European Journal of Internal Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Derivation and validation model for hospital hypoglycemia

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ARTICLE INFO

Article history:
Received 27 December 2016
Received in revised form 26 August 2017
Accepted 27 August 2017
Available online xxxx

Keywords:
Hypoglycemia
Hospital
Prediction rule
Diabetes mellitus

ABSTRACT

Background: An objective and simple prognostic model for hospitalized patients with hypoglycemia could be helpful in guiding initial intensity of treatment.
Methods: We carried out a derivation rule for hypoglycemia using data from a nationwide retrospective cohort study of patients with diabetes or hyperglycemia carried out in 2014 (n = 839 patients). The rule for hypoglycemia was validated using a second data set from a nationwide retrospective cohort study carried out in 2016 (n = 561 patients). We derived our prediction rule using logistic regression with hypoglycemia (glucose less than 70 mg/dL) as the primary outcome.
Results: The incidence of hypoglycemia in the derivation cohort was 10.3%. Patient's characteristics independently associated with hypoglycemia included episodes of hypoglycemia during the previous three months (odds ratio [OR]: 6.29, 95% confidence interval [95%CI]: 3.37–11.79, $p < 0.001$) estimated glomerular filtration rate lower than 30 mL/min/1.73 m^2 (OR: 2.32, 95%CI: 1.23–4.35, $p = 0.009$), daily insulin dose greater than 0.3 units per Kg (OR: 1.74, 95%CI: 1.06–2.85, $p = 0.028$), and days of hospitalization (OR: 1.03, 95%CI: 1.01–1.04, $p = 0.001$). The model showed an area under the curve (AUC): 0.72 (95%CI: 0.66–0.78, $p < 0.001$). The AUC in the validation cohort was: 0.71 (95%CI: 0.63–0.79, $p < 0.001$).
Conclusions: The rule showed fair accuracy to predict hypoglycemia. Implementation of the rule into computer systems could be used in guiding initial insulin therapy.

1. Introduction

Hypoglycemia is a common complication in type 1 and type 2 diabetes [1]. Patients suffering from hypoglycemia very often require acute management by relatives, healthcare personnel or physicians at emergency departments [2]. Most patients with hypoglycemia attending emergency departments are discharged after treatment; however, approximately 30% require hospital admission. Patients suffering from hypoglycemia in the hospital have longer length of stay and mortality than control population [3]. Characteristically hypoglycemia appears in frail elderly patients, with long duration of diabetes disease and with number of comorbidities [3]. Recent studies showed the association between hypoglycemia with angina, myocardial infarction and acute cerebrovascular events, which results in an increased risk of cardiovascular disease and all-cause mortality [4–6]. The association between hypoglycemia and increased risk of mortality in an intensive care unit and general ward settings has also been demonstrated [7–9].

Guidelines have established recommendations for blood glucose monitoring, preferred insulin regimens and glycemic goals within the hospital setting. Current standard of care recommends random glucose target less than 180 mg/dL and a premeal target less than 140 mg/dL in medical and surgical hospitalized patients [10,11]. Nevertheless, clinical judgment combined with ongoing evaluation of patients´ clinical condition, including concomitant medications, nutritional status, severity of illness and underlying diseases should be considered when deciding insulin doses and glucose targets. Several ambulatory studies in patients

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http://dx.doi.org/10.1016/j.ejim.2017.08.024
0953-6205/

with diabetes have shown increased risk of hypoglycemia among those with older age, chronic kidney disease, congestive heart failure, cardiovascular disease, depression, higher A1C levels, and in users of insulin, sulfonylureas, or beta-blockers [11–13]. Few studies; however have reported on predictors and risk factors for hypoglycemia in hospitalized patients with diabetes. An accurate, objective, and simple clinical prediction rule may be helpful in guiding initial intensity of hyperglycemia treatment on admission. It is clear that individualization of care is necessary when initiating insulin therapy in hospitalized patients; in one hand, patients with estimated low risk of hypoglycemia can be managed with intensive control as suggested by published guidelines [9], whereas patients at high risk of hypoglycemia may be benefit from a less intensive therapy and less stringent glucose targets. We report a practical clinical prediction rule for hospitalized patients with hypoglycemia that relies on standard clinical parameters to tailor insulin therapy during the hospital stay.

2. Methods

2.1. Patient identification and eligibility

We identified patients with inpatient hypoglycemia from a nationwide cohort study carried out in 111 hospitals in 2014 [14]. We included patients older than 15 years admitted to internal medicine departments with hyperglycemia (glucose values above 140 mg/dL) or known diabetes between June 23rd and July 8th, 2014 who were followed-up during the hospital stay.

2.2. Baseline predictor variables and outcome measures

To derive our prediction rule, we used clinical variables routinely available on admission that have been associated with hypoglycemia in previous studies. These variables included age, gender, most recent HbA1c value, estimated glomerular filtration rate by MDRD4 (Modification of Diet in Renal Disease), presence of cognitive impairment assessed by global deterioration scale, history of cardiovascular disease, previous hypoglycemia episodes in the last 3 months, insulin regimen, daily insulin dose, and length of hospitalization. The study outcome used to derive our prediction rule was the development of hypoglycemia during hospitalization. We defined hypoglycemia as a glucose concentration less than 70 mg/dL, either in the presence or absence of hypoglycemia symptoms [15]. Severe hypoglycemia was defined as a glucose concentration below 50 mg/dL.

2.3. Derivation of the prediction rule

We derived our prediction rule using stepwise logistic regression, with hypoglycemia during hospitalization as the primary outcome, and the demographic and clinical variables previously reported as predictors. On the basis of the beta-coefficients of the model, we generated a point score that divided patients into different risk classes.

2.4. Validation of the prediction rule

To validate the prediction rule we used the data of patients participating in a nationwide cohort study carried out two years later, between June 27th and July 3rd, 2016. A total of 86 hospitals and 561 patients participated in the validation cohort. We included patients who met the same criteria described in the derivation cohort to obtain clinical and laboratory variables.

2.5. Statistical analyses

Descriptive statistics are presented using mean and standard deviations for continuous variables and count and percentages for categorical variables. The Chi-squared test was used for comparison of categorical variables and the Student's *t*-test was used for comparison of continuous variables between groups. A p-value of <0.05 was considered statistically significant. Logistic regression analysis was used with the derivation sample to estimate the probability of hypoglycemia (no interactions were tested). To build the derivation model of hypoglycemia we tested those variables with a p-value < 0.10 obtained in the univariate analysis. Odds ratios (ORs) and their 95% confidence intervals (95%CI) were derived from the coefficients. A number of models were built and the most parsimonious and explicative model, based on the Hosmer and Lemeshow goodness of fitness test, was selected for evaluation in the validation cohort. The R squared of Nagelkerke was used to estimate the proportion of variation explained by the model. The diagnostic performance of the final model was assessed by constructing receiver operating characteristic (ROC) curve and evaluated by calculating the area under the ROC curve (AUC). Finally, on the basis of the beta-coefficients of the model, we generated a point score that divided patients into different risk classes for hypoglycemia. Statistical analysis was performed using SPSS (Version 24.0. Armonk, NY: IBM Corp).

3. Results

3.1. Patient characteristics in derivation and validation cohorts

Patients in the derivation cohort (n = 839) were slightly younger, with lower prevalence of established cardiovascular disease and comorbid illnesses defined by the Charlson score as well as better glucose control than patients in the validation cohort (n = 561) (Table 1).

In the derivation cohort a total of 100 (12.25%) patients suffered from hypoglycemia whereas in the validation cohort there were 50 (9.94%) patients with hypoglycemia (0.85 vs. 0.81 episodes per 100 patient-days, p = 0.74). Severe hypoglycemia (capillary glucose < 50 mg/dL) was observed in 24 patients in the derivation cohort and in 14 patients in the validation cohort (incidence 0.23 vs. 0.22 episodes per 100 patient-days, p = 0.91).

3.2. Derivation of the prediction rule

We carried out a univariate analysis to determine the variables associated with development of hypoglycemia during hospital admission (Table 2). Significant variables included eGRF, cognitive impairment, treatment with oral antihyperglycemic drugs during hospitalization, treatment with sulfonylureas, insulin regimen and daily insulin dose, history of hypoglycemia during the previous three months, hypoglycemia on admission, Charlson comorbidity index, recent hospitalization during the previous three months, and length of stay. Several logistic regression models were built with variable combinations to finally select the most simple and explanatory of them.

The final model identified 4 independent variables associated with hypoglycemia: eGFR less than 30 mL/min/1.73 m^2, insulin dose greater than 0.3 units/Kg/day, length of stay, and a previous episode of hypoglycemia during the three-month before admission (Table 3). The p-value of the Hosmer-Lemeshow goodness-of-fit statistic with 3 degrees of freedom is 0.901. The R square of Nagelkerke was 0.133.

The model showed an area under ROC of 0.72 (95%CI: 0.66–0.78; $p < 0.001$) (Fig. 1). The performance of the model for a probability greater than 0.15 of suffering from hypoglycemia during hospitalization had a sensitivity of 40.2%, and a specificity of 87.2%. The proportion of true results (both true positive and true negative) among the total number of cases examined was 81.7%.

A scoring system based on the estimated β coefficients of the regression model was used to quantify the magnitude of the association of each of these 4 factors with hypoglycemia. A total point score for a given patient is obtained by summing the points for each applicable characteristic and summing the patient's length of hospitalization in days. This scoring system allowed estimate the probability of hypoglycemia in day 1 of hospitalization: less than 10 points (6%); 10 points

Please cite this article as: Ena J, et al, Derivation and validation model for hospital hypoglycemia, Eur J Intern Med (2017), http://dx.doi.org/10.1016/j.ejim.2017.08.024