** (77 - 92)	**94** (89 - 99)	**87** (80 - 94)	**93** (88 - 98)	**91** (85 - 97)
Birt Hogg Dube Syndrome (N = 16)					
Rad-specialists 1-2	**78** (70 - 86)	**99** (97 - 99)	**94** (89 - 99)	**96** (92 - 99)	**95** (91 - 99)
Rad-specialists 3-4	**56** (46 - 66)	**98** (95 - 99)	**90** (84 - 96)	**92** (87 - 97)	**91** (86 - 97)
Pulmonary Specialists	**56** (46 - 66)	**94** (90 - 99)	**68** (58 - 77)	**92** (86 - 97)	**88** (82 - 95)
Round 1 Non-specialists	**81** (73 - 89)	**94** (89 - 99)	**73** (64 - 82)	**96** (92 - 99)	**92** (86 - 97)
Round 2 Non-specialists	**77** (69 - 85)	**97** (94 - 99)	**86** (79 - 93)	**96** (91 - 99)	**94** (89 - 99)
All Readers	**75** (66 - 84)	**96** (92 - 99)	**81** (73 - 89)	**95** (91 - 99)	**93** (87 - 98)
Langerhans Cell Histiocytosis (N = 13)					
Rad-specialists 1-2	**88** (82 - 95)	**95** (91 - 99)	**76** (67 - 84)	**98** (96 - 99)	**94** (90 - 99)
Rad-specialists 3-4	**85** (77 - 92)	**92** (87 - 98)	**68** (59 - 77)	**98** (95 - 99)	**91** (86 - 97)
Pulmonary Specialists	**58** (48 - 68)	**92** (87 - 98)	**54** (44 - 64)	**93** (88 - 98)	**88** (81 - 94)
Round 1 Non-specialists	**75** (66 - 84)	**86** (79 - 93)	**47** (37 - 57)	**96** (92 - 99)	**85** (78 - 92)
Round 2 Non-specialists	**68** (59 - 78)	**92** (87 - 97)	**59** (49 - 69)	**95** (91 - 99)	**89** (83 - 95)
All Readers	**73** (64 - 82)	**90** (85 - 96)	**57** (47 - 67)	**96** (92 - 99)	**88** (82 - 94)
Lymphocytic Interstitial Pneumonia (N = 7)					
Rad-specialists 1 - 2	**86** (79 - 93)	**95** (91 - 99)	**61** (51 - 70)	**99** (97 - 99)	**94** (90 - 99)
Rad-specialists 3 - 4	**57** (47 - 67)	**92** (87 - 98)	**51** (41 - 61)	**97** (93 - 99)	**90** (84 - 96)
Pulmonary Specialists	**64** (55 - 74)	**96** (91 - 99)	**56** (46 - 66)	**97** (94 - 99)	**93** (88 - 98)
Round 1 Non-specialists	**36** (26 - 45)	**97** (94 - 99)	**56** (46 - 65)	**95** (91 - 99)	**93** (88 - 98)
Round 2 Non-specialists	**76** (68 - 85)	**93** (88 - 98)	**47** (37 - 57)	**98** (95 - 99)	**92** (86 - 97)
All Readers	**60** (51 - 70)	**95** (90 - 99)	**52** (42 - 62)	**97** (93 - 99)	**92** (87 - 98)
Cystic Lung Disease Mimics (N = 24)					
Rad-specialists 1 - 2	**96** (92 - 99)	**97** (93 - 99)	**91** (85 - 97)	**99** (96 - 99)	**96** (93 - 99)
Rad-specialists 3 - 4	**90** (84 - 96)	**94** (89 - 99)	**83** (76 - 92)	**96** (93 - 99)	**93** (88 - 98)
Pulmonary Specialists	**84** (77 - 91)	**94** (90 - 99)	**85** (78 - 92)	**95** (90 - 99)	**92** (86 - 97)
Round 1 Non-specialists	**80** (71 - 88)	**96** (92 - 99)	**88** (81 - 94)	**93** (88 - 98)	**92** (86 - 97)
Round 2 Non-specialists	**77** (69 - 86)	**97** (94 - 99)	**92** (86 - 97)	**93** (87 - 98)	**92** (87 - 98)
All Readers	**81** (74 - 89)	**96** (92 - 99)	**89** (83 - 95)	**94** (89 - 99)	**92** (87 - 98)

Table 4. Performance of cyst characteristics in diagnosing cystic lung diseases by non-specialists.

Cyst Type	Sensitivity	Specificity	PPV	NPV	Accuracy
Simple Cyst (LAM)					
Non-specialists	**88** (83 - 91)	**91** (89 - 93)	**83** (78 - 96)	**94** (92 - 96)	**90** (88 - 92)
Simple Cyst + Female* (LAM)					
Non-specialists	**91** (86 - 94)	**94** (91 - 95)	**86** (82 - 89)	**96** (94 - 97)	**92** (91 - 94)
BHD-type					
Non-specialists	**76** (68 - 82)	**98** (96 - 99)	**86** (80 - 91)	**95** (94 - 96)	**94** (92 - 96)
LIP-type					
Non-specialists	**73** (60 - 83)	**93** (91 - 95)	**45** (38 - 52)	**98** (97 - 99)	**92** (89 - 93)
PLCH-type					
Non-specialists	**38** (30 - 48)	**96** (94 - 97)	**59** (49 - 69)	**91** (90 - 92)	**88** (86 - 90)

*If both simple cyst and female as criteria for Dx of LAM

3.4. Causes of Misdiagnosis

There was a subset of cases that accounted for the majority of the remaining diagnostic errors. For 22 cases (23%) in Round 1, ≤50% of observers (0 - 7/14 observers) correctly diagnosed disease. For 22 cases (23%) in Round 2, ≤55% of observers (0 - 5/9 observers) correctly diagnosed disease. Seven cases were the uncommon cystic diseases discussed previously and two were cases where superimposed emphysema confused the case. The majority of misdiagnosed cases were confined to a small number of the common causes of cystic lung disease: LAM, PLCH, BHD and LIP (5 LIP, 3 LAM, 2 BHD and 2 PLCH in Round 1 and 4 BHD, 3 LAM, 3 PLCH, 1 LIP and 4 cystic mimics in Round 2).

3.5. Evaluation of Diagnostic Strategies

We employed two different teaching strategies. Round 1 used a combination of cyst characteristics and cyst number to inform a diagnosis similar to current conventional teaching strategies. Round 2 relied exclusively on the recognition of five cyst types: 1) simple-type, 2) BHD-type, 3) PLCH-type, 4) LIP-type and 5) cheerio-type. Strategy 2 slightly outperformed strategy 1, predominantly because of improved diagnosis of LIP. Two individuals, non-specialists 2 and 5 were involved in both rounds of testing and both improved with the second strategy.

The performance characteristics of the various cyst types for their respective diseases are listed in Table 4. In general, the cyst types are moderately to highly specific for the disease with specificities from 91% - 100%. However, with the exception of simple cysts for the diagnosis of LAM, the sensitivity of cyst types was moderate to low.

4. Discussion

Our study and others [2] [3] [13] [19] indicate that cystic lung diseases can be accurately diagnosed based solely on imaging characteristics, with a correct first-choice

diagnosis of as high as 86% by the best-performing specialists. This accuracy is principally due to the diagnosis of the most common cystic lung diseases: LAM (combined accuracy 91%), BHD (combined accuracy of 93%), LIP (combined accuracy of 92%) and PLCH (combined accuracy of 88%). Previous reports have shown similar accuracy in the diagnosis of LAM and LIP but lesser accuracy in the diagnosis of PLCH [2].

Previous studies have suggested that pulmonologists and trainees perform less well than chest radiologists [2], a finding we also showed when comparing non-specialists with our highest-performing chest radiologists. However, we have demonstrated that with minimal training, non-specialist radiologists and pulmonologists can also have high performance with the correct first choice diagnosis of as high as 82% which is similar to some specialists.

We devised two training strategies, both of which helped non-specialist readers achieve moderate to high accuracy in the diagnosis of common cystic lung diseases. The second training strategy performed slightly better than the first. This second strategy is simpler and is based on the recognition of 4 cyst types: Simple-type, BHD-type, PLCH-type and LIP-type cysts that are moderate to highly predictive of LAM, BHD, PLCH and LIP respectively.

Misdiagnosis related to the cheerio sign, small thick-walled cysts, was an important cause of reduced accuracy, a finding that has not been noted by prior studies. This sign, which is commonly associated with PLCH, was therefore interpreted as PLCH by nearly all reviewers in Round 1. However, in our database, metastasis, another known cause of the cheerio sign [7] [15], accounted for half of the cases. In Round 2, the training document specifically noted that the cheerio sign could be caused by both metastasis and PLCH and suggested that lower predominant cheerio signs are likely metastasis and upper predominant cheerio signs are likely PLCH. This strategy reduced, by half, diagnostic errors of cheerio-type cysts. Other reported causes of the cheerio sign include, amyloidosis (present in our database) adenocarcinoma spectrum lesions, primary lung carcinoma, granulomatosis with polyangiitis, rheumatoid nodules and pulmonary meningothelial-like nodules [20] [21]. If our database is representative of the general population, cheerio-type cysts are caused by metastasis and PLCH in approximately equal frequency.

To simulate clinical practice, we included lung diseases such as emphysema, cystic bronchiectasis and severe honeycombing that might be confused with cystic lung disease, a confounding factor that previous studies have not included [2] [3] [13] [19]. We have shown that readers can usually distinguish cystic lung diseases from mimics with a combined accuracy of 92%.

In our database, a significant fraction of diagnostic errors were due to rare causes of cystic lung disease including cystic metastases, amyloidosis, neurofibromatosis, sarcoidosis, and idiopathic pulmonary fibrosis. With the exception of cystic metastasis, none of these diagnoses were correctly diagnosed. Imaging alone is usually not adequate to diagnose these cases.

The majority of the remainder of diagnostic errors occurred in a small subset

of cases, 13 - 15 of 97 cases, or 13% - 15% in our database. This finding suggests that in most cases, approximately 85% - 87%, of LAM, BHD, PLCH and LIP produce cysts with the characteristic cyst features outlined in this report and can be identified by trained non-specialists. However, there are small subsets of LAM, BHD, PLCH and LIP that produce cysts that are not characteristic of the disease or for other reasons are easily misclassified.

Our study has strengths related to a large number of cases and large number and varied experiences of readers. In addition, our training algorithm is a teaching tool that can be readily and widely utilized in clinical practice. The principal limitation of the study is the source of the cases. Sixty percent of cases were obtained by retrospective review of the medical records or from teaching files. There is a possibility that biases regarding cyst appearance were introduced in this process. There were no normal exams and the relative frequency of cystic disease and cystic mimics was not controlled. This may have increased reader performance compared with the daily practice where cystic diseases are rarely seen and cystic mimics are more common. The low number of pulmonologists participating in the study is another limitation such that little can be deduced about differences in performance between radiologists and pulmonologists.

5. Conclusion

In conclusion, most cases of cystic lung diseases can be accurately diagnosed from their appearance on thin-section CT utilizing a novel strategy based on 5 cyst appearances: 1) Simple-type, 2) BHD-type, 3) PLCH-type, 4) LIP-type and 5) Cheerio-type. With limited training, non-specialist radiologists and non-specialist pulmonologists can perform as well or better than some diffuse lung disease specialists, although not as well as the highest-performing specialists.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

LAM: Lymphangioleiomyomatosis;

PLCH: Langerhans Cell Histiocytosis;

LIP: Lymphocytic Interstitial Pneumonia;

BHD: Birt-Hogg-Dubé Syndrome;

IPF: Idiopathic Pulmonary Fibrosis;

CTD: Connective Tissue Disease Related Interstitial Lung Disease;

PPV: Positive Predictive Value;

NPV: Negative Predictive Value;

ILD: Interstitial Lung Disease.