**PROBAST**

Study:

Prediction of Nocturnal Hypoglycemia in Adults with Type 1 Diabetes under Multiple Daily Injections Using Continuous Glucose Monitoring and Physical Activity Monitor

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?**

SVM

**What is the outcome of interest?**

Hypoglycemia detection

Step 3: Assess risk of bias

**Domain 1: Participants**

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

Patients enrolled in the study met the following inclusion criteria: aged > 18 years, with T1D for at least 5 years, treated with multiple doses of insulin (MDI), using a rapid acting insulin analogue such as prandial insulin and a basal insulin analogue, with HbA1c within 6.5% and 9.5%, practicing carbohydrate (CH) counting, able to understand and follow the instructions of the study including the use of an intermittently scanned continuous glucose monitoring (CGM)system and to perform > 4 self-monitoring blood glucose measurements (SMBG) per day. In addition, they fulfilled the following: >4 hypoglycemia/week (<3.9 mmol/l (70 mg/dl), including day and night), in the last 2 weeks and/or one severe hypoglycemia (needing third party assistance) during the last year and/or impaired awareness hypoglycemia (IAH, Clarke Test > 3). Exclusion criteria included: serious illness that may impair study participation, pregnancy or breastfeeding, history of drug use or alcohol abuse, and the use of an experimental drug or device during the past 30 days.

**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?**

N

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

High

**Rationale of bias rating**

There are a lot of different inclusion and exclusion criteria. Combined they limit the generalizability of the findings from this study population. Particularly limiting are >18, the intensive management requirements, the hypoglycemia history and the use of specific insulin devices.

**Domain 2: Predictors**

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

During this period, every patient used the CGM FreeStyle Libre (FSL) system (Abbott Diabetes Care, Alameda, CA, USA) to monitor interstitial glucose concentration and the Fitbit Alta HR wristband (Fitbit, Inc., San Francisco, CA,USA) to obtain the data related with physical activity and sleeping periods.

Patients were instructed to manually enter the information of every insulin dose (rapid-acting and long-acting),as well as the estimation of CH content for every meal consumed during the study, into the reader device.

**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 applicable and independent

**Domain 3: Outcome**

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

Class labeling was performed 6 h after the beginning of sleep considering the following: if any interstitial glucose concentration reading was lower than3.9 mmol/l (70 mg/dl), it was considered an event. Such an instance was labeled as Class 1 (night with hypoglycemia). Otherwise, Class 0 (night without hypoglycemia) was assigned.

**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**

Independent outcome. Objective labeling based on CGM value.

**Domain 4: Analysis**

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

A total of ten subjects were enrolled to participate in the study

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

Personalized predictive models were generated using two supervised ML algorithms which have been widely applied in supervised learning: multilayer perceptron networks (MLP) [34] and support vector machines (SVM).

An exhaustive feature selection method was applied and 2048 feature vectors were evaluated. For each combination of features, stratified random sampling was performed, and thus the balance was maintained between classes

**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)**

Later, k-fold cross validation (k = 5) was conducted, and the results for that iteration were obtained.

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

SEN, SPE, ACC, GMean

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

None. All subjects completed the study.

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

The imputation of missing data was performed in a straightforward way: any gap in interstitial glucose concentration data lower or equal to 120 min was imputed through linear interpolation. In cases of gaps larger than120 min, no imputation was performed.

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

Y

**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?**

U

**Risk of bias introduced by the analysis**

Low

**Rationale of bias rating**

Good amount of outcomes. Proper handling of missing data and all participants included in analysis.

**Overall Risk of bias**

Low