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Original Research

Derivation and Validation of a Risk-Prediction Tool for Hypoglycemia in Hospitalized Adults With Diabetes: The Hypoglycemia During Hospitalization (HyDHo) Score

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Key Messages

- Many patients on medical inpatient units do not experience hypoglycemia during their hospitalizations, so they may not require intensive glucose monitoring.
- A risk-prediction model using 5 key clinical variables can predict hypoglycemia risk at the time of admission.

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ABSTRACT

Objectives: We sought to develop the Hypoglycemia During Hospitalization (HyDHo) scoring system, to predict the risk for hypoglycemia during hospitalization in patients with diabetes at the time of admission to a general medical unit.
Methods: We randomly selected 300 patients with diabetes who had been admitted to a medical inpatient unit at a teaching hospital. Hypoglycemia was defined as any point-of-care glucose test result $\leq$3.9 mmol/L. Demographic and clinical predictors of hypoglycemia were identified through review of the hospitalization record. Bivariate associations between each predictor variable and hypoglycemia were used to choose variables for a logistic regression model. Model coefficients were converted into an integer points score. The selected model was applied to a validation dataset from 300 similar randomly selected patients admitted to a different teaching hospital.
Results: In the derivation cohort, 72 (25%) patients experienced hypoglycemia during their hospitalizations. The final selected model included 5 variables: age, emergency department visit 6 months prior, insulin use, use of oral agents that do not induce hypoglycemia, and severe chronic kidney disease. With a score of $\geq$9, sensitivity was 86% and specificity was 32%. The model had adequate discrimination and good calibration in the validation cohort.
Conclusions: A parsimonious risk prediction model that uses 5 key clinical variables predicts hypoglycemia during hospitalization at the time of admission. More than one-quarter of patients at low risk for hypoglycemia had scores below the threshold. They could be identified at the time of admission by applying the HyDHo scoring system and may need less intensive glucose monitoring while in hospital.

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RÉSUMÉ

Objectifs : Nous avons cherché à établir le score Hypoglycemia During Hospitalization (HyDHo) pour prédire le risque d'hypoglycémie durant l'hospitalisation chez les patients diabétiques lors de l'admission dans une unité de médecine générale.
Méthodes : Nous avons sélectionné de manière aléatoire 300 patients diabétiques admis dans une unité d'hospitalisation de médecine d'un hôpital d'enseignement. Nous avons défini l'hypoglycémie comme suit : tout résultat de dosage du glucose hors laboratoire ≤3,9 mmol/l. Nous avons déterminé les prédicteurs démographiques et cliniques de l'hypoglycémie par la revue des dossiers d'hospitalisation. Nous avons utilisé les associations bivariées entre chacune des variables de prédiction et l'hypoglycémie pour choisir les variables d'un modèle de régression logistique. Nous avons converti les coefficients des modèles en un score de points entiers. Nous avons appliqué le modèle sélectionné à un ensemble de données de validation de 300 patients similaires sélectionnés de manière aléatoire qui avaient été admis dans un hôpital d'enseignement différent.
Résultats : Dans la cohorte de dérivation, 72 (25 %) patients ont manifesté une hypoglycémie durant leur hospitalisation. Le modèle final sélectionné regroupait 5 variables : l'âge, les visites au service des urgences dans les 6 mois précédents, l'utilisation de l'insuline, l'utilisation par voie orale de médicaments qui ne provoquent pas l'hypoglycémie, et la maladie rénale chronique grave. Un score de ≥9 indiquait une sensibilité de 86 % et une spécificité de 32 %. Le modèle montrait une capacité discriminante adéquate et une bonne calibration dans la cohorte de validation.
Conclusions : Un modèle parcimonieux de prédiction du risque qui utilise 5 variables cliniques prédit au moment de l'admission une hypoglycémie durant l'hospitalisation. Plus d'un quart des patients exposés à un risque faible d'hypoglycémie avaient des scores en dessous du seuil. En appliquant le score HyDHo, les patients pourraient être identifiés au moment de l'admission et auraient besoin de moins de surveillance du glucose en continu au cours de leur séjour à l'hôpital.

Introduction

Hypoglycemia is common in hospitalized patients with diabetes and is documented in 12% to 26% of patients admitted to general medical wards (1–3). Several studies have shown that patients who experience hypoglycemia in hospital have longer lengths of stay and an increased likelihood of mortality, both during their admission and after they have been discharged (4–8). Even after adjustment for age and comorbidities, hypoglycemia increased the risk of death 2- to 3-fold (8), and 1-year mortality was increased by 66% for each day that involved a hypoglycemic episode (9). Clinical practice guidelines recommend higher glycemic targets for inpatients than in usual outpatient care because management during acute illness can be challenging, because evidence suggests that extremely tight glycemic control may not benefit all inpatients, and because tight targets require careful monitoring of blood glucose levels (10–12). However, more than a quarter of patients with diabetes maintain entirely normal glucose levels throughout their hospitalizations (13) and, therefore, might not need to have their glucose levels monitored as frequently. Currently, there is no objective way to identify, at the time of admission to hospital, which patients are at risk for hypoglycemia during their hospitalizations. Our goal was to develop the Hypoglycemia During Hospitalization (HyDHo) scoring sysem, a risk tool to predict hypoglycemia for patients with diabetes who are admitted to general medical wards.

Methods

Derivation cohort

The derivation cohort consisted of 300 randomly selected patients with diabetes who had been admitted to a medical inpatient unit between November 2009 and October 2010 at Sunnybrook Health Sciences, a tertiary-care teaching hospital in Toronto, Ontario, Canada. We did not specify type of diabetes as an inclusion criterion; however, the vast majority of hospitalized adult patients have type 2 diabetes. All point-of-care glucose tests taken for the selected patients during their hospital stays were collected, and patients were defined as having experienced hypoglycemia if they had point-of-care glucose test results ≤3.9 mmol/L at any time during the hospitalization. We did not ascertain whether these readings were correlated with symptoms because any glucose readings below this threshold would be considered clinically significant in an inpatient setting. The frequency of point-of-care testing for admitted patients was at the discretion of the admitting physician. The hospital used the Nova StatStrip glucose meter (Nova Biomedical, Waltham, Massachusetts, United States) during the period of the study.

Through review and abstraction from the hospitalization records, we collected a variety of demographic and clinical data for each patient. The goal was to create a risk-prediction tool that could be used at hospital admission; therefore, only objective variables that would be commonly available when a patient is admitted were selected. Demographic variables included age and sex. Measures of comorbidity included previous hospitalizations at the same institution within the prior 28 days and previous emergency department visits at the same institution within the prior 6 months. Patient use of the following medication classes prior to admission was recorded: systemic corticosteroids, inhaled corticosteroids, beta agonists, beta blockers (excluding ophthalmic preparations), alpha blockers, insulin, hypoglycemia-inducing oral diabetes agents (sulfonylureas or glitinides) and other oral diabetes agents. We captured whether patients were ordered nil per os on admission. Fever was defined as an admission temperature ≥38°C. Anemia was defined as admission hemoglobin levels ≤114 g/L for women and ≤129 g/L for men. An elevated white blood cell count was defined as $\geq 11.1 \times 10^9$/L. Admission values for creatinine were collected and converted to estimated glomerular filtration rates using the modification of diet in renal disease equation (14), then categorized into ≥60 mL/min/1.73 m^2, ≥30 and <60 mL/min/1.73 m^2, and <30 mL/min/1.73 m^2. We also examined severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2) as a dichotomous variable.

Validation cohort

We then identified 300 randomly selected patients admitted to a medical inpatient unit between November 2009 and October

2010 at Mount Sinai Hospital, which is another tertiary care teaching hospital in Toronto. Point-of-care glucose tests were obtained for the patients, and the same demographic and clinical data were collected through review and abstraction of the hospitalization records. During the period of the study, the hospital used the LifeScan SureStep glucose meter (LifeScan, Milpitas, California, United States).

Statistical analysis

Descriptive statistics were calculated for all variables. Continuous measures were summarized using means and standard deviations, whereas categorical measures were summarized using counts and percentages.

In the derivation cohort, we examined the bivariate association between each baseline characteristic and hypoglycemia by using t tests for continuous variables, Wilcoxon rank sum tests for continuous variables with non-normal distributions and chi-square tests for dichotomous or categorical variables. We then selected those candidate variables with $p \leq 0.1$ for inclusion in a multivariable logistic regression to determine the independent association of these variables with hypoglycemia during the hospitalizations. Model regression coefficients were converted into an integer points score using the method of Sullivan et al (15), and a receiver operating characteristic curve was plotted to determine a threshold score. As a sensitivity analysis, we examined regression models using a threshold of ≤3.4 mmol/L to define hypoglycemia.

We then determined the performance of the model selected from the derivation dataset in the validation dataset. The discrimination of the model was assessed using the c-statistic, which represents the area under a receiver operating characteristic curve. Calibration was assessed by comparing observed vs. predicted rates of hypoglycemia using the Hosmer-Lemeshow goodness-of-fit test.

All analyses were carried out using SAS v. 9.4 (SAS Institute, Cary, North Carolina, United States).

Ethics

The study was approved by the research ethics boards of Sunnybrook Health Sciences Centre and Mount Sinai Hospital, both in Toronto.

Results

In the derivation cohort, 14 patients had missing data for key variables, so the model was derived using the remaining 286 patients. In the validation cohort, 1 patient was excluded because no point-of-care glucose test results were available, leaving 299 in the cohort. The baseline characteristics of the derivation and validation cohort patients are shown in Table 1.

In the derivation cohort, 72 (25%) patients had hypoglycemia during their hospitalizations. Patients had a median of 3.0 point-of-care glucose tests per day (interquartile range 2.0 to 4.0). Bivariate associations between each baseline characteristic and hypoglycemia are presented in Supplementary Table 1. The final selected multivariate model included 5 variables: age, emergency department visit during the 6 months prior, insulin use, other oral agent use (nonhypoglycemia inducing) and severe chronic kidney disease. Figure 1 shows the calculation of the HyDHo score derived using this model; Figure 2 shows the receiver operating characteristic curve for the score. Sensitivity and specificity were maximized with a threshold score of ≥14, resulting in a sensitivity of 65% (95% confidence interval [CI] 54% to 75%) and a specificity of 69% (95% CI 62% to 75%) to predict hypoglycemia. Alternatively, to improve sensitivity, using a score of ≥9 resulted in a sensitivity of 86% (95% CI 76% to 92%), but the specificity declined to 32% (95% CI 26% to 39%). There were 79 patients (28%) with scores below this threshold, and their risk for hypoglycemia was 13%.

Table 1
Characteristics of the derivation and validation cohorts

	Derivation cohort	Validation cohort
n	286	299
Age (years, mean ± SD)	70.5±14.5	69.3±16.9
Sex		
Male	167 (58)	139 (46)
Female	119 (42)	160 (54)
Previous admission during prior 28 days	45 (16)	32 (11)
Emergency department visit during prior 6 months	104 (36)	122 (41)
Systemic corticosteroids	22 (8)	35 (12)
Inhaled corticosteroids	34 (12)	42 (14)
Beta agonists	38 (13)	50 (17)
Beta blockers	127 (44)	100 (33)
Alpha blockers	34 (12)	23 (8)
Insulin	91 (32)	73 (24)
Hypoglycemia-inducing oral diabetes drugs	80 (28)	75 (25)
Other oral diabetes drugs	140 (49)	131 (44)
NPO within the first 24 h	68 (24)	41 (14)
Fever	23 (8)	39 (13)
Creatinine (μmol/L, median [IQR])	96 (72–145)	91 (63–143)
eGFR (mL/min/1.73 m^2)		
≥60	151 (53)	168 (56)
≥30 and <60	85 (30)	81 (27)
<30	50 (17)	50 (17)
Severe chronic kidney disease	50 (17)	50 (17)
Anemia	148 (52)	166 (56)
Elevated white blood cell count	83 (29)	123 (41)

Note: Values are n (%) except where indicated.
eGFR, estimated glomerular filtration rate; *IQR*, interquartile range.

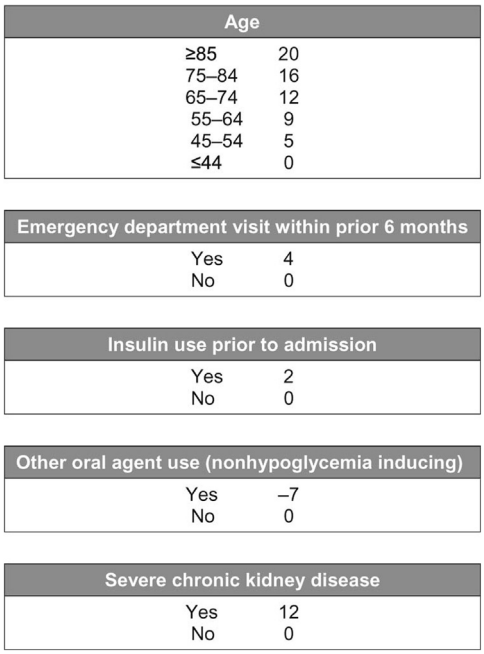

Figure 1. Hypoglycemia during hospitalization (HyDHo) scoring system to predict the risk for hypoglycemia during hospitalization.

In the sensitivity analysis, using a glucose threshold of ≤3.4 mmol/L, 51 (18%) patients experienced hypoglycemia. The regression model coefficients were very similar to those of the primary analysis (data not shown).

In the validation cohort, 94 (31%) patients experienced hypoglycemia during their hospitalizations. The model had a c-statistic

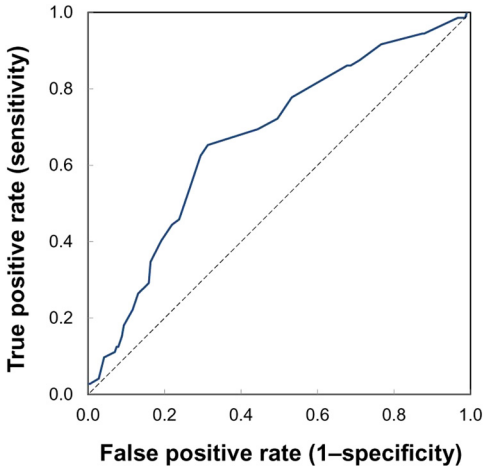

Figure 2. Receiver operating characteristic curve for the hypoglycemia during hospitalization (HyDHo) score to predict hypoglycemia.

of 0.642, and the Hosmer-Lemeshow test had a p value of 0.134, demonstrating adequate discrimination and good calibration. In the validation cohort, a threshold of ≥9 gave a sensitivity of 77% (95% CI 67% to 84%) and a specificity of 28% (95% CI 22% to 34%). There were 79 (26%) patients in the validation cohort who had scores below this threshold.

Discussion

We developed a parsimonious risk-prediction model that used 5 key clinical variables to predict, at the time of admission to a general medical unit, the risk for a patient with diabetes to experience hypoglycemia during hospitalization. The variables included in the HyDHo score are objective and commonly available when a patient is admitted: age, emergency department visit in the prior 6 months, insulin use, use of oral agents other than those that induce hypoglycemia, and severe chronic kidney disease (admission estimated glomerular filtration rate <30 mL/min/1.73 m^2). The model is moderately discriminative in the validation cohort and has good calibration. The points score that was derived from the regression model could be used by clinicians at the bedside to identify a patient's risk for hypoglycemia. A threshold score of ≥9 identified patients at highest risk for hypoglycemia during their hospitalizations, with good sensitivity in both the derivation and the validation cohorts. Patients with scores below this threshold represented more than one-quarter of the patients in both cohorts, and they had a low risk for hypoglycemia. Therefore, they may need less intensive glucose monitoring during hospitalization. The median number of glucose tests was 3.0 per day, suggesting that patients are receiving point-of-care testing before most meals and at bedtime. Application of the HyDHo scoring system to thoughtfully reduce the frequency of glucose monitoring for selected patients could free up nursing resources for use elsewhere and could improve patient experiences. The score could also be used to identify patients who are at particularly high risk for hypoglycemia and to target them for other interventions, including intensive glucose monitoring.

A previous study created a risk-prediction tool for hypoglycemia in inpatients. Elliott et al (16) examined more than 3,000 inpatients receiving insulin who had hypoglycemia. Models to predict the risk for glucose levels <3.9 mmol/L and <3.3 mmol/L were derived. Both models had the same parameters: basal insulin dose, meal insulin use, adjustment scale insulin use, sulfonylurea use and weight and creatinine clearance. However, these models were not validated. Notably, our model also found that both insulin use and renal function were predictors of hypoglycemia; and although sulfonylurea use was not predictive of an increased hypoglycemia risk in our model, the use of other classes of oral agents was protective. Many of the other variables included in our study were not examined in this previous study. Kinnare et al (17) examined predictors of hypoglycemia in hospitalized patients receiving parenteral nutrition and insulin. Factors that were associated with point-of-care glucose tests <3.3 mmol/L included days on parenteral nutrition, intensive care unit admissions, use of an insulin infusion and histories of diagnosed diabetes.

There are some limitations in our study that should be highlighted. Although the HyDHo scoring system was validated in an independent population at another hospital, it was in the same city and under the same health-care system as the hospital at which the model was derived. Validation in a completely different geographic and health system environment would improve the generalizability of the model. In addition, hypoglycemia was defined based only on the point-of-care glucose test results. There was no correlation with symptoms or clinical consequences; hence, these results may not represent the most clinically relevant hypoglycemic episodes. All point-of-care tests were examined, including both those that were part of routine glucose monitoring in hospital and those that may have been done emergently because the patient was having symptoms or signs of hypoglycemia. Thus, the study is likely to be overestimating the frequency of hypoglycemia that is detected by routine monitoring of hospitalized patients. However, this also means that patients with low HyDHo scores were truly at low risk for hypoglycemia. Finally, we did not examine risks for hyperglycemia because it is less urgent than hypoglycemia; however, intensive glucose monitoring may be indicated for some patients to detect hyperglycemia.

Conclusions

In summary, the HyDHo scoring system can be applied at the time of admission to a general medical unit using commonly available objective data to identify patients with diabetes who are at risk for having hypoglycemic episodes during their hospitalizations. Patients are at increased risk if they score ≥9; this includes all patients taking nonhypoglycemia-inducing oral agents (such as metformin) who are ≥75 years of age and all patients not taking these agents who are ≥55 years of age. However, patients scoring <9 have a low risk for hypoglycemia and, therefore, may need less intensive glucose monitoring, improving their experiences in hospital. Applying the HyDHo scoring system could allow clinicians to make more informed decisions about personalizing care, thereby optimizing nursing and other resource utilization. Future research will examine how implementation of the HyDHo score to streamline point-of-care glucose testing for general medical patients affects inpatient care.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at www.canadianjournalofdiabetes.com.

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Author Disclosures

None.

Author Contributions

BRS and JML conceived of and designed the study. SW acquired the data. AK analyzed the data. All authors interpreted the data. BRS drafted the manuscript. All authors revised it for important intellectual content.

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Supplementary Material

Supplementary Table 1
Bivariate associations between baseline characteristics and hypoglycemia in the derivation cohort

	Hypoglycemia		p value
	Yes	No	
N	72	214	
Age (years, mean±SD)	72.9±13.3	69.7±14.8	0.10
Sex			0.41
Male	45 (62%)	122 (57%)	
Female	27 (38%)	92 (43%)	
Previous admission 28 days prior	10 (14%)	35 (16%)	0.62
Emergency department visit 6 months prior	32 (44%)	72 (34%)	0.10
Systemic corticosteroids	7 (10%)	15 (7%)	0.45
Inhaled corticosteroids	9 (12%)	25 (12%)	0.85
Beta agonists	10 (14%)	28 (13%)	0.86
Beta blockers	36 (50%)	91 (43%)	0.27
Alpha blockers	11 (15%)	23 (11%)	0.30
Insulin	29 (40%)	62 (29%)	0.07
Hypoglycemia-inducing oral diabetes drugs	25 (35%)	55 (26%)	0.14
Other oral diabetes drugs	24 (33%)	116 (54%)	0.002
NPO within the first 24 h	16 (22%)	52 (24%)	0.72
Fever	9 (12%)	14 (7%)	0.11
Creatinine (μmol/L, median and IQR)	110 (72–206)	92 (72–138)	0.05
eGFR (mL/min/1.73 m^2)			0.01
≥60	32 (44%)	119 (56%)	
≥30 and <60	19 (26%)	66 (31%)	
<30	21 (29%)	29 (14%)	
Severe chronic kidney disease	21 (29%)	29 (14%)	0.003
Anemia	42 (58%)	106 (50%)	0.20
Elevated white blood cell count	20 (28%)	63 (29%)	0.79

eGFR, estimated glomerular filtration rate; *IQR*, interquartile range.