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Efficacy of model-based iterative reconstruction in cystic fibrosis assessment using CT

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ARTICLE INFORMATION

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AIM: To evaluate the efficacy of model-based iterative reconstruction (MBIR) constructed non-enhanced ultra-low dose (ULD) computed tomography (CT) of the chest to evaluate cystic fibrosis (CF) pathology.

MATERIALS AND METHODS: ULD-CT was compared with chest X-ray and standard adaptive statistical iterative reconstructed (ASIR) non-enhanced low-dose CT (LD-CT). The effective radiation dose was calculated from the recorded dose–length product (DLP) values and compared between the two CT methods. Identification of pathology was compared between ULD-CT and chest X-ray. It was hypothesised that ULD-CT would be superior to chest X-ray in the identification of CF pathology at lower doses than LD-CT.

RESULTS: The mean effective radiation dose of ULD-CT was 0.073 mSv, comparable to one chest X-ray, which was a 94% reduction compared to LD-CT. Compared to chest X-ray, ULD-CT detected on average, 2.3 more regions of bronchiectasis per study and better delineated varicose and cystic forms of bronchiectasis ($p \leq 0.0001$). ULD-CT identified four-times more mucous plugging than chest X-ray ($p < 0.000001$) and twice the amount of consolidation ($p = 0.0002$).

CONCLUSION: ULD-CT is superior to chest X-ray in quantifying CF disease and achieves remarkable radiation doses significantly lower than LD-CT, comparable to one chest radiograph. The present results suggest that MBIR-constructed ULD-CT is an effective imaging technique for CF surveillance, with potential applications in other disease settings.

Introduction

Cystic fibrosis (CF) is a common genetic condition causing chronic respiratory and multi-organ diseases. Predicted survival is now 37.4 years[1,2]; however, pulmonary exacerbations remain a leading cause of morbidity[3] and mortality.[4,5] Timely intervention is crucial, but requires early detection of pulmonary pathologies.[3,6] Plain chest radiography[7,8] has been the primary disease surveillance mechanism[9] and has an average radiation dose of 0.01–0.2 mSv.[10] Other investigations, including pulmonary function testing, have limited predictive value in the assessment of disease extent.[11,12] Over the last 15 years, the use of computed tomography (CT) for CF imaging has increased nearly sixfold[13] as pulmonary lesions are better identified and quantified on CT[14]; however, routine chest CT confers radiation doses of 5–6 mSv per scan.[15] Cumulative radiation doses exceeding 50 mSv a year or 100 mSv a lifetime may be incurred, at which stochastic effects are likely to occur.[16,17]

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Current CT image reconstruction techniques include filtered back projection (FBP) and adaptive statistical iterative reconstruction (ASIR). FBP is one of the earliest CT reconstruction techniques. It allows speed and simplicity; however, it is sensitive to signal and noise levels. ASIR uses a proportion of FBP and the full statistical iterative reconstruction to create a blended image. ASIR reduces quantitative image noise, with similar diagnostic confidence[18] and dose reductions of 32–65% compared to FBP.[19]

MBIR is the latest and most advanced CT iterative reconstruction technique that incorporates the three-dimensional nature of the X-ray source, image voxel, and detectors in its iterative process. With backwards and forwards projections, MBIR matches the reconstructed image to the acquired data iteratively by manipulating data using a statistical metric[20,21] in cycles (Fig 1). MBIR reduces radiation dose without increasing noise. It significantly reduces noise magnitude and improves noise spatial uniformity.[22] Texture enhancement functions[23] and specific algorithms[24] can then be employed to improve image quality. MBIR has been shown to construct clinically acceptable non-contrast CT chest for detection of lung disease at 70–80% reduced radiation dose,[25,26] a level comparable to plain chest radiography (Fig 2).

The present retrospective study was undertaken to evaluate the efficacy of ULD-CT using MBIR image reconstruction technique in the imaging assessment of CF compared to chest X-ray and LD-CT, in the effective radiation dose and identification of major pulmonary pathology.

Materials and methods

Patient cohort and CT protocol

Low-risk ethics approval was obtained from the institution's ethics committee for this retrospective study. There was no change in the referral pattern or scanning practice.

CF patients who had undergone non-iodinated contrast medium-enhanced ULD-CT and chest X-ray within 7 days of the chest CT examination from July 2014 to June 2017 were included in the study. Patients who received standard non-iodinated contrast medium-enhanced chest LD-CT during the study period when ULD-CT was not available, were also included if the chest X-ray (PA and lateral) was performed within 7 days. Studies were excluded if CT was markedly degraded by motion artefact, iodinated contrast medium

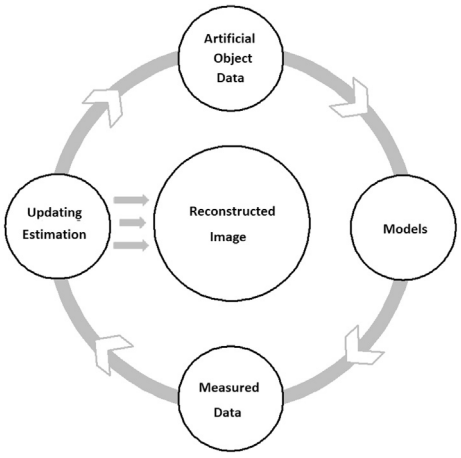

Figure 1 MBIR.

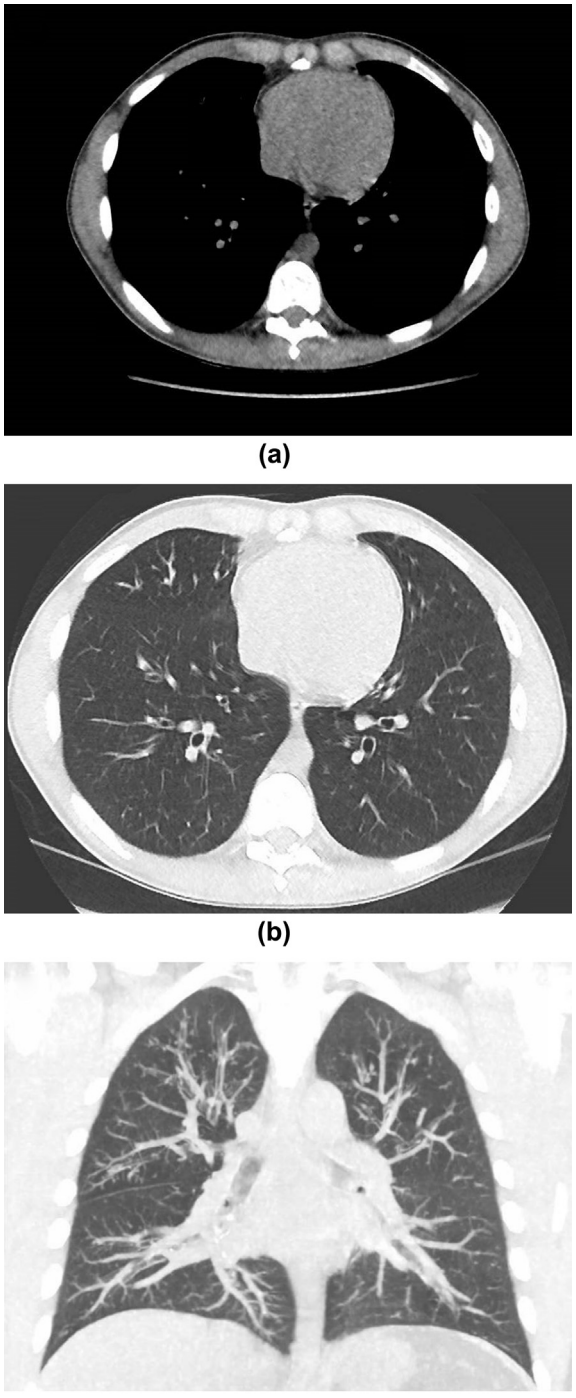

Figure 2 Appearances of MBIR CT chest in (a) axial soft-tissue window, (b) axial lung window, and (c) coronal lung window reformat in an adult patient. Scanning parameters were 80 kVp, 10 mA, and 0.4 second rotation time. DLP of the CT was 5.15 mGy·cm (effective dose 0.072 mSv).

was given, radiation dose data were not available, or chest radiographs were performed outside the 7-day period. CT protocols are described in Table 1. CT dose index ($CTDI_{vol}$) and dose–length product (DLP) were recorded for each study. The effective CT dose was calculated by multiplying DLP with a k value of 0.014. Patient demographics including age, gender, and body mass index (BMI) were recorded. Studies were de-identified and readers were blinded.

Image analysis

Two blinded radiologists with 6 and 28 years of chest CT and plain radiography experience randomly examined the ULD-CT de-identified chest images on the picture archiving and communication system (PACS). Chest radiographs were blindly and randomly examined at separate settings with no reference to CT images. De-identified standard three image planes (axial, sagittal, and coronal) of each CT study were displayed on standard PACS windows, with windowing permitted for the observer's comfort.

The presence, type, severity, and distribution of bronchiectasis was assessed and compared between ULD-CT and chest radiographs. Severity was graded according to the bronchiectasis severity component of the Bhalla scoring system.[27] The severity of bronchiectasis was scored as none (absent), mild (bronchial lumen being slightly greater than adjacent vessel), moderate (bronchial lumen being two to three times the adjacent vessel), severe (bronchial lumen being over three times the adjacent vessel). The exact lobes of the lung (upper, lower, right middle, and lingula lobes) where bronchiectasis was found in each patient's CT were recorded. The presence of mucous plugging was recorded and quantified on each study. The total number of mucous plugs were counted and compared.

Additional findings included the presence of other assessed pathologies including tree-in-bud, suspected pulmonary hypertension with enlarged pulmonary arteries, pneumothorax, peribronchial thickening, nodules, mucous plugging, lymphadenopathy, ground glass, emphysema, effusion, consolidation, cavity, and atelectasis. Features were assessed on a binary scale of whether they were appreciable or not on chest X-ray and ULD-CT.

Table 1
Ultra-low (ULD-CT) and low-dose computed tomography (LD-CT) protocols.

	ULD-CT	LD-CT
No. of scans (image quality)	169	21
CT scanner	64-slice gemstone Multi-detector CT (MDCT) GE HealthCare, Milwaukee, USA	256-slice MDCT iCT, Philips Healthcare, Cleveland, USA
Scan parameters	100 kVp, 10 mA, 0.625 mm collimation, 1.3 pitch, 0.4 second rotation	100 kVp, 250–400 mA with automatic exposure, 0.5 mm collimation, 1.3 pitch, 0.275 second rotation
Reconstruction parameter	MBIR protocol (VEO, GE Healthcare, Milwaukee, WI, USA) Slice thickness: 5 mm axial, coronal and sagittal planes Mediastinal and lung windows Coronal MIPs images in lung window	ASIR: level 4 iDose (iDose, Philips Healthcare, Cleveland, OH, USA) Slice thickness: 5 mm axial, coronal and sagittal planes Mediastinal and lung windows Coronal MIPs images in lung window

Statistical analysis

Microsoft Excel 2007 and MedCalc for Windows, version 17.8.6 (MedCalc Software, Ostend, Belgium) were used. Shapiro–Wilk test and graphical visualisation were used to evaluate normality. Non-normal variables were analysed by median, interquartile range (IQR), and the Mann–Whitney U-test for independent samples to compare medians. Fisher's exact test was used to compare proportions. p-Values <0.05 were considered significant.

Results

Baseline characteristics

During the study period, 240 CT examinations (219 ULD-CT and 21 LD-CT) of 103 CF patients were undertaken. Overall, 75% of the CT examinations were performed for acute presentations and 25% for follow-up. Of the 219 ULD-CT examinations, one was excluded as the CTDI and DLP data were not available, five were excluded due to administration of intravenous iodinated contrast medium, and 44 were excluded as they lacked a chest X-ray within 7 days of the CT. After exclusions, 169 ULD-CT studies with chest X-rays within 7 days were available for assessment. Of the 21 LD-CT examinations performed, 19 patients also underwent ULD-CT, with a mean time difference between scans of 30 months (range 1–76 months). Many patients underwent more than one ULD-CT examination, as depicted in Table 2.

The baseline patient characteristics are displayed in Table 3. There was a statistically significant difference between BMI of the two groups ($p=0.0065$) even after removal of four outliers ($p=0.0092$) with higher values within the ULD-CT group (Fig 3). Age and gender of both CT groups were not significantly different.

Table 2
Scans performed per patient.

No. of ULD-CT examinations per patient	No. of patients
1	31
2	24
3	10
4	4
5	2
6	3
7	1
8	0
9	1

Table 3
Baseline characteristics.

	ULD-CT	LD-CT	*p*-Value
Total no. of scans	169	21	
Median BMI [IQR]	21.37 [19.72–23.10]	20.02 [19.08–21.19]	0.0065 0.0092 (outliers removed)
Mean age [SD]	27.57 [7.29]	25.29 [7.41]	0.1786
Female patients	72 (42.6%)	9 (43%)	1.0000
Male patients	97 (57.4%)	12 (57%)	

ULD-CT, ultra-low-dose computed tomography; LD-CT, low-dose computed tomography; BMI, body mass index.

CT dose

DLP was similar in patients with low to normal BMI, but increased in patients with BMI >25 (15% of patients; Fig 4). The median DLP and ED for ULD-CT were 5.24 mGy·cm (interquartile range [IQR]: 4.98–5.53) and 0.073 mSv (IQR: 0.070–0.077), and these for LD-CT were 86.82 mGy·cm (IQR: 70.145–150.51) and 1.22 mSv (IQR: 0.98–2.11). Both the median DLP and ED in the ULD-CT cohort were significantly lower than LD-CT ($p<0.0001$). Despite higher BMIs in the ULD-CT cohort, the ED was still much lower and achieved statistical significance.

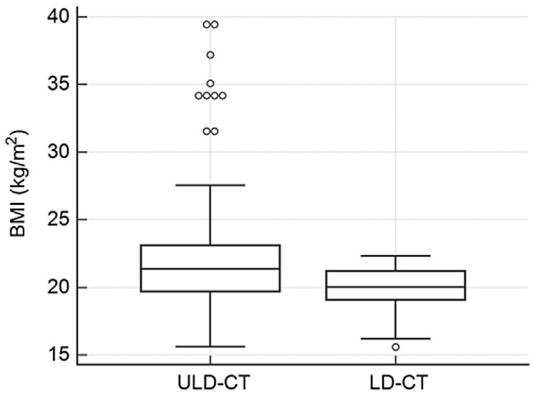

Figure 3 Distribution of patient BMI in both groups.

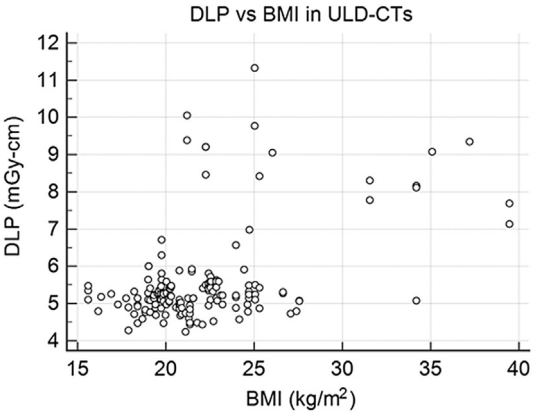

Figure 4 DLP versus BMI in ULD-CT.

Identification of pathology

Nineteen of the 21 LD-CT examinations performed had overlapping ULD-CT studies on the same patient and had exact identification of pathology, thus only ULD-CT was compared with plain chest radiographs for detection of pulmonary pathology. ULD-CT was considered the reference standard due to its high sensitivity and accuracy (Fig 5).

Bronchiectasis

The overall prevalence of bronchiectasis was 93.5% on chest X-rays and 95.9% on ULD-CT examinations ($p=0.47$) in the CF patients. In four patients (2.47%), bronchiectasis was not detected on chest X-rays, but was seen on ULD-CT. ULD-CT was better at identifying varicose and cystic types of bronchiectasis ($p\leq0.0001$), but equivalent in assessing the cylindrical type (Fig 6). The severity of bronchiectasis was

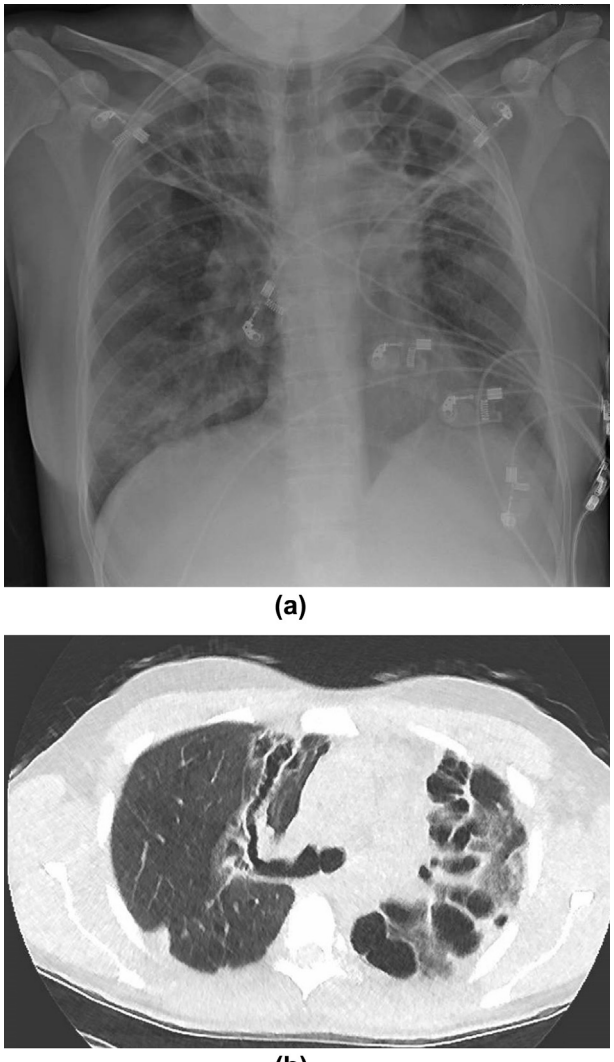

Figure 5 Cystic and varicose bronchiectasis. (a) Chest X-ray and (b) MBIR ULD-CT.

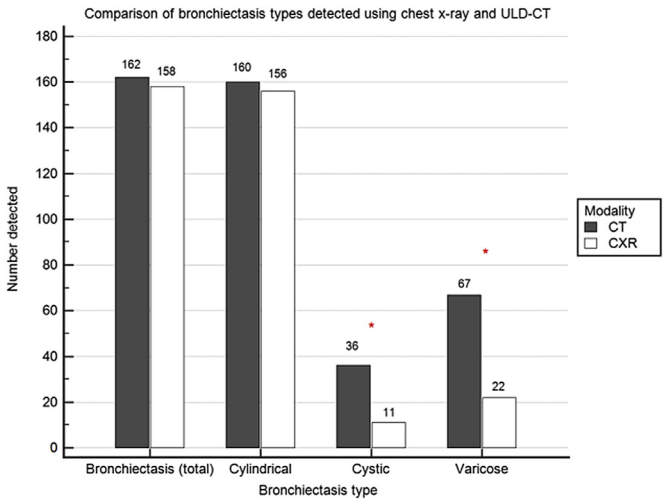

Figure 6 Assessment of bronchiectasis using chest X-ray and ULD-CT.

assessed equally on chest X-ray and ULD-CT (Table 4). Dividing the lungs into six lobes (upper, lower, right middle, and lingula lobes), ULD-CT was able to identify 389 more lobes of bronchiectasis compared to chest X-ray: an average of 2.3 more lobes of bronchiectasis were identified per study.

Mucous plugging

Mucous plugging was detected on 138 ULD-CT examinations (82%) and 35 chest X-rays (21%; $p<0.000001$), which is statistically significant. Where mucous plugging was present, ULD-CT was able to identify on average 7.4 more regions of mucous plugging compared to chest X-ray when each plug was considered separately (Fig 7).

Additional findings

In nearly all cases, ULD-CT was able to identify pathology with greater accuracy than chest X-ray (Fig 8). Table 5 provides reference *p*-values for each comparison. Consolidation was detected on twice the number of ULD-CT examinations compared to chest X-ray ($p=0.0002$). Markers of disease activity, such as atelectasis, peribronchial thickening, cavities, tree-in-bud, inflammatory nodules, and lymphadenopathy, were much better evaluated using ULD-CT (Figs 9 and 10). Interestingly, emphysema was only seen in three cases (1.2%) on ULD-CT and not on chest X-ray at all.

Table 4
Bronchiectasis severity (number detected).

	Chest X-ray	ULD-CT	*p*-Value
None	7	7	1.000
Mild	56	56	1.000
Moderate	86	85	1.000
Severe	20	21	1.000

ULD-CT, ultra-low dose computed tomography.

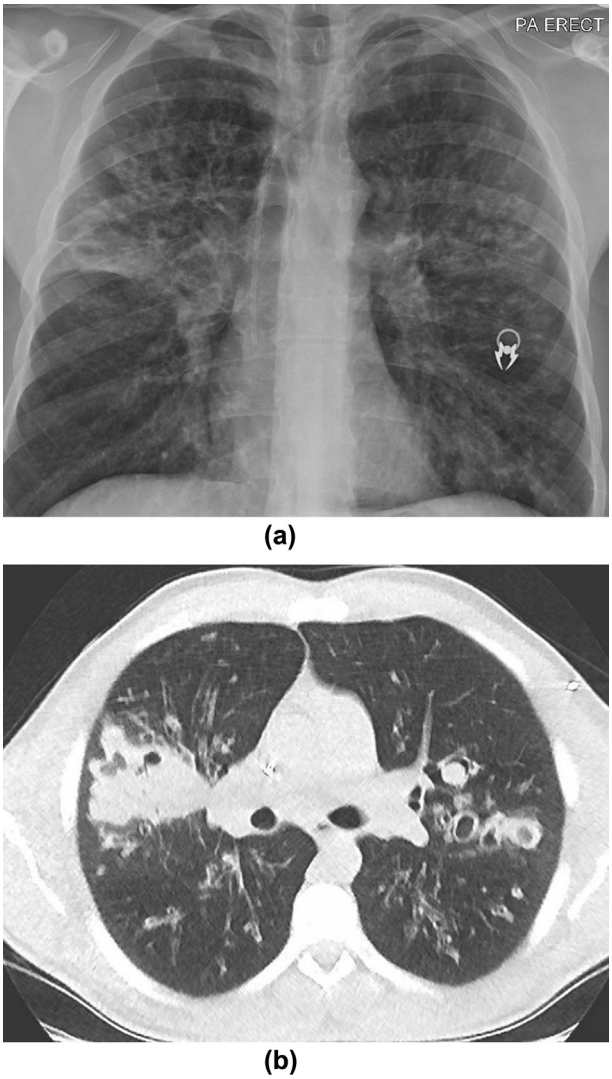

Figure 7 (a) Chest X-ray performed 1 day before (b) MBIR CT showing right upper lobe opacity and bilateral upper lobe bronchiectasis. CT confirmed multiple bronchocoeles, consolidation, and bronchiectasis.

Discussion

Iterative CT image reconstruction is available with most modern CT systems. The latest CT systems would have the advanced MBIR or hybrid-MBIR. The calculated median effective dose of ULD-CT reconstructed with MBIR was 0.073 mSv in the present study. This was 94% lower than the standard LD-CT with a median effective dose of 1.22 mSv and comparable to doses of 0.16 and 1.13 mSv previously reported in the literature.[26,28] As expected, a higher BMI necessitated higher $CTDI_{vol}$, DLP, and effective doses; however, even in patients with BMI >35, the estimated effective dose remained far lower than LD-CT.

Chest X-ray has been the most widely used imaging method for CF evaluation as it is readily available and easy to perform; however, it has well-published miss rates of 19% and 24% for lung cancer, as well as limited sensitivity for subtle pathology.[29–31] The present study showed that chest X-ray could detect bronchiectasis as well as ULD-CT in CF

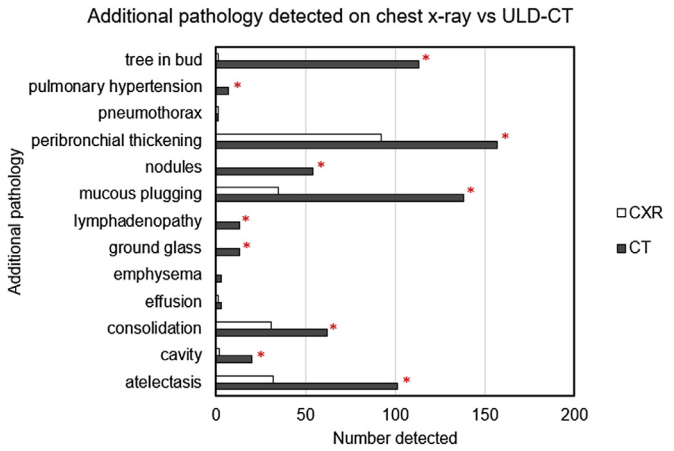

Figure 8 Additional pathology detected on CXR versus ULD-CT. Asterisk indicates statistical significance (see Table 5 for *p*-values).

Table 5
Additional pathology detected on chest X-ray versus ultra-low dose (ULD) computed tomography (CT).

Pathology	Chest X-ray	ULD-CT	p-Value
Tree in bud	1	113	<0.000000001
Pulmonary hypertension	0	7	0.014665824
Pneumothorax	1	1	1.00
Peribronchial thickening	92	157	<0.000000001
Nodules	0	54	<0.000000001
Mucous plugging	31	137	<0.000000001
Lymphadenopathy	0	13	0.000192107
Ground glass	0	13	0.000192107
Emphysema	0	3	0.247774481
Effusion	1	3	0.622764516
Consolidation	31	62	0.000235873
Cavity	2	20	0.000074315
Atelectasis	32	101	<0.000000001

patients who normally have these marked changes in their lungs, but often missed mucous plugging and other markers of pulmonary disease. To improve sensitivity, multiple scoring systems have been developed to evaluate chest X-ray in CF patients; however, a universally accepted system has not yet been identified.[27,32,33] The main limitations of the scoring systems were interobserver variability of identifying pathologies and an inability to discriminate between moderate and gross changes on plain radiographs.

Conventional CT has the greatest sensitivity for parenchymal and small airways disease amongst all imaging methods, but is limited by radiation dose and expense. In the literature, CT is superior to chest X-ray in evaluating early disease and correlates most closely with clinical progress of CF patients.[34–36] Mucous plugging is the first radiological manifestation of bacterial overgrowth, and bronchiectasis the first sign of irreversible lung disease[36]—time points where early intervention is crucial.[37] When a formal CT scoring system was used, results were reproducible across the board, and had good correlation with forced expiratory volume in 1 second (FEV_1).[5]

The present study shows that MBIR can achieve superior diagnostic quality images with radiation exposure comparable to that of one chest radiograph. ULD-CT detected more

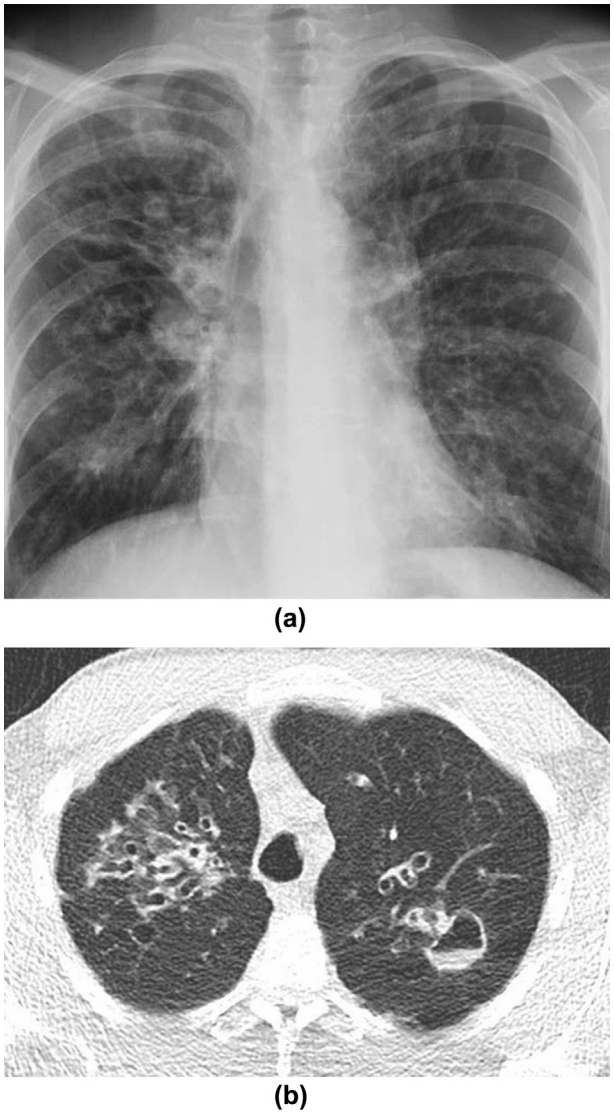

Figure 9 Left upper lobe cavity is difficult to see on (a) chest X-ray, but is easily defined on (b) MBIR ULD-CT.

bronchiectasis, mucous plugging, consolidation and other markers of disease activity compared to chest X-ray. Bronchiectasis is considered an early sign of irreversible lung injury, correlates with exacerbation rate, and has been shown to progress faster than spirometry in both paediatric and adult populations.[38] Mucous plugging as an early sign is, however, potentially reversible, thus early detection may guide treatment.[8] Similarly, evidence of consolidation seen on ULD-CT may initiate faster treatment and alleviation of infection. In the present study, 75% of ULD-CT examinations were performed for acute presentations and 25% for follow-up; however, pulmonary disease can progress in the absence of symptoms. Therefore, ULD-CT may even be an effective screening tool for asymptomatic patients.

Emphysema was detected at ULD-CT in three patients, but not on plain radiographs. Emphysema is an important marker of potentially irreversible small airways disease and is difficult to assess on chest X-ray. Even at the ultra-low dose level, emphysema can be visualised on CT due to the

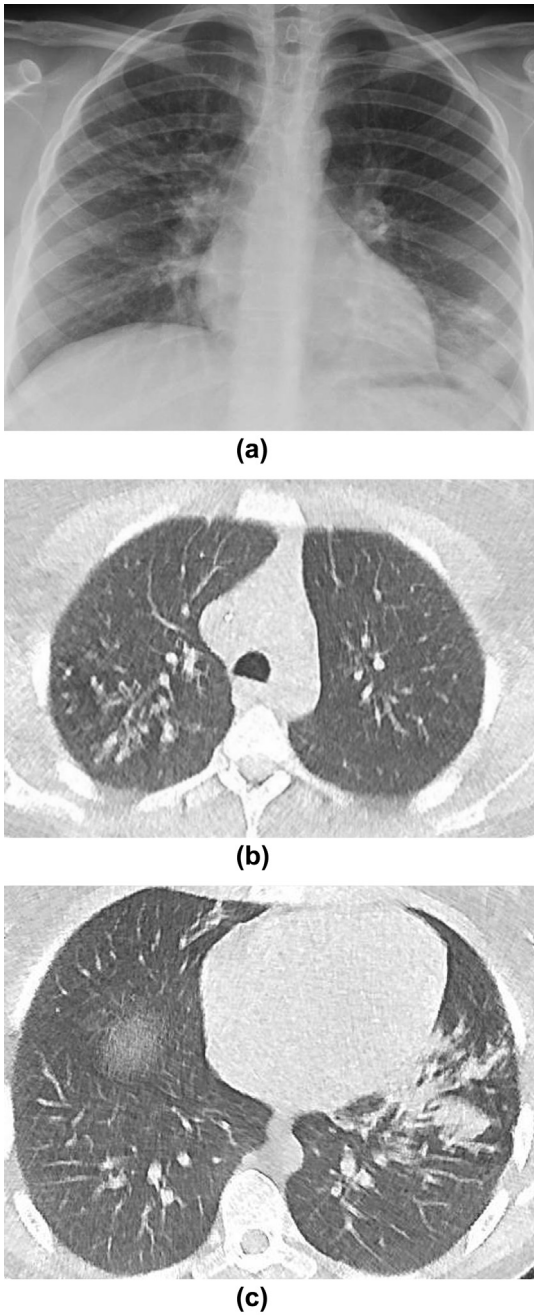

Figure 10 (a) Chest X-ray demonstrates left lower lobe consolidation and right upper lobe bronchiectasis. (b–c) MBIR ULD-CT confirms these findings and also shows mucous plugging in the right upper lobe.

reduced image noise. Emphysema is generally difficult to appreciate on plain radiographs and it can be obscured by other gross parenchymal changes in CF patients.[39,40] The addition of end-expiratory imaging in patients suspected of severe small airways disease would further clarify, but the radiation dose would double.

In CF patients, accurate evaluation and prediction of pulmonary disease changes using CT guides clinicians on early intervention and prevention of permanent lung damage. Certain CT scores have also been shown to correlate with mortality while on the lung transplant waiting list, as well as post-transplant mortality,[41,42] with potential roles in transplant allocation. Bronchiectasis-based CT scores have shown correlations with the number of respiratory exacerbations and even shown predictive value in some paediatric studies.[43,44] In adults, high-resolution CT (HRCT) findings deteriorate more rapidly than spirometry, with the most common abnormalities being bronchiectasis, mucous plugging, and peribronchial thickening.[12] A study by Shah in adult patients identified mucous plugging, peribronchial thickening, and air–fluid levels on HRCT as reversible findings in acute exacerbations and HRCT severity scores correlating with spirometry.[45] The Bhalla scoring system evaluates lung impairment and is more sensitive than spirometry in detecting initial changes[46] in all ages. These studies demonstrate the role of imaging in CF assessment in both adults and children.

Ivacaftor is an oral transmembrane conductance regular (CFTR) potentiator used in CF patients with G551D mutation. Monitoring of treatment response to ivacaftor has been demonstrated with HRCT scanning, demonstrating the role of imaging in treatment surveillance.[47] Further research involving gene therapy is currently underway and MBIR-based CT would be invaluable in identifying prospective patients and evaluating treatment response.

Several studies have compared FBP, ASIR, and MBIR techniques in chest imaging. The largest was a systematic review by Den Harder *et al.*,[24] who found that objective image quality, diagnostic confidence, and acceptability of IR algorithms were equal or improved compared to FBP in most studies.[24] Dodge *et al.*[48] used a phantom study to compare FBP, ASIR, and MBIR over a range of typical to low dose intervals. They found that ASIR had 1.2–1.8 times greater contrast-to-noise ratio (CNR) compared to FBP. MBIR on the other hand, had a CNR that was five-times higher at low dose levels compared to FBP.[48] MBIR has been shown to provide greater potential than ASIR for diagnostically acceptable LD-CT.[49]

MBIR has extremely high computational requirements and generally requires 30–40-minute processing times. The recently developed hybrid-MBIR has shortened this processing time down to few minutes. In the future, higher computing power will further lessen the time of this iterative requirement. MBIR CT images appear different to FBP CT, and have been described as “plastic” due to the lack of image noise. This may challenge some radiologists who may require some time to adjust.

The main limitation of the present study was a lack of “gold standard” conventional dose CT chest, typically around 5–6 mSv dose, for comparison; however, there was 90% patient overlap in LD-CT and ULD-CT groups in the present study, with imaging features being similar. As such, ULD-CT was mainly used as a reference standard as it identified more pathology than chest X-ray. Given the availability of ULD-CT at the authors’ institution, the LD-CT examinations were requested by Accident and Emergency physicians after hours, who were unaware of the availability of ULD-CT.

In conclusion, MBIR CT of the chest achieves remarkably low radiation doses in the imaging of CF patients, with

significantly better diagnostic accuracy compared to chest radiography. The present median effective dose of 0.073 mSv is lower than previously published values in CF patients. This is a significant advancement for CF patients requiring regular imaging assessment. The MBIR algorithm will likely also have broader applications in other forms of chest and body imaging. The present study has clearly demonstrated the superiority of MBIR ULD-CT in the imaging of CF patients.

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Conflict of interest

The authors declare no conflict of interest.

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