Predicting inpatient hypoglycaemia in hospitalized patients with diabetes: a retrospective analysis of 9584 admissions with diabetes

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Title: Predicting inpatient hypoglycaemia in hospitalized patients with diabetes: a retrospective analysis of 9,584 admissions with diabetes

Running head: Predicting inpatient hypoglycaemia in hospitalized patients with diabetes

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Conflicts of interest
None.

What's new?
- Hypoglycaemia is associated with worse outcomes in inpatients with diabetes. At present there is no targeted and validated prediction model for identifying patients with an increased risk of hypoglycaemia.
- We performed a retrospective analysis of inpatient admissions with diabetes to develop a prediction model for hypoglycaemia incorporating routinely collected biochemical data.
- We found that the occurrence of hypoglycaemia could be predicted by a model incorporating background medication, ethnicity, age, admission type and laboratory measurements.
- Model performance indicates potential clinical utility to identify patients at risk of hypoglycaemia during their inpatient stay, which could lead to improved patient management and outcomes.

Abstract

Aims

Inpatient hypoglycaemia in patients with diabetes mellitus is associated with excess mortality, increased length of stay and increased complication rate. The objective of this study was to explore whether a quantitative approach to identify hospitalized patients with diabetes at risk of hypoglycaemia could be feasible by incorporating routine biochemical, haematological and prescription data.

Methods

A retrospective cross-sectional analysis of all diabetic admissions (n=9,584) from 1st January 2014 to 31st December 2014 was performed. Hypoglycaemia was defined as a blood glucose level of < 4 mmol/L. The prediction model was constructed using multivariable logistic regression, populated by clinically important variables and routine laboratory data.

Results

Using a pre-specified variable selection strategy, it was shown that the occurrence of inpatient hypoglycaemia could be predicted by a combined model taking into account background medication (type of insulin, use of sulphonylurea), ethnicity (Black and Asian), age (75+ years old), type of admission (emergency) and laboratory measurements (eGFR, CRP, sodium and albumin). ROC curve analysis revealed that the Area Under the Curve (AUC) was 0.733 (95% CI 0.719 to 0.747). The cut-off point chosen to maximize both sensitivity and specificity was 0.15. AUC obtained from internal validation did not differ from the primary model (0.731 (95% CI 0.717 to 0.746)).

Conclusions

The inclusion of routine biochemical data, available at the time of admission, can add prognostic value to demographic and medication history. The predictive performance of the constructed model indicates potential clinical utility to identify patients at risk of hypoglycaemia during their inpatient stay.

Introduction

Hospitalised patients with diabetes have high infection rates [1-4], longer length of stay [5-7] and increased mortality (10% higher) [8]. Hypoglycaemia is one of the important determining events for this worse prognosis, which can be reflected in excess mortality, increased length of stay and increased complications amongst patients with diabetes [9-11]. Hence, predicting the risk of hypoglycaemia in hospitalized patients with diabetes mellitus and preventing its occurrence in a selected, high-risk subset of them through active monitoring or therapeutic modifications may be an efficient way to improve outcomes.

However, a targeted and validated prediction model for identifying inpatients with diabetes at an increased risk of hypoglycaemia is still missing. The main reason is the heterogeneity in populations, thresholds for hypoglycaemia, underlying diseases and co-morbidities across relevant studies [11-19]. This is why the Joint British Diabetes Societies' (JBDS) position currently advocates a non-quantitative approach with regard to risk of inpatient hypoglycaemia in patients with diabetes [20]. Specifically, the recommended approach would be to consider medical or lifestyle risk factors, such as strict glucose management, history of severe hypoglycemic events, duration of insulin use, severe liver failure, renal failure, terminal illness or increasing age and alcohol use respectively.

To explore whether a quantitative approach to identify hospitalized patients with diabetes at risk of hypoglycaemia could be feasible and construct a relevant prediction model incorporating routine biochemical data collected at admission, we performed a retrospective analysis of admissions with diabetes.

Methods

All hospitalized adult (>16 years old) patients with diabetes mellitus in the general ward of our Institution were considered as potentially eligible, irrespective of the primary diagnosis. The observation period was from 1st January 2014 to 31st December 2014. The diagnosis of diabetes mellitus was consolidated by the presence of relevant Patient Administration System (PAS) discharge codes for diabetes or the presence of a continuous anti-hyperglycemic medication in the electronic medical record system (Patient Information and Communication System (PICS)). The diagnosis of diabetes was also ensured by cross-checking the PAS database for the International Classification of Diseases version 10 (ICD-10) diabetes codes (E10 – E14) retrospectively for the previous 10 years, up to 2004. Prescription of metformin or short acting insulin in the absence of a diabetes code was considered an exclusion criterion to ensure case (diabetes mellitus) definition. Patients admitted to ITU were excluded from the analysis.

The outcome of interest was the occurrence of hypoglycaemia, which was defined as a blood glucose level of < 4 mmol/L (point of care or laboratory blood glucose measurement).

Statistical Analysis

Baseline differences in continuous data between hypoglycaemic and non hypoglycaemic groups were explored using the Student's T-test or Mann-Whitney U test according to distribution. Differences in dichotomous data were explored using a Chi-squared test.

The prediction model was constructed on the basis of a multivariable logistic regression model with hypoglycaemia as the dependent outcome. This model was populated by clinically important variables, as identified by previous literature, including laboratory results as recorded in PICS. All variables with a *p*-value at significance level of 20% (p = 0.20) in the univariate analysis were included in the multivariable logistic regression model (Supplementary Table 1). In cases where two variables were statistically significant but highly correlated, one was chosen based on clinical familiarity. Continuous data (for example age) were also analyzed as categories to inspect potential non-linear effects. Area Under the Curve analysis was performed to assess the predictive performance of the final model. A decision threshold was selected with the intent of maximizing both sensitivity and specificity. Positive and negative predictive values were calculated using the prevalence of hypoglycaemia in this dataset.

Internal validation was assessed using bootstrapping, in which sample datasets the same size as the original dataset are repeatedly resampled, with replacement, and model parameters are re-estimated and averaged over the samples [21]; this identifies any shrinkage necessary to reduce model over-optimism due to over-fitting. Missing data were handled by a chained multiple imputation technique with predictive mean matching. Bootstrapped results from each of the imputed datasets were combined using Rubin's rule. In sensitivity analysis, missing values were replaced by values in

the normal range for the given clinical pathology test. Model calibration was assessed by plotting predicted probability of hypoglycaemia against observed probability. Significance level was set at 5% and all analyses were implemented in Stata 13.0.

Results

Flow chart

From a total of 106,580 patients admitted to our Institution during 2014, 57,922 admissions were eligible (emergency or elective admissions) and of those, 9,584 admissions were in patients with diabetes. Hypoglycaemia occurred in 1,327 (13.8%) admissions with diabetes while the remaining 8,257 (86.2%) did not have a hypoglycaemic event. A flow chart summarizing the selection process along with reasons for exclusion is presented in Figure 1.

6,187 unique patients made up the 9,584 admissions included in the analysis. Of the 1,792 patients who contributed two or more admissions, 664 experienced a hypoglycaemic episode; none of these 664 patients had a hypoglycaemic episode in more than one admission.

Baseline characteristics

A table summarizing differences in the baseline demographics and medication history is presented in Table 1 and 2. Patients in the hypoglycaemia group were older, more deprived, with higher comorbidities and more likely to belong to an ethnic minority group compared to the group without hypoglycaemia. Insulin use and sulphonylureas were also proportionally more common in the hypoglycaemia group (Table 2). A table summarizing differences in the baseline laboratory measurements is presented in Table 3. Patients in the hypoglycaemia group were more likely to have elevated

inflammation markers (C-reactive protein, CRP levels), electrolyte disturbances or have anaemia.

Final model

Using a pre-specified variable selection strategy, younger age categories, female gender, hyperkalaemia, an elevated neutrophil count and anaemia were not found to be significant predictors of hypoglycaemia in the multivariable logistic regression. Elderly greater than 75 years, Insulin and sulphonylureas therapy, Black and Asian ethnicity, emergency admissions, lower eGFR, higher CRP, hyponatraemia (<125mmol/L) and hypo-albuminaemia were the strongest predictors of hypoglycaemia in patients with diabetes mellitus admitted in the general ward. The final model (prior to bootstrapping) is presented in the Table 4.

In sensitivity analysis, we used multilevel modelling (xtlogit) to allow for any possible correlation between multiple admissions for an individual patient; this made very little difference to the model parameters.

Model performance and internal validity

ROC curve analysis revealed that the Area Under the Curve (AUC) was 0.733 (95% CI 0.719 to 0.747) (Figure 2). The cut-off point chosen to maximize both sensitivity and specificity was 0.15 predicted probability of hypoglycaemia, with these corresponding values being 59.3% and 73.7% respectively. At this cut-off the positive predictive value was 26.6% and the negative predictive value was 91.8%. A confusion matrix describing model performance is shown in Figure 3. The model was internally validated by bootstrapping; model coefficients were unchanged and test statistics were similar to the primary model, indicating no evidence of over-fitting: AUC 0.731 (95% CI 0.717 to 0.746), sensitivity 59.3%, specificity 73.4%, positive predictive value 26.4%, and negative predictive value 91.8%. Visual assessment of the

calibration plot (Figure 4) suggests that model calibration is good (i.e. predicted probabilities of hypoglycaemia are similar to observed probabilities).

In sensitivity analysis, missing clinical pathology test results were replaced with values in the normal range (Supplementary Table 2). This had little effect on the model performance: AUC 0.735 (95% CI 0.721 to 0.749), sensitivity 60.4%, specificity 73.4%, positive predictive value 26.8%, and negative predictive value 92.0%.

Discussion

In this retrospective analysis of all diabetic admissions, we found that the occurrence of inpatient hypoglycaemia could be predicted by a combined model taking into account background medication (type of insulin, use of sulphonylurea use), ethnicity (Black and Asian), age (75+ years old), type of admissions (emergency) and laboratory measurements (eGFR, CRP, sodium and albumin).

Considering that inpatient hypoglycaemia is significantly associated with inpatient mortality and increased length of hospital stay [10, 11] and that real-time generated alerts using a validated computerized predictive algorithm may significantly reduce its occurrence [16], the findings of the present study could provide a robustly validated basis to improve inpatient safety and outcomes. Importantly, this study also showed that the inclusion of routine biochemical data (such as CRP, albumin, eGFR and sodium), available at the time of admission, could add prognostic value to demographic and medication history, thus providing a more holistic and optimized approach in the prediction of hypoglycemic events.

On the other hand, the findings of the present study should be interpreted in the context of its limitations. First external validity, that is assessing the model in a

different environment on a different population, would be a prerequisite before recommending its adoption in clinical practice. Moreover, the extent of missing data with regard to glycated hemoglobin (HbA1c) prevented the plausible exploration of tight versus poor glycemic control as a predictor of hypoglycaemia. The study used routinely collected observational data, and therefore there may be unobserved confounding for which it was not possible make adjustments in the analysis. However, this does not vitiate the utility of the model or the observed association between the predictor variables and the outcome.

Taking the above into consideration and using the largest dataset of diabetic admissions to date, we suggest that the occurrence of inpatient hypoglycaemia may be predicted by a combined model using background medication ethnicity, age, type of admission and routine laboratory measurements as independent predictors. The predictive performance of the constructed model indicates potential clinical utility in identifying patients at high risk of inpatient hypoglycaemia.

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Conflicts of interest

None.

Author contributions

KS, NA and KN developed the model. AS advised on the statistical analysis. KT, TM, GR, SG, SM and KN provided clinical input. All authors wrote the paper or revised it critically for important intellectual content.

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Table 1. Baseline demographics

Patient Demographics	Normoglycaemia (>3.9 mmol/L; N= 8,257)	Hypoglycaemia (≤3.9 mmol/L; N= 1,327)	P-value
Age median (IQR)	68 (56-78)	70 (57-80)	0.032
Age categories N (%)			< 0.001
16-44	723 (8.8)	128 (9.7)	
45-54	1,118 (13.5)	154 (11.6)	
55-64	1,574 (19.1)	218 (16.4)	
65-74	2,095 (25.4)	294 (22.2)	
75-84	1,858 (22.5)	361 (27.2)	
≥ 85	889 (10.8)	172 (13.0)	
Sex N (%)[0]			0.026
Male	4,566 (55.4)	691 (52.1)	
Female	3,682 (44.6)	636 (47.9)	
Ethnicity N (%)[0]			< 0.001
Caucasian	5,657 (68.5)	855 (64.4)	
Black	455 (5.5)	117 (8.8)	
Asian	1,765 (21.4)	298 (22.5)	
Other	380 (4.6)	57 (4.3)	
IMD deprivation quintile N (%)[0]			0.025
Least deprived 1	366 (4.5)	47 (3.6)	
2	531(6.5)	85 (6.5)	
3	1,657 (20.4)	239 (18.3)	
4	1,675 (20.6)	246 (18.8)	
Most deprived 5	3,915 (48.1)	689 (52.8)	
Type of Admission N (%)			< 0.001
Elective	1,882 (22.8)	144 (10.9)	
Emergency	6,375 (77.2)	1,183 (89.2)	
Modified† Charlson Comorbidity score N (%)			< 0.001
0	3,807 (46.1)	429 (32.3)	
1	1,524 (18.5)	214 (16.1)	
2 or more	2,926 (35.4)	684 (51.5)	

IMD: Index of Multiple Deprivation. Missing Data: [0] <1.5%, otherwise nil.

†Charlson score with diabetes scores removed.

Table 2: Medication history

Patient Medications	Normoglycaemia (>3.9 mmol/L; N= 8,257)	Hypoglycaemia (<3.9 mmol/L; N= 1,327)	P-value
Insulin N (%)			
Short Acting	887 (10.7)	373 (28.1)	< 0.001
Intermediate Acting	184 (2.2)	88 (6.6)	< 0.001
Long Acting	1,085 (13.1)	381 (28.7)	< 0.001
Sulphonylureas N (%)	1,370 (16.6)	334 (25.2)	< 0.001
Metformin N (%)	3,145 (38.1)	501 (37.8)	0.816
Thiazolidinediones N (%)	139 (1.7)	29 (2.2)	0.196
Incretin mimetics N (%)	107 (1.3)	13 (1.0)	0.336
DPP-4 inhibitors N (%)	691 (8.4)	124 (9.3)	0.237
Other antidiabetic medications† N (%)	36 (0.4)	14 (1.1)	0.004

Reg.: Regulator. † Alpha-glucosidase, prandial glucose regulator, SGLT2 inhibitors. Common combinations of medications are shown in Supplementary Table 3.

Table 3. Baseline laboratory characteristics considered for the prediction model

Patient Laboratory Results	Normoglycaemia (>3.9 mmol/L; N= 8,257)	Hypoglycaemia (≤3.9 mmol/L; N= 1,327)	P-value
Electrolytes and renal function			
Sodium mean (SD)◊	137.0 (4.8)	136.3 (5.7)	< 0.001
Sodium N (%)◊			< 0.001
< 125 mmol/L	110 (1.6)	43 (3.4)	
125-134 mmol/L	1,611 (23.1)	377 (29.9)	
135-144 mmol/L	5,076 (72.9)	796 (63.2)	
145-154 mmol/L	160 (2.3)	37 (2.9)	
≥ 155 mmol/L	8 (0.1)	7 (0.6)	
Potassium mean (SD) ◊	4.5 (0.6)	4.6 (0.8)	< 0.001
Potassium N (%)◊			< 0.001
< 3 mmol/L	28 (0.4)	9 (0.8)	
3-6 mmol/L	6,139 (97.2)	1,046 (94.2)	
≥ 6 mmol/L	150 (2.4)	56 (5.0)	
Creatinine median (IQR) ◊	88 (68, 127)	105 (75, 173)	< 0.001
eGFR median (IQR)◊	66 (43, 88)	51.5 (30, 78)	< 0.001
eGFR N (%)◊			< 0.001
≥ 90	1,686 (24.2)	230 (18.3)	
60-89	2,352 (33.8)	303 (24.1)	
30-59	1,860 (26.7)	411 (32.7)	
15-29	533 (7.7)	168 (13.4)	
< 15	524 (7.5)	146 (11.6)	
Infection / Inflammation marker			
CRP median (IQR)*	13 (4, 47)	24 (6, 77)	< 0.001
CRP N (%)*			< 0.001
< 10 mg/L	2,622 (44.1)	413 (34.3)	
10-49 mg/L	1,902 (32.0)	377 (31.3)	
50-99 mg/L	689 (11.6)	175 (14.5)	
≥ 100 mg/L	728 (12.3)	240 (19.9)	
Haematology Tests			
Haemoglobin mean (SD)◊	120.8 (21.4)	115.5 (21.4)	< 0.001
Haemoglobin ◊			< 0.001
< 80 g/L	220 (3.2)	60 (4.8)	
80-109 g/L	1,732 (25.2)	413 (33.0)	
≥ 110 g/L	4,911 (71.6)	780 (62.3)	
Neutrophil median (IQR)◊	6.3 (4.5, 8.9)	7.0 (4.8, 10.3)	< 0.001
Neutrophil N (%)◊			< 0.001
< 2	157 (2.3)	32 (2.5)	
2-7.9	4,476 (65.0)	718 (57.1)	
≥ 8	2,261 (32.8)	508 (40.3)	
Liver function test			
Albumin mean (SD)◊	40.1 (5.4)	37.9 (6.3)	< 0.001
Albumin N (%)◊			< 0.001
< 25	77 (1.8)	34 (2.8)	
25-35	862 (13.1)	305 (24.7)	
≥ 35	5,654 (85.8)	898 (72.6)	
Bilirubin median (IQR)◊	7 (5, 11)	7 (5, 12)	0.742

Missing Data: ◊ 5-20%, * 21-30%

Table 4. Results of the multivariable logistic regression analysis

Variables (n, % observations with imputed data)	Regression Coefficient (95% CI)	OR (95% CI)	P-value
Age categories			
16-44	0.19 (-0.08 to 0.45)	1.20 (0.92 to 1.58)	0.177
*45-54	-	1	-
55-64	0.03 (-0.20 to 0.26)	1.03 (0.82 to 1.30)	0.786
65-74	0.03 (-0.20 to 0.25)	1.03 (0.82 to 1.28)	0.823
≥ 75	0.25 (0.04 to 0.46)	1.28 (1.04 to 1.59)	0.022
Sex			
*Male	-	1	-
Female	0.06 (-0.07 to 0.18)	1.06 (0.94 to 1.20)	0.362
Ethnicity			
*Caucasian	-	1	-
Black	0.53 (0.30 to 0.77)	1.71 (1.35 to 2.16)	< 0.001
Asian	0.17 (0.02 to 0.33)	1.19 (1.02 to 1.39)	0.027
Other	0.20 (-0.10 to 0.50)	1.22 (0.90 to 1.66)	0.198
Admission Type			
*Elective	-	1	-
Emergency	0.70 (0.51 to 0.89)	2.01 (1.66 to 2.43)	< 0.001
Insulin			
Short Acting	0.86 (0.71 to 1.02)	2.37 (2.03 to 2.78)	< 0.001
Intermediate Acting	0.71 (0.42 to 0.99)	2.03 (1.53 to 2.69)	< 0.001
Long Acting	0.70 (0.55 to 0.85)	2.02 (1.73 to 2.35)	< 0.001
Sulphonylureas	0.57 (0.42 to 0.72)	1.77 (1.53 to 2.05)	< 0.001
Sodium (1,350, 14.1%)			
<125 mmol/L	0.55 (0.16 to 0.93)	1.73 (1.17 to 2.54)	0.006
125-134 mmol/L	0.08 (-0.07 to 0.23)	1.08 (0.93 to 1.25)	0.291
*135-144 mmol/L	-	1	-
145-154 mmol/L	0.09 (-0.30 to 0.48)	1.09 (0.74 to 1.61)	0.668
≥ 155 mmol/L	1.09 (-0.01 to 2.19)	2.97 (0.99 to 8.91)	0.052
Potassium (2,147, 22.4%)			
< 3 mmol/L	0.34 (-0.47 to 1.14)	1.40 (0.63 to 3.13)	0.413
*3 – 6 mmol/L	-	1	-
≥ 6 mmol/L	0.08 (-0.28 to 0.43)	1.08 (0.76 to 1.54)	0.672
eGFR (1,362, 14.2%)			
*≥ 90	-	1	-
60-89	-0.02 (-0.22 to 0.17)	0.98 (0.80 to 1.19)	0.815
30-59	0.34 (0.14 to 0.54)	1.40 (1.15 to 1.71)	0.001
15-29	0.54 (0.28 to 0.79)	1.71 (1.32 to 2.20)	< 0.001
< 15	0.41 (0.14 to 0.67)	1.50 (1.16 to 1.95)	0.002
CRP (2,429, 25.3%)			
*0 - 10	-	1	-
10 - 49	0.10 (-0.06 to 0.26)	1.10 (0.94 to 1.30)	0.230
50 - 99	0.27 (0.05 to 0.49)	1.31 (1.06 to 1.63)	0.014
≥ 100	0.37 (0.15 to 0.58)	1.44 (1.16 to 1.78)	0.001
Albumin (1,745, 18.2%)			
< 25	0.61 (0.17 to 1.06)	1.85 (1.19 to 2.88)	0.007
25-35	0.49 (0.31 to 0.66)	1.63 (1.37 to 1.94)	< 0.001
*≥ 35	-	1	-
Neutrophil count (1,423, 14.8%)			
<2	0.11 (-0.29 to 0.52)	1.12 (0.75 to 1.66)	0.584
*2-8	-	1	-
≥ 8	0.06 (-0.08 to 0.20)	1.06 (0.92 to 1.23)	0.405
Haemoglobin (1,459, 15.2%)			
< 80	-0.03 (-0.35 to 0.30)	0.98 (0.70 to 1.35)	0.880
80-110	0.02 (-0.12 to 0.17)	1.02 (0.88 to 1.19)	0.742
*≥ 110	-	1	-
Constant	-3.57 (-3.86 to -3.27)		< 0.001

Figure 1. Flow diagram of included patients with diabetes

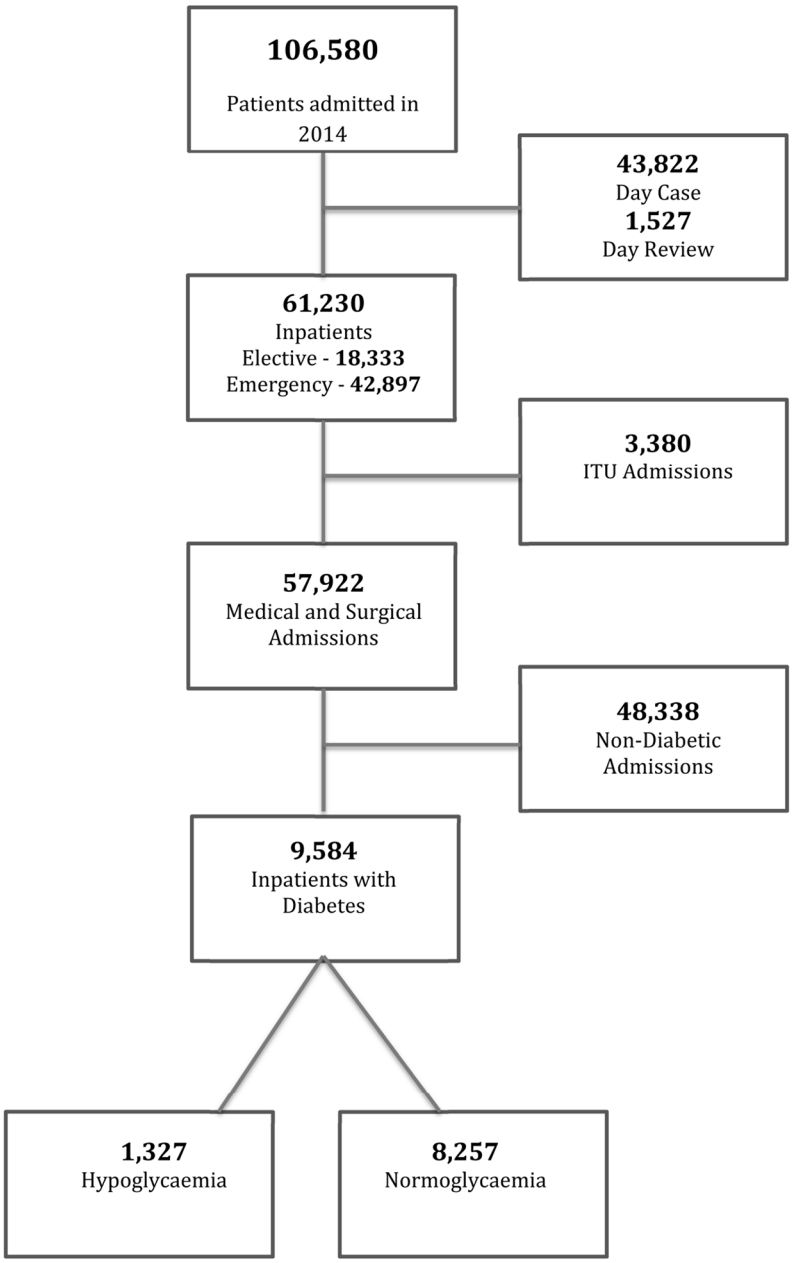


Figure 2. ROC curve for fitted model

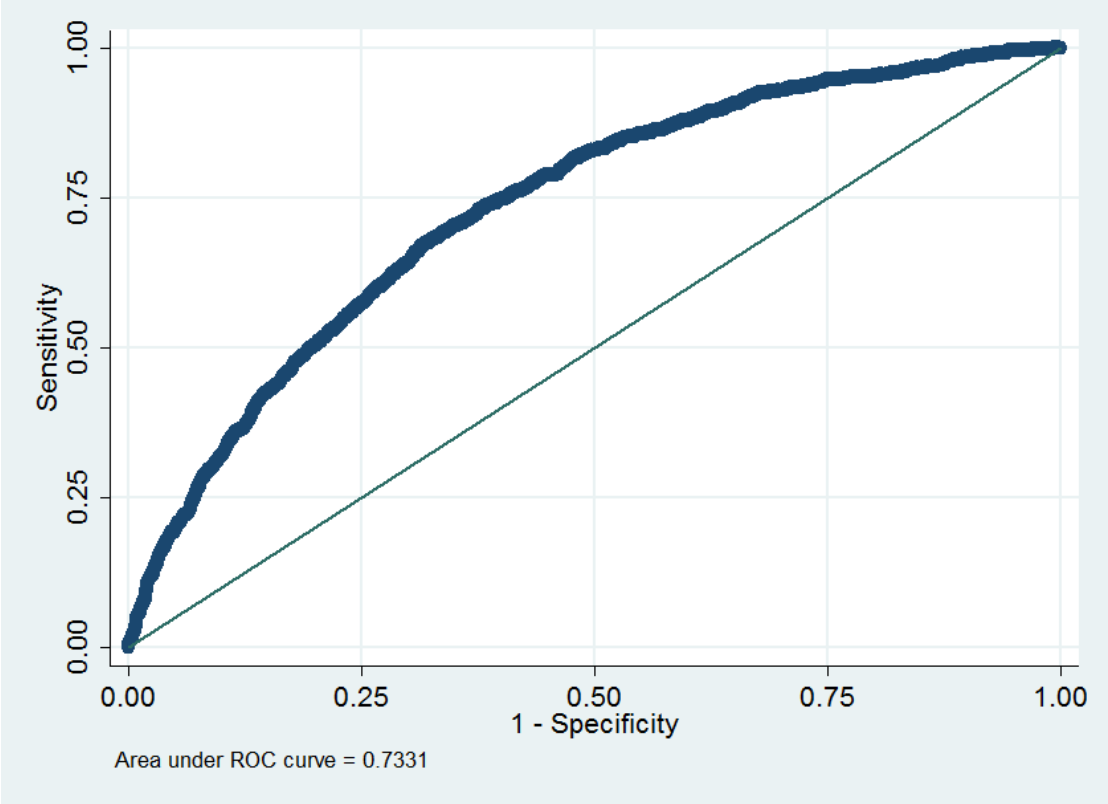
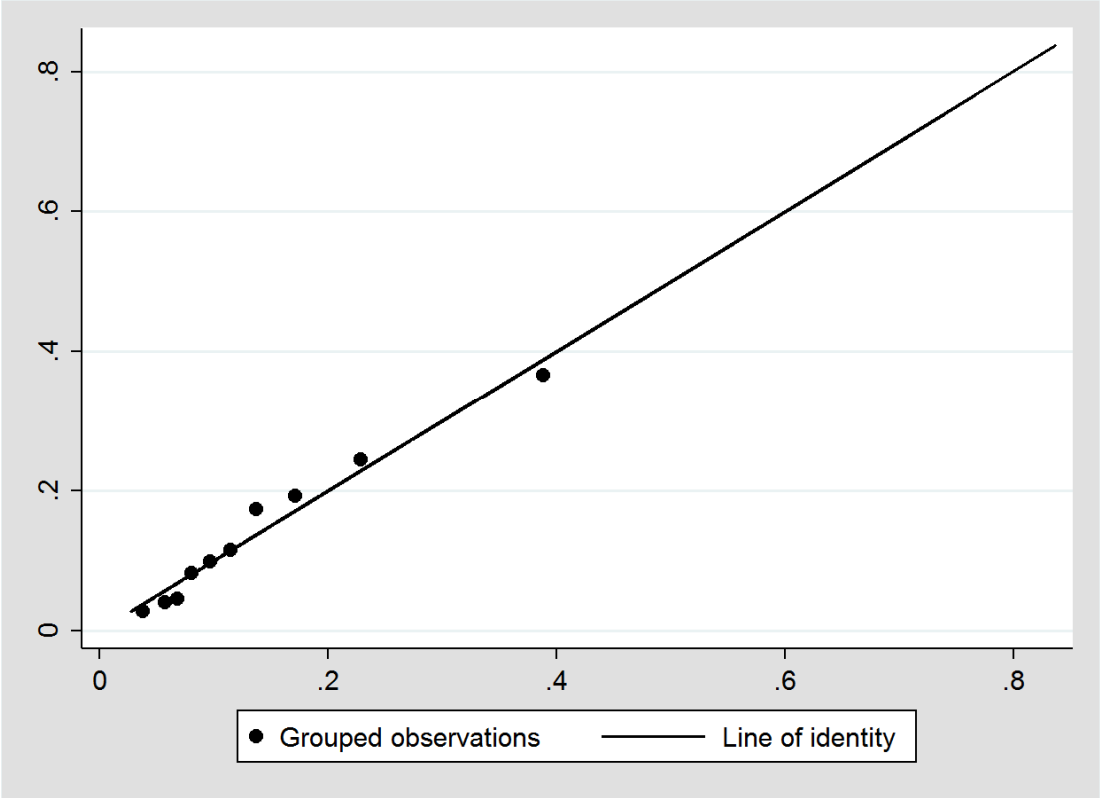


Figure 3. Confusion matrix showing actual and predicted numbers of hypoglycaemic outcomes

n=9,584		Predicted Yes	Predicted No	
Actual	Yes	787	540	1,327
	No	2,182	6,075	8,257
		2,969	6,615	

Figure 4. Calibration plot showing predicted and observed probabilities of hypoglycaemia



Supplementary Table 1. Findings of the univariate analyses.

Variables	Odds Ratio	95% CI	P-value
Age categories			
16-44	1.29	1.00 to 1.65	0.051
*45-54	1	-	-
55-64	1.01	0.81 to 1.25	0.961
65-74	1.02	0.83 to 1.25	0.861
≥ 75	1.41	1.16 to 1.71	< 0.001
Gender			
*Male	1	-	-
Female	1.14	1.02 to 1.28	0.026
Ethnicity			
*Caucasian	1	-	-
Black	1.70	1.37 to 2.11	< 0.001
Asian	1.12	0.97 to 1.29	0.127
Other	0.99	0.74 to 1.32	0.959
IMD deprivation quintile			
*Least deprived 1	1	-	-
2	1.25	0.85 to 1.82	0.256
3	1.12	0.81 to 1.57	0.494
4	1.14	0.82 to 1.59	0.428
Most deprived 5	1.37	1.00 to 1.88	0.049
Type of Admission			
*Elective			
Emergency	2.43	2.02 to 2.90	<0.001
Modified† Charlson			
*0	1	-	-
1	1.25	1.05 to 1.48	0.013
≥ 2	2.07	1.82 to 2.36	< 0.001

IMD: Index of Multiple Deprivation. †Modified Charlson: Charlson score minus Diabetes.

Variables	Odds Ratio	95% CI	P-value
Insulin			
Short Acting	3.25	2.83 to 3.73	< 0.001
Intermediate Acting	3.12	2.40 to 4.05	< 0.001
Long Acting	2.66	2.33 to 3.05	< 0.001
Any	3.36	2.98 to 3.79	< 0.001
Sulphonylureas	1.69	1.47 to 1.94	< 0.001
Metformin	0.99	0.87 to 1.11	0.816
Thiazolidinediones	1.30	0.87 to 1.96	0.197
Incretin mimetics	0.75	0.42 to 1.34	0.338
DPP-4 inhibitors	1.13	0.92 to 1.38	0.237

Variables	Odds Ratio	95% CI	P-value
Sodium			
<125 mmol/L	2.49	1.73 to 3.58	< 0.001
125-134 mmol/L	1.53	1.34 to 1.75	< 0.001
*135-144 mmol/L	1	-	-
145-154 mmol/L	1.46	1.01 to 2.11	0.044
≥155 mmol/L	5.78	2.06 to 16.24	0.001
Potassium			
<3 mmol/L	1.78	0.85 to 3.75	0.129
*3-6 mmol/L	1	-	-
≥6 mmol/L	2.26	1.66 to 3.06	< 0.001
eGFR			
*≥ 90	1	-	-
60-89	0.93	0.77 to 1.12	0.424
30-59	1.62	1.35 to 1.93	< 0.001
15-29	2.34	1.86 to 2.94	< 0.001
< 15	2.12	1.69 to 2.67	< 0.001
CRP			
*0-10	1		
10-49	1.32	1.13 to 1.53	< 0.001
50-99	1.74	1.43 to 2.11	< 0.001
≥ 100	2.28	1.91 to 2.72	< 0.001
Albumin			
< 25	2.79	1.84 to 4.23	< 0.001
25-35	2.25	1.93 to 2.61	<0.001
*≥ 35	1	-	-
Neutrophil count			
< 2	1.21	0.83 to 1.77	0.330
*2-8	1	-	-
≥ 8	1.44	1.27 to 1.63	< 0.001
Haemoglobin			
< 80	1.76	1.31 to 2.37	< 0.001
80-109	1.49	1.31 to 1.70	< 0.001
*≥ 110	1	-	

*Comparator.

Supplementary Table 2. Results of analysis replacing missing clinical pathology test results with values in the normal range.

Variables	Regression Coefficient (95% CI)	P-value	Boostrapped Regression Coefficient (95% CI)	P-value
Age categories				
16-44	0.20 (-0.07 to 0.47)	0.139	0.20 (-0.07 to 0.48)	0.144
*45-54	-	-	-	-
55-64	0.02 (-0.21 to 0.26)	0.836	0.02 (-0.21 to 0.26)	0.836
65-74	0.01 (-0.21 to 0.23)	0.934	0.01 (-0.22 to 0.23)	0.935
≥ 75	0.24 (0.02 to 0.45)	0.029	0.24 (0.02 to 0.45)	0.033
Sex				
*Male	-	-	-	-
Female	0.05 (-0.07 to 0.18)	0.395	0.05 (-0.07 to 0.18)	0.399
Ethnicity				
* Caucasian	-	-	-	-
Black	0.56 (0.33 to 0.80)	< 0.001	0.56 (0.32 to 0.80)	< 0.001
Asian	0.18 (0.02 to 0.33)	0.025	0.18 (0.02 to 0.34)	0.029
Other	0.23 (-0.07 to 0.54)	0.131	0.23 (-0.07 to 0.54)	0.132
Admission Type				
*Elective	-	-	-	-
Emergency	0.50 (0.30 to 0.70)	< 0.001	0.50 (0.30 to 0.70)	< 0.001
Insulin				
Short Acting	0.82 (0.66 to 0.98)	< 0.001	0.82 (0.65 to 0.99)	< 0.001
Intermediate Acting	0.68 (0.40 to 0.97)	< 0.001	0.68 (0.38 to 0.98)	< 0.001
Long Acting	0.69 (0.54 to 0.84)	< 0.001	0.69 (0.53 to 0.85)	< 0.001
Sulphonylureas	0.54 (0.40 to 0.69)	< 0.001	0.54 (0.39 to 0.70)	< 0.001
Sodium				
<125 mmol/L	0.57 (0.18 to 0.96)	0.004	0.57 (0.17 to 0.97)	0.005
125-134 mmol/L	0.06 (-0.08 to 0.21)	0.413	0.06 (-0.09 to 0.22)	0.440
*135-144 mmol/L	-	-	-	-
145-154 mmol/L	0.08 (-0.31 to 0.48)	0.672	0.08 (-0.35 to 0.51)	0.700
≥ 155 mmol/L	1.05 (-0.05 to 2.14)	0.061	1.05 (-0.21 to 2.30)	0.102
Potassium				
< 3 mmol/L	0.42 (-0.39 to 1.23)	0.311	0.42 (-0.37 to 1.22)	0.300
*3 – 6 mmol/L	-	-	-	-
≥ 6 mmol/L	0.02 (-0.33 to 0.36)	0.931	0.02 (-0.35 to 0.38)	0.934
eGFR				
*≥ 90	-	-	-	-
60-89	0.03 (-0.15 to 0.21)	0.727	0.03 (-0.15 to 0.21)	0.729
30-59	0.39 (0.21 to 0.57)	< 0.001	0.39 (0.20 to 0.57)	< 0.001
15-29	0.57 (0.33 to 0.81)	< 0.001	0.57 (0.33 to 0.81)	< 0.001
< 15	0.40 (0.15 to 0.65)	0.002	0.40 (0.14 to 0.66)	0.003
CRP				
*0 - 10	-	-	-	-
10 - 49	0.23 (0.08 to 0.39)	0.003	0.23 (0.07 to 0.39)	0.004
50 - 99	0.41 (0.20 to 0.62)	< 0.001	0.41 (0.19 to 0.62)	< 0.001
≥ 100	0.49 (0.28 to 0.70)	< 0.001	0.49 (0.27 to 0.71)	< 0.001
Albumin				
< 25	0.62 (0.18 to 1.07)	0.006	0.62 (0.16 to 1.09)	0.009
25-35	0.48 (0.31 to 0.65)	< 0.001	0.48 (0.30 to 0.66)	< 0.001
*≥ 35	-	-	-	-
Neutrophil count				
<2	0.15 (-0.26 to 0.56)	0.475	0.15 (-0.25 to 0.55)	0.467
*2-8	-	-	-	-
≥ 8	0.06 (-0.08 to 0.20)	0.379	0.06 (-0.08 to 0.21)	0.383
Haemoglobin				
< 80	-0.01 (-0.34 to 0.31)	0.935	-0.01 (-0.34 to 0.31)	0.936
80-110	0.03 (-0.12 to 0.18)	0.663	0.03 (-0.12 to 0.19)	0.676
*≥ 110	-	-	-	-
Constant	-3.43 (-3.69 to -3.16)	< 0.001	-3.43 (-3.70 to -3.16)	< 0.001

Supplementary Table 3. Common drug combinations.

Drug combination		n	% of study population (n = 9,584)
2 drugs	Sulphonylureas + metformin	1,012	10.6
	Insulin + metformin	743	7.8
	Metformin + DPP-4 inhibitors	458	4.8
	Insulin + sulphonylureas	370	3.9
	Sulphonylureas + DPP-4 inhibitors	351	3.7
	Insulin + DPP-4 inhibitors	233	2.4
3 drugs	Sulphonylureas + metformin + DPP-4	223	2.3
	Sulphonylureas + insulin + metformin	201	2.1