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Lung Hyperinflation Is Associated with Pulmonary Exacerbations in Adults with Cystic Fibrosis

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Abstract

***Background*: Forced expiratory volume 1 second (FEV_1) has traditionally been used as a readily available marker of health in adult cystic fibrosis (CF). However, due to the obstructive nature of this disease, it is possible that lung hyperinflation could be more closely related to disease severity than is FEV_1. The purpose of this study was to determine if hyperinflation is more closely associated with quality of life, functional status, and pulmonary exacerbations than FEV_1 in patients with CF. *Methods*: Sixty-eight adult patients with CF were evaluated in this retrospective study. We used IC and functional residual capacity (FRC) and their ratios to total lung capacity (TLC) as measures of lung hyperinflation. We used bivariate correlations and backwards regression analysis to assess possible associations between FEV_1, lung hyperinflation, and measures of disease severity including questionnaire based quality of life, pulmonary exacerbation frequency, and mortality. The respiratory component of the Cystic Fibrosis Questionnaire–Revised (CRQ-R-Respiratory) was used as a measure of quality of life. *Results*: Both FEV_1 and IC were negatively correlated with pulmonary exacerbations over a 3 year period ($p = 0.004$, $r^2 = 0.127$; $p < 0.001$, $r^2 = 0.307$, respectively), while FRC/TLC correlated positively with exacerbations ($p = 0.007$). Backwards regression analysis showed that among pulmonary function variables, IC had the strongest relationship with exacerbations over 3 years. A lower CFQ-R-Respiratory score was associated with greater mortality ($p = 0.005$). However, no statistically significant relationships were found between lung function and mortality. *Conclusions*: FEV_1 and lung hyperinflation-as measured by IC and FRC/TLC-are both associated with pulmonary exacerbation frequency. This suggests that chronic dynamic hyperinflation contributes significantly to disease severity in adult cystic fibrosis.**

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Keywords

Cystic Fibrosis, Hyperinflation, Inspiratory Capacity, Quality of Life

1. Introduction

Cystic fibrosis (CF) is a progressive, multisystem disorder characterized by excessive production of thickened exocrine secretions. Bronchial secretions obstruct airflow and predispose individuals to recurrent respiratory infections, resulting in progressive airflow limitation, ventilation inhomogeneities [1]-[3], impaired gas exchange, and impaired respiratory muscle function [4]. Forced expiratory volume 1 second (FEV_1) percent predicted is often used as a marker of disease severity in CF. However, others have only been able to identify no [5] or weak although significant associations between FEV_1 and quality of life (Spearman rho correlations 0.32 to 0.57) [6]. In addition, psychological and educational factors may be better predictors of work status than FEV_1 in adults with cystic fibrosis [7].

Studies in COPD show that tidal expiratory flow limitation (tEFL) is more closely related to dyspnea than is FEV_1 [8]. In COPD, tEFL has been associated with chronic dynamic hyperinflation during tidal breathing [9] defined as end-expiratory lung volume exceeding the relaxation volume of the respiratory system during quiet breathing. Tidal EFL leads to dynamic hyperinflation during exercise in patients with COPD as reflected by reduced inspiratory capacity (IC) and increased residual volume (RV), resulting in exercise intolerance [10]-[13]. Others have shown that the ratio of IC to total lung capacity (IC/TLC) is an independent predictor of mortality in patients with COPD [14]-[16]. In particular, in patients with the emphysematous phenotype of COPD an IC/TLC ratio of <25% is a significant predictor for mortality (hazard ratio 2.4, $p < 0.0001$) [16]. Hyperinflation and its relation to morbidity and exercise intolerance have been assessed in children with CF [2], but not in adult CF patients.

The purpose of this study was to determine if hyperinflation is more closely associated with functional status and pulmonary exacerbations than is FEV_1 in adult patients with CF, using IC, functional residual capacity (FRC), residual volume (RV), and their ratios to TLC as indices of hyperinflation. In addition, we wanted to determine if baseline lung volume data including IC and IC/TLC best predicted pulmonary exacerbations and mortality over the 3 years following the first set of lung function measurements were obtained.

2. Patients and Methods

2.1. Data Collection

This retrospective data analysis was derived from clinical and lung function data obtained from adult CF patients evaluated in the CF Clinic at the Keck Medical Center, a 400-bed tertiary referral center of the University of Southern California, from 1999 to 2014. The data for the cohort were reviewed according to the following inclusion criteria: i) diagnosis of CF based on characteristic phenotypic features [17] [18]; ii) confirmed by pilocarpine iontophoresis sweat test measuring sodium and chloride values; iii) genotype identification using extended mutation screening of both alleles [19] [20]; and iv) documentation of at least 1 set of complete lung function testing. Patients who had received a lung transplant were excluded. The study was approved by the institutional review board of USC Health Sciences Center.

Spirometry, lung volumes by body plethysmography and diffusion capacity were obtained in seated position (MedGraphics, System 1070, St. Paul, MN, USA). Measurements were obtained at least 4 hours after bronchodilator treatment. The cut-off point of FEV_1/FVC for COPD was 0.7 [21]. Predicted values for post-bronchodilator FEV_1, FVC and FEV_1/FVC were from Schoenberg *et al*. [22], and for subdivisions of lung volume from Crapo *et al*. [23]. IC, IC/TLC and FRC/TLC were used as measures of lung hyperinflation. Predicted values for IC were obtained from the difference between the predicted values for TLC and FRC [24]. All lung function testing was performed according to ATS/ERS guidelines [25].

Pulmonary exacerbations—defined by necessity for intravenous antibiotics, administered during hospitalization—were documented yearly for three consecutive years. One and 3 year exacerbations represent the number of pulmonary exacerbations within the first 1 and first 3 calendar years, respectively, of the subject's initial

evaluation. All cause mortality was recorded. The respiratory domain of the standard Cystic Fibrosis Questionnaire-Revised (CFQ-R-Respiratory) [26] was used as a measure of quality of life. The respiratory domain includes 6 questions each worth 4 points. CFQ-R-Respiratory score was recorded as a percentage of the total 24 points possible within the respiratory domain, with a higher number indicating a more favorable score [27]. All patients received bronchodilators, hypertonic saline and mucolytics, and some were prescribed inhaled antibiotics for chronic suppression of pathogens.

2.2. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics. Bivariate correlations using Pearson's coefficient were used to assess for associations between lung function, number of pulmonary exacerbations and CFQ-R-Respiratory [28]. One-way analysis of variance (ANOVA) was used to compare exacerbation frequency, lung function, and CFQ-R-Respiratory between individuals who expired during the 15-year study period and individuals who survived. Backwards regression analysis was used to determine the order of magnitude of correlation between exacerbation frequency and lung function variables. A $p \leq 0.05$ was taken as significant.

3. Results

The records of 200 patients were reviewed. Of these, 68 patients met inclusion and exclusion criteria. Their anthropometric and physiologic data are shown in **Table 1**. The population was predominantly Caucasian (84%) with a small minority of Hispanics and African Americans. Six participants had a history of pulmonary hypertension. Three had a history of lobectomy, 38 had cystic fibrosis-related diabetes, and one had a history of pneumothorax. Twenty-six individuals were homozygous for F508del, 32 were heterozygous for F508del, 8 individuals had other mutations, and 1 was unknown. Mean baseline CFQ-R-Respiratory score was 75%. Mean FEV_1/FVC, IC, IC/TLC and FRC/TLC was 64%, 90%, 43% and 57%, respectively.

The number of acute exacerbations requiring hospitalization were (mean ± SD) 2 ± 0.9, 2.5 ± 1, and 2 ± 1 in years 1, 2, and 3, respectively. As shown in **Table 2**, FEV_1, FVC, FEV_1/FVC, IC, IC/TLC, FRC/TLC and RV/TLC all correlated with number of exacerbations over 1 and 3 years. Both FEV_1 and IC were negatively correlated with pulmonary exacerbations over a 3 year period ($p = 0.004$, $r^2 = 0.127$; $p < 0.001$, $r^2 = 0.307$, respectively), while FRC/TLC correlated positively with exacerbations ($p = 0.007$). TLC alone did not correlate with exacerbations, while FRC alone exhibited a weak correlation. As expected, FEV_1, FVC, IC and their ratios with TLC correlated negatively with exacerbation frequency, while FRC/TLC and RV/TLC exhibited positive relationships. Backwards regression analysis between exacerbations over the first year and lung function showed that the highest correlation was with FEV_1 % predicted ($r^2 = 0.251$, $p = 0.001$ **Table 3(a)**). The next closest correlation was with FVC % predicted ($r^2 = 0.271$, $p = 0.002$). Backwards regression analysis over 3 years showed that the highest correlation was with the IC % predicted ($r^2 = 0.311$, $p < 0.001$ **Table 3(b)**). The next closest correlation was with FEV_1 % predicted ($r^2 = 0.330$, $p < 0.001$). We found no correlation between lung function and CFQ-R-Respiratory score. The relationship of FEV_1, FVC, IC, and FRC/TLC to 3-year exacerbations is depicted in **Figure 1**. The numbers of exacerbations above and below critical cutoff values for normality of the same variables are shown in **Figure 2**.

Twelve out of the 68 individuals originally included in the analysis expired over the 15-year study period. We examined differences in pulmonary exacerbations, CFQ-R-Respiratory and lung function by mortality status (**Figure 3** and **Figure 4**). Only CFQ-R-Respiratory was lower in individuals who had expired during the study period in comparison to survivors ($p = 0.005$). Mortality, however, did not correlate with baseline FEV_1, FVC, IC/TLC, FRC/TLC or RV/TLC (**Figure 4**).

4. Discussion

Finding clinically relevant parameters of disease severity provides useful guideposts in the ongoing management of CF. While disease severity can be measured in many ways in CF, we focused on examination of the CFQ-R-Respiratory score, pulmonary exacerbations, and mortality because these values provide a patient-centered measurement of health. To our knowledge this is the first study to demonstrate that lung hyperinflation, as measured by IC and FRC/TLC, correlates with frequency of pulmonary exacerbations in adults with cystic fibrosis. We have also confirmed the utility of the CFQ-R-Respiratory score by demonstrating its association with

Table 1. Anthropometric and physiologic data.

	n (%), mean (SD)
Gender (% female)	35 (52%)
Age	29 (8.9)
Body Mass Index (kg/m^2)	23 (3.7)
Ethnicity	
Caucasian	57 (84%)
Hispanic	9 (13%)
African-American	2 (3%)
Medical History	
Pulmonary Hypertension	6 (9%)
Cystic Fibrosis Related Diabetes	38 (56%)
Pneumothorax	1 (2%)
Lobectomy	3 (4%)
Genotype	
F508del Homozygous	26 (38%)
F508del Heterozygous	33 (49%)
Other	8 (12%)
Mortality (% expired)	13 (20%)
Total exacerbations over 1 year	0.7 (0.9)
Total exacerbations over 3 years	2.3 (2.5)
CFQ-R-Respiratory Score (%)	75 (15)
Lung Function	
FEV_1 (% pred)	61 (27)
FVC (% pred)	74 (20)
FEV1/FVC (%)	64 (15)
TLC (% pred)	102 (15)
IC (% pred)	90 (23)
IC/TLC (%)	43 (11)
FRC (% pred)	107 (31)
FRC/TLC (%)	57 (11)
RV (% pred)	176 (79)
RV/TLC (%)	43 (16)

Values above are expressed as n (%) or mean (±SD) as appropriate. **Expired** subjects defined as subjects that were expired at the end of the 15 year data collection period. Abbreviations: **BMI** body mass index, **FEV_1** forced expiratory volume 1 second, **FVC** forced vital capacity, **IC** inspiratory capacity, **FRC** functional residual capacity, **RV** residual volume, **TLC** total lung capacity, **CFQ-R-Respiratory** cystic fibrosis questionnaire revised respiratory domain.

Table 2. Bivariate correlations comparing lung function to pulmonary exacerbations and CFQ-R.

		1 Year Exacerbations	3 Year Exacerbations	CFQ-R-Respiratory Score
FEV_1 (% pred)	Pearson Coef	−0.326**	−0.356**	0.213
	p-value	0.007	0.004	0.193
FVC (% pred)	Pearson Coef	−0.252*	−0.345**	0.18
	p-value	0.041	0.006	0.273
FEV_1/FVC	Pearson Coef	−0.338**	−0.295*	0.242
	p-value	0.005	0.018	0.132
TLC (% pred)	Pearson Coef	0.156	0.04	−0.019
	p-value	0.223	0.76	0.912
IC (% pred)	Pearson Coef	−0.425**	−0.554**	0.172
	p-value	0.004	<0.001	0.315
IC/TLC	Pearson Coef	−0.389**	−0.412**	0.099
	p-value	0.01	0.007	0.573
FRC (% pred)	Pearson Coef	0.308*	0.197	−0.069
	p-value	0.045	0.212	0.695
FRC/TLC	Pearson Coef	0.389*	0.412**	−0.098
	p-value	0.01	0.007	0.574
RV/TLC	Pearson Coef	0.361**	0.323*	−0.141
	p-value	0.003	0.011	0.392

Abrreviations: **1 and 3 year exacerbations** number of pulmonary exacerbations within the first 1 and first 3 years, respectively, of the subject's initial evaluation. **FEV_1** forced expiratory volume 1 second, **FVC** forced vital capacity, **IC** inspiratory capacity, **FRC** functional residual capacity, **RV** residual volume, **TLC** total lung capacity, **CFQ-R-Respiratory** cystic fibrosis questionnaire revised respiratory domain. **Correlation is significant at the 0.01 level (2. tailed). *Correlation is significant at the 0.05 level (2. tailed).

Table 3. (a) Backward regression analysis of lung function vs exacerbations over 1 year. (b) Backward regression analysis of lung function vs exacerbations over 3 years

(a)

	r^2	p value
Model 1[a]	0.322	0.074
Model 2[b]	0.321	0.043
Model 3[c]	0.321	0.023
Model 4[d]	0.310	0.014
Model 5[e]	0.296	0.008
Model 6[f]	0.291	0.004
Model 7[g]	0.271	0.002
Model 8[h]	0.251	0.001

Backward regression analysis pulmonary functions as independent variables and exacerbations over 1 year as the dependent variable. Independent variables are removed from each consecutive model as detailed below: a. Predictors: FEV_1 % pred, TLC % pred, RV/TLC % pred, IC/TLC, IC % pred, FVC % pred, FEV_1/FVC, FRC % pred; b. Predictors: FEV_1 % pred, TLC % pred, RV/TLC % pred, IC/TLC, IC % pred, FVC % pred, FEV_1/FVC; c. Predictors: FEV_1 % pred, TLC % pred, IC/TLC, IC % pred, FVC % pred, FEV_1/FVC; d. Predictors: FEV_1 % pred, TLC % pred, IC/TLC, IC % pred, FVC % pred; e. Predictors: FEV_1 % pred, IC/TLC, IC % pred, FVC % pred; f. Predictors: FEV_1 % pred, IC % pred, FVC % pred; g. Predictors: FEV_1 % pred, FVC % pred; h. Predictors: FEV_1 % pred.

(b)

	r^2	p value
Model 1[a]	0.454	0.006
Model 2[b]	0.454	0.003
Model 3[c]	0.444	0.001
Model 4[d]	0.423	0.001
Model 5[e]	0.393	0.001
Model 6[f]	0.359	0.001
Model 7[g]	0.330	<0.001
Model 8[h]	0.311	<0.001

Backward regression analysis pulmonary functions as independent variables and exacerbations over 3 years as the dependent variable. Independent variables are removed from each consecutive model as detailed below: a. Predictors: RV/TLC % pred, TLC % pred, FEV_1/FVC, IC/TLC, FVC % pred, IC % pred, FRC % pred, FEV_1 % pred; b. Predictors: RV/TLC % pred, TLC % pred, FEV_1/FVC, IC/TLC, FVC % pred, IC % pred, FEV_1 % pred; c. Predictors: RV/TLC % pred, TLC % pred, FEV_1/FVC, FVC % pred, IC % pred, FEV_1 % pred; d. Predictors: RV/TLC % pred, TLC % pred, FEV_1/FVC, IC % pred, FEV_1 % pred; e. Predictors: RV/TLC % pred, FEV_1/FVC, IC % pred, FEV_1 % pred; f. Predictors: RV/TLC % pred, IC % pred, FEV_1 % pred; g. Predictors: IC % pred, FEV_1 % pred; h. Predictors: IC % pred.

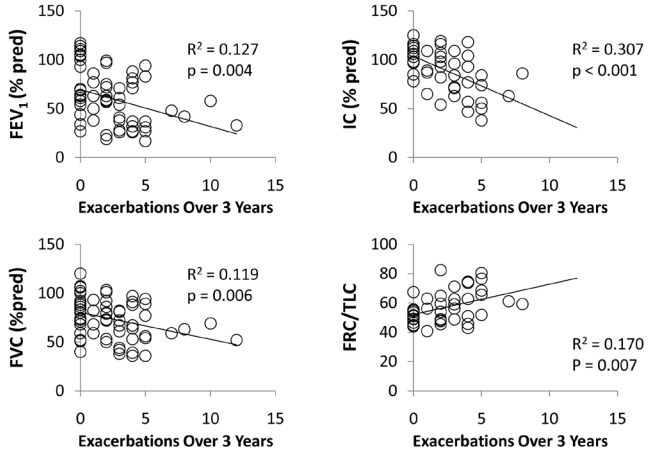

Figure 1. Correlations between lung function and exacerbations over 3 years. Relation of lung functions to total number of exacerbations over three years. Abbreviations: FEV_1 forced expiratory volume 1 second, FVC forced vital capacity, TLC total lung capacity, IC inspiratory capacity, FRC functional residual capacity.

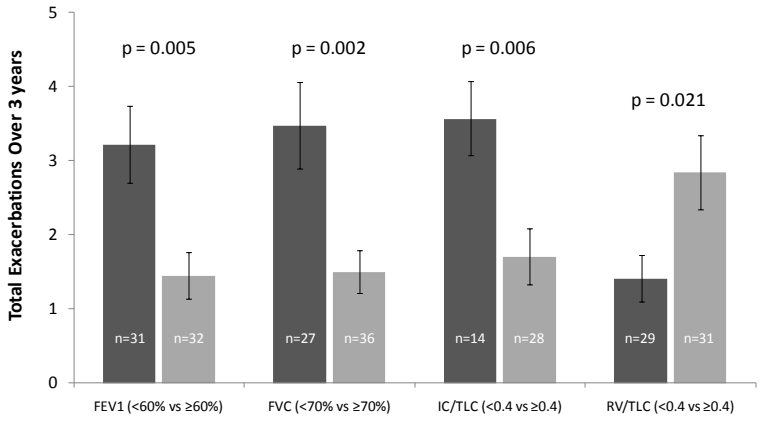

Figure 2. Comparison of mean exacerbations among high vs low lung function. Lung function is shown along the x-axis and is dichotomized into two groups. Cutoff values defining high and low groups are shown along the x-axis. Error bars represent mean ± SEM. Mean exacerbations over three years is compared between groups. Abbreviations: FEV_1 forced expiratory volume 1 second, FVC forced vital capacity, TLC total lung capacity, IC inspiratory capacity, RV residual volume.

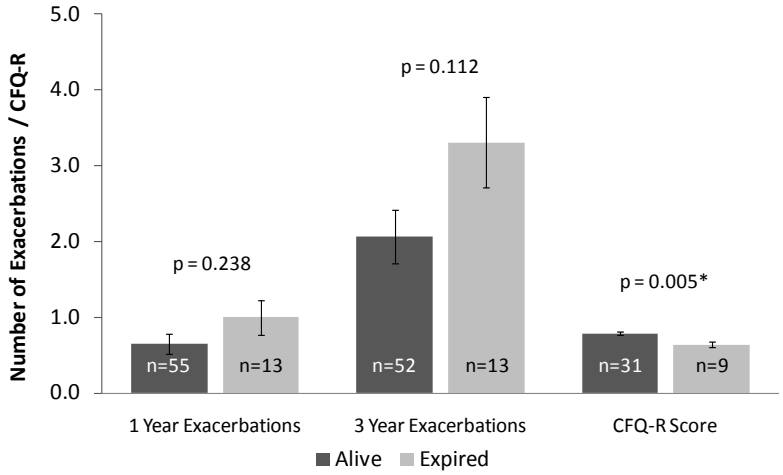

Figure 3. Comparisons of means of pulmonary exacerbations and CFQ-R grouped by mortality status. 1 and 3 year exacerbations denote total number of pulmonary exacerbations within the first 1 and 3 years, respectively, of the subjects' initial evaluation. Alive and expired denote subjects who were living or deceased respectively at the end the 15 year data collection period. CFQ-R-Respiratory cystic fibrosis questionnaire revised respiratory domain. Error bars represent mean ± SEM.

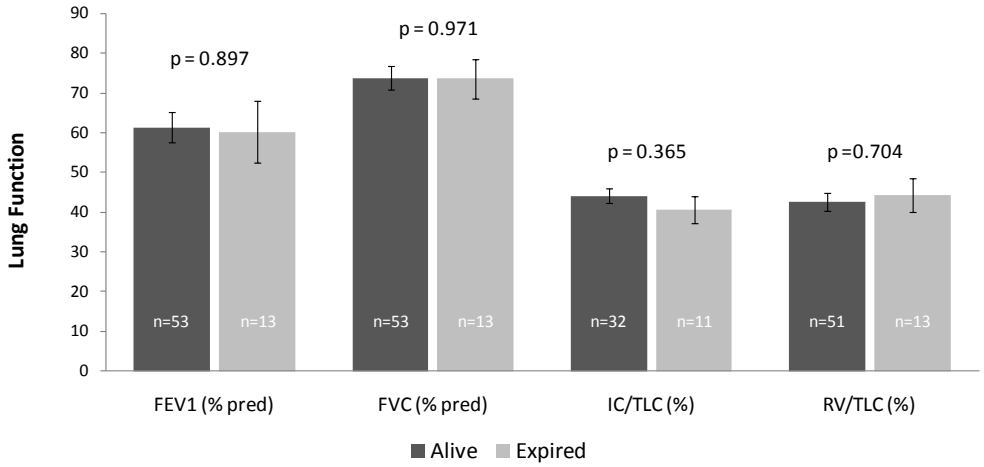

Figure 4. Comparisons of means of lung function grouped by mortality status. Alive and expired denote subjects who were living or deceased respectively at the end the 15 year data collection period. Abbreviations: FEV_1 forced expiratory volume 1 second, FVC forced vital capacity, TLC total lung capacity, IC inspiratory capacity, RV residual volume. Error bars represent mean ± SEM.

mortality. Our findings suggest that lung hyperinflation is as important as FEV_1 in relation to frequency of pulmonary exacerbations.

It might be expected that patients with the most severe airflow limitation would be the most dyspneic. Yet, some patients with severe airway obstruction, as reflected by the FEV_1, have few symptoms, while others with minimal flow limitation exhibit severe dyspnea. In patients with COPD, smoking and advanced age contribute to peripheral airway closure as a result of which, closing volume exceeds FRC [29] [30]. Sequential opening and closing of the airways produces epithelial injury in respiratory and membranous bronchioles. Similar changes likely result from chronic inflammation with intercurrent infectious exacerbations in patients with CF, resulting in peripheral airway closure and increase in closing volume, and eventually hyperinflation. Use of the negative expiratory pressure technique during quiet tidal breathing has demonstrated that tEFL at rest is associated with lower IC [11]. Since maximal tidal volume correlates with IC during exercise, patients with tEFL at rest exhibit an increase in end-expiratory lung volume and a further decrease in IC with concomitant exercise limitation. By contrast, in non-tEFL patients IC is usually normal, and FEV_1/FVC is the sole predictor of exercise limitation

[10]. This is mainly due to the fact that a low FEV_1/FVC ratio is associated with a maximal expiratory flow-volume curve with an upward concavity with little expiratory flow over the resting tidal volume range. Using the NEP technique, Goetghebeur *et al*. [31] found that in CF patients severe chronic dyspnea and tidal flow limitation during resting breathing in seated position are uncommon and seen only when the FEV_1 is <50% predicted (14% prevalence in their CF patients, with FEV1 < 30% predicted). The prevalence of tEFL was lower than in a study of COPD patients [8], attributed to lower lung elastic recoil and more peripheral lung disease in the COPD patients, and possibly due to persistent inspiratory muscle contraction resulting increased EELV thus avoiding tEFL. Thus patients without tEFL at rest but with a low FEV_1/FVC are more likely to exhibit tEFL during exercise than patients who have a normal FEV_1/FVC.

That lung hyperinflation would correlate significantly with pulmonary exacerbations but not with CFQ-R-Respiratory or mortality is not surprising. Recent studies suggest that disease severity in CF is impacted by a large number of factors, reflective of the multi-system nature of the disease. Lung function as measured by FEV_1 correlates with most domains of the CFQ-R but not all, and furthermore depressive symptoms correlate strongly with total CFQ-R scores even when controlling for FEV_1 [6]. Britto *et al*. [5] similarly reported a correlation between number of exacerbations and some domains of questionnaire based measures of quality of life but not others. Burker *et al*. [7] demonstrated the importance of employment status and education level on quality of life. Lung hyperinflation, exacerbations, questionnaire-based quality of life, and mortality are interrelated in complex ways in CF as they are in COPD [32]-[34].

There were limitations to our study. Unfortunately, not enough patients (n = 12) completed a 6MWD to allow analysis of this variable in relation to lung hyperinflation. Analysis of the full CFQ-R was not included in this study because only data on the respiratory domain was available retrospectively. In addition, we would have preferred to express the numbers of exacerbations and their relation to lung function variables on a per-year basis; however, as is often a challenge with retrospective studies, this was not possible as lung function testing subsequent to the baseline measurements was performed at random, irregular intervals, making it difficult to match up the exacerbations and lung functions within discreet time segments. We therefore elected to examine the total number of exacerbations within 1- and 3-year time frames with respect to baseline functional variables only. Moreover, the lack of difference amongst baseline lung function variables between living and expired patients does not exclude the effects of lead time: that is, the possibility that some patients may have experienced a rapid decline in lung function within the 15-year period that, had sequential testing been performed, might have predicted which patients were likely to develop respiratory failure and to have died from their illness. Lastly, this study was underpowered to detect associations between lung hyperinflation and mortality. A number of future inquiries are possible at this time. Namely, a large-scale prospective trial examining the relationship between lung function and disease severity and outcome in adult CF patients is missing from current literature.

5. Conclusion

FEV_1 and lung hyperinflation—as measured by IC and FRC/TLC—are both associated with pulmonary exacerbation frequency. This suggests that chronic hyperinflation contributes significantly to disease severity in adult cystic fibrosis.

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