




RESEARCH ARTICLE

Using different methods to process forced expiratory volume in one second (FEV₁) data can impact on the interpretation of FEV₁ as an outcome measure to understand the performance of an adult cystic fibrosis centre: A retrospective chart review [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract


Background: Forced expiratory volume in one second (FEV₁) is an important cystic fibrosis (CF) prognostic marker and an established endpoint for CF clinical trials. FEV₁ is also used in observation studies, e.g. to compare different centre's outcomes. We wished to evaluate whether different methods of processing FEV₁ data can impact on a centre's outcome.

Methods: This is a single-centre retrospective analysis of routinely collected data from 2013-2016 which included 208 adults with CF. Year-to-year %FEV₁ change was calculated by subtracting best %FEV₁ at Year 1 from Year 2 (i.e. negative values indicate %FEV₁ decline), and compared using Friedman test. Three methods were used to process %FEV₁ data. First, %FEV₁ calculated with Knudson equation was extracted directly from spirometer machines. Second, FEV₁ volume were extracted then converted to %FEV₁ using clean height data and Knudson equation. Third, FEV₁ volume were extracted then converted to %FEV₁ using clean height data and GLI equation. In addition, %FEV₁ decline calculated using GLI equation was adjusted for baseline %FEV₁ to understand the impact of case-mix adjustment.

Results: There was a trend of reduction in %FEV₁ decline with all three data processing methods but the magnitude of %FEV₁ decline differed. Median change in %FEV₁ for 2013-2014, 2014-2015 and 2015-2016 was -2.0, -1.0 and 0.0 respectively using %FEV₁ in Knudson


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	Invited Reviewers		
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1. **Edward McKone**, St Vincent's Hospital, Dublin, Ireland

2. **Pierre-Régis Burgel** , Paris Descartes University, Paris, France

3. **Clive Osmond** , University of Southampton, Southampton, UK

Any reports and responses or comments on the

equation whereas the median change was -1.1, -0.9 and -0.3 respectively using %FEV₁ in the GLI equation. A statistically significant p-value (0.016) was only obtained when using %FEV₁ in Knudson equation extracted directly from spirometer machines.

Conclusions: Although the trend of reduction in %FEV₁ decline was robust, different data processing methods yielded varying results when %FEV₁ decline was compared using a standard related group non-parametric statistical test. Observational studies with %FEV₁ decline as an outcome measure should carefully consider and clearly specify the data processing methods used.

Keywords

Cystic fibrosis, epidemiology, patient outcome assessment, forced expiratory volume

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article can be found at the end of the article.

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Author roles: Hoo ZH: Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft Preparation; El-Gheryani MSA: Data Curation, Investigation, Writing – Review & Editing; Curley R: Data Curation, Formal Analysis, Investigation, Writing – Review & Editing; Wildman MJ: Conceptualization, Methodology, Project Administration, Supervision, Visualization, Writing – Review & Editing

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Introduction

Cystic fibrosis (CF) is a multi-system genetic condition but the two main affected organs are lungs (resulting in recurrent infections and respiratory failure) and gastrointestinal tract (resulting in fat malabsorption and poor growth)¹. Median survival has improved to 45 years, in part because of improvement in care quality². An important quality improvement initiative is benchmarking, which involves identifying high-performing centres and the practices associated with outstanding performance^{3–5}. Since forced expiratory volume in one second (FEV_1) is an important CF prognostic marker^{6–9}, it is often used as an outcome measure for benchmarking^{3–5,10}.

Different statistical methods of analysing FEV_1 data can yield different results¹¹, but there is scant attention paid to the methods of processing FEV_1 data. We previously reported a statistically significant reduction in % FEV_1 decline for our CF centre from 2013–2016¹². We now set out to understand the impact of using different FEV_1 data processing methods on our CF centre's outcome.

Methods

This is a single-centre retrospective analysis of routinely collected clinical data from 2013–2016. Regulatory approval for the analysis was obtained from NHS Health Research Authority (IRAS number 210313). All adults with CF diagnosed according to the **UK CF Trust criteria** aged ≥ 16 years were included, except those with lung transplantation or on ivacaftor. These treatments have transformative effects on % FEV_1 ^{13–15}, thus may affect the interpretation of % FEV_1 decline.

Demographic data (age, gender, genotype, pancreatic status, CF related diabetes, *Pseudomonas aeruginosa* status), body mass index (BMI) and FEV_1 data were collected by two investigators (HZH and RC / HZH and MEG) independently reviewing paper notes and electronic records. Where data from the two investigators differ, the original data from paper notes or electronic records were reviewed to by both investigators to ensure the accuracy of abstracted data. This process ensures the accuracy of abstracted data and helps avoid potential bias from inaccurate or inconsistent data collection¹⁶. FEV_1 data were processed with three different methods prior to analysis. First, % FEV_1 readings (calculated with Knudson equation¹⁷ and available in whole numbers) were directly extracted from spirometer machines. Second, FEV_1 volumes (in litres, to two decimal places) were extracted and clean height data were used to calculate % FEV_1 (as whole numbers) with Knudson equation¹⁷. Third, FEV_1 volumes (in litres, to two decimal places) were extracted and clean height data were used to calculate % FEV_1 with GLI equation¹⁸ using an **Excel Macro** (Microsoft Excel 2013).

Best % FEV_1 , i.e. the highest % FEV_1 reading in a calendar year for each study subject was used for analysis since it is most reflective of the true baseline % FEV_1 ¹⁹. Year-to-year % FEV_1 change was calculated by subtracting best % FEV_1 at Year 1 from Year 2 (i.e. negative values indicate % FEV_1 decline and positive values indicate increase in % FEV_1). In addition to calculating year-to-

year % FEV_1 change using three different FEV_1 data processing methods, % FEV_1 change calculated with GLI equation was also adjusted for baseline % FEV_1 using reference values from Epidemiologic Study of CF (ESCF)²⁰. The ESCF study found median % FEV_1 change of $-3\%/year$, $-2\%/year$ and $-0.5\%/year$ for baseline % $FEV_1 \geq 100\%$, $40–99.9\%$ and $<40\%$ respectively²⁰. Adjusted % FEV_1 change was calculated by subtracting median ESCF % FEV_1 change from actual % FEV_1 change. Thus, an adjusted % FEV_1 change >0 meant the subject's % FEV_1 decline was less than expected (indicating better health outcome) whilst an adjusted % FEV_1 change <0 meant the subject's % FEV_1 decline was more than expected (indicating worse health outcome). % FEV_1 change from 2013–2014 to 2015–2016 calculated using different FEV_1 data processing methods were compared using Friedman test. Analyses were performed using **SPSS v24** (IBM Corp) and p-value <0.05 was considered statistically significant.

Results

This analysis included 208 adults, with 147 adults providing data for all four years. Overall, the cohort was ageing but baseline % FEV_1 increased from 2014 onwards (see **Table 1**).

The % FEV_1 increase was in part due to younger adults with higher % FEV_1 transitioning from paediatric care because % FEV_1 tended to decline from year to year (see **Table 2**). However, different % FEV_1 decline results were obtained with different FEV_1 data processing methods. There was statistically significant reduction in the rate of % FEV_1 decline using % FEV_1 readings as recorded in spirometer machines ($p=0.016$). Cleaning of height data and standardisation of % FEV_1 calculation with Knudson equation¹⁷ did not alter the magnitude of % FEV_1 decline, but the p-value was no longer statistically significant ($p=0.062$). The use of GLI equation altered the magnitude of % FEV_1 decline although the trend of reduction in % FEV_1 decline persisted ($p=0.135$). Adjustment for baseline % FEV_1 further increased the p-value ($p=0.210$).

Dataset 1. Sheffield forced expiratory volume in one second (FEV_1) data

<http://dx.doi.org/10.5256/f1000research.14981.d205603>

Discussion

We demonstrated that different centre-level % FEV_1 decline results were obtained using different FEV_1 data processing methods. In particular, year-on-year % FEV_1 decline was smaller in magnitude when % FEV_1 was calculated using GLI equation¹⁸ instead of Knudson equation¹⁷. This is in part due to the demographic of our centre which has a relatively young adult population. A previous study found a near-linear % FEV_1 decline from childhood to adulthood with GLI equation, whereas there was accelerated % FEV_1 decline during adolescence and young adulthood when % FEV_1 was calculated with Knudson equation²¹. One advantage of using the GLI equation, which is seamless across all ages, is that it improves the interpretation of % FEV_1 decline^{21,22}. Another advantage is that % FEV_1 decline can be adjusted for baseline % FEV_1 using ESCF reference values (since the ESCF values for % FEV_1 decline were calculated using the GLI equation²⁰).

Table 1. Characteristics of study subjects from 2013 to 2016.

	2013	2014	2015	2016
Excluded				
Lung transplantation, n	6	6	9	7
On ivacaftor, n	7	7	9	13
Included, n	166	170	185	186
Age in years, median (IQR)	25 (19 – 31)	26 (20 – 32)	27 (20 – 34)	27 (21 – 34)
Female, n (%)	76 (45.8)	80 (47.1)	87 (47.0)	90 (48.4)
Genotype status: [¶]				
≥1 unknown mutation(s), n (%)	11 (6.6)	13 (7.6)	16 (8.6)	15 (8.1)
≥1 class IV-V mutation(s), n (%)	26 (15.7)	29 (17.1)	36 (19.5)	34 (18.3)
Homozygous class I-III, n (%)	129 (77.7)	128 (75.3)	133 (71.9)	137 (73.7)
Pancreatic insufficient, [†] n (%)	137 (82.5)	135 (79.4)	142 (76.8)	145 (78.0)
CF related diabetes, [‡] n (%)	39 (23.5)	42 (24.7)	42 (22.7)	54 (29.0)
<i>P. aeruginosa</i> status: [§]				
No <i>P. aeruginosa</i> , n (%)	60 (36.1)	57 (33.5)	74 (40.0)	78 (41.9)
Intermittent <i>P. aeruginosa</i> , n (%)	37 (22.3)	36 (21.2)	31 (16.8)	29 (15.6)
Chronic <i>P. aeruginosa</i> , n (%)	69 (41.6)	77 (45.3)	80 (43.2)	79 (42.5)
BMI, median (IQR)	22.3 (19.7 – 24.6)	22.7 (20.0 – 25.0)	23.0 (20.3 – 26.0)	23.2 (20.4 – 26.0)
Best %FEV ₁ , median (IQR)	78.7 (54.1 – 92.5)	76.6 (54.4 – 89.7)	77.8 (60.4 – 89.0)	78.5 (58.5 – 89.6)

[¶] Genotype status as defined by international consensus²³. Homozygous class I-III mutations indicate 'severe genotype'.

[†] Pancreatic insufficiency was diagnosed by the clinical team on the basis of ≥2 faecal pancreatic elastase levels <200µg/g stool and symptoms consistent with maldigestion and malabsorption, in accordance to the [UK Cystic Fibrosis \(CF\) Trust guideline](#).

[‡] CF related diabetes was diagnosed by the clinical team on the basis of oral glucose tolerance test and continuous subcutaneous glucose monitoring results, in accordance to the [UK CF Trust guideline](#).

[§] *Pseudomonas aeruginosa* status was determined according to the Leeds criteria²⁴.

Table 2. Discrepancies in %FEV₁ decline with different methods of processing forced expiratory volume in one second (FEV₁) data.

Methods of processing FEV ₁ data:	Change in %FEV ₁ , median (IQR)			Friedman test p-values
	2013 to 2014 (n = 158)	2014 to 2015 (n = 162)	2015 to 2016 (n = 170)	
(1) %FEV ₁ (calculated with Knudson equation) extracted from spirometer machines used for analysis [†]	-2.0 (-6.0 to 1.0)	-1.0 (-3.3 to 2.0)	0.0 (-3.0 to 2.0)	0.016
(2) FEV ₁ volume (in L) extracted and height data were cleaned, then %FEV ₁ calculated using Knudson equation [‡]	-2.0 (-5.0 to 1.0)	-1.0 (-4.0 to 1.0)	0.0 (-3.8 to 2.0)	0.062
(3) FEV ₁ volume (in L) extracted and height data were cleaned, then %FEV ₁ calculated using GLI equation [§]	-1.1 (-4.6 to 1.5)	-0.9 (-3.2 to 1.5)	-0.3 (-2.9 to 1.8)	0.135
(4) FEV ₁ volume (in L) extracted and height data were cleaned, then %FEV ₁ calculated using GLI equation, then change %FEV ₁ adjusted for baseline %FEV ₁ using ESCF reference values [§]	0.7 (-2.4 to 3.6)	1.1 (-1.4 to 3.5)	1.6 (-1.3 to 3.7)	0.210

ESCF - Epidemiologic Study of cystic fibrosis

[†] The vast majority of the %FEV₁ data were from spirometer machines at the Sheffield Adult cystic fibrosis (CF) centre, which were calculated with Knudson equation¹⁷ in whole numbers. Some %FEV₁ data were from spirometer machines at the Pulmonary Function Unit which operationalised the Knudson equation differently; by calculating age to one decimal place to determine the predicted FEV₁. These spirometer machines also provided %FEV₁ to two decimal places, but this was rounded to whole numbers for the purpose of analysis. These results were presented at the 2017 North American CF Conference and were published as an abstract in *Pediatric Pulmonology*¹².

[‡] FEV₁ volumes were available in litres to two decimal places from spirometer machines. Height data were also extracted to allow the calculation of predicted FEV₁. This led us to uncover the inconsistency recording of height, which affected 30–40% of the study subjects and would have introduced erroneous variability to the %FEV₁, because all equations for predicted %FEV₁ are dependent on height. Height data were cleaned to weed out error. Where there was uncertainty regarding the height, the higher value was used to obtain a conservative estimate of %FEV₁. To replicate calculation process of the spirometer machines at the Sheffield Adult CF centre, age was rounded down to a whole number and predicted FEV₁ in volume were calculated to two decimal places using Knudson equation¹⁷. This was used to derive the %FEV₁, which was then rounded to whole numbers for the purpose of analysis.

[§] FEV₁ and height data were extracted as above. %FEV₁ was calculated using the GLI equation¹⁸ using an Excel Macro available at the [European Respiratory Society website](#).

[§] %FEV₁ calculated using the GLI equation¹⁸ as described above, then adjusted for baseline %FEV₁ as described in the 'Methods' section. An adjusted %FEV₁ change of >0 meant the subject's %FEV₁ decline was less than expected for his / her baseline %FEV₁, indicating better health outcomes.

The limitation for all single-centre analysis is the potential lack of generalisability. Another limitation of our analysis is that the ESCF reference values used to adjust %FEV₁ decline were derived using a cohort from around 15 years ago²⁰, and may not represent the current population. Our results nonetheless highlighted that %FEV₁ decline can be extremely sensitive to the FEV₁ data processing methods. This is one of the challenges of using %FEV₁ decline to infer quality of care. Another challenge is that %FEV₁ lacks sensitivity as an outcome measure. A recent sample size estimation using the UK CF registry data suggests that 273 adults per centre are needed to detect a 5% FEV₁ difference at the 95% significance level²⁵. The sensitivity of measures used to detect variations in care quality is particularly pertinent to CF because a relatively small population is spread across many centres. Indeed, only 6/28 (21.4%) of all **UK adult CF centres** have ≥273 adults. That means process measures, e.g. medication adherence, is important to detect variations in quality of CF care. Mant & Hicks previously demonstrated that measuring processes of care proven in randomised controlled trials to reduce death allows detection of meaningful differences in care quality for myocardial infarction with just 75 cases, whereas 8179 cases would be needed if mortality was used as the quality indicator²⁶.

Given the limitations of FEV₁ as an outcome measure in CF, results of centre comparisons based on FEV₁ data should be carefully interpreted. Observational studies with %FEV₁ decline as an outcome measure should carefully consider and clearly specify the data processing methods used.

Ethical considerations

Regulatory approval for the analysis was obtained from NHS Health Research Authority (IRAS number 210313).

Data availability

Dataset 1: Sheffield forced expiratory volume in one second (FEV₁) data [10.5256/f1000research.14981.d205603](https://doi.org/10.5256/f1000research.14981.d205603)²⁷

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this piece of work.

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Pierre-Régis Burgel 

Pulmonary Department and Adult CF CentreGroupe Hospitalier Cochin-Hotel Dieu, Paris Descartes University, Paris, France

The authors performed a retrospective analysis of FEV1% predicted data over 3 years in an adult CF center in the UK. They examined FEV1 decline from year to year by calculating variation in best FEV1 during two consecutive years and examined the impact of using data obtained using Knudson equation (directly extracted from the spirometer or recalculated with the appropriate height) vs. GLI equation. They also performed an adjustment using ESCF data.

The authors concluded that trends in FEV1 decline were robust among methods, although the results were somewhat different using different methods/equations.

The study has some interest in highlighting problems associated with these type of calculations, especially when used for benchmarking (as in the UK).

I have the following comments for improvement:

1. An important drawback of Knudson equation is related to the change of FEV1 in the transition from pediatric to adults. This is why the GLI is nowadays often used in mixed pediatric/adult population. The authors used the UK definition of adults (over 16 years) and suggested that some of the difference in their results between Knudson and GLI data are due to the younger patients in this cohorts. I would be happier if the authors could perform a sensitivity analysis using only patients 18 years and over? This would minimize the Knudson/GLI age bias and would make these results more relevant to the adult centres outside of UK. Looking at Table 1, it seems that only a minority of patients were below 18 years.
2. I think the word FEV1 decline is inappropriate in this manuscript. A year to year variation (even over 3 years) is not a decline. For calculating a decline, you would need multiple data points (at the very least 3 data points) and perform more complicated analyses (e.g., mixed model analysis). I would suggest to remove the word decline from the manuscript as the main goal of the authors did not appear to be FEV1 decline but mostly year to year FEV1

variation which is used for benchmarking in the UK.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Adult pulmonologist with experience in the care of adults with cystic fibrosis. Researcher.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 12 Aug 2018

Zhe Hui Hoo, University of Sheffield, Sheffield, UK

We thank Prof Burgel for the review and we will iterate the manuscript taking into account the two very useful suggestions, i.e.

1. we will perform a sensitivity analysis for the results in Table 2 using only adults aged 18 years and above
2. we will replace the term "FEV1 decline" with "year-to-year FEV1 variation"

Competing Interests: No competing interests were disclosed

Reviewer Report 06 July 2018

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**Edward McKone**

Department of Respiratory Medicine, St Vincent's Hospital, Dublin, Ireland

FEV1 as a percent of predicted is widely used as an outcome measure in patients with cystic fibrosis and is one of the metrics used to compare centres or countries in benchmarking exercises.

This manuscript presents data showing that differences in data processing and the use of different reference equations used to estimate FEV1 as a percent predicted can result varying estimates of lung disease changes and potentially impact comparisons of centres/countries.

The paper supports the standardization of FEV1 collection and reference equations which is currently in development by CF International Registries. It also highlights that different approaches to data collection can impact the interpretation of statistical analyses.

Comments:

Differences in FEV1 percent predicted using different equations is well known (Rosenfeld et al¹ and more recently in the cited UK/US comparison study). For this reason, the GLI have been recently accepted as the standard for most CF registries.

Although year to year subtraction is a method of looking at longitudinal changes, regression methodology is preferable to analyse these changes, especially, as in this case, where you have 3 time points. This also allows to adjust for baseline factors such as lung disease severity.

The method of adjustment for baseline lung function is a bit crude. The medians subtracted are from a US population over 10 years ago and are likely to overestimate lung function decline in this population. In the Morgan et al, J Pediatr 2016 paper cited, the benefits of using this type of adjustment was shown using regression.

Did their statistical approach factor in that these were repeated measures in the same patients?

Bland & Altman plots comparing different reference equations could be considered.

The results suggest that height inaccuracy is impacting the results. As this is a single centre study, it is difficult to determine if this is a more universal problem.

References

1. Rosenfeld M, Pepe MS, Longton G, Emerson J, et al.: Effect of choice of reference equation on analysis of pulmonary function in cystic fibrosis patients. *Pediatr Pulmonol*. 2001; **31** (3): 227-37 [PubMed Abstract](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 12 Aug 2018

Zhe Hui Hoo, University of Sheffield, Sheffield, UK

We thank Prof McKone for the review and we will iterate the manuscript taking into account the suggestion to compare the different reference equations (Knudson vs GLI) using Bland-Altman analysis.

We concur the GLI has been recently accepted as the standard for most CF registries.

We concur that regression analyses is preferable to determine FEV1 decline. As recommended by Prof Burgel, we will replace the term "FEV1 decline" with "year-to-year FEV1 variation" in the revised manuscript.

We concur that the method used to adjust year-to-year FEV1 variation for baseline FEV1 is crude. The displayed data from the ESCF paper is only presented according to the four FEV1 categories, hence our choice of adjustment method. Given the limited number of subjects within the Sheffield dataset, we felt it is more appropriate to use reference values for suitably large datasets instead of simply calculating the predicted %FEV1 change using the Sheffield dataset. There are more recent reference values for FEV1 from the ECFSPR (Boëlle et al, 2012) and Canadian registry (Kim et al, 2018); however those papers do not provide reference values for year-to-year FEV1 variation.

Our statistical method account for repeated FEV1 measures since:

1. by using best FEV1, there is only x1 FEV1 reading per person per year
2. only x1 FEV1 reading per person was used to calculate the year-to-year FEV1 variation

As mentioned in the discussion section, we concur that a single-centre study may not be generalisable. However, inaccurate data recording within routine datasets (e.g. CF registries) is unlikely to be an isolated problem. For example, the letter by Hartley et al (2016) in JCF revealed that 6% of the adults with CF at the Manchester Adult CF Centre had incorrect genotype data recorded in the UK CF registry.

Competing Interests: No competing interests were disclosed

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