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Review

A systematic review of studies examining the rate of lung function decline in patients with cystic fibrosis

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EDUCATIONAL AIMS

The reader will come to appreciate:

- Development of lung disease progression models is essential to understand the natural history of lung function changes over age in patients with cystic fibrosis and to determine risk factors influencing the progression.
- Overall lung function progression is shown to be nonlinear and have high variability in the rate of decline over a life time in patients with cystic fibrosis.
- Clinical observations and a summary of the presented literature data do not agree with the commonly used constant rate model used to describe lung function decline over a patient's life time in individual studies
- Patients with cystic fibrosis who experienced *Pseudomonas aeruginosa* infection and pancreatic insufficiency were more likely to have a lower baseline and more rapid FEV_1%predicted decline compared to their peers

ARTICLE INFO

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nonlinear decline

SUMMARY

A systematic review was performed (i) to describe the reported overall rate of progression of CF lung disease quantified as FEV_1%predicted decline with age, (ii) to summarise identified influencing risk factors and (iii) to review methods used to analyse CF lung disease progression data. A search of publications providing FEV_1%predicted values over age was conducted in PUBMED and EMBASE. Baseline and rate of FEV_1%predicted decline were summarised overall and by identified risk factors. Thirty-nine studies were included and reported variable linear rates of lung function decline in patients with CF. The overall weighted mean FEV_1%predicted over age was graphically summarised and showed a nonlinear, time-variant decline of lung function. Compared to their peers, *Pseudomonas aeruginosa* infection and pancreatic insufficiency were most commonly associated with lower baseline and more rapid FEV_1%predicted declines respectively. Considering nonlinear models and drop-out in lung disease progression, analysis is lacking and more studies are warranted.

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Abbreviations: CF, cystic fibrosis; FEV_1, forced expiration volume in the first second; FEV_1%predicted, percentage predicted of forced expiration volume in the first second; CFTR, cystic fibrosis transmembrane conductance regulator; WIRCT, Wisconsin randomized clinical trial project; CFQA, German CF quality assurance; CGS, Canadian Consortium for CF Genetic Studies; NBS, newborn screening; MI, meconium ileus; CFRD, cystic fibrosis related diabetes; PI, pancreatic insufficiency; PS, pancreatic sufficiency; BMI, body mass index; *P.aeruginosa*, *Pseudomonas aeruginosa*; MRSA, methicillin resistant *Staphylococcus aureus*; NTM, non-tuberculosis mycobacterium; ABPA, allergic bronchopulmonary aspergillosis; GEE, general estimating equations; LMEM, linear mixed effect model; ANCOVA, analysis of covariance; ANOVA, analysis of variance.

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INTRODUCTION

Cystic fibrosis (CF) is a life-shortening autosomal recessive disorder caused by mutations in the gene encoding cystic fibrosis transmembrane conductance regulator (CFTR) [1]. The median predicted survival age continues to increase and in the United States survival age increased from 35.9 years in 2009 to 41.2 years in 2012 [2,3]. Lung disease is still the main determinant of mortality and morbidity in patients with CF. Patients with CF have a progressive decline in lung function mainly attributed to recurrent vicious cycles of lung infection, inflammation and obstruction [4]. Maintaining lung health and reducing progression of lung disease are the main goals in CF management, which is guided by research [5]. Besides structural changes in the lungs, CF lung disease progression is mainly described as deterioration in lung function over time [6]. A decline in forced expiratory volume in the first second (FEV_1) has been suggested to be predictive of mortality [7] and is recommended as a clinical primary endpoint of respiratory function in CF clinical trials [8]. Determining the rate of decline in FEV_1 (expressed as percentage predicted) through the development of disease progression models allows for a better understanding of the lung disease progression and permits identification of factors that might slow, modify or accelerate the lung trajectory over time [9–11]. Numerous studies have quantified the rate of decline in FEV_1%predicted over time to describe CF lung disease progression. Furthermore, a number of risk factors have been identified that influence FEV_1%predicted decline [7,9–36]. Sex, genotype, newborn screening, meconium ileus and pancreatic status are the most common non-modifiable risk factors that may influence the lung function decline. The influence of these factors generally does not change over time (time independent). Infection, nutritional status, pulmonary exacerbation and respiratory illnesses vary over time and are the most commonly reported modifiable risk factors that influence CF lung function decline.

The rate of decline reported varies greatly from study to study and predictors of the variability are not yet fully understood. Determining the rate of lung function progression overall and determining influential factors that can predict future progression are critical to facilitate and to assess the potential impact of clinical treatments over time and for supporting future clinical trial design [37]. Describing CF lung disease progression requires longitudinal measurement of FEV_1%predicted and a predictive model that describes the true trend of disease progression in this population, considers correlation between FEV_1%predicted measurements, identifies relationships between risk factors and the progression rate and is able to account for time-variant factors [38]. Consequently, methods of analysis used to describe CF lung disease progression need to be reviewed simultaneously when comparing reported progression rates.

A structured review of studies that describe lung function progression over age in CF patients was performed to (i) describe the reported progression rate of CF lung disease quantified as decline of FEV_1%predicted over age, (ii) summarise the influence of identified risk factors on lung function progression and (iii) review methods used to describe CF lung disease progression.

METHODS

Structured literature search

Data for this review were identified by structured review of publications listed in PUBMED and EMBASE databases. The PubMed search terms were 'cystic fibrosis' [MESH] AND 'lung disease' [MESH], 'cystic fibrosis' [MESH] AND 'lung disease' [MESH] AND 'progression', 'cystic fibrosis' [MESH] AND 'lung disease' [MESH] AND 'progression model' AND 'risk factors'. The EMBASE search used combination of the Emtree terms "cystic fibrosis lung disease", "cystic fibrosis lung disease progression" and "cystic fibrosis lung disease progression model". The search was limited to publications in English language that were published after January 1990 to October 2015. Additional publications were identified by reviewing study reference lists and consulting expert review articles identified through the search.

Inclusion criteria

Inclusion of studies was based on (i) original studies describing progression of lung function as FEV_1%predicted over patient's age (either graphically or as mathematical equation), (ii) reported the baseline value and the slope of FEV_1%predicted decline (either graphically or as mathematical equation). Risk factors investigated across studies had to have the same definition, be presented in the same units or convertible units, and measured by a similar suitable method, to be included in a separate subanalysis. Only studies published after 1990 were included to minimise historical cohort effects, particularly regarding diagnostics and treatment strategies, which are not informative for current clinical treatment of CF lung disease.

Data extraction

The baseline FEV_1%predicted value and rate of FEV_1%predicted decline were extracted and separated by influencing risk factors originally identified in the study. Baseline FEV_1%predicted was defined as the FEV_1%predicted value at the start of a study. Rate of decline in FEV_1%predicted is represented by the slope of FEV_1%predicted decline over age. Values were extracted from equations or from graphics using digitizeIt software version 1.6.1 (© I.Bormann 2001-2013). Extracted data was used to identify baseline and slope of FEV_1%predicted values, assuming a linear model, unless specified differently. Slopes and baseline values from graphics with nonlinear appearance were obtained through piecewise linear regression of the extracted data using R studio software (version 0.99.486, RStudio, Inc., Boston, MA, http://www.rstudio.com/) [39]. Here, FEV_1%predicted values associated with the specific age at the breakpoints of the separate line segments served as additional intercept values.

Analysis

Reported lung function progression for each risk factors was summarised graphically and in tabular form. For the graphical summary FEV_1%predicted versus age for each risk factor reported in all studies was overlaid with the weighted mean FEV_1%predicted of all risk factors at every age. A minimum of three FEV_1%predicted values at each particular age had to be presented in the graph. Further, subgroups were individually summarised graphically by presenting the FEV_1%predicted at every age for each risk factor for individual studies and overlaid with the weighted mean FEV_1%predicted over age for the particular risk factor. For a subgroup analysis more than five studies were required to sufficiently represent the subgroup. The weighted mean FEV_1%predicted was calculated using the equation 1 and 2 below:

$$w_{Za} = \frac{w_{Za}}{w_{Za} + w_{Zb} + w_{Zc} + \ldots w_{Zi}} * N_Z \quad (1)$$

$$\overline{X}_{mi} = \frac{w_{1a}X_{1a} + w_{1b}X_{1b} + w_{2a}X_{2a} + w_{2b}X_{2b} \ldots w_{Zi}X_{Zi}}{w_{1a} + w_{1b} + w_{2a} + w_{2b} + \ldots . w_{Zi}} \quad (2)$$

where w is the number of participants contributing data to the analysis for the i^{th} factor in the Z^{th} study is the weight applied, N is the total number of participants in Z^{th} study. X is FEV_1%predicted at

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