Using Recursive Logistic Regression to Develop a Patient-Reported Outcome in Non-Cystic Fibrosis Bronchiectasis

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Middlemore Clinical Trials
Future of healthcare

AUT

EMBRACE Trial

This work is an extension to the trial: Wong, C., et al. *Lancet* (2012) vol. 380, pp. 660–7

Articles

Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial

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Lancet 2012; 380: 660–67

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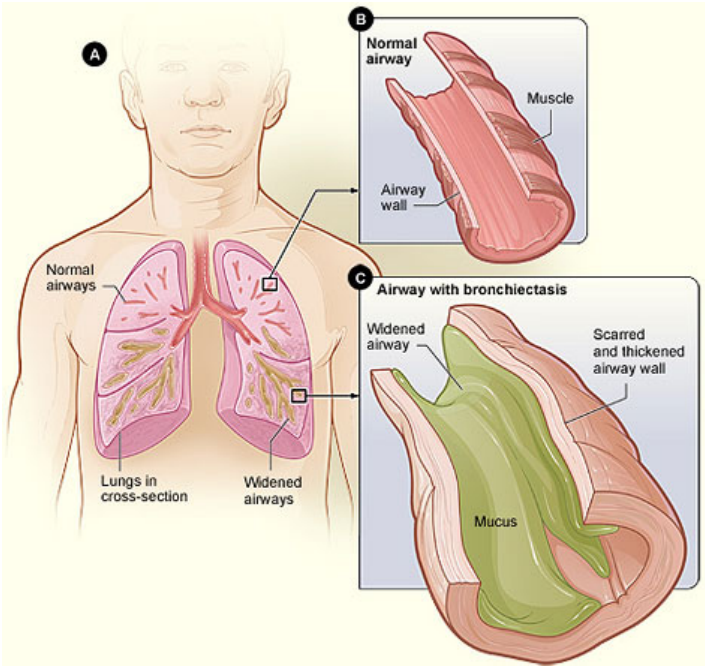
Summary

Background Azithromycin is a macrolide antibiotic with anti-inflammatory and immunomodulatory properties. We tested the hypothesis that azithromycin would decrease the frequency of exacerbations, increase lung function, and improve health-related quality of life in patients with non-cystic fibrosis bronchiectasis.

Methods We undertook a randomised, double-blind, placebo-controlled trial at three centres in New Zealand. Between Feb 12, 2008, and Oct 15, 2009, we enrolled patients who were 18 years or older, had had at least one pulmonary exacerbation requiring antibiotic treatment in the past year, and had a diagnosis of bronchiectasis defined by high-resolution CT scan. We randomly assigned patients to receive 500 mg azithromycin or placebo three times a week for 6 months in a 1:1 ratio, with a permuted block size of six and sequential assignment stratified by centre. Participants, research assistants, and investigators were masked to treatment allocation. The coprimary endpoints were rate of event-based exacerbations in the 6-month treatment period, change in forced expiratory volume in 1 s (FEV_1) before bronchodilation, and change in total score on St George's respiratory questionnaire (SGRQ). Analyses were by intention to treat. This study is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12607000641493.

Findings 71 patients were in the azithromycin group and 70 in the placebo group. The rate of event-based exacerbations was 0·59 per patient in the azithromycin group and 1·57 per patient in the placebo group in the 6-month treatment period (rate ratio 0·38, 95% CI 0·26–0·54; p<0·0001). Prebronchodilator FEV_1 did not change from baseline in the

Bronchiectasis



- Respiratory condition.
- Caused by chronic infection of airways.
- Signs and symptoms:
  - chronic inflammation of airways
  - bacterial infection
  - recurring exacerbations
  - increased mortality.
  - disabling cough
  - production of large quantities of sputum
  - reduced quality of life.

EMBRACE Design

Objectives	Assess the effect of *azithromycin* on health-related quality of life and lung function in patients 18–80 years with bronchiectasis (diagnosed by CT scan).
Design	Multicenter (3), double-blind, placebo-controlled, parallel group (1:1), 141 pts total.
Intervention	500mg azithromycin capsule vs. placebo, 3 days per week, for 6 months.
Follow-up	6 months (treatment period) and 12 months.
1° Endpoints	i) Rate of Event Based Exacerbations (EBEs) over 6 mo. treatment period; ii) Change in St. George's Respiratory Questionnaire (tot. score); (+ *others*).
2° Endpoints	Symptom scores for: sputum purulence, sputum volume, dyspnoea; (+ *others*).

Exacerbations

- Exacerbations and symptom scores recorded prospectively in patient diaries.
- Each patient-day judged *exacerbation* or *no exacerbation*.
- Key symptoms of an exacerbation are
  - Sputum volume
  - Sputum purulence (colour)
  - Dyspnoea (shortness of breath, coughing).
- Two types: Event-based (EBE) and Symptom-based (SBE).

EBE Incidence

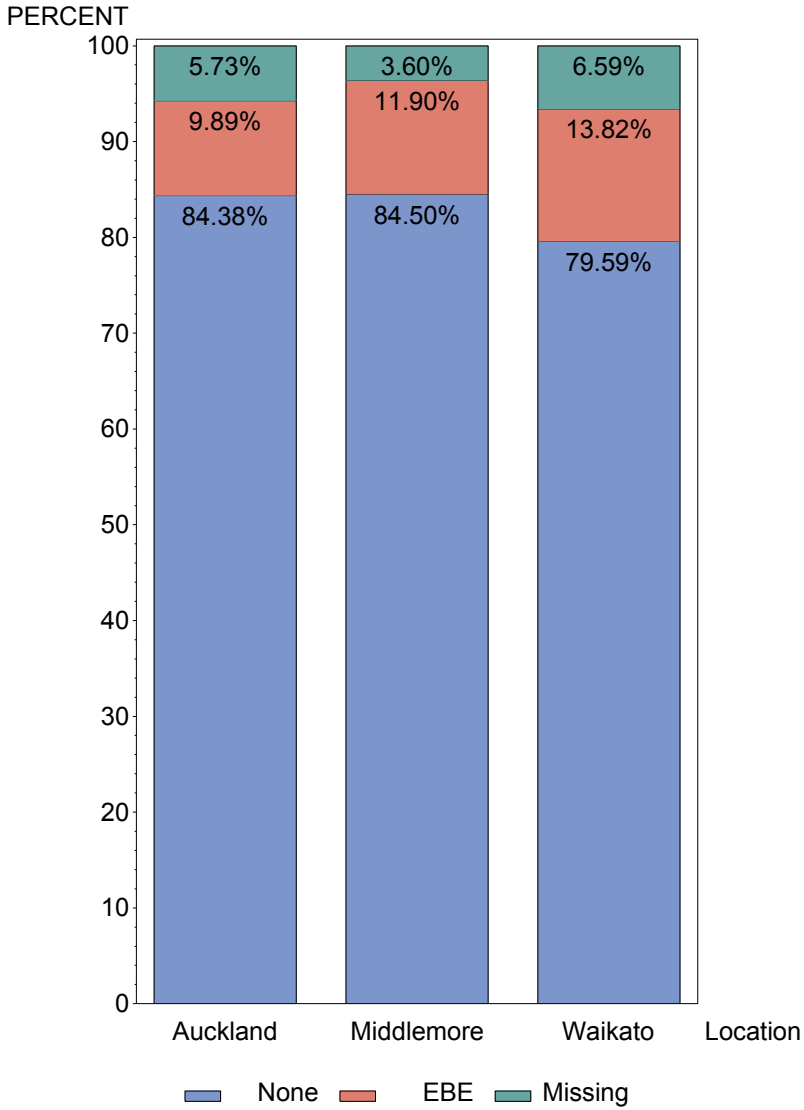


Figure : Diarized days by Event-based exacerbations status for each EMBRACE location, all patient-days.

Exacerbations

EBE is Physician-Determined

- EBEs require treatment with antibiotics.
- Ascertainment of EBE requires contact with clinician.

SBE is Patient-Determined

- SBEs are adjudicated using daily symptom diaries completed by patients.
- Patients have input into evaluation of their own health status.
- This is a patient-reported outcome.

Manually Adjudicated SBEs (manSBEs)

- Adjudication of SBEs originally done by manual review of diaries.
- This was laborious and time-consuming.
- Eventually abandoned.

Goals

Automatically Adjudicate SBEs

- Automatically adjudicate SBEs.
- In the process, revisit the definition $\Rightarrow$ New SBE.

Validate New SBE Against EBE

- Estimate performance of new SBE as a predictor of EBE.
- Assess treatment sensitivity of new SBE.

(Goals II)

Jointly Validate Against Patient-Reported Wellbeing

- Patients also reported their general wellbeing in the diaries.
- Assess, and improve, performance of new SBE as a measure of wellbeing.

Method

Data

- Observed $\sim$ 50 000 patient-days observed on 141 patients across 3 centres over 6 months.
- **Symptoms**: patients rated severity of
  - Sputum purulence, sputum volume, dyspnoea

  on a validated 5-point scale, 0 "no symptom" $\rightarrow$ 4 "very much".
- **Wellbeing**: "I feel well", 1 "strongly agree" $\rightarrow$ 5 "strongly disagree".

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Table : Example data

			Symptoms				
Pat.	Day	EBE	SP	SV	DY	Well B	SBE
1	0	0	1	1	1	1	$\uparrow$
1	1	1	3	3	4	1	$\uparrow$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	Adjudicated
1	17	1	2	1	5	2	$\downarrow$
1	18	0	1	0	0	3	$\downarrow$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\downarrow$

Goal is a Model for Prediction

- Statistical goal is a model to predict a time-ordered, clustered, binary outcome, $\text{EBE}_{i,t}$.
- $\Rightarrow$ propose a model (somehow!).
- Verify it has good predictive power.

Model Selection

- Based on *manSBE* procedure, decided to use symptom scores and EBE at an earlier time-point ($\text{EBE}_{i,t-\delta}$, $0 < \delta$) as explanatory variables.
- Used a GLMM, logit link, with random intercepts for patient.

$$\begin{aligned} \text{EBE}_{i,t} &\sim \text{Bern}\left(p_{i,t}\right) \\ \text{logit}\, p_{i,t} \mid \left(\mathbf{x}, b_i\right) &= \mathbf{x}'_{i,t}\boldsymbol{\beta} + b_i \\ b_i &\sim \text{Normal}(0, \tau^2) \end{aligned}$$

- $\mathbf{x}_{i,t}$ contains symptom scores averaged over two time windows (contemporaneous, earlier), and $\text{EBE}_{i,t-\delta}$:

$$\mathbf{x}'_{i,t} = \begin{bmatrix} 1 & \overline{\text{SV}}_{i,\text{cont.}} & \overline{\text{SP}}_{i,\text{cont.}} & \overline{\text{DY}}_{i,\text{cont.}} \\ & & & \overline{\text{SV}}_{i,\text{earl.}} & \overline{\text{SP}}_{i,\text{earl.}} & \overline{\text{DY}}_{i,\text{earl.}} & \text{EBE}_{i,t-\delta} \end{bmatrix}$$

Model Selection

- Dichotomize using a threshold, c, such that sensitivity $=$ specificity:

$$\text{SBE} \equiv \widehat{\text{EBE}}_{i,t} = \begin{cases} 1 & \text{if } \widehat{p}_{i,t} > c \\ 0 & \text{if } \widehat{p}_{i,t} \leq c \end{cases}$$

Design parameters are: $\mathbf{x}$, δ, c.

$\mathbf{x}$, δ Time windows, averaging method, EBE offset chosen to give good in-sample predictive performance (using AUC). $\delta = 5$

c Two-stage estimation of c.

Model Performance

Two-fold Cross-validation

- Split data into a training set and a hold-out set for validation.
- Randomly select 70 percent of the patients and allocate all their observations to the training set.
- The remainder go into the hold-out set.

Prospective Prediction

- The selected model is **retrospective** in that today's prediction depends on earlier GP-adjudicated EBEs.

$$\text{logit}\, p_{i,t} \mid \left(\text{EBE}_{i,t-5}, \cdot\right) = \mathbf{x}_i'\beta + b_i \tag{1}$$

- We want a **prospective** model based on patient-reported outcomes $\Rightarrow$ must use its own earlier predictions.

$$\text{logit}\, p_{i,t} \mid \left(\widehat{\text{EBE}}_{i,t-5}, \cdot\right) = \mathbf{z}_i'\beta + b_i \tag{2}$$

- (1) is a *recursive logistic* model (Bonney, 1986, 1987).
- To fit (2), a sequential procedure was used.

Sequential Approach

1. Initialize by generating retrospective predictions, $\widehat{\text{EBE}}_{i,1}^{[\text{ret}]}, \ldots,$ $\widehat{\text{EBE}}_{i,5}^{[\text{ret}]}$, using $\widehat{\beta}$ and threshold, $c^{[\text{ret}]}$, from the retrospective model.

Using the training set:

2. Sequentially generate prospective predictions $\widehat{\text{EBE}}_{i,6}^{[\text{pro}]}, \widehat{\text{EBE}}_{i,7}^{[\text{pro}]}, \ldots.$
   - Use "population level" predictions
   - Use $c^{[ret]}$ to threshold the predicted probabilities (we have to because this is the only c currently available).
3. Re-estimate the binary threshold $\rightarrow c^{[pro]}$.

Using the hold-out set:

4. Repeat 2 using $c^{[pro]}$.

Method Overview

1. Build a **retrospective** prediction model for EBE_t using
   - symptom scores
   - GP-adjudicated EBE status at times $t \in [t - \delta, t_0)$.
2. Convert to a "prospective" model for EBE_t using
   - retrospective design
   - patient-report-derived EBE status at times $t \in [t - \delta, t_0)$.
3. Estimate its predictive performance.

Results

Dataset	Model	c (used)	c (Opt.)	Sens. (%)	Spec. (%)
Training	Retro.	0.093	0.093	90	92

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Training	Retro.	0.093	0.093	90	92
	Prosp.	0.093	0.048	76	88
	Prosp.	0.048	0.048	83	83
Hold-out	Prosp.	0.048	—	90	79

- Our prospective SBE predictor,
  - misses 10 percent of the EBEs (1 in 10)
  - calls an EBE 21 percent of time there isn't one (1 in 5).
- Relative to using the whole dataset,
  - Estimated sensitivity equal,
  - Specificity is 86 percent ($\downarrow$ 13 percentage points).

Patient-Reported Wellbeing

- Patients also reported wellbeing each day using a 1–5 scale.

DIARY CARD Subject Initials: ☐ ☐ ☐ Subject No: ☐ ☐ ☐

Study week number: ☐ ☐

Wellbeing I feel well	1 Strongly agree	2 Agree	3 Neither agree nor disagree	4 Disagree	5 Strongly disagree

- Ultimately, we're interested in a patient-reported outcome that is sensitive to both changes in physical state and patient-reported wellbeing.
- How is our new definition of SBE associated with wellbeing?
- Do we get "closer" to wellbeing with SBE rel. to EBE?

Wellbeing and SBE

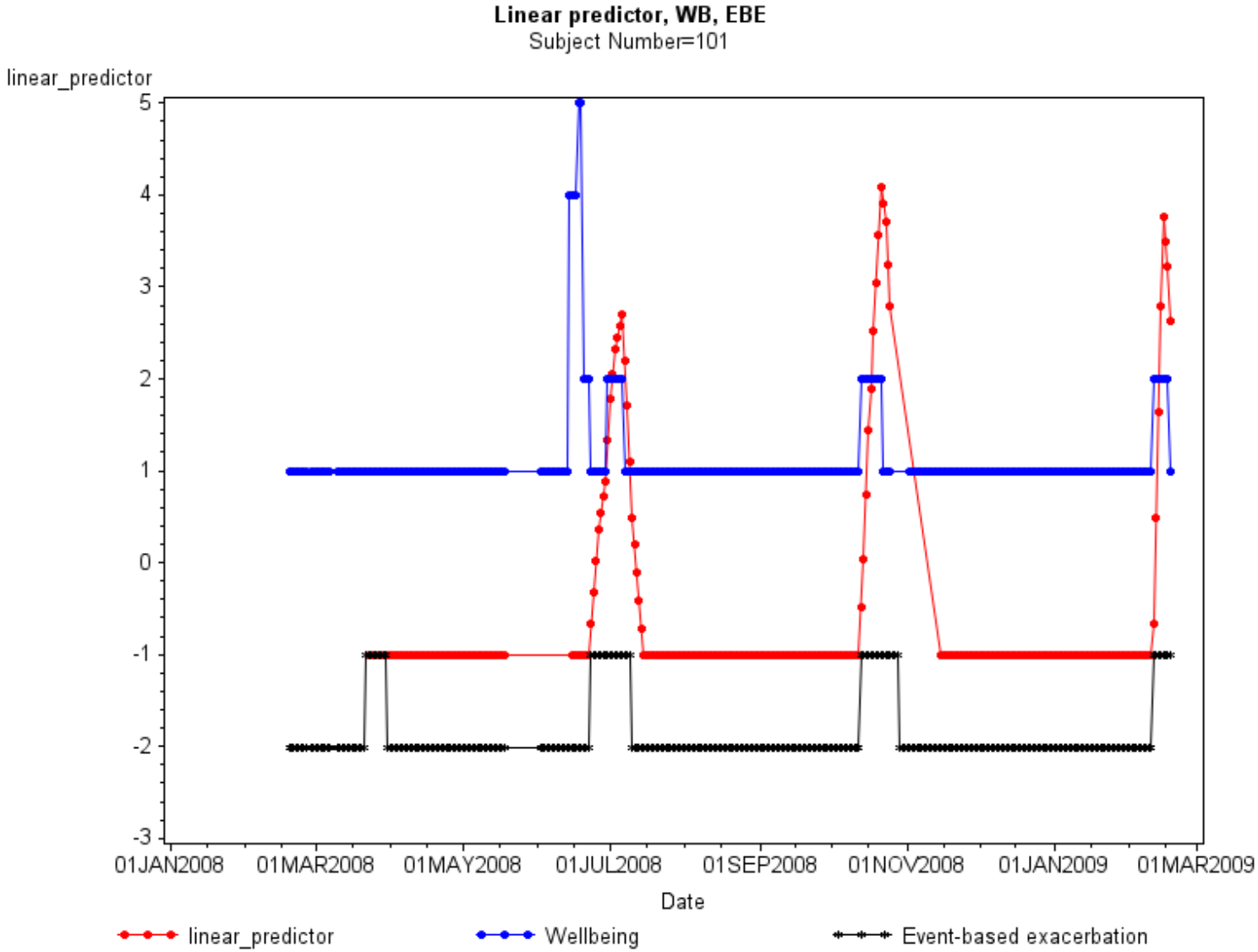

Figure : Wellbeing and SBE linear predictor for patient no. 101.

Wellbeing and SBE

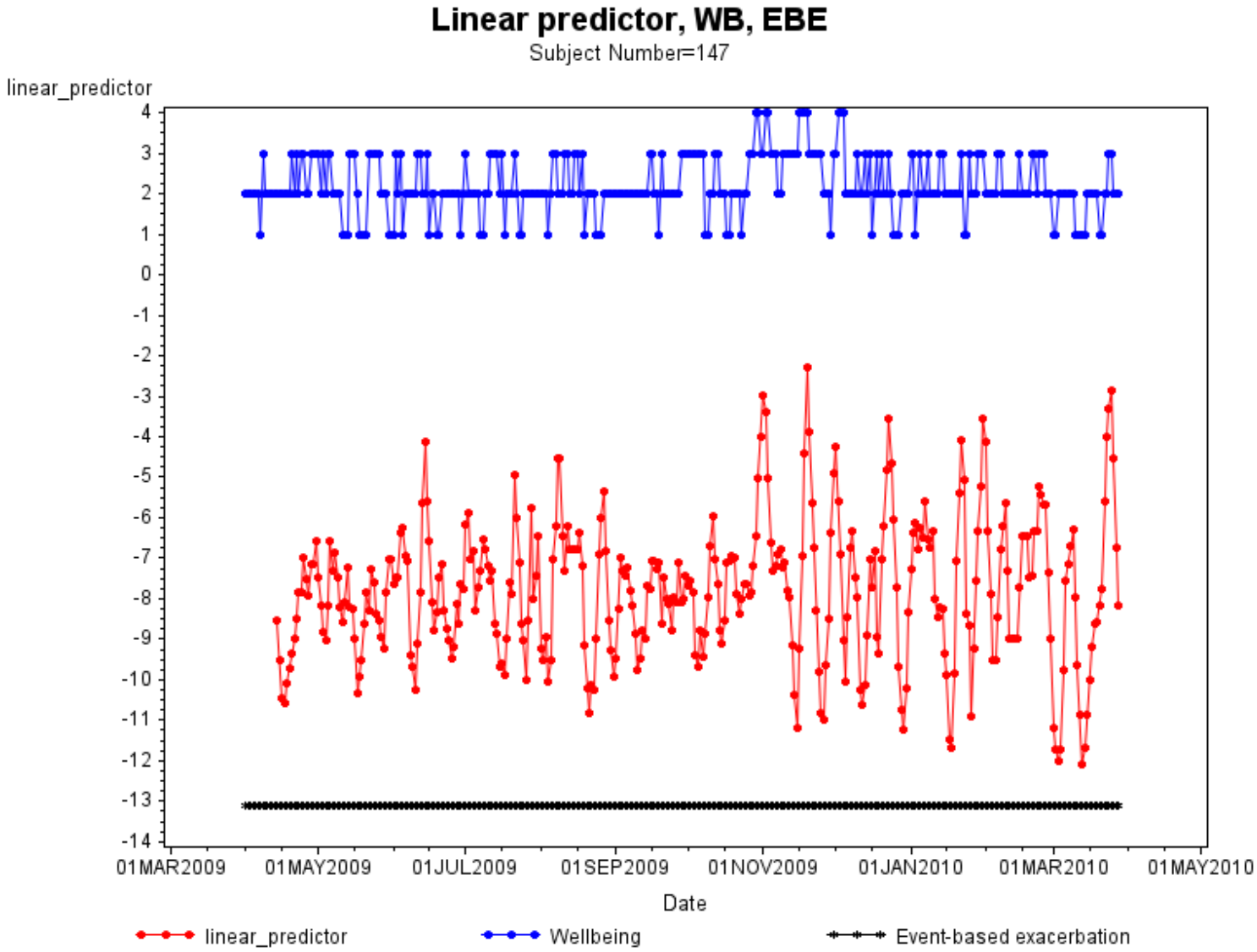

Figure : Wellbeing and SBE linear predictor for patient no. 147.

Wellbeing and SBE

- Weighted Pearson correlation between wellbeing and the linear predictor from the SBE model is $\widehat{\rho} = 0.33$.
- Future: combine the SBE prediction model with a similar one for wellbeing.

Summary

- Exacerbations are an outcome of interest in the study of bronchiectasis.
- Ascertainment of event-based exacerbations (EBEs) requires clinical assessment.
- Symptom-based exacerbations (SBEs) are ascertained from patient-reported symptom scores and exacerbation history, coded "by hand".
- We used logistic regression to develop an "automatic" coding scheme; changes in symptoms that are associated with changes in physical state (EBE).
- As a classifier of EBE the performance was quite good (sens. 90%, spec. 79%).

Bibliography

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