Pulmonary fibrosis is the preferred general term for the permanent replacement of lung parenchyma by connective tissue and is typically associated with functional impairment. A variety of insults cause focal or diffuse lung injury (mechanical, infectious, inflammatory, and iatrogenic). Lung repair culminates in fibrosis with volume loss and architectural distortion.

Terminology

In certain cases, fibrosis may be focal and may be stable over time. In others, fibrosis can be progressive and follow a recognisable CT pattern such as UIP or NSIP. Interstitial lung abnormality refers to early fibrotic lung disease which may progress.

Pathology

Fibrosis in the lung is a process that occurs in the interstitium. Pulmonary fibrosis can be localized, segmental, or lobar or affect the entirety of the lung(s). Among the many conditions associated with pulmonary fibrosis are:

- significant acute insult to the lungs
    - adult respiratory distress syndrome [4]
    - from a significant pulmonary infection
        - Post COVID fibrosis, especially in patients admitted to ICU and needing intubation/ventilation
    - diffuse alveolar damage from any source
- inhaled substances
    - coal/silica: progressive massive fibrosis
    - asbestos: asbestos-related pulmonary fibrosis
- chronic microaspiration [9]
- radiation: radiation-induced pulmonary fibrosis
- congenital conditions
    - cystic fibrosis
    - Hermansky-Pudlak syndrome
- autoimmune conditions
- connective tissue disorders
- granulomatous conditions
    - sarcoidosis: pulmonary manifestations of sarcoidosis
    - tuberculosis: pulmonary manifestations of tuberculosis
    - granulomatosis with polyangiitis: pulmonary manifestations of granulomatosis with polyangiitis
- others

- airway-centered interstitial fibrosis
- chronic conditions
  - chronic hypersensitivity pneumonitis
  - chronic eosinophilic pneumonia
- polymyalgia rheumatica (occasional case reports [6])
- medications: drug-induced lung disease
- combined pulmonary fibrosis and emphysema'
- aging
  - some studies report thin-section CT findings associated with interstitial lung disease to some degree are frequently seen in "asymptomatic" elderly individuals [7,8]
- idiopathic pulmonary fibrosis

Radiographic features

CT

Early pulmonary fibrosis [12]:

- irregular interlobular septal thickening
- irregular pleural thickening
- intralobular reticular opacity

This can progress with increasing reticulation and

- traction bronchiectasis and bronchiolectasis
- honeycombing
- architectural distortion

Treatment and prognosis

Antifibrotic medication provides benefit for patients with progressive pulmonary fibrosis [12].

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Objective

Chest computed tomography (CT) demonstrates superior sensitivity compared to chest radiograph (CR) in diagnosing and monitoring the progression of lung disease in people with Cystic Fibrosis (PWCF). Nevertheless, many healthcare facilities frequently prefer CR as the initial imaging modality, largely due to radiation concerns. Our study aimed to evaluate and compare the efficacy of Chest CT to CR using a specialised locally designed ultra-low dose CT protocol for surveillance purposes in

Methods/materials

In this prospective single-centre study, paediatric patients as part of surveillance imaging underwent both an ultra-low dose CT (ULDCT) of the chest and a CR during the same clinical visit. Demographic data and the radiation dose for each scan were recorded, using metrics such as the volume CT dose index, the dose length product (DLP), the effective dose and size-specific dose estimate. Two consultant radiologists independently assessed the ULDCTs using the Brody II scoring system, while the

Results

Forty-five paediatric patients, mean age 10.1 years (range 4.5–15.7 years), underwent both an ULDCT of the chest and a CR. The average Brody II score across the cohort was 5.62, with excellent inter-rater reliability and intra-class correlation coefficient (ICC) of 0.98 (95% CI = 0.96, 0.99). The average Chrispin-Norman score was 0.93 with moderate inter-rater reliability and ICC of 0.64 (95% CI = 0.19, 0.83). The mean effective dose for ULDTchestwas 0.066 +/- 0.013 mSv, a dose range

Conclusions

In light of its superior diagnostic capabilities, minimal radiation dose penalty, and higher interobserver reliability, we advocate for ULDCT to be the preferred modality for surveillance imaging in paediatric PWCF.

Objectives

The European Cystic Fibrosis Society - Clinical Trial Network (ECFS-CTN) is focused on optimising the use of chest CT, necessitating an understanding of current practices, dose reduction strategies, and variations across centres. These practices can differ significantly influenced by local expertise, available imaging modalities, and physician confidence. This study aimed to survey European centres to gain a detailed insight into chest CT practices and dose reduction techniques across the

Methods

The survey, developed by ECFS-CTN experts, included 86 items tailored to CF specialist pulmonologist, radiologist and radiographer groups. It covered six domains including indications, protocols, optimisation practices, considerations for low-dose protocols, alternative imaging preferences, and perspectives on imaging scoring systems used for people with cystic fibrosis (PWCF).

Results

The survey attracted 54 respondents fromvarious disciplines in CF centres across 11 European countries. Over 83% of radiologists and radiographers preferred using low-dose CT (LDCT) protocols for surveillance imaging of adult and paediatric PWCF, with 60% having a specific protocol for this purpose. There was no consensus on CT protocol optimisation, with varied approaches to designing low-dose protocols. Common strategies included iterative reconstruction (23/30), reducing mA (17/30),

Conclusion

This study highlights the variability in imaging practices across disciplines and locations, emphasising the need for evidence-based guidelines to optimise and harmonise CT protocols for PWCF.

Objectives

The ‘Exercise as an Airway Clearance Technique in Cystic Fibrosis (ExACT-CF)’ trial was a 28-day randomised, pilot feasibility trial comparing daily ExACT (stopping all other ACTs) with usual care (chest physiotherapy daily). ExACT-CF was co-designed with the UK CF community. Key secondary aims were to evaluate the safety of asking people with CF (pwCF) to stop all traditional ACT and replace it with ExACT.

Methods

In this two-arm randomised pilot trial conducted at two UK CF centres (Edinburgh and Southampton), 50 pwCF (≥10 years, forced expiratory volume in 1 second [FEV_1] >40% predicted; who were stable on Elexacaftor/Tezacaftor/Ivacaftor [ETI]), were recruited and randomly assigned (1:1 allocation using minimisation) to an ExACT programme (stopping all other ACTs) or usual care for 28-days. Safety was assessed by the change in lung clearance index ($LCI_{2.5}$) over the 28-days, change in FEV_1 over the

Results

Fifty participants (58% male) were recruited across the two centres (mean (standard deviation) age: 20.3 (11.6) years). Forty-eight participants were randomised to either usual care or ExACT. We will present data on changes in lung clearance index ($LCI_{2.5}$), spirometry (FEV_1 and forced vital capacity) from baseline through to 28-days, for both study arms. In addition, we will report rates of AEs and SAEs for each study arm. Qualitative findings also revealed that pwCF involved in the trial felt

Chest x-rays (CXR) are commonly performed as part of the evaluation of patients presenting with increased respiratory symptoms in Cystic Fibrosis (CF). There is little evidence to support this practice. Repeated CXR carry a degree of risk, cost and inconvenience for patients. We sought to establish current practice amongst UK Adult CF consultants and to evaluate the diagnostic utility of CXR in adults attending the CF unit in Leicester with new symptoms.

Methods

UK Adult CF consultants were surveyed regarding their use of CXR via a WhatsApp poll. A retrospective case note review was then undertaken of CXR use in Leicester CF adults over a 2-year period. Consultant radiologist reports were recorded alongside evidence showing any changes in diagnosis or treatment based on CXR findings. CXR performed for routine monitoring of CF lung disease were excluded.

Results

35 UK CF consultants took part in our poll. 63% routinely request CXR for all patients attending with increased symptoms; 37% request CXR only if a specific complication is suspected eg pneumothorax. In Leicester 191 CXRs from individual care episodes were reviewed in 73 patients. 82% of CXR showed no new changes from previous films; 17% showed new changes compatible with acute infection and 1% showed evidence of general disease progression. CXR findings made a material contribution to

Conclusions

The routine use of CXR to evaluate CF patients presenting with a change in respiratory symptoms remains widespread. Most CXR do not showany changes from baseline and do not alter the final diagnosis or management. CXR was only useful in our data set in patients presenting with chest pain where it either offered reassurance or lead to further evaluation with CT scanning.

Abstract:

A 65-year-old man, former smoker, developed exertional dyspnea and a dry cough. After a progressive worsening of symptoms, the patient was referred to a pulmonologist. Physical examination showed bilateral crackles at the lower fields of the lungs, a very typical sign of interstitial lung diseases (ILDs). Therefore, a high-resolution computed tomography of the lungs was performed. This showed typical radiological features of “usual interstitial pneumonia,” including subpleural reticulation, honeycombing, and traction bronchiectasis, suggesting an idiopathic pulmonary fibrosis (IPF). Pulmonary function tests revealed a restrictive lung impairment and a moderate reduction of lung diffusion for carbon monoxide. For diagnostic completeness, signs of connective tissue diseases (CTDs) were investigated and a specific antibody panel for CTDs and precipitins was carried out. After a multidisciplinary discussion, the diagnosis of IPF was made and the patient started antifibrotic therapy and a periodic follow-up to monitor disease progression. The chapter deals with the challenging diagnostic workout and the therapeutic choices of IPF, a rare condition that involves lung parenchyma with progressive fibrosis. The lack of specific respiratory symptoms can lead to misdiagnosis of more frequent respiratory diseases such as chronic obstructive

pulmonary disease and consequent diagnostic delay. In this context, the integration of several specific competencies, achieved through the establishment of multidisciplinary teams, is essential.

Objectives

Traditional spirometry involves forced maneuvers that are unphysiological, and the use of a mouthpiece alters normal breathing. Dynamic Chest radiography (DCR) is a novel cinematic imaging technique that visualizes the thorax in motion over 10–20 seconds without using forced maneuvers or a mouthpiece, with a radiation dose similar to a standard chest film. We wished to investigate the relationship between DCR and spirometry.

Methods

Using DCR, a semi-automated calculation of projected lung area (PLA) throughout inspiration and expiration was made, where PLA was recorded at its maximum during inspiration (PLA_{max}) and minimum during expiration (PLA_{min}). Percentage change between these points was also recorded. We compared this with traditional spirometry recorded within 24 hours of DCR acquisition in 20 adult people with cystic fibrosis (pwCF).

Results

The mean (SD) FEV_1 was 70.9 (23.4) % predicted. Mean (SD) PLA_{max} and PLA_{min} was 44164.2 (7873) mm^2 and 32577.4 (8355) mm^2 respectively. The mean (SD) percentage change in PLA between PLA_{max} and PLA_{min} was 25.92% (9.1). There was a significant correlation between lung function in the form of FEV_1 and percentage change of PLA_{max} to PLA_{min} ($r = 0.69$, $p < 0.0001$) and also FEV_1 and expiratory PLA_{min} ($r = -0.44$, p-0.0006). Therewas however no significant correlation between FEV_1 and inspiratory PLA_{max}

Conclusion

DCR metrics correlate with simple lung function in pwCF. DCRs are quick to perform, impart a low radiation dose, and may be better tolerated by pwCF than conventional spirometry. Given the unphysiological nature of forced maneuvers in the measurement of lung function, we are further exploring the utility of DCR in pwCF.

Objectives

This prospective, longitudinal observational multicenter TRACK-CF study aims to gain further insights into the onset and development of early cystic fibrosis (CF) lung disease. Our analysis now focuses on the longitudinal development of the lung clearance index ($LCI_{2.5}$) measured by multiple-breath washout (MBW) and chest magnetic imaging (MRI) scores and the comparison of these two methods with age.

Methods

The study design includes annual MRI and MBW in children spanning the entire pediatric age range. MRI scans were evaluated using a dedicated semi-quantitative morphofunctional score. The spiroware 3.3.1 for the Exhalyzer D device was used. The data exclusively focus on modulator-naïve children.

Results

So far, 163 childrenwere examined repeatedly with a mean age of 4.45 (±4.71) years at their first visit. The study cohort consists of 90 males and 73 females. Of all children, 42.8%were F508del

homozygous and 43.4% of the children were heterozygous with one F508del allele. In the total cohort, the mean $LCI_{2.5}$ was 6.6 (±0.4) in the first year of life and increased to 11.1 (±2.7) at age 18 ($P < 0.001$). The MRI global score increased from 7.1 (±4.8) to 16.3 (±7.8) ($P < 0.001$). Similarly, the MRI

Conclusions

The prospective, observational TRACK-CF study demonstrates that non-invasive methods such as MBWand MRI are sensitive to detect early changes and the longitudinal progression of CF lung disease in modulator-naive children. These findings supports MBW and MRI as complementary outcome measures for monitoring and early intervention trials in children with CF.

Background

SHIP-CT showed that 48-week treatment with inhaled 7% hypertonic saline (HS) reduced airway abnormalities on chest CT using the manual PRAGMA-CF method relative to isotonic saline (IS) in children aged 3-6 years with cystic fibrosis (CF). An algorithm was developed and validated to automatically measure bronchus and artery (BA) dimensions of BA-pairs on chest CT. Aim of the study was to assess the effect of HS on bronchial wall thickening and bronchial widening using the BA-analysis.

Methods

The BA-analysis (LungQ, version 2.1.0.1, Thirona, Netherlands) automatically segments the bronchial tree and identifies the segmental bronchi (G_0) and distal generations (G_1-G_{10}). Dimensions of each BA-pair are measured: diameters of bronchial outer wall (B_{out}), bronchial inner wall (B_{in}), bronchial wall thickness (B_{wt}), and artery (A). BA-ratios are computed: B_{out}/A and B_{in}/A to detect bronchial widening and B_{wt}/A and B_{wa}/B_{oa} (=bronchial wall area/bronchial outer area) to detect bronchial wall thickening.

Results

113 baseline and 102 48-week scans of 115 SHIP-CT participants were analysed. LungQ measured at baseline and 48-weeks respectively 6,073 and 7,407 BA-pairs in the IS-group and 6,363 and 6,840 BA-pairs in the HS-group. At 48 weeks, B_{wt}/A (mean difference 0.011; 95%CI, 0.0017 to 0.020) and B_{wa}/B_{oa} (mean difference 0.030; 95% 0.009 to 0.052) was significantly higher (worse) in the IS-group compared to the HS-group representing more severe bronchial wall thickening in the IS-group (p=0.025 and p=0.019 respectively). B_{wt}/A and B_{wa}/B_{oa} decreased and B_{in}/A remained stable from baseline to 48 weeks in the HS while it declined in the IS-group (all p<0.001). There was no difference in progression of B_{out}/A between two treatment groups.

Conclusion

The automatic BA-analysis showed a positive impact of inhaled HS on bronchial lumen and wall thickness, but no treatment effect on progression of bronchial widening over 48 weeks.

Keywords

Cystic fibrosis

Structural airway disease

Hypertonic saline

Bronchial wall thickening

Artificial intelligence

Computed tomography

Abbreviations

CF

cystic fibrosis

CT

computed tomography

SHIP

the Saline Hypertonic in Preschoolers study

SHIP-CT

the Saline Hypertonic in Preschoolers + CT study

$LCI_{2.5}$

lung clearance index

PRAGMA-CF

Perth-Rotterdam Annotated Grid Morphometric Analysis for CF

BA

bronchus and artery

AI

artificial intelligence

TLC

total lung capacity

FRC

functional residual capacity

B_{in}

bronchial inner diameter

B_{out}

bronchial outer diameter

B_{wt}

bronchial wall thickness

A

artery diameter

B_{out}/A

bronchial outer diameter divided by adjacent artery diameter

B_{in}/A

bronchial inner diameter divided by adjacent artery diameter

B_{wt}/A

bronchial wall thickness divided by adjacent artery diameter

B_{wa}/B_{oa}

bronchial wall area divided by bronchial outer area

TLC-CT

total lung capacity measured on inspiratory chest CT scan

TLC-CT%

total lung capacity measured on inspiratory chest CT scan as a percentage of the predicted value

G

segmental generation

MBW

multiple breath washout

CFTR

cystic fibrosis transmembrane regulator

1. Introduction

Cystic fibrosis (CF) lung disease is characterized by impaired mucociliary clearance which contributes to a vicious cycle of airway inflammation and infection resulting in structural lung damage [1,2]. This damage can be observed on chest computed tomography (CT) early in life [3], [4], [5], [6], [7], [8], [9], [10], and is associated with later decline in lung function [3,[5], [6], [7],10], more frequent exacerbations [5,8], and poorer quality of life [7,9]. Thus, effective therapies should be started in early childhood to delay the onset and progression of lung damage and improve the long-term trajectory of lung disease for individuals with CF [7,11].

For the treatment of CF lung disease, inhaled hypertonic saline is used as an osmotic therapeutic agent to maintain mucus hydration, facilitating effective mucociliary clearance in CF. The efficacy of inhaled hypertonic saline in children aged 3-6 years was evaluated in two randomized controlled trials: the Saline Hypertonic in Preschoolers (SHIP) study [12] and the Saline Hypertonic in Preschoolers + CT (SHIP-CT) study [3]. Both studies showed a positive effect of hypertonic saline after 48-week treatment on the lung clearance index ($LCI_{2.5}$). Moreover, in the SHIP-CT study, a positive effect of hypertonic saline compared to isotonic saline was demonstrated on lung structure as assessed by chest CT. For the SHIP-CT study, chest CTs were scored by a certified observer using the manual Perth-Rotterdam Annotated Grid Morphometric Analysis for CF (PRAGMA-CF) method.

PRAGMA-CF [4] is a morphometric scoring system that computes the volume fraction of structural lung components using a grid overlaying ten equally spaced axial CT slices. The primary outcome for SHIP-CT was PRAGMA-CF %Disease which is the percentage of total lung volume occupied by airways that show bronchiectasis, mucus plugging, and/or airway wall thickening. SHIP-CT showed that patients treated with hypertonic saline had lower %Disease compared to the group who were treated with isotonic saline. In addition, the hypertonic saline group also showed significantly less bronchiectasis which was a secondary outcome measure. One limitation of the PRAGMA-CF method is the use of a hierarchical system to annotate the airway abnormalities, therefore, specific contributions to total lung disease ranked following bronchiectasis such as mucus plugging and bronchial wall thickening can be under-estimated due to the hierarchical approach. Furthermore, the diagnoses of bronchial widening and bronchial wall thickening are not made based on precise measurements, but through eyeballing by the observer. The accurate differentiation between mild bronchial widening and bronchial wall thickening using PRAGMA-CF is difficult, which may affect the accuracy and sensitivity to measure bronchial changes over time. Finally, a set of only ten equally spaced slices are annotated to achieve PRAGMA-CF scores which may limit its' sensitivity for monitoring progression.

A more objective method to diagnose bronchial wall thickening and bronchial widening is to measure bronchus and artery (BA) dimensions using a three-dimensional image of the lung reconstructed from a chest CT. This was previously done manually in a proof of concept study in a limited number of school-aged children [13] and preschool children [14] with CF and in matched controls with normal chest CTs. The manual analysis was shown to be sensitive to detect bronchial wall thickening and bronchial widening even in young children [14]. Furthermore, the manual analysis showed more severe structural airway changes in the small airways relative to the more central larger airways [13,14]. A major disadvantage of the manual analysis is that it is extremely time-consuming, as it can take anywhere between 1 and 5 days to analyse a single CT, depending on the size of the subject. For this reason, an automatic artificial intelligence (AI) BA-analysis algorithm was developed and validated [15], [16], [17]. This automatic BA-analysis can detect a large number of BA-pairs in children older than 6 years with CF from segmental bronchi as segmental generation 0 up to the 12^{th} segmental generation [16,17]. Substantial differences in BA-dimensions between 11 CFs and 12 controls aged 6- 14 years were detected (data on file) and cut-off values to define bronchial wall thickening and bronchial widening were established [17]. Furthermore, the automatic BA-analysis outcomes for bronchial widening demonstrated a moderate to good correlation with corresponding PRAGMA-CF scores in children older than 6 years with CF [16]. Finally, using the automatic BA-analysis, progression of bronchial widening could be detected in two external CF cohorts [15,17]. In the original SHIP-CT analysis plan, BA-analysis outcomes were secondary outcomes. However, at the time of completion of SHIP-CT, the algorithm was still in its' validation stage and therefore was not included in the primary analysis. As the automatic BA-analysis has now been validated and certified for use in adults but not yet in children, we aimed to analyse all CTs to evaluate the effect of hypertonic saline inhalation on BA-dimensions.

We hypothesized that the automatic BA-analysis would be a sensitive and accurate tool to detect changes over time in bronchial wall thickening and bronchial widening and that BA-outcomes would correlate with functional measures of airway disease such as $LCI_{2.5}$ among participants in the SHIP-CT study.

2. Methods

2.1. Study population

The SHIP-CT study was a multicentre, randomized, double-blinded, controlled, parallel group trial conducted between May 2016 and December 2019 at 23 centres in Europe, North America, and Australia [3]. The details of the study have been reported previously [3]. Key inclusion criteria were a diagnosis of CF; age 36-72 months; ability to cooperate with chest CT imaging except for participants in Australia who underwent chest CT under general anaesthesia; and ability to comply with twice daily hypertonic or isotonic saline inhalations. Eligible participants were randomized 1:1 to inhale twice daily 7% hypertonic saline (treatment arm) or 0.9% isotonic saline (control arm) for 48 weeks.

The trial was registered (ClinicalTrials.gov identifier NCT02950883) and approved by the Institutional Review Boards and Human Research Ethics committee at each participating centre and written informed consent was obtained.

2.2. Chest CT scanning

Chest CT scans were performed at baseline and at 48 weeks according to a specific scan protocol for each centre, which was developed by the Erasmus Medical Centre Lung Analysis Core Laboratory (Rotterdam, the Netherlands) with the aim of standardizing image quality and lung volume. Participants in centres in Australia had their CTs obtained under general anaesthesia as per their routine clinical protocol. All other centres followed a technician or spirometry guided breath hold protocol without sedation. Participants were trained in the chest CT-related breath hold manoeuvres at each visit with the aim to optimize the lung volume and breath hold manoeuvre for the chest CT acquisition. The aim for the inspiratory CT scan was to obtain a volume level as close as possible to total lung capacity (TLC). If the participant had difficulties in following the volume specific manoeuvre, only an inspiratory chest CT was conducted at the best obtainable lung volume between functional residual capacity (FRC) and TLC.

2.3. Bronchus and artery analysis

The automatic BA-analysis was performed using LungQ (version 2.1.0.1, Thirona, Nijmegen, The Netherlands). LungQ is an AI-based medical image analysis platform that automatically identifies patient-specific anatomical features, structural abnormalities, and diseases from chest CT scans. The AI-based algorithms of LungQ are trained with a large variety of datasets to ensure robust performance against variation in patient characteristics (age, gender, BMI), variation in disease populations (chronic obstructive pulmonary disease, asthma, CF, interstitial lung disease, chronic bronchitis, bronchiectasis, COVID-19), and variation in image characteristics (manufacturer, dose, convolutional kernel, voxel spacing). To ensure a robust performance in patients with CF, additional training was performed on around 1.5 million training samples (including data augmentation techniques) from bronchus-artery matches in CT scans of CF patients.

The BA-analysis utilize two AI-based algorithms on the inspiratory CT scan: 1) to segment the bronchial tree from CT for bronchi with a visible lumen, and 2) to match each centreline point within the identified bronchial tree to the adjacent artery. For each matched (paired) centreline points, the bronchial inner diameter (B_{in}), bronchial outer diameter (B_{out}), bronchial wall thickness (B_{wt}), and artery diameter (A) are computed perpendicular to the longitudinal bronchus or artery axis. The bronchi quantification utilises a proprietary intensity profile quantification algorithm that allows for sub-resolution quantification for bronchial wall thickness. The algorithm quantifies each individual bronchus cross-section perpendicular to the local bronchial direction by calculating the bronchial dimensions in a multitude of radial intensity profiles with a sampling distance of higher resolution than the resolution of the scan. These measurements are used to compute the following BA-ratios: B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} (=bronchial wall area/bronchial outer area). The BA-dimensions of

each individual bronchial branch is computed as the average of all measurements within that branch. Separate from the quantification analysis, anatomical branches are identified to determine the segmental generations within the bronchial branch. This information is combined with the quantifications of each branch to provide bronchial quantifications per generation. Furthermore, information of segmental generation, segmental parent, and lobe is registered for each BA-pair.

The cut-off values to determine bronchial wall thickening and bronchial widening are based on the automatic BA-analysis of a previously manual annotated dataset of chest CTs from 11 patients with CF and from 12 normal CTs of age-matched control subjects (mean [range] age is 11.8 [6-14] years) [14]. Based on this analysis, the cut-off value for bronchial wall thickening (B_{wt}/A) was set as 0.14 and for bronchial widening (B_{out}/A) was set at 1.1 (data on file).

2.4. PRAGMA-CF

All chest CT scans for the SHIP-CT study were previously analysed by PRAGMA-CF, which is a manual morphometric method using a grid projected over ten equally spaced axial CT slices. PRAGMA-CF computes a volume fraction of the following structural lung components hierarchically on the inspiratory CT scans: %Bronchiectasis, %Mucus plugging, %Airway wall thickening, %Atelectasis, and %Healthy. The composite score %Disease reflects all airway associated abnormalities and is defined as the sum of %Bronchiectasis, %Mucus plugging and %Airway wall thickening. More details can be found in the SHIP-CT study publication [3].

2.5. Lung volume

We also used LungQ (version 2.1.0.1, Thirona, Nijmegen, the Netherlands) to compute lung volumes as lung volume is an important determinant of the BA-ratios [18,19]. LungQ segments the left and right lung separately from which TLC-CT could be computed. TLC-CT measurements are expressed in millilitres and as a percentage of the predicted value for TLC-CT% using the Global Lung Function Initiative correcting for age (>5 years old), sex, and height of the study subject (online calculator http://gli-calculator.ersnet.org/index.html) [20]. For children younger than 5 years old, we inputted the age as 5 years in the predicted lung volume calculation as the proportion of children <5 years did not differ between treatment groups.

2.6. Lung clearance index

The nitrogen multiple breath washout (MBW) testing was performed on the same day as chest CT scanning at baseline, 24, and 48 weeks using an open-circuit, bias-flow system (Exhalyzer D, EcoMedics, Duernten, Switzerland) and associated software (Spiroware) according to a standardized protocol defined by the MBW Resource Centre at the Hospital for Sick Children (Toronto, Canada). From the MBW test, the corrected values of $LCI_{2.5}$ is derived. For this study, we aimed to compare the changes in BA-dimensions to the changes in $LCI_{2.5}$. For this comparison, we compared the difference in BA-dimensions between baseline and 48 weeks with the changes in $LCI_{2.5}$. Additional $LCI_{2.5}$ results have been reported in the SHIP-CT study publication(3).

2.7. Outcomes

In the SHIP-CT study, the primary outcome was the difference in PRAGMA-CF %Disease at 48 weeks between treatment groups, adjusted for baseline PRAGMA-CF %Disease and baseline age. Secondary outcomes included differences in PRAGMA-CF sub-scores (%Bronchiectasis, %Mucus plugging, %Airway wall thickening, %Atelectasis and %Trapped air) at 48 weeks and changes in PRAGMA-CF %Disease and its sub-scores, and $LCI_{2.5}$ from baseline to 48 weeks [3].

Secondary outcomes of the SHIP-CT study included the difference in BA-ratios at 48 weeks and change in BA-ratios from baseline to 48 weeks between treatment groups. These outcomes were not reported in the SHIP-CT publication as the automatic BA-analysis was not validated at the time of the completion of the SHIP-CT study. For this study, the key outcome was difference in BA-ratios at 48 weeks and change in BA-ratios from baseline to 48 weeks, adjusted for baseline PRAGMA-CF %Disease (to correct for baseline differences in disease severity between treatment groups) and time-dependent TLC-CT.

2.8. Statistical analysis

Data are summarized as mean (standard deviation, SD) or median (interquartile range, IQR). The difference in BA-ratios at 48 weeks and change in BA-ratios from baseline to 48 weeks between treatment groups were assessed by a linear mixed-effects model. The model assumed time, treatment group, baseline age, sex, genotype, baseline height, baseline weight, TLC-CT (time-dependent), baseline PRAGMA-CF %Disease, and the interaction between time and treatment as fixed effects and accounted for the correlation between measurements that are taken from the same individual, measurements that are taken from the same segmental generation, and measurements that are taken from the same lobes as random effects. This interaction between time and treatment allows the effect of treatment on the outcomes to be different from baseline to 48 weeks. Sensitivity analysis was done by assuming the same model using different subsets of centrally segmental generations (G_1-G_6, G_1-G_{10}, or each segmental generation separately). Due to large variability in deeper generations, we investigated whether the differences between treatment groups were changed. Logarithmic transformation was used for BA-ratios expect for B_{wa}/B_{oa} since the normality (of the residuals) and homoscedasticity assumptions were not met. To facilitate the interpretation of the results, we generated effect plots to present predicted BA-ratios, which are the estimated outcomes when assuming specific values (mean) for the above mentioned variables.

Comparison between BA-ratios and $LCI_{2.5}$ were assessed by Spearman correlation analysis. Multiple measurements of BA-ratios per scan are first summarized as a median, and Spearman correlation coefficients were obtained. A correlation coefficient lower than 0.2 was rated as very weak, 0.2-0.4 as weak, 0.4-0.6 as moderate, 0.6-0.8 as strong, and 0.8-1 as excellent.

Statistical significance was accepted for p-values less than 0.05. No correction for multiple testing was performed [21]. Statistical analyses were done with R (version 4.0.5, packages: nlme, effects).

3. Results

3.1. Study population

A total of 220 scans of 116 participants were collected from SHIP-CT dataset. Five CT scans had to be excluded because of inconsistent slice spacing (n=4) and poor image quality (n=1). A total of 113 baseline and 102 48-week CT scans of 115 participants were included this study, 60 participants were in the isotonic saline group and 55 participants were in the hypertonic saline group. 100 participants have paired baseline and 48-week scans. Two participants have only 48-week scans because their baseline scans had poor image quality (n=1) and inconsistent slice spacing (n=1). Thirteen participants have only baseline scans because of lost to follow-up (n=11) and inconsistent slice spacing (n=2). Seven CTs from five participants from Australia were made under general anaesthesia. Thirteen CTs from eleven participants were made between FRC and TLC as participants had difficulties in following the volume specific manoeuvre. Median age at enrolment was 55 months. Clinical characteristics of the treatment groups are summarized in Table 1. Imaging characteristics per treatment group are shown in Table 2.

Table 1. Demographic characteristics of SHIP-CT participants at baseline.

Characteristic	**Isotonic saline group (n=60)**	**Hypertonic saline group (n= 55)**
Age (months)	54.6 (43.6, 65.7)	55.1 (50.0, 63.7)
Sex		
Male	30 (50%)	28 (51%)
Female	30 (50%)	27 (49%)
CFTR genotype		
Homozygous ΔF508	21 (35%)	27 (49%)
Compound heterozygote ΔF508	30 (50%)	23 (42%)
Other	9 (15%)	5 (9%)
Race		
Caucasian	56 (93%)	53 (96%)
Asian	1 (2%)	0
Pacific	1 (2%)	0
Indian	1 (2%)	1 (2%)
Other	1 (2%)	1 (2%)
Ethnicity		
Hispanic or Latino	3 (5%)	2 (4%)
Non-Hispanic or Latino	57 (95%)	53 (96%)
Weight (kg)	18.0 ± 3.3	17.9 ± 2.9
Height (cm)	105.6 ± 7.7	106.7 ± 7.5

Data are median (IQR), n (%), or mean ± SD. CFTR= cystic fibrosis transmembrane conductance regulator.

Table 2. Chest CT-related characteristics at baseline and 48 weeks.

Empty Cell	**Isotonic saline group (n=60)**		**Hypertonic saline group (n=55)**	
Empty Cell	**Baseline**	**48 weeks**	**Baseline**	**48 weeks**
BA-outcomes*				
BA-pair count	105±54	137±61	116±65	142±70
B_{out}/A	0.983 (0.824, 1.170)	0.990 (0.834, 1.175)	0.989 (0.820, 1.189)	1.002 (0.834, 1.210)
B_{in}/A	0.619 (0.494, 0.768)	0.642 (0.526, 0.784)	0.629 (0.513, 0.771)	0.673 (0.537, 0.827)
B_{wt}/A	0.173 (0.134, 0.224)	0.165 (0.126, 0.212)	0.170 (0.131, 0.223)	0.160 (0.122, 0.210)
B_{wa}/B_{oa}	0.588 (0.497, 0.672)	0.562 (0.467, 0.646)	0.573 (0.498, 0.661)	0.544 (0.459, 0.625)
Lung Volume				
TLC-CT (ml)	1208 (924, 1498)	1477 (1158, 1854)	1191 (956, 1526)	1549 (1036, 1762)
TLC-CT%	87 (75, 105)	96 (84, 105)	88 (68, 103)	93 (74, 109)
PRAGMA-CF				
%Disease	1.03 (0.40, 1.93)	1.45 (0.63, 4.31)	0.91 (0.44, 2.03)	1.16 (0.37, 2.37)
%Bronchiectasis	0.62 (0.20, 1.56)	1.19 (0.51, 3.08)	0.70 (0.24, 1.86)	0.95 (0.22, 2.18)
%Airway wall thickening	0.03 (0.00, 0.30)	0.03 (0.00, 0.27)	0.00 (0.00, 0.19)	0.00 (0.00, 0.12)

Data are mead ± SD or median (IQR). BA = bronchus and artery. B_{out}/A = bronchial outer diameter divided by adjacent artery diameter. B_{in}/A = bronchial inner diameter divided by adjacent artery diameter. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. B_{wa}/B_{oa}= bronchial wall area divided by bronchial outer area. TLC-CT = total lung capacity measured on inspiratory chest CT scan. TLC-CT% = total lung capacity measured on inspiratory chest CT scan as a percentage of the predicted value. PRAGMA-CF = Perth-Rotterdam Annotated Grid Morphometric Analysis for cystic fibrosis. %Disease = total volume of abnormal airways expressed as a percentage of total lung volume. %Bronchiectasis = total volume of bronchiectasis expressed as a percentage of the total lung

volume. %Airway wall thickening = total volume of airway wall thickening expressed as a percentage of total lung volume. *BA-outcomes included all segmental generations (G_0- G_{10}). Baseline BA-outcomes were assessed from 58 participants in the isotonic saline group and 55 participants in the hypertonic saline group. 48-week BA-outcomes were assessed from 54 participants in the isotonic saline group and 48 participants in the hypertonic saline group.

3.2. Bronchus and artery analysis

The automatic BA-analysis detected and quantified 6,073 BA-pairs (n=58) at baseline and 7,407 BA-pairs (n=54) at 48 weeks from segmental generation G_0 up to G_{10} in the isotonic saline group and 6,363 BA-pairs (n=55) at baseline and 6,840 BA-pairs (n=48) at 48 weeks from G_0 up to G_9 in the hypertonic saline group. In the isotonic saline group, a mean of 105 (SD, 54) BA-pairs per CT at baseline and 137 (SD, 61) BA-pairs per CT at 48 weeks were detected. In the hypertonic saline group, a mean of 116 (SD, 65) BA-pairs per CT at baseline and 142 (SD, 70) BA-pairs per CT at 48 weeks were detected. Participants in both treatment groups had the highest number of BA-pairs detected in segmental generation G_2 (Fig. 1). As 99% of BA-pairs were detected in segmental generations G_1-G_6, only BA-ratios in segmental generations G_1-G_6 were used for further analysis.

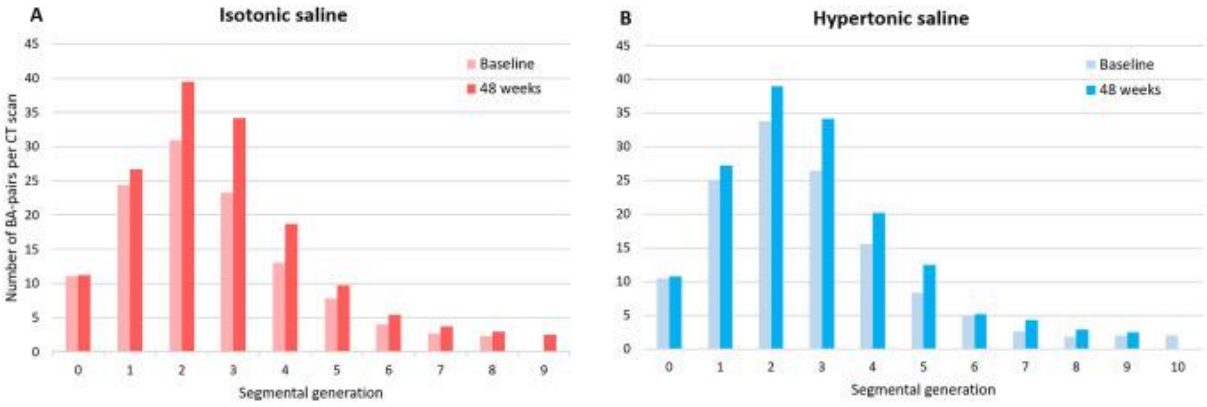

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Fig. 1. Average number of BA-pairs per segmental generation at baseline and 48 weeks between treatment groups. The figure shows (A) the average number of BA-pairs per segmental generation in isotonic saline group at baseline (light red) and 48 weeks (dark red). (B) The average number of BA-pairs per segmental generation in hypertonic saline group at baseline (light blue) and 48 weeks (dark blue). BA = bronchus and artery. Note that the highest number of BA-pairs in both treatment groups could be detected in segmental generation G_2 and more BA-pairs could be detected at 48 weeks compared to baseline which can be the result of growth and/or disease progression [14].

Baseline imaging characteristics were balanced between treatment groups (Table 2). The mixed-effects model analyses (Table S1, main effect: treatment) showed that at 48 weeks, B_{wt}/A and B_{wa}/B_{oa} was significantly higher in the isotonic saline group compared to the hypertonic saline group (p=0.025 and p=0.019, respectively; Figure S4 and S5 for sensitivity analysis). As shown in Fig. 2, mean predicted B_{wt}/A in the in the isotonic saline group was 0.171 (95%CI, 0.164 to 0.178) and in the hypertonic saline group was 0.160 (95%CI, 0.154 to 0.167) with a mean difference of 0.011 (95% CI, 0.0017 to 0.020) adjusted for the mean of age, height, weight, lung volume, PRAGMA-CF %Disease or mode of sex, race, and genotype. Mean predicted B_{wa}/B_{oa} in the isotonic saline group was 0.585 (95%CI, 0.567 to 0.602) and in the hypertonic saline group was 0.554 (95%CI, 0.536 to 0.572) with a

mean difference of 0.030 (95% CI, 0.009 to 0.052). There was no significant difference in B_{out}/A (p=0.94) and B_{in}/A (p=0.21) at 48 weeks between treatment groups (Fig. 2; Figure S2 and S3 for sensitivity analysis). Mean predicted B_{out}/A at 48 weeks was 0.983 (95%CI, 0.947 to 1.021) in the isotonic saline group and 0.986 (95%CI, 0.949 to 1.024) in the hypertonic saline group. Mean predicted B_{in}/A at 48 weeks was 0.614 (95%CI, 0.582 to 0.647) in the isotonic saline group and 0.644 (95%CI, 0.610 to 0.679) in the hypertonic saline group.

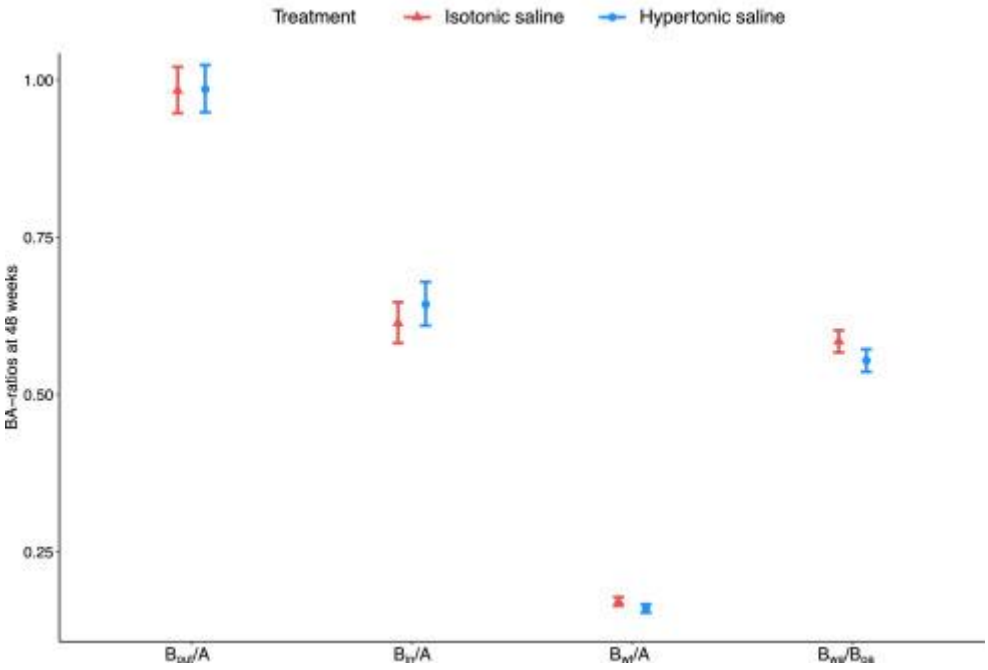

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Fig. 2. Comparison of predicted B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} in segmental generations G_1-G_6 at 48 weeks between treatment groups. Mean predicted (95%CI) values of B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} in segmental generations G_1-G_6 at 48 weeks were estimated from mixed-effects model. Significant differences at 48 weeks between treatment groups were found in B_{wt}/A (p=0.025) and B_{wa}/B_{oa} (p=0.019) but not in B_{out}/A (p=0.94) and B_{in}/A (p=0.21). Predicted BA-ratios are the estimated outcomes when assuming specific values (mean) for other variables. B_{out}/A = bronchial outer diameter divided by adjacent artery diameter. B_{in}/A = bronchial inner diameter divided by adjacent artery diameter. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. B_{wa}/B_{oa} = bronchial wall area divided by bronchial outer area. G=segmental generation. Error bars indicate 95%CI.

The mixed-effects model analyses (Table S1, main effect: interaction between time and treatment) showed that changes in B_{wt}/A, B_{in}/A, and B_{wa}/B_{oa} from baseline to 48 weeks were significantly different between treatment groups favouring the hypertonic saline group (all p<0.001; Figure S6 for sensitivity analysis). As shown in Fig. 3, mean predicted B_{wt}/A in segmental generations G_1-G_6 increased from 0.156 (95%CI, 0.150 to 0.163) at baseline to 0.171 (95%CI, 0.164 to 0.178) at 48 weeks in the isotonic saline group and from 0.152 (95%CI, 0.146 to 0.159) to 0.160 (95%CI, 0.154 to 0.167) in the hypertonic saline group. Mean predicted B_{wa}/B_{oa} in segmental generations G_1-G_6 increased from 0.551 (95%CI, 0.534 to 0.569) at baseline to 0.585 (95%CI, 0.567 to 0.602) at 48 weeks in the isotonic saline group and from 0.541 (95%CI, 0.523 to 0.559) to 0.554 (95%CI, 0.536 to 0.572) in the hypertonic saline group. Mean predicted B_{in}/A decreased from 0.633 (95%CI, 0.601 to

0.668) at baseline to 0.614 (95%CI, 0.582 to 0.647) at 48 weeks in the isotonic saline group and was stable at 0.642 (95%CI, 0.608 to 0.678) at baseline and 0.644 (95%CI, 0.610 to 0.679) at 48 weeks in the hypertonic saline group. Progressive B_{out}/A was found in both treatment groups (Table S1, main effect: time, p<0.001), but there was no significant difference between hypertonic saline and isotonic saline groups (p=0.39). Mean predicted B_{out}/A increased from 0.968 (95%CI, 0.932 to 1.005) to 0.983 (95%CI, 0.947 to 1.021) in the isotonic saline group and from 0.964 (95%CI, 0.928 to 1.002) at baseline to 0.986 (95%CI, 0.949 to 1.024) in the hypertonic saline group (Fig. 3).

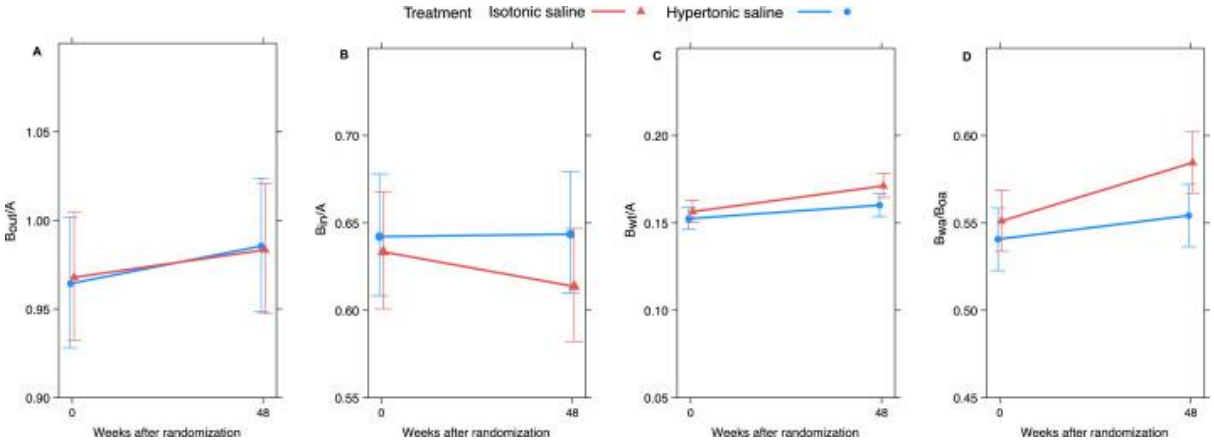

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Fig. 3. Change in B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} in segmental generations G_1- G_6 from baseline to 48 weeks between treatment groups. Change in B_{out}/A (A), B_{in}/A (B), B_{wt}/A (C), and B_{wa}/B_{oa} (D) in segmental generations G_1-G_6 from baseline to 48 weeks between treatment groups were estimated with mixed-effect models for repeated measures. Significant differences in change from baseline to 48 weeks between treatment groups were found in B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} (all p<0.001), but not in B_{out}/A (p=0.39). Predicted B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} are the estimated outcomes when assuming specific values (mean) for other variables. B_{out}/A = bronchial outer diameter divided by adjacent artery diameter. B_{in}/A = bronchial inner dimeter divided by adjacent artery diameter. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. B_{wa}/B_{oa} = bronchial wall area divided by bronchial outer area. G = segmental generation. Error bars indicate 95%CI.

Distribution of bronchial wall thickening as defined by $B_{wt}/A > 0.14$ and bronchial widening as defined by $B_{out}/A > 1.1$ of each lobe in both groups at baseline is shown in Fig. 4. Bronchial wall thickening was present between 64% and 75% and bronchial widening was present between 28% and 40% of total BA-pairs in different lobes. The right upper lobe was the most affected lobe.

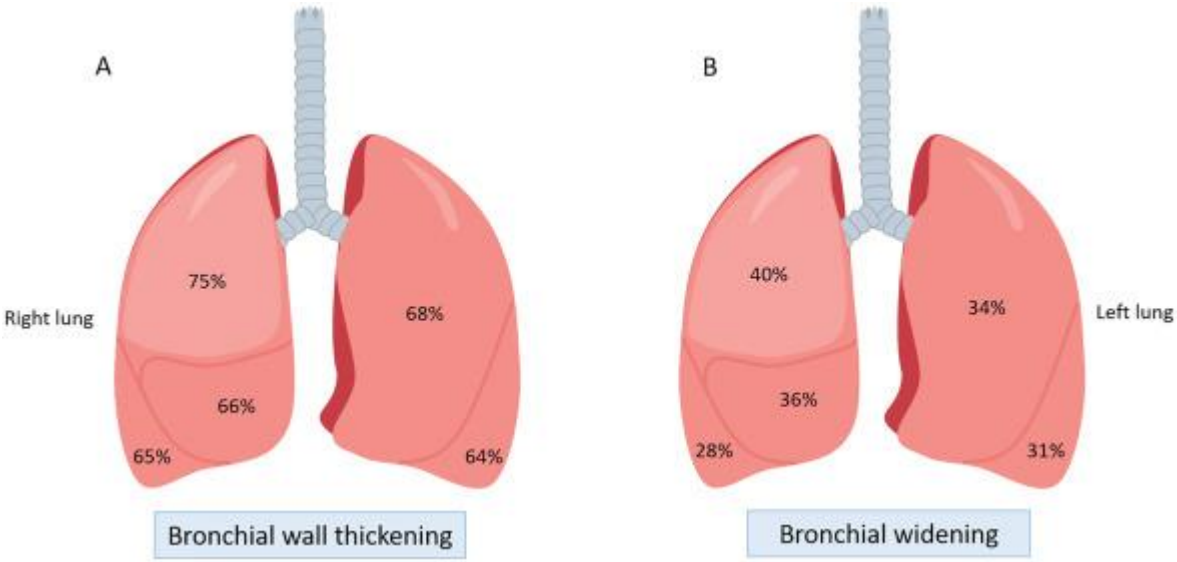

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Fig. 4. Radiological distribution of bronchial wall thickening and bronchial widening of each lobe at baseline in both groups. The figure shows the percentages of bronchus-artery pairs for each lobe showing bronchial wall thickening (A) and bronchial widening (B) at baseline in both groups. Bronchial wall thickening is defined by a ratio between bronchial wall thickness and artery (B_{wt}/A) >0.14. Bronchial widening is defined by a ratio between bronchial outer diameter and artery (B_{out}/A) >1.1. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. B_{out}/A = bronchial outer dimeter divided by adjacent artery diameter.

3.3. Lung volume

At baseline, median TLC-CT was 1,191mL (IQR, 926, 1,526) and median TLC-CT% was 88% (IQR, 71, 105). At 48 weeks, the median TLC-CT was 1,527mL (IQR, 1,155, 1,820) and the median TLC-CT% was 95% (IQR, 81, 108). There was a considerable variability in the trajectories of TLC-CT% from baseline to 48 weeks in both treatment groups (Figure S1).

3.4. Comparison between BA-ratios and $LCI_{2.5}$ outcomes

The correlation coefficients between BA-ratios and $LCI_{2.5}$ are shown in Table S2 (Appendix). B_{wt}/A correlated weakly with $LCI_{2.5}$ at both baseline and 48 weeks but correlated very weakly when analysing changes over time. For the comparison between B_{wt}/A and $LCI_{2.5}$, there were 104 participants who had paired B_{wt}/A- $LCI_{2.5}$ data at baseline and 85 participants at 48 weeks. To evaluate the changes over time, there were 85 participants who had paired baseline and 48-week $LCI_{2.5}$ and paired B_{wt}/A data. In 16/40 (40%) participants in the hypertonic saline group and 23/45 (51%) participants in the isotonic saline group, change in $LCI_{2.5}$ from baseline to 48 weeks was discordant with the change in B_{wt}/A (Fig. 5). As shown in Figure S7, there was a variability in the trajectories of $LCI_{2.5}$ and B_{wt}/A per participant from baseline to 48 weeks in both treatment groups.

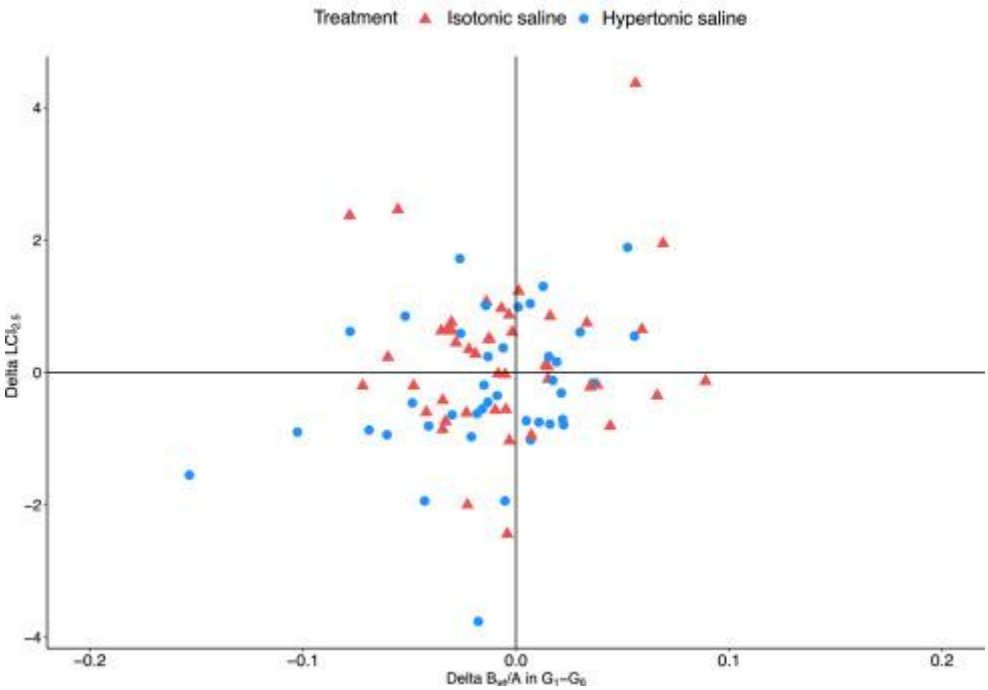

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Fig. 5. Scatter plot of the change in $LCI_{2.5}$ and change in median B_{wt}/A in segmental generations G_1-G_6 from baseline to 48 weeks between treatment groups. Change in $LCI_{2.5}$ and change in B_{wt}/A in segmental generations G_1-G_6 between baseline and 48 weeks were assessed from 47 participants in the isotonic saline group and 41 participants in the hypertonic saline group. $LCI_{2.5}$ = lung clearance index. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. Delta $LCI_{2.5}$ = the difference in $LCI_{2.5}$ between baseline and 48 weeks. Delta B_{wt}/A in G_1-G_6 = the difference in median B_{wt}/A in segmental generations G_1-G_6 between baseline and 48 weeks. G = segmental generation. Note that in 16/40 (40%) participants in the hypertonic saline group and 23/45 (51%) participants in the isotonic saline group, delta $LCI_{2.5}$ from baseline to 48 weeks was discordant with delta median B_{wt}/A in segmental generations G_1- G_6.

4. Discussion

Using an automatic analysis to measure dimensions of visible BA-pairs, the automatic BA-analysis was able to detect and quantify a large number of BA-pairs on chest CT scans in children aged 3-6 years with CF. We showed that CTs of children randomized to the hypertonic saline group had significantly thinner bronchial walls and larger bronchial lumens over 48 weeks relative to the isotonic saline group. There was no difference in progression of bronchial widening between treatment groups.

The bronchial wall observed on chest CT scans became significantly thinner with the treatment of hypertonic saline over 48 weeks. The mean difference between treatment groups in B_{wt}/A at 48 weeks was 0.011 (95%CI, 0.0017 to 0.020) which might seem small. To put this difference into perspective, we can express this difference as a percentage of the ratio as observed in a control population of children aged 3-6 years with normal chest CTs where BA-pairs can be detected up to the 5^{th} segmental generation. The median B_{wt}/A for segmental generations G_1-G_5 was 0.18 (data on file). The mean difference between treatment groups in the SHIP-CT study thus corresponds to an increase of 0.011/0.18=6% in the B_{wt}/A ratio. This means children aged 3-6 years with CF who were

treated with hypertonic saline had a 6% thinner bronchial wall over 48 weeks relative to the isotonic saline group. Similarly, B_{wa}/B_{oa}, which is the ratio between the bronchial wall area and the bronchial outer area, provides information on the degree of bronchial wall thickening independent of artery diameter changes. A significant smaller progression in B_{wa}/B_{oa} was observed in the hypertonic saline group relative to isotonic saline group. A reduction in bronchial wall thickening can reflect both more effective clearance of mucus and/or reduction of inflammatory thickening.

We speculate that the reduced bronchial wall thickness from baseline to 48 weeks in the hypertonic saline group compared to the isotonic saline group can be explained by two possible mechanisms. Firstly, hypertonic saline is likely to reduce bronchial wall thickness due to improved mucus clearance. Hypertonic saline allows water to move from the submucosa to the bronchial lumen facilitating mucociliary clearance [22], [23], [24]. As more mucus is cleared from the bronchi, the bronchial wall on CT may become thinner and the bronchial inner diameter becomes larger [25]. Secondly, improved mucociliary clearance is likely to facilitate the clearance of microorganisms, reduce inflammation and its' associated mucosal swelling [23,[26], [27], [28], [29]]. Using chest CT, mucus cannot be differentiated from the bronchial wall when the bronchus is completely obstructed, however, this only accounts for a small fraction of the full set of observable bronchi. It could theoretically be that some (inflamed/obstructed) bronchi are missed in the analysis. Therefore, the true difference in bronchial wall thickness between treatment groups may have been to some extent underestimated. Despite this fact the algorithm was sensitive enough to measure bronchial wall thickness and even detect a significant difference between the two treatment groups. The impact of inflammation on bronchial dimensions is probably much smaller than that of mucus adherent to the mucosa [22]. The reduced bronchial wall thickness, lower volumes of low attenuation regions and lower $LCI_{2.5}$ as reported previously [3] all consistently point towards more efficient mucociliary clearance in the bronchial in the hypertonic saline group relative to the isotonic saline group.

Using the automatic BA-analysis, we found a significant but small progression in bronchial widening using B_{out}/A in both treatment groups over 48 weeks. B_{out}/A is the most accurate quantitative metric for the diagnosis of bronchial widening (or bronchiectasis) [13,30,31]. However, there was no significant difference in progression of B_{out}/A between hypertonic saline and isotonic saline groups. This result contrasts with our previous report which showed that the PRAGMA-CF %Bronchiectasis score, a secondary outcome measure for SHIP-CT, was significantly lower in the hypertonic saline group at 48 weeks compared to the isotonic saline group [3]. This discrepancy can be explained by differences in the methodology. PRAGMA-CF [4] is a scoring method where the observer annotates all grid cells on ten equally spaced axial slices using the following hierarchical order: 1) Bronchiectasis, 2) Mucus plugging, 3) Airway wall thickening. For the diagnosis of bronchiectasis, the observer compares the outer diameter of the bronchus to the diameter of an adjacent artery by visual assessment and not by actual measurements. In cases where the bronchial outer diameter is substantially greater than that of the adjacent artery in combination with a thickened bronchial wall, the observer will easily classify such a bronchus as bronchiectasis. However, it is likely that especially in early stages of disease, bronchi showing thickening but no widening are more readily misclassified by the observer as bronchiectasis. With the automatic BA-analysis, we now show that in the hypertonic saline group, less bronchi at 48 weeks had thickened bronchial walls. Bronchi with a normal thin wall are less likely to be misclassified as bronchiectasis using PRAGMA-CF. In addition, improved mucus clearance in the hypertonic saline group might also have resulted in a lower number of bronchi easily visible to the observer. The automatic BA-analysis quantifies BA-dimensions in cross section throughout the bronchial tree with high precision, differentiating with strict rules between normal size and widening. Thus, we consider the assessment of bronchial widening being a hallmark of bronchiectasis by the automatic BA-analysis as more precise and more reliable than that of

PRAGMA-CF. However, the findings of our automatic BA-analysis are in line with that of SHIP-CT, which showed a positive response in the primary outcome measure, PRAGMA-CF %Disease, which includes all bronchi-related abnormalities [3]. Based on our automatic BA-analysis, we can conclude that the reduction in %Disease was primarily driven by clearance of mucus in the hypertonic saline group and not by a reduction in bronchial widening (bronchiectasis) [23].

The automatic BA-analysis allows us to address several issues related to the current challenges of defining bronchial widening (or bronchiectasis). Firstly, the automatic BA-analysis is capable of measuring a large number of visible BA-pairs, including small airways in the periphery of the lung. Secondly, it provides objective measurements of BA-ratios by automatically measuring BA-dimensions rather than relying on subjective human-observation. Thirdly, the automatic BA-analysis allows for the assessment of both bronchial wall thickening and bronchial widening independently. This analysis provides a more comprehensive evaluation of bronchial dimensions and morphology, allowing for a more accurate and detailed characterization of bronchial remodelling of lung disease. Finally, the output of the automatic BA-analysis also supplies information specified by segmental generation, segmental parent and lobe. This allows to locate bronchiectasis even in non-diffuse lung diseases.

We observed only weak correlations between changes in bronchial wall thickness as measured by the automatic BA-analysis and the changes in $LCI_{2.5}$ outcome. Similarly, in previous studies, poor correlations were observed between CT changes as measured by various scoring methods and functional outcomes as measured by spirometry and MBW [10,32,33]. The weak correlation between BA-outcomes and $LCI_{2.5}$ can be explained by the differences in the compartment measured by their techniques. $LCI_{2.5}$ is a measure of ventilation inhomogeneity which is thought to be especially sensitive to abnormalities of the small airways [34]. Small airways are defined as bronchi of 2 mm or less. In a 25-year old male without lung disease this corresponds to bronchi ranging from the 19^{th} generation to 25^{th} generation starting from the trachea as G_0 [27]. This would be equivalent to sub-segmental generation G_{15} and higher in our automatic BA-analysis. The automatic BA-analysis can measure bronchi down to a diameter of 2 mm as determined by the resolution of the CT scanner. Hence, for the SHIP-CT study, bronchi down to the 10^{th} segmental generation could still be detected. This means a large number of smaller bronchi in higher generations that are likely to contribute to the $LCI_{2.5}$ are not visible on CT in these young children. In our study, 39/85 participants were discordant when comparing changes in CT as measured by B_{wt}/A and $LCI_{2.5.}$ This finding is similar to a previous study where 50% of children had discrepancy between changes in CT and $LCI_{2.5}$ outcomes over two years [35]. Therefore, both structural CT outcomes and functional $LCI_{2.5}$ outcomes should be considered as outcome measures to monitor CF lung disease in young children as they measure different aspects of the disease.

A limitation of measuring BA-dimensions and BA-ratios is that these outcomes may vary depending on the level of inspiration [18,19,30,36]. As can be seen on the lung volumes computed from the CT (Appendix Figure S1), there was quite some variability in lung volume both at baseline and at 48 weeks for these children aged 3-6 years. These differences in lung volume between baseline and 48 weeks is likely to have reduced the sensitivity of the method to detect differences between the two treatment groups. In older more cooperative children with lung volumes closer to TLC during CT acquisition, the sensitivity of the BA-analysis to track disease is likely to be better. Another limitation of the automatic BA-analysis for young children is related to the relatively poor spatial resolution as discussed above. However, it is important to note that geometrical changes in central airways are correlated with changes in more peripheral airways [37]. Furthermore, small airway disease can be reflected as low attenuation regions on expiratory scans [38,39]. The recently introduced photon-

counting CT with superior resolution and lower radiation exposure is able to detect structures up to 0.2 mm in size [40]. This innovation in CT technology will therefore be of great importance for the sensitive detection and monitoring of small airways disease in children aged 3-6 years.

5. Conclusion

The automatic BA-analysis is able to detect and measure a large number of BA-pairs on chest CTs in children aged 3-6 years with CF who participated in the SHIP-CT study. We showed that twice daily hypertonic saline inhalation reduced bronchial wall thickness relative to the isotonic saline group. There was no difference in progression of bronchial widening between treatment groups.
The automatic analysis of BA-dimensions allows for objective and sensitive detection of bronchial wall thickening and bronchial widening which is important not only for clinical studies but also for clinical care to monitor the effect of CF transmembrane regulator (CFTR) modulator therapy on structural airway changes. Future clinical care for patients across different age groups who respond positively to CFTR modulator therapy, which are currently being investigated in several real-life studies such as RECOVER (NCT04602468), MODUL-CF (NCT04301856), and ENRICH (Grant003138121).

Background

Airway clearance therapy is prescribed to patients with bronchiectasis, but limited evidence exists demonstrating the effectiveness of medical device treatment options.

Research Question

What is the impact of high-frequency chest wall oscillation therapy (HFCWO) on health care resource use (HCRU) and economic outcomes in patients with bronchiectasis in the United States?

Study Design and Methods

A retrospective pre-post cohort study was conducted using the PharMetrics Health Plan Claims Database. The study included commercially insured adult patients with bronchiectasis receiving HFCWO between January 2009 and February 2018. Health care claims were compared 12 months before and after initiation of HFCWO. End points included all-cause and disease-specific HCRU and costs. Comparisons were conducted using McNemar's test for categorical variables and the Wilcoxon signed-rank test for continuous variables.

Results

A total of 255 patients were included. Mean age was 55.6 years, and 58% were high risk. Compared with baseline, significant reductions in all-cause hospital length of stay (9 vs 6 days; *P* = .05), oral antibiotics (89% vs 80%; *P* = .002), IV antibiotics (12% vs 6%; *P* = .01), and radiology examinations (96% vs 92%; *P* = .03) were observed. For disease-specific outcomes, significant reductions in hospitalizations (8% vs 3%; *P* = .004), acute exacerbations (7% vs 2%; *P* = .007), outpatient physician office visits (87% vs 78%; *P* < .001), radiology examinations (58% vs 34%; *P* < .0001), and laboratory services (51% vs 38%; *P* = .001) were found. Significant reductions in disease-specific costs were identified, including inpatient hospitalizations, pulmonologist visits, and radiology examinations; however, despite these reductions, all-cause total cost data were similar for both periods because of the cost of the device.

Interpretation

HFCWO therapy is associated with lower HCRU 12 months after initiation of therapy. Further health economic studies are required to determine if cost savings offset cost of the device after 1 year.

ey Words

airway clearance therapy

bronchiectasis

HCRU

HFCWO

Abbreviations

ACT

airway clearance therapy

HCRU

health care resource use

HFCWO

high-frequency chest wall oscillation therapy

HRCT

high-resolution CT

ICD

International Classification of Diseases

Take-home Point

STUDY QUESTION: Is high-frequency chest wall oscillation (HFCWO) therapy associated with reduced health care resource use and medical costs in patients with bronchiectasis?

RESULTS: This retrospective claims-based database study of 255 patients with bronchiectasis found significant reductions in hospital length of stay, antibiotic use, acute exacerbations, office visits, and disease-specific inpatient hospitalization costs 12 months after initiation of HFCWO therapy, with total all-cause cost and disease-specific data showing a reduction in cost in services except for ancillary and total outpatient services, because the postindex cost was higher because of the cost of the HFCWO device.

INTERPRETATION: HFCWO therapy is associated with lower health care resource use 12 months after initiation of therapy; however, further health economic studies are required to determine if associated cost savings offset the cost of the device after 1 year.

Bronchiectasis is a heterogenous chronic lung condition characterized pathologically by irreversible dilation of the large airways, bronchi, and bronchioles. The term *non-cystic fibrosis bronchiectasis*, referred to as *bronchiectasis* hereafter,[1] includes all cases of bronchiectasis arising from causes other than cystic fibrosis. Once considered an orphan disease,[2] this has changed recently, primarily because of an aging US population[3] and improved diagnostics, specifically the increased availability of high-resolution CT (HRCT) imaging. A 2017 study estimated that diagnostic rates increase almost

8% annually and that up to 522,000 Americans are being treated for bronchiectasis.[3] Bronchiectasis has a significant economic impact on health care services. A global systematic review conducted by Goeminne et al[4] in 2019 suggested that the economic burden of bronchiectasis on the health care system is significant and likely underestimated.

Medical management of bronchiectasis aims to control symptoms, to reduce the incidence of exacerbations, to prevent disease progression, and to improve quality of life. This is achieved through a multifaceted approach that may include airway clearance therapies (ACTs), mucolytic therapies, exercise, antibiotics, antiinflammatory therapies, and treatment of the underlying cause, if identified. Despite medical management via these interventions, hospitalizations still occur, and these events carry a significant burden. ACTs are recommended by internationally published bronchiectasis guidelines,[5], [6], [7], [8] and they are considered standard of care for the management of bronchiectasis. High-frequency chest wall oscillation (HFCWO) is a type of ACT administered with a vest-like garment capable of generating airflow oscillations to produce cough-like shear forces to help decrease secretion viscosity.[9] Several studies have tested various HFCWO devices on patients with bronchiectasis and have found improvement in lung function parameters[10] and quality-of-life measures[10,11] compared with chest physiotherapy, as well as a decrease of severe exacerbations and antibiotic use.[12,13] However, more real-world evidence is needed to better understand the performance of HFCWO therapy on patients with bronchiectasis.

The authors hypothesized that use of HFCWO therapy is associated with reductions in all-cause and disease-specific health care resource use (HCRU) and medical costs. The aim of this study was to investigate the impact of HFCWO therapy on HCRU and economic outcomes in patients with bronchiectasis in the United States using claims derived from the IQVIA PharMetrics Health Plan Claims Database.

Study Design and Methods

Study Design

A retrospective pre-post cohort study was conducted using the IQVIA PharMetrics Health Plan claims database. The population of interest was patients with bronchiectasis receiving HFCWO for airway clearance between January 1, 2009, and February 28, 2018. HCRU and associated medical costs were compared in the 12 months before and 12 months after the index periods. The date of first prescription of an HFCWO device was used as the index date. Baseline demographics, clinical characteristics, and the following outcomes were assessed:
hospitalization; bronchiectasis exacerbations; medication use; and outpatient, inpatient, and diagnostic services (e-Table 1). The study was considered exempt from institutional review board review under 45 CFR 46.101(b)(4).

Settings and Participants

The data were sourced from the IQVIA PharMetrics Health Plan claims database, which comprises fully adjudicated medical and pharmaceutical claims for nearly 91 million unique patients from 91 health plans across the United States. The database includes both inpatient and outpatient diagnoses (in International Classification of Diseases [ICD], Ninth Revision, Clinical Modification format) and procedures (in Current Procedural Terminology, Fourth Edition, and Health Care Common Procedure Coding System formats) as well as both retail and mail order prescription records. Available data on prescription records include the National Drug Code and the Generic Product Identification code, as well as the quantity of the medication dispensed. Amounts charged by providers and amounts allowed and paid by health plans are available for all services rendered, as well as dates of services

for all claims. Additional data elements include demographic variables, product type, payer type, provider specialty, and start and stop dates of health plan enrollment. The Health Insurance Portability and Accountability Act-compliant data generally are representative of the national commercially insured population in terms of age and sex.

The study population included adult patients enrolled in continuous health plan for ≥ 12 months immediately preceding the index date (pre-index period) and ≥ 12 months immediately after the index date (postindex period). Inclusion also required one or more medical claims with a diagnosis code for bronchiectasis during the 12-month pre-index period and evidence of HRCT scan of the thorax before the diagnosis code of bronchiectasis or one or more medical claims (inpatient or outpatient) with a record of receipt of HFCWO or non-HFCWO treatments. Patients were not be eligible for the study if data were incomplete, if they were aged 65 years or older at the index date and not covered by Medicare Risk or with Medicare Cost coverage or State Health Insurance Assistance Program (SCHIP), or if they had a diagnosis of cystic fibrosis during the entire study period.

Patients aged 65 years or older at the index date and covered by Medicare Risk, Medicare Cost coverage, or State Health Insurance Assistance Program also were included. All costs were converted to 2019 US dollars using the medical component of the Consumer Price Index. Patients with incomplete data and patients with one or more medical claim for cystic fibrosis during the entire study period were excluded.

To identify patients with bronchiectasis, ICD, Tenth Revision, Clinical Modification, diagnosis codes J47.9 and J47.1 and ICD, Ninth Revision, Clinical Modification diagnosis codes 494.0 and 494.1 were used. Health Care Common Procedure Coding System code E0483 was used to identify claims for HFCWO.

Outcomes of Interest

All-cause and disease-specific HCRU and costs were measured and compared between the 12-month preindex and postindex periods among HFCWO users. Disease-specific use and associated costs were defined as claims having a primary or secondary diagnosis code for bronchiectasis in an outpatient setting or any admit or discharge diagnosis of bronchiectasis in an inpatient setting. Similarly, the primary diagnosis code for bronchiectasis was used for the identification of a bronchiectasis acute exacerbation. Disease-specific use and associated costs were included within all-cause use and costs. The cost of the HFCWO device is included within ancillary costs for both all-cause and disease-specific categories. HCRU and costs were expressed as both the proportion of patients with such use as well as per-patient mean ± SD and median for costs and use. Use and costs were calculated on a per-patient basis and were averaged across the cohort. All costs were converted to 2019 US dollars using the medical component of the Consumer Price Index.

Statistical Analyses

Comparisons between the preindex period (baseline) and postindex period were conducted using McNemar's test for categorical variables (frequency and percentage [No. (%)]) and the Wilcoxon signed-rank test for continuous variables (median) and paired *t* test (mean ± SD), as appropriate. Analyses were conducted using SAS release 9.3 software (SAS Institute, Inc.).

Results

From the PharMetrics Health Plan claims database of 91 million patients, 4,002 patients met selection criteria, of whom 255 were identified as having an HFCWO prescription (e-Table 2). Table 1 describes the baseline demographics and clinical characteristics of the 255 patients

included in the study analysis. The mean ± SD age of patients was 55.6 ± 14.5 years, with most participants (46%) older than 60 years. Female patients accounted for 67% of the cohort. Data on race were unavailable. Most patients (58%) were covered by commercial insurance and 12% were covered by Medicare Risk. Pulmonology was the physician specialty most associated with first observed bronchiectasis diagnosis (46%) and device prescription (52%; data not shown). Most patients (58%) were identified as high risk according to the Bronchiectasis Aetiology and Comorbidity Index. The five most common comorbidities for the study patient population (e-Table 3) were included for the Bronchiectasis Aetiology and Comorbidity Index computation, of which COPD was the most common comorbidity, presenting in 64% of patients. In the preintervention period, 14% of patients showed Pseudomonas aeruginosa colonization and 14% harbored comorbid nontuberculous mycobacteria infection. The following results describe the impact of HFCWO by comparing HCRU data and associated medical costs 12 months before and 12 months after initiation of therapy for all-cause findings and disease-specific findings.

Table 1. Demographic and Baseline Characteristics of Patients Using HFCWO Therapy

Baseline Characteristics	**HFCWO Therapy Group (N = 255) n(%)**
Age, y	
Mean ± SD	55.6 ± 14.5
Median	58.0
Age group, y	
18-44	48 (19)
45-54	47 (18)
55-59	44 (17)
60+	116 (46)
Sex	
Male	84 (33)
Female	171 (67)
Unknown	7 (3)
Payer type	
Commercial	147 (58)

Baseline Characteristics	HFCWO Therapy Group (N = 255) n(%)
Medicaid	23 (9)
Medicare Risk	31 (12)
Self-insured	24 (9)
Unknown	30 (12)
Charlson comorbidity index	
0	0 (0.0)
1	130 (51)
2	41 (16)
3+	84 (33)
BACI risk score	
Low (0)	38 (15)
Intermediate (1-5)	70 (28)
High (≥ 6)	147 (58)
Comorbid included in BACI	
COPD	163 (64)
Asthma	131 (51)
Comorbid conditions of interest	
Sinus disease	95 (37)
Gastroesophageal reflux disease	93 (36.5)
Dysphagia, abnormal swallow	31 (12.2)
Connective tissue, autoimmune disease, inflammatory disorders	55 (21.6)

Baseline Characteristics	HFCWO Therapy Group (N = 255) n(%)
P aeruginosa	35 (13.7)
Nontuberculous mycobacteria	35 (13.7)
Aspergillus fumigatus	12 (4.7)
MRSA	5 (2.0)
Allergic bronchopulmonary aspergillosis	9 (3.5)
Alpha-$_1$ antitrypsin deficiency	4 (1.6)
Use of nebulizer	99 (39.8)
Use of inhaler	68 (26.7)

Data are presented as No. (%), unless otherwise indicated. BACI = Bronchiectasis Aetiology and Comorbidity Index; HFCWO = high-frequency chest wall oscillation therapy; MRSA = Methicillin-resistant *Staphylococcus aureus*.

Inpatient Hospitalizations and Length of Stay

All-cause findings data showed that 12 months after starting HFCWO therapy, inpatient hospitalizations trended down by 11%, although this was not statistically significant (Fig 1). The median length of stay among patients with one or more hospitalizations reduced from 9 to 6 days, a 33% reduction (P = .05) (Fig 2). The mean number of inpatient visits was 2.04 before index vs 1.82 after index (data not shown).

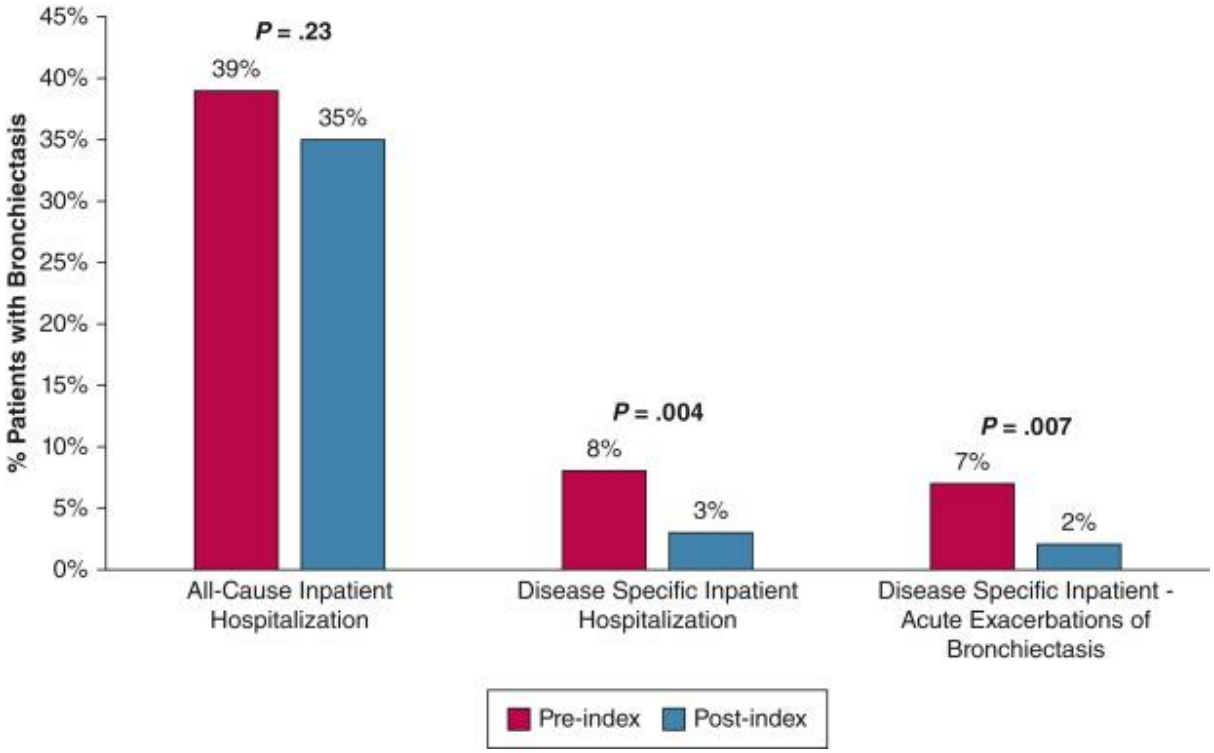

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Figure 1. Bar graph showing all-cause and disease-specific inpatient hospitalizations.

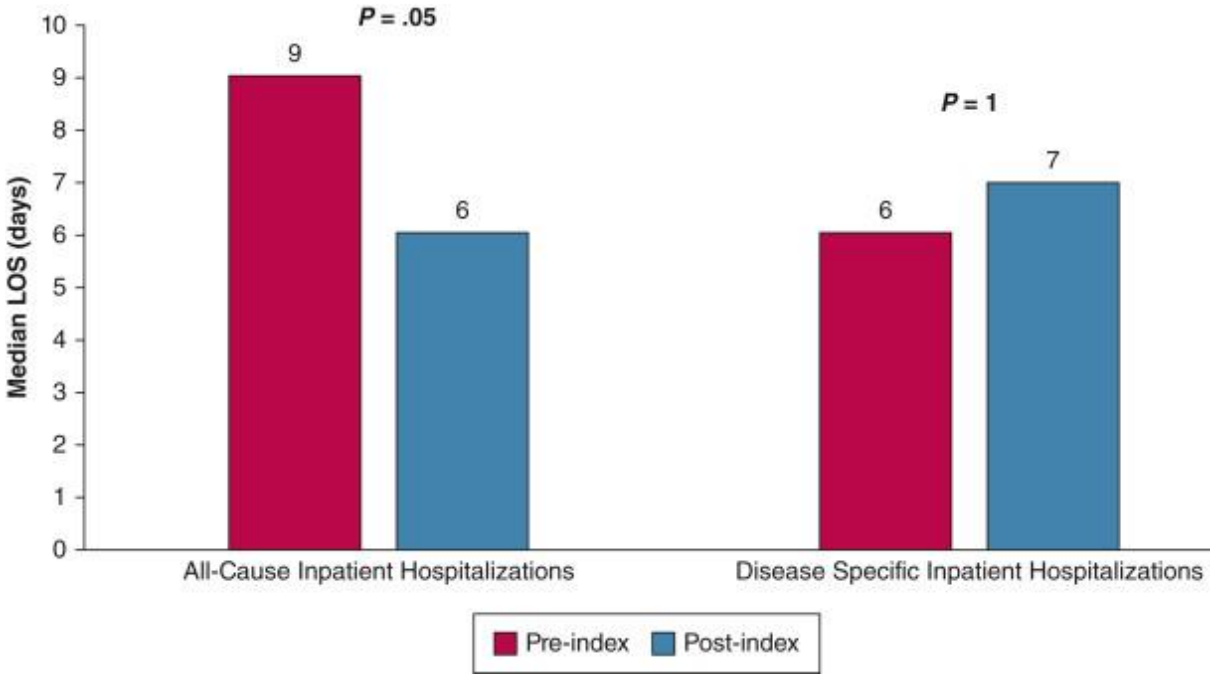

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Figure 2. Bar graph showing all-cause and disease-specific inpatient hospitalizations LOS. LOS = length of stay.

For disease-specific findings, inpatient hospitalizations decreased significantly by 67% (*P* = .004) (Fig 1). However, median length of stay increased among patients with one or more hospitalizations from 6 to 7 days (Fig 2). Although unable to be confirmed because of the nature of the data source, this slight increase may be the result of the high severity and morbidity of the hospitalized patients. Bronchiectasis acute exacerbations were reduced by 67% (*P* = .007) (Fig 1). These exacerbations were defined and identified as claims having a primary diagnosis code for bronchiectasis in any admit or discharge diagnosis of bronchiectasis in an inpatient setting. The mean number of disease-specific inpatient visits, among those with one or more hospitalizations, was 1.19 before index vs 1.14 after index (data not shown).

Antibiotic Use

All-cause findings data revealed the proportion of patients prescribed antibiotics was reduced significantly in the postindex period compared with the preindex period (Table 2). Specifically, use of oral antibiotics decreased by 9% (*P* < .002) and IV antibiotic use decreased by 47% (*P* = .01). Clarithromycin, azithromycin, and erythromycin were selected as antibiotics specific for treatment of bronchiectasis, given their usefulness in the prevention of exacerbations. Multiple clinical trials14, 15, 16 support clinical use of macrolides to help reduce bronchiectasis exacerbations. The analysis of disease-specific findings for antibiotic use revealed that no significant differences in antibiotic use was found for the preindex vs postindex periods (Table 2). See e-Table 4 for additional data regarding all-cause pharmacy services.

Table 2. Trends in Health Care Resource Utilization: All-Cause and Disease-Specific Antibiotic Use

Characteristic	Preindex (N = 255)	Postindex (N = 255)	Change, %	*P* Value
All-cause pharmacy services	250 (98)	244 (96)	–2	.03
Specific medications of interest	243 (95)	237 (93)	–3	.08
Oral antibiotics	226 (89)	205 (80)	–9	.002
IV antibiotics	30 (12)	16 (6)	–47	.011
Disease-specific pharmacy services	135 (53)	136 (53)	+1	.91
Specific medications of interest	135 (53)	136 (53)	+1	.91
Antibiotics	135 (53)	136 (53)	+1	.91

Data are No. (%) of patients requiring antibiotic use at least once, unless otherwise indicated.

Outpatient Visits and Laboratory and Radiology Services

All-cause findings data showed that all patients had at least one outpatient encounter and that total visits to pulmonologists decreased by 10% (*P* < .001) (Table 3). Also a significant reduction was observed for all-bronchoscopy use by 65% (*P* < .0001), for sputum analysis evaluations by 37% (*P* < .0001), and for radiology services by 4% (*P* = .03), specifically chest radiography by 24% (*P* < .0001)

(Table 4). A trend toward reduction, although not statistically significant, was seen for ED visits by 16%, for pulmonary rehabilitation by 33%, for HRCT imaging services by 43% (data not shown in Table 4), for laboratory tests by 2%, and for chest physiotherapy services by 38%. Primary care office visits increased by 4%.

Table 3. Trends in Health Care Resource Use: All-Cause and Disease-Specific Outpatient Visits and Services

Characteristic	Preindex (N = 255)	Postindex (N = 255)	Change, %	*P* Value
All-cause outpatient services	255 (100)	255 (100)	…	…
ED visits	112 (44)	94 (37)	–16	.06
Physician office visits	255 (100)	255 (100)	…	…
Pulmonologists	192 (75)	172 (68)	–10	< .0001
PCP	200 (78)	207 (81)	+4	.26
All-cause medical and surgical services	172 (68)	150 (59)	–13	.01
Bronchoscopy	60 (24)	21 (8)	–65	< .0001
All Cause ancillary services	254 (100)	255 (100)	…	…
Pulmonary rehabilitation	9 (100)	6 (2)	–33	.32
Chest physiotherapy by a respiratory therapist	8 (3)	5 (2)	–38	.41
Disease Specific outpatient services	241 (95)	249 (98)	+3	.05
ED visits	16 (6)	9 (4)	–44	.14
Physician office visits	222 (87)	199 (78)	–10	.001
Pulmonologists	146 (57)	131 (51)	–10	.05
PCP	74 (29)	58 (23)	–22	.03
Disease-specific medical and surgical services	36 (14)	16 (6)	–56	.003

Characteristic	Preindex (N = 255)	Postindex (N = 255)	Change, %	*P* Value
Bronchoscopy	27 (11)	10 (4)	–63	.002
Disease-specific ancillary services	193 (76)	248 (97)	+29	< .0001
Pulmonary rehabilitation	5 (2)	3 (1)	–40	.32
Chest physiotherapy by a respiratory therapist	8 (3)	2 (1)	–75	.058

Data are presented as No. (%) of patients requiring outpatient visits and services at least once, unless otherwise indicated. PCP = Primary care physicians.

Table 4. Trends in Health Care Resource Use: Laboratory and Radiology Services

Characteristic	Preindex Period (N = 255)	Postindex Period (N = 255)	Change, %	*P* Value
All-cause laboratory use				
All services	246 (97)	241 (95)	–2	.2
Sputum analysis	160 (63)	101 (40)	–37	< .0001
All-cause radiology examinations	245 (96)	235 (92)	–4	.03
Chest radiography	195 (77)	149 (58)	–24	< .0001
Disease-specific laboratory use				
All services	129 (51)	97 (38)	–25	.001
Sputum analysis	71 (28)	49 (19)	–31	.011
Disease-specific radiology examinations	149 (58)	87 (34)	–42	< .0001
Chest radiography	66 (26)	45 (18)	–32	.01

Data are presented as No. (%) of patients requiring laboratory and radiology services at least once.

Disease-specific findings showed that although outpatient encounters increased by 3% (*P* = .05), physician office, pulmonologist, and primary care physician visits decreased significantly by 10% (*P* = .001), 10% (P = .05), and 22% (*P* = .03), respectively (Table 3). A statistically significant

decrease also was observed for bronchoscopy use by 63% (*P* = .002), for laboratory services by 25% (*P* = .001), for sputum analysis evaluations by 31% (*P* = .011) (Table 4), for radiology services by 42% (*P* < .0001), and for chest radiography by 32% (*P* = .01). No change was observed in HRCT imaging services (data not shown in Table 4; 0% change was observed from the preindex to postindex period). Overall use of outpatient ancillary services increased by 28% (*P* < .0001); however, decreases in pulmonary rehabilitation services of 40% and in chest physiotherapy of 75% were observed, although these were not statistically significant. Note that changes to laboratory outcomes show a change in the number of laboratory sample draws (ie, times laboratory tests were performed), rather than a change in the laboratory test value.

Cost Data

All-cause findings data showed for the 12-month preindex and postindex periods, the mean total all-cause costs of care were similar ($56,053 vs $57,775) (Table 5). Significant reductions in laboratory costs ($1,798 vs $1,227; *P* < .001) and radiology costs ($2,157 vs $1,510; *P* = .001) were observed in the postindex period. Costs for inpatient visits ($20,429 vs $14,546) and ED visits ($920 vs $627) were lower in the postindex period, although this was not statistically significant. Ancillary services costs roll into the total of outpatient services cost, both of which were significantly higher in the postindex period: $8,849 vs $19,537 (*P* < .001) for ancillary services and $19,440 vs $27,372 (*P* < .001) for total outpatient services. However, this difference is associated primarily with the cost of the device (average device cost of $10,887.80; median, $11,770.30), which if subtracted from the postindex amount shows a decrease for both ancillary ($8,849 vs $8,649) and total ($19,440 vs $16,484) outpatient services costs. It is important to note that the cost of the HFCWO device is included within ancillary costs for both all-cause and disease-specific categories.

Table 5. Trends in All-Cause Cost Before and After Initiation of HFCWO Therapy

Variable	Preindex Period (N = 255)		Postindex Period (N = 255)		*P* Value, Mean
	Mean ± SD	Median	Mean ± SD	Median	
All-cause costs (allowed amount)					
Total costs	$56,053 ± $97,873	$29,253	$57,775 ± $77,979	$34,084	.77
Inpatient hospitalization costs	$20,429 ± $72,969	$0	$14,546 ± $59,007	$0	.3
Oral antibiotics costs	$638 ± $1,943	$192	$499 ± $1,605	$84	.021
IV antibiotics costs	$633 ± $4,765	$0	$481 ± $3,515	$0	.43

Variable	Preindex Period (N = 255)		Postindex Period (N = 255)		*P* Value, Mean
	Mean ± SD	Median	Mean ± SD	Median	
Outpatient services costs[a]	$19,440 ± $29,260	$12,694	$27,372 ± $35,730	$20,248	< .001
ED visits	$920 ± $2,249	$0	$627 ± $1,940	$0	.11
Physician office visits[b]	$3,447 ± $7,064	$2,281	$2,666 ± $3,584	$1,827	.05
Pulmonologist visits[b]	$506 ± $575	$348	$344 ± $560	$175	< .001
Medical and surgical services	$2,268 ± $5,833	$353	$1,804 ± $4,602	$155	.26
Bronchoscopies[b]	$411 ± $1,399	$0	$134 ± $680	$0	< .001
Ancillary services[a]	$8,849 ± $20,723	$4,045	$19,537 ± $31,112	$15,067	< .001
Laboratory[b]	$1,798 ± $3,396	$800	$1,227 ± $3,451	$493	< .001
Radiology examinations[b]	$2,157 ± $2,838	$1,193	$1,510 ± $2,593	$592	.001
Disease-specific costs (allowed amount)					
Total costs[a]	$4,522 ± $7,731	$1,586	$12,492 ± $7,752	$12,691	< .0001
Inpatient hospitalization costs[b]	$1,607 ± $6,051	$0	$468 ± $3,319	$0	.008
Antibiotics costs	$111 ± $323	$7	$117 ± $316	$7	.73
Outpatient services costs[a]	$2,803 ± $3,873	$1,386	$11,907 ± $6,690	$12,386	< .0001

Variable	Preindex Period (N = 255)		Postindex Period (N = 255)		*P* Value, Mean
	Mean ± SD	Median	Mean ± SD	Median	
ED visits	$66 ± $357	$0	$55 ± $577	$0	.81
Physician office visits[b]	$552 ± $653	$364	$433 ± $531	$302	.01
Pulmonologist visits	$234 ± $334	$113	$190 ± $313	$61	.05
Medical and surgical services	$192 ± $777	$0	$120 ± $1,085	$0	.38
Bronchoscopies	$147 ± $658	$0	$45 ± $282	$0	.011
Ancillary services[a]	$1,296 ± $2,581	$170	$10,907 ± $5,962	$11,719	< .0001
Laboratory[b]	$320 ± $886	$0	$200 ± $574	$0	.05
Radiology examinations[b]	$378 ± $766	$52	$192 ± $528	$0	.0005

HFCWO = high-frequency chest wall oscillation therapy.

a

Increases significantly.

b

Decreases significantly.

An analysis of disease-specific findings found that mean total costs were 2.8 times higher in the postindex period ($4,522 vs $12,492; *P* < .0001) (Table 5), primarily because of costs associated with the HFCWO device, as reflected in the outpatient ancillary services costs. If we consider preindex and postindex costs, not including the cost of the HFCWO device, we see a decrease for disease-specific total costs ($4,522 vs $1,604). Costs associated with physician office visits ($552 vs $433; *P* = .006), laboratory use ($320 vs $200; *P* = .05), and radiology use ($378 vs $192; *P* = .0005) were significantly lower. Mean inpatient hospitalization costs were 3.4 times lower ($1,607 vs $468; *P* = .008).

Discussion

This retrospective claims database analysis evaluated HCRU in patients with bronchiectasis treated with HFCWO therapy. This analysis showed that HFCWO therapy is associated with lower HCRU 12 months after therapy initiation compared with the 12-month baseline period for patients with bronchiectasis. These results are particularly significant given that many patients with bronchiectasis who were prescribed HFCWO therapy had severe illness.

Findings from this study are consistent with other studies of HFCWO.[12] A comparative retrospective cohort study from a database of patients with bronchiectasis found that antibiotic use and number

of exacerbations requiring hospitalization were reduced after initiation of an algorithm for mucociliary clearance that included initiation of HFCWO.[12]

For all-cause outcomes, a statistically significant reduction was identified for pulmonologist visits, bronchoscopies, sputum analyses, use of oral and IV antibiotics, and chest radiography in the 12 months after starting HFCWO therapy. Although not statistically significant, reductions in all-cause hospitalizations, outpatient services such as ED visits, pulmonary rehabilitation, and chest physiotherapy were seen.

For disease-specific findings, in the 12 months after HFCWO therapy onset, a significant improvement in bronchiectasis acute exacerbation and disease-specific hospitalizations also was observed. Disease-specific significant reductions in physician office visits, including pulmonologist and primary care physicians, bronchoscopies, sputum analysis, and chest radiography were found. A trend toward reduction of pulmonary rehabilitation and chest physiotherapy was identified.

Significant decrease in HCRU was found; however, this was not reflected on the overall annual costs because of the cost associated with the HFCWO device. An average cost of $10,887.80 (median, $11,770.30) was associated with the HFCWO device. Total outpatient costs, specifically outpatient ancillary services costs that included the cost of the device, were the major driver of postindex total costs. However, when the average cost of the HFCWO device is subtracted from the total outpatient costs, which includes the outpatient ancillary services, we do observe a decrease in postindex costs. For all-cause and disease-specific inpatient and outpatient services, all other cost data were less in the postindex period.

Preliminary data from a study of pre-post HFCWO therapy for 3-year data for health care cost and use showed total cost reduction at year 2 ($2,065; $P < .01$) and year 3 ($3,459; $P < .01$),[17] which included the HFCWO device cost. Further work is required to understand better the impact of HFCWO therapy on health care costs beyond 1 year.

Overall, this study shows the potential reduction of hospitalizations and HCRU for patients with bronchiectasis prescribed HFCWO therapy. Future studies need to examine the impact of the HFCWO device on longer-term HCRU and costs among patients with bronchiectasis because the cost of an HFCWO device typically is incurred during the first year of initiation, despite device life being much longer. Further analysis of patient subgroups that would benefit most from the therapy is warranted. An analysis of a Medicare patient population also is recommended.

This analysis has many limitations, including high variability in practice among physicians, difficulty securing a sufficiently large sample size based on inclusion criteria and patient matching, and challenges associated with patients switching insurance providers. Given the inclusion and exclusion criteria and the evaluation time frame (12-month preindex and postindex dates), patients who did not meet these criteria because of death or insurance switching were excluded.

Claims database studies pose unique challenges. For the purposes of the study, exacerbations were identified via claims with a primary diagnosis code for bronchiectasis in any admit or discharge diagnosis of bronchiectasis, and we are unable to confirm a bronchiectasis pulmonary exacerbation as defined by the European Respiratory Society.[18] Our approach for defining exacerbation admissions using bronchiectasis as the primary reason for hospitalization may underestimate the actual number of exacerbation hospitalizations. Additionally, misclassification bias from inaccurate coding of ICD, Ninth Revision, diagnosis codes indicating a bronchiectasis diagnosis is possible. Some studies analyzing use of ICD, Ninth Revision, codes have shown that records can underestimate or overestimate an actual diagnosis rate in various respiratory diseases like COPD.[19,20] To mitigate

overestimating bronchiectasis diagnoses and HFCWO use, patients included in this study had to have a bronchiectasis diagnosis confirmed by HRCT imaging and an alternative ACT had to have failed.[21] Prescription of HFCWO is associated with concurrent interventions for the patient with non-cystic fibrosis bronchiectasis, all of which have not been accounted for, limiting the analysis of the impact of multiple interventions to the outcomes.

Additionally, selection bias resulting from use of a commercial claims database excludes the uninsured and those with Medicare fee-for-service coverage, and thus, our results cannot be generalizable to these populations. Only 12% of the population in our data set were Medicare Risk, meaning patients who received Medicare benefits through a Medicare Risk provider. It is also impossible to confirm treatment adherence because the frequency of use and adherence to the therapy are unavailable; we only can confirm the patients in the data set were prescribed the HFCWO device. This limitation again may underestimate the benefit of the technology because limited use likely would demonstrate little to no benefit.

Interpretation

In patients with bronchiectasis, HFCWO therapy resulted in improved HCRU and economic outcomes 12 months after starting therapy. Use of HFCWO was associated with a reduction in all-cause antibiotic use and radiology examinations. A decline in disease-specific hospitalizations, bronchiectasis acute exacerbations, disease-specific physician office visits, and laboratory and radiologic examinations was observed. A decrease in HCRU was observed; however, the total average for all-cause cost did not decrease. Although a significant increase for disease-specific total cost average was found, we identified a significant reduction in HCRU including total inpatient hospitalization costs and length of stay. The increase in disease-specific total cost primarily is the result of the costs associated with the HFCWO. In the absence of large-scale prospective clinical trials, our findings add to the body of evidence regarding the effectiveness of HFCWO therapy in this patient population with increasing prevalence, significant morbidity, and economic burden. Further study is needed.

Methods: Study databases were combined for this analysis. Clinical characteristics at baseline and 6 months on ETI common to both studies include sex at birth, CFTR genotype group, prior modulator use, age, ppFEV1, SwCl, and the Cystic Fibrosis Questionnaire–Revised (CFQ-R). Participants with SwCl measured at baseline and 6 months are included in this analysis. Multivariate logistic regression was used to estimate features associated with achieving SwCl levels of less than 30 mmol/L after 6 months of ETI. Results: Data are available from 499 participants in the combined analysis set (RECOVER, n = 116; PROMISE, n = 383). The cohort consisted of mostly adolescents (aged 12–17, n = 186, 37.3%) and young adults (aged 18–30, n = 165, 33.1%), with 28 (5.6%) younger than 12. The RECOVER population is younger than that of PROMISE (75.8% vs. 32.9% < 0.02) and at 6 months (RECOVER: 39.4 mmol/L, 95% CI, 35.9, 42.9 mmol/L; PROMISE: 45.7 mmol/L, 95% CI, 43.6, 47.9 mmol/L) ($p < 0.01$). Average changes were similar (both mean change −42.0 mmol/L, 95% CI, −43.8, −40.2 mmol/L). Six-month SwCl less than 30 mmol/L was achieved in 23.7% of the cohort (n = 118), but neither ppFEV1 change (both mean increasae 9.5 mmol/L, 95% CI, 8.6, 10.4 mmol/L) nor CFQ-R change (17.7 vs. 17.2, $p > 0.05$) was different between those below or above 30 mmol/L. Sex at birth, genotype group, younger age, and lower baseline SwCl were associated with SwCl less than 30 mmol/L at 6 months (OR, 4.2, 95% CI 2.4, 7.2 for female participants; OR, 1.8, 95% CI, 0.6, 5.3 for FG vs. FF, OR, 0.3, 95% CI, 0.2, 0.6 for FM vs. FF). There odds were higher for normalized SwCl for every 10-year lower baseline age (OR, 1.4, 95% CI, 1.03, 1.8) and every 10 mmol/L lower baseline SwCl (OR, 1.7. 95% CI, 1.5, 2.0). Prior modulator use and baseline ppFEV1 were not associated with normalization of SwCl when accounting for other variables. Conclusions: Female and younger PwCF

were found to be more likely to achieve normalization of SwCl in this preliminary analysis. Further analysis in the entire population is required to understand these findings more completely. The independent association of genotype suggests that effective targeting of both alleles is important for achieving the greatest CFTR rescue. As more data become available in RECOVER and PROMISEPeds (aged 6–12), unified analyses will yield greater power and generalizability. Acknowledgements: Support from CFF (several grants) for RECOVER and PROMISE. References [1] Nichols DP, Paynter AC, Heltshe SL, Donaldson SH, Frederick CA, Freedman SD, et al. Clinical effectiveness of elexacaftor/tezacaftor/ ivacaftor in people with cystic fibrosis: a clinical trial. Am J Respir Crit Care Med 2022;205(5):529–39. [2] https://clinicaltrials.gov/ct2/show/NCT04602468 142 Elexacaftor-tezacaftor-ivacaftor and spirometry-controlled chest CT scores in children with cystic fibrosis aged 6 to 11 K. Lester1 , P. McNally1,2, J. Davies3,4, B. Elnazir5,6, D. Cox2,7, M. Williamson2 , B. Linnane8,9, L. Kirwan10, P. O'Regan10, E. McKone11, E. Twomey2 , T. Persaud2 , D. Rea2 , M. Bonte12, H. Tiddens12, T. Semple3,13. 1 Royal College of Surgeons in Ireland University of Medicine and Health Sciences, Dublin, Ireland; 2 Children's Health Ireland, Dublin, Ireland; 3 Royal Brompton and Harefield Hospitals, part of Guys and St Thomas' Trust, London, UK; National Heart and Lung Institute, Imperial College London, London, UK; 4 European Cystic Fibrosis Society, Lung Clearance Index Core Facility, London, UK; 5 Children's Health Ireland at Tallaght, Dublin, Ireland; 6 Trinity College Dublin, Ireland; 7 University College Dublin, Dublin, Ireland; 8 School of Medicine, University of Limerick, Limerick, Ireland; 9 University Hospital, Limerick, Ireland; 10Cystic Fibrosis Registry of Ireland, Dublin, Ireland; 11St Vincent's University Hospital, Dublin, Ireland; 12Erasmus University Medical Centre, Rotterdam, the Netherlands; 13Centre for Paediatrics and Child Health, Imperial College London, London, UK Background: Elexacaftor-tezacaftor-ivacaftor (ETI) is associated with improvements in pulmonary function, sweat chloride, and nutrition in people with CF (PwCF) with the F508del mutation. RECOVER (NCT04602468) is a multicenter post-approval study examining the impact of ETI in PwCF. We have previously demonstrated significant improvements in chest CT scores after 1 year of treatment with ETI in people aged 12 and older. We sought to establish the impact of ETI on CT scores over 1 year of treatment in children aged 6 to 11. Methods: Before the study, CT scanners at all sites were standardized in terms of scanning protocol and scanner output under the supervision of the European Cystic Fibrosis Society Clinical Trials Network CT imaging core facility at the Erasmus Medical Centre Rotterdam. PwCF aged 6 to 11 were recruited to the study before initiating ETI. Spirometry-controlled CT scans were performed at baseline and 1 year in subjects enrolled in this aspect of the study. CT scan images were anonymized, sent for analysis at Erasmus, and scored using the Perth Rotterdam Annotated Grid Morphometric Analysis (PRAGMA) scoring system. PRAGMA scores are divided into percentage disease, percentage bronchiectasis, percentage trapped air, percentage mucus plugging, and percentage bronchial wall thickening. Data are expressed as mean values, and differences in means are assessed using Mann-Whitney t tests. Results: CT scans have been performed in 39 children aged 6 to 11 at baseline, of which 17 have been scored. One-year scans are ongoing and will be scored and available for presentation at the conference. In comparison with baseline scans for people aged 12 and older, at baseline, children aged 6 to 11 had significantly lower mean PRAGMA-CF scores in the areas of percentage disease (3.182 v 7.126, p = 0.001), percentage trapped air (7.134 v 18.64, p = 0.003), percentage mucus plugging (0.475 v 2.054, p = 0.003) but not percentage bronchiectasis (2.184 v 3.947, p = 0.08). Data collection and analysis of baseline and 1-year scans in children aged 6 to 11 is ongoing. Conclusions: PRAGMA-CF CT scores and subscores are substantially lower in people with CF aged 6 to 11 than those aged 12 and older. Analysis of the full dataset of baseline versus 6-month scores will be presented at the conference. Acknowledgements: We would like to thank our study participants and their parents, the RECOVER study team, collaborators, and staff. Funding from CFF, UK Cystic Fibrosis Trust, and Cystic Fibrosis Ireland. 143 High-dose vitamin D treatment of

cystic fibrosis pulmonary exacerbations modulates the correlation profile of plasma immune mediators D. Moncada-Giraldo1,2, V. Giacalone1,2, J. Alvarez3 , C. Margaroli4 , V. Tangpricha5,6, R. Tirouvanziam1,2. 1 Department of Pediatrics, School of Medicine, Emory University, Atlanta, GA; 2 Center for Cystic Fibrosis and Airways Disease Research, Children's Healthcare of Atlanta, Atlanta, GA; 3 Division of Endocrinology, Metabolism, and Lipids, Department of Medicine, School of Medicine, Emory University, Atlanta, GA; 4 Division of Molecular and Cellular Pathology, Department of Pathology, University of Alabama at Birmingham, Birmingham, AL; 5 Department of Medicine, School of Medicine, Emory University, Atlanta, GA; 6 Emory+Children's Center for Cystic Fibrosis and Airways Disease Research, School of Medicine, Emory University and Children's Healthcare of Atlanta, Atlanta, GA Background: In people with CF, pulmonary exacerbations (PEx) are associated with morbidity and mortality. Vitamin D has been studied as an important mediator to maintain lung homeostasis, but its underlying mechanisms of action are ill defined. In a prior multicenter, double-blind, randomized, placebo-controlled clinical trial (RCT), vitamin D administration to treat CF PEx did not improve clinical outcomes including time to next exacerbation, 12-month mortality, or lung function [1], although lack of improvement in clinical outcomes does not preclude changes in inflammatory mediators. We conducted an ancillary analysis of plasma samples from the parent RCT to determine if high-dose oral vitamin D administration (250,000 IU given as a single bolus) at the time of admission of a CF PEx affected circulating immune mediators. Methods: To quantify immune mediators, venous blood was collected in K2 ethylenediaminetetraacetic acid tubes during inpatient visits at the time of hospital admission for a PEx (V1) and 3 months after the PEx (V2) in vitamin D (n = 30) and placebo (n = 29) groups. Blood was centrifuged at 400 × g to separate cells from plasma, and plasma was removed and centrifuged again at 3,000 × g to remove platelets. Platelet-free plasma was frozen at −80°C until use for immune mediator quantification using a 10- plex chemiluminescent assay (U-PLEX, Meso Scale Diagnostics). Immune mediator levels between the two visits were compared within each group (vitamin D and placebo) (subject-matched samples; Wilcoxon signed-rank test) and between groups at both visits (Wilcoxon rank sum test) and assessed for correlations (Spearman test). Results: Six mediators changed significantly between V1 and V2 for both groups (TNF-α, CXCL10, macrophage colony-stimulating factor (CSF) (higher at V2); IL-6, vascular endothelial growth factor A, IL-1RA (lower at V2)). IFN-γ was significantly lower at V2 for the vitamin D group only. Twenty positive correlations among immune mediators were identified in the placebo group and 19 correlations (18 positive and 1 negative) for the vitamin D group. Five correlations were conserved between groups, 15 were unique to the placebo group, and 13 were unique to the vitamin D group. Positive correlations between pro-and anti-inflammatory mediators such as IL-1β and IL-10 were unique for patients under vitamin D treatment. Mediator correlation profiles for neutrophils and monocytes were switched between placebo and vitamin D groups, featuring positive correlations centered on CXCL8, IL-1β, IL-18, and granulocyte CSF (proneutrophil) for the placebo group and CCL2, CXCL11, and M-CSF (promonocyte) for the vitamin D group. Conclusions: A large bolus dose of vitamin D given at the time of CF PEx does not alter plasma immune mediator levels measured at PEx and 3 months after PEx, although a different mediator correlation pattern in the vitamin D group suggests a switch from a pro-neutrophilic to a promonocytic poise (Figure 1). Acknowledgements: CFF (TANGPR11A0). Reference [1] Tangpricha V, Lukemire J, Chen Y, Binongo JNG, Judd SE, Michalski ES, et al. Vitamin D for the immune system in cystic fibrosis (DISC): a double-blind, multicenter, randomized, placebo-controlled clinical trial. Am J Clin Nutr 2019;109(3):544–53. doi: 10.1093/ajcn/nqy291. 144 Changes in airway nitric oxide in people with cystic fibrosis taking elexacaftor-tezacaftor-ivacaftor—Results from the RECOVER study K. Lester1 , P. McNally1,2, J. Davies3,4, B. Elnazir5,6, D. Cox2,7, M. Williamson2 , B. Linnane8,9, L. Kirwan10, P. O'Regan10, E. McKone11, H. Grasemann12. 1 Royal College of Surgeons in Ireland, University of Medicine and Health Sciences, Dublin, Ireland; 2 Children's Health Ireland, Dublin, Ireland; 3 Royal Brompton and

Harefield Hospitals, part of Guys and St Thomas' Trust, London, UK; National Heart and Lung Institute, Imperial College London, London, UK; 4 European Cystic Fibrosis Society, Lung Clearance Index Core Facility, London, UK; 5 Children's Health Ireland at Tallaght, Dublin, Ireland; 6 Trinity College Dublin, Ireland; 7 University College Dublin, Dublin, Ireland; 8 School of Medicine, University of Limerick, Limerick, Ireland; 9 University Hospital, Limerick, Ireland; 10Cystic Fibrosis Registry of Ireland, Dublin, Ireland; 11St Vincent's University Hospital, Dublin, Ireland; 12Respirology, SickKids, Toronto, Canada Background: Fraction of exhaled nitric oxide (FeNO) is a well-established noninvasive airway biomarker. Low FeNO in people with CF (PwCF) is associated with lower lung function and infection with certain pathogens. The CFTR modulator ivacaftor has been shown to increase in FeNO significantly in treated PwCF, suggesting that FeNO may have the potential to serve as biomarker of restored CFTR function in response to CFTR modulators. We sought to determine whether elexacaftor-tezacaftorivacaftor (ETI) therapy was associated with changes in FeNO in PwCF. Methods: RECOVER is a multicenter postapproval study of ETI in Ireland and the United Kingdom. FeNO was measured at baseline and after 6 months and 1 year on ETI treatment using the NioX Vero analyzer. Because ETI was approved in PwCF aged 12 and older before it became available for children aged 6 to 11, the effects of ETI on FeNO were analyzed separately in these two age groups. Airway secretions of participants were bio-banked for later studies of inflammatory markers and of the L-arginine-NO metabolism. Background

To evaluate the chest CT appearance of patients with a clinicopathologic diagnosis of hypersensitivity pneumonia.

Methods

IRB approval was obtained for a retrospective review of patients with a preoperative CT scan, a surgical pathology report from a transbronchial biopsy or wedge resection consistent with hypersensitivity pneumonitis, and a pulmonary consultation, which also supported the diagnosis. The pathology report was evaluated for granulomas, airway-centered fibrosis, microscopic honeycombing, and fibroblast foci. The medical records were reviewed for any known antigen exposure. Patients were separated into two groups; those with and without a known antigen exposure. The CT scans were assessed for distribution of fibrosis: upper lobe or lower lobe predominance, airway-centered versus peripheral distribution, three-density pattern, and honeycombing.

Results

264 pathology reports included the term chronic hypersensitivity pneumonitis (CHP). Thirty-eight of the patients had a pulmonologist who gave the patient a working diagnosis of CHP. The average age of these patients was 64 years, and 21/38 were women. Seventeen of the 38 patients had at least one antigen exposure described in the medical records. All the patients had fibrosis along the airways on chest CT. Both known antigen exposure and no known antigen patients had upper and lower lung-predominant fibrosis. There were more patients with hiatal hernias in the unknown antigen group. Honeycombing was an uncommon finding.

Conclusion

Airway-centered fibrosis was present on chest CT in all 38 patients with CHP (100%), with or without known antigen exposure.

Introduction

Chronic hypersensitivity pneumonitis (CHP) is a clinical diagnosis that requires exposure to an identifiable antigen [1,2]. The classic histopathologic description, which is the result of antigen inhalation, is airway-centered cellular bronchiolitis, interstitial pneumonia, poorly formed granulomas, and multinucleated giant cells. The chronic form of the disease may be associated with fibroblast foci and microscopic honeycombing, as is seen with usual interstitial pneumonitis (UIP) [3,4] (see Fig. 1, Fig. 2, Fig. 3).

CT imaging of CHP shows a pattern of fibrosis that surrounds the airways, and inspiration is associated with mosaic attenuation and expiration with air trapping [[5], [6], [7]] which resembles “head cheese” because of its heterogeneity [8]. The term “head cheese” has been largely replaced by the term “three-density pattern.” The three-density pattern on inspiratory CT has well-demarcated areas of high attenuation, low attenuation, and a normal lung. The low attenuation areas were associated with small airway disease. The high-attenuation areas are GGOs associated with infiltration [9]. The purpose of the present study was to describe the chest CT patterns of pulmonary fibrosis in patients with a histopathologic diagnosis of hypersensitivity pneumonitis, with and without exposure to a known antigen.

Patients and methods

The study was approved by the Institutional Ethics Committee of Columbia University School of Medicine (IRB-AAAS1829, October 12, 2018), which waived the requirement for written informed consent for this retrospective study.

Patients with a pathology report from a wedge resection or a transbronchial biopsy consistent with hypersensitivity pneumonitis between the years 2016 and 2017 and a Pulmonary consultation, which also supported the diagnosis, were included in the study. The patients were

Results

A total of 264 pathology reports from 264 patients included the term “chronic hypersensitivity pneumonitis.” Thirty-eight of these patients were rendered a working diagnosis of CHP by the treating pulmonologist. All 38 patients had at least one chest CT scan available for review. Seventeen (44%) of the 38 patients had at least one antigen exposure. The remaining 21 (56%) patients had no known antigen exposure. There was no statistically significant difference between the average ages and gender

Discussion

Chronic hypersensitivity pneumonitis was first described in 1713 when Bernardino Ramazzini identified patients with lung disease following antigen exposure. Since then, many antigens have been identified, including avian feces, mycobacteria, and fungi [10]. Diagnosis is important because the primary treatment is to separate the patient from the causative antigen [11].

Pathologically, CHP demonstrates granulomas and/or architectural remodeling centered on airways due to the inhalational nature of

Conclusions

The diagnosis and differentiation of fibrotic lung diseases are challenging. A thorough review of the HRCT pattern offers an opportunity to improve outcomes by narrowing the list of differential diagnoses, potentially guiding steps towards earlier diagnosis and intervention. This is especially true for CHP, which has the potential to improve after protecting the patient from exposure to the

antigen. The imaging feature that was most compatible with a clinical diagnosis of CHP was fibrosis along

Rationale and Objectives

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators have revolutionised the treatment of cystic fibrosis (CF). Chest computed tomography (CT) is key in the diagnosis and follow-up of anatomical damage to the lungs. Our study aimed to evaluate changes on lung CT scans of patients with CF after receiving elexacaftor-tezacaftor-ivacaftor (ETI) therapy for one year.

Materials and Methods

We conducted a retrospective, observational, single-centre study between 2018 and 2021 on adult patients with CF administered ETI. We reviewed chest CT scans before and at least one year after starting ETI. The Brody-II score (BSII) was measured by two experienced radiologists who were blinded to the treatment. Paranasal sinus CT scans and clinical and functional data were also compared. Wilcoxon tests were used to compare differences, and Spearman's correlation coefficient was used to evaluate changes in forced expiratory volume in one second (FEV_1) and total BSII.

Results

In the period, 63 patients were given ETI, and 12 met the criteria for analysis. The inter-observer reproducibility of BSII was satisfactory (intraclass correlation coefficient = 0.83, 95% confidence interval 0.57–0.91). The BSII decreased after one year of treatment (−18 ± 16, $p = 0.002$) due to lower mucous plugging (−7 ± 4, $p < 0.001$) and peribronchial thickening (−9 ± 10, $p = 0.002$) scores. Bronchial, parenchymal, and hyperinflation scores were unchanged. Clinical and functional parameters were significantly improved, except for total lung capacity. The correlation between ΔFEV_1 and Δtotal BSII was strong ($r = 0.88$, $p < 0.001$). The paranasal sinus CT score significantly improved with ETI treatment.

Conclusions

ETI decreased pulmonary and sinus morphological abnormalities after one year of treatment.

Introduction

Cystic fibrosis (CF), an autosomal recessive disease, is one of the most common lethal genetic diseases in Caucasian populations [1]. This disease is caused by mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein [2]. CFTR protein dysfunction can affect various organs, especially the lungs, leading to progressive airway mucus obstruction, bronchiectasis, persistent bacterial infection, and inflammation [3]. Life expectancy has greatly increased over the past few decades due to pharmacological approaches and lung transplantation [4]. The recent triple combination in elexacaftor-tezacaftor-ivacaftor (ETI) therapy has revolutionised CF treatment. Elexacaftor and tezacaftor are CFTR correctors that act together to increase the amount of CFTR protein reaching the cell membrane [5]. Ivacaftor is a CFTR potentiator that helps mutated and normal CFTR proteins stay open longer at the cell membrane to allow more chloride to leave the cell and reduce sodium absorption [6]. Since December 2019, this therapy has been US Food and Drug Administration-approved for patients who are over 12 years old and have at least one allele with the f508del mutation. ETI significantly improves respiratory function, especially the percentage-predicted forced expiratory volume in 1 s (FEV_1), with gains of 10% in patients with homozygous mutations when compared to tezacaftor-ivacaftor treatment [7] and 13.8% in patients

with heterozygous mutations when compared to placebo, leading to reduced pulmonary exacerbations and improved quality of life [8].

Currently, chest computed tomography (CT) is considered the best imaging modality to evaluate the extent of the disease, assess complications such as infectious exacerbation, perform angiography in cases of haemoptysis, and follow up with patients. Abnormalities noted on imaging can help differentiate between bronchiectasis, mucous plug, bronchial thickening, and parenchymal lesions. Changes observed on chest CT in patients receiving previously available pharmacological therapies have been explored, and the mucous plugging and bronchial thickening scores seem to improvObjective

A small but relevant proportion of patients with cystic fibrosis develop severely asymmetric chest cavities during the course of their disease. For these patients, the best surgical approach for lung transplantation (LTx) and optimal size matching strategies are controversial.

Methods

All cystic fibrosis patients with asymmetric chest cavities who underwent LTx at the Medical University of Vienna between 2003 and 2017 were identified (n = 13). Patients were grouped according to different surgical strategies: unilateral full-size and contralateral lobar transplantation (n = 4), standard double LTx after mobilization/repositioning of the mediastinum (n = 3), oversized single LTx followed by pneumonectomy on the smaller contralateral side (n = 4), and single LTx after a remote contralateral pneumonectomy (n = 2).

Results

Compared with cystic fibrosis patients with symmetric chests (n = 276, control group), the perioperative management of patients with asymmetric chests was often more complicated. Consequently, 90-day mortality was heightened (23.1% vs 6.5%). Despite this, long-term survival was good with a 5-year survival rate of 69% compared with 78%. Of note, outcome seemed superior for patients who surgery was undertaken with a bilateral compared with a unilateral approach.

Conclusions

Severely asymmetric chest cavities present challenges in regard to the surgical strategy, size matching, and postoperative management. However, in carefully selected patients, LTx provides an adequate long-term outcome.

Abbreviations and Acronyms

CF

cystic fibrosis

CPB

cardiopulmonary bypass

CT

computed tomography

DLTx

double lung transplantation

ECMO

extracorporeal membrane oxygenation

LTx

lung transplantation

PGD

primary graft dysfunction

POD

postoperative day

SLTx

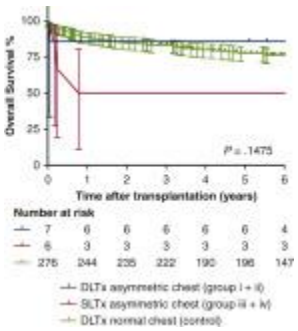
single-lung transplantation

TLC

total lung capacity

VA

venoarterial



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Survival rates of cystic fibrosis patients after lung transplantation.

Central Message

Lung transplantation can be offered to carefully selected CF patients with severe chest asymmetries. It provides adequate long-term outcome, especially when bilateral transplantation is feasible.

Perspective

Severely asymmetric chest cavities represent a challenging situation in lung transplantation. This case series shows that although the perioperative management was often complicated, long-term survival was good in carefully selected cystic fibrosis patients with asymmetric chests. Our data also suggest that—when technically feasible—a bilateral approach should be preferred.

See Commentaries on pages 664 and 666.

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease in Europe with 1 in 2000 to 3000 children being affected. Although treatment of patients with CF has improved significantly, especially with the development of therapies targeting defects in the CF transmembrane conductance regulator,[1] average life expectancy without lung transplantation usually does not exceed the fifth decade of life. Progressive respiratory insufficiency is still the main cause of death in CF patients and lung transplantation remains the only available treatment.[2]

A significant percentage of CF patients develop asymmetric chest cavities in the course of their disease. Prevalence of scoliosis in CF patients ranges from 9.9% to 15.5%[3,4] which is 5 to 10 times higher than the frequency recorded in the general population.[5] CF patients with more severe lung disease have a higher incidence of scoliosis. Because those patients are usually rejected for an orthopedic repair due to their poor pulmonary condition, progressive scoliosis often leads to secondary chest wall deformities. This may result in technical difficulties for lung transplantation (LTx).[6] Another reason for asymmetric chest cavities in patients with CF are recurrent infections leading to atelectasis of major parts of the lung. This can result in chronic consolidation and shrinking of a lobe, a mediastinal shift, elevation of the diaphragm and consequently a significant asymmetry of 1 hemithorax.

Asymmetric chest cavities should not be considered a contraindication for LTx; however, size matching and perioperative handling can be challenging. Current literature is limited to a few case reports of CF patients with chest wall deformities and/or previous pneumonectomy receiving LTx.[7], [8], [9] Of note, none of these case reports have provided long-term follow-up and survival data.

The aim of this study was to evaluate short- and long-term outcome in patients with severe asymmetric chest cavities undergoing LTx as well as to compare different surgical strategies.

Materials and Methods

Study Population and Definitions

In this single-center, retrospective cohort study, all CF patients with a severe chest deformity who underwent LTx at the Medical University of Vienna between 2003 and 2017 were included. Asymmetry of the chest cavity was defined as either a significant retraction of 1 hemithorax (at least 30% smaller compared with the contralateral side), a shift of the mediastinum resulting in a big unilateral and a small contralateral thoracic cavity, or a severe scoliosis (with spinal curve >40°). Patients with an asymmetric chest cavity seen on computed tomography (CT) scan, a history of remote pneumonectomy, or severe scoliosis were presented and discussed in our weekly pretransplant meeting, including transplant surgeons, transplant pulmonologists, psychologists, and transplant coordinators. The decision for each surgical procedure was based on the assessment of the patient's CT scan, considering the size and shape of the chest. Retransplantions as well as multiorgan and living-donor lobar transplants were excluded. Peri- and postoperative parameters were retrieved from the hospital documentation system and from the institutional transplant database. Results were compared with CF patients without chest deformities transplanted within the same time period (ie, control group). None of the control group patients received an unplanned pneumonectomy during the study period (eg, anastomotic failure, malignancy, or central pulmonary embolism with subsequent graft necrosis). In addition, we did not perform single LTx (SLTx) for CF patients with symmetric chests because SLTx should be avoided in CF patients due to the presence of highly resistant organisms and the constant risk of infectious spreading to the transplanted lung.[10]

Primary graft dysfunction (PGD) was calculated according to the latest recommendation of the International Society for Heart and Lung Transplantation.[11] In the absence of bilateral infiltrations, a

PGD0 was documented. In case of radiological signs of reperfusion edema, PGD1 was assigned when PaO2/FiO2 (P/F) ratio was >300 mm Hg, PGD2 for a P/F ratio of 200 to 300 mm Hg, and PGD3 for P/F ratio <200 mm Hg. Patients on postoperative extracorporeal membrane oxygenation (ECMO) were classified as PGD3 if chest radiograph showed bilateral infiltrations. In case of clear radiographs, ECMO patients were classified as PGD ungradable. End of mechanical ventilation was defined as extubation without early reintubation (<5 days). In case of reintubation, end of mechanical ventilation was reached after the final extubation. In tracheostomized patients, end of mechanical ventilation was documented when a patient tolerated mere oxygen insufflation for more than 6 consecutive hours. The study was approved by the ethics board on human research from the Medical University of Vienna (No. EK 1264/2020). Patient written consent for the publication of the study data was waived by the institutional ethics board due to the retrospective analysis. The study rationale is summarized in Figure 1.

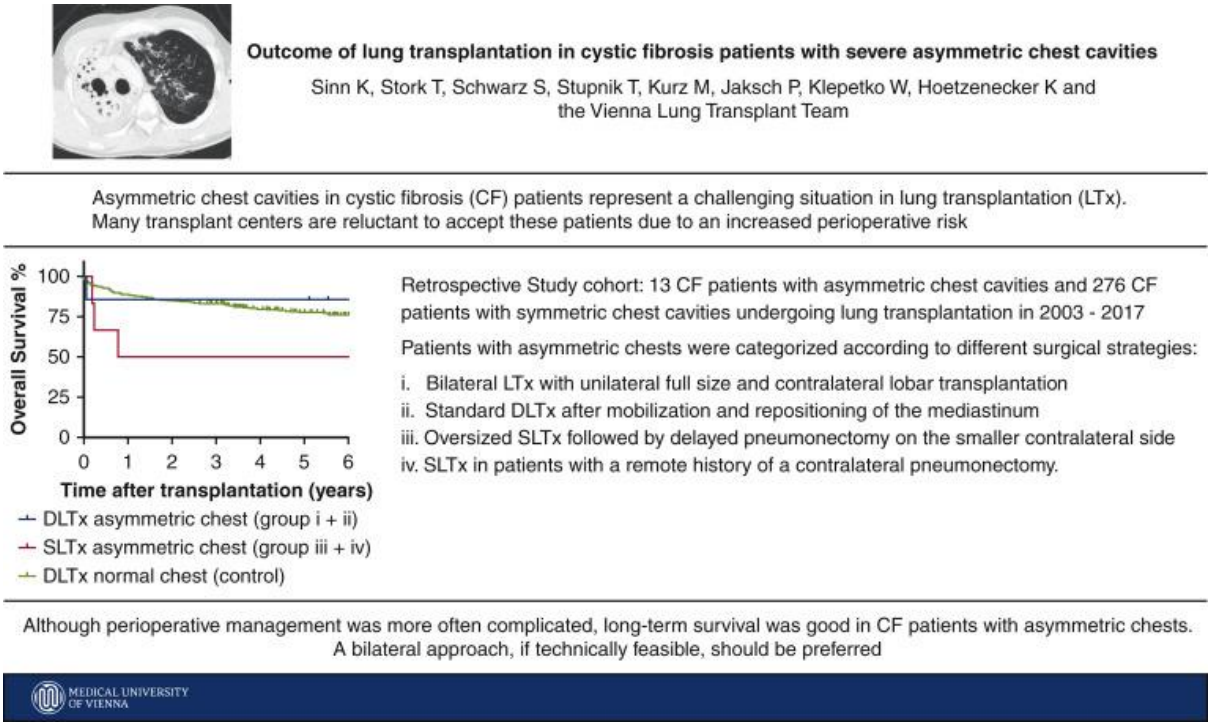

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Figure 1. Summary of rationale, key points, and conclusion of the study. This retrospective cohort study aimed to analyze outcome of cystic fibrosis (*CF*) patients with asymmetric chest cavities undergoing lung transplantation (*LTx*). Patients with asymmetric chests were grouped according to different surgical strategies and results were compared with CF patients with symmetric chests. Adequate long-term outcome can be provided for CF patients with asymmetric chest cavities, especially when bilateral transplantation is feasible. *DLTx*, Double-lung transplantation; *SLTx*, single-lung transplantation.

Statistical Analysis

Due to the small sample size, this is a mainly descriptive study. Statistical analysis was performed using SPSS version 24.0 (IBM-SPSS Inc, Armonk, NY). Normal distributed data were presented by mean and standard deviation, otherwise by median and interquartile range (IQR); categorical variables were reported by absolute frequencies and percentages. The *t* test or Wilcoxon test were

applied to test differences of continuous variables. The χ^2 test was employed for categorical variables. The Kaplan-Meier estimate was used to calculate overall survival. Survival differences of the different subgroups were compared by long-rank tests. GraphPad Prism 8 (GraphPad Prism, GraphPad Software, La Jolla, Calif) was used to produce graphs.

Results

A total of 13 CF patients with asymmetric chests were identified (median age, 24.2 years; IQR, 18.8-31.5 years; 8 women [62%]). Eleven patients experienced a volume-reduced hemithorax with shifting of the mediastinum due to a size discrepancy of the native lungs (n = 9) or due to a previous pneumonectomy (n = 2). Two patients had severe scoliosis in addition to their chest deformity. Retrospective 3-dimensional volumetry of the chest cavity (n = 6 out of 13) was performed and the results are shown in Table E1. During the same time period, 276 CF patients with symmetric chest cavities (median age, 24.8 years; IQR, 19.7-31.7 years; 147 women [53.3%]) underwent transplantation and served as a control group. Detailed patient demographic characteristics are shown in Table 1.

Table 1. Donor and recipient characteristics

Empty Cell	**Group i DLTx: Unilateral full size + contralateral lobe (n = 4)**	**Group ii DLTx: Mediastinal mobilization (n = 3)**	**Group iii SLTx: Followed by delayed pneumonectomy (n = 4)**	**Group iv SLTx: Patients with a remote pneumonectomy (n = 2)**	**Control group (n = 276)**	***P* valu**
Donor						
Age (y)	49.5 (14-63)	53.0 (53-55)	44.0 (18-52)	51.0 (50-52)	38.0 (5-79)	.031
Gender (%)						.020
Male	75	0	50	50	44	
Female	25	100	50	50	56	
Type of donation (%)						.015
DBD	100	100	100	100	97	
DCD	0	0	0	0	3	
Smoking						
Yes	0 (0)	0 (0)	0 (0)	0 (0)	39 (14.1)	.048
No	3 (75)	2 (66.7)	2 (50)	2 (100)	135 (48.9)	

Empty Cell	**Group i DLTx: Unilateral full size + contralateral lobe (n = 4)**	**Group ii DLTx: Mediastinal mobilization (n = 3)**	**Group iii SLTx: Followed by delayed pneumonectomy (n = 4)**	**Group iv SLTx: Patients with a remote pneumonectomy (n = 2)**	**Control group (n = 276)**	***P* valu**
Unknown	1 (25)	1 (33.3)	2 (50)	0 (0)	135 (48.9)	
Abnormal radiograph	1 (25)	0 (0)	0 (0)	0 (0)	33 (12)	.053
Last Po_2	504.3 ± 124.8	388.7 ± 49.7	377.1 ± 82.9	466.0 ± 22.6	452.7 ± 94.5	.709
Last Pco_2	39.7 ± 6.4	54.2 ± 26.6	42.2 ± 6.0	52.3 ± 16.6	39.2 ± 7.3	.503
Recipient						
Age (y)	18.8 (17-23)	30.8 (22-41)	30.9 (28-41)	20.3 (16-24)	24.8 (6-56)	.854
Gender (%)						.777
Male	50	0	50	50	47	
Female	50	100	50	50	53	
High urgent status	1 (25)	0 (0)	1 (25)	1 (50)	34 (12.3)	.331
LAS†	51.3 (37.7-64.9)	37.5 (–)	–	62.4 (–)	38.8 (28.6-100)	.906
Bridged with MV	0 (0)	0 (0)	0 (0)	0 (0)	34 (12.3)	.378
Bridged with ECLS	0 (0)	0 (0)	1 (25)	0 (0)	37 (13.4)	.690
Incision						
Clamshell	4 (100)	3 (100%)	0 (0)	1 (50)	276 (100)	< .00
Thoracotomy	0 (0)	0 (0)	4 (100)	1 (50)	0 (0)	
Type of support						

Empty Cell	**Group i DLTx: Unilateral full size + contralateral lobe (n = 4)**	**Group ii DLTx: Mediastinal mobilization (n = 3)**	**Group iii SLTx: Followed by delayed pneumonectomy (n = 4)**	**Group iv SLTx: Patients with a remote pneumonectomy (n = 2)**	**Control group (n = 276)**	***P* valu**
No ECMO	0 (0)	1 (33.3)	0 (0)	0 (0)	48 (17.4)	.705
Pre- and intraoperative ECMO	0 (0)	0 (0)	1 (25)	0 (0)	38 (13.8)	
Intraoperative ECMO	4 (100)	2 (66.7)	3 (75)	0 (0)	188 (68.1)	
CPB	0 (0)	0 (0)	0 (0)	2 (100)	2 (0.7)	
Surgical time (min)	311.7 ± 41.9	315.3 ± 80.5	201.3 ± 73.1	285.0 ± 28.3	397.0 ± 70.3	.450
Postoperative ECMO	2 (50)	1 (33.3)	3 (75)	1 (50)	44 (15.9)	.003
Induction therapy						
Alemtuzumab	2 (50)	2 (66.7)	0 (0)	1 (50)	140 (50.7)	.361
Antithymocyte globulin	2 (50)	1 (33.3)	2 (50)	1 (50)	106 (38.4)	
No	0 (0)	0 (0)	2 (50)	0 (0)	30 (10.9)	

Values are presented as median (range), n (%) or mean ± standard deviation, unless otherwise noted. *DLTx*, Double lung transplantation; *SLTx*, single lung transplantation; *DBD*, donation after brainstem death; *DCD*, donation after circulatory death; Po_2, oxygen tension; Pco_2, carbon dioxide tension; *LAS*, lung allocation score; *MV*, mechanical ventilation; *ECLS*, extracorporeal life support; *ECMO*, extracorporeal membrane oxygenation; *CPB*, cardiopulmonary bypass.

*

P values are all asymmetric chest groups versus control group.

†

LAS was implemented during December 2011 in the Eurotransplant region; therefore, it is only available for patients listed after December 2011.

Surgical Approach

Patients with asymmetric chests were grouped according to the following surgical strategies: Group i: Double LTx (DLTx) with unilateral full size and contralateral lobar transplantation (n = 4), Group ii: Standard DLTx after mobilization and repositioning of the mediastinum (n = 3), Group iii: Oversized SLTx followed by delayed pneumonectomy of the smaller contralateral side (n = 4), and Group iv: SLTx in patients who had a remote history of a contralateral pneumonectomy before they were presented to our lung transplant program (n = 2). CT scans of representative patients from each group are shown in Figure 2. In addition, we produced schematic drawings highlighting the different extent of chest asymmetry and the postoperative situs of each group (Figure 3). Allocation and donor selection was primarily based on donor and recipient total lung capacity (TLC). However, we measured the chest radiograph and the CT scan of the recipient before transplantation and adapted acceptable donor TLC ranges accordingly. Before finally accepting a donor lung, the size and shape of the donor were always evaluated during explantation by the explant surgeon.

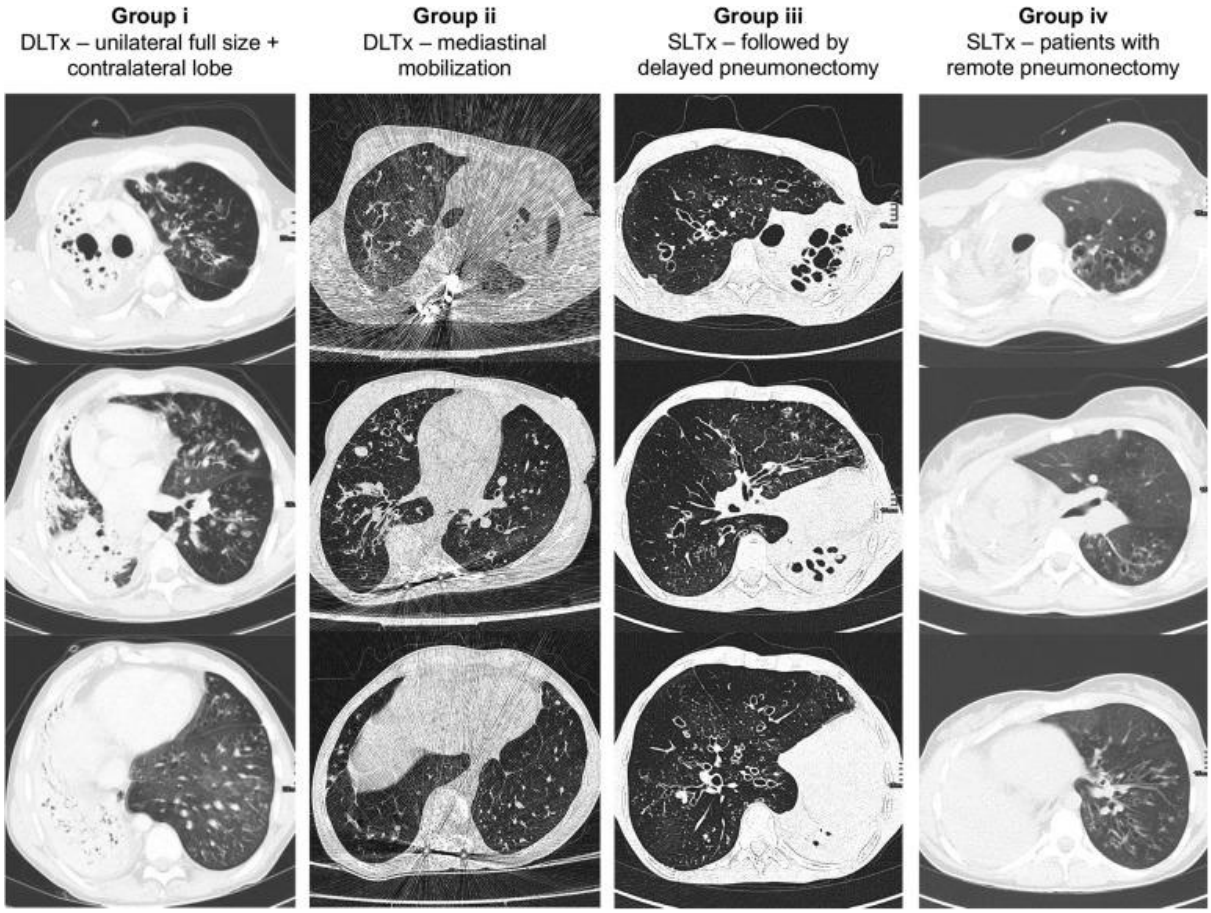

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Figure 2. Standardized sections of preoperative computed tomography (CT) scans of representative patients with asymmetric chests. Group i: Double-lung transplantation (*DLTx*) with unilateral full size and contralateral lobar transplantation; Group ii: Standard DLTx after mobilization and repositioning of the mediastinum; Group iii: Oversized single-lung transplantation (*SLTx*) followed by delayed pneumonectomy of the smaller contralateral side; Group iv: SLTx in patients with a remote history of a contralateral pneumonectomy.

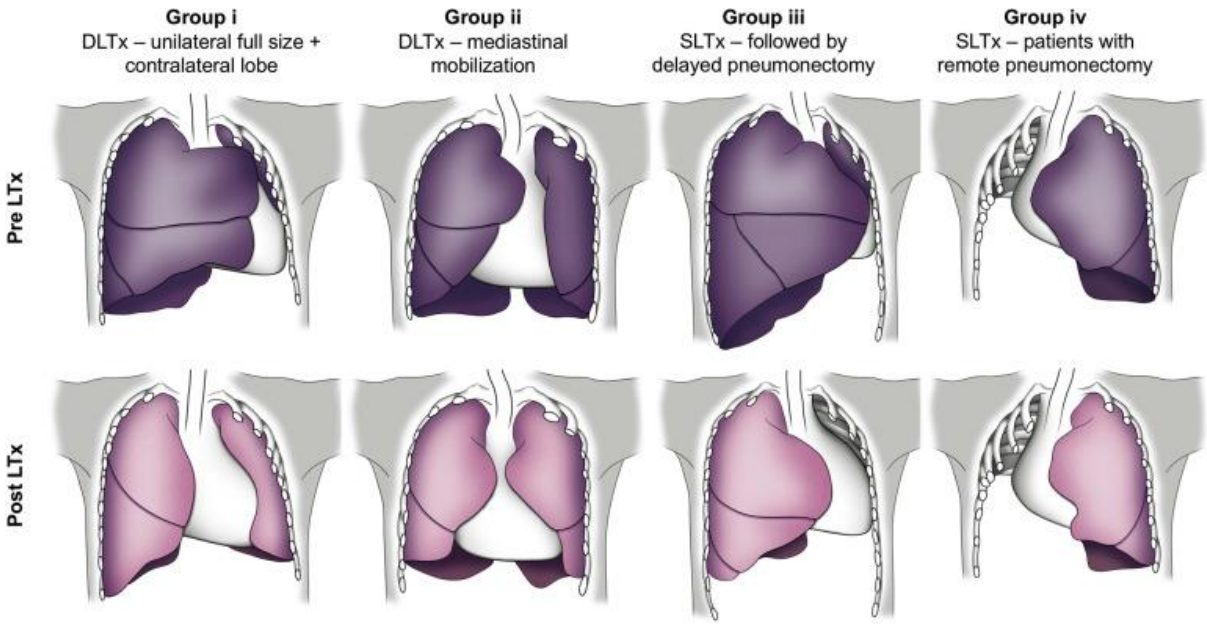

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Figure 3. Pre- and postoperative schematic drawings of the different study groups. Group i: double-lung transplantation (*DLTx*) with unilateral full size and contralateral lobar transplantation; Group ii: Standard DLTx after mobilization and repositioning of the mediastinum; Group iii: Oversized single-lung transplantation (*SLTx*) followed by delayed pneumonectomy of the smaller contralateral side; Group iv: SLTx in patients with a remote history of a contralateral pneumonectomy. *LTx*, Lung transplantation.

The recipient chest was accessed through a clamshell incision in all DLTx cases (n = 7) or through an anterior thoracotomy in 5 of the 6 SLTx recipients. In 1 SLTx case the sternum had to be split to get sufficient access to the hilar structures. In patients of Group i (DLTx: Unilateral full size + contralateral lobe), the decision between upper or lower lobe was based on the shape of the donor lung and the space of the smaller hemithorax. In case of a relatively broad upper chest and a narrow lower chest we used the upper lobe, in case of a relatively narrow upper chest and a broad lower chest the lower lobe was used. Mobilization and repositioning of the mediastinum (Group ii) was performed by complete separation of the upper mediastinum from the sternum and the anterior chest wall. This usually results in a medialization of the heart and correction of mild to moderate size discrepancy between the 2 chest cavities. Six out of 8 DLTx patients were intraoperatively supported by a central venoarterial (VA) ECMO. Patients who underwent SLTx with a planned contralateral pneumonectomy were either transplanted on femofemoral VA ECMO (n = 3) or central VA ECMO (n = 1). The mean duration of the delayed pneumonectomy was 158.8 ± 61.7 minutes. The number of blood products administered during SLTx and delayed pneumonectomy in Group iii are presented in Table E2. Cardiopulmonary bypass (CPB) was used in the 2 SLTx patients with a previous contralateral pneumonectomy. Intraoperative parameters of all patients are summarized in Table 1.

Perioperative Results

Compared with the control group, the perioperative course was more often complicated in CF patients with an asymmetric chest. There was a significant difference in PGD grades at 72 hours (PGD0 or 1: 46.2% vs 22.5%, PGD2: 0% vs 3.6%, PGD3: 23.1% vs 1.8%) (Table 2). This translated into a

prolonged duration of mechanical ventilation (>7 days) in 7 out of 13 patients (53.8%), whereas only 12.3% of patients in the control group were still ventilated on POD7. In 5 (38.5%) patients, a tracheostomy was required. Three patients had to be brought back to the operating room for evacuation of a hemothorax (n = 2) or encapsulated pleural effusion (n = 1). CF patients with asymmetric chests required transient renal replacement therapy more often than control patients (30.8% vs 7.3%); however, the kidney function fully recovered in all patients and none remained hemodialysis-dependent.

Table 2. Outcome

Empty Cell	**Group i DLTx: Unilateral full size + contralateral lobe (n = 4)**	**Group ii DLTx: Mediastinal mobilization (n = 3)**	**Group iii SLTx: Followed by delayed pneumonectomy (n = 4)**	**Group iv SLTx: Patients with a remote pneumonectomy (n = 2)**	**Control group (n = 276)**	***P* valu**
PGD at 72 h						
PGD 0	1 (25)	2 (66.7)	1 (25)	0 (0)	48 (17.4)	.003
PGD 1	0 (0)	0 (0)	1 (25)	1 (50)	14 (5.1)	
PGD 2	0 (0)	0 (0)	0 (0)	0 (0)	10 (3.6)	
PGD 3	1 (25)	0 (0)	1 (25)	0 (0)	5 (1.8%)	
PGD ungradable	1 (25)	0 (0)	1 (25)	1 (50)	15 (5.4)	
Extubated	1 (25)	1 (33.3)	0 (0)	0 (0)	183 (66.3)	
Tracheostomy	0 (0)	1 (33.3)	3 (75)	1 (50)	64 (23.2)	.200
Length of mechanical ventilation (d)	2.5 ± 2.7	6.3 ± 7.0	27.8 ± 21.0	25.4 ± 26.6	3.7 ± 6.4	< .001
Prolonged weaning >7 d	0 (0)	1 (33.3)	4 (100)	2 (100)	34 (12.3)	< .001
Kidney replacement	1 (25)	0 (0)	3 (75)	0 (0)	20 (7.3)	.031
Acute re-transplantation	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	.045
ICU stay (d)	14.3 ± 5.0	11.3 ± 8.6	49.3 ± 28.7	30	15.6 ± 25.7	.077

Empty Cell	**Group i DLTx: Unilateral full size + contralateral lobe (n = 4)**	**Group ii DLTx: Mediastinal mobilization (n = 3)**	**Group iii SLTx: Followed by delayed pneumonectomy (n = 4)**	**Group iv SLTx: Patients with a remote pneumonectomy (n = 2)**	**Control group (n = 276)**	***P* valu**
Hospital stay (d)	26.7 ± 11.2	35.3 ± 23.1	68.8 ± 37.6	47.5 ± 31.8	32.5 ± 28.3	.150
90-d mortality rate	1 (25)	0 (0)	2 (50)	0 (0)	18 (6.5)	.059
1-y survival rate	3 (75)	3 (100)	2 (50)	1 (50)	245 (88.7)	.058
ACR	1 (25)	0 (0)	1 (25)	0 (0)	5 (1.8%)	.035
AMR	0 (0)	0 (0)	1 (25)	0 (0)	14 (50.7)	.507
CLAD	0 (0)	0 (0)	2 (50)	0 (0)	62 (22.5)	.307

Values are presented as n (%) or mean ± standard deviation. *DLTx*, Double lung transplantation; *SLTx*, single lung transplantation; *PGD*, primary graft dysfunction; *ICU*, intensive care unit; *ACR*, acute cellular rejection; *AMR*, antibody mediated rejection; *CLAD*, chronic lung allograft dysfunction.

*

P values: All asymmetric chest groups versus control group.

One patient of Group iii (SLTx with a delayed contralateral pneumonectomy) had to be listed for acute retransplantation due to severe PGD. Despite insertion of a peripheral VA ECMO, the patient did not stabilize and received a second single lung on postoperative day (POD) 3. The further course was prolonged and the pneumonectomy of the contralateral side was finally performed on POD33. The patient fully recovered and could be discharged on POD109 in good clinical condition. She lived for 15 years with an excellent quality of life and died in 2018 after a pneumonia leading to multiorgan failure.

One patient in Group i (DLTx with unilateral full-size and contralateral lobe) developed acute cellular rejection and died on POD19 after exhaustion of all therapeutic options. Two patients in Group iii (SLTx followed by delayed contralateral pneumonectomy) died on POD61 and POD86 due to infectious multiorgan failure and antibody-mediated rejection. This resulted in a 90-day mortality of 23.1% in the asymmetric chest group, which was higher compared with the control group (6.5%).

A subanalysis of the 4 groups with asymmetric chests revealed that procedure-related complication rates as well as early outcome was significantly worse in the 2 SLTx groups. These patients had a high likelihood for prolonged mechanical ventilation, renal replacement therapy, or procedure-related complications. Although the numbers of patients were too low to allow a meaningful statistical comparison, 2 out of 4 patients in Group iii (50%) and 1 out of 2 in Group iv (50%) died within 1 year after transplantation. Perioperative outcome and complications of all 4 groups are summarized in Tables 2 and 3.

Table 3. Complications

Empty Cell	**Group i DLTx: Unilateral full size + contralateral lobe (n = 4)**	**Group ii DLTx: Mediastinal mobilization (n = 3)**	**Group iii SLTx: Followed by delayed pneumonectomy (n = 4)**	**Group iv SLTx: Patients with a remote pneumonectomy (n = 2)**	**Control group (n = 276)**	***P* val**
Wound infection	0 (0)	1 (33.3)	0 (0)	0 (0)	15 (5.4)	.531
Hemothorax	0 (0)	0 (0)	2 (50)	0 (0)	11 (4.0)	.053
Pleural effusion/empyema	0 (0)	1 (33.3)	0 (0)	0 (0)	7 (2.5)	.268
DIOS/paralytic ileus	1 (25)	1 (33.3)	1 (25)	0 (0)	6 (2.7)	.008
PRES	0 (0)	0 (0)	1 (25)	0 (0)	10 (40.5)	.413
Other	1 (25)	0 (0)	3 (75)	0 (0)	7 (2.5)	< .00
ECMO/CPB-related complications						
Groin infection	0 (0)	1 (50)	0 (0)	1 (50)	2 (0.2)	.259
Thromboembolic event	0 (0)	0 (0)	0 (0)	0 (0)	10 (4.6)	.467
Bleeding cannulation site	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	.098

Values are presented as n (%). *DLTx*, Double lung transplantation; *SLTx*, single lung transplantation; *DIOS*, distal intestinal obstruction syndrome; *PRES*, posterior reversible encephalopathy syndrome; *ECMO*, extracorporeal membrane oxygenation; *CPB*, cardiopulmonary bypass.

*

P values: All asymmetric chest groups versus control group.

Long-Term Outcome

Two patients (15.4%) with an asymmetric chest cavity developed acute cellular rejection >A2 compared with 5 patients (1.8%) in the control group. During the follow-up, 15.4% of patients in the asymmetric chest wall group developed chronic lung allograft dysfunction compared with 22.5% in the control group, the median time to the diagnosis of chronic lung allograft dysfunction was 949 days versus 1054 days.

Survival data are depicted in Figure 4. Median time of follow-up was 9.0 years (IQR, 5.6-12.0 yeras). Mean overall survival was 10.2 years (95% confidence interval, 6.03-14.38 yeras) in patients with asymmetric chest cavity versus 12.95 years (95% confidence interval, 12.0-13.82 years) in the control group, without any statistical significance between groups. Cause of death in CF patients with an asymmetric chest and CF patients with a symmetric chest are listed in Table 4. Detailed follow-up data of each patient in the asymmetric chest group are listed in Table E3. Although early mortality was high in the 2 SLTx groups (Group iii and Group iv), long-term survival could be achieved after overcoming the critical early postoperative period. Of note, survival in the 2 DLTx groups (Group i and Group ii) was similar to the control group. None of the long-term survivors developed late physical deformity or scoliosis.

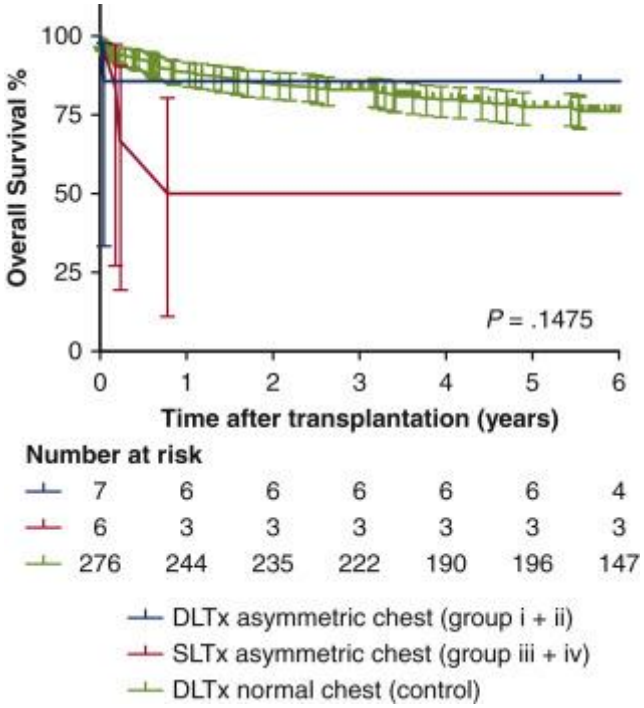

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Figure 4. Overall survival of cystic fibrosis (CF) patients with asymmetric chests receiving double-lung transplantation (*DLTx*) (Group I + ii, *blue*) and single-lung transplantation (*SLTx*) (Group iii + iv, *red*) compared with CF patients with normal chest cavities (control group, *green*). There was no significant difference between the groups. Vertical bars represent 95% confidence limits.

Table 4. Causes of death

Empty Cell	**Asymmetric chest (n = 6)**	**Control (n = 75)**
MOF	4 (66.6)	39 (52)
AMR	1 (16.7)	0 (0)
ACR	1 (16.7)	1 (1.3)

Empty Cell	**Asymmetric chest (n = 6)**	**Control (n = 75)**
Malignancy	0 (0)	7 (9.3)
CLAD	0 (0)	14 (18.7)
Bleeding	0 (0)	3 (4)
Other	0 (0)	7 (9.3)
Unknown	0 (0)	4 (5.3)

Values are presented as n (%). *MOF*, Multiorgan failure; *AMR*, antibody mediated rejection; *ACR*, acute cellular rejection; *CLAD*, chronic lung allograft dysfunction.

Discussion

A significant proportion of CF patients have asymmetric chest cavities due to scoliosis, chest wall deformities, or a significant mediastinal shift. Mild-to-moderate chest wall asymmetries are usually irrelevant for transplantation, but significant asymmetries make LTx challenging. Therefore, some transplant centers consider severe asymmetric chests as a contraindication for LTx. The main concerns are difficult pneumonectomy, especially in cases with a shrunken, consolidated lung; problems in finding a graft that fits to both chest cavities; and reduced chest compliance that significantly influences postoperative mucus clearance. Although sporadic case reports exist describing LTx in patients with asymmetric chests, there is no structured evaluation of a larger case series analyzing perioperative risks and long-term results.

This work could show that LTx can be offered to carefully selected CF patients with severe chest asymmetries. It provides adequate long-term outcome, especially when DLTx is feasible. However, overall prognosis was significantly impaired for the subgroup of SLTx recipients.

Many patients with a long-standing chest asymmetry have a limited compliance and mucus clearance can be impaired in the early postoperative period. This can lead to prolonged respiratory weaning and recurrent infections. Early tracheostomy should be advocated in these patients. A tracheostomy helps to reduce the sedation requirement and therefore allows a gradual weaning of the ventilator and early mobilization. In addition, it facilitates removal of secretions by deep suction or bronchoscopy.

The assessment of the correct dimensions for the donor lung requires exceptional attention because typical parameters such as the real and predicted TLC are not sufficient for size-matching because they do not reflect anatomic conditions of the recipient. The size of the recipient's chest has to be calculated and judged based on CT scans—chest radiograph is not sufficient. For a planned SLTx, it has to be considered that due to mediastinal shifting, 1 hemithorax is much larger compared with the diminutive chest volume of the contralateral side. Thus, the donor has to be considerably taller than the recipient, so that a single lung graft can fill out the enlarged hemithorax. We retrospectively performed 3-dimensional volumetry of recipient CT scans to better quantify the volume of both chest cavities. Unfortunately, only 6 out of 13 CT scans were electronically still available. In our opinion, 3-dimensional volumetry is an interesting additional tool that can be used to determine the best surgical strategy of CF patients with asymmetric chests. However, we believe that the shape and configuration of the chest is equally important and should be considered in the decision making.

There are only few published case reports describing LTx in patients with severe asymmetric chests, including 2 cases with scoliosis from the Cleveland Clinic and 1 Chinese patient with severe mediastinal shift to the left who received a full-sized right allograft and lobar transplantation on the left side. Postoperative complications of these three patients included reoperation for bleeding and prolonged weaning; however, long-term outcome was good.[12], [13], [14] This is in line with results from our cohort of DLTx recipients where we could demonstrate good long-term results and only 1 death within the first 90 days.

In this case series, patients of the DLTx groups (Groups i and ii) showed better survival compared with the SLTx groups (Groups iii and iv). Possible negative prognostic factors in patients after SLTx and contralateral pneumonectomy are worse posttransplant respiratory physiology and less lung volume, which can function as reserve in case of respiratory infection or graft rejection.

SLTx is usually contraindicated in CF patients as the remaining bronchiectatic lung inevitably endangers the graft, especially in patients who are colonized with multidrug-resistant pathogens.[15] Thus, the concept of SLTx combined with a contralateral pneumonectomy was developed.[16] However, such a strategy was not widely adopted as it was associated with significantly worse short- and long-term outcome as compared to DLTx. However, if surgical options are limited to a SLTx due to a severe asymmetric chest cavity, pneumonectomy of the contralateral lung has to be performed. The question about the optimal timing of the pneumonectomy is crucial. SLTx with simultaneous contralateral pneumonectomy has the advantage that only 1 operation has to be performed and a spillage of bacteria to the transplanted graft is avoided, on the other hand the surgical trauma is greater and a sternal-sparing approach is hardly possible. Because many of the patients need intraoperative cardiopulmonary support (ECMO or even CPB) there is a substantial risk of bleeding into the pneumonectomy cavity. Delayed pneumonectomy after SLTx might result in a shorter operating time and a reduced risk of bleeding. The arguments against a 2-stage approach include a second operation, which can interfere with the recovery and can lead to longer reconvalescence. The ultimate decision whether a pneumonectomy can be safely done immediately after SLTx or whether a cooling-down period of a couple of days is better, has to be left to the surgeon's discretion and the intraoperative situation.

A distinct subgroup of our study cohort are patients who had previously undergone pneumonectomy long before the patient was presented to our LTx program. To the best of our knowledge, only 1 case exists in the literature where a DLTx was performed successfully in such a patient.[17] Apart from this case, there is general agreement among transplant surgeons that a SLTx is the only reasonable option. Piotrowski and colleagues[8] reported in 1997 an SLTx performed 8 months after contralateral pneumonectomy in a young CF patient with an asymmetric chest. The postoperative course was complicated by severe reperfusion injury; however, after overcoming this complication, the patient recovered and could be discharged in good clinical condition.[8] SLTx after a previous pneumonectomy is technically challenging and the following technical principles have to be considered: First, the pneumonectomy cavity should not be opened due to a high-risk of bacterial spreading which might lead to a postpneumonectomy empyema. Second, such transplants require CPB and in most cases the main pulmonary artery needs a vent. Third, central cannulation may be difficult due to the often extensive mediastinal shift and a peripheral cannulation should be considered. Postoperative care is also particularly demanding and holds special risks. Adequate fluid management is essential to avoid lung edema and PGD3. If a negative fluid balance cannot be achieved by conservative management, then renal replacement therapy should be liberally started. We have previously shown that an early implementation of renal replacement therapy for fluid management leads to improved pulmonary outcomes and long-term kidney function is not impaired by such an approach.[18]

The fact that early outcome of CF LTx recipients with chest asymmetry is lower than survival of the control CF group cannot be used to justify to exclude these patients from receiving a life-saving treatment. We believe that as long as a patient has a realistic chance to fully recover after a LTx, such a procedure should be offered. Weighing the outcomes of different indications to decide whether or not a patient can be listed is problematic and will result in only accepting easy patients with the best perioperative outcome. The key aspects to consider when accepting CF patients with severe chest asymmetry for LTx are shown in Figure E1.

This study has several limitations. First, it is a retrospective single-center study, which poses a potential bias and variabilities between different transplant centers are neglected. Furthermore, due to the long study period of almost 15 years, the study cannot account for changes in allocation standards, advances in surgical techniques, and immunosuppressive protocols. Another major limitation of this work is the small number of patients with asymmetric chests undergoing LTx. This may impair the statistical comparability of outcomes with the control group. We plan to reach out to other CF centers and provide a multi-institutional experience with patients with asymmetric chest cavities.

Conclusions

Although our cohort of patients with asymmetric chests is small, it clearly favors a (size-reduced) bilateral over a single LTx. Despite a higher perioperative morbidity and mortality long-term survival is comparable to CF patients with symmetric chests.

e with ivacaftor [9], [10] and the combination of lumacaftor and ivacaftor [11], [12]. Although improvement is also expected with ETI therapy, the effect of ETI on pulmonary and sinus morphological changes has not yet been evaluated on CT for over 1 year.

This study aimed to assess changes in lung CT lesions based on a score in patients with CF after one year of ETI therapy. The secondary objectives were to evaluate changes in the other clinical and functional parameters, measure the correlation between the change in FEV_1 and the CT score, and investigate the difference in paranasal sinus obstruction CT score.

Population

This was a retrospective, observational, non-interventional, single-centre study conducted at the French CF centre of Marseille University Hospital (Hôpital Nord, Assistance Publique- Hôpitaux de Marseille, France) from April 2018 (date of the oldest chest CT scan) to November 2021. The study included adult patients with CF (≥18 years) who were heterozygous or homozygous for the f508del mutation and were included in the French early access program for the use of ETI from December 2019

Population

During the study period, 160 non-transplanted patients were followed up in our adult CF centre; 63 were treated with ETI, 41 of whom were excluded due to the lack of a chest CT scan before or after ETI treatment. In the remaining 12 patients, two chest CT scans had been performed—one before treatment initiation and another at least one year after starting treatment (Fig. 1). The 12 patients had a mean age of 36 ± 10 years, and they were retrospectively included for analysis. The patient

Discussion

ETI therapy significantly improved the visual Brody-II score in patients with advanced CF after one year of treatment.

The decrease in the Brody-II score in this cohort was −18 points or 21%. Despite the small number of patients in this sample, the significant results were not associated with a lack of power in our study. The mucous plugging and peribronchial thickening scores were reduced by 50%; to our knowledge, this is the first time that such results have been seen on chest CT in patients

Background

Brasfield scoring system is utilized to compare people with cystic fibrosis (pwCF) chest radiographs and to measure disease burden in individual patients. The emergence of CFTR modulator elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) presents cutting-edge advancement in cystic fibrosis care. Studies exploring chest radiographic changes post-modulator therapy are scarce.

Objectives

Our aim is to assess the impact of modulator therapy on radiographs, and the relation of FEV1 changes with Brasfield score.

Methods

Forty-six adult pwCF had their pre- and post-modulator chest X-rays scored using Brasfield scoring system by a cystic fibrosis clinical fellow (August 2018- December 2022). Radiographs done in the context of exacerbations were excluded. Best FEV1 (Laboratory or best handheld measure) pre- and post-modulator therapy were included.

Results

Ninety-two chest X-rays for forty-six pwCF were scored between August 2018-December 2022. Brasfield score ranged from 5 to 25 (mean 17.7) pre-modulator and 6 to 25 post-modulator (mean 19.6). No pwCF had a lower score following the modulator introduction. Nine pwCF had no change in the Brasfield score, these had baseline scores ranging from 22 to 25. The remaining thirty-seven pwCF had a score increase between 1 and 7 points. Twenty showed improvement in Brasfield score of 5–15%. Fifteen of

Conclusions

Brasfield scoring system verifies the positive outcome of ELX/TEZ/IVA modulator therapy on chest radiographs. Furthermore, pwCF with no improvement in FEV1 demonstrate improvements in Brasfield scores. Further statistical analysis in graph format to look at the correlation of FEV1 with Brasfield score will be included.

Objectives

The aim of this study was to compare high-resolution computed tomography (HRCT) thoracic cage volume and lung volume measured by body plethysmography in adult patients with cystic fibrosis (CF), and to identify parameters that influence the difference between measurements (Dvol = V_{HRCT}-V_{PFT}).

Methods

HRCT, pulmonary function tests (PFTs) were performed in 48 adults with CF (21 M/27 F, aged–18–46 years, medians of age = 25 years, height = 1,66 m, BMI = 19,2 kg/m^2). HRCT was used to measure chest volume and assess lung structural changes using the modified Bhalla score. Measurements were taken by an experienced radiologist using the Vitrea automated station (Lung Analysis

application, Canon Aquilion Prime SP, 160 slices, slice thickness 1 mm). PFTs results were evaluated using GLI reference

Results

Median chest volume at HRCT and volume measured by body plethysmography were 5227 (4199–6167) mL and 4350 (3695–5100) mL, respectively. The median Dvol was 656 (292–1376) mL. All patients had bronchiectasis. Mucus plugging (92%), acinar nodule (75%) and peribronchial thickening (62%) were present in most patients. The median composite HRCT score was 13. There was a strong significant correlation between chest volume at HRCT and lung volume measured by body plethysmography ($R = 0,78$, $p < 0,001$).

Conclusion

In adult patients with CF, there is a strong correlation between chest volume at HRCT and lung volume measured by body plethysmography. The difference between these measurements depends on the severity of structural and functional disorders of the lung and BMI.

Acknowledgements: This work was supported by grants from the Cystic Fibrosis Foundation (THORNT21F0, CAVERL20Y5) and the National Institutes of Health (5R01-HL-136647). 115 Efficacy of home respiratory culture kits in people with cystic fibrosis M. Gulati1 , Y. Wang2 , K. Hall1 , N. Zedro1 , V. Downer1 , E. Ong1 , S. Jia1 , T. Sisson1 . 1 Division of Pulmonary and Critical Care, University of Michigan, Ann Arbor, MI; 2 Department of Biostatistics, University of Michigan, Ann Arbor, MI Background: Respiratory cultures are an important part of clinical care for people with cystic fibrosis (CF). Telemedicine visits during the COVID-19 pandemic have not allowed for routine collection. To address this, the University of Michigan Adult Cystic Fibrosis Program mailed home culture kits to patients. We hypothesized that results from home sputum samples would be consistent with prior cultures obtained in sputum collected in clinic but that self-collected throat swabs would provide false-negative results. We also sought to determine percentage return rate. Methods: Adults with CF were sent culture kits containing a specimen cup and a throat swab. Patients had the choice to submit either sample for processing. Medical personnel provided written instructions with the culture kits and, on occasion, instructed patients on proper collection techniques via phone. Samples were then refrigerated for up to 24 hours before a delivery service returned the specimen to a University of Michigan laboratory for analysis. Data collected from December 2020 to December 2021 (N = 77) included percentage return rate, result, source, and presence of microorganisms. Pairwise culture data of samples collected in clinic versus home-collected samples within 1 year were included in the analysis. Descriptive statistics and Cohen κ correlation coefficients were computed for all culture data and subgroups (Table 1A–E). Results: Of 77 culture kits returned, 46 had corresponding clinic samples collected using the same method, and the remaining 21 were collected using different methods (throat swab vs sputum sample). Overall, approximately 200 kits were mailed to patients, with a return rate of 38.5%. A similar percentage of positive culture results was obtained with same method of collection: sputum and throat samples (Table 1C, D, E), although the discordance rate between cultures collected in clinic and at home ranged from approximately 10% to 30%. Correlation between clinic and home culture data was generally good throughout, except for clinic versus home throat swabs, probably because of a low event rate in the small sample size. Conclusions: The data suggest that, overall, clinic and home culture kits provide similar positive results, although discordance in specific culture results was common. This may be due to natural fluctuations from culture to culture in people with CF. A limitation of this study is that the cultures being compared in our study were not completed on the same day. Nevertheless, our data also indicate that collection technique may influence results for certain microorganisms. How these

differences might influence antibiotic selection and treatment outcomes in the era of telemedicine requires more investigation. The return rate was found to be relatively low, demonstrating the need for interventions to improve patient outreach and compliance. 116 Associations between lung T1 magnetic resonance imaging, chest computed tomography, and multiple-breath washout in young children with mild cystic fibrosis lung disease C. Ren1,1, J. Slaven3 , S. Nasr4 , K. McBennett5,6, C. Flask7 . 1 Children's Hospital of Philadelphia, Philadelphia, PA; 2 Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 3 Department of Biostatistics and Health Data Science, Indiana University School of Medicine, Indianapolis, IN; 4 University of Michigan, Ann Arbor, MI; 5 Internal Medicine and Pediatrics, Case Western Reserve University, Cleveland, OH; 6 University Hospitals Cleveland Medical Center, Cleveland, OH; 7 Case Western Reserve University, Cleveland, OH Background: Structural and physiologic evidence of lung disease is present in a large proportion of children with cystic fibrosis (CF) even in the setting of normal forced expiratory volume in 1 second. Chest computed tomography (CT) can detect changes in lung structure in children with CF, but it exposes them to ionizing radiation. Multiple-breath washout (MBW) can detect ventilation inhomogeneity in children with mild CF lung disease, but it can be time consuming to perform and requires a high degree of operator expertise. Lung T1-magnetic resonance imaging (MRI) can assess pulmonary perfusion and can be quickly performed on clinical MRI scanners using conventional acquisitions and no inhaled or injectable MRI contrast agent. We hypothesized that lung T1-MRI is a sensitive measure of early and mild lung disease in children with CF. To test this hypothesis, we performed T1-MRI, chest CT, and MBW in a cohort of children with CF aged 6 to 11. Table 1 (abstract 115): Analysis of respiratory culture results for (A) all cultures, (B) different collection, and (C, D, E) same collection method. *$p < 0.05$. Cohen κ correlation coefficient between groups: poor agreement < 0.001) PEx states ($p < 0.001$) (Figure 1c). The male-female differential between mean cytokine levels widened (>71.8% of mean value) during PEx for cytokines CXCL10, tumor necrosis factor alpha, granulocyte colony-stimulating factor, interferon lambda, and macrophage inflammatory protein 1 alpha, although these differences were not statistically significant. Conclusions: Sputum IL-1β and SPLUNC1 levels are markers of PEx in all CF participants. SPLUNC1 is predictive of PEx at 60 days, whereas IL-6 is not. IL-6 is higher in men than in women at baseline and even higher during PEx, suggesting that IL-6 may be a sex-specific PEx marker. This highlights the importance of considering sex-based differences when interpreting inflammation marker values as a clinical resource in CF care. The wide sexbased differences in sputum cytokine levels during PEx suggest that sexspecific differences contribute to clinical sexual dimorphism that should be further investigated to define their contribution to CF lung disease, PEx frequency, and mortality in women with CF. Acknowledgements: This work was supported by National Institutes of Health (NIH) R01-HL081160 and R21-AI083475 (LC), NIH T32-HL007778, National Heart, Lung, and Blood Institute, NIH K01-HL125514-01, and the Cystic Fibrosis Foundation Fifth Year Clinical Fellowship and Pilot and Feasibility Award (CB), American Thoracic Society Foundation Unrestricted Research Award (CB). 118 Antibiotic regimen changes during pediatric pulmonary exacerbation treatment J. Cogen1 , D. Sanders2 , J. Slaven3 , A. Faino4 , C. Ren5,6. 1 Division of Pulmonary and Sleep Medicine Department of Pediatrics, Seattle Children's Hospital, University of Washington Seattle, WA; 2 Pediatrics, Indiana University, Indianapolis, IN; 3 Department of Biostatistics and Health Data Science, School of Medicine, Indiana University, Indianapolis, IN; 4 Children's Core for Biostatistics, Epidemiology and Analytics in Research, Seattle Children's Research Institute, Seattle, WA; 5 Children's Hospital of Philadelphia, Philadelphia, PA; 6 Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA Background: Previous respiratory culture results or past PEx antibiotic treatment are typically used to guide antibiotic selection for in-hospitaltreated pulmonary exacerbations (PEx). In the absence of clinical improvement during PEx treatment, antibiotics are frequently changed to find a particular regimen that alleviates symptoms and restores lung function, but the clinical benefits of

changing antibiotics in clinical practiceA qualitative needs assessment of people with cystic fibrosis and research coordinators to inform future clinical trials incorporating home spirometry as an endpoint M. Rosenfeld1,2, E. Nguyen3,4, B. Fogarty5 , A. Berlinski6,7, G. Sawicki8,9, A. Hartzler10. 1 Department of Pediatrics, School of Medicine, University of Washington, Seattle, WA; 2 Department of Epidemiology, School of Medicine, University of Washington, Seattle, WA; 3 Biomedical Informatics and Medical Education, University of Washington, Seattle, WA; 4 Community-Oriented Public Health Practice, University of Washington, Seattle, WA; 5 Therapeutics Development C, Seattle Children's, Seattle, WA; 6 Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR; 7 Arkansas Children's Research Institute, Little Rock, AR; 8 Boston Children's Hospital, Boston, MA; 9 Harvard Medical School, Boston, MA; 10Department of Biomedical Informatics and Medical Education, School of Medicine, University of Washington, Seattle, Washington Background: Home spirometry holds promise as a primary endpoint for clinical trials. Qualitative needs assessments describing the practices and perspectives of people with cystic fibrosis (PwCF), caregivers of PwCF, and research coordinators (RCs) regarding home spirometry can inform strategies for incorporating home spirometry into clinical trials. Methods: We conducted a series of focus groups that engaged PwCF, caregivers, or RCs (separately), led by an experienced facilitator and conducted via videoconference. PwCF aged 14 and older and caregivers with experience performing home spirometry were recruited through the Cystic Fibrosis Foundation (CFF) Community Voice. RCs with experience coaching home spirometry were recruited through the CFF Therapeutics Development Network from sites participating in the PROMISE study. Participants provided informed consent and completed an online survey before the focus group to describe their demographic characteristics and home spirometry devices. Focus groups elicited current experiences and barriers to and facilitators of home spirometry across six target areas, followed by discussion and prioritization. Target areas for PwCF and caregivers included research incentives, burden of procedures, reminders, remote coaching, training, and spirometry results. Target areas for RCs included participant and RC training, remote coaching, monitoring progress, participant engagement, and institution-specific issues. Qualitative analyses followed the deductive approach of template analysis [1]. Common themes identified in each session were reviewed in all PwCF or RC sessions to identify areas of consensus, which were used to formulate recommendations for future clinical trials. Results: From September to November 2021, 27 PwCF and six caregivers stratified according to age and role (teens, adults aged 18–39, adults aged ≥40, caregivers) participated in seven sessions, and 24 RCs participated in five sessions. Groups identified barriers to and facilitators of use of home spirometry. Although most PwCF and caregivers found home spirometry convenient, many experienced technical barriers, reported a learning curve to home measurement, and expressed uncertainty about the quality and reliability of measurements. Major barriers that RCs identified involved tailoring participant training to individual needs, scheduling remote coaching, and performing effective coaching remotely. Participants offered age-specific recommendations in key domains: training materials and procedures (for PwCF and RCs), remote coaching, monitoring progress, maintaining engagement, and other areas, including differences in the conduct and interpretation of research versus clinical and home versus office spirometry. Conclusions: Recommendations from this qualitative needs assessment of PwCF, caregivers, and RCs regarding home spirometry in the research setting have been incorporated into the design of OUTREACH, a CFFfunded, multicenter, prospective study of the accuracy, variability, feasibility, and acceptability of home spirometry as a clinical trial endpoint. Our results can also help inform the design of future remote clinical trials. Acknowledgements: This work was supported by CFF ROSENF21A0. We thank all the focus group participants. Reference [1] Crabtree A. A template approach to text analysis: Developing and using code-books. Doing Qualitative Research 1992;3:93–109. 183 Chest computed tomography assessment to monitor cystic fibrosis structural lung disease progression in

bronchiectasis during late childhood and adolescence Y. Chen1,2, H. Tiddens1,2, C. Byrnes3 , J. Carlin4 , J. Cheney5,6, P. Cooper7 , K. Grimwood8 , M. Kemner-van de Corput1,2, J. Massie9,10, C. Robertson9,11, P. Sly12, S. Vidmar13, C. Wainwright5,6. 1 Department of Paediatric Pulmonology and Allergology, Sophia Children's Hospital, Erasmus MC, Rotterdam, the Netherlands; 2 Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, the Netherlands; 3 Starship Children's Health and Department of Paediatrics, University of Auckland, Auckland, New Zealand; 4 Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute, Melbourne and Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia; 5 Department of Respiratory and Sleep Medicine, Queensland Children's Hospital, Brisbane, Queensland, Australia; 6 School of Medicine, University of Queensland, Brisbane, Queensland, Australia; 7 Department of Respiratory and Sleep Medicine, Children's Hospital at Westmead, Sydney, New South Wales, Australia; 8 School of Medicine and Menzies Health Institute Queensland, Griffith University Gold Coast Campus and Departments of Infectious Diseases and Paediatrics, Gold Coast Health, Gold Coast, Queensland, Australia; 9 Department of Respiratory Medicine, Royal Children's Hospital, Melbourne, Victoria, Australia; 10Children's Bioethics Centre, Royal Children's Hospital, Melbourne, Victoria, Australia; 11Department of Paediatrics, University of Melbourne, Australia; 12Child Health Research Centre, University of Queensland, Brisbane, Queensland, Australia; 13Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute, Melbourne and Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia Background: Cystic fibrosis (CF) lung disease is characterized by progressive bronchiectasis and airway wall thickening (AWT) starting in early childhood. Using the Perth-Rotterdam Annotated Grid Morphometric Analysis for CF (PRAGMA-CF), the follow-up of the Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study (CF-FAB study) showed that the extent of lung disease in young children with CF (CwCF) was an important risk factor for progressive structural lung disease in adolescence [1]. Recently, a fully automated method was developed and validated to measure airway and artery (AA) dimensions for sensitive detection of bronchiectasis and AWT. The aim of our study was to monitor progression of bronchiectasis and AWT over late childhood into adolescence in a longitudinal follow-up study (CF-FAB) of the ACFBAL cohort using the AA method and PRAGMA-CF. Methods: CF-FAB enrolled CwCF who completed the ACFBAL study in Australia and New Zealand. Computed tomography (CT) scans were obtained at two time points approximately 18 months apart. CT scans were analyzed using manual PRAGMA-CF and the automated AA method (LungQ-AA, v2.1.0, Thirona, the Netherlands). PRAGMA-CF computes the volume fraction of the following structural lung components on the inspiratory CT scan: % bronchiectasis, mucus plugging (%MP), %AWT, and atelectasis (%Atelec). The composite score %Disease (%Dis) is defined as the sum of % bronchiectasis, %MP, and %AWT. LungQ-AA automatically segments the bronchial tree and identifies segmental (G0) and distal (G1- 13) airway generation. For each identified airway, the following dimensions are quantified: diameters of airway outer edge (Aout), airway lumen wall (Alumen), artery (A) and airway wall thickness (Awt), and AA-ratios: Aout/A, Alumen/A, and Awt/A. Bronchiectasis was defined as Aout/A greater than 1.1 or Alumen/A greater than 0.8 and AWT as Awt/A greater than 0.3. Mixedeffects models were used for analysis. Results: One hundred twenty CwCF with a mean baseline age of 12.8 ± 1.6 were enrolled, and 115 baseline and 110 follow-up CT scans were obtained with a mean interval of 26 months. Coded CT scans were manually scored in random order using PRAGMA-CF. %Dis increased by 0.44% per year (p = 0.03) and % bronchiectasis increased by 0.38% per year (p = 0.01), respectively. No significant progression was observed for %AWT (p = 0.98). One hundred eighty-five CT scans from 100 CwCF could be analyzed using LungQ-AA (39 excluded because slice thickness was greater than 1.5 mm and 1 for reason unknown). On baseline CT scans (n = 96), 30,792 AA pairs and on follow-up CT scans (n = 89) 32,024 AA pairs were detected from G1 to G13 and analyzed; significant progressions were found in Aout/A and

S378 S107 Alumen/A (all p < 0.001), but not in Awt/A (p = 0.35). Between 64% and 66% of AA pairs were defined as bronchiectasis and 59% as AWT. Conclusions: Progressive bronchiectasis can be observed in CwCF during late childhood into adolescence. AA analysis results agree with PRAGMACF results to monitor disease progression in CwCF. Acknowledgements: On behalf of the ACFBAL and CF-FAB study groups. This study was supported by grants from the Australian National Health and Medical Research Council (9937868, 351541, 1044829). C.E. Wainwright was supported through Practitioner Fellowship through the Children's Hospital Foundation Brisbane (RG0692016). Reference [1] Wijker NE, Vidmar S, Grimwood K, Sly PD, Byrnes CA, Carlin JB, et al. Early markers of cystic fibrosis structural lung disease: Follow-up of the ACFBAL cohort. Eur Respir J 2020;55(4). 184 Effects of elexacaftor/tezacaftor/ivacaftor therapy on lung clearance index and magnetic resonance imaging in patients with cystic fibrosis and one or two F508del alleles S. Graeber1,2,3,4, D. Renz5 , M. Stahl1,2,3,4, S. Pallenberg6,7, O. Sommerburg8,9, L. Naehrlich10,11, J. Berges8,9, M. Dohna5 , F. Ringshausen7,12, F. Doellinger13, J. Röhmel1,2,4, S. Hämmerling8 , S. Barth10,11, C. Rückes-Nilges10,11, M. Wielpütz9,13, G. Hansen6,7,14, J. Vogel-Claussen5,7, B. Tümmler6,7, M. Mall1,2,3,4, A. Dittrich6,7. 1 Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany; 2 Cystic Fibrosis Center, Charité-Universitätsmedizin Berlin, Berlin, Germany; 3 Berlin Institute of Health, Charité-Universitätsmedizin Berlin, Berlin, Germany; 4 German Center for Lung Research, Berlin, Germany; 5 Department of Radiology, Hannover Medical School, Hannover, Germany; 6 Department of Pediatric Pneumology, Allergology and Neonatology, Hannover Medical School, Hannover, Germany; 7 German Center for Lung Research, Biomedical Research in Endstage and Obstructive Lung Disease, Hannover Medical School, Hannover, Germany; 8 Division of Pediatric Pulmonology and Allergy and Cystic Fibrosis Center, Department of Pediatrics, University of Heidelberg, Heidelberg, Germany; 9 Department of Translational Pulmonology, Translational Lung Research Center Heidelberg, German Center for Lung Research, University of Heidelberg, Heidelberg, Germany; 10Department of Pediatrics, Justus-Liebig-University Giessen, Giessen, Germany; 11University of Giessen and Marburg Lung Center, German Center for Lung Research, Giessen, Germany; 12Department of Pneumology, Hannover Medical School, Hannover, Germany; 13Department of Radiology, Charité-Universitätsmedizin Berlin, Berlin, Germany; 14Cluster of Excellence RESIST (EXC 2155), German Research Foundation, Hannover Medical School, Hannover, Germany Background: We recently demonstrated that triple combination cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator therapy with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) improves CFTR function in airway and intestinal epithelia to 40% to 50% of normal in patients with CF with one or two F508del alleles. In previous studies, this improvement in CFTR function was shown to improve clinical outcomes, but effects on the lung clearance index (LCI) determined using multiplebreath washout and abnormalities in lung morphology and perfusion detected using magnetic resonance imaging (MRI) have not been studied. The aim of this study was to examine the effect of ELX/TEZ/IVA on LCI and lung MRI scores in people with CF and one or two F508del alleles aged 12 and older. Methods: This prospective, observational, multicenter, postapproval study assessed LCI and lung MRI scores before and 8 to 16 weeks after initiation of ELX/TEZ/IVA. Results: Ninety-one people with CF, including 45 heterozygous for F508del and a minimal function mutation (MF) and 46 homozygous for F508del, were enrolled. Treatment with ELX/TEZ/IVA improved LCI in F508del/MF (−2.4, interquartile range (IQR) −3.7 to −1.1; p < 0.001) and F508del homozygous (−1.4, IQR −2.4 to −0.4; p < 0.001) patients. ELX/TEZ/IVA also improved the MRI global score in F508del/MF (−6.0, IQR −11.0 to −1.3; p < 0.001) and F508del homozygous (−6.5, IQR −11.0 to −1.3; p < 0.001) patients. Conclusions: Our data demonstrate that improvement in CFTR function with ELX/TEZ/IVA improves lung ventilation and abnormalities in lung morphology, including airway mucus plugging and wall thickening in adolescents and adults with CF and one or two F508del alleles in a realworld postapproval setting. Acknowledgements: This study was supported by an

independent medical grant from Vertex Pharmaceuticals Incorporated (IIS-2018- 107555), the German Center for Lung Research funded by the German Federal Ministry of Education and Research (82DZL009B1, 82DZL002A1, 82DZL005B1, 82DZL004B1), and the German Research Foundation (CRC 1449–431232613 Z02). The funders had no role in design, management, data collection, analyses, or interpretation of the data or in the writing of the abstract or the decision to submit to the North American Cystic Fibrosis Conference. S.T.P. is a member of the Else-Kröner Forschungskolleg TITUS. S.Y.G. and M.S. are participants of the BIH-Charité Clinician Scientist Program funded by the Charité-Universitätsmedizin Berlin and the BIH. 185 Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for F508del-CFTR and a gating or residual function mutation J. Chmiel1 , P. J. Barry2 , C. Colombo3 , E. De Wachter4 , I. Fajac5 , M. Mall6 , K. McBennett7 , E. McKone8 , P. Mondejar-Lopez9 , B. Quon10, B. Ramsey11, P. Robinson12, S. Sutharsan13, N. Ahluwalia14, M. Lu14, S. Moskowitz14, V. Prieto-Centurion14, S. Tian14, D. Waltz14, T. Weinstock14, F. Xuan14, L. Zelazoski14, Y. Zhang14, D. Polineni15, for the VX18-445-110 Study Group. 1 Indiana University School of Medicine, Indianapolis, IN; 2 Manchester University NHS Foundation Trust, Manchester, UK; 3 University of Milan, Milan, Italy; 4 Univeritair Ziekenhuis Brussel, Brussels, Belgium; 5 Universite de Paris, Hopital Cochin, Paris, France; 6 Charité-Universitätsmedizin, Berlin, Germany; 7 University Hospitals Cleveland Medical Center, Cleveland, OH; 8 St.Vincent's Hospital, Dublin, Ireland; 9 Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain; 10St. Paul's Hospital, Vancouver, Canada; 11Seattle Children's Hospital, Seattle, WA; 12Royal Children's Hospital, Melbourne, Australia; 13University Medicine Essen-Ruhrlandklinik, Essen, Germany; 14Vertex Pharmaceuticals Incorporated, Boston, MA; 15University of Kansas Medical Center, Kansas City, KS Background: The triple combination regimen of elexacaftor/tezacaftor/ ivacaftor (ELX/TEZ/IVA) was shown to be safe and efficacious in people with CF aged 12 years and older with cystic fibrosis (CF) and heterozygous for F508del-CFTR and either a CFTR gating mutation (F508del-gating genotypes) or a residual function mutation (F508del-residual function genotypes). A 96-week, Phase 3, open-label extension study was conducted to assess long-term safety and efficacy in these participants. Methods: Participants received ELX 200 mg once daily/TEZ 100 mg once daily/IVA 150 mg every 12 hours. The primary endpoint was safety and tolerability; secondary endpoints included absolute changes in percent predicted FEV1 (ppFEV1), sweat chloride concentration, body mass index (BMI), body weight, and Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score. Results: 251 participants (F508del-gating genotypes, n = 92; F508delresidual function genotypes, n = 159) were enrolled and dosed. Mean (SD) exposure to ELX/TEZ/IVA was 89.3 (20.0) weeks. Overall, 241 participants (96.0%) had an adverse event (AE), which for most were mild (32.3%) or moderate (55.0%) in severity. The exposure-adjusted rates of AEs and serious AEs (589.36 and 13.38 events per 100 patient years) were lower than in the 8-week parent study (1033.98 and 26.74 events per 100 patient years). Thirteen patients (5.2%) had AEs that led to treatment discontinuation (increased liver function tests [n = 6], psychiatric events [n = 4], other events [n = 3]), and there was one death due to an operative complication during resection of a cecal mass, which was not considered related to ELX/TEZ/IVA. Following a 4-week run-in period with either IVA or TEZ/IVA, participants who received ELX/TEZ/IVA in the parent study had improvements in ppFEV1, sweat chloride concentration, and CFQ-R respiratory domain score that were maintained to Week 96 of this extension study, while participants who started ELX/TEZ/IVA in the extension study had similar improvements from parent study baseline at Week 96 (Table 1) Background

Idiopathic pulmonary fibrosis (IPF) is a fatal interstitial lung disease characterized by an unpredictable decline in lung function. Predicting IPF progression from the early changes in lung function tests have known to be a challenge due to acute exacerbation. Although it is unpredictable, the neighboring

regions of fibrotic reticulation increase during IPF's progression. With this clinical information, quantitative characteristics of high-resolution computed tomography (HRCT) and a statistical learning paradigm, the aim is to build a model to predict IPF progression.

Design

A paired set of anonymized 193 HRCT images from IPF subjects with 6–12 month intervals were collected retrospectively. The study was conducted in two parts: (1) Part A collects the ground truth in small regions of interest (ROIs) with labels of “expected to progress” or “expected to be stable” at baseline HRCT and develop a statistical learning model to classify voxels in the ROIs. (2) Part B uses the voxel-level classifier from Part A to produce whole-lung level scores of a single-scan total probability's (STP) baseline.

Methods

Using annotated ROIs from 71 subjects' HRCT scans in Part A, we applied Quantum Particle Swarm Optimization–Random Forest (QPSO-RF) to build the classifier. Then, 122 subjects' HRCT scans were used to test the prediction. Using Spearman rank correlations and survival analyses, we ascertained STP associations with 6–12 month changes in quantitative lung fibrosis and forced vital capacity.

Conclusion

This study can serve as a reference for collecting ground truth, and developing statistical learning techniques to predict progression in medical imaging.

Introduction and background

Statistical Learning is an integral component of Artificial Intelligence (AI) in medical imaging [1]. However, broadly implementing AI in medical imaging can result in several issues, such as, lack of reproducibility, generalizability, and computational power [[1], [2], [3]]. Thus, it is important to develop algorithms that maintain adequate repeatability and reproducibility by using one or more independent sets of data for clinical validation [4]. Generally, there are three steps involved in

Objectives

The purpose of this study is to predict disease progression in the natural follow-up of 6–12 months in subjects with IPF using the baseline HRCT. IPF is a rare and fatal interstitial lung disease (ILD) with a median survival time of 3 to 5 years after diagnosis [21]. Progression in IPF is known to have heterogeneous and unpredictable patterns of progression - stable, slow progression or, rapid progression [21,22]. Although gender, age, and pulmonary function tests (GAP) and usual interstitial

Results

We now present results from the three steps in our algorithm in the following order: (1) model development, (2) analytic validation, and (3) clinical validation.

Discussion

Building a robust model to produce results for clinical validation requires careful consideration of the processes that include the targeted population for a training data set [60,61]. Overall, our proposed STP score is significantly associated with the changes in QLF scores, where both scores are derived from HRCT images. However, the STP score was not associated with the expected changes in the percent predicted FVC. There are several possible reasons for this observation. One of the main

Conclusions

Recent medical research is completed to analyze and make an inference because of increasingly huge data set. Standard statistical methods may no longer be adequate and modern analytic tools can be used. Increasingly, this involves statistical learning techniques and nature-inspired metaheuristic algorithms, such as quantum particle swam optimization, or some hybridization thereof. Our initial work of a statistical learning paradigm is an integrate approach, coupled with a hybrid of quantum

Objectives: Forced oscillations technique (FOT) data at the low frequency of 5 Hz are sparse in patients with cystic fibrosis (CF). Our aim was to measure respiratory resistance and reactance at 5 Hz (Rrs5 and Xrs5, respectively) in a population of children, adolescents, and young adults with CF, and relate the FOT parameters to the severity of lung disease. Methods: Forty-six patients with CF (age 16.2 ± 5.8 years, range 6.9–27 years; 41.3% males) underwent spirometry, Multiple Breath nitrogen Washout (N2MBW), and FOT at frequencies of 5, 11, and 19 Hz. Outcomes included the FEV1 z-score, the Lung Clearance Index (LCI), the N2MBW indices Scond and Sacin, and the Rrs5 and Xrs5. The correlation among the above parameters was assessed by Spearman's coefficient and the relationship between FOT and N2MBW indices by linear regression after adjustment for age and FEV1 z-score. Results: Rrs5 was strongly correlated with LCI ($r = 0.74$; $P < 0.001$) and Scond ($r = 0.79$; $P < 0.001$) and moderately correlated with Sacin ($r = 0.44$; $P = 0.009$). Xrs5 was also strongly correlated with LCI ($r = 0.80$; $P < 0.001$), while its correlation with Scond and Sacin was moderate ($r = 0.58$ and $r = 0.57$, respectively; $P < 0.001$). Rrs5 emerged as significant predictor of LCI (beta = 0.381; $P = 0.009$) and Scond (beta = 0.823; $P < 0.001$), independently of FEV1 z-score and age. Xrs5 was a significant predictor of LCI (beta = 0.671; $P < 0.001$), Scond (beta = 0.435; $P = 0.031$) and Sacin (beta = 0.725; $P < 0.001$), again independently of FEV1 z-score and age. Conclusion: In children and young individuals with CF, changes in respiratory resistance and reactance at the frequency of 5 Hz are consistent with ventilation heterogeneity and may assist in monitoring the progression of lung disease. WS19.04 Lung ultrasound in cystic fibrosis bronchiectasis I. Ciuca1 , L.L. Pop1 , M. Dediu2 , D. Popin3 . 1 University of Medicine and Pharmacy "Victor Babes", Pediatrics, Timisoara, Romania; 2 University of Medicine and Pharmacy "Victor Babes", Pediatric Department, Timisoara, Romania; 3 Clinical County Hospital Timisoara, Pediatric Pulmonology Unit, Timisoara, Romania Objectives: Cystic fibrosis (CF) lung disease dictates the disease's outcome. For lung assessment, computed tomography (CT) is the gold standard, but also irradiating. Lately, lung ultrasound (LUS) proves to be reliable for diagnosis of consolidations, atelectasis or bronchiectasis. The aim of our study was to evaluate the value of a newly conceived LUS score comparing it to CT score and to evaluate the correlation between the score and the lung clearance index (LCI). Methods: Patients with CF were screened by LUS, calculation LUS score, followed by CT scan. Results: Ninety-eight patients with CF were screened and 57 were included in the study; the mean age was 11.8 ± 5.5 SD years. The mean LUS score was 5.88 ± 5.4 SD. LUS CF score had a very strong correlation with the CT score of $rs = 0.87$ ($p = 0.000$). LUS showed a good sensibility for detecting atelectasis Se = 83.7% and consolidations (Se = 94.4%). A lower Se = 77.7%, and Sp = 9%, was found for cylindrical bronchiectasis. Conclusion: Our study has shown that LUS lung CF score is a parameter that can be used with a complementary role in the diagnosis and monitoring of CF lung disease of children, not being recommended for incipient structural changes. WS19.05 Arterialised partial pressure of oxygen: an alternative to FEV1% for tracking cystic fibrosis lung disease in childhood? R. Gaupmann1 , B. Böhm1 , B. Mersi1 , A. Graf2 , S. Gruber1 , Z. Szepfalusi1 , S. Renner1 , E. Dehlink1 . 1 Medical University of Vienna, Department of Paediatrics, Division of Paediatric Allergy, Pulmology, and Endocrinology, Vienna, Austria; 2 Medical University of Vienna, Institute for Medical Statistics, Centre for Medical Statistics, Informatics and Intelligent Systems, Vienna, Austria Objectives: Maintaining good lung function is one of the major therapeutic objectives in the treatment of cystic fibrosis (CF). As spirometry is unreliable at young

ages, early airway disease often remains unrecognised. To overcome this “silent phase,” other, more sensitive, and more feasible methods for tracking CF-lung disease are warranted. Methods: This retrospective observational single-centre cohort study aims to characterise abnormalities in arterialised gas exchange in relation to annual best lung function (percent predicted forced expiratory volume of the first second, FEV1%) and its predictive impact on the clinical course in 96 paediatric CF-patients (age range: 6 to 18 years, 44 females/52 males). Results: A significant correlation of annual best FEV1% and corresponding arterialised partial pressure of oxygen (cPaO2) was detected over the observational period of 13 years ($p < 0.001$). At the age of 5 years, already 39 of 96 CF-patients (40.6%) were hypoxemic (cPaO2 < 85 mmHg, Mean ± SD 79.57 ± 4.59 mmHg). Interestingly, 34 of those 39 hypoxemic patients (87.2%) had normal FEV1% at this time. In a multivariable linear mixed model, the FEV1% decline over time was significantly more pronounced in the group that had been hypoxemic at baseline ($p = 0.0004$). Lower cPaO2 at early ages significantly shortened the time to onset of CF-related diseases, such as the first episode of allergic bronchopulmonary aspergillosis, ABPA ($p = 0.016$) and tended to shorten the time to a diagnosis of CFRelated Diabetes, CFRD ($p = 0.06$, Kaplan-Meier analysis). No association with the onset of chronic Pseudomonas aeruginosa colonisation was found ($p = 0.102$). Conclusion: We were able to detect abnormal gas exchange despite preserved lung function already at the age of 5 years, which was associated with an earlier onset of CF-related complications. cPaO2 may play a role as an alternative to pulmonary function tests, especially at younger ages. WS19.06 Validation of airway-artery algorithm to detect and monitor airway disease on chest computed tomography in the ataluren cystic fibrosis cohort Q. Lv1,2, L. Gallardo Estrella3 , E.-R. Andrinopoulou4 , P. Ciet2,1, J.-P. Charbonnier3 , M. P.C. Kemner - van de Corput2 , D. Caudri1 , M. de Bruijne2 , H. A.W.M. Tiddens1,2. 1 Erasmus MC, Sophia Children’s Hospital, Department of Pediatric Pulmonology and Allergology, Rotterdam, Netherlands; 2 Erasmus MC, Department of Radiology and Nuclear Medicine, Rotterdam, Netherlands; 3 Thirona, Nijmegen, Netherlands, 4 Erasmus MC, Department of Epidemiology, Rotterdam, Netherlands Background: CF lung disease is characterised by progressive airway wall thickening (AWT) and bronchiectasis (BE) which can be detected on chest computed tomography (CT) scans using PRAGMA-CF. Aim: To investigate whether an artificial intelligence-based algorithm to measure airway and artery (AA) dimensions of all visible AA-pairs on chestCTs can detect prevalence and progression of AWT and BE. Methods: Erasmus-MC LungAnalysis and Thirona jointly developed and validated a fully automated AA-method (LungQ, Thirona) which: (1) detects the airway tree and matching arteries; (2) identifies airway generation (G) for each AA-pair; (3) measures for each AA-pair: outer airway diameter (Aout), lumen airway diameter (Alumen), airway wall thickness (Awt) and diameter of the paired artery (A); (4) computes for each AA-pair Aout/A, Alumen/A, and Awt/A ratios; (5) presents ratios from the segmental bronchi (G0) up to the highest visible generation. In the ataluren study, non-volume controlled chest CTs from 190 patients were made at the start of study (SOS) and after 48 weeks at end of study (EOS). Mean (SD) age at SOS was 22.7 (9.7) years. Mixed-effects models were used to explore the 48-weeks changes in Aout/A, Alumen/A, and Awt/A from G0 to the highest detected generation adjusted for gender, age, weight, and height. Results: From G0 to G20 104, 965 AA-pairs were quantified on 332 CTs of 190 patients: SOS 45,828 AA pairs on 176 CTs and EOS 59,137 AA-pairs on 156 CTs. Over the 48-week period, Aout/A, Alumen/A, and Awt/A increased (all $p < 0.001$). This progression was significant for G1 to G6 for Aout/A (all adjusted $p < 0.001$) and Alumen/A (all adjusted $p < 0.02$) and for Awt/A for G2, G3,G5 (all adjusted $p < 0.03$). Conclusions: The AA-method detected progression of CF-related airway changes over 48 weeks. The AA-method appears to be a sensitive outcome to detect disease progression and therefore a promising outcome measure to study the effect of potential disease-modifying drugs on CF lung disease. Table 1. Overview of microbiological samples and clinic visits November 2017–2021 Nov 2017 Nov 2018 Nov 2019 Nov 2020 Nov 2021 Sputum samples 208 (98.6%) 232 (96.7%) 170 (97.7%)

79 (97.5%) 96 (83.5%) Cough swabs 3 (1.4%) 8 (3.3%) 4 (2.3%) 2 (2.5%) 19 (16.5%) Total samples 211 240 174 81 115 In-hospital clinic attendance 261 (100%) 300 (100%) 245 (100%) 158 (48.2%) 151 (67.7%) Virtual clinic attendance 0 (0%) 0 (0%) 0 (0%) 170 (51.8%) 72 (32.3%) Total Visits 261 300 245 328 223 Conclusions: There has been a marked reduction in microbiological samples in the years 2020 and 2021 despite relative preservation of total clinic appointments. This appears to be partly due to an increase in virtual clinic attendance without adequate remote sampling. The disproportionate increase in cough swabs in 2021 can be attributed to ELX/TEZ/IVA availability resulting in decreased sputum burden. This work identifies challenges in monitoring patients established on highly effective modulator therapy in new clinic models. P102 Prevalence of sensitisation to common inhaled allergens in a Belgian adult cystic fibrosis population and its impact on respiratory outcomes H. Marissiaux1 , A. Haccuria1 , I. Etienne1 , A. Michils1 , A. Van Muylem1 , C. Knoop1 . 1 Université Libre de Bruxelles, CUB Erasme, Chest Department, Brussels, Belgium Introduction: Constant therapeutic improvements over the last decades have considerably prolonged life expectancy of cystic fibrosis (CF) patients and consequently, about 65% of Belgian CF patients have reached adulthood. In parallel, atopic sensitisation reaches a peak in the young adult population, and concerns 40% of the adult population in Belgium (1). Therefore, atopy and CF are very likely to coexist in adulthood, but the consequences of this overlap in respiratory health are unknown. Materials and methods: We retrospectively analysed inhaled corticosteroid (ICS) daily intake, frequency of exacerbations and forced expiratory volume in one second (FEV1) between 2015 to 2020 in all non-transplanted adult CF patients followed up at our institution. Data on IgE levels specific of house dust mites, grass pollen, tree pollen, cat, dog, and Aspergillus fumigatus were also collected for the same period. Results: Seventy-nine patients were included, of whom two-thirds disclosed a least 1 sensitisation (specific IgE >0.35 kU/L). Sensitisation rates to house dust mites, grass and tree pollens were at least as high as in the non-CF Belgian adult population (Fig. 1). CF (N = 79) Belgian general population (1) >1 specific IgE 53 (67%) 40% Grass pollen 23/78 (29.5%) 25.9% Tree mix/birch 18/78 (23.1%) 13.2% Dermatophagoïdes pteronyssinus/farinae 19/62 (36.5%) 25.9% Aspergillus fumigatus (AF) 27/79 (34.2%) No data AF + IgE tot >500 kU/L 18/79 (22.8%) No data Blomme K. Int Arch Allergy Immunol. 2013 Fig. 2 Non-atopic Atopic Sensitization other than AF Sensitization with AF p FEV1 decline(%) 0.17[-18.19– 26.82] 0.2[-16.4– 9.35] 0.858 ICS (µg) 310.34[0–3631.58] 709.33[0– 2211.54] 0.002 Exacerbations. year−1 0.83 [0– 11.81] 1.52 [0– 4.36] 1.43 [0–4.36] * 1.60[0–4.36] ** 0.005 0.033* 0.002** Atopy did not seem to influence yearly lung function decline (0.17% [-18.19–26.82] versus 0.2% [-16.4–9.35], p = 0.858), but was positively correlated with a higher exacerbation rate (1.52 [0–4.36] versus 0.83 [0– 11.81], p = 0.005) and higher daily ICS intake (709.33 µg equivalent beclometasone [0–2211.54]vs 310.34 µg [0–3631.58]), p = 0.002) (Fig. 2). Conclusions: Atopic sensitisation concerns two-thirds of Belgian adult CF patients and is more frequent than in the non-CF adult population. It is associated with poorer respiratory outcomes such as significantly higher exacerbation rate and doubling of ICS intake. We therefore suggest allergy screening for common inhaled allergens in the usual CF work-up for optimal management of those patients. P103 Evaluation of patient opinion about the current and future pharmacy service for an adult cystic fibrosis clinic D. McCabe1 . 1 Western General Hospital, NHS Lothian, Pharmacy, Edinburgh, United Kingdom Objectives: To evaluate patients' preferences for future developments to the pharmacy service for CF. Methods: A questionnaire was devised, tested, updated and the completed by patients attending routine appointments over a 2-month period (September to November 2021). Results: https://create.piktochart.com/output/56691994-cf-survey 43 patients were surveyed about medication supply. They generally were happy with supply overall. Getting prescriptions from GP and community pharmacy were the most problematic and supply via homecare was the least problematic. Patients prefer supply close to home or delivered to home and least prefer traveling to hospital for supply. 36 patients were surveyed about IV antibiotic therapy.

Some patients were happy making IV antibiotics at home while some patients find making IV's time consuming and get in the way of normal life Most patients would prefer IV's to come in a ready-made form The majority prefer the home setting, but like to be able to choose hospital when they need it. The reasons for setting choice were: preference of hospital environment, impact on normal life, ability to choose setting and degree of confidence in giving IV's at home. Conclusion: Homecare supply should be an option for patients who prefer this route of supply and have issues with accessing supply in the community. Ready-made IV antibiotics should be available for some patients. P104 Exploring the value of annual chest radiographs in people with cystic fibrosis: an observational study from a single UK centre C. Stovin1 , H. Robbie2 , C. Fang2 , S. Norton3,4, J. Bedford5 , F. Perrin6 , M.D. Waller6,7. 1 King's College Hospital NHS Foundation Trust, London, United Kingdom; 2 King's College Hospital NHS Foundation Trust, Department of Radiology, London, United Kingdom; 3 Institute of Psychiatry Psychology & Neuroscience, Department of Psychology, London, United Kingdom; 4 King's College London, Faculty of Life Sciences & Medicine, London, United Kingdom; 5 York and Scarborough Teaching Hospitals NHS Foundation Trust, York, United Kingdom; 6 King's College Hospital NHS Foundation Trust, Department of Adult Cystic Fibrosis, London, United Kingdom; 7 King's College London, Centre of Human & Applied Physiological Sciences, London, United Kingdom Objectives: Annual chest x-rays (CXR) are recommended to monitor progression of CF lung disease (CF Trust, 2011; ECFS, 2018), yet insufficient evidence supports their utility or relationship with clinical outcomes. As life expectancy increases, the value of annual CXR in people with CF (pwCF) needs consideration. This study evaluates this and explores correlations with other markers of disease severity. Methods: Single-centre, retrospective analysis of annual CXR in clinical stability pwCF (≥18 years) across ≥10 years. A novel CXR score for lung disease (airway thickness, bronchiectasis, nodules, atelectasis, opacities and cavities, all rated 0–10) was developed. Randomised annual CXR were scored by 2 senior radiologists. CXR scores were matched with spirometry and BMI. S92 Poster Sessions / Journal of Cystic Fibrosis 21S1 (2022) S61–S140 Results: Twenty-eight patients, aged 33.0 (31.0–39.5) yrs, were included (mean(SD) follow-up = 11.4(1.9) yr). A total of 304 CXR were scored (mean = 10.9/patient). Overall inter-observer agreement was good for each CXR variable (all Gwet's AC>0.6). Annual rate of change in CXR score over time was 0.11 (total), and 0.00 to 0.06 (individual CXR variables). No or very weak relationship was found between changes in (i) total CXR score or (ii) individual CXR variables, and changes in any clinical parameter (Table 1). Table 1. Spirometry, body mass index and total CXR score at baseline, annual change, and correlation with annualised change for each variable with total CXR score (Pearson coefficient). Baseline (Median (IQR)) Annual Change (Mean (SD)) Correlation between annualised change in variable and total CXR score Total CXR score 6.0 (3.5–16.5) −0.11 (4.0) – ppFEV1 (%) 56.4 (31.4–68.6) −0.48 (8.76) −0.09 (p = 0.16) ppFVC (%) 63.1 (46.9–82.7) −0.64 (10.31) −0.07 (p = 0.26) BMI (kg/m2) 22.7 (20.9–24.3) 0.18 (1.52) −0.15 (p = 0.02) Conclusions: Our new simple CXR score shows annual changes in CXR in adults with CF are insufficiently sensitive to detect disease progression, and show no relationship to changes in other clinical parameters. These data suggest little value in performing annual CXR in stable pwCF. P105 Home spirometry is reliable and of consistent quality in children with cystic fibrosis C.F. O'Toole1 , S. Irving1,2, S. Stanojevic3 , U. Emem-Fong4 , S. Carr2,1. 1 Imperial College London, Faculty of Medicine, London, United Kingdom; 2 Royal Brompton Hospital, Department of Paediatrics, London, United Kingdom; 3 Dalhousie University, Department of Community Health and Epidemiology, Halifax, Canada; 4 Royal Brompton Hospital, Department of Adult Respiratory Medicine, London, United Kingdom Background: Respiratory management of cystic fibrosis (CF) relies on accurate monitoring of trends in lung function. The COVID-19 pandemic accelerated uptake of home spirometers at our paediatric & adult CF centres. Objectives: To establish the reliability and consistency of home-measured spirometry compared to clinic spirometry in children with CF. Methods: A single centre retrospective study. A timeline was constructed for each

individual consisting of 3 pre-pandemic hospital clinic sessions and 3 subsequent virtual sessions. The acceptable period between sessions was 3–12 weeks. Remote devices were Nuvoair® Next or Spirobank® Smart. Control data from CF adults with concurrent clinic and home Nuvoair® data in 2019. Accepted FVC & FEV1session values were used to calculate coefficient of variance (CoV). Sessions graded as 'F' (ATS guidelines) were noted but excluded. GLI percent predicted values were used, with height values interpolated from growth charts if necessary. Results: Sequential spirometry data and baseline demographics are shown in table 1 (n = 139). The proportion of acceptable and unacceptable spirometry (ATS) did not differ between Nuvoair® and hospital measurements. There were more A grades and fewer F grades with hospital spirometry. Conclusions: Routine home spirometry had acceptable variability and quality compared to hospital measures. The step-up in home spirometry measurements for children using Nuvoair® was not seen in pre-pandemic adult data. The differences between home and hospital measures in children suggest an influence of isolation above that of equipment differences. P106 Upper airway disease in adults with cystic fibrosis: a cross-sectional study S. Uyttebroek1,2, L. Dupont3,4, L. Van Gerven1,2,5. 1 UZ Leuven, Department of Otorhinolaryngology, Leuven, Belgium; 2 KU Leuven, Department of Neurosciences, Experimental Otorhinolarygology, Rhinology Research, Leuven, Belgium; 3 UZ Leuven, Department of Pneumology, Leuven, Belgium; 4 KU Leuven, Department of Chronic Diseases and Metabolism, Respiratory Diseases and Thoracic Surgery, Leuven, Belgium; 5 KU Leuven, Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group, Leuven, Belgium Objectives: Chronic rhinosinusitis (CRS) is highly prevalent in patients with cystic fibrosis and is often refractory to conventional treatments. Uncontrolled CRS might negatively influence the lower airways leading to a reduced lung function, bacterial colonisation and graft failure after lung transplantation. Additionally, CRS has an impact on the quality of life due to persisting complaints and the need for (sometimes repetitive) sinus surgeries. The goal of this cross-sectional study is to provide an overview of upper airway manifestations in adults with CF. Methods: Adult CF patients were recruited at the outpatient pneumology clinic. All patients underwent nasal endoscopy, sinus sampling and a CT scan. Furthermore, they were asked to fill in a questionnaire on sinonasal complaints and QoL. These data were combined in a patient Registry. Results: Out of 100 included CF patients, the diagnosis of CRS with and without nasal polyps was made in 63% and 24%, respectively. Objectively, a mean Lund-Kennedy endoscopy and Lund-Mackay radiology score of 5/12 and 10/24 were observed. S. aureus and P. aeruginosa could be isolated in 29% and 10% of the cases, with presence of multidrug resistant strains in 13%. Patient-reported scores were rather low, with a mean SNOT-22 score of 19/110. Complaints of nasal obstruction, rhinorrhea and postnasal drip were reported in 51%, 37% and 42% of the cases. Altogether, CRS was well controlled in only 20% of the patients, despite the use of standard-of-care treatments in 62% and previous surgery in 44%. In 51% of the patients, CFTR-gene modulators were prescribed. Conclusion: CRS is highly prevalent in CF and affects 87% of the patients in this cohort. Despite the use of standard-of-care treatments, CRS is only well-controlled in the minority of the patients. Nasal endoscopy and baseline CT sinuses should be part of routine CF investigations, as there is a high discrepancy between patient-reported symptoms and the extent of the disease. Table 1. (abstract: P105) Cohort Age (mean ± SD) Lung Function Hospital spirometry Home spirometry 1 2 3 CoV 4 5 6 CoV CoV with sequence 4 removed Paediatric Nuvoair® N = 70 10.1 (±2.87) FVC (mean, ±SD) 94.9 (14.8) 94.6 (14.8) 93.9 (14) 5.2 (2.6) 100.4 (15.4) 101 (15.9) 99.5 (16.6) 5.9 (3.8) 5.9 (3.9) FEV1 (mean, ±SD) 88.2 (16.5) 87.5 (15.5) 86.8 (15.9) 5.46 (3.1) 91.3 (16.4) 93.4 (16.9) 91.8 (17.4) 7 (5.07) 6.1 (4.1) Paediatric spirobank N = 14 10.3 (±3.14) FVC (mean, ±SD) 96.8 (11.7) 97.5 (11.2) 98.1 (10.4) 94.0 (12.7) 97.9 (15.4) 96.8 (10.6) FEV1 (mean, ±SD) 94.7 (11.5) 93.6 (10.9) 95.3 (11.7) 92.5 (14.3) 94.6 (16.9) 94.9 (14.9) Adult Nuvoair® N = 55 33.1 (±10.5) FVC (mean, ±SD) 81.7 (17.8) 83.1 (19.4) 80.8 (19.2) 78.6 (18.3) 79.3 (18.6) 79.5 (19.6) 5.1 (2.6) 4.5 (2.7) FEV1 (mean, ±SD) 60.6 (21.2) 60.3 (22.4) 59.5 (21.9) 61.2 (20.7) 61.3 (21.8) 61.9 (22.1)

5.9 (3.2) 5.1 (3.3) Objective: To evaluate the use of the 3-minST to identify pulmonary exacerbations in children and adolescents with CF. Methods: This is a cross-sectional study including patients aged 6 years and older. Demographic, anthropometric and lung function data were collected. The presence of pulmonary exacerbation was assessed using the Kanga score. The 3-minST was performed using a 15 cm step and heart rate (HR), peripheral oxygen saturation (SpO2), subjective sensation of dyspnea and leg fatigue were measured before, after and during recovery from the test. Quadriceps muscle strength was also assessed. The study was approved by the local ethic committee. The student t test, correlation tests and ROC curve analysis were performed. Results: Sixty-two patients (n = 62) with a mean age of 11.1 ± 4.3 years were included. Mean FEV1 (z-score) was − 1.46 ± 2.0 and Kanga score was 16.4 ± 4.1. A Kanga score above 20 (severe) was found in 25.8% of patients. HR (bpm) and SpO2 (%) at the end of the test were, respectively, 126.7 ± 16.9 and 95.4 ± 3.0. Significant differences ($p < 0.05$) between patients with a Kanga score below or above 20 were found for age, FEV1, final and 1-min recovery HR and SpO2. Kanga score significantly and moderately correlated with age (r = 0.41), FEV1 (r = -0.40), final SpO2 (r = 0.43) and 1-min recovery HR (r = 0.40) and SpO2 (r = 0.44). ROC curve analysis have shown that 1-min recovery HR was the best variable to predict pulmonary exacerbations, with an area under the curve of 0.734 (95%CI 0.60–0.87), 62.5% sensibility and 72% specificity for a cut-off value of 111 bpm. Conclusion: The present results show that the 3-minST may be a complementary tool in the evaluation of pulmonary exacerbation in paediatric patients with CF. P214 A comparison of airway clearance devices in adult cystic fibrosis patients: NIPPY Clearway2 versus Intermittent Positive Pressure Breathing (IPPB) R. Brown1 , K. Giannoulatos1 , L.E. Wadsworth1 . 1 Manchester Adult Cystic Fibrosis Centre, Manchester University NHS Foundation Trust, Manchester, United Kingdom Objectives: The IPPB device is a well-established airway clearance technique, benefiting patients who primarily present with an increased work of breathing, sputum retention or atelectasis. Yet IPPB is no longer being manufactured and will soon become an obsolete physiotherapy treatment option across UK respiratory areas. The Breas NIPPY Clearway2 offers patients an IPPB airway clearance mode as an alternative treatment option to the IPPB device keeping with the same principles. Our aim was to compare the 2 devices and evaluate if the Clearway2 could be a suitable alternative to the IPPB device within our CF service. Methods: Adult CF patients who were admitted to hospital with a CF exacerbation between 4–26 October 2021 used the Clearway2 and the IPPB device on alternative consecutive days. Patients who declined to participate or who had contraindications to positive pressure devices were excluded. Patients were randomly allocated to use the Clearway2 or IPPB on day 1 and then the alternative device on day 2. Sputum volumes and device settings were recorded pre and post treatment session. Patients provided feedback on both devices via a questionnaire (0 = Disliked,10 = Liked). Results: Ten adult CF patients, 6 males participated.Mean age 31 years, FEV1 (%) 1.75 (51), FVC (%) 3.12 (77). No changes were observed in sputum volumes between the two devices. Device settings (mean) are tabled below. Device Settings: Mean (SD) Inspiratory Pressure (cmH2O) Flow Rate (L/min) Inspiratory Sensitivity (IPPB) Trigger Level (NIPPY Clearway 2) Plateau IPPB 20 (7.8) 31 (5.6) 5.5 (2.4) n/a N/A NIPPY Clearway 2 19 (6.1) 62 (19.3) N/A 5 (1.5) Not used Total patient questionnaire feedback for the Clearway2 was 64/100 compared to 69/100 for the IPPB device. Conclusion: Both devices are well perceived by adult CF patients. IPPB was marginally the preferred device in this small cohort, however the NIPPY Clearway2 mode can be used as an alternative option to IPPB if obsolete. Inspiratory pressure settings were found to be similar, however flow rate delivery between the two devices differed. The Clearway2 required a higher flow rate setting, which was likely due to the turbine flow versus compressed gas delivery. P215 Airway clearance physiotherapy and health-related quality of life in cystic fibrosis - a substudy of a series of n-of-1 randomised controlled trials S. Gursli1 , A. Quittner2 , R.B. Jahnsen3,4, B. Skrede5 , B. Stuge6 , E. Bakkeheim1 . 1 Oslo University Hospital, National Resource Centre for Cystic Fibrosis, Oslo, Norway; 2 Behavioral Health Systems

Research, Miami, Florida, United States; 3 Oslo University Hospital, Norwegian Quality and Surveillance Registry for Cerebral Palsy, Neurosciences for children, Oslo, Norway; 4 University of Oslo, Faculty of Medicine, Research Center of Habilitation and Rehabilitation Models and Services, Oslo, Norway; 5 Oslo University Hospital, Department of Pulmonary Medicine, Oslo, Norway; 6 Oslo University Hospital, Division of Orthopaedic Surgery, Oslo, Norway Objectives: Airway clearance physiotherapy is recommended in cystic fibrosis, but limited evidence supports the efficacy or duration and frequency. A pilot study investigated the safety, efficacy and participants' perceptions of a novel airway clearance technique, specific cough technique (SCT). A sub-study assessed changes in health-related quality of life (HRQoL) and the association with sputum weight and lung function. Methods: We conducted randomised, controlled individual trials (N-of-1 RCTs) with six adults. Each trial included eight weeks of treatment, twice a week, using saline inhalation in horizontal positions, one with SCT and one with forced expiration technique, in random order. Efficacy was measured by sputum wet weight (g). Lung function was measured at baseline and at end of study. HRQoL was measured using the Cystic Fibrosis QuestionnaireRevised (CFQ-R) at baseline and at the end of study. Individual HRQoL scores (0–100) were coded and analysed using CFQ-R Software Program, version 2.0. Results: Correlations were found between total sputum weight (g) and positive changes in CFQ-R Respiratory Symptoms Scores (CFQ-R-RSS) ($r = 0.94$ ($p < 0.01$)) and between changes in lung function (delta FEF50) and CFQ-R-RSS ($r = 0.84$ ($p = 0.04$)). In a linear regression model with sputum weight as the dependent variable, the effect size of CFQ-R-RSS was Beta (CI) 16.4 (8.1, 24.8) g ($p = 0.006$). With both sputum weight and lung function in the analysis, only sputum weight was associated with CFQ-R-RSS. Conclusion: There was a strong correlation between total sputum weight (g) and positive changes in CFQ-R-RSS. The univariate association between CFQ-R-RSS and changes in lung function highlights the relationship between symptoms, clinical variables and HRQoL. More studies examining optimised treatments are needed. A long-term study may reveal beneficial effects on other clinically meaningful endpoints, such as pulmonary exacerbations, high-resolution computed tomography scores and HRQoL. P216 The short-term influence of chest physiotherapy on lung function parameters in children with cystic fibrosis and primary ciliary dyskinesia D. De Beuckeleer1 , B. Vandervoort1 , E. Huenaerts2 , M. Schülte2 , F. Vermeulen2,3, M. Proesmans3,2, T. Troosters1 , M. Vreys1,2, M. Boon2,3. 1 Catholic University Leuven, Department of Rehabilitation Sciences, Leuven, Belgium; 2 University Hospital Leuven, Pediatrics, Leuven, Belgium; 3 Catholic University Leuven, Department of Development and Regeneration, Leuven, Belgium Objectives: Chest physiotherapy is one of the basic treatments for patients with bronchiectasis to improve mucociliary clearance. The progression of lung disease in patients with bronchiectasis can be evaluated by spirometry and Multiple Breath Washout (MBW) and it is advised to monitor these on a regular basis. However, the short-term effect of chest physiotherapy on spirometry and MBW parameters is insufficiently clear and this variability may impact standardisation. For cystic fibrosis (CF), scarce data did not show a short-term effect in children; however, for primary ciliary dyskinesia (PCD), no data are available. S126 Poster Sessions / Journal of Cystic Fibrosis 21S1 (2022) S61–S140 Methods: We performed a single-centre, prospective cross-over study to evaluate the short-term effect of an airway clearance therapy (ACT) session using positive expiratory pressure mask on FEV1 and Lung Clearance Index (LCI), compared to no intervention in paediatric patients with CF and PCD. Results: A total of 31 paediatric patients was included: 14 with PCD and 17 with CF. For the whole group, there was no difference in median change of FEV1 pp between the treatment and the control group (0.969), nor in median change of LCI (0.294). For CF, the mean change in FEV1 pp with ACT was − 1.4% (range − 9; +5) versus − 0.2% (range − 6; +5) for the control group (p 0.271); the mean change in LCI with ACT was +0.10 (range − 0.7; 1.2) versus +0.17 (range − 0.5; 2.8) for the control group (p 0.814). In PCD, the mean change in FEV1 pp with ACT was +1.0 (range − 7; +8) versus − 0.3 (range − 6; +5) for the control group (p 0.293) and the mean change in LCI with ACT was − 0.46 (range − 3.7; +0.9) versus −

0.11 (range − 1.4; 1.3) for the control group (p 0.178). There was no difference between PCD and CF for change in FEV1 after ACT (p = 0.208), nor for LCI (p = 0.095). Conclusion: No significant short-term effect of ACT was found on lung function parameters in children with CF and PCD. Further research in a larger study group including adults is needed. P217 Exercise as airway clearance therapy (ExACT) in cystic fibrosis: a UKbased e-Delphi survey of patients, caregivers and health professionals Z. Saynor1,2, S. Cunningham3,4,5, L. Morrison6 , E. Main7 , S. Reid8 , D. Urquhart4,5. 1 University of Portsmouth, Physical Activity, Health and Rehabilitation Thematic Research Group, School of Sport, Health and Exercise Science, Portsmouth, United Kingdom; 2 University Hospitals Southampton NHS Foundation Trust, Wessex Cystic Fibrosis Unit, Southampton, United Kingdom; 3 University of Edinburgh, Centre for Inflammation Research, Edinburgh, United Kingdom; 4 Royal Hospital for Children and Young People, Department of Paediatric Respiratory and Sleep Medicine, Edinburgh, United Kingdom; 5 University of Edinburgh, Department of Child Life and Health, Edinburgh, United Kingdom; 6 Queen Elizabeth University Hospital (The Southern General Hospital), West of Scotland Adult Cystic Fibrosis Unit, Glasgow, United Kingdom; 7 UCL Great Ormond Street Institute of Child Health, Physiotherapy Section, London, United Kingdom; 8 Person with Cystic Fibrosis, Glasgow, United Kingdom Background: Establishing whether exercise could replace traditional airway clearance therapy (ACT) in people with cystic fibrosis (pwCF) is a top research priority. We aimed to gauge consensus amongst United Kingdom key stakeholders on whether exercise can be used for ACT and develop consensus on the type, duration and intensity of exercise considered equivalent to ACT. Methods: Our panel comprised CF physiotherapists and doctors, adults with CF and parents/partners of pwCF. Using e-Delphi methodology, respondents ranked agreement on a 9-point Likert scale with statements relating to exercise ACT. Consensus was defined as >70% agreement (scores 7–9). Results: Eighty-three participants completed Round 1, with 60 (72%) completing all three rounds: fifteen (25%) pwCF, 24 (40%) physiotherapists, 11 (18%) doctors, and 10 (17%) parents/partners. 75% (63/83) considered exercise could be potentially be equivalent to ACT. 88% (52/60) would participate in a clinical trial to answer the question and 89% (74/83) would adopt exercise for ACT if supported by trial evidence. Exercise ACT was considered to be aerobic activity, of 21–30 minutes duration (modal average), and an intensity that elicits deep breathing (90%, 60/67). Assessment breaths and coughs and huffs (during and/or after exercise) should accompany exercise to remove loose secretions (80%, 48/60), however, it should be noted the physiotherapy subgroup had significantly higher agreement with this statement than other groups. Traditional ACT is considered to remain integral to care during an exacerbation (73%, 44/60). Conclusions: Our panel support the research priority ‘exercise as a substitute for traditional ACT’. The consensus recommended exercise considered equivalent to traditional ACT and may serve as a reference for developing new ACT strategies and also enable clinical trials to investigate the safety of substituting such exercise for traditional ACT in pwCF. P218 Calibration and cross-validation of accelerometry in children and adolescents with cystic fibrosis M. S. Bianchim1 , M. A. McNarry2 , R. Evans3 , L. Thia4 , A. R. Barker5 , C.A. Williams5 , S. Denford5 , K. A. Mackintosh2 . 1 Swasnea University, Applied Sports, Technology, Exercise and Medicine Research Centre, Swansea, United Kingdom; 2 Swansea University, Applied Sports, Technology, Exercise and Medicine Research Centre, Swansea, United Kingdom; 3 Morriston Hospital, Paeditric Department, Swansea, United Kingdom; 4 Noah’s Ark Children’s Hospital for Wales, Cardiff, United Kingdom; 5 University of Exeter, Children’s Health and Exercise Research Centre, Exeter, United Kingdom Objectives: Available cut-points to classify physical activity (PA) intensity have primarily been generated and validated in healthy populations and may misclassify PAwhen applied to people with cystic fibrosis (CF). The aim of this study was to develop and cross-validate condition-specific PA cutpoints in children and adolescents with CF. Methods: Children and adolescents with CF (n = 35, 15 girls; 11.6 ± 2.8 years) and 28 healthy controls (16 girls; 12.2 ± 2.7 years), energy expenditure and triaxial acceleration were measured during 6 daily activities of

varying intensities. Euclidean Norm Minus One (ENMO) and Mean Amplitude Deviation (MAD) were extracted from the raw acceleration data using both GENEActiv (both wrists) and ActiGraph GT9X (both wrists and right waist) accelerometers. Receiver Operator Characteristic curves were used to determine healthy and CF-specific raw acceleration cut-points for sedentary time (SED), moderate physical activity (MPA) and vigorous physical activity (VPA). Results: The PA cut-points were generally lower in CF compared to healthy peers for both ENMO (60.2–73.1 vs. 63.5–86.8 mg) and MAD (58.9–85.2 vs. 75.9–93.7 mg). The accuracy of the CF-specific ENMO and MAD cut-points varied from fair to excellent according to brand and placement, with greater accuracy for SED (73–98%) and VPA (66–99%), than MPA (66–87%). Raw acceleration differed between placements within brand. Waist and non-dominant wrist generated lower ENMO and MAD values, particularly for VPA. Conclusion: The substantial inter-cut-point differences modifies the accuracy of previous studies reporting PA in youth with CF, supporting the need for disease-specific cut-points to be utilised. P219 Establishing a review process for patients using non-invasive ventilation for airway clearance in the St. Bartholomew's cystic fibrosis adult population G. Goodwin1 , P. Wilson1 , D. Watson1 , N. Shafi1 . 1 St Bartholomew's Hospital, Barts Health NHS Trust, Adult Cystic Fibrosis, London, United Kingdom Objectives: There is no specific guidance on the review process of cystic fibrosis patients using non-invasive ventilation (NIV). The CF trust physiotherapy standards of care and good clinical practice suggest review in various settings and as patients require. The aim was to create local guidance for patients using NIV for airway clearance (ACT) at St Bartholomew's hospital. Methods: A survey was created and sent to the Association of Chartered Physiotherapists in Cystic Fibrosis members working in CF centres across the UK via the email distribution list, to establish current practice of reviewing CF patients using NIV for ACT. Four questions were asked: How many of your CF cohort use NIV for ACT? How often do you review these patient's ACT settings? How do you review these patients? Please give any further information about your NIV for ACT reviews Results: Twenty responses were received. Two respondents reported no patients used NIV for ACT, 1 reported >20 patients, and the other 17 respondents reported 1–20 patients. Seven respondents reviewed patients quarterly, 5 reviewed patients yearly, 4 reviewed patients at their request or on admission and the other 2 reviewed 8-weekly or 6-monthly. Ten respondents reviewed patients face-to-face, 2 reviewed virtually, 2 reviewed on home visits and 6 used a combination of methods.