GLI equations improve interpretation of FEV\textsubscript{1} decline among patients with cystic fibrosis

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Running Title: FEV\textsubscript{1} decline using GLI

Word Count: 990

Key Words: Cystic fibrosis, spirometry, reference values, serial measurements

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Introduction

The prognosis for individuals with cystic fibrosis (CF) has improved markedly over the last 50 years, with most countries now reporting that 50% of the population reach at least 35 years of age.[1-3] Despite this improvement, the average age at death is still in the late 20’s and varies enormously between CF centres and countries.[4] To further improve the trajectory of lung disease, it is critical to identify patients that would benefit most from early intervention.

Although current markers of disease progression rely on spirometric measures of lung function (Forced Expiratory Volume in 1 second; FEV₁), it is well recognised that choice of reference equation may have a dramatic effect on the apparent rate of decline in lung function. The recently published Global Lung Function Initiative (GLI) equations[5] present a novel opportunity to appropriately investigate longitudinal trends in lung function in patients with CF. Cross-sectional analysis of data from the UK CF Trust Registry demonstrated important differences in interpretation of spirometry results between the internationally endorsed GLI equations and those of Knudson[6], Wang[7] and Hankinson[8]. While overall results summarised as %predicted FEV₁ according to each equation differed by only a few percent, individual patient results were quite discrepant, particularly in young children, those over 50 years, and adolescents. The discrepancies observed during adolescence are of particular concern since this population is recognised to be at risk of rapid progression of CF lung disease.[9, 10]

In this study we aimed to investigate the impact of the GLI equations on estimates of population level decline in %predicted FEV₁ with age.
Methods

Data Sources

Data were extracted from the Toronto CF database containing 1,023 subjects with 27,868 measurements over 23 years (1990-2013), and the UK CF Registry containing 6,043 subjects with 20,013 measurements over 5 years (2007-2011). In the encounter-based Toronto Registry patients had an average of 49 observations (range 1-150), while in the annual-based UK Registry patients had an average of 4 observations (range 1-5). Patients were included irrespective of number of observations, transplant status, age of diagnosis or death. Spirometric outcomes were interpreted using %predicted FEV\textsubscript{1} calculated from GL[5], Knudson[6] and Wang-Hankinson[7, 8]. These were chosen to reflect current practice by many CF Registries. Analyses were limited to Caucasian patients > 6 years of age to permit appropriate comparison between equations. Patients >30 years of age or with %predicted FEV\textsubscript{1} >130% were excluded to minimise the impact of survival bias and reduce undue influence of outlier values.

Statistical Analysis

A non-linear mixed effects approach using a shape invariant spline curve model was used to simultaneously estimate the average change in lung function with age, while adjusting for subject-specific random intercepts and slopes, assuming that all patients follow the same underlying curve shape.[11] The average change in lung function with age was fitted as a natural cubic spline where degrees of freedom (d.f) were chosen to minimise the Bayesian Information Criterion (BIC). We compared the complexity (d.f) of the average lung function decline curve described by each of the three spirometry reference equations. Analysis was done in the statistical program R, using the sitar package.[12]
Results

Selecting the simplest model with best fit for each reference equations demonstrated that the pattern of FEV$_1$ decline at population level differed according to the reference equations (Figure 1). GLI models were best fit with steady and near-linear decline starting at younger ages, whereas the other equations required more complex models and suggest greater decline during adolescence and early adulthood. Similar patterns were observed in the Toronto and UK populations (Figure 1A & 1B). Overall >85% of variance was explained by each of the models. Thus, while the estimated pattern of lung function decline was influenced by reference equation, model fit was not.
Discussion

The GLI equations demonstrated a near-linear decline throughout childhood with no acceleration or deceleration during adolescence. These findings suggest that the well-established adolescent decline described at a population level may be an artefact of the spirometry reference equations used, rather than reflecting the true clinical course. The ability to interpret rate of decline in lung function accurately is even more important for individual patients in whom inaccurate tracking of FEV₁ may prompt unnecessary intervention, including invasive procedures and aggressive treatments. Equally, these findings suggest that current practice may be missing a critical opportunity for intervention earlier in childhood.

The GLI equations are seamless across all ages, thus avoiding artifactual changes which can occur when transitioning from paediatric to adult reference equations. Unlike many paediatric spirometry equations, the GLI equations take both age and height into account, such that predicted values are higher in older than younger individuals of the same height. Thus GLI reference equations model growth appropriately during the adolescent period (Quanjer et al erj 2010, changes in FEV/FVC) and highlight the relative importance of early childhood in understanding the progression of CF lung disease. In addition the current study confirms that non-linear growth models are appropriate to describe patterns of lung function decline.[13]

The pattern of %predicted FEV₁ decline differed according to the spirometry reference equation used. While such differences have been reported previously, this is the first study to use both the GLI equations, (which model changes during adolescence more appropriately (Quanjer 2010)) and employ a non-linear mixed approach to analysis, which takes account of repeated measures within individuals over time. The largest discrepancies were observed for the Knudson equations, which are a composite of three separate equations, each based on a relatively small
sample. The Wang-Hankinson equations, which are based on bigger samples with join points carefully chosen to minimise discontinuity between equations, match the GLI more closely. Nonetheless, use of these older equations may exaggerate the rate of decline during adolescence.

**Limitations**

Our study population was inclusive of patients irrespective of clinical status, therefore the observed pattern of lung function decline may not be comparable to previous studies. The analyses excluded subjects younger than 6 years of age; however lung function decline may start much earlier emphasising the need for early markers of lung disease for this population. In addition the analysis was limited to a spirometric outcome, FEV₁, which itself may not be sensitive enough to detect early pathological changes.

Our decision to base models on %predicted values is in line with current clinical practice and widespread use in epidemiological studies, together with the fact is the only basis on which results can be readily calculated when using the Knudson or Wang-Hankinson equations. However, this may introduce an age, sex and height bias, especially when interpreting results from adults, which can be avoided by alternative ways of using FEV₁ (Miller erj), including the use of z-scores, (Stanojevic breathe) which can be readily calculated when using GLI equations. To further investigate the potential benefits of these alternative approaches when interpreting longitudinal changes, it will be essential to link changes in lung function to clinical outcomes within individuals. Whereas the clinical interpretation of change over time in %predicted FEV₁ (including its inherent challenges) is familiar to the CF community, longitudinal changes in z scores are less well understood and require further detailed analysis which is beyond the scope of the current brief report.
Conclusion

These findings challenge previously held beliefs about population trends in disease progression in patients with CF, particularly the rapid FEV$_1$ decline during adolescence. It is crucial that we better understand the nature and relationship of disease progression, as inaccurate tracking of lung function will make targeted intervention for at-risk individuals less effective.
**Figure Legend**

Figure 1. Overall pattern of %predicted FEV$_1$ with age at the population level as defined by three spirometric reference equations, GLI (solid line), Wang-Hankinson (dashed line) and Knudson (dotted line). Data are presented for the Toronto CF database (A) and the UK CF Registry (B). In the Toronto dataset GLI and Wang-Hankinson equations show steady rate of decline in childhood, whereas the Knudson equations show periods of accelerated decline in adolescence. In the UK dataset, both Wang-Hankinson and Knudson equations show periods of accelerated decline in adolescence, with GLI equations showing steady decline starting in childhood.
References