Validation of Individualized Prediction of Lung Function Decline in Patients Diagnosed with COPD

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Background

Rationale

- Early initiation of therapies may reduce lung function decline in patients with chronic obstructive pulmonary disease (COPD) at-risk of rapid lung function decline.[1,2]
- Prediction model for the natural history of FEV_1 decline over time in patients with mild-moderate COPD, developed by Zafari et al [3], may be valuable to identify patients who would benefit from early intervention.

The Zafari Model Equation

- Mixed-effects regression models to predict future FEV_1 decline over 11 years (available at http://resp.core.ubc.ca/ipress/FEV1Pred) [3]
- Data from the Lung Health Study: multicentre clinical trial from 1993
- Patients: Smokers aged 35-59 years with FEV_1 %predicted 55-90% and FEV_1/FVC<0.7
- Clinical and demographic variables as predictors:
  - Age, sex, height, weight at baseline
  - Smoking behaviour during first 5 years of follow-up
  - Type of intervention: usual care vs. smoking cessation (with or without short-acting bronchodilator)
- Validated in two external datasets

Aim

- We aim to validate this prediction model against FEV_1 measurements, recorded before initiation of maintenance therapy, within primary care records from the United Kingdom.

Methods

Study design

- Historical cohort study using data from two large UK primary care databases:
  1. Optimum Patient Care Research Database (OPCRD)
  2. Clinical Practice Research Datalink (CPRD)
- Patients identified from date of FEV_1 recording which fell within 3 months prior to and 12 months after first COPD diagnosis (index date)
- Patients followed-up until date of initiation of first maintenance therapy

Patient selection

Inclusion Criteria
1. A diagnostic Read code for COPD
2. Valid spirometry recorded around diagnostic Read code for COPD
3. Evidence of obstruction recorded ever, defined as FEV_1/FVC<0.7
4. Mild or moderate COPD (FEV_1 % predicted ≥50% and ≤90%) at index date
5.Age ≥ 35 years
6. ≥1 year of medical records prior to index date for baseline characterisation
7. History of tobacco smoking
8. Recorded height at adult age (≥21 years) and weight within 5 years of index date
9. ≥1 valid spirometry records after index date before initiation of maintenance therapy

Exclusion criteria:
1. Active asthma at index date or follow-up
2. History of other chronic lower respiratory conditions

Methods

Predicted FEV1 value calculation

- All follow-up FEV_1 values recorded between index date and initiation of maintenance therapy were compared with predicted values.
- Predicted FEV_1 values were calculated conditional on FEV_1 at index date using the following predictors (all variables of the original Zafari model):

  1. Age at index
  2. Sex
  3. Height
  4. Weight
  5. Smoking status throughout the first 5 years

  6. Smoking cessation intervention within 3 months after index date
  7. Short-acting bronchodilator prescription within 3 months after index date

Validation of FEV1 prediction model

- Scatterplots were produced to:
  1. Visualize observed and predicted values of each measurement (**Figure 1**)
  2. Plot differences between observed and predicted values by time since baseline (**Figure 2**)
  3. Plot differences between observed and predicted values against the mean with limits of agreement (range mean difference ±1.96 standard deviation; **Figure 3**)
- Overall root mean squared error (RMSE) of predicted versus observed FEV_1 values was calculated as follows, where e_i is the individual differences between predicted and observed.

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n} e_i^2}$$

- Coverage probability was calculated, defined as proportion of observed FEV_1 values falling within 95% prediction interval.
- Patients identified by the model to be at high risk of rapid decline, defined as patients with ≥75% probability of an average annual decline of 30 and 40 ml/year over 11 years for women and men respectively, were quantified.

Results

Patient population

- 451,518 patients with COPD diagnosis or Read code identified from both databases.
- Following inclusion and exclusion, 8,091 COPD patients were included in analyses.
- A total of 13,725 follow-up FEV_1 values during minimal therapy (no therapy or short-acting bronchodilator only) after baseline spirometry were available
- The median (IQR) number of follow-up FEV1 recordings was 1.0. Median (IQR) time between index and initiation was 1.83 (1.00-3.17) years

Results

Patient Baseline Characteristics

Characteristic		N=8,091
Age (years)	Mean (SD)	65.5 (9.9)
Sex	Male, n (%)	4,530 (56.0)
Weight (kg)	Mean (SD)	75.9 (18.3)
Height (m)	Mean (SD)	1.68 (0.10)
BMI	Mean (SD)	26.9 (5.5)
BMI categorised	Underweight, n (%)	292 (3.6)
	Normal Weight, n (%)	2,952 (36.5)
	Overweight, n (%)	2,781 (34.4)
	Obese, n (%)	2,066 (25.5)
Smoking status at baseline	Ex-smoker, n (%)	3,244 (40.1)
	Current smoker, n (%)	4,224 (52.2)
	Not recorded, n (%)	623 (7.7)
Smoking status up to 5 years of follow-up	Sustained quitter, n (%)	2,161 (26.7)
	Intermittent quitter, n (%)	2,587 (32.0)
	Continuous smoker, n (%)	2,761 (34.1)
	Not recorded, n (%)	582 (7.2)
Smoking cessation intervention first 3 months	Yes, n (%)	2,863 (35.4)
Short-acting bronchodilator prescription first 3 months	Yes, n (%)	4,520 (55.9)

SD=standard deviation; n=number; kg=kilogram; m=metre

Validation results
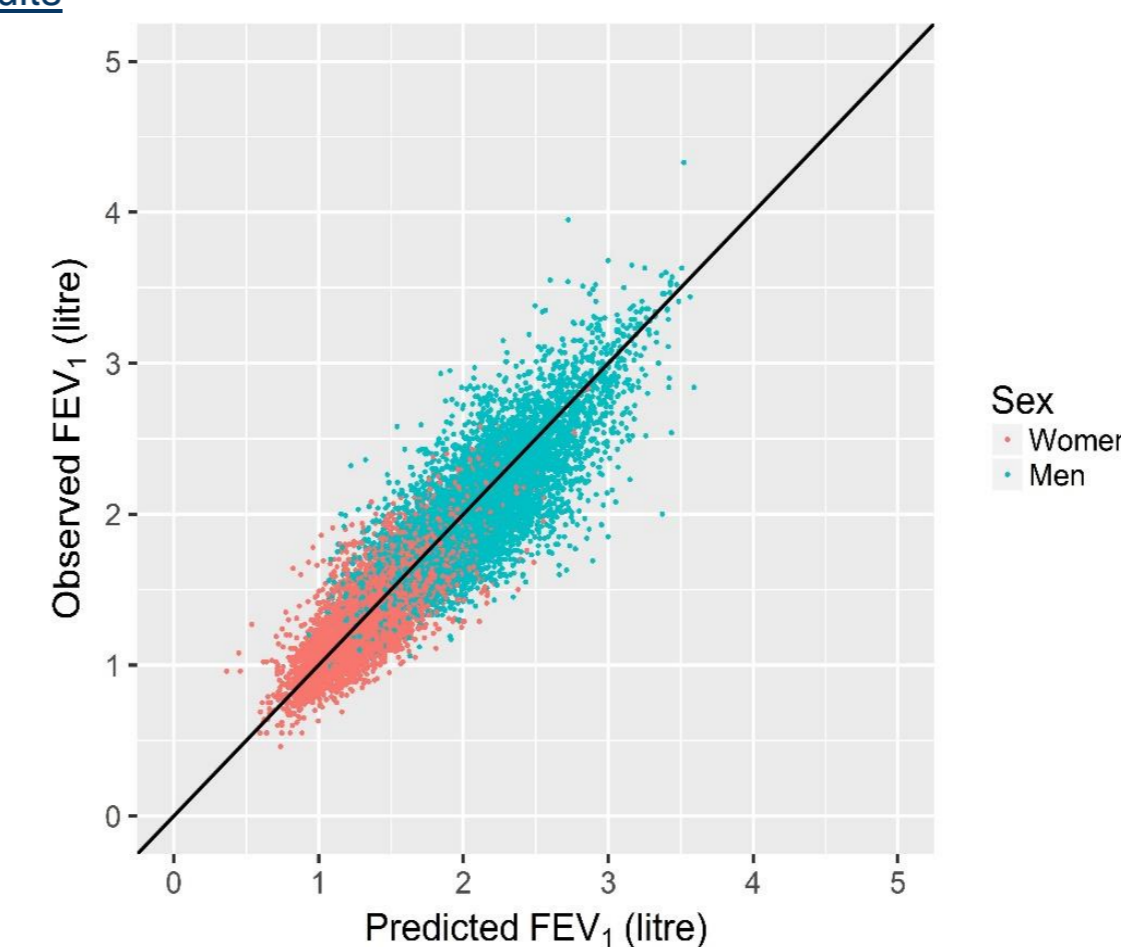
Figure 1. Plot of observed by predicted FEV_1 values

- RMSE was 232 ml for follow-up FEV_1 values. The coverage probability was 90%
- There was no clear evidence of error increasing over time (**Figure 2**)
- Observed values were on average 42 ml lower than predicted values (**Figure 3**)
- A high risk of rapid decline was found in 23% of women and 31% of men of whom 99% and 79% were continuous smokers respectively
- 60% of female and 78% of male continuous smokers had a high risk of rapid decline

Results
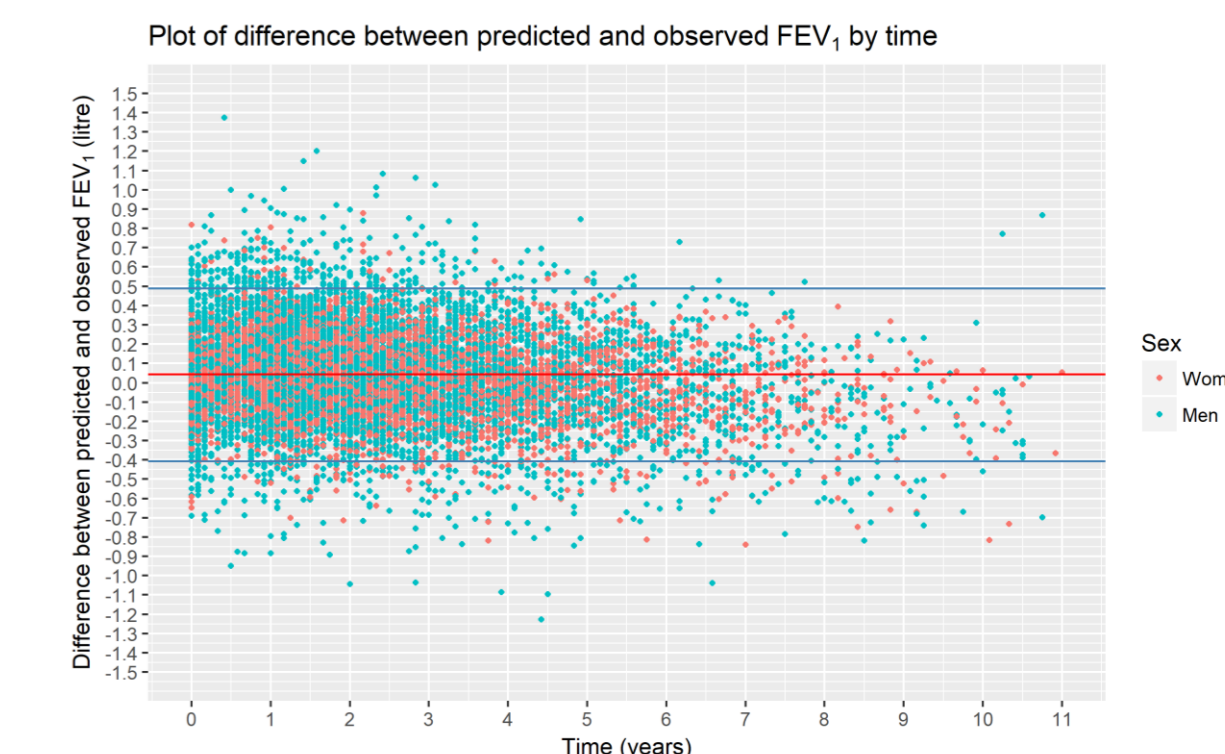
Figure 2. Plot of difference between predicted and observed FEV_1 values by time since baseline spirometry at diagnosis
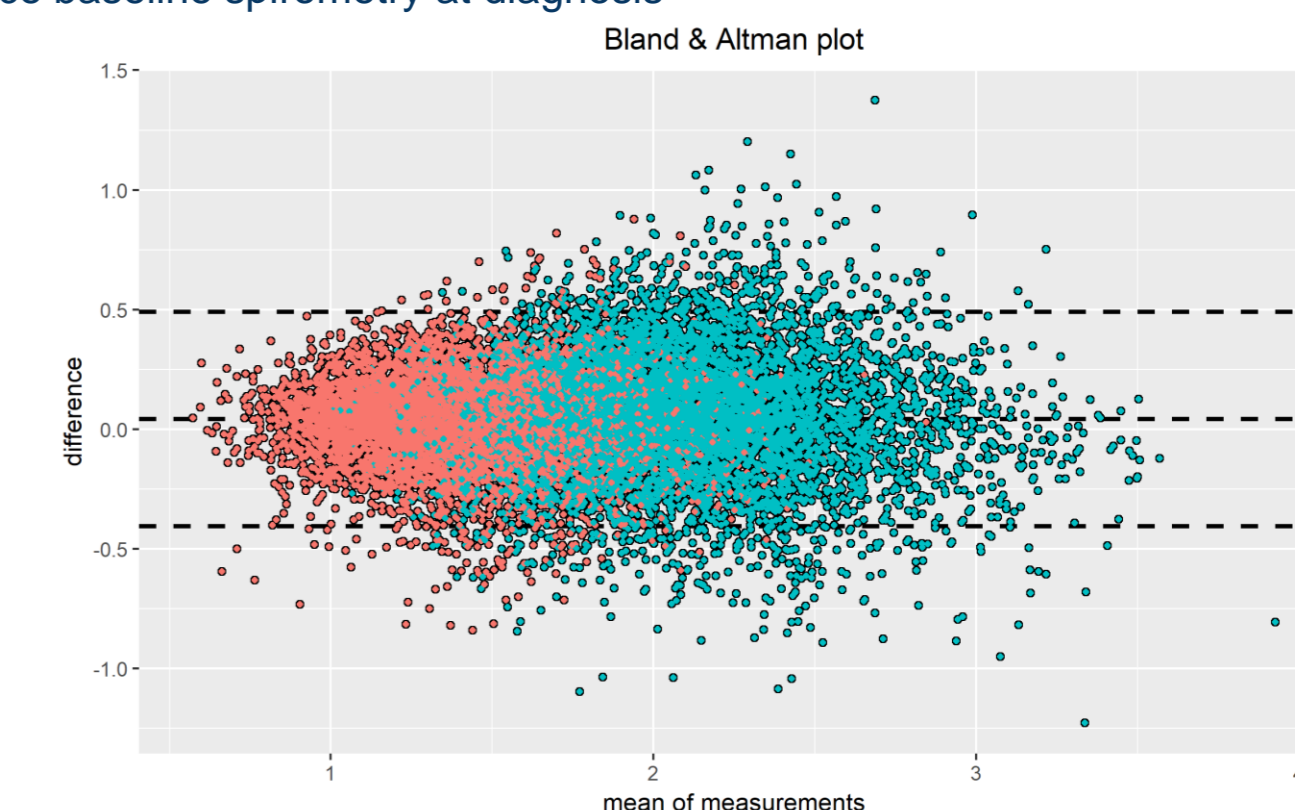
Figure 3. Bland & Altman plot of difference between predicted and observed FEV_1 values by mean of both measurements (litre)

Conclusion

- The Zafari equation predicting future FEV_1 values performed robustly in UK electronic medical data, similar to reported values from the external validation cohort published by Zafari et al.
- When used to identify rapid decliners, the model will predominantly select continuous smokers.
- Current model does not include past exacerbations as a predictor. Further analyses are required to examine the association between lung function deterioration and exacerbation.

References

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2. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med. 2008;178(4):332-338.
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