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Investigating the Severity of Lung Disease Using Lung CT Scan and Pulmonary Function Tests in Children with Cystic Fibrosis

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Abstract

Background: Cystic Fibrosis (CF) is an autosomal recessive disease that has a negative impact on the quality of life in patients. Various methods for assessing lung function and airway obstruction in patients with CF can be used to diagnose and recognize the progression of the disease.

Methods: This is a cross-sectional study with a descriptive approach conducted on 45 CF patients aged 5-18 years. This study investigated the relation between pulmonary disease severity in lung computed tomography (CT) scans, and pulmonary function tests in cystic fibrosis patients referred to our paediatric hospital.

Results: The average age of the patients was 8.33 ± 2.95 years. 73.3% had bronchiectasis with different degrees. In oscillometry (IOS) evaluation, 8.9% had central obstruction, 28.9% had total airway obstruction, 37.8% had peripheral obstruction, and 24.4% had no obstruction. The spirometry results revealed that 53.3% of patients had normal spirometry, 35.6% showed a mild obstruction pattern, and 11.1% had a moderate obstruction. The results obtained from spirometry and IOS revealed that the total resistance in moderate airway obstruction was significantly higher than other resistances, and there was a significant increase in the severity of moderate obstruction of total airway resistance (P=0.022).

Conclusion: Our study showed that CT scan could reveal the complications of cystic fibrosis earlier than pulmonary tests, and it is a reliable tool in evaluating the progress of cystic fibrosis complications and should be considered in the follow-up of patients. Moreover, IOS can help interpret spirometry findings.

Key Words: Bronchiectasis, CT scan findings, Cystic fibrosis, Oscillometry, Pulmonary function tests, Spirometry.

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1- INTRODUCTION

Cystic Fibrosis (CF) is a life threatening and multi-systemic disease that mainly leads to dysfunction of the exocrine glands. It is inherited as an autosomal recessive disease, responsible for a mutation in the CFTR protein (cystic fibrosis transmembrane conductance regulator). This mutation impaired the exchange of ions (chloride, sodium) and water. As a consequence of this disruption, hyper concentration in mucus and reduction in clearance of mucociliary can cause airway inflammation and chronic endobronchial infection, which ensue in the progression of severe lung disease and damage the airways, leading to the formation of cysts, abscesses, fibrosis, and bronchiectasis (1, 2).

There are various methods to evaluate lung function and assess airway obstruction in CF patients, such as spirometry, lung computed tomography (CT) scan, and Impulse oscillometry (IOS). Pulmonary function test and CT scan are used to diagnose, investigate the progression of lung disease and assess the response to treatment in these patients (3, 4).

In PFT, forced expiratory volume in 1 sec (FEV1) is the gold standard measurement of lung function in patients with CF. However, in patients with mild or moderate lung dysfunction, FEV1 is usually in the normal range and children must be cooperative enough to accomplish ventilatory manoeuvres, so they must be at least 3 years of age to perform PFT correctly (5, 6).

CT scans are considered as a gold standard technique for evaluating the pulmonary structural disease in CF patients. Most studies have mentioned that performing CT scan along with PFT can reduce the progression of disease and increase the life quality and long term outcomes in patients (7, 8).

The oscillometric technique, which requires only passive cooperation from the patients, has the potential to evaluate respiratory system impedance and airflow for the youngest and disabled children. Nevertheless, it cannot show early damage of the respiratory disease in CF patients (9, 10).

Each method has some limitations; therefore, we need to validate the methods to select the most applicable ones for monitoring lung dysfunction in CF patients. A limited number of studies have evaluated CF pulmonary complications with PTF and CT scan, and some studies have conflicting results on the findings of these methods. This study was, then, conducted to correlate the severity of lung disease in lung CT scan, using the pulmonary function test, in cystic fibrosis patients referred to Taleghani Children's Hospital.

2- MATERIAL AND METHODS

2-1. Design and sampling

This cross-sectional study was conducted on 45 CF patients in the age range of 5-18 years referring to Taleghani Hospital, Gorgan, Iran. Between January 2020 to august 2021, all patients diagnosed with CF and referred to our paediatric centre hospital were asked to participate in this study. The diagnosis of CF was confirmed with a positive sweat chloride level test (positive result amount ≥60 mmol/L) and gene mutation analysis. Then, in order to evaluate respiratory function, we performed spirometry, IOS, and CT scan while they were stable in their clinical conditions.

2-2. Inclusion and exclusion criteria

The inclusion criteria encompassed all cystic fibrosis patients referred to our paediatric centre between 2020 to 2021, aged between 5 to 18 years old, whose tests were successfully conducted at a stable clinical condition. The exclusion

criteria were having any underlying disease and/or being clinically unstable and/or unable to carry out forced expiration.

2-3. Data collection

First, we performed IOS measurements because forced expiratory manoeuvres would change the bronchial motor tone. We tested patients in a sitting position, using the nose clip with an extended neck. For measuring the impedance of the total respiratory system, we used an oscillometry system (Jaeger Master Screen, Wurzburg, Germany). During the test, we asked the patients to do 20 to 30-sec breathing (for reducing the energy, the hands of the investigator helped the patients) and to avoid swallowing, coughing, vocalisation, and the impulse generator produced brief pressure pulses at intervals of 0.2 sec. For a test to be considered appropriate, during at least 20 secs, the time segment chosen for analysis had to be free of any disruption.

Oscillometric can gauge the Respiratory Resistance (Rrs) and reactance (Xrs) at a number of frequencies. We apply the Rrs, Xrs, and respiratory impedance at 5 Hz (R5, X5, Zr), and the resonance frequency (Fres) as the IOS parameters. The results of raw values by using the manufacturer reference values in the Dencker study were evaluated as a predicted percent derived from a predictive equation in relation to standing height and weight in healthy children and CF patients.

In the Spirometry test (Flowhandy ZAN100, Germany), forced expiratory flows measured the Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), and Forced mid-Expiratory Flow (FEF25–75). Also, the findings of the spirometry test were expressed as raw values and percent of predicted values.

A High-Resolution Computed Tomography (HRCT) scan was performed on all patients included in the study by the use of a multiple detector CT scanner. CT scans were obtained from apices to bases of lungs in supine position and at a full inspiration condition. All scans were investigated by a paediatric pulmonologist physician and a consultant radiologist experienced in reporting HRCT scans.

To determine the grade of bronchiectasis in the HRCT scan, the grading of bronchiectasis in the CT score with the Bronchiectasis Radiological Index (BRICS) is used. Based on the ratio of the diameter of the lumen to the adjacent vessel and the number of bronchopulmonary segments with emphysema, the degree of bronchiectasis is divided into three groups: mild, moderate, and severe. Part one is about the presentation of bronchiectasis. In the absence of bronchiectasis, the score is zero. If the lumen diameter is just more than the adjacent vessel, it gets one score; if it is 2-3 times more than the adjacent vessel, it gets two scores; and if it is three times more than the adjacent vessel, it gets three scores. Part two concerns the number of bronchopulmonary segments with emphysema in CT scans. Zero scores are considered when there is no bronchopulmonary segment with emphysema. If there are 1-5, it gets one score; if there are more than five, it gets two scores. Overall, score one is considered mid, 2-3 is moderate, and 4-5 is severe.

2-4. Data analysis

For all statistical analyses, the Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS, Chicago, IL) was used. Continuous variables were expressed as mean ± Standard Deviation (SD), median, and categorical variables were expressed as counts (percentage). Comparisons of continuous paired variables were performed using the Wilcoxon t-test and comparisons of continuous variables between groups were

performed using the Mann–Whitney Test. Correlation between continuous variables was performed with Spearman Correlation Analysis. A two-sided p-value<0.05 was considered significant for all the tests in the study.

3- RESULT

In this study, forty-five CF patients referred to Taleghani paediatric Hospital were included. The average age of the children was 8.33 ± 2.95 years. The frequency of gender showed that 53.3% were boys and 46.7% were girls.

In the lung CT scan findings, 26.7% of patients had no bronchiectasis and 73.3% had bronchiectasis with different degrees. As presented in **Table 1**, 155 lobes (57.4%) out of a total of 270 lobes, did not have any bronchiectasis, 25.6% of the lobes were mildly involved, 14.4% of the lobes had moderate, and 2.6% of the lobes had severe bronchiectasis (**Table 1**).

Table-1: Frequency of severity of bronchiectasis in all lung lobes

Variable	Severity of bronchiectasis	Abundance	Percent
A total of 270 lobes	No lung involvement	155	57.4
	mild	69	25.6
	moderate	39	14.4
	severity	7	2.6

Among the different lobes of the lung, the highest frequency of lobes affected by bronchiectasis was related to the right and left lower lobes, which ranked first with a frequency of 48.9%. Second, the right upper lobe has a frequency of 46.7%, and then, the right middle lobe and the left upper lobe with 40% and 37.8%. The Lingular lobe with a frequency of 33.3% has the lowest involvement of bronchiectasis considering among the different lobes of the lung.

In the current study, the overall prevalence of bronchiectasis in the lower lobes is higher than that in the upper lobes. However, in severe bronchiectasis, the upper lobes are more involved than the other ones.

In IOS evaluation, the mean change percentages of central, peripheral and total airway resistance was measured and the frequency of airway obstruction was determined. Among 45 patients, 8.9% had central obstruction, 28.9% had total airway obstruction, 37.8% had peripheral obstruction, and 24.4% had no obstruction. The findings of IOS, further, showed that the peripheral airways are more involved than the central airways, and CF disease in children tends to involve the peripheral airways in a form of peripheral obstruction pattern (**Tables 2** and **3**).

The spirometry results of our study revealed that 53.3% of our patients had normal spirometry test results, 35.6% of them showed a mild obstruction pattern, and the rest (11.1%) had a moderate obstruction. Spirometry values are shown in **Table 4**.

Table-2: Changes of airway resistance

Variable	Mean	Standard deviation	Maximum	Minimum
Total airway resistance (R5)	101.58	35.709	161.00	19.10
Large airway resistance (R20)	112.31	41.559	184.90	28.9
Small airway resistance (R5-20)	155.38	96.136	331.8	29.60

Table-3: Percentage of airway obstruction

airway obstruction	Frequencies	Percentage
Normal	11	24.4
Central or large airway obstruction	4	8.9
Total obstruction of airways	13	28.9
Peripheral or small airway obstruction	17	37.8

Table-4: Changes in pulmonary function tests

Variable	Mean	Standard deviation	Maximum	Minimum
FVC	74.8	23.5	107.8	45.7
FEV1	63.3	27.6	104.2	33.1
FEV1/FVC	66.1	13.4	91.9	40.6
FEF25-75	52.9	19.2	70.2	43.2

FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, FEF25–75: forced mid-expiratory flow

The findings of spirometry suggested that the amounts of FVC, FEV1, and FEF25-75 decrease, as the severity of bronchiectasis increases; but this reverse correlation was not significant (P=0.061, P=0.054, P=0.078).

Although in the results of IOS, CT scan, and spirometry, we observed an increase in central, peripheral, and total airways resistance along with the increase in severity of bronchiectasis in patients, statistical significance was not confirmed for all of the correlations. However, central airways resistance statistically correlated with severity of bronchiectasis (P-value=0.06). The results obtained from spirometry and IOS revealed that the total resistance in moderate airway obstruction was significantly higher than those of other resistances and there was a significant increase in the severity of moderate obstruction of total airway resistance (P=0.022) (**Table 5**).

Table-5: Relations between airway resistance and moderate obstruction

Oscillometry	Mean	Standard deviation	P-value*
R5	129.07	49.787	0.022
R20	148.13	48.514	0.472
R5-20	75.73	36.305	0.221

R5: total airways resistance, R20: large airways resistance, R5-20: small airways resistance. *P-value <0.05 considered significant for all the tests in the study.

4- DISCUSSION

CF is a progressive hereditary disease and the Advanced CF Lung Disease (ACFLD) is the most common cause of morbidity and mortality in these patients. ACFLD is associated with decreasing the quality of life, increasing the clinical symptoms and complications, enhancing exacerbation rate, and causing a lot of cost to the healthcare facilities (2, 7, 8, 11-14).

CF patients must be evaluated repeatedly for lung function status and disease

severity. The median survival of CF patients in 1960 was less than ten years. Today, with the advancements in treatment, control of complications, and prevention of progression, the quality of life and median survival has increased to 47 years (1, 2, 15).

Physicians face challenges in treating CF patients. Low socioeconomic status, lower birth weight, worse nutritional status, and worse lung function can affect the treatment protocol, burden, and costs of treatment. Long-term complications of the disease can cause disability, lung transplant, neurological and psychiatric diseases (3, 6, 16, 17).

In CF patients, different methods should be investigated for diagnosing pulmonary function status in stable patients, for early determination of pulmonary damage and for increasing the effectiveness of antibiotic treatment in exacerbations (18, 19).

In this study, using a lung CT scan, the location, extension, and severity of bronchiectasis in different lung lobes were determined. The CT scan findings were compared with the results of the IOS and spirometry revealing that the patients with severe bronchiectasis had milder IOS and spirometry findings. This finding indicated that CT scan can reveal the complications of CF earlier than lung tests and it is a reliable tool in evaluating the progress of CF complications; and should be considered in the follow-up of patients. Similar to our findings, in the study by Bayfield (2021), it is mentioned that bronchiectasis and lung function disorder are presented in early ages of CF patients. In their study, 91% of the patients in school-age had bronchiectasis in their lung CT scan. They concluded that CT scan can be a gold standard method for the diagnosis of bronchiectasis in CF patients (1, 17, 20, 21).

Our results also revealed that despite the prevalence of bronchiectasis being higher in the lower lobes, in the setting of severe bronchiectasis, upper lobes are more involved than others. In contrast to this finding, Straten (2020) indicated that based on the severity of bronchiectasis, different lobes can be affected. In most cases, lung CT scans have shown that bronchiectasis tends to contain upper lobes in CF patients (12, 18, 19, 22).

IOS values are influenced by various factors such as the stability or exacerbation of the disease, treatment phase, prescribed medicine or physiotherapy; and its data analysis can help early detection of disease complications and its progression, along with selecting appropriate treatments. In IOS results, we observed an increase in the resistance of entire airways, but this increase in resistance and their percentage changes were within the normal range. According to IOS findings, it was suggested that in CF children, peripheral airways with peripheral obstructive patterns are more prevalent. In line with our findings, Gokcen (2021) comparing IOS values before and after the treatment with a bronchodilator reported that there was a decrease in peripheral airway resistance after treatment (9, 12, 23, 24).

Based on the results of spirometry, most patients had normal or mild obstruction patterns, which indicates the stable condition of the patients in this study. 40% of patients had a response to bronchodilator whereas 60% had no response, which is in concordance with the nature of the disease. Pollak et al. (2021) reported that the response to bronchodilators in spirometry tests of CF patients was not adequate. So early detection of complications and exacerbations is not possible by spirometry alone and requires the use of a CT scan or IOS.

As presented in our results, along with the increase in the severity of bronchiectasis, a decrease in spirometry parameters (FEV1, EVC, FEF25-75) was observed, though this relation was not statistically significant. Therefore, spirometry results should not be considered alone to evaluate the complications and progression of the disease and should be utilised as a complementary method along with a CT scan or IOS (13, 18, 21, 23).

In this study, we elucidated that the CT scan findings have a direct correlation with the results of IOS. Higher severity of bronchiectasis is correlated with increased airway resistance. Therefore, we can use IOS for assessing CF complications. The results of spirometry are not helpful in investigating the complications and progress of CF alone, and there is a need for a complementary method. CT scan is a more useful method than spirometry and IOS in diagnosing early complications and progression of the disease (7, 15, 18, 21, 24).

Based on the study results and the progressive and destructive nature of the disease, early detection of complications increases the survival and quality of life, and reduces further complications, hospitalisation, frequency of exacerbations, and treatment duration of patients. All of these conditions lead to a reduction in the burden of treatment costs and informing patients and their families about the importance of follow-up, referral, and treatment on time (9, 13, 17, 22, 23).

5- STRENGTHS AND LIMITATIONS

The strength of this study is to evaluate the severity of pulmonary disease in children with CF using three methods, CT scan, oscillometry, and spirometry with a significant number of samples, based on which we presented significant results regarding the interpretation of the findings. Limitations of our study were as follows. We could not evaluate IOS or spirometry findings in the exacerbation or treatment conditions compared to the stable condition. In this study, bronchiectasis was investigated, and other complications such as air trapping, mucus plaque, and consolidation were not investigated. Moreover, children over five years of age were compared due to the comparison of IOS and spirometry findings, and children under five were excluded from the study due to limitations in performing spirometry.

6- ETHICAL CONSIDERATIONS

Informed consent was obtained from all individual participants' legal guardians and a copy of the written consent is available. The purpose of this study was completely explained to the participants' legal guardians and they were assured that all the information would be kept confidential by the authors. This study was conducted in line with principles of the declarations of Helsinki. The ethical committee of Golestan University of Medical Sciences approved the study under the code of IR.GOUMS.REC.1401.538

7- DATA AVAILABILITY

Data and material of this article are not publicly available due to ethical matters but are available from the corresponding author on reasonable requests.

8- AUTHOR CONTRIBUTIONS

L.Sh and B.K suggested the study of conception and design. D.A reported all the lung CT scans. L.Sh and B.K performed material preparation and data collection, and M.M performed Data analysis. N.L and M.M wrote the first draft of the manuscript, and all authors commented on previous versions. All authors read and approved the final manuscript.

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