ความแปรปรวนของระดับน้ำตาลหลังอดอาหารที่วัดในแต่ละครั้งของการมารับบริการที่โรงพยาบาลมีความสัมพันธ์กับการนอนโรงพยาบาลด้วยภาวะน้ำตาลต่ำหรือไม่ :การศึกษาศูนย์เดียวในโรงพยาบาลเชียงรายประชานุเคราะห์ ประเทศไทย

ชินพร รัตนสะอาด พ.บ.**

บทคัดย่อ

ความเป็นมา : การนอนโรงพยาบาลด้วยภาวะน้ำตาลต่ำเป็นภาวะแทรกซ้อนที่สำคัญอย่างหนึ่งที่อาจเกิดขึ้นได้ในการรักษาโรคเบาหวานชนิดที่ 2 แม้ว่าแนวปฏิบัติจากสมาคมโรคเบาหวานไทยไม่ได้กล่าวถึงการวัดความแปรปรวนของระดับน้ำตาล แต่ American Diabetes Association ในปี 2022 ได้กล่าวถึงความเกี่ยวโยงระหว่างความแปรปรวนของระดับน้ำตาลกับการเกิดภาวะน้ำตาลต่ำ และมีคำแนะนำตั้งเป้าหมายควบคุมความแปรปรวนของระดับน้ำตาลโดยใช้ค่าเปอร์เซ็นต์ของสัมประสิทธิ์ความแปรปรวน (%CV; percent coefficient of variation) ที่วัดจากเครื่อง continuous glucose monitor (CGM) ผู้วิจัยเกิดความสงสัยว่าระดับน้ำตาลหลังอดอาหารที่วัดเป็นครั้งๆ ในการมารับบริการอาจสามารถบ่งชี้ถึงการนอนโรงพยาบาลด้วยภาวะน้ำตาลต่ำ จึงได้ทำการศึกษาเพื่อพิสูจน์ความเกี่ยวข้องนี้

วัตถุประสงค์ : เพื่อพิสูจน์ความสัมพันธ์ระหว่างความแปรปรวนของระดับน้ำตาลหลังอดอาหารในแต่ละครั้งของการมารับบริการกับการนอนโรงพยาบาลด้วยภาวะน้ำตาลต่ำ

วิธีการศึกษา : งานวิจัยแบบศึกษาตามรุ่นย้อนหลัง (retrospective cohort) ในประชากรผู้ใหญ่ที่ป่วยด้วยโรคเบาหวานชนิดที่ 2 และได้มารับบริการที่โรงพยาบาลเชียงรายประชานุเคราะห์ในปี พ.ศ. 2562 ถึง พ.ศ. 2564 รวมทั้งหมด 15,039 คน เหลือเข้าสู่การวิเคราะห์ 9,239 คน หลังการคัดออก วัดความแปรปรวนของระดับน้ำตาลหลังอดอาหารด้วยค่าสัมประสิทธิ์ความแปรปรวน (CV-FBS) โดยคำนวณจากค่าระดับน้ำตาลหลังอดอาหาร 3 ค่าที่สุ่มปีละ 1 ค่าใน 3 ปี ด้วยคอมพิวเตอร์ แบ่งกลุ่มผู้ป่วยออกเป็น 4 กลุ่ม ตามควาร์ไทล์ของ CV-FBS ทำการคำนวณ Kaplan-Meier curves, Log-rank test และ Cox proportional hazard regression

ผลการศึกษา : ควาร์ไทล์ที่ 1 มี CV-FBS 0.00 - 0.06 หรือ 0.00% - 5.89% ควาร์ไทล์ที่ 2 มี CV-FBS 0.06 - 0.11 หรือ 5.89% - 10.54% ควาร์ไทล์ที่ 3 มี CV-FBS 0.11 - 0.18 หรือ 10.54% - 18.35% ควาร์ไทล์ที่ 4 มี CV-FBS 0.18 - 0.89 หรือ 18.37% - 89.37% ได้ทำ Kaplan-Meier curves แสดงถึงโอกาสการนอนโรงพยาบาลด้วยภาวะน้ำตาลต่ำที่สูงขึ้นในควาร์ไทล์ที่สูงขึ้น Log-rank test พบ p-value <0.001 เมื่อเทียบกับควาร์ไทล์ที่ 1 แล้วพบว่า ควาร์ไทล์ที่ 2 มีค่า hazard ratio เท่ากับ 1.36 (p-value 0.229; 95%CI 0.82 - 2.25) ควาร์ไทล์ที่ 3 มีค่า hazard ratio เท่ากับ 1.87 (p-value 0.008; 95%CI 1.17 - 2.97) และควาร์ไทล์ที่ 4 มีค่า hazard ratio เท่ากับ 2.82 (p-value <0.001; 95%CI 1.78 - 4.46) ฉะนั้น ความแปรปรวนของระดับน้ำตาลหลังอดอาหารมีผลเพิ่มโอกาสการนอนโรงพยาบาลด้วยภาวะน้ำตาลต่ำอย่างมีนัยสำคัญในควาร์ไทล์ที่ 3 และควาร์ไทล์ที่ 4

สรุปและข้อเสนอแนะ : ความแปรปรวนของระดับน้ำตาลหลังอดอาหารในแต่ละครั้งของการมารับบริการมีความสัมพันธ์กับการนอนโรงพยาบาลด้วยภาวะน้ำตาลต่ำ โดยค่า CV-FBS สูงตั้งแต่ 0.11 หรือ 10.54% ขึ้นไปควรถือว่าเป็นปัจจัยเสี่ยงหนึ่งของการเกิดภาวะน้ำตาลต่ำ

คำสำคัญ : เบาหวานชนิดที่ 2 ความแปรปรวนของระดับน้ำตาล สัมประสิทธิ์ความแปรปรวนระดับน้ำตาลหลังอดอาหาร การนอนโรงพยาบาลด้วยภาวะน้ำตาลต่ำ

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IS VISIT-TO-VISIT FASTING GLUCOSE VARIABILITY ASSOCIATED WITH OCCURRENCE OF HYPOGLYCEMIA HOSPITALIZATION IN ADULT TYPE 2 DIABETIC PATIENTS? A SINGLE-CENTER POPULATION STUDY IN CHIANGRAI PRACHANUKROH HOSPITAL, THAILAND.

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ABSTRACT

BACKGROUND: Hospitalizations due to hypoglycemia is an important potential complication in the treatment of type 2 diabetes mellitus. Although, Thai Diabetes Association guideline did not mention measuring the glycemic variability, whereas American Diabetes Association (ADA) in 2022, mentioned that its influence on hypoglycemia events and made a glycemic target recommendation based on percent coefficient of variation (%CV) from continuous glucose monitoring (CGM) devices. Suspecting that visit-to-visit fasting glucose variation which reflects long-term glycemic variability might have a prognostic value on the incidences of hypoglycemia hospitalization, we investigate their association.

OBJECTIVE: To ascertain the association between visit-to-visit fasting glucose variability and the incidences of hypoglycemia hospitalization.

METHODS: A population-based retrospective observational cohort study was conducted. Medical records of 15,039 adult type 2 diabetic patients having a visit at Chiangrai Prachanukroh Hospital from 2019 to 2021 were reviewed, of which 9,239 patients were analyzed after exclusion. Measuring the visit-to-visit fasting glucose variation coefficient of variation (CV-FBS) calculated from three values of fasting glucose randomly selected by a computer program once per year for three years. Patients were divided into 4 groups according to quartiles of CV-FBS. Kaplan-Meier curves, Log-rank test and Cox proportional hazard regression were then calculated.

RESULTS: The first quartile has CV-FBS 0.00 - 0.06 or 0.00% - 5.89%, the second quartile 0.06 - 0.11 or 5.89% - 10.54%, the third quartile 0.11 - 0.18 or 10.54% - 18.35%, and the fourth quartile 0.18 - 0.89 or 18.37% - 89.37%. Kaplan-Meier curves were calculated showing higher event probability in the higher quartiles. Log-rank test yielded p-value <0.001. Compared to the first quartile, the second quartile had a hazard ratio of 1.36 (p-value 0.229; 95%CI 0.82 - 2.25); the third quartile had a hazard ratio of 1.87 (p-value 0.008; 95%CI 1.17 - 2.97); and the fourth quartile with had a hazard ratio of 2.82 (p-value <0.001; 95%CI 1.78 - 4.46). Thus, the impact of visit-to-visit fasting glucose variability on the risk of hypoglycemia hospitalization is statistically significant in the third and fourth quartiles.

CONCLUSIONS AND RECOMMENDATIONS: Visit-to-visit fasting glucose variation is associated with occurrence of hypoglycemia hospitalizations. High CV-FBS ≥ 0.11 or 10.54% should be considered a risk factor of hypoglycemia hospitalizations.

KEYWORDS: Type 2 diabetes, glycemic variability, coefficient of variation, fasting glucose, hypoglycemia hospitalization

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Background

Diabetes is a disease with high burden with a prevalence of 9.5% in 2020 as reported by the Diabetes Association of Thailand,[1,] and a prevalence of 11.6% or 38.4 million Americans in 2021 as reported by the American Diabetic Association (ADA).[2] Treatment of diabetes involves lowering the concentration of glucose in the blood circulation. Through an interplay of both absolute and relative insulin excess, hypoglycemic episodes may occur. Severe hypoglycemia is defined as "an event requiring the assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions[3] and episodes may lead to hospitalizations. Glucose is an essential fuel for the functioning and survival of the brain, and it is dependent on a continuous supply from the circulation.[4] This thus creates a dilemma in the treatment of diabetes: too much insulin and hypoglycemia develop with its devastating effects;[5] too little insulin and glycemic targets are not achieved resulting in further complications.[6]

The 2023 Thai diabetes guideline prescribes fasting blood sugar (FBS), 2-hr post-prandial blood sugar, and hemoglobin A1c (HbA1c) goals.[1] HbA1c integrates both basal and postprandial hyperglycemia.[7] However, the glycemic disorders in type 2 diabetes are not limited to just chronic sustained hyperglycemia, but also acute upward and downward changes. Oscillating blood glucose can have a more deleterious effect on the blood vessels than sustained chronic hyperglycemia. Control of glycemic variability would thus be beneficial in reducing the risk of diabetes complications.[8]

This is reflected in the ADA Guideline 2022 with glycemic variability goal in terms of percent coefficient of variation (%CV) ≤36.00% as measured by a continuous glucose monitoring (CGM) device to provide protection against hypoglycemia.[9] But CGM devices are scarcely available in Thailand.

From clinical experiences, we suspect that long-term glycemic variability itself has a prognostic value for incidence of hypoglycemia hospitalization. Though there were trials that established glycemic variability and severe hypoglycemia including hospitalizations,[10-12] none was performed in Thailand or resource-limited settings. Therefore, we conducted this study to ascertain the association in our primary care setting.

Objective

To ascertain the association between visit-to-visit fasting glucose variability and the incidences of hypoglycemia hospitalization.

Materials and Methods

Study Design

We conducted a retrospective cohort study using routine practice data of visits from January 1, 2019 to December 31, 2021 from Chiangrai Prachanukroh Hospital electronic medical record database. All adults aged 18 years or more with type 2 diabetes, defined the presence ICD-10 code E11 and anti-diabetic medicine prescriptions in the medical records, were evaluated without any sampling. Individuals who had fewer than one measurement of fasting glucose per year or had less than three years of fasting glucose data were excluded.

$$CV = \frac{SD}{Mean}$$

Visit-to-visit fasting glucose variability was measured by calculating the coefficient of variation (CV-FBS), which is a mean-normalized variability measure, from three values of fasting plasma glucose randomly selected by a computer program once per year in the last three years. The range of CV-FBS in the first quartile is between 0.00 (0.00%) and 0.06 (5.89%), the second quartile 0.06 (5.89%) and 0.11 (10.54%), the third quartile 0.11 (10.54%) and 0.18 (18.35%), and the fourth quartile 0.18 (18.37%) and 0.89 (89.37%).

Hypoglycemia hospitalization was defined as hospitalization for in-patient treatment with a provisional diagnosis in one of the ICD-10 codes E11.64, E16.0, E16.1, or E16.2. All were then manually reviewed. Person-time calculations were done in multiple intervals with different factors to account for patients with multiple visits or multiple hypoglycemia hospitalizations.

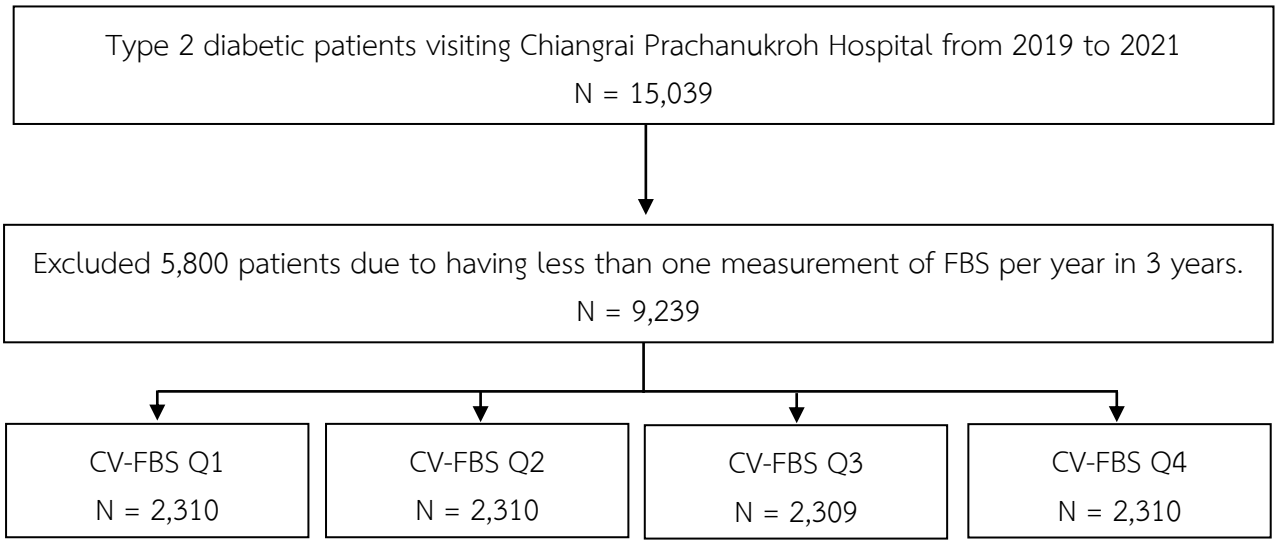

FIGURE 1 Study flow

Statistical Analysis

Baseline characteristics of the included patients are reported as mean with standard deviation (SD) for continuous variables, or as N with percent for categorical variables.

Continuous variables were compared using ANOVA, and categorical variables were compared using a chi-squared test.

Patients were divided into four groups based on quartiles of CV-FBS, with Q4 being most variable, and Q1 being least variable. Five Cox proportional hazard models were then computed with Q1 as reference. Model 1 was adjusted for demographic factors: sex, age, and insurance. Model 2 was adjusted for model 1 plus lifestyle factors: smoking, and drinking. Model 3 was adjusted for model 2 plus diabetes-related factors: use of insulin secretagogues, use of insulin injections, and presence of hypoglycemia hospitalization in the past 1 year. Model 4 was adjusted for model 3 plus comorbidity factors: polypharmacy (> 4 drugs), albuminuria, obesity (BMI ≥ 27 kg/m^2), chronic kidney disease (ICD10 code N18), cardiovascular disease (ICD10 codes I21, I22, I23, I24, and I25), dyslipidemia (ICD10 code E78), cerebrovascular disease (ICD10 codes I62, I63, and I69), hypertension (ICD code I10), and major depressive disorder (ICD10 code F32). Model 5 was adjusted for model 4 plus biological indices: systolic blood pressure (SBP), diastolic blood pressure (DBP), last triglyceride (TG), last total cholesterol (Chol), last low-density cholesterol (LDL), last high-density cholesterol (HDL), last creatinine (Cr), and last hemoglobin A1c (HbA1c)

The probability of hypoglycemia hospitalization for each quartile was modeled using multiple-event Cox hazard regression models with Efron method for ties, and Kaplan-Meier survival curves were calculated for each quartile.

All statistical analyses were performed using STATA version 16.1 and p-values <0.05 were considered significant.

ETHICAL CONSIDERATION

This study was approved by the Chiangrai-Prachanukroh Hospital Ethics Committee. Ref. no. CR 0033.102/EC 650

Results

Table 1 lists the baseline characteristics of the patients grouped by quartiles of CV-FBS. There were more females than males. Those in the highest quartile of CV-FBS had more insulin injection use, more medications prescribed, more chronic kidney disease, more cerebrovascular disease, and higher average HbA1c than the lowest quartile.

Figure 2 shows the Kaplan-Meier curves visualizing the higher probability of hypoglycemia hospitalizations in the higher quartiles over the three-year period. The log-rank test was performed, and the p-value was <0.001.

A total of 265 hypoglycemia hospitallization events was observed, yielding an overall incidence of 2.72% per person, or 3.89 events per 100000 person-days.

TABLE 1 Baseline characteristics

	Q1	Q2	Q3	Q4	p-value
N (%)	2,310 (25.00%)	2,310 (25.00%)	2,309 (24.99%)	2,310 (25.00%)	
Demographic factors					
Male	931 (40.30%)	959 (41.52%)	921 (39.89%)	1,028 (44.50%)	0.006
Age (years)	62.84 (10.64)	61.75 (10.53)	60.90 (11.06)	59.62 (11.84)	<0.001
Insurance					<0.001
None	15 (0.65%)	11 (0.48%)	13 (0.56%)	28 (1.21%)	
Universal coverage	1,582 (68.48%)	1,640 (71.00%)	1,734 (75.10%)	1,685 (72.94%)	
Government	557 (24.11%)	460 (19.91%)	374 (16.20%)	379 (16.41%)	
Social security	156 (6.75%)	199 (8.61%)	188 (8.14%)	218 (9.44%)	
Lifestyle factors					
Smoking	60 (2.60%)	68 (2.94%)	77 (3.33%)	89 (3.85%)	0.088
Drinking	175 (7.58%)	209 (9.05%)	219 (9.48%)	198 (8.57%)	0.118
Diabetes-related factors					
Use insulin secretagogues	529 (22.90%)	634 (27.45%)	698 (30.23%)	674 (29.18%)	<0.001
Use insulin injections	88 (3.81%)	140 (6.06%)	272 (11.78%)	506 (21.90%)	<0.001
Has hypoglycemia hospitalization in 1 year	13 (0.56%)	12 (0.52%)	22 (0.95%)	68 (2.94%)	<0.001
Comorbidity factors					
Polypharmacy (> 4 drugs)	1,781 (77.10%)	1,801 (77.97%)	1,852 (80.21%)	1,924 (83.29%)	<0.001
Albuminuria	1,012 (45.08%)	1,113 (49.29%)	1219 (54.06%)	1,369 (60.68%)	<0.001
Obesity (BMI ≥ 27 kg/m^2)	736 (32.49%)	798 (35.14%)	803 (35.41%)	745 (32.94%)	0.081
Chronic kidney disease	556 (24.07%)	610 (26.41%)	675 (29.23%)	844 (36.54%)	<0.001
Cardiovascular disease	211 (9.13%)	234 (10.13%)	244 (10.57%)	274 (11.86%)	0.023
Cerebrovascular disease	190 (8.23%)	188 (8.14%)	188 (8.14%)	255 (11.04%)	0.001
Dyslipidemia	2,203 (95.37%)	2,218 (96.02%)	2,203 (95.41%)	2171 (93.98%)	0.011
Hypertension	2,190 (94.81%)	2,185 (94.59%)	2,189 (94.80%)	2167 (93.81%)	0.395
Major depressive disorder	50 (2.16%)	29 (1.26%)	41 (1.78%)	51 (2.21%)	0.059
Biological indices					
SBP, mean (S.D.); mmHg	135.86 (17.25)	136.64 (17.15)	136.64 (17.54)	137.38 (19.31)	<0.001
DBP, mean (S.D.); mmHg	74.74 (11.54)	75.48 (11.44)	75.02 (11.64)	74.98 (11.87)	0.319
Triglyceride, mean (S.D.); mg/dL	148.22 (98.24)	155.14 (95.37)	160.20 (115.36)	160.63 (111.75)	<0.001
Cholesterol, mean (S.D.); mg/dL	170.61 (38.05)	172.10 (38.46)	172.29 (40.98)	171.98 (44.88)	<0.001
LDL, mean (S.D.); mg/dL	96.92 (32.32)	98.77 (32.90)	98.94 (95.22)	98.89 (37.99)	<0.001
HDL, mean (S.D.); mg/dL	49.49 (13.06)	48.68 (12.97)	47.38 (12.52)	47.30 (13.97)	<0.001
Creatinine, mean (S.D.); mg/dL	1.09 (0.84)	1.15 (1.08)	1.25 (1.32)	1.53 (1.87)	<0.001
HbA1c, mean (S.D.); %	7.09 (1.22)	7.30 (1.28)	7.66 (1.52)	8.21 (2.11)	<0.001

SBP=systolic blood pressure, DBP= diastolic blood pressure, LDL= low-density lipoprotein, HDL= high-density lipoprotein, HbA1c= glycated hemoglobin A1c

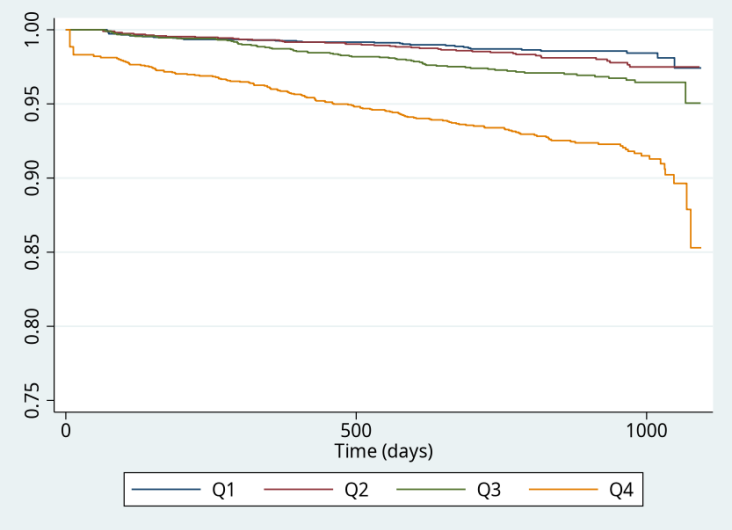

FIGURE 2 Kaplan-Meier survival curves

TABLE 2 Incidences of hypoglycemia hospitalization

	Person-days	Events	Rate (per 100000 person-days)	95%CI
Q1	1,702,399	28	1.64	1.14 - 2.38
Q2	1,675,455	39	2.33	1.70 - 3.19
Q3	1,713,455	64	3.74	2.92 - 4.77
Q4	1,716,633	134	7.81	6.59 - 9.25

After adjusting for all covariates, the third and fourth quartiles of CV-FBS are significantly associated with hypoglycemia hospitalization with hazard ratios of 1.87 (p-value 0.008; 95%CI 1.17 - 2.97) and 2.82 (p-value <0.001; 95%CI 1.78 - 4.46), respectively. The effect was most pronounced in the fourth quartile. There was no violation of the proportional hazard assumption.

TABLE 3 Cox proportional hazard models

	Model 1, HR (p-value; 95%CI)	Model 2, HR (p-value; 95%CI)	Model 3, HR (p-value; 95%CI)	Model 4, HR (p-value; 95%CI)	Model 5, HR (p-value; 95%CI)
CV-FBS					
Q1	REFERENCE	REFERENCE	REFERENCE	REFERENCE	REFERENCE
Q2	1.46 (0.176; 0.84 - 2.52)	1.46 (0.176; 0.84 - 2.52)	1.40 (0.204; 0.83 - 2.36)	1.37 (0.219; 0.83 - 2.27)	1.36 (0.229; 0.82 - 2.25)
Q3	2.37 (0.001; 1.44 - 3.90)	2.37 (0.001; 1.44 - 3.90)	1.94 (0.007; 1.20 - 3.13)	1.85 (0.011; 1.15 - 2.96)	1.87 (0.008; 1.17 - 2.97)
Q4	5.14 (<0.001; 3.22 - 8.18)	5.09 (<0.001; 3.20 - 8.11)	3.11 (<0.001; 1.94 - 5.00)	2.82 (<0.001; 1.77 - 4.48)	2.82 (<0.001; 1.78 - 4.46)
Demographic factors					
Male	1.12 (0.429; 0.85 - 1.47)	1.20 (0.207; 0.90 - 1.59)	1.10 (0.462; 0.85 - 1.42)	0.96 (0.766; 0.73 - 1.26)	1.07 (0.650; 0.80 - 1.42)
Age (years)	1.04 (<0.001; 1.03 - 1.05)	1.04 (<0.001; 1.02 - 1.05)	1.03 (<0.001; 1.02 - 1.05)	1.02 (0.004; 1.01 - 1.04)	1.02 (0.016; 1.00 - 1.04)
Insurance					
None	REFERENCE	REFERENCE	REFERENCE	REFERENCE	REFERENCE
Universal coverage	1.80 (0.560; 0.25 - 13.16)	1.84 (0.547; 0.25 - 13.46)	1.56 (0.659; 0.22 - 11.35)	1.55 (0.665; 0.22 - 11.08)	1.59 (0.645; 0.22 - 11.54)
Government	1.40 (0.743; 0.19 - 10.35)	1.41 (0.736; 0.19 - 10.47)	1.30 (0.795; 0.18 - 9.57)	1.35 (0.769; 0.18 - 9.85)	1.24 (0.836; 0.17 – 9.07)
Social security	1.66 (0.636; 0.20 - 13.41)	1.70 (0.620; 0.21 - 13.69)	1.36 (0.769; 0.17 - 10.81)	1.58 (0.664; 0.20 - 12.40)	1.35 (0.776; 0.17 - 10.62)
Lifestyle factors					
Smoking		0.95 (0.915; 0.39 - 2.31)	1.06 (0.893; 0.44 - 2.57)	0.91 (0.855; 0.35 - 2.40)	0.96 (0.930; 0.36 - 2.55)
Drinking		0.57 (0.043; 0.34 - 0.98)	0.60 (0.117; 0.39 - 1.11)	0.75 (0.276; 0.44 - 1.26)	0.72 (0.224; 0.42 - 1.23)
Diabetes-related factors					
Use insulin secretagogues			1.20 (0.245; 0.88 - 1.63)	1.17 (0.324; 0.86 - 1.60)	1.20 (0.257; 0.88 - 1.64)
Use insulin injections			2.90 (<0.001; 2.10 - 3.99)	2.50 (<0.001; 1.78 - 3.50)	2.35 (<0.001; 1.67 - 3.32)
Has hypoglycemia hospitalization in 1 year			8.00 (<0.001; 5.54 - 11.56)	6.56; <0.001; 4.51 - 9.53)	6.13 (<0.001; 4.22 – 8.90)

TABLE 3 (Cont.)

	Model 1, HR (p-value; 95%CI)	Model 2, HR (p-value; 95%CI)	Model 3, HR (p-value; 95%CI)	Model 4, HR (p-value; 95%CI)	Model 5, HR (p-value; 95%CI)
Comorbidity factors					
Polypharmacy (> 4 drugs)				0.90 (0.664; 0.56 - 1.45)	0.94 (0.785; 0.59 - 1.50)
Albuminuria				1.11 (0.514; 0.81 - 1.52)	1.03 (0.862; 0.75 - 1.41)
Obesity (BMI >= 27 kg/m^2)				0.77 (0.075; 0.58 - 1.03)	0.82 (0.193; 0.62 - 1.10)
Chronic kidney disease				2.18 (<0.001; 1.55 - 3.08)	2.03 (<0.001; 1.43 - 2.89)
Cardiovascular disease				1.14 (0.393; 0.84 - 1.56)	1.08 (0.626; 0.79 - 1.49)
Cerebrovascular disease				1.31 (0.133; 0.92 - 1.85)	1.28 (0.169; 0.90 - 1.83)
Dyslipidemia				0.62 (0.159; 0.32 - 1.21)	0.61 (0.159; 0.31 - 1.21)
Hypertension				0.74 (0.501; 0.31 - 1.77)	0.66 (0.356; 0.28 - 1.59)
Major depressive disorder				1.51 (0.285; 0.71 - 3.22)	1.66 (0.174; 0.80 – 3.46)
Biological indices					
SBP, mean (S.D.); mmHg					1.01 (0.018; 1.00 - 1.01)
DBP, mean (S.D.); mmHg					0.98 (0.017; 0.97 - 1.00)
Triglyceride, mean (S.D.); mg/dL					1.00 (0.698; 1.00 - 1.00)
Cholesterol, mean (S.D.); mg/dL					1.00 (0.219; 1.00 - 1.01)
LDL, mean (S.D.); mg/dL					0.99 (0.028; 0.99 - 1.00)
HDL, mean (S.D.); mg/dL					1.01 (0.107; 1.00 - 1.02)
Creatinine, mean (S.D.); mg/dL					1.05 (0.064; 0.99 - 1.10)
HbA1c, mean (S.D.); %					1.02 (0.593; 0.95 - 1.09)

CV-FBS, coefficient of variation of visit-to-visit fasting blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin A1c

CONCLUSIONS AND RECOMMENDATIONS:

Our retrospective study, we established that long-term glycemic variability, measured with visit-to-visit CV-FBS, is associated with higher incidences of hypoglycemia hospitalization. We recommend monitoring of long-term glycemic variability in addition to the standard parameters in the current Thai practice guidelines. High variability of fasting blood glucose (CV-FBS ≥ 0.11 or 10.54%) should be considered a risk factor of hypoglycemia hospitalization.

Hypoglycemia is a common complication in the treatment of diabetes.[13] Risk factors for hypoglycemia hospitalization were identified in prior studies, including potentially modifiable risk factors such as the choice of glucose-lowering agents.[14-16] The treatment of diabetes must always be balanced with the risk of iatrogenic complications including hypoglycemia. Episodes of hypoglycemia leads to fear of hypoglycemia which may interfere with treatments of diabetes, including attempts by the patient to keep his/her blood sugar high or self-adjusting treatment regimens.[17] If not managed by the physician properly, treatment goals may not be achieved.

There were similar studies that investigated the association between glycemic variability and severe hypoglycemia. The DEVOTE study was a trial that demonstrated the association between day-to-day fasting glycemic variability and severe hypoglycemia and cardiovascular events. However, it was performed on patients receiving insulin injections only; none of the participants were treated with oral agents.[12] Similarly, a post hoc analysis using data from the ACCORD trial measured glycemic variability with standard deviations of FBS and HbA1C also found the association with severe hypoglycemia.[10] However, the ACCORD trial was done in the US and Canada population which may limit its generalizability to other populations.[18]

Currently, Thai practice guidelines do not prescribe recommendations regarding glycemic variability,[1] but the ADA in its 2022 guideline indicated the link between glycemic variability and hypoglycemia events, and prescribes a glycemic target based on %CV as measured by CGM devices.[9] There were also prior studies that demonstrated negative consequences of glycemic variability, including cardiovascular events, strokes, and mortality.[19-21]

Our study demonstrates the utility of CV-FBS as a statistically significant risk factor of hypoglycemia hospitalization in the third quartile and up (CV-FBS ≥ 0.11 or 10.54%). Its use as a measure of glycemic variability in resource-limited settings where CGM devices are unavailable might be helpful. However, the exact cut-off value for the Thai people remains to be studied.

To the best of our knowledge, this is the first study to evaluate the association between visit-to-visit fasting glucose variability and hypoglycemia in Thailand. The strength of our study is that only routine practice data were used, and thus can be applied directly without additional measurements or instructions to the patients. This is especially important in resource-limited and rural primary care settings, where even access to fasting blood glucose measurement is scarce.

Limitations

This study has several limitations. Firstly, being a population-based study in the Muang district of Chiangrai, Thailand, caution must be exercised in applying our results to other populations. Secondly, being a retrospective observational study using routine practice data, unrecognized confounding variables, recording errors, and right-censoring may be unaccounted for. Thirdly, we did not include laboratory results obtained from outside sources that were not entered into the central laboratory database but nevertheless were used in clinical practice.

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