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Predicting Future Lung Function Decline in Cystic Fibrosis Patients: Statistical Methods and Clinical Connections

Rhonda D. Szczesniak, PhD[*],
Division of Biostatistics and Epidemiology/Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Gary L. McPhail, MD,
Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Dan Li, MS,
Department of Mathematical Sciences, University of Cincinnati, Cincinnati, Ohio

Raouf S. Amin, MD, and
Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

John P. Clancy, MD
Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

To the Editor

We read the article by Rosenfeld and colleagues[1] with great interest and applaud the authors for investigating the predictive value of decline in (observed) lung function on subsequent decline in lung function in patients with cystic fibrosis (CF). As the authors indicated, there is a dearth of literature on this particular research question, although it is of great CF clinical and epidemiological interest. The authors utilized a large data source to examine the predictive value for a variety of spirometric variables; they clearly defined their calculations and statistical approach. We focus on one of the spirometric variables presented in the study, forced expiratory volume in one second of percent predicted (hereafter, FEV_1%p); however, the comments may be generalized to the other spirometric variables that the authors examined.

The authors calculated a two-point slope for each CF patient over a two-year interval by taking the difference between maximum FEV_1%p for a given year of age and the subsequent two-year value. The authors used the magnitude of the estimated Pearson correlation coefficient to quantify the extent to which reference slopes were predictive of subsequent two-year slopes; these correlations were performed overall and by defined age strata. Correlations between reference slopes and follow-up levels (as opposed to slopes) were also estimated. Contrary to what they had anticipated, the authors found low correlation estimates for associations between reference and subsequent slopes; the authors found

[*]Correspondence to: R.D. Szczesniak, PhD, Division of Biostatistics and Epidemiology (MLC 5041), 3333 Burnet Avenue, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229. rhonda.szczesniak@cchmc.org.

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moderate correlation between reference slopes and subsequent level (as opposed to slope). The statistical approach and findings raise questions regarding how to best assess the potential prognostic utility of FEV_1%p decline.

Patient-specific predictions can be made using a selected statistical model or summary measure, such as the two-point FEV_1%p slopes used by the authors. Clinicians and researchers in CF have often operationalized rate of decline in lung function as a slope, which intuitively corresponds to rise over run. The authors' illustrations and plots of median two-year slopes depict nonlinear age-related FEV_1%p progression across CF patients. Their results suggest the need to characterize individual rates of decline in terms of derivatives using quantities related to velocity and acceleration. A previous study of the Cystic Fibrosis Foundation Patient Registry revealed similar trends in age-related FEV_1%p decline, as well as acceleration and deceleration, using flexible (nonlinear) modeling via semiparametric regression.[2]

The two-point slopes provide an easily interpretable approximation to how the population progresses with regard to FEV_1%p decline, but statistical models that can incorporate the aforementioned nonlinearity, as well as covariate information (e.g., weight-for-age percentile), between-subject variation and longitudinal correlation, are needed to characterize observed FEV_1%p decline in the individual patient and forecast disease progression. Although such models require assumptions, insights may be gained about individualized fluctuations in FEV_1%p and predictions, possibly improving the ability to forecast subsequent FEV_1%p decline. A previous study of the Danish Cystic Fibrosis Patient Registry, which the authors cited, incorporated stochastic variation in FEV_1%p response in the form of model covariance to improve predictive accuracy.[3]

The authors' work provides new epidemiological insight into the population-based predictive utility of observed lung function decline. To gain understanding of how this work could be translated into clinical settings or used to plan clinical trials, it may be helpful to consider dynamic models targeted at predicting individual FEV_1% p progression. The collection of longitudinal FEV_1%p data on a given CF patient may be thought of as a time series. This composition of FEV_1%p fluctuations are often viewed as a nuisance in epidemiologic studies, but are often of great interest for individual predictions. For example, in a clinical setting, it may be advantageous to model the complete observed time series of individual CF patients, as opposed to maximum or average FEV_1%p calculated annually or quarterly. Statistical models allow for "borrowing" of information across CF patients' longitudinal courses although utilizing all observed data on the patient of interest, and can more accurately forecast the patient's FEV_1%p progression over a subsequent time frame of interest (e.g., time of next quarterly clinic visit), compared to selecting only the maximum FEV_1%p value per year and using this value to assess individual progression.

Another issue mentioned by the authors and reported in the previously referenced studies is survival bias. This induces a type of informative dropout that is a difficult statistical issue to address. In order to account for survival bias and simultaneously improve predictive accuracy, many analysts jointly model the longitudinal and time-to-event data. Indeed, an application involving a joint longitudinal FEV_1%p-survival model of CF patient data has

been presented by one of the authors and his colleagues.[4] The longitudinal FEV_1%p submodel that results from this type of approach is adjusted for survival bias and may be used to more accurately forecast FEV_1%p progression, including individual FEV_1%p data points and other features, such as rate of decline. Joint models are widespread in the statistical literature but have made somewhat limited appearances in the clinical literature. This may be due in part to the computational drawbacks.

Regardless of whether FEV_1%p (level or slope) predictions are obtained from a dynamic model or an aggregate calculation of observed data, the quality and stability of the predictions must be examined. The authors use Pearson correlation coefficient estimates to quantify the level of predictive value, but other measures, such as mean squared error (commonly referred to as MSE) or average predicted squared error in the case of more complex longitudinal models and forecasting, are often employed for this purpose.[5]

Assessing the predictive utility of lung function decline can be approached in numerous ways, beginning with how to operationalize the rate of decline and ending with evaluating forecasting ability and clinical interpretation. The authors' work provides additional insights and a path forward to further investigate the predictive utility of rate of decline in lung function, however it is operationalized or measured, in CF. Furthermore, this work demonstrates the need to translate existing statistical approaches that account for bias and other issues into CF clinical practice and trials planning.

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