**PROBAST**

Study:

Predicting the risk of exacerbation in patients with chronic obstructive pulmonary disease using home telehealth measurement data.

Step 2: Type of prediction study

**Is the study a diagnostic or a prognostic study?**

Prognostic

**Is the study a development only, development and validation or validation only study?**

Development only

**What is the model of interest?**

CART model

**What is the outcome of interest?**

Predict future AECOPD

Step 3: Assess risk of bias

**Domain 1: Participants**

**Describe the sources of data and criteria for participant selection**

The home telehealth database employed in the development of the algorithm consists of data from twenty-one patients with moderate-to-severe COPD (six males, fifteen females, aged 71 ± 10years (mean ± SD)). Data were acquired between February 2007and January 2008, using a home monitoring unit (TeleMed-Care Health Monitor: TMC-Home, TeleMedCare Pty. Ltd., Sydney, Australia) placed in the patients’ homes. The database was generated from a randomized controlled study comparing standard best practice care (SBPC) with SBPC plus remote monitoring-triggered intervention. Only data collected from the intervention group were used here. The study was conducted within the catchment area of Austin Hospital in the state of Victoria, Australia. The participant inclusion criteria were: (i) English fluency; (ii) finger dexterity to use a keyboard and mouse; (iii) willingness to use a computer in health self-management; (iv) living independently; (v) no major motor deficit that could prevent use of the home monitoring device;(vi) able to give informed consent; (vii) confirmed moderate/severe COPD; and, (viii) at least one hospital presentation in the last 12months. Exclusion criteria were: (i) significant co-morbidities (e.g.,cancer, renal failure); (ii) documented cognitive impairment; and,(iii) participation in another trial

**1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?**

Y

**1.2 Were all inclusions and exclusions of participants appropriate?**

Y

**Risk of bias introduced by selection of participants:**

Low

**Rationale of bias rating**

Only patients from intervention group used so all patients are comparable. Reasonable eligibility criteria

**Domain 2: Predictors**

**List and describe predictors included in the final model, e.g. definition and timing of assessment**

Each patient was asked to complete physiological measurements and questionnaires on a daily basis using the TMC-Home device, i.e., to measure blood pressure, lung function, pulse oximetry, body temperature and body weight. The questionnaire delivered by the TMC-Home device queried the patients on their respiratory symptoms and general feeling of wellbeing. Moreover, medication information relating to patient respiratory management was recorded in order to acquire a history of medication changes throughout the monitoring period.

**2.1 Were predictors defined and assessed in a similar way for all participants?**

Y

**2.2 Were predictor assessments made without knowledge of outcome data?**

Y

**2.3 Are all predictors available at the time the model intended to be used?**

Y

**Risk of bias introduced by predictors or their assessment**

Low

**Rationale of bias rating**

Predictors are assessed the same way and are all applicable

**Domain 3: Outcome**

**Describe the outcome, how it was defined and determined, and the time interval between predictor assessment and outcome determination:**

The reference standard development was adapted from the definition of COPD exacerbation provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document and literature [14,15]. In the symptom questionnaires, patients were asked if there had been any changes in their symptoms, namely: increase in sputum amount; change in sputum colour or consistency; or, worsening breathlessness. Similarly, in thedaily medication questionnaires, patients were asked if they had increased their dosage, or had started the use of a respiratory medication on that day. Examples of the questions asked are shown in Appendix A. Worsening in any one of the symptoms that warranted an increased dosage, or initiating the usage of a respiratory med-ication, indicated that the patient may have undergone anexacerbation episode on that particular day [14,16]. The threesymptoms used below in the definition of risk of exacerbation for this study are:

• an increase in sputum volume;

• an increase in breathlessness; and,

• a darkening in sputum colour.

Henceforth, one of two categorization labels (high risk or low risk of developing an exacerbation) was assigned to the patient’s health condition on each day for which there was a documented worsening in their health condition, based on the rules below. Patients were categorized as being at a high risk of exacerbation if:(i) they had any two of the three symptoms, and had started oral corticosteroids and/or antibiotics on the same day, and this day was not within two weeks of the previous exacerbation,or,(ii) they had any one of the three symptoms, and had increased their rescue inhaler use on the same day, and this day was not within two weeks of the previous high risk of exacerbation. Otherwise, patients were categorized as low risk of exacerbation f they had only one of the three symptoms, and:(i) this symptom was occurring for the first time, or,(ii) this symptom occurred within two weeks after the patient was previously defined as being at high risk of exacerbation, or,(iii) this symptom occurred within two weeks after a worsening of the same symptom.

**3.1 Was the outcome determined appropriately?**

Y

**3.2 Was a pre-specified or standard outcome definition used?**

Y

**3.3 Were predictors excluded from the outcome definition?**

Y

**3.4 Was the outcome defined and determined in a similar way for all participants?**

Y

**3.5 Was the outcome determined without knowledge of predictor information?**

Y

**3.6 Was the time interval between predictor assessment and outcome determination appropriate?**

Y

**Risk of bias introduced by the outcome or its determination**

Low

**Rationale of bias rating**

Outcome is defined based on clinically validated standard for COPD exacerbation and applied consistently. Due to future predictions outcome is independent of predictors.

**Domain 4: Analysis**

**Describe number of participants, number of candidate predictors, outcome events and events per candidate predictor**

Twenty-one subjects were enrolled in the trial for a combined total of 6542 days. They performed at least one type of measurement for 4641 days and answered questionnaires for 4230 days. 1211 out of 4230 days were determined to show a worsening in symptoms concomitant with changes in respiratory medication records. Of these 1211 records, 215 days of measurement data were deemed to contain outliers and were thus excluded from the analysis, leaving a total of 996 useable training days/instances. Based on the health status reference standard, patients were labelled as having a high risk of exacerbation for 90 days out of 996 and patients were labelled as having low risk for 112 days; giving a total of 202 labelled days

**Describe how the model was developed, predictor selection and risk group definition**

CART model

Multivariate classification

**Describe whether and how the model was validated, either internally (cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, different type of participants)**

Once the tree has been constructed, its performance is evaluated using leave-one-out cross validation (LOOCV). The cross validation process, used to estimate the expected generalized classification performance, is described as follows. Using data from twenty sub-jects (from the twenty-one available subjects), the CART is trained. The data from the remaining subject is later introduced for testing. This is repeated twenty-one times.

**Describe the performance measures of the model, e.g. calibration, discrimination, classification, net benefit, and whether they were adjusted for optimism**

ACC, SPE, SEN, PRE, REC, Cohens kappa

**Describe any participants who were excluded from the analysis**

None

**Describe missing data on predictors and outcomes as well as methods used for missing data**

Firstly, some of the features in the dataset obtained from the home telehealth database were missing, as patients only recorded approximately 71% (4641 out of 6542 days)of their scheduled physiological measurements (cf., Table 1). Currently, this problem is overcome by labelling the missing feature as unknown. The CART classifier is capable of handling missing values[31], but the incompleteness of the data and labelling can lead to poorer prediction accuracy.

**4.1 Were there a reasonable number of participants with the outcome?**

PY

**4.2 Were continuous and categorical predictors handled appropriately?**

Y

**4.3 Were all enrolled participants included in the analysis?**

Y

**4.4 Were participants with missing data handled appropriately?**

Y

**4.5 Was selection of predictors based on univariable analysis avoided?**

Y

**4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls)**

**accounted for appropriately?**

Y

**4.7 Were relevant model performance measures evaluated appropriately?**

Y

**4.8 Were model overfitting and optimism in model performance accounted for?**

Y

**4.9 Do predictors and their assigned weights in the final model correspond to the results**

**from multivariable analysis?**

Y

**Risk of bias introduced by the analysis**

Low

**Rationale of bias rating**

Reasonable amount of outcomes and proper handling of missing data. No exclusion of

**Overall Risk of bias**

Low