Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis

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ABSTRACT
Background Decline in forced vital capacity (FVC) over time reliably predicts mortality in patients with idiopathic pulmonary fibrosis. The use of this measure in clinical practice is recommended by current evidence-based guidelines. It is unknown if the method of calculating decline in FVC (relative vs absolute change) impacts its frequency or its ability to predict mortality.

Methods Patients with idiopathic pulmonary fibrosis from two prospective cohorts were included if they had a baseline and 12-month follow-up FVC. A ≥10% decline in FVC from baseline was calculated in two ways: a relative decline of 10% (eg, from 60% predicted to 54% predicted) and an absolute decline of 10% (eg, from 60% predicted to 50% predicted). The frequency of a ≥10% decline in FVC and its ability to predict 2-year transplant-free survival were compared between these two methods. Declines in FVC of ≥5% and ≥15% were similarly compared. Analyses were performed unadjusted and adjusted for age, gender, use of oxygen, baseline FVC and baseline diffusion capacity for carbon monoxide.

Results The frequency of any given FVC decline was significantly greater using the relative change in FVC method. For ≥10% decline, both methods predicted 2-year transplant-free survival with similar accuracy, and remained significant predictors after adjusting for baseline characteristics. The absolute change method appeared more predictive for ≥5% decline.

Conclusions Using the relative change in FVC maximises the chance of identifying a ≥10% decline in FVC without sacrificing prognostic accuracy. This may not hold true for ≥5% decline in FVC. These findings have important implications for clinical practice and the design of clinical trials.

What is the key question?
► Is the frequency of a decline in forced vital capacity (FVC) influenced by the method used to calculate the change in patients with idiopathic pulmonary fibrosis?

What is the bottom line?
► Using a relative (instead of an absolute) change in FVC maximises the chance of identifying a ≥10% decline without sacrificing prognostic accuracy.

Why read on?
► The choice of the method used to calculate a change over time in FVC has potential implications for both clinical practice and clinical trial design.

INTRODUCTION
Serial change in forced vital capacity (FVC) is an accepted measure of the disease course in patients with idiopathic pulmonary fibrosis (IPF).1–7 FVC decline has been used as the primary endpoint in several randomised controlled drug trials.6–13 and the European Medicines Agency recently approved pirfenidone for use in patients with IPF based on studies using this endpoint.13 A ≥10% decline in FVC has been reliably correlated with worse survival time in IPF,1–5 and recent evidence-based guidelines recommend that an absolute decrease in FVC of ≥10% can be used as a surrogate marker of mortality.14 In addition, recent studies have suggested that an FVC decline of ≥5% may also have clinical significance.1,5 A ≥10% decline in FVC can be a relative decline of 10% (eg, from 4 to 3.6litres or from 60% predicted to 54% predicted) or an absolute decline of 10% (eg, from 60% predicted to 50% predicted). Some clinical trials in patients with IPF have used the relative change from baseline in FVC (or VC),15–17 while other clinical trials and cohort studies have used the absolute change from baseline.1–5,9 10 12 13 18 The frequency and predictive abilities of relative and absolute changes in FVC have not been directly compared.

The frequency and prognostic value of any given decline in FVC may depend on which method of calculation is used. Such differences would have important implications for clinical practice and clinical trial design. Consequently, we sought to evaluate how the method of calculation (relative vs absolute) impacted the frequency and prognostic value of declines in FVC in patients with IPF.

METHODS
Patients
Consecutive patients with a new diagnosis of IPF based on international guidelines19 were identified from two independent longitudinal cohorts at the University of California, San Francisco (UCSF) and the Mayo Clinic (Rochester, Minnesota, USA).
Patients were included in the study if they had two serial FVC measurements 12 months apart. The Institutional Review Boards at each institution approved the protocol.

**Predictor and outcome variables**

The primary predictor variable was a ≥10% decline in FVC, defined as the difference between the baseline FVC and the 12-month FVC (±3 months, figure 1). The change in FVC was calculated as relative change (FVC\(_{\text{baseline}}\) − FVC\(_{\text{12 months}}\)/FVC\(_{\text{baseline}}\), using either FVC in litres or % predicted FVC) and absolute change (FVC\(_{\text{baseline}}\) − FVC\(_{\text{12 months}}\), using % predicted FVC). Since the two methods of calculating relative change are mathematically equivalent, we only report the data from relative change in % predicted FVC (data for the relative change in FVC in litres is included in table 1 in the online data supplement). Secondary analysis included the predictor variable of ≥5% and ≥15% declines in FVC. Additional predictor variables included were age, gender, oxygen use, FVC and diffusion capacity for carbon monoxide (DLCO). FVC and DLCO were measured according to previous guidelines\(^{20, 21}\) and % predicted FVC was recalculated from the raw data using the National Health and Nutrition Examination Survey (NHANES) equation.\(^{22}\)

The primary outcome was 2-year transplant-free survival, defined as the absence of death or lung transplant at 2 years measured from the date of the 12-month FVC (ie, 2 years after the change in FVC was observed). Secondary outcomes included survival at 2 years, transplant-free survival at 1 year, survival at 1 year, time to death or lung transplant, and time to death. For survival outcomes, lung transplant was either not considered an event (survival at 2 years, survival at 1 year) or subjects were censored on the date of transplant (time to death). Vital status and transplantation status were determined from review of the medical record and use of the Social Security Death Registry (accessed on 27 Jun 2011 at http://ssdi.rootsweb.ancestry.com).

**Statistical analysis**

The frequency of decline in FVC was determined for both methods and compared using McNemar’s \(\chi^2\) test (test of symmetry). The impact of baseline FVC on frequency of decline in FVC was evaluated by considering baseline FVC as a continuous variable and by stratifying baseline FVC above or below the median value. Logistic regression was used to determine the association of dichotomised decline in FVC with 2-year transplant-free survival. Unadjusted analyses were performed, followed by adjustment for age, gender, oxygen use and baseline % predicted FVC and DLCO. The utility of adding change in FVC to the nested baseline variables was tested using a likelihood ratio test. These analyses were repeated for secondary endpoints (logistic regression and Cox proportional hazards). The predictive ability of each method was compared using OR or HRs and the area under the receiver operating characteristic (AUROC) curve or c-statistic as appropriate. We compared test characteristics subjectively since there is no formal means to directly compare these non-nested models. Analyses were repeated excluding patients with severe disease by physiological criteria (FVC <50% or DLCO <35% predicted). All data analysis was performed using Stata V.11.0 (Stata Corp).

**RESULTS**

**Patient population**

A total of 142 patients were included in the primary analysis (88 from UCSF and 54 from Mayo Clinic, table 1). Included patients did not differ in baseline characteristics or survival from those excluded due to lack of a 12-month follow-up FVC (n=189; data not shown). The mean age at the time of diagnosis was 67 years, most patients were men with a history of smoking, and more than half had surgical lung biopsy. The mean FVC at baseline was 2.7 litres (68% predicted) and mean DLCO was 12.4 ml/min/mm Hg (49% predicted). Patients had a wide range of disease severity, with a broad distribution of baseline FVC and DLCO (see figure 1 in the online data supplement). There were 108 patients that met physiological inclusion criteria commonly used for intervention studies (FVC ≥50% predicted and DLCO ≥35% predicted).

**Frequency of decline in FVC over 12 months**

The frequency of a ≥10% decline in FVC over 12 months was almost twice as high using the relative change in FVC than using the absolute change in FVC (50% vs 18%, p<0.001) (table 2). There was no significant relationship between baseline FVC and the prevalence of ≥10% decline in FVC over 12 months using either method (see table 2 and figure 2 in the online data supplement). The results were similar for 5% and 15% declines in FVC and when excluding patients with severe disease (table 2).

Baseline patient characteristics were not different when comparing patients without a ≥10% decline in FVC by either method (n=99), patients with a ≥10% decline only by the relative method (n=17), and patients with decline by both methods (n=26) (data not shown). Median transplant-free survival was 4.7 years for patients without a ≥10% decline in FVC by either method, 2.6 years for patients with a ≥10% decline only by the relative method, and 2.0 years for patients with a ≥10% decline by both methods (p value=0.001 for the difference between all groups).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD or %)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.0 (9.0)</td>
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<tr>
<td>Male gender</td>
<td>74%</td>
</tr>
<tr>
<td>History of smoking</td>
<td>69%</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>1.4%</td>
</tr>
<tr>
<td>Biopsy proven disease</td>
<td>56%</td>
</tr>
<tr>
<td>Current or previous prednisone use</td>
<td>35%</td>
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<tr>
<td>Long-term oxygen therapy</td>
<td>19%</td>
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<tr>
<td>FVC, litres</td>
<td>2.70 (0.78)</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>67.6 (16.1)</td>
</tr>
<tr>
<td>DLCO (ml/min/mm Hg)</td>
<td>12.4 (4.2)</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>48.5 (15.1)</td>
</tr>
</tbody>
</table>

DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity.

**Figure 1** Methods of 12-month decline in forced vital capacity (FVC) calculation. Two methods of calculating change in FVC over 12 months were used. The time interval for 12-month follow-up FVC was set at 9–15 months to allow for adequate numbers of patients.
Excluding patients with severe disease (n = 12 months)

Whole cohort (n = 142)

<table>
<thead>
<tr>
<th>Method of calculation</th>
<th>12-month FVC decline</th>
<th>12-month FVC decline</th>
<th>12-month FVC decline</th>
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<tbody>
<tr>
<td></td>
<td>≥5%</td>
<td>≥10%</td>
<td>≥15%</td>
</tr>
<tr>
<td>Relative change</td>
<td>70 (49.3)</td>
<td>43 (30.3)</td>
<td>30 (21.1)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>52 (36.6)</td>
<td>26 (18.3)</td>
<td>11 (7.7)</td>
</tr>
<tr>
<td>p Value for difference</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Excluding patients with severe disease (n = 108)*

<table>
<thead>
<tr>
<th>Method of calculation</th>
<th>12-month FVC decline</th>
<th>12-month FVC decline</th>
<th>12-month FVC decline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥5%</td>
<td>≥10%</td>
<td>≥15%</td>
</tr>
<tr>
<td>Relative change</td>
<td>58 (53.7)</td>
<td>36 (33.3)</td>
<td>25 (23.2)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>46 (42.6)</td>
<td>22 (20.4)</td>
<td>7 (6.5)</td>
</tr>
<tr>
<td>p Value for difference</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data presented as number of patients (% of patients) meeting the stated threshold.

*Patients were excluded from this analysis if baseline FVC <50% or DLCO <35%.

DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity.

Predictive value of decline in FVC over 12 months

Both methods of calculating ≥10% decline in FVC predicted transplant-free survival at 2 years, using both unadjusted and adjusted analysis (table 3 and figure 2). The adjusted ORs for death or transplant at 2 years were 3.59 (95% CI 1.14 to 10.07) for the relative method and 4.52 (95% CI 1.27 to 16.12) for the absolute method, with overlapping CIs. Using the relative or absolute method, the AUROC was 0.82 with the addition of ≥10% decline in FVC to the baseline variables age, gender, oxygen use, % predicted FVC and % predicted DLCO. The addition of ≥10% FVC decline to baseline variables significantly improved model performance for both the relative and absolute methods (likelihood ratio test p value = 0.02 for both methods). A ≥5% decline in FVC over 12 months predicted a greater risk of death or transplant at 2 years on adjusted analysis using only the absolute method of calculation (table 3). Adjustment for each individual covariate (age, gender, oxygen use, baseline FVC and baseline DLCO) increased the OR of death or transplant at 2 years. The greatest increase in OR was seen with the adjustment for baseline FVC. A ≥15% decline in FVC over 12 months predicted a greater risk of death or transplant at 2 years on unadjusted and adjusted analysis using only the relative method of calculation (table 3). The results were qualitatively similar for all secondary outcomes, including the direction and magnitude of the effect (OR and HRs; see tables 3–5 in the online data supplement), and the overall predictive accuracy of the models (AUROC curve and c-statistic; data not shown). The results were also similar for all analyses when excluding patients with severe disease (table 3).

DISCUSSION

Recent evidence-based guidelines for the management of IPF state that an absolute decline in FVC of ≥10% over time is an acceptable method to assess disease progression and estimate risk of future mortality in patients with IPF.14 As a consequence, a ≥10% decline in FVC affects management decisions (eg, enrolment in a clinical trial, start of a therapy, referral for lung transplant evaluation) and the counselling of patients. Our results show that the method used to calculate change in FVC has a significant impact on the frequency of a decline in FVC over 12 months in patients with IPF, and suggest that a ≥10% relative decline in FVC may be preferable to an absolute ≥10% decline in assessing disease progression.

The choice of method has potential implications for both clinical practice and clinical trial design. Clinically, the use of the absolute method to calculate a ≥10% decline in FVC fails to identify almost half of patients with a ≥10% decline in FVC calculated using the relative method. These ‘relative-method positive, absolute-method negative’ patients had a similar 2-year transplant-free survival to patients with a ≥10% decline by both methods. This suggests that using the absolute method to calculate ≥10% decline in FVC will miss some patients that have a clinically meaningful decline in FVC, which could lead to delays in important management decisions.

Our findings also demonstrate the potential impact of the method used to calculate a ≥10% decline in FVC on the design and results of clinical trials. Almost twice as many patients...
would be required to adequately power a clinical trial to ≥10% decline in FVC using the absolute method than using the relative method (figure 3). Put another way, using the relative method to calculate ≥10% decline in FVC would substantially increase the number of events in such a trial, reducing sample size requirements and increasing feasibility. In theory, trials that used a ≥10% decline in FVC as part of their primary endpoint (eg, as a component of progression-free survival) could yield different results depending on the choice of relative or absolute method. This difference between methods applies to our cohort as a whole and to the subgroup of patients with less severe IPF who would meet the inclusion criteria for the most recent randomised clinical trials.

Recently, it has been reported that declines in FVC smaller than 10% predict mortality. Unlike our findings for a ≥10% decline in FVC, we found that a ≥5% decline in FVC over 12 months was predictive of 2-year transplant-free survival only when calculated as an absolute change, and only when adjusting for baseline variables. This apparent difference between our study and previous studies may be due to different study populations. Specifically, previous studies showing that small declines in FVC are predictive of mortality have limited the number of patients with severely reduced baseline FVC by either requiring surgical lung biopsy for diagnosis, or by excluding patients with severe disease. In our study, the most powerful modifier of the predictive power of a relative 5% decline in FVC was baseline FVC, suggesting that baseline severity may be an important factor in evaluating the significance of small changes in FVC. This suggests that for clinicians and clinical researchers who decide to use declines of <10%, the absolute method may be more appropriate. This may be due to an increased risk of identifying random, clinically insignificant fluctuations in FVC using the relative method. Interestingly, we found that a ≥15% decline in FVC over 12 months was predictive of 2-year transplant-free survival only when calculated as a relative change. However, the lack of statistical significance for the absolute change is likely related to the small number of events when using this method.

Our results are limited by the retrospective nature of the study design; not all patients had an FVC measurement recorded 12 months after initial evaluation. Importantly, there were no significant clinical or physiological differences between those patients who had a 12-month follow-up FVC measurement and those patients who did not (data not shown). A second limitation is that the numbers of patients with relatively normal or with severely reduced pulmonary function were small, and thus our results may not apply to all patients with IPF. However, the findings of this study do not appear to change with stratification or adjustment for baseline FVC. Finally, our results are applicable to a 12-month change in FVC, but may not apply to other intervals of change. We chose to evaluate a 12-month change in FVC primarily because change in FVC over 12 months is commonly reported in clinical trials. An additional advantage of using a 12-month interval is that every individual will age exactly 1 year. This eliminates distortion in % predicted FVC values that would occur with other time intervals in which only some individuals would have a birthday that resulted in ageing-related changes in their predicted FVC. This birthday phenomenon would not affect change in FVC reported in litres.

In summary, this study demonstrates that the method used to calculate change in FVC in patients with IPF is important as it affects the frequency of any given decline in FVC, the most commonly used measure of disease progression in clinical practice and clinical trials. We believe that clinicians and clinical researchers should consider using the relative change in FVC when calculating a ≥10% decline in FVC. This approach maximises the chances of identifying clinically meaningful change without sacrificing prognostic accuracy.

Acknowledgements
The authors wish to acknowledge the assistance of Sally McLaughlin and Jane Berkeley for their efforts in caring for many of these patients and their assistance with managing the clinical data. We would also like to acknowledge the providers in the community for partnering with us in the care of patients with IPF and referring patients to our centres for participation in clinical research. Finally, we would like to acknowledge the patients and family members whose generosity and selflessness in participating in research makes progress possible.

Contributors
Conception and design: LR, CJR, HRC; analysis and interpretation: LR, CJR, JSL, PJW, LLK, TEK, HRC; drafting the manuscript for important intellectual content: LR, CJR, JSL, PJW, LLK, BL, BME, KDJ, TEK, JHR, HRC.

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Correction notice
This article has been corrected since it was published online first. The author names now read Brett Ley and Brett M Elicker. The following sentence has been updated to read: 'The mean age at the time of diagnosis was 67 years, most patients were men with a history of smoking, and more than half had surgical lung biopsy.’

Competing interests
None to declare.

Patient consent
Obtained.

Ethics approval
Ethics committee of UCSF and Mayo Clinic.

Provenance and peer review
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REFERENCES


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