

Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis: MR Imaging of Airway Mucus Contrasts as a Tool for Diagnosis¹

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Purpose:

To assess the diagnostic accuracy of mucus contrast characterization by using magnetic resonance (MR) imaging to discriminate allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis (CF).

Materials and Methods:

The study was approved by the local Ethics Committee, and all patients or their parents gave written informed consent. One hundred ten consecutive patients with CF were screened between January 2014 and July 2015. All patients underwent a non-contrast material-enhanced MR protocol that included routine T1-weighted and T2-weighted sequences. The presence of mucus with both high T1 and low T2 signal intensities and the so-called inverted mucoid impaction signal (IMIS) sign was qualitatively and quantitatively assessed by two physicians who were blinded to all other data. The reference standard for a diagnosis of ABPA was the criteria of the Cystic Fibrosis Foundation Consensus Conference. ABPA status was followed up for 1 year. Reproducibility was assessed by using the κ test, correlation was assessed by using the Spearman coefficient, and diagnostic accuracy was assessed by calculating the sensitivity and specificity of IMIS.

Results:

One hundred eight patients with CF were included (mean age, 20 years $\pm$ 11 [standard deviation]; range, 6–53 years): 18 patients with ABPA and 90 patients without ABPA. At the lobar level, inter- and intrareader reproducibility were very good ($\kappa > 0.90$). IMIS had 94% sensitivity (95% confidence interval [CI]: 73%, 99%) and 100% specificity (95% CI: 96%, 100%) for the diagnosis of ABPA. A complete resolution of IMIS was observed in patients with ABPA after 3 months of specific treatment that was significantly correlated with decrease in total immunoglobulin E level ($p = 0.47$; $P = .04$).

Conclusion:

The IMIS sign was both specific and sensitive for the diagnosis of ABPA in CF. Allergic fungal inflammation appears to induce characteristic modifications of mucus contrasts that are assessable by using a noninvasive, contrast material-free, and radiation-free method.

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Patients with cystic fibrosis (CF) are especially prone to fungal respiratory infections because of altered fluid thickness and mucus composition, which provide a favorable environment for the development of pulmonary aspergillosis (1). Thus, *Aspergillus fumigatus* is the most frequent fungal pathogen and is found in the sputum of up to 58% of patients with CF (2). In CF, inhalation of *Aspergillus* conidia can result in four clinical scenarios (3): *Aspergillus* colonization, bronchitis, sensitization, or allergic bronchopulmonary aspergillosis (ABPA). The latter scenario is critical to diagnose because ABPA in CF is associated with more severe worsening and lung damage and requires specific therapeutic management (4). Criteria of ABPA in CF have been established during the Cystic Fibrosis Foundation Consensus Conference (CFFC) (5–7). However, the diagnosis of ABPA remains difficult in CF because of overlap in clinical, microbiologic, radiologic, and immunologic features, and thus, prolonged repetition of testing may be part of the diagnosis process. Therefore, there is a need for an efficient diagnostic tool to confirm ABPA early and improve ABPA management. In the field of imaging, it has been shown that the presence of mucous plugging impaction with hyperattenuating mucus (HAM) at computed tomography (CT) is a 100% specific criterion of ABPA in

patients without CF and thus may be considered pathognomonic (8,9). This specific feature was subsequently transposed to lung magnetic resonance (MR) imaging as a radiation-free technique, then corresponding to modification in combined T1-weighted and T2-weighted contrasts, ascribed to an increase in calcium salt, iron, and/or manganese contents (10). Mucoid impactions have been described with both T1 hyperintensity and T2 hypointensity at MR imaging. We will call this the inverted mucoid impaction signal (IMIS) sign (11). However, to our knowledge, no study has been performed so far to evaluate the diagnostic accuracy of MR imaging to discriminate ABPA in a population of patients with CF, and we hypothesized that IMIS could share similar diagnostic performance to that of HAM at CT. Thus, the aim of this study was to assess the diagnostic accuracy of mucus contrast characterization by using MR imaging to discriminate ABPA in CF.

Materials and Methods

Patients

The study was approved by the local Ethics Committee (ClinicalTrials identifier: NCT02853175). Verbal assent was obtained from all patients, and all patients or their parents in the case of minors (patients < 18 years of age) gave written informed consent. The study was funded by the Laboratory of Excellence Translational Research and Advanced Imaging Laboratory, ANR-10-LABX-57. All coauthors had full control over the data. The study was observational and prospective and was performed between January 2014 and August 2015. All consecutive patients

with CF followed up in the children's hospital and the adult hospital of Bordeaux were screened during a routine visit 3 months before their yearly follow-up and then included at this time. Clinical, functional, biologic, microbiologic, and radiologic examinations (in particular, a complete assessment of ABPA status [5,12]) were performed the same day according to guidelines. Inclusion criteria were a diagnosis of CF proven by sweat chloride and/or genetic testing and age older than 6 years. The diagnosis of ABPA was established by multidisciplinary sessions involving pediatricians, pneumologists, physicians, immunologists, physiologists, and mycologists with full knowledge of the patient's medical history. The CFFC criteria were used as the standard of reference (5) (Appendix E1 [online]). Patients were not included when they had a contraindication to MR imaging such as claustrophobia ($n = 2$), a pacemaker ($n = 0$), or iron material ($n = 0$). There were no additional exclusion criteria.

Advances in Knowledge

- At nonenhanced MR imaging, the inverted mucoid impaction signal (IMIS) was 100% (95% confidence interval [CI]: 96%, 100%) specific and 94% (95% CI: 73%, 99%) sensitive for the diagnosis of allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis (CF).
- A complete resolution of IMIS was observed after a treatment of oral corticosteroid and itraconazole; this resolution was significantly correlated with the decrease in total immunoglobulin E level ($p = 0.47$, $P = .04$).

Implication for Patient Care

- Lung MR imaging is specific and sensitive for the diagnosis of ABPA in CF and thus may be a tool to assist clinicians in discriminating those patients who may benefit from ABPA treatment from among patients with polymicrobial inflammations.

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Abbreviations:

ABPA = allergic bronchopulmonary aspergillosis
CF = cystic fibrosis
CFFC = Cystic Fibrosis Foundation Consensus Conference
CI = confidence interval
HAM = hyperattenuating mucus
IgE = immunoglobulin E
IgG = immunoglobulin G
IMIS = inverted mucoid impaction signal
ISHAM = International Society for Human and Animal Mycology

Author contributions:

Guarantors of integrity of entire study, G.D., J.R., J.M., S.B., F.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, G.D., P.B., J.R., J.M., S.B., L.D., R.M., M.F.; clinical studies, G.D., J.R., J.M., S.B., M.M., J.F.C., M.F., F.L.; experimental studies, G.D., J.R., J.M., L.D.; statistical analysis, G.D., P.B., J.R.; and manuscript editing, G.D., P.B., J.R., L.D., M.M., J.F.C., R.M., M.F., F.L.

Conflicts of interest are listed at the end of this article.

Figure 1

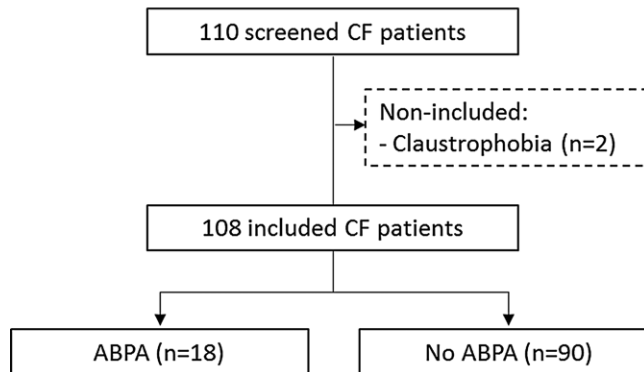


Figure 1: Study flowchart.

For additional analysis, patients were also classified by using alternative diagnostic criteria from the International Society for Human and Animal Mycology (ISHAM) (13) or according to a modified immunologic classification (3) (Appendix E1 [online]). The minimum number of patients necessary for assessing, at least, a sensitivity of 30% with 100% specificity in association with 10% variability (14), and a prevalence of 15% according to published data (3) was calculated. Finally, ABPA status was followed up over 1 year. A flowchart of the protocol is given in Figure 1. Eighteen patients were classified by consensus into the ABPA group and 90 patients were classified into the no-ABPA group. There was no difference between the ABPA and no-ABPA groups regarding demographics, genetics, associated comorbidities, or pulmonary function test results, and treatments were similar (Table 1). No patient had a history of hemoptysis. Table E1 (online) provides additional information on pathogens that were isolated from sputum cultures. There was no significant association between the presence of these pathogens and ABPA status, except for *A. fumigatus* (odds ratio = 38 [95% CI: 2, 661]; $P = .01$). At CT, the proportion of patients with collapse or consolidation and mucoid impaction was higher in the ABPA group. Conversely, there were no significant differences related to the presence of central bronchiectasis, bronchiectasis extent, or severity (Table 1).

Imaging Techniques

MR imaging (15,16) and CT (12,17) were completed at the time of inclusion on the same day. Details on lung MR technical parameters are provided in Appendix E1 (online). Briefly, examinations were performed with a 1.5-T MR imaging unit (Magnetom Avanto; Siemens Healthcare, Erlangen, Germany), without contrast material injection. For the study purpose, complementary evaluation of mucoid impaction contrasts was assessed by using routine T1-weighted and T2-weighted sequences (18).

CT of the chest was performed with a Somatom Definition 64 scanner (Siemens Healthcare). The volumetric CT dose index (CTDI_{vol}) ranged from 1.5 to 3.0 mGy, and dose-length product ranged from 50 to 150 mGy · cm. In addition, effective diameter ranged from 20 to 28 cm, and size-specific dose estimates of CTDI_{vol} ranged from 1.2 to 1.9 mGy (19).

Imaging of Mucoid Impaction Analysis

Details on imaging analysis are given in Appendix E1 (online). Briefly, two physicians, one junior and the other senior, with, respectively, 4 years (J.R. [reader 1]) and 30 years (F.L. [reader 2]) of experience in medical imaging analyzed the examinations after anonymization in random order. The physicians were blinded to the study purpose, patient characteristics, other imaging results, and the other reader's evaluation. Regarding qualitative MR

imaging evaluation, readers were asked to assess the presence of mucoid impaction at the lobar level by using a binary scale (present = 1). When a mucoid impaction was considered to be present, readers had to then evaluate whether its signal intensity was similar to that of the previously published "waterlike" MR imaging appearance (ie, hypointensity on T1-weighted images and hyperintensity on T2-weighted images [18,20]) or if it was defined by the novel IMIS sign, which is hyperintense on T1-weighted images and hypointense on T2-weighted images (10). Readers also had to locate it in the central or peripheral region of the lung, the latter corresponding to the third external part of the lung (8). According to CT literature on HAM, IMIS was primarily searched within central airways, whereas peripheral airways were analyzed independently (4,8,9,13,14,21). Finally, a consensus reading was completed, during which both readers performed the evaluation together. In cases of discrepancy, a third reading by a senior physician with 25 years of experience (P.B.) who was blinded to any other data was allowed. For additional quantitative MR evaluation, round or oval region of interest measurements of mucus signal intensity were performed on both T1-weighted and T2-weighted images and had to measure at least 7 mm² (9,13,14).

Qualitative and quantitative CT evaluations were performed by the same readers in sessions separated by 1 month. In particular, readers were asked to specify the presence of HAM (9). Additional attenuation measurement was performed on paraspinal muscle on the same imaging section for normalization purposes. On each CT or MR section where airway mucus was quantified, round or oval regions of interest were placed manually within both corresponding right and left paraspinal muscles to include at least two-thirds of muscle surface. All measurements were made independently by both readers (J.R. and F.L.) and were averaged to obtain a single value per patient whereas the reproducibility of evaluation was assessed.

Table 1

Baseline Patient Characteristics

Characteristic	Patients with ABPA (n = 18)	Patients without ABPA (n = 90)	P Value
Age (y)			
Median	14 (12, 19)	18.5 (16, 23)	.34
Range	6–53	6–50	NA
Body mass index (kg/m ²)	20 (17, 21)	20 (19, 20)	.96
Tobacco consumption/no tobacco consumption	0/18	1/89	>.99
Homozygosity for <i>DeltaF508</i> mutation/heterozygosity for <i>DeltaF508</i> mutation	8/10	41/49	.95
Pulmonary function testing results			
FEV ₁ (percentage predicted value)	80 (62, 87)	78.5 (72, 83)	.86
FEV ₁ /FVC (%)	74.4 (68, 82)	76 (74, 80)	.99
RV (percentage predicted value)	115 (81, 166)	124 (110, 134)	.63
TLC (percentage predicted value)	95 (85, 101)	100.5 (98, 105)	.13
Comorbidities			
Hepatobiliary disease (yes/no)	6/12	26/64	.55
Pancreatic exocrine insufficiency (yes/no)	14/4	64/26	.51
Diabetes mellitus (yes/no)	2/16	14/76	.85
Inhaled treatment			
Corticosteroid (yes/no)	11/7	40/50	.15
β ₂ mimetic (yes/no)	9/9	29/61	.10
Leukotriene (yes/no)	2/16	8/82	.40
Mucolytic (yes/no)	18/0	90/0	NA
Oral treatment			
Antihistamine (yes/no)	2/16	13/77	.96
Corticosteroid (yes/no)	0/18	0/90	NA
Antifungal therapy (yes/no)	0/18	0/90	NA
CT findings			
Central bronchiectasis (yes/no)	16/2	74/16	.45
Bronchiectasis extent (no. of segments per patient)	5.5 (4, 11)	5.4 (5, 9)	.77
Bronchiectasis severity*	2.1 (1, 3)	1.9 (1, 2)	.85
Mucoid impaction (yes/no)	18/0	63/27	.007
Consolidation or collapse (yes/no)	13/6	38/52	.02
Total IgE level (IU/mL)	1101 (600, 1524)	56 (36, 83)	<.001
Level of anti- <i>A fumigatus</i> IgE (IU/mL)	9.3 (3.7, 25.3)	0.09 (0.09, 0.09)	<.001
Anti- <i>A fumigatus</i> IgG status			
Positive (≥ 10 U/mL)	13	14	<.001
Intermediate (≥ 5 and < 10 U/mL)	5	3	<.001
Negative (< 5 U/mL)	0	73	<.001
Eosinophil status			
Total eosinophil count (cells/μL)	750 (600, 990)	185 (160, 220)	<.001
Past history of elevation (yes/no)	13/5	11/79	<.001
<i>A fumigatus</i> colonization (positive/negative)	18/0	44/46	<.001

Note.—Data are medians, with 95% confidence intervals (CIs) in parentheses, for continuous variables and are numbers of patients for categorical variables. FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, IgE = immunoglobulin E, IgG = immunoglobulin G, NA = not applicable, RV = residual volume, TLC = total lung capacity.

* Bronchiectasis severity scale: 0 = normal; 1 = more than 1 times the diameter of the adjacent vessel; 2 = more than 2 times the diameter of the adjacent vessel; 3 = more than 3 times the diameter of the adjacent vessel.

Statistical Analysis

For continuous variables, data were expressed as medians with 95% CIs. Comparisons of medians between

groups were performed by using the Mann-Whitney test. Comparison of paired groups was performed by using paired *t* tests. Relationships between

variables were assessed by calculating Spearman coefficients. For categorical variables, data were expressed as absolute values, and percentages were expressed with 95% CIs. Comparison of percentages between groups was performed by using the χ^2 test. The relationship between categorical variables was assessed by calculating odds ratios (22).

Diagnostic accuracy was analyzed by measuring sensitivity, specificity, positive predictive value, and negative predictive value. Reproducibility was analyzed by using the κ test and Bland-Altman analysis (23). *P* < .05 was considered to indicate a significant difference.

Results

Qualitative and Quantitative Assessment of Lung MR Images

Regarding the consensus analysis, IMIS was present in 17 of 18 patients who fulfilled the CFFC ABPA criteria. IMIS was noticed in central airways only and manifested in two different forms, either bronchoceles alone (*n* = 14) (Fig 2) or bronchoceles within collapse or consolidation (*n* = 12) (Fig E1 [online]). Conversely, seven patients with ABPA also had bronchiolar centrilobular nodules with the “tree-in-bud” appearance, whereas IMIS was not noticed in the peripheral lung. There was no case of mucus signal compatible with fresh blood (ie, hypointense on T1-weighted images and hypointense on T2-weighted images [20]). At MR imaging, there was very good agreement in identifying the presence or the absence of IMIS (κ > 0.90) at both inter- and intra-reader evaluation (Table 2). Regarding results from sputum cultures, the sole pathogen significantly associated with the presence of IMIS was *A fumigatus* (odds ratio = 17 [95% CI: 2, 139]; *P* = .006).

Qualitative subjective assessment of IMIS was completed by means of a quantitative measurement of signal intensity (Table E2 [online]). This measurement was feasible in all 17 patients with IMIS, whereas only 41 of

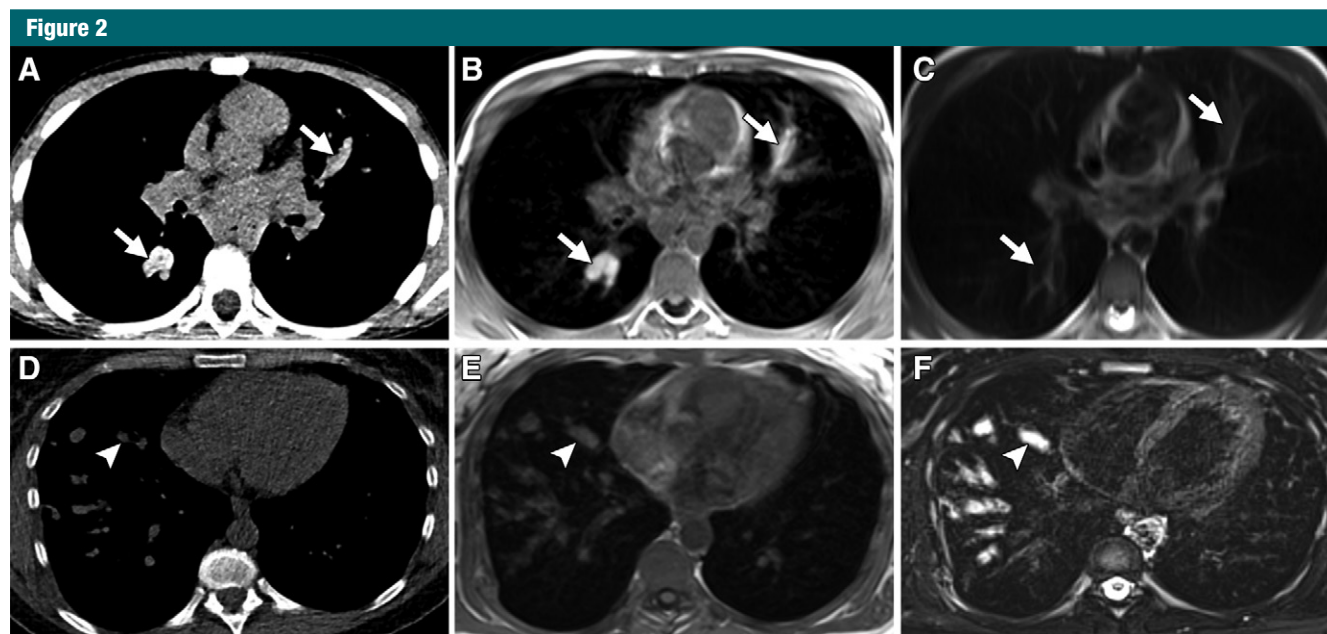


Figure 2: CT and MR images acquired in, *A, B, C*, a patient with ABPA and, *D, E, F*, a patient without ABPA. *A*, In a 9-year-old patient with ABPA, arrows = central mucoid impaction with increased attenuation at CT. *B, C*, Corresponding MR images show contrasts (arrows) on, *B*, a T1-weighted MR image (repetition time msec/echo time msec, 3.8/1.18; flip angle, 8°), which shows hyperintense signal, and, *C*, a T2-weighted MR image (2000/27; flip angle, 150°), which shows hypointense signal. *D, E, F*, In a 10-year-old patient without ABPA but with a positive culture for *A. fumigatus*, arrowhead = marked differences in contrast—that is, complete reversal of CT attenuation (on *D*), as well as MR imaging contrast on, *E*, T1-weighted and, *F*, T2-weighted MR images.

90 patients without IMIS had a central mucoid impaction available for measurement. The interobserver mean difference for normalized T1 mean signal intensity measurement was 0.03 (95% CI: -0.4, 0.5), whereas it was -0.08 (95% CI: -1.4, 1.2) for normalized T2 mean signal intensity. There were significant differences between groups regarding normalized T1 and T2 measurements (Fig 3, Table E3 [online]).

Diagnostic Performance of Lung MR Imaging

All evaluations (independently or in consensus between readers) were consistent with 100% specificity of evaluation (95% CI: 96%, 100%) (Table 3). There was no discrepancy during consensus reading, and the final result was a sensitivity of 94% (95% CI: 73%, 99%).

Areas under the receiver operating characteristic curves of normalized T1 and T2 mean signal intensity measurements ($n = 58$) were both 1.00 (95% CI: 0.94, 1.00). However, mucoid impactions

Table 2

Inter- and Intrareader Agreement in Assessing the Presence of Mucoid Impaction at MR Imaging in 540 Pulmonary Lobes of 108 Patients with CF

Parameter and Measure	Interreader Agreement		Intrareader Agreement	
	κ Value	95% CI	κ Value	95% CI
IMIS positive				
Per lobe	0.96	0.93, 0.98	0.97	0.95, 0.99
Per patient	0.96	0.89, 1.00	1.00	1.00, 1.00
IMIS negative				
Per lobe	0.94	0.91, 0.96	0.95	0.92, 0.97
Per patient	0.93	0.86, 1.00	0.93	0.86, 1.00

were not quantified in one patient with ABPA and in 49 patients without ABPA (Table E4 [online]). In these 50 patients, mucoid impactions were found to be either absent or peripheral, and thus, mucus contrasts were not measurable.

Diagnostic Accuracy of MR Imaging by Using Other ABPA Classifications

By using the diagnostic criteria of the ISHAM (5), there was difficulty in classifying five patients with a total IgE level of

less than 1000 IU/mL and all minor criteria but a specific IgG level that was not negative nor positive but “intermediate” (6,7,24) at both screening and diagnostic phases. Therefore, the sensitivity and specificity of IMIS could be either 100% and 94% or 94% and 100%, if the intermediate results were to be considered negative or positive, respectively.

Referring to a modified immunologic classification, patients who could not be classified into an ABPA-I group

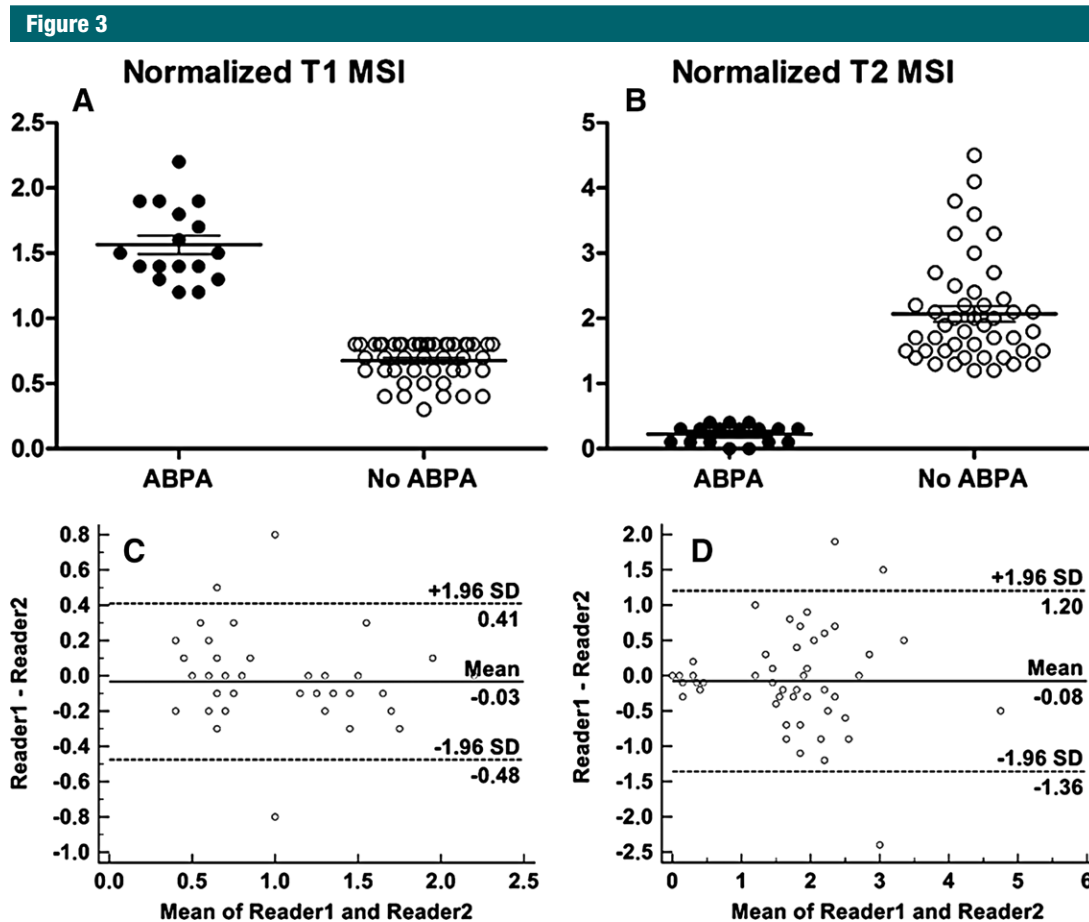


Figure 3: Graphs show results of comparison of MR mucus signal intensity measurements between groups. Quantitative measurements were not available in one patient with ABPA and in 49 patients without ABPA. On *A* and *B*, ● = measurements in patients with ABPA and ○ = measurements in patients without ABPA. *C* and *D* show results of Bland-Altman analyses of reproducibility between reader 1 and reader 2 of, *C*, T1-weighted and, *D*, T2-weighted quantitative measurements of normalized signal intensities. On *C* and *D*, solid line = mean difference between readers, and dashed lines = 95% limits of agreement. *MSI* = mean signal intensity.

Table 3

Diagnostic Accuracy of IMIS Sign at MR Imaging for the Presence of ABPA in 108 Patients with CF

Reading	No. of TP Results	No. of TN Results	No. of FP Results	No. of FN Results	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Reader 1	17	90	0	1	94 (73, 99)	100 (96, 100)	100 (80, 100)	99 (94, 99)
Reader 2	16	90	0	2	89 (65, 98)	100 (96, 100)	100 (79, 100)	98 (92, 99)
Consensus	17	90	0	1	94 (73, 99)	100 (96, 100)	100 (80, 100)	99 (94, 99)

Note.—Data in parentheses are 95% CIs. FN = false-negative, FP = false-positive, NPV = negative predictive value, PPV = positive predictive value, TN = true-negative, TP = true-positive.

($n = 90$) were patients with *Aspergillus* sensitization ($n = 23$), *Aspergillus* bronchitis ($n = 12$), and no *Aspergillus*-related disease ($n = 58$). The specificity of MR imaging in the assessment of ABPA-I among other *Aspergillus*-related disorders ranged from 94% to 100%,

depending on five patients with intermediate specific IgG results.

ABPA Status Follow-up over 1 Year

All 18 patients with ABPA were treated with a combination of oral corticosteroids and itraconazole. At 3 months,

the patients improved their status to no ABPA (Table E5 [online]), while a complete resolution of IMIS was observed in all patients (Figs E2 and E3 [online]). There was significant correlation between the decrease in total IgE and that of IMIS ($\rho = 0.47$, $P = .04$) (Fig 4).

Figure 4

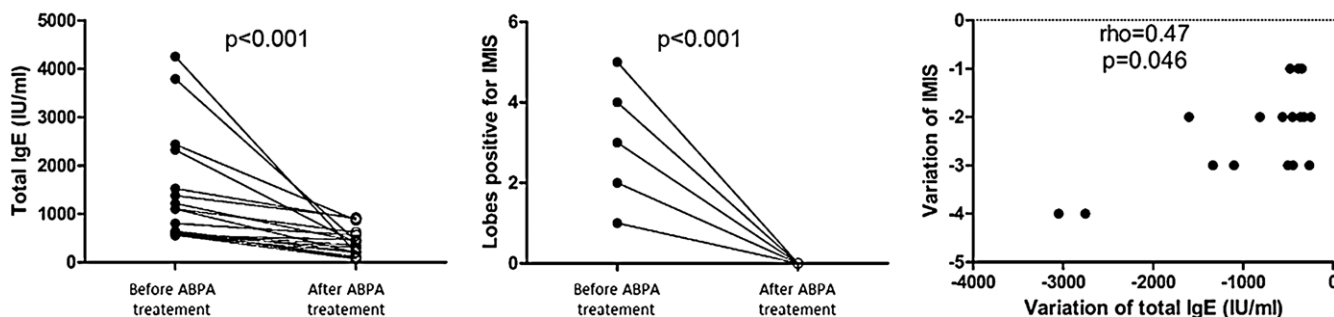


Figure 4: Graphs show results of pretreatment and posttreatment examinations performed in 18 patients with ABPA who were treated with oral corticosteroids and itraconazole. There is a significant decrease in both total IgE level (left) and in the number of lung lobes positive for IMIS of central airways (middle) after 3 months of treatment. The variation in measurements was calculated as the difference between results obtained after treatment and those obtained before treatment. Right: There was significant correlation between both total IgE and IMIS variations.

Conversely, none of the 88 patients without ABPA fulfilled either the minimum or the classic criteria for ABPA at follow-up. However, two patients had clinical exacerbation while IMIS appeared at MR imaging. All criteria for ABPA were positive, although total IgE levels were found to be 210 and 410 IU/mL. The MR imaging abnormalities did not disappear after 1 month of first-line antibiotic therapy, and the CFFC criteria were compatible with ABPA 3 months later, with a total IgE level of more than 500 IU/mL.

Diagnostic Performance of Chest CT

Data on the reproducibility of qualitative and quantitative measurements of HAM at CT are given in Tables E2, E3, and E6 (online). Qualitative subjective assessment of HAM was found to have 72% (95% CI: 46%, 90%) sensitivity and 100% (95% CI: 95%, 100%) specificity. The presence of HAM was 100% concordant with the presence of IMIS, whereas four patients with ABPA had IMIS but no HAM. A threshold of attenuation of less than 59 HU had a 95% specificity with 88% sensitivity. With a threshold of normalized attenuation higher than 1, the specificity was 93% and the sensitivity 88% (Fig E3, Table E4 [online]).

Discussion

To the best of our knowledge, this study is the first evaluating the diagnostic accuracy of lung MR imaging to diagnose

ABPA in CF. Results demonstrate that, by using a radiation-free and contrast material-free method, MR imaging is specific for diagnosing ABPA in a population of patients with CF, in particular in discriminating it from other polymicrobial inflammations and thus helping to adjust treatment.

To establish the diagnosis of ABPA in CF is of particular importance, because ABPA requires specific treatments (4,5). However, with standard biomarkers, the diagnosis may be difficult and may require repetition of testing over months (5,13). However, the ISHAM working group has indicated that, in the special condition of CF, the diagnosis of ABPA cannot rely on the sole standard of immunologic findings (5,13), and the current standard of reference to overcome difficulties remains the criteria of the CFFC (13). In particular, in the CFFC criteria, it is stated that a valuable alternative to specific IgG is a therapeutic test to check whether newly developed radiologic abnormalities persist with antibiotic therapy (5). In this study, all patients suspected of having ABPA developed this pejorative imaging outcome. Conversely, all of them improved with ABPA treatment, thus confirming that the disease was relieved. However, such repetition of testing may raise concern, over the long term, regarding iterative radiation exposures and risks of antibiotic resistance development. However, patients with CF with untreated ABPA

are prone to more severe outcomes. Furthermore, the prevalence of ABPA was found to be 16.6%, close to that of the maximum prevalence of 15% reported in the literature (3) and consistent with previous works indicating that *Aspergillus* diseases are not rare in CF (25).

The 100% specificity of HAM at CT for the diagnosis of ABPA in patients without CF has already been reported by Agarwal and colleagues (9) and has been consistently supported by similar results from other teams worldwide (4,21,26). HAM has also been described in Japanese patients with both ABPA and another form of allergic bronchopulmonary mycosis due to *Schizophyllum commune* (27). Therefore, there is compelling evidence that HAM can be considered pathognomonic for bronchial fungal allergy, unlike other forms of airway inflammations. Recent literature has also suggested that HAM may be part of the diagnostic criteria of ABPA in CF (4,28). Lung MR imaging has been reported to be valuable in transposing HAM into a radiation-free technique and could be a novel paradigm for lung MR imaging (10). Our results indicate that, according to CFFC criteria, IMIS shares similar 100% specificity to HAM for the diagnosis ABPA in CF. The number of patients was enough to assess a 95% CI of less than 5%. In addition, *A. fumigatus* was the sole pathogen significantly associated with the presence of

IMIS (odds ratio = 17 [95% CI: 2, 139]; $P = .006$), whereas a complete resolution of IMIS was achieved by using an association of oral corticosteroid and itraconazole. Thus, we found no other rationale to relate IMIS presence to an inflammatory process other than fungal allergy. Therefore, it suggests that MR imaging could be useful in following up the regional extent of this diagnostic sign noninvasively.

Interestingly, we observed an unexpected high sensitivity of IMIS alone as compared with previous published data on HAM (4,8,14,21). Nevertheless, the sensitivity of MR imaging for tissue characterization is known, because contrast variations with MR imaging do not rely solely on molecular concentrations but also rely on tissue components (29). Therefore, there were marked contrast differences between the ABPA and no-ABPA groups, from bright to dark appearances, thus making additional quantification of signal intensity more optional. In addition, CF alters the mucociliary clearance, and thus, we hypothesized that ABPA-related mucus abnormalities (8–10,14) may be prone to accumulate in CF (30). Moreover, patients with CF undergo imaging at least once a year (12). Therefore, acute inflammatory manifestations may be detectable earlier than in patients without CF (13). In this study, IMIS was systematically a precursor for the development of bronchiectasis during follow-up. This suggests that IMIS may be an early sign of ABPA.

Finally, tissue characterization using a combination of routine T1-weighted and T2-weighted sequences was performed without contrast material injection, and the contrast material-free MR imaging protocol was reproducible and highly acceptable. The use of lung MR imaging has recently been emphasized in both acute (31) and long-term follow-up of CF, either alone (15) or in combination with CT (17). In addition, recent progress in structural imaging with ultrashort echo times (32,33) may eventually enable MR imaging to provide both high-resolution morphology and tissue contrast characterization (18) in a single examination.

Our study had some limitations. First, in agreement with the CT literature on HAM, IMIS was reported in the central part of the lung only. It could be discussed that the discrimination of lumen from wall abnormalities was below the spatial resolution of the MR imaging technique in the lung periphery and, thus, this point was not assessable in patients without central airway IMIS. Nevertheless, this known inaccuracy (16) was not prone to impair the specificity of IMIS, because nonvisible structures cannot be related to false-positive results but only to false-negative results. However, at the population level, both intra- and interobserver reproducibility were very good ($\kappa > 0.90$), whereas only one in 18 cases of ABPA was missed using the IMIS sign. Second, in our study, we did not find allergic bronchopulmonary mycoses (ABPMs) other than that related to *A fumigatus* (34). However, MR imaging features of other ABPMs have not yet been described in CF, whereas all ABPMs are part of the same disease spectrum related to fungal allergy and require the same treatment. Third, recent ABPA biomarkers such as basophil activation (6) and sputum galactomannan (3) were not evaluated here. However, combining MR imaging with these novel immunologic biomarkers should be well suited for a better understanding of the disease to select homogeneous groups of patients with similar characteristics for future clinical trials. Fourth, the natural history of ABPA is not well known, and thus, the present radiation-free technique may be used longitudinally to decipher this issue. Fifth, the population was small because CF is an uncommon disease, although it is the most frequent and lethal genetic disorder in Caucasians. However, this study is a first attempt to assess the diagnostic accuracy of MR imaging for ABPA in CF, and a further multicenter larger cohort is thus needed for better precision in measurement, especially regarding sensitivity. Sixth, follow-up after treatment was available over the short term only; further investigation may require further randomized trials with long-term follow-up.

Last, although complete resolution of IMIS was achieved with specific ABPA treatment, the diagnostic accuracy of MR imaging, not explanation of IMIS, was the aim of this study. Further correlation studies should be worth doing.

Finally, we have shown that noninvasive characterization of the inflammatory process involved in CF is feasible using MR imaging. In particular, the presence of the IMIS criterion was highly specific in the diagnosis of ABPA with good sensitivity, thus suggesting that it may be useful in assisting clinicians in discriminating patients who may benefit from treatment for ABPA among other polymicrobial inflammations. Because ABPA diagnosis requires a combination of criteria, including imaging criteria (4,5,13), this study suggests that IMIS is a valuable alternative to HAM for the care of patients with CF, without concern about radiation dose accumulation (35) during lifelong treatment.

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Appendix E1

Supplemental Methods

Study Design

The diagnosis of CF was made with sweat chloride testing (>60 mmol/L according to the quantitative iontophoresis test) and/or documentation of two identifiable *CFTR* mutations and one or more clinical features consistent with CF. The *CFTR* genotype was confirmed by using the Elucigene CF29 assay (Tepnel Diagnostics, Manchester, England).

Yearly follow-up of patients from birth to inclusion was performed according to French national guidelines, including a medical consultation at least every 3 months and more often in case of disease exacerbations. A full assessment of CF disease was also completed once a year, including clinical status and functional, biologic, microbiologic, immunologic, and imaging examinations with complete follow-up of ABPA status (12). Lung function was tested by using spirometry and American Thoracic Society criteria. Serology levels (total IgE and anti-*A fumigatus* immunoglobulin E antibodies) were measured by using standard ImmunoCAP assays (Phadia, Uppsala, Sweden) (3,6) according to the manufacturer's instructions. Serum anti-*A fumigatus* IgG antibodies were determined with an enzyme-linked immunoassay (Bio-Rad, Marnes-la-Coquette, France). In particular, according to the manufacturer's instructions and recent publications, the threshold for considering the results of the anti-*A fumigatus* IgG test to be strictly negative was less than 5 U/mL; the threshold for considering the test results as strictly positive was greater than 10 U/mL; when the level was between 5 and 10 U/mL, the result was intermediate (6,7,24).

The study design was observational and prospective, and the study was performed between January 2014 and August 2015. All consecutive patients with CF who were followed in both a children's hospital (Bordeaux, France) and an adult hospital (Pessac, France) were screened during a routine examination 3 months before their annual visit, the latter corresponding to the date of inclusion. The diagnosis of ABPA was performed in multidisciplinary sessions involving pediatricians, pneumonologists, physicians, immunologists, physiologists, and mycologists, with full knowledge of the patient's medical history. Criteria for screening and diagnosis of ABPA were those recommended by the Cystic Fibrosis Foundation Consensus Conference (CFFC) (5).

Thus, CFFC criteria for screening ABPA in CF were as follows:

- “1. Maintain a high level of suspicion for ABPA in patients >6 years of age.
2. Determine the total serum IgE concentration annually. If the total serum IgE concentration is > 500 IU/mL, determine immediate cutaneous reactivity to *A fumigatus* or use an in vitro test for IgE antibody to *A fumigatus*. If results are positive, consider diagnosis on the basis of minimal criteria.
3. If the total serum IgE concentration is 200–500 IU/mL, repeat the measurement if there is increased suspicion for ABPA, such as by a disease exacerbation, and perform further

diagnostic tests (immediate skin test reactivity to *A fumigatus* in vitro for IgE antibody to *A fumigatus*, *A fumigatus* precipitins, or serum IgG antibody to *A fumigatus*, and chest radiography.”

Following the screening phase, patients were classified into ABPA group according to whether they fulfilled the criteria established by the CFFC (5):

“- Classic case.

1. Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, decline in pulmonary function, increased sputum) not attributable to another etiology

2. Serum total IgE concentration of 1000 IU/mL (2400 ng/mL), unless patient is receiving systemic corticosteroids (if so, retest when steroid treatment is discontinued)

3. Immediate cutaneous reactivity to *Aspergillus* (prick skin test wheal of 13 mm in diameter with surrounding erythema, while the patient is not being treated with systemic antihistamines) or in vitro presence of serum IgE antibody to *A fumigatus*

4. Precipitating antibodies to *A fumigatus* or serum IgG antibody to *A fumigatus* by an in vitro test

5. New or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.

- Minimal diagnostic criteria

1. Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, change in pulmonary function, or increased sputum production) not attributable to another etiology.

2. Total serum IgE concentration of 500 IU/mL (1200 ng/mL). If ABPA is suspected and the total IgE level is 200–500 IU/mL, repeat testing in 1–3 months is recommended. If patient is taking steroids, repeat when steroid treatment is discontinued.

3. Immediate cutaneous reactivity to *Aspergillus* (prick skin test wheal of 13 mm in diameter with surrounding erythema, while the patient is not being treated with systemic antihistamines) or in vitro demonstration of IgE antibody to *A fumigatus*.

4. One of the following: (a) precipitins to *A fumigatus* or in vitro demonstration of IgG antibody to *A fumigatus*; or (b) new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.”

However, in our study, data from chest radiography were replaced with data from lung MR imaging (36).

Alternative criteria for diagnosing ABPA in CF were as follows:

Additional analysis was performed by using alternative diagnostic criteria.

First, the following criteria from the ISHAM working group were used (13):

“- Predisposing conditions: bronchial asthma, cystic fibrosis

- Obligatory criteria (both should be present)

Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *A fumigatus*

Elevated total IgE levels (> 1000 IU/mL)*

- Other criteria (at least two of three)

Presence of precipitating or IgG antibodies against *A fumigatus* in serum

Radiographic pulmonary opacities consistent with ABPA§

Total eosinophil count > 500 cells/ μ L in steroid naïve patients (may be historical)

*If the patient meets all other criteria, an IgE value < 1000 IU/mL may be acceptable”

§The chest radiographic features consistent with ABPA may be transient (ie, consolidation,

nodules, tram-track opacities, toothpaste/finger-in-glove opacities, fleeting opacities) or permanent (ie, parallel line and ring shadows, bronchiectasis, and pleuropulmonary fibrosis)”

- ABPA in special situations

“ABPA in CF: (...) The diagnosis of ABPA in CF cannot be based solely on serology and skin test results, as patients with CF may demonstrate variable responses to *A.fumigatus* and prolonged testing might be required to make a definite diagnosis. To overcome these difficulties, an international consensus conference has made recommendations for diagnosis and management of ABPA in CF (5).”

Of note, the ISHAM working group indicates that, in the special situation of CF, criteria to overcome serologic difficulties are those of the CFFC. In this study, data from chest radiography were replaced by data from lung MR imaging (36)

Second, we used a pure immunologic classification of ABPA (“ABPA-I”). For this, we used a modification of the Manchester classification proposed by Baxter and colleagues (3). Indeed, in the current study, measurements from real time-PCR and sputum galactomannan were not performed, and thus, the modified immunologic classification was as follows:

1. Nondiseased patients with CF with or without *Aspergillus* in sputum but no measurable immunologic response.

2. Immunologic ABPA (ABPA-I) with all immunologic markers being high.*

3. *Aspergillus* sensitization with or without *Aspergillus* isolated in sputum but negative *A fumigatus* IgG and/or total IgE not being high.*

4. *Aspergillus* bronchitis with negative IgE markers but positive *A fumigatus* IgG.

*The threshold for considering total IgE to be elevated was set at 180 IU/mL, as indicated by Baxter and colleagues (3).

Imaging Techniques and Analysis

Lung MR imaging examinations were performed by using a 1.5-T MR imaging unit (MAGNETOM Avanto; Siemens Healthcare), without contrast material injection (16).

Acquisitions were performed in the axial plane by using a 12-channel thorax/spine body coil. For the study purpose, T1-weighted fast sequence parameters were as follows: repetition time msec/echo time msec, 3.8/1.18; flip angle, 8°; averaging, 1; voxel size, $1.4 \times 1.4 \times 3 \text{ mm}^3$, and acquisition time, 18 seconds with breath holding. A T2-weighted sequence was performed with respiratory gating with a navigator placed on the diaphragm to obtain images at end-normal expiration (ie, functional residual capacity). Parameters for this sequence were as follows: 2000/27; flip angle, 150°; averaging, 1; voxel size, $1.4 \times 1.4 \times 3 \text{ mm}^3$; and acquisition time, 4–8 minutes.

Low-dose CT of the chest was performed with a Somatom Definition 64 scanner (Siemens). Tube voltage was adapted to patient weight and was 80 kV for patients weighing less than 35 kg and 110 kV for patients weighing more than 35 kg. A modulating tube current (CareDose4D; Siemens Medical Solutions) with an effective reference tube current was used. Patients were instructed orally before and during examination to hold their breath at functional residual capacity. Effective dose ranged from 1.2 to 1.5 mSv. No spirometric gating or contrast material injection was used.

Image Analysis

Image evaluation was performed, independently and then in consensus, by two observers with 4 years (J.R., reader 1) and 30 years (F.L., reader 2) of experience in medical imaging. The observers were blinded to any clinical, functional, microbiologic, or biologic data. Regarding qualitative MR image evaluation, readers had to assess the presence of mucoid impaction at the lobar level on a binary scale (present = 1; absent = 0) by using the ultrashort echo time sequence. When a mucoid impaction was scored as present, readers had to characterize the T1-weighted and T2-weighted contrasts of the found mucoid impaction to evaluate whether it would appear with usual “waterlike” MR imaging contrasts (ie, either hypointense on T1-weighted images and hyperintense on T2-weighted images or hypointense on T1-weighted images and hypointense on T2-weighted images [20,37]) or with the IMIS sign, which is hyperintense on T1-weighted images and hypointense on T2-weighted images (10). The location of the mucus was performed at the lobar level by discriminating between the central and the peripheral parts of the lung. The peripheral part was the third external part of the lung, as previously described (8).

For quantitative MR evaluation, region of interest measurements of central mucoid impaction signal intensity (SI) were performed on both T1-weighted and T2-weighted images, with careful delineation between the lumen and bronchial wall to avoid wall SI. Because of the limited spatial resolution of the MR imaging technique, mucoid impactions located in the peripheral part of the lung were considered not to be measurable. One measurement in IMIS and/or non-IMIS mucoid impaction was performed and averaged to get a single value per lobe. All lobar measurements were then averaged to get a final single value per patient. Additional measurements were performed in the paraspinal muscles on corresponding sections to normalize mucus SI with medullar SI so that:

$$\text{Normalized mucus SI} = \text{mucus SI} / \text{muscle SI} \cdot 100.$$

Similar qualitative and quantitative evaluations were performed by the same readers on CT images. This time, evaluation of areas of mucus contrast was divided between those that appeared to represent HAMs and those that showed hypo- or isoattenuation. Patients who were

positive for the HAM sign were expected to have ABPA (9). Additional measurement was performed in the paraspinal muscle to normalize mucus attenuation as previously described (9):

$$\text{Normalized mucus attenuation} = \text{mucus attenuation/muscle attenuation} \cdot 100.$$

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Table E1. Bacterial, Mycobacterial, and Fungal Pathogens Found in Sputum Cultures from 108 Patients with CF

Organism Type and Organism	Patients with ABPA (n = 18)	Patients without ABPA (n = 90)	Odds Ratio (n = 108)	P Value of Odds Ratio
Bacteria				
<i>Staphylococcus aureus</i>	7	40	0.79 [0.28; 2.23]	.66
<i>Streptococcus pneumoniae</i>	5	32	0.60 [0.20; 1.81]	.52
<i>Pseudomonas aeruginosa</i>	6	38	0.68 [0.23; 1.98]	.48
<i>Burkholderia cepacia</i>	0	10	0.21 [0.01; 3.69]	.28
<i>Burkholderia multivorans</i>	0	2	0.95 [0.04; 20.76]	.97
<i>Burkholderia vitaminensis</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Stenotrophomonas maltophilia</i>	0	9	0.23 [0.01; 4.16]	.32
<i>Haemophilus influenzae</i>	0	12	0.16 [0.00; 2.99]	.22
<i>Alcaligenes xyloxydans</i>	1	6	0.82 [0.09; 7.28]	.86
<i>Proteus mirabilis</i>	0	3	0.67 [0.03; 13.64]	.79
<i>Achromobacter xyloxydans</i>	0	4	0.52 [0.02; 10.07]	.66
<i>Neisseria saprophytes</i>	0	2	0.95 [0.04; 20.76]	.97
<i>Serratia sp</i>	1	8	0.60 [0.07; 5.14]	.64
Mycobacteria				
<i>Mycobacterium intracellulare</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Mycobacterium avium</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Mycobacterium abscessum</i>	0	1	1.61 [0.06; 41.15]	.77
Fungi				
<i>Aspergillus fumigatus</i>	18	44	38.66 [2.26; 661.06]	.01
<i>Aspergillus terreus</i>	0	2	0.95 [0.04; 20.76]	.97
<i>Aspergillus flavus</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Aspergillus nidulans</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Candida albicans</i>	5	28	0.85 [0.27; 2.62]	.77
<i>Candida parapsilosis</i>	0	1	1.61 [0.06; 41.15]	.77

<i>Candida krusei</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Candida lusitanae</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Candida tropicalis</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Scedosporium spp</i>	0	3	0.67 [0.03; 13.64]	.79
<i>Rhizopus orizae</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Geotrichum candidum</i>	0	2	0.95 [0.04; 20.76]	.97
<i>Geotrichum silvicola</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Penicillium chrysogenum</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Penicillium citroenum</i>	0	2	0.95 [0.04; 20.76]	.97
<i>Penicillium subrubescens</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Penicillium dipodomyis</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Pseudallescheria multispora</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Hexagonia hydroides</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Paecilomyces sp</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Alternaria alternata</i>	0	1	1.61 [0.06; 41.15]	.77
<i>Schizophyllum commune</i>	0	1	1.61 [0.06; 41.15]	.77

Note.—Unless otherwise specified, data are numbers of patients with a positive culture. Data in brackets are 95% CIs. Odds ratios are measurements between results of pathogen cultures and positivity of ABPA classification and/or IMIS findings. Where zeroes caused problems with computation of the odds ratios or their standard errors, 0.5 was added to all values according to Deeks JJ and Higgins JP, 2010. *P* values of odds ratios were calculated according to Seskin DJ, 2004. *P* < .05 was considered to indicate a significant difference.

Table E2. Results of Bland-Altman Analysis of Inter- and Intrareader Reproducibility of Measurements at CT and MR Imaging in 58 Patients with CF and Measureable Mucus Contrasts

Modality and Measurement	Interreader Reproducibility		Intrareader Reproducibility	
	MD	95% LOA	MD	95% LOA
MR imaging				
T1 mucus SI	5.2	[−87.2; 97.5]	−2.7	[−48.6; 43.1]
T1 muscle SI	2.7	[−61.1; 66.5]	−3.0	[−29.9; 24]
Normalized T1 MSI (%)	0.03	[−0.4; 0.5]	−0.01	[−0.3; 0.3]
T2 mucus SI	19.6	[−224.3; 263.5]	−5.9	[−135.1; 123.3]
T2 muscle SI	17.3	[−171.5; 206.1]	−4.4	[−108.3; 99.5]
Normalized T2 MSI (%)	−0.08	[−1.4; 1.2]	0.07	[−0.6; 0.7]
CT				
Mucus attenuation (HU)	0.4	[−74; 74.8]	−0.9	[−34.5; 32.7]
Muscle attenuation (HU)	−2.8	[−30.1; 24.6]	1.2	[−16; 18.3]
Normalized mucus attenuation (%)	0.08	[−1.2; 1.4]	−0.07	[−0.8; 0.7]

Note.—Quantitative measurements were not available in one patient with ABPA and in 49 patients without ABPA. LOA = limits of agreement, MD = mean difference, MSI = mean signal intensity, SI = signal intensity.

Table E3. Comparison of Quantitative Mucus MR Imaging and CT Measurements in Patients with CF with ABPA and Those without ABPA

Modality and Measurement	Patients with ABPA (<i>n</i> = 17)	Patients without ABPA (<i>n</i> = 49)	<i>P</i> Value
MR imaging			
T1 SI			

Mucus	173 [140; 191]	73.5 [60; 80]	<.001
Muscle	116 [100; 130]	110 [100; 120]	.82
Normalized T1 MSI	1.5 [1.4; 1.8]	0.7 [0.6; 0.8]	<.001
T2 SI			
Mucus	40 [20; 79]	307 [264; 344]	<.001
Muscle	185 [150; 238]	160 [130; 197]	.22
Normalized T2 MSI	0.3 [0.1; 0.3]	1.9 [1.6; 2.1]	<.0001
CT			
Attenuation			
Mucus (HU)	86 [73; 121]	32 [26; 40]	<.001
Muscle (HU)	49 [43; 54]	55 [50; 57]	.06
Normalized attenuation	2 [1.4; 2.5]	0.6 [0.5; 0.7]	<.001

Note.—Quantitative measurements were not available in one patient with ABPA and in 49 patients without ABPA. MSI = mean signal intensity, SI = signal intensity.

Table E4. Diagnostic Accuracy of MR Imaging and CT Measurements according to Variable Thresholds in 58 Patients with CF with Measureable Mucus Contrasts

Parameter	Criterion	Sensitivity (%)	95% CI	Specificity (%)	95% CI	Positive LR	Negative LR
Normalized T1 MSI	≥0.3	100	[80.5–100]	0	[0–7.7]	1	
	>0.8	100	[80.5–100]	100	[92.3–100]		0
	>2.2	0	[0–19.5]	100	[92.3–100]		1
Normalized T2 MSI	<0	0	[0–19.5]	100	[92.3–100]		1
	≤0.4	100	[80.5–100]	100	[92.3–100]		0
	≤4.5	100	[80.5–100]	0	[0–7.7]	1	
HAM	≥7	100	[80.5–100]	0	[0.0–7.7]	1	
	>22	100	[80.5–100]	28.26	[16.0–43.5]	1.39	0
	>23	94.12	[71.3–99.9]	30.43	[17.7–45.8]	1.35	0.19
	>32	94.12	[71.3–99.9]	52.17	[36.9–67.1]	1.97	0.11
	>33	88.24	[63.6–98.5]	54.35	[39.0–69.1]	1.93	0.22
	>59	88.24	[63.6–98.5]	95.65	[85.2–99.5]	20.29	0.12
	>73	70.59	[44.0–89.7]	95.65	[85.2–99.5]	16.24	0.31
	>74	70.59	[44.0–89.7]	97.83	[88.5–99.9]	32.47	0.3
	>76	64.71	[38.3–85.8]	97.83	[88.5–99.9]	29.76	0.36
	>80	58.82	[32.9–81.6]	100	[92.3–100]		0.41
	>151	0	[0.0–19.5]	100	[92.3–100]		1
	≥0.1	100	[80.5–100]	0	[0.0–7.7]	1	
Normalized HAM	>0.3	100	[80.5–100]	21.74	[10.9–36.4]	1.28	0
	>0.4	94.12	[71.3–99.9]	26.09	[14.3–41.1]	1.27	0.23
	>0.6	94.12	[71.3–99.9]	58.7	[43.2–73.0]	2.28	0.1
	>0.7	88.24	[63.6–98.5]	67.39	[52.0–80.5]	2.71	0.17
	>1	88.24	[63.6–98.5]	93.48	[82.1–98.6]	13.53	0.13
	>1.2	82.35	[56.6–96.2]	95.65	[85.2–99.5]	18.94	0.18
	>1.3	82.35	[56.6–96.2]	97.83	[88.5–99.9]	37.88	0.18
	>1.6	58.82	[32.9–81.6]	97.83	[88.5–99.9]	27.06	0.42
	>1.7	58.82	[32.9–81.6]	100	[92.3–100]		0.41

	>4.8	0	[0.0–19.5]	100	[92.3–100]		1
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Note.—LR = likelihood ratio. MSI = mean signal intensity.

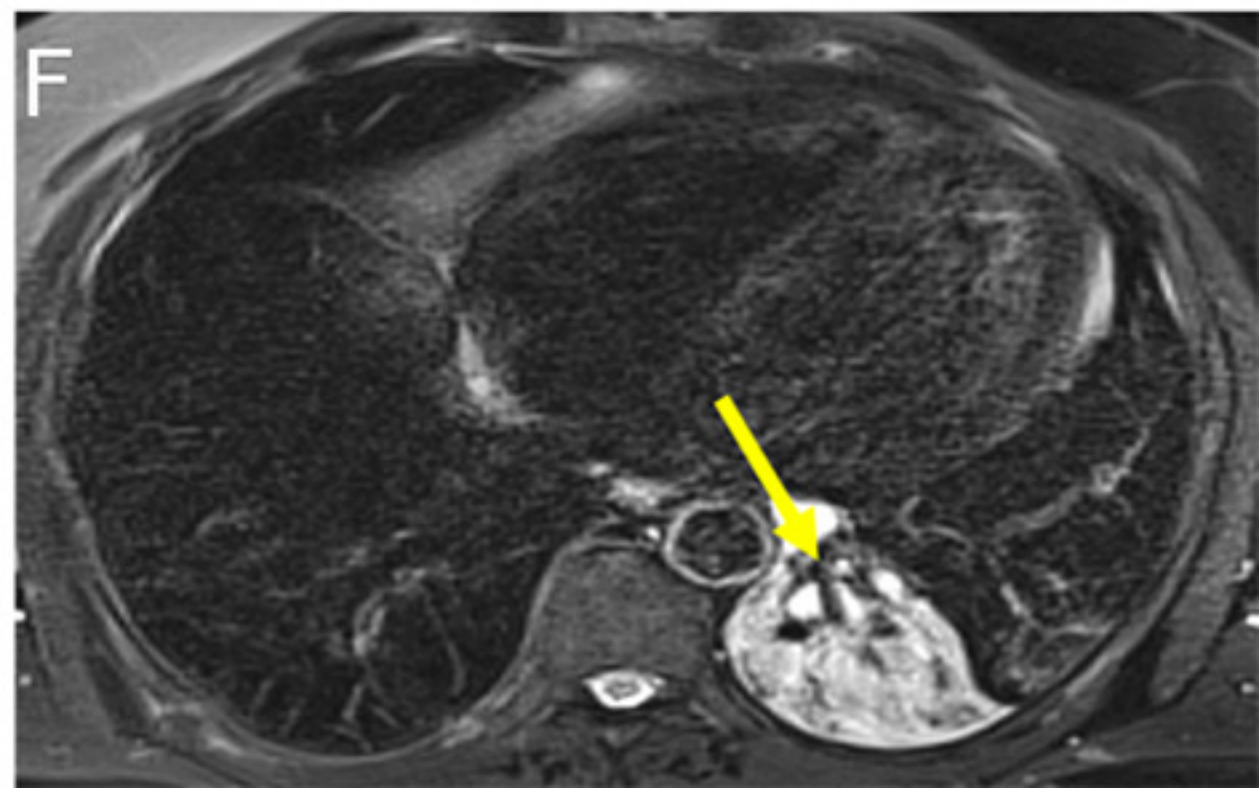
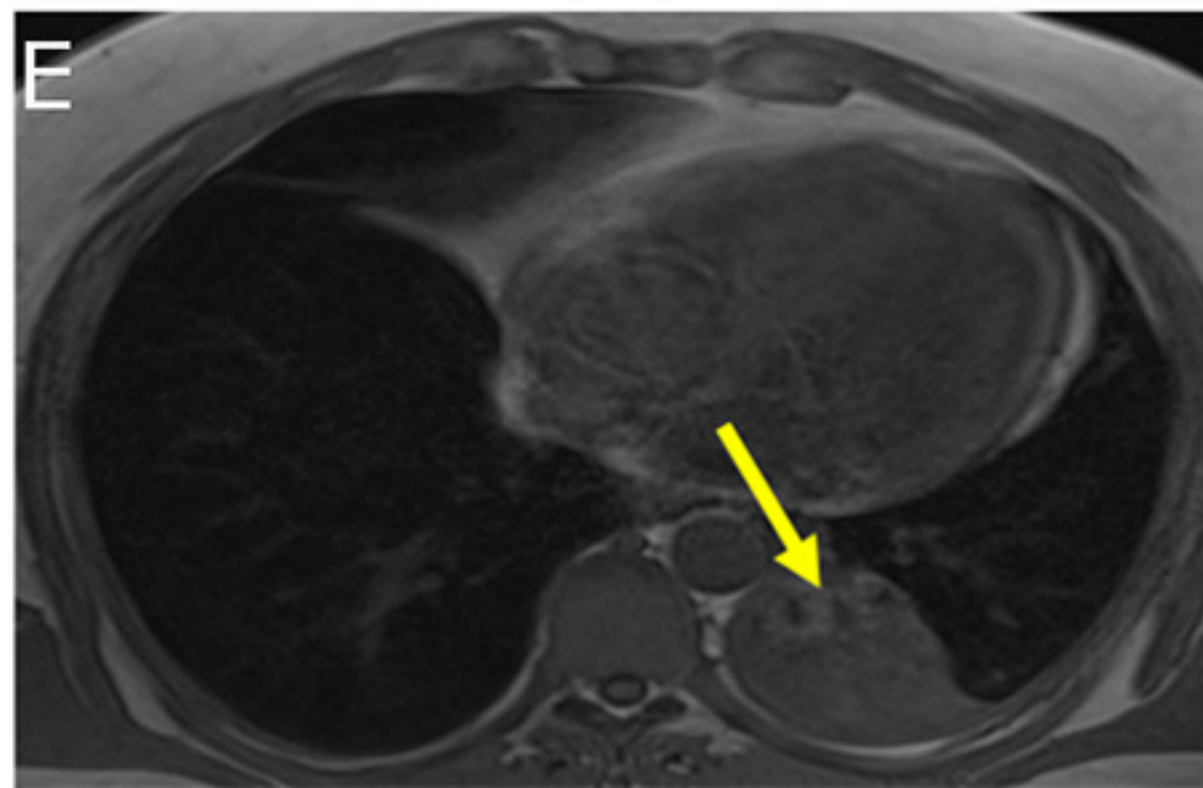
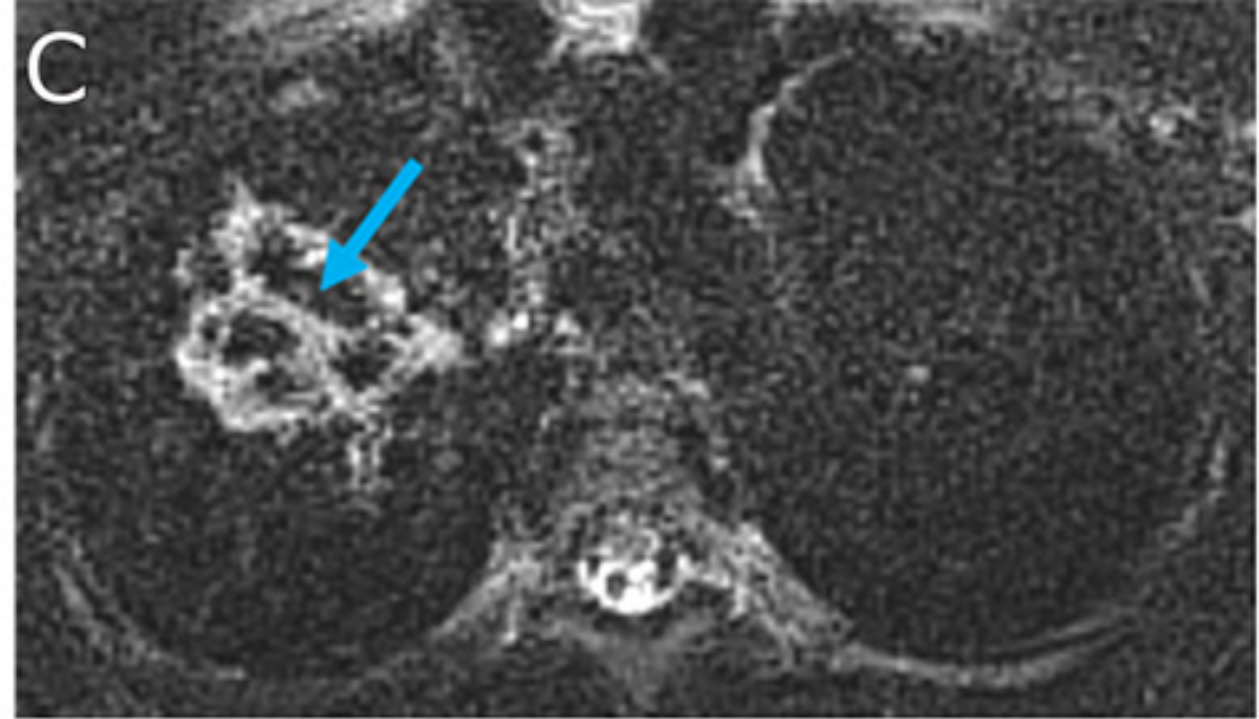
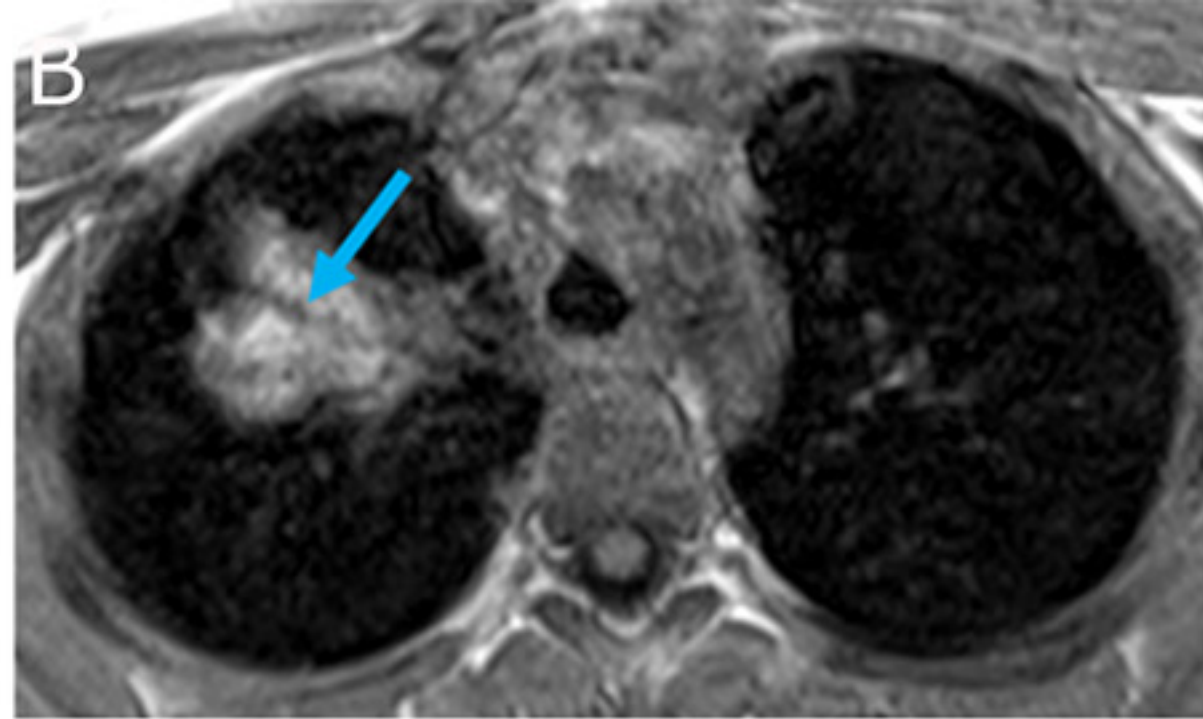
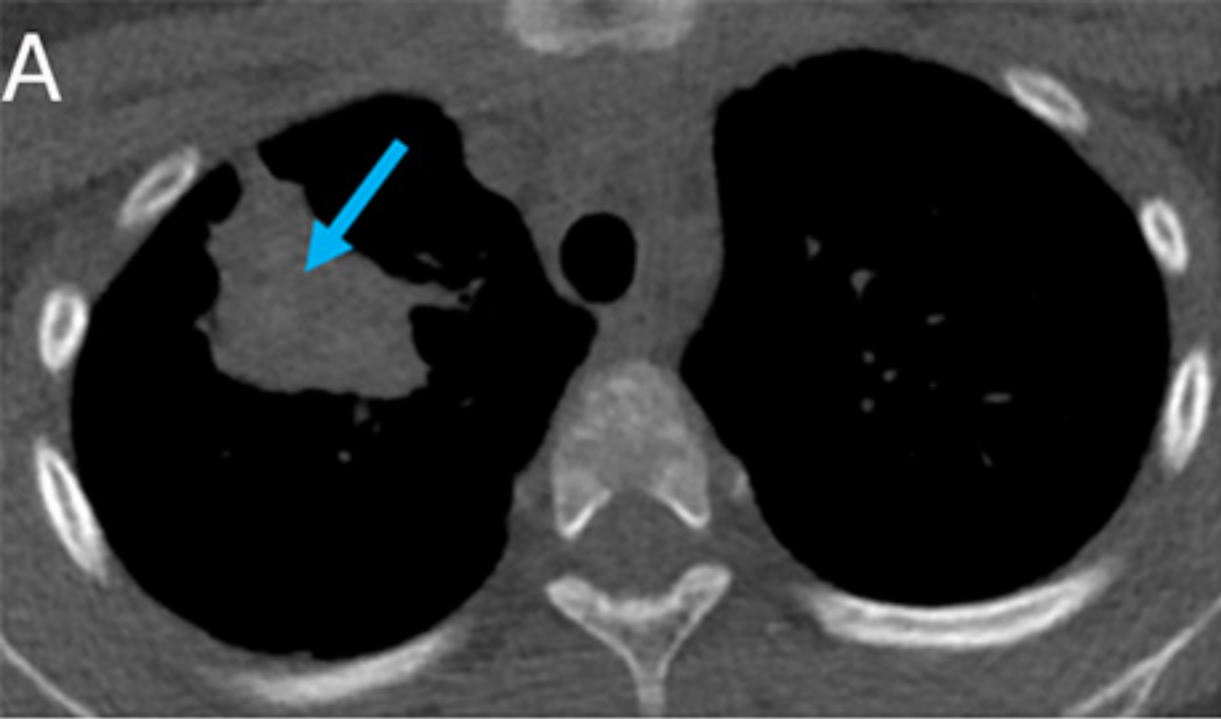
Table E5. Patient Characteristics before and after Treatment in 18 Patients with ABPA

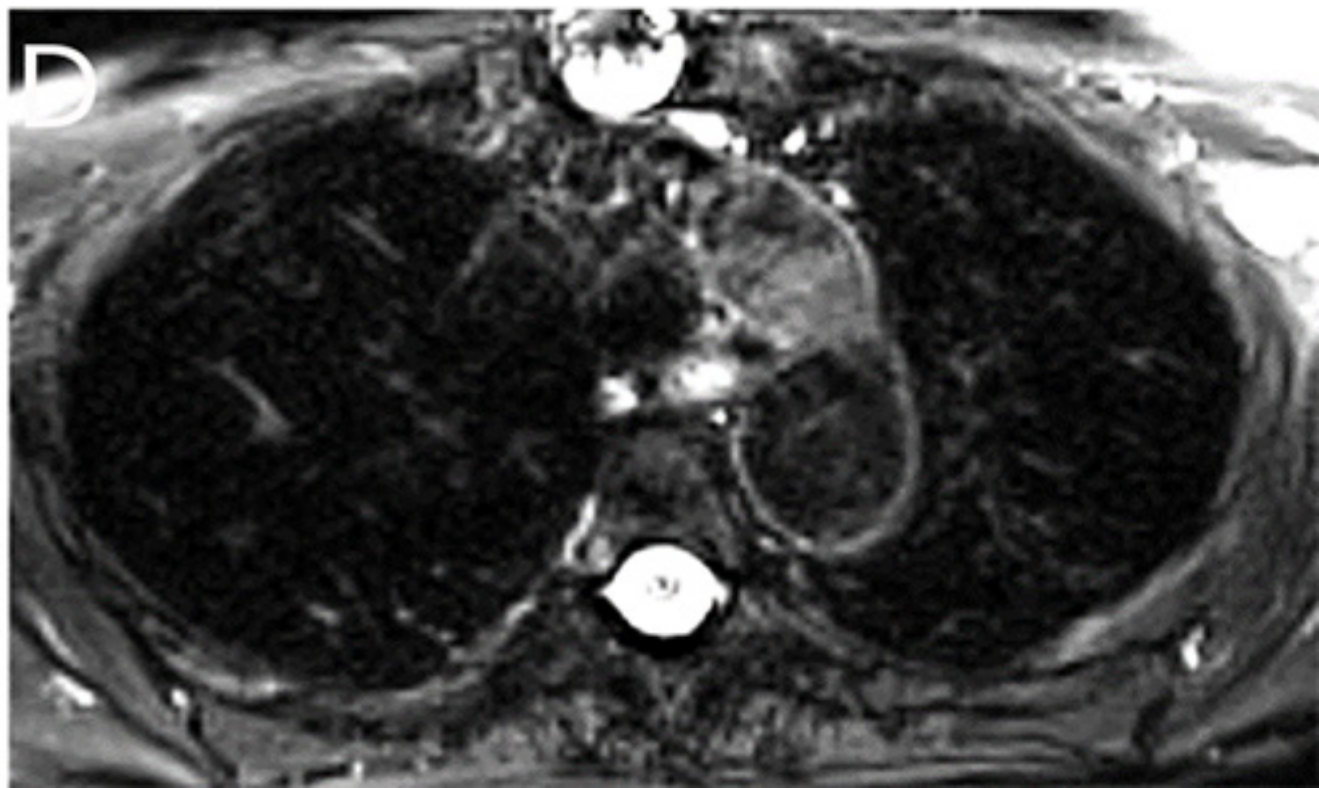
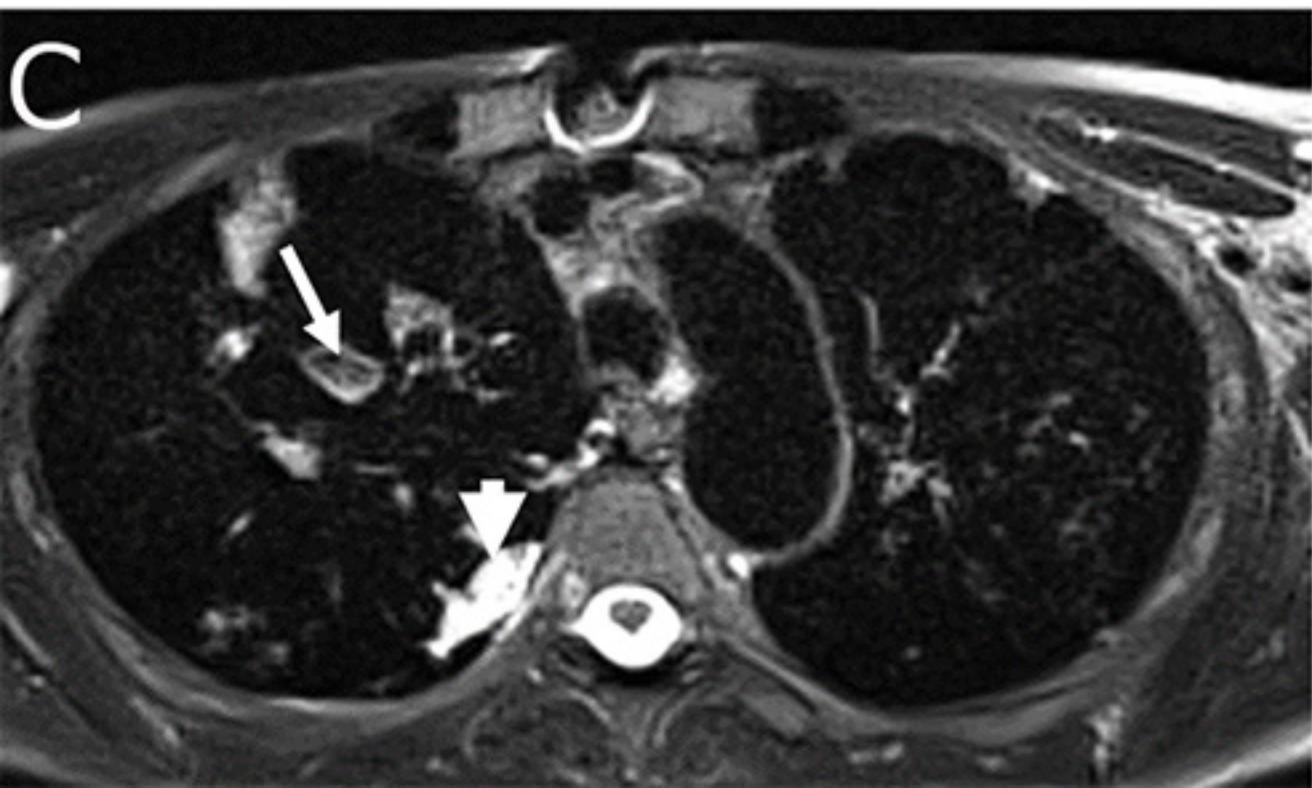
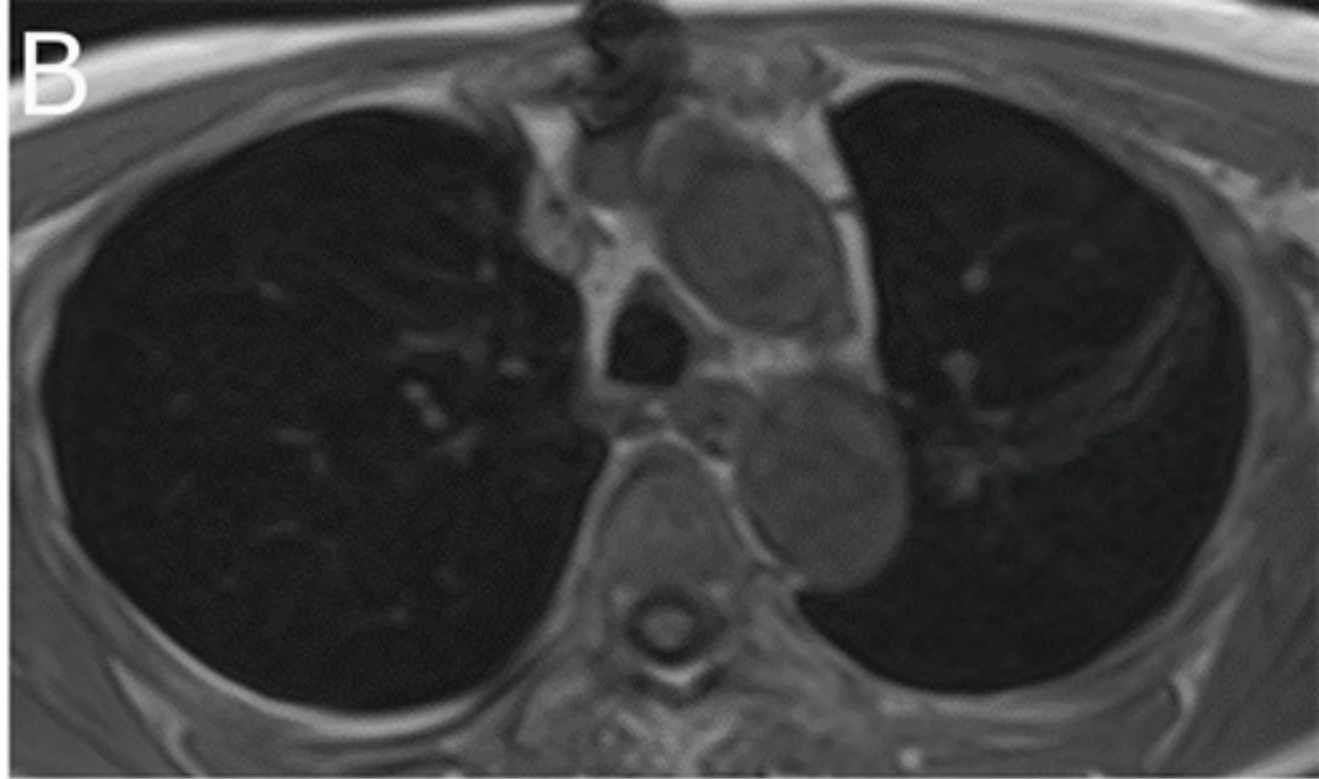
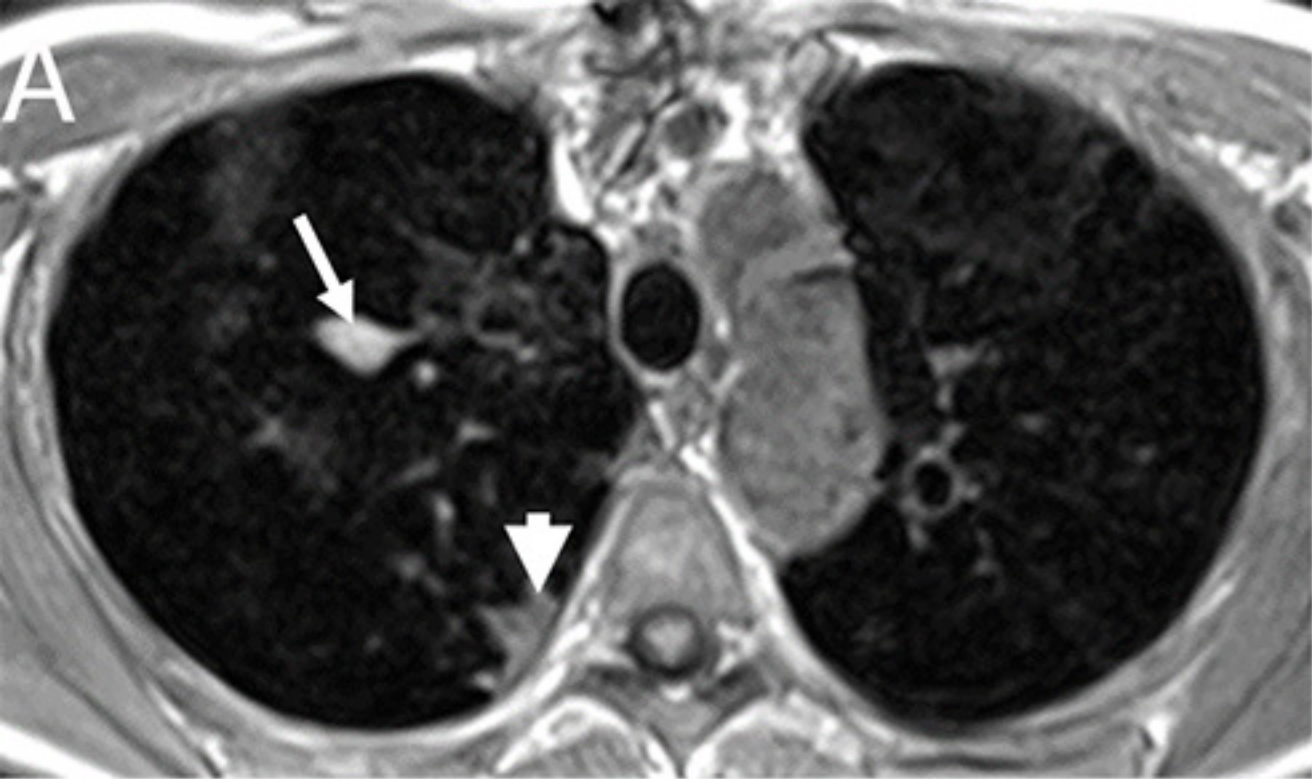
Parameter	Before Treatment	After Treatment	P Value
Exacerbations (yes/no)	18/0	0/18	NA
FEV ₁ (percentage predicted)	80 [62; 87]	84.6 [73; 95]	<.001
Total IgE (IU/mL)	1101 [600; 1524]	415 [320; 690]	<.001
Anti- <i>Aspergillus</i> IgE (IU/mL)	9.3 [3.7; 25.3]	8.1 [2.6; 23]	.40
Anti- <i>Aspergillus</i> IgG			
Positive	13	6	<.001
Intermediate	5	2	<.001
Negative	0	0	NA
<i>Aspergillus</i> culture (positive/negative)	18/0	3/15	<.001
IMIS of central airways (positive/negative)	17/1	0/18	<.001
Peripheral mucus plugs (positive/negative)	7/11	3/16	<.001

Note.—Data are medians with 95% CIs in brackets for continuous variables and are absolute numbers for categorical data. FEV₁ = forced expiratory volume in 1 second. NA = not applicable.

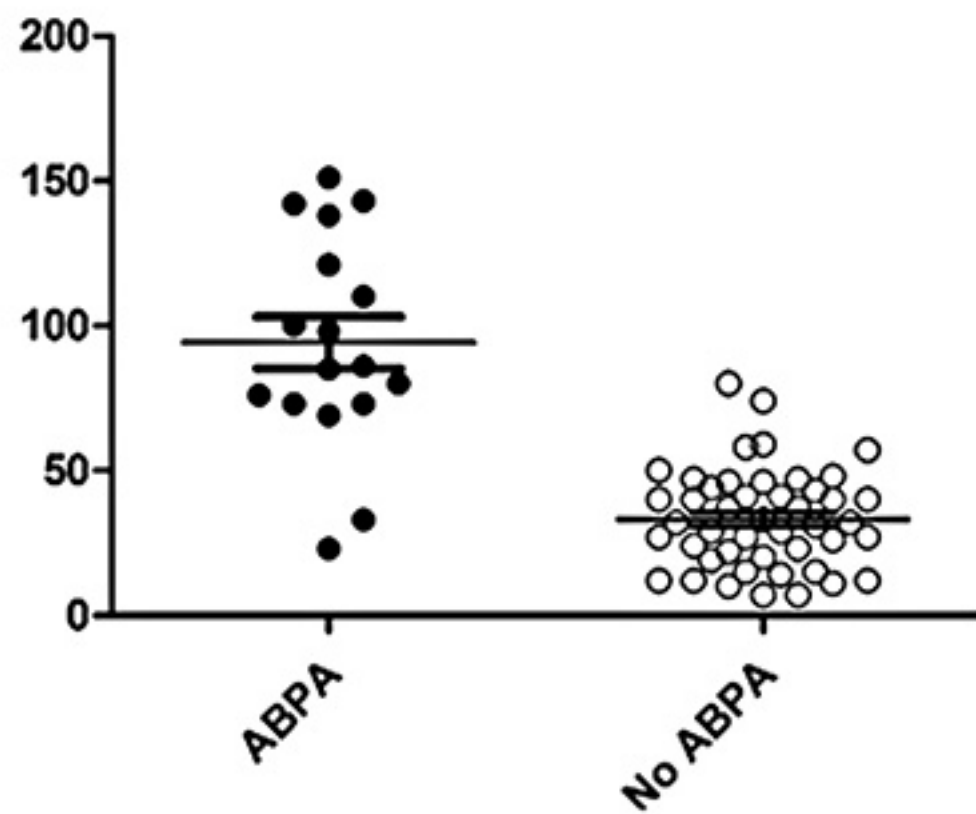
Table E6. Inter- and Intrareader Agreement in Assessing the Presence of Muroid Impaction at CT in 540 Pulmonary Lobes of 108 Patients with CF

Parameter and Analysis Type	Interreader Agreement		Intrareader Agreement	
	κ Value	95% CI	κ Value	95% CI
Positive for HAM sign				
Per lobe	0.81	[0.70; 0.92]	0.84	[0.74; 0.94]
Per patient	0.92	[0.80; 1]	1	[1; 1]
Negative for HAM sign				
Per lobe	0.87	[0.83; 0.92]	0.95	[0.92; 0.98]
Per patient	0.92	[0.83; 0.99]	0.87	[0.78; 0.97]

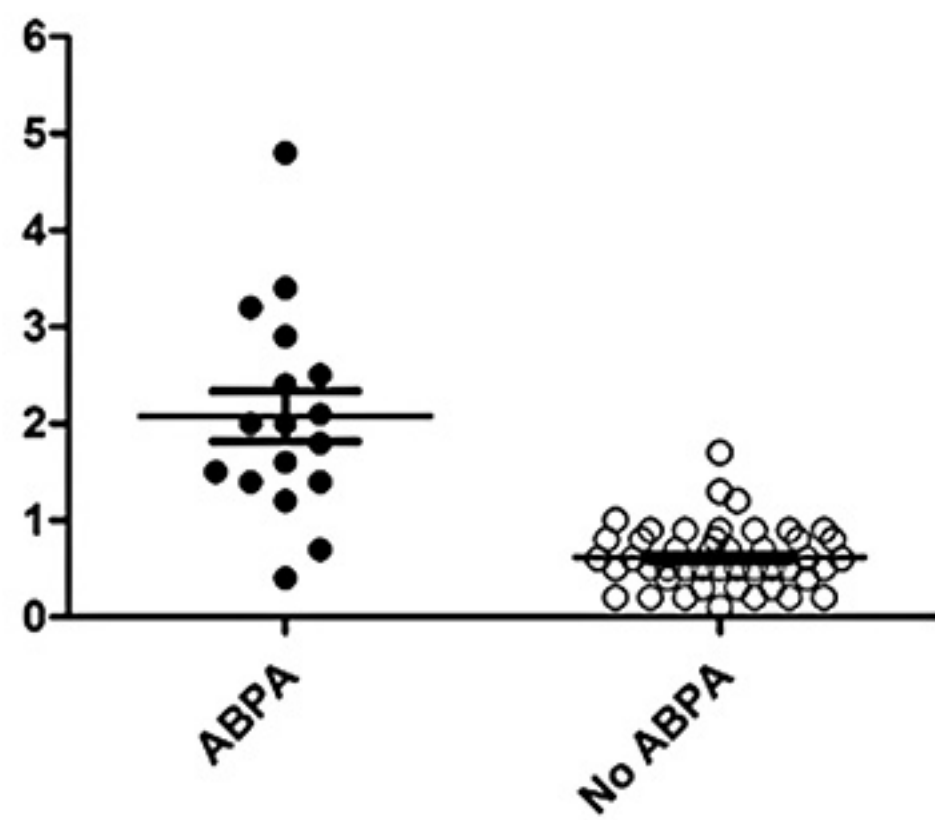




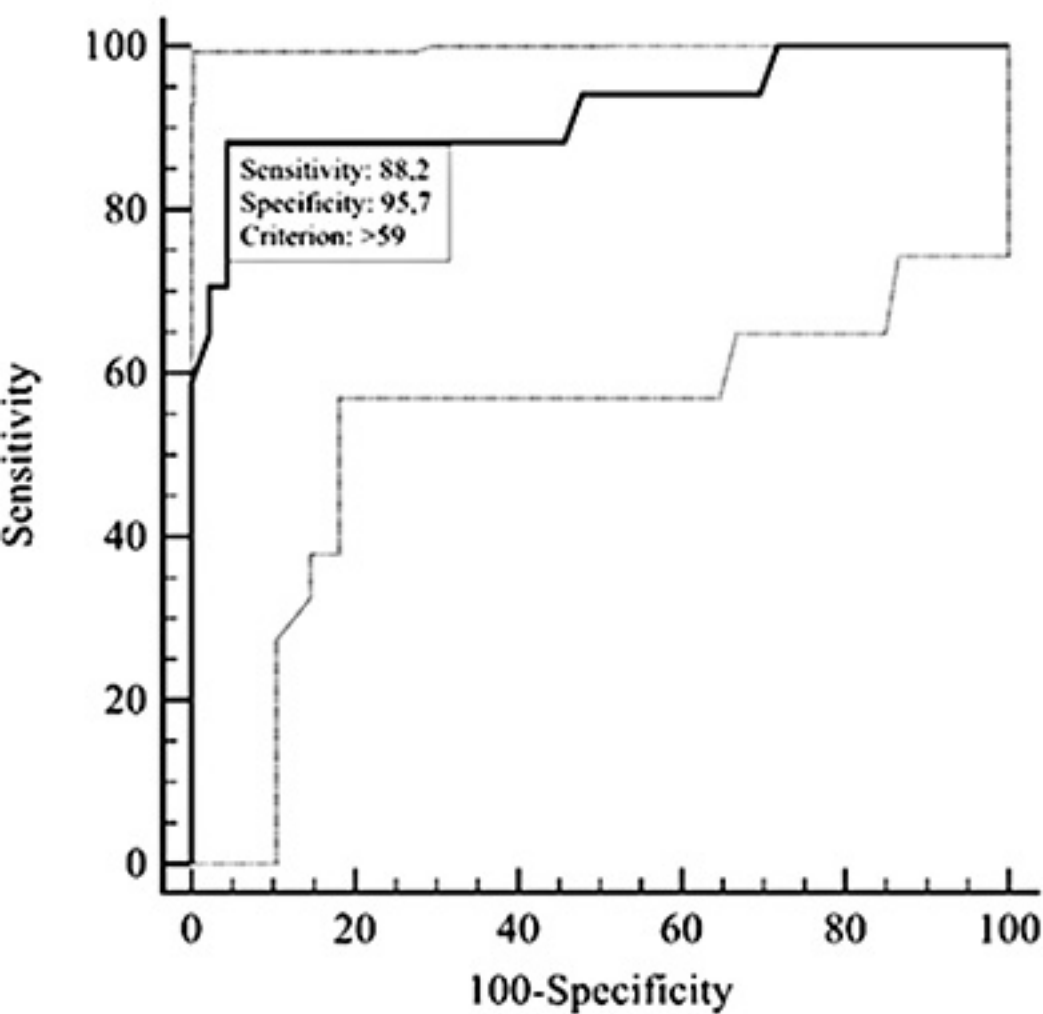
Mucus attenuation



Normalized attenuation



Attenuation



Normalized attenuation

