

Analysis of Factors Associated with FEV1 Decline in Alpha-1 Antitrypsin Deficient Patients: a Comparison of Statistical Approaches

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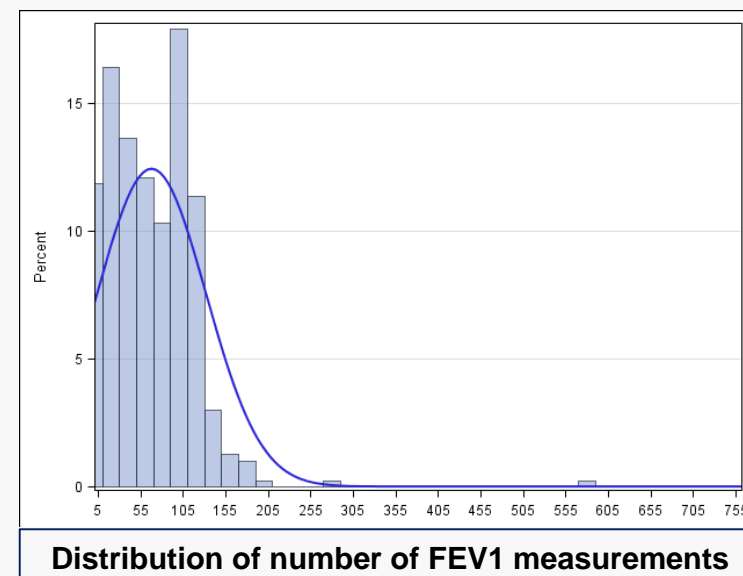


Introduction

- In longitudinal studies examining pulmonary function, one of the main statistical challenges is heterogeneity of the data, which must be accounted for via robust statistical modeling. Some of the most commonly-used statistical methods to examine risk factors associated with a longitudinal decline in FEV1 include linear regression on individual patient's slopes and Linear Mixed Models (LMM).
- The present study utilizes uniquely rich spirometry data of the Step Forward Study (SFS) to examine pulmonary function among population with Alpha1-Antitrypsin Deficiency (AATD) and to identify factors associated with FEV1 decline.

Spirometry

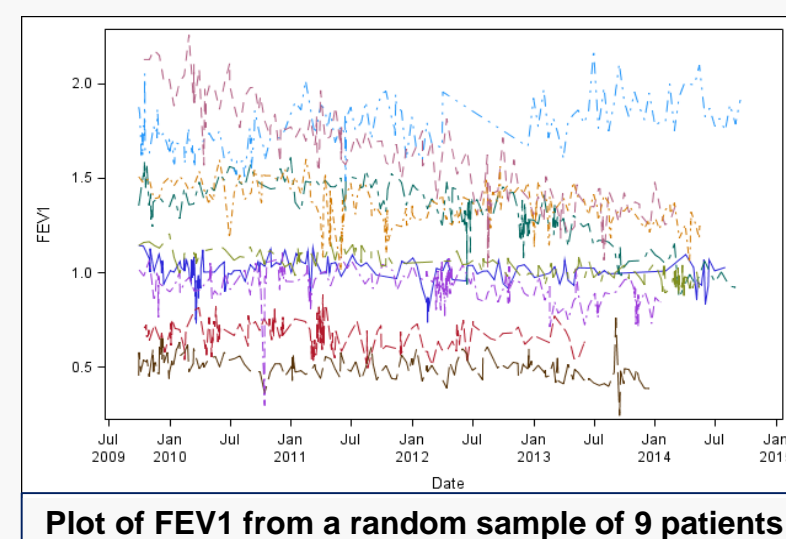
- Throughout the 5-year-long follow-up period, spirometry data was collected on a bi-weekly and daily (during exacerbations) basis with over twenty thousand valid pulmonary function data observations.
- Spirometry was assessed by providing each participant a high-end NDD EasyOne mass-flow sensing spirometer pre-programmed with the subject's height, birth date, sex, and race. Spirometry, including FEV1, FVC, FEF25-75, and PEF was obtained using strict ATS criteria as designed into the unit.



- Each participant received telephonic training by AlphaNet Coordinators in proper spirometer use and spirometer data download. Data was transferred to AlphaNet via mailing of flash memory cards from each spirometer every two-three months.

Materials and Methods

- To gain a better understanding of the factors associated with FEV1 decline in patients with Alpha-1 Antitrypsin deficiency (AATD), FEV1 data collected during AlphaNet's SFS Study were analyzed using two statistical methods: 1) a two-stage approach that includes linear regression on individual patient's slopes, and 2) LMM.
- The following variables were considered as potential predictors in both statistical methods: baseline FEV1, baseline age, gender, marital status, hospitalizations, exacerbations, smoking, history of pneumonia and/or asthma, regular exercise, and following guidelines of the Alpha-1 Disease Management and Prevention Program (ADMAPP). The significance level was set at 0.05. All statistical analyses were performed using SAS v9.4.



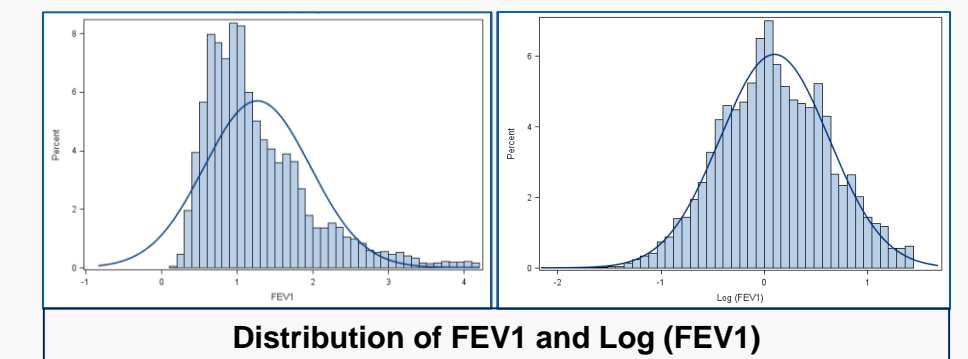
Statistical Methods

Method 1: Linear Regression on Individual Slopes

- The two-stage approach utilized weighted median linear regression on individual FEV1 slopes with the reciprocal of the standard error of the estimated slope of each patient as the weights.
- In the first stage, we estimated the slope of FEV1 over time for each patient using a median linear regression using Proc Quantreg program of SAS, where FEV1 was the outcome variable and age of respondents at each measurement was the independent variable. The resulting estimated slope described patient-specific annual FEV1 decline.
- In the second stage, we used a weighted linear regression model where the estimated slopes were used as an outcome variable.
- Standard errors were calculated for each patient's slope and inverse of the standard errors of each individual's slope estimate were used as weights.

Method 2: Linear Mixed Model

- The second method utilized LMM with a random intercept and slope in addition to the fixed effects. Fixed effects have interpretation of population averaged values, where random effects are subject-specific.
- An unstructured covariance matrix was used for the random effects to allow for a possible correlation between random slope and random intercept, and logged FEV1 was the outcome variable.
- Age at each FEV1 observation was used as a meta-meter of follow-up time, and age at baseline was included in the model.
- Final model included the following variables: baseline age, baseline log (FEV1), and following ADMAPP guidelines (based on the smallest AIC).



Results

- Data were analyzed from 387 participants. Mean age was 57.9 (± 9.2) years. The majority of participants were female (54.0%), married (74.3%), with ZZ genotype of AATD (89.3%), and a history of smoking (75.3%). Mean baseline FEV1 (L) was 1.24 (± 0.69), equivalent to 39.6 (± 21.5) % predicted. Mean follow-up time was 3.2 (± 1.6) years. Mean number of spirometry measurements was 73.9 (± 211.5 , range 2-848).

Select characteristics of the study sample at baseline, n=387

Age at baseline, mean (SD), years	57.9 (9.2)
Female, n (%)	206 (54.0)
Married, n (%)	286 (74.3)
ZZ Phenotype of AATD, n (%)	318 (89.3)
Hospitalizations in the past year, mean (SD)	0.34 (0.81)
Exacerbations in the past year, mean (SD)	1.96 (1.68)
History of Ever Smoking, n (%)	283 (75.3)
History of Pneumonia, n (%)	56 (15.1)
History of Asthma, n (%)	168 (45.0)
Regular Exercise, n (%)	203 (53.6)
Following ADMAPP guidelines, n (%)	215 (58.7)
Baseline FEV1	
Mean (SD), L	1.24 (0.69)
Mean (SD), % predicted	39.6 (21.5)
Follow-up time, mean (SD), years	3.2 (1.6)
Number of spirometry measurements per individual	
mean (SD)	73.9 (211.5)
min, max	2 - 848

Method 1: Results

- Results of the two-stage approach indicated that baseline FEV1 was a significant predictor of FEV1 decline ($p < 0.01$). Higher baseline FEV1 was associated with greater decline. The median slope of FEV1 decline was 22.5 ml per year.

Method 2: Results

- The LMM method demonstrated a significant effect of baseline age ($p < .0001$), following ADMAPP guidelines ($p = 0.0265$), and baseline FEV1 ($p < .0001$), as well as an effect of time ($p < .0001$).
- Adjusting for the baseline FEV1 and age, patients who did not follow guidelines of ADMAPP had 10.2% greater decline in FEV1 per year compared to those who complied.

Conclusions

- The two-stage regression approach demonstrated an association between FEV1 decline and baseline FEV1.
- LMM was more robust to heterogeneity of the data, and revealed an association between FEV1 decline and two additional predictors: baseline age and participation in ADMAPP.

References

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