**PROBAST**

Study:

Prediction of Asthma Exacerbations in Children by Innovative Exhaled Inflammatory Markers: Results of a Longitudinal Study

Step 2: Type of prediction study

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

Diagnostic

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

Development only

**What is the model of interest?**

**What is the outcome of interest?**

Asthma exacerbations

Step 3: Assess risk of bias

**Domain 1: Participants**

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

Children between 6 and 18 years old with doctor-diagnosed asthma were recruited for this one year observational cohort study (clinicaltrial.gov NCT 01239238). All children had been treated for asthma at the outpatient clinic of 2 specialized pediatric pulmonology centers for at least 6months and used inhaled corticosteroids during the year preceding the study. Asthma was defined by the criteria of the Global Initiative for Asthma (GINA) and the guideline of the Dutch Society of Pediatrics as: 1) presence of asthma symptoms and use of ICS during the year pre-ceding the study [2, 4]; 2) reversibility to a β2-agonist defined as an increase in FEV1 of 9% of predicted value [4, 14], as described before [9]; and/or 3) presence of bronchial hyperresponsiveness (defined as a >20% drop in FEV1 after the inhalation of histamine with a concentration 8 mg/ml) [4].

Exclusion criteria were: 1) technical unsatisfactory performance of lung function measurements, 2) presence of cardiac abnormalities, 3) mental retardation, 4) congenital abnormalities or existence of a syndrome, 5) active smoking, or 6) treatment with immunotherapy during the study.

**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?**

PN

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

High

**Rationale of bias rating**

Asthma patients with unsatisfactory performance of lung function measurements excluded ( as well as smoking and various other conditions). This limits generalizability of results to other asthma patients.

**Domain 2: Predictors**

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

The lung function measurements consisted of 3 maneuvers with maximal effort to achieve FEV1. The highest FEV1 value of each day was selected for each patient

Exhaled breath condensate

Fractional nitric oxide

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

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

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

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

**Rationale of bias rating**

**Domain 3: Outcome**

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

**3.1 Was the outcome determined appropriately?**

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

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

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

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

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

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

**Rationale of bias rating**

**Domain 4: Analysis**

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

96 children. 48% of all 94 children experienced 1or more exacerbations during the study. Of all exacerba-tions 5 were severe in 5 children and 72 exacerbations were moderate.

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

**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)**

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

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

During the study 13 children dropped out. Of these children, 2 were excluded from the statistical models because these children were only present during the first clinical visit and it was unknown whether they experienced an exacerbation in the following 2 months

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

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

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

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

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

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

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

**accounted for appropriately?**

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

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

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

**from multivariable analysis?**

**Risk of bias introduced by the analysis**

**Rationale of bias rating**

**Overall Risk of bias**