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Glucose variability during the early course of acute pancreatitis predicts two-year probability of new-onset diabetes: A prospective longitudinal cohort study

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Abstract

Background: Acute pancreatitis (AP) is the largest contributor to diabetes of the exocrine pancreas. However, there is no accurate predictor at the time of hospitalisation for AP to identify individuals at high risk for new-onset diabetes.

Objective: To investigate the accuracy of indices of glucose variability (GV) during the early course of AP in predicting the glycated haemoglobin (HbA1c) trajectories during follow-up.

Methods: This was a prospective longitudinal cohort study of patients without diabetes at the time of hospitalisation for AP. Fasting blood glucose was regularly measured over the first 72 h of hospital admission. The study endpoint was the HbA1c trajectories - high-increasing, moderate-stable, normal-stable - over two years of follow-up. Multinomial logistic regression analyses were conducted to investigate the associations between several common GV indices and the HbA1c trajectories, adjusting for covariates (age, sex, and body mass index). A sensitivity analysis constrained to patients with non-necrotising AP was conducted.

Results: A total of 120 consecutive patients were studied. All patients in the high-increasing HbA1c trajectory group had new-onset diabetes at 18 and 24 months of follow-up. Glycaemic lability index had the strongest significant direct association (adjusted odds ratio = 13.69; $p = 0.040$) with the high-increasing HbA1c trajectory. High admission blood glucose, standard deviation of blood glucose, and average real variability significantly increased the patients' odds of taking the high-increasing HbA1c trajectory by at least two-times. Admission blood glucose, but not the other GV indices, had a significant direct association (adjusted odds ratio = 1.46; $p = 0.034$) with the moderate-stable HbA1c trajectory. The above findings did not change materially in patients with non-necrotising AP alone.

Conclusions: High GV during the early course of AP gives a prescient warning of worsening HbA1c pattern and new-onset diabetes after hospital discharge. Determining GV during hospitalisation could be a relatively straightforward approach to early identification of individuals at high risk for new-onset diabetes after AP.

KEYWORDS
acute pancreatitis, diabetes, glucose variability, predictors, prospective cohort study

INTRODUCTION

Diabetes of the exocrine pancreas constitutes around 1.6% of all new-onset diabetes in adults.[1] Its most common subtype, post-pancreatitis diabetes mellitus, is associated with a 13% higher risk of all-cause mortality than type 2 diabetes.[2] Further, the efficacy of common antidiabetic medications differs considerably between post-pancreatitis diabetes mellitus and type 2 diabetes.[3] A 2021 population-based study demonstrated that individuals with post-pancreatitis diabetes mellitus have worse glycaemic control (as evidenced by elevated glycated haemoglobin (HbA1c)) than those with type 2 diabetes.[4] Post-pancreatitis diabetes mellitus is a common sequela of acute pancreatitis (AP). A 2014 meta-analysis and meta-regression of 24 cross-sectional and case-control studies showed that new-onset diabetes develops in 23% of AP patients during follow-up and the severity of AP is not a predictor of diabetes.[5] The latter finding was corroborated in subsequent large scale population-based studies.[6,7] Those studies showed that individuals with mild AP were at a more than two-times higher risk of developing new-onset diabetes (in comparison with the general population), which was not dissimilar to individuals with non-mild AP. Therefore, identification of high-risk individuals at the time of recovery from an attack of AP is of importance and it is one of the core elements of the 'holistic prevention of pancreatitis' framework.[1]

The LACERTA project was the first longitudinal cohort study of consecutive non-selected patients with AP who had no diabetes (either diagnosed or undiagnosed) and who were prospectively followed up at regular intervals after hospital discharge.[8] Several studies conducted in the settings of acute diseases other than AP showed that in-hospital hyperglycaemia may be a predictor of new-onset diabetes and its associated complications.[9–12] Further, significant associations between increased glucose variability (GV) in hospitalised patients (not requiring intensive care unit admission) and worse short- and long-term outcomes were demonstrated.[13,14] We hypothesised that GV during the course of AP reflects latent disturbances in glucose metabolism that set the individual on the path to overt diabetes after hospital discharge. The aim was to investigate whether common indices of GV during the early course of AP can accurately predict patients who develop new-onset diabetes after AP.

Key summary

Summarise the established knowledge on this subject

- The high burden of deranged glucose metabolism after an attack of acute pancreatitis, irrespective of its severity, is being increasingly appreciated.
- There is currently no scientific evidence on how to identify patients at high risk of new-onset diabetes after acute pancreatitis.
- HbA1c trajectories during follow-up is a robust clinical endpoint that suits well longitudinal studies of patients after an attack of pancreatitis.

What are the significant and/or new findings of this study?

- Glucose variability during hospitalisation for acute pancreatitis accurately predicts future risk of developing deranged glucose metabolism, including new-onset diabetes after acute pancreatitis.
- High glycaemic lability index significantly increases the odds of taking the high-increasing HbA1c trajectory (and developing new-onset diabetes) by 13 times.
- Admission blood glucose significantly increases the odds of both taking the high-increasing HbA1c trajectory and taking the moderate-stable HbA1c trajectory by approximately two times.

METHODS

Source of data

The study was a prospective longitudinal cohort study of patients with AP admitted to non-referral hospital that serves a population of approximately 500,000 people (Auckland City Hospital). This study was conducted by the COSMOS group as part of the LACERTA project (approved by the Health and Disability Ethics Committee (13/STH/182)). The study complied with the Helsinki Declaration and the TRIPOD reporting guidelines for prognostic studies.[15]

Participants

Consecutive individuals aged 18 years or above with a primary diagnosis of AP, established prospectively based on international guidelines,[16] were invited to participate. All participants provided written informed consent. Individuals who had diabetes mellitus before hospitalisation or at the time of hospitalisation (defined as HbA1c $\geq$ 6.5% (48 mmol/mol) and/or use of antidiabetic medications[17]), definite chronic pancreatitis, post-endoscopic retrograde cholangiopancreatography pancreatitis, pancreatic surgery, endoscopic or percutaneous necrosectomy or drainage of pancreatic fluid collections, autoimmune diseases (e.g., autoimmune pancreatitis, celiac disease), malignancy (except non-melanoma skin cancer), severe

systemic illness, diseases that may affect HbA1c levels (e.g., chronic kidney disease, disorders of iron metabolism), took medications that may affect glycaemic status (e.g., systemic corticosteroids, systemic immunosuppressants, antipsychotics), or were pregnant/postpartum were excluded from the study.

All participants underwent regular (including weekends and public holidays) blood glucose measurements by the COSMOS group in the fasted state during the first 72 h after hospital admission for AP using the same finger-prick test (FreeStyle®, Abbot). The first glucose measurement was taken within 24 h of hospitalisation (when all participants were nil-by-mouth, in line with the standard of care in our institution). Then fasting glucose measurements were taken every 24 h over the following two days. If an in-hospital diet was introduced, glucose measurements were done after at least 8 h of fasting. All study participants received standard up-to-date management during the course of AP[18] and none received parenteral nutrition or intravenous infusion of dextrose during the first 72 h after hospital admission.[19] All participants were prospectively followed up by the COSMOS group every 6 months for up to two years and none of them followed a diabetes prevention protocol or received a treatment for diabetes.

Outcome

The study outcome was membership in one of the three mutually exclusive groups based on the within-person change in glycaemia over two years of follow-up. The process of categorising individuals into the trajectory-based glycaemia groups was described in detail elsewhere.[8] The groups were termed 'normal-stable glycaemia', 'moderate-stable glycaemia', and 'high-increasing glycaemia' (Figure 1). Given that diabetes status (as a static binary variable) can change in two directions during follow-up, the use of trajectories enabled the robust identification of a subgroup of AP individuals with consistently worsening HbA1c pattern during follow-up (i.e., high-increasing glycaemia). These individuals progressed from borderline normoglycaemia/prediabetes at the time of hospitalisation to overt diabetes within 18-24 months of prospective follow-up. This means that all patients with high-increasing glycaemia had new-onset diabetes after AP. Glycated haemoglobin was measured at our hospital's accredited laboratory using an enzymatic colourimetric assay (Trinity Biotech, Ireland), which is certified by the National Glycohaemoglobin Standardisation Program and standardised to the Diabetes Control and Complications Trial reference assay.

Predictors

Predictors were derived from fasting blood glucose measurements during the first 72 h of hospitalisation for AP. Four predictors were calculated as follows:

1. Admission blood glucose (ABG) (mmol/L) was determined as the first fasting glucose measurement taken within 24 h of admission.
2. Standard deviation of blood glucose (SD_{BG}) was calculated as the arithmetic standard deviation.
3. Average real variability (ARV) (mmol/L) was calculated using the equation: $ARV = 1/(N-1)\sum_{i=1}^{N-1}|Glucose_{i+1} - Glucose_i|$; where N denotes the number of valid glucose readings, and i is the order of measurements.
4. Glycaemic lability index (GLI) (mmol/L) was calculated using the equation: $GLI = \sum \frac{\lambda^2}{t}$; where λ is the squared difference between two consecutive glucose measurements, and t is the time between the measurements (24 h).[20]

Covariates

Body mass index (BMI) (kg/m^2) was determined using a digital medical scale with a stadiometer (Health o metre®) and patients were categorised as 'normal'(<25 kg/m^2), 'overweight' (25 to 29.9 kg/m^2), or 'obese' (≥30 kg/m^2). Aetiology of AP was categorised as biliary AP, alcohol-related AP, and other. Recurrence of AP was defined as two or more episodes of confirmed AP (at least 30 days apart) prior to enrolment into the study. Pancreatic necrosis was determined based on computed tomography during hospitalisation.

Missing data

Missing in-hospital glucose values were replaced with the most plausible values using the MI procedure in SAS (Supporting Information).

Statistical analysis

The differences in baseline characteristics of patients between the three glycaemia groups (i.e., normal-stable, moderate-stable, and high-increasing) were evaluated using one-way analysis of variance test and chi-square test. Data were presented as mean ± SD and frequency. The subsequent statistical analyses were conducted in two steps. First, multinomial logistic regression analyses were conducted to investigate the associations between membership in the glycaemia groups during follow-up as the dependent variable and the predictors (ABG, SD_{BG}, ARV, and GLI) during hospitalisation as the independent variables. For all analyses, normal-stable glycaemia was set as the reference. All analyses were conducted using two models: model 1 was the unadjusted model and model 2 was adjusted for age, sex, and BMI. Second, a pre-specified sensitivity analysis was conducted with a view to exploring the effect of pancreatic necrosis on the estimates. This analysis was constrained to individuals with non-necrotising AP only. Data were presented as odds ratio (OR) with corresponding 95% confidence interval (CI) in the above analyses. For all analyses, p values < 0.05 were deemed to be statistically

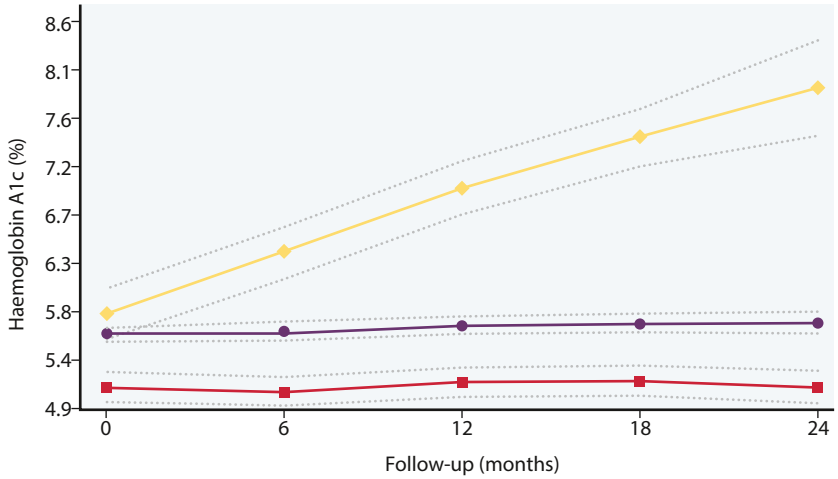

FIGURE 1 Distinct HbA1c trajectories after an attack of acute pancreatitis. Trajectories were determined using group-based trajectory modelling in 120 individuals. Red line (□) represents 'normal-stable glycaemia', purple line (○) represents 'moderate-stable glycaemia', yellow line (◊) represents 'high-increasing glycaemia'

significant. A receiver-operating characteristic (ROC) curve was generated from multivariate models (adjusted for age, sex, and BMI). The area under the curve (AUC) was calculated to determine the prognostic accuracy for each GV index as a predictor of high-increasing and moderate-stable glycaemia. Cut-off thresholds, sensitivity and specificity values, and Youden's index (J statistic) were calculated for each predictor. All statistical analyses were conducted using SPSS 25.0 and SAS 9.4 for Windows (USA).

RESULTS

Characteristics of the study groups

The study included a total of 120 patients with AP. The normal-stable glycaemia group ($n = 40$) included individuals with a mean (95% CI) HbA1c of 5.1% (5.0–5.3) at baseline that remained relatively stable at 5.1% (4.9–5.2) at 6 months, 5.2% (5.0–5.3) at 12 months, 5.2% (5.0–5.3) at 18 months, and 5.1% (5.0–5.3) at 24 months of follow-up. The moderate-stable glycaemia group ($n = 72$) included individuals with a mean (95% CI) HbA1c of 5.6% (5.6–5.7) at baseline that remained relatively stable at 5.6% (5.6–5.7) at 6 months, 5.7% (5.6–5.8) at 12 months, 5.7% (5.6–5.8) at 18 months, and 5.7% (5.6–5.8) at 24 months of follow-up. The high-increasing glycaemia group ($n = 8$) included individuals with a mean (95% CI) HbA1c of 5.8% (5.6–6.0) at baseline that progressively increased to 6.4% (6.1–6.6) at 6 months, 7.0% (6.7–7.2) at 12 months, 7.5% (7.2–7.7) at 18 months, and 7.9% (7.5–8.4) at 24 months of follow-up. While the three study groups were significantly different in terms of sex ($p = 0.012$), the groups did not differ significantly in terms of age ($p = 0.155$) and BMI ($p = 0.353$) (Table 1). None of the patients was diagnosed with pancreatic cancer during follow-up. Other characteristics of the study groups are presented in Table 1.

Admission blood glucose in the study groups

Admission blood glucose was significantly associated with high-increasing glycaemia in both the unadjusted and adjusted models (Table 2). For every mmol/L increase in ABG, the odds of taking the high-increasing trajectory during follow-up increased by OR (95% CI) of 2.19 (1.13, 4.24), $p = 0.020$, in the adjusted model (Table 2). The ROC curve for ABG in the high-increasing HbA1c glycaemia versus the normal-stable HbA1c glycaemia is presented in Figure 2. Admission blood glucose was significantly associated with moderate-stable glycaemia in both the unadjusted and adjusted models. For every mmol/L increase in ABG, the odds of taking the moderate-stable trajectory during follow-up increased by OR (95% CI) of 1.46 (1.03, 2.07), $p = 0.034$, in the adjusted model (Table 2). The ROC curve for ABG in the moderate-stable glycaemia versus the normal-stable glycaemia is presented in Figure 3. The ABG cut-off thresholds for predicting high-increasing glycaemia and moderate-stable glycaemia are presented in Table 3. The above associations did not change materially in the sensitivity analysis constrained to individuals with non-necrotising AP (Table 4).

Standard deviation of blood glucose in the study groups

Standard deviation of blood glucose was significantly associated with high-increasing glycaemia in both the unadjusted and adjusted models (Table 2). For every unit increase in SD_{BG}, the odds of taking the high-increasing trajectory during follow-up increased by OR (95% CI) of 3.36 (1.10, 10.31), $p = 0.034$, in the adjusted model. The ROC curve for SD_{BG} in the high-increasing glycaemia versus the normal-stable glycaemia is presented in Figure 2. The SD_{BG} cut-off

TABLE 1 Characteristics of study participants

Characteristic	Glycaemia groups during follow-up			p
	Normal-stable	Moderate-stable	High-increasing	
Age (years)	48 ± 16	54 ± 16	53 ± 20	0.155
Sex (*n*, %)				0.012[a]
Men	18 (45)	44 (61)	8 (100)	
Women	22 (55)	28 (39)	0 (0)	
Body mass index (kg/m^2)				0.353
Normal	17 (43)	19 (26)	2 (25)	
Overweight	13 (32)	25 (35)	2 (25)	
Obese	10 (25)	28 (39)	4 (50)	
Pancreatic necrosis (n, %)				0.468
Yes	1 (2)	4 (6)	1 (12)	
No	39 (98)	68 (94)	7 (88)	
Recurrence (*n*, %)				0.219
Yes	15 (37)	18 (25)	1 (12)	
No	25 (63)	54 (75)	7 (88)	
Aetiology (*n*, %)				0.510
Biliary	21 (53)	38 (53)	5 (63)	
Alcohol-related	8 (20)	15 (21)	3 (37)	
Others	11 (27)	19 (26)	0 (0)	

Note: Body mass index was categorised as normal (<25 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2). Participant-related characteristics are presented as frequency or mean ± standard deviation.

[a]Statistically significant *p* values (<0.05).

TABLE 2 Associations between indices of glucose variability during the early course of acute pancreatitis and the trajectory-based glycaemia groups during follow-up in the overall cohort

Index	Overall cohort Mean ± SEM	Model	Moderate-stable glycaemia OR (95% CI)	p	High-increasing glycaemia OR (95% CI)	p
ABG (mmol/L)	6.20 ± 0.01	1	1.54 (1.11, 2.13)	0.011[a]	2.07 (1.18, 3.63)	0.012[a]
		2	1.46 (1.03, 2.07)	0.034[a]	2.19 (1.13, 4.24)	0.020[a]
SD_{BG}	1.15 ± 0.01	1	0.99 (0.53, 1.84)	0.966	2.84 (1.09, 7.42)	0.033[a]
		2	0.94 (0.49, 1.78)	0.847	3.36 (1.10, 10.31)	0.034[a]
ARV (mmol/L)	1.28 ± 0.01	1	1.03 (0.58, 1.83)	0.924	2.43 (1.00, 5.92)	0.051
		2	1.00 (0.55, 1.81)	0.795	2.83 (1.01, 7.94)	0.048[a]
GLI (mmol/L)	0.28 ± 0.01	1	0.97 (0.21, 4.34)	0.962	7.07 (1.02, 48.73)	0.047[a]
		2	0.86 (0.19, 4.02)	0.850	13.69 (1.12, 167.17)	0.040[a]

Note: Model 1: unadjusted; Model 2: adjusted for age, sex, and body mass index. 'Normal-stable glycaemia' was set as the reference.

Abbreviations: ABG, admission blood glucose; ARV, average real variability; CI, confidence interval; GLI, glycaemic lability index; OR, odds ratio; SD_{BG}, standard deviation of blood glucose; SEM, standard error of the mean.

[a]Statistically significant *p* values (<0.05).

threshold for predicting high-increasing glycaemia is presented in Table 3. Standard deviation$_{BG}$ was not significantly associated with moderate-stable glycaemia in both the unadjusted and adjusted models (Table 2). The ROC curve for SD_{BG} in the moderate-stable glycaemia versus the normal-stable glycaemia is presented in Figure 3. The above associations did not change materially in the

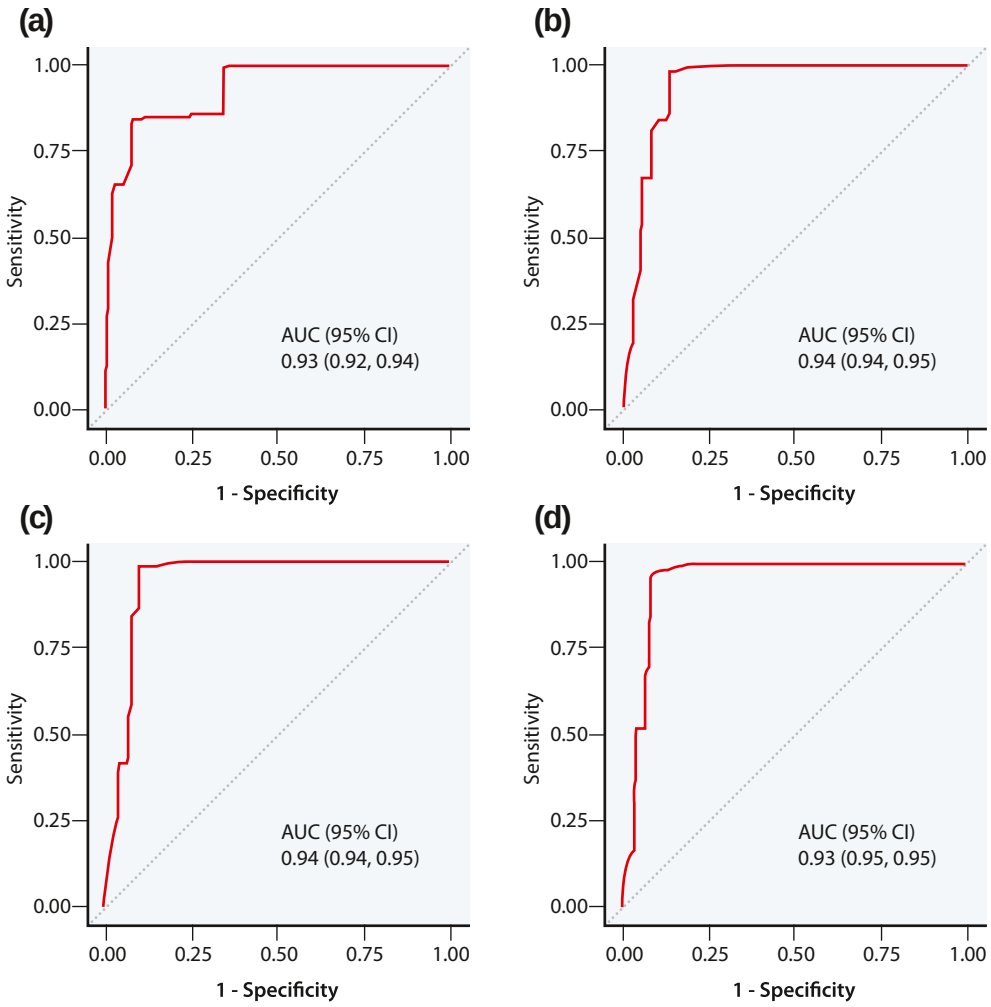

FIGURE 2 Receiver-operating characteristic curves of the studied predictors in the high-increasing glycaemia group versus the normal-stable glycaemia group (a) Admission blood glucose; (b) Standard deviation of blood glucose; (c) Average real variability; (d) Glycaemic lability index. The curves were generated from multivariate analyses adjusted for age, sex, and body mass index. Solid line represents 'high-increasing glycaemia' and dotted line represents the chance of differentiating the groups to be as good as flipping a coin

sensitivity analysis constrained to individuals with non-necrotising AP (Table 4).

Average real variability in the study groups

Average real variability was significantly associated with high-increasing glycaemia in the adjusted model only (Table 2). For every mmol/L increase in ARV, the odds of taking the high-increasing trajectory during follow-up increased by OR (95% CI) of 2.83 (1.01, 7.94), $p = 0.048$, in the adjusted model. The ROC curve for ARV in the high-increasing glycaemia versus the normal-stable glycaemia is presented in Figure 2. The ARV cut-off threshold for predicting high-increasing glycaemia is presented in Table 3. Average real variability was not significantly associated with moderate-stable glycaemia in both the unadjusted and adjusted models (Table 2). The ROC curve for ARV in the moderate-stable glycaemia versus the normal-stable glycaemia is presented in Figure 3. The above associations did not change materially in the sensitivity analysis constrained to individuals with non-necrotising AP (Table 4).

Glycaemic lability index in the study groups

Glycaemic lability index was significantly associated with high-increasing glycaemia in both the unadjusted and adjusted models (Table 2). For every mmol/L increase in GLI, the odds of taking the high-increasing trajectory during follow-up increased by OR (95% CI) of 13.69 (1.12, 167.17), $p = 0.040$, in the adjusted model. The ROC curve for GLI in the high-increasing glycaemia versus the normal-stable glycaemia is presented in Figure 2. The GLI cut-off threshold for predicting high-increasing glycaemia is presented in Table 3. Glycaemic lability index was not significantly associated with moderate-stable

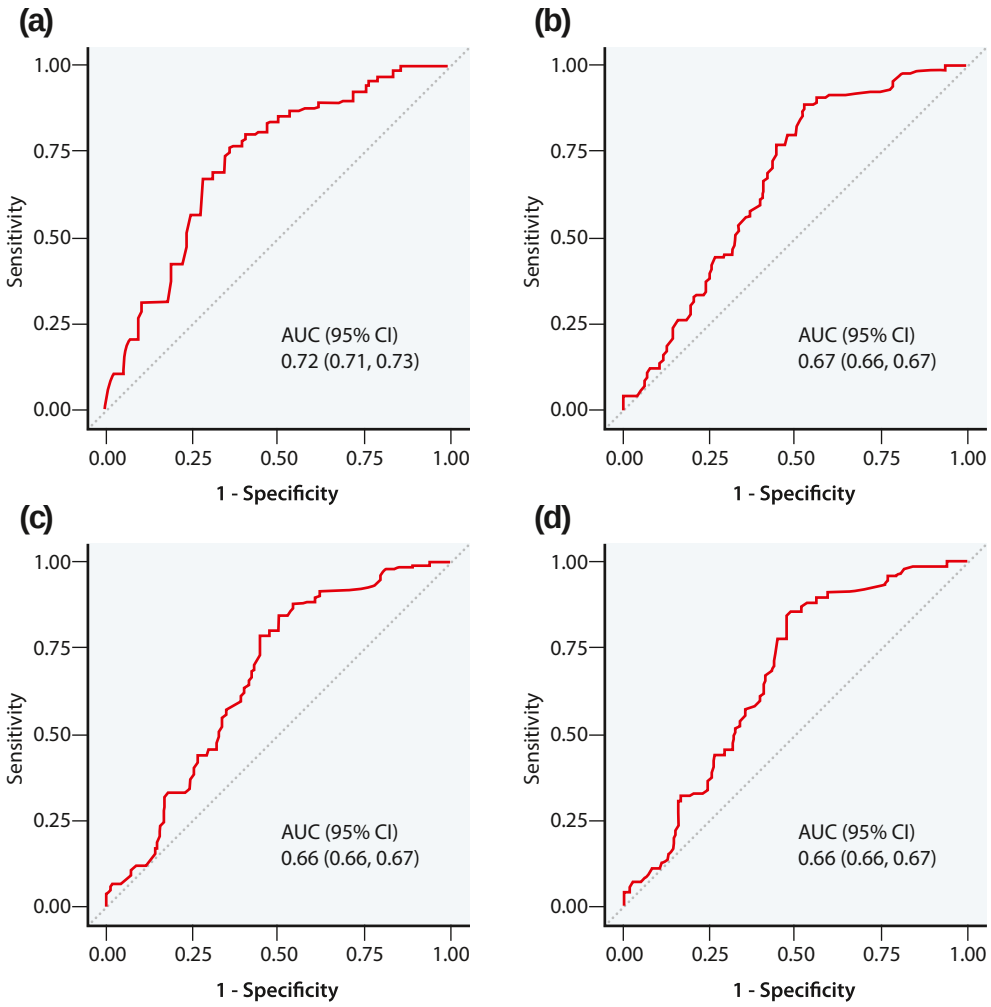

FIGURE 3 Receiver-operating characteristic curves of the studied predictors in the moderate-stable glycaemia group versus the normal-stable glycaemia group (a) Admission blood glucose; (b) Standard deviation of blood glucose; (c) Average real variability; (d) Glycaemic lability index. The curves were generated from multivariate analyses adjusted for age, sex, and body mass index. Solid line represents 'high-increasing glycaemia' and dotted line represents the chance of differentiating groups to be as good as flipping a coin

TABLE 3 Accuracy of the studied indices in predicting moderate-stable and high-increasing trajectories of glycaemia

		Moderate-stable glycaemia			High-increasing glycaemia		
Index	**Cut-off value**	**Sensitivity**	**Specificity**	**J**	**Sensitivity**	**Specificity**	**J**
ABG	6.29 mmol/L	41%	81%	0.22	50%	80%	0.30
SD_{BG}	1.66	80%	20%	−0.01	69%	72%	0.41
ARV	1.85 mmol/L	82%	18%	0.00	70%	76%	0.46
GLI	0.30 mmol/L	77%	23%	0.01	72%	71%	0.43

Note: Based on the overall cohort data. 'Normal-stable glycaemia' was set as the reference.

Abbreviations: ABG, admission blood glucose; ARV, average real variability; GLI, glycaemic lability index; J, Youden's index; SD_{BG}, standard deviation of blood glucose.

glycaemia in both the unadjusted and adjusted models (Table 2). The ROC curve for GLI in the moderate-stable glycaemia versus the normal-stable glycaemia is presented in Figure 3. The above associations did not change materially in the sensitivity analysis constrained to individuals with non-necrotising AP (Table 4).

DISCUSSION

This was the first prospective longitudinal cohort study to investigate whether fluctuations in fasting blood glucose levels (as evidenced by standard GV indices) during the course of AP can identify individuals

TABLE 4 Associations between indices of glucose variability during the early course of acute pancreatitis and the trajectory-based glycaemia groups during follow-up in patients without pancreatic necrosis

		Moderate-stable glycaemia		High-increasing glycaemia	
Index	**Model**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
ABG (mmol/L)	1	1.52 (1.10, 2.10)	0.011[a]	2.11 (1.22, 3.66)	0.008[a]
	2	1.45 (1.03, 2.06)	0.034[a]	2.27 (1.19, 4.32)	0.012[a]
SD_{BG}	1	1.03 (0.55, 1.94)	0.916	2.97 (1.10, 8.04)	0.032[a]
	2	0.97 (0.51, 1.87)	0.933	3.27 (1.04, 10.27)	0.042[a]
ARV (mmol/L)	1	1.06 (0.60, 1.88)	0.846	2.47 (1.00, 6.08)	0.050
	2	1.02 (0.56, 1.87)	0.935	2.73 (0.96, 7.77)	0.059
GLI (mmol/L)	1	1.06 (0.23, 4.77)	0.943	7.66 (1.04, 56.20)	0.045[a]
	2	0.92 (0.19, 4.36)	0.917	12.90 (1.02, 162.65)	0.048[a]

Note: Model 1: unadjusted; Model 2: adjusted for age, sex, and body mass index. 'Normal-stable glycaemia' was set as the reference.

Abbreviations: ABG, admission blood glucose; ARV, average real variability; CI, confidence interval; GLI, glycaemic lability index; OR, odds ratio; SD_{BG}, standard deviation of blood glucose.

[a]Statistically significant *p* values (<0.05).

who are at high risk for developing progressively worsening hyperglycaemia and new-onset diabetes after hospital discharge. To date, GV has mostly been investigated only as a risk factor for mortality in critically ill patients.[21,22] Further, high GV (assessed with the use of continuous glucose monitoring) has been shown to be significantly associated with the presence of diabetes in cross-sectional studies in the setting of chronic pancreatitis.[23,24] However, changes in GV (and, by extension, possible usefulness of continuous glucose monitoring) in unselected AP patients is an unchartered territory. In the present study, for the first time, we explored the usefulness of in-hospital GV as a predictive marker of consistently worsening HbA1c pattern (and resulting new-onset diabetes) long after hospital discharge from AP. A strength of the present study was that patients with pre-existing diabetes (either diagnosed or undiagnosed) were excluded. All participants (regardless of aetiology of AP or the presence of pancreatic necrosis) were assessed at several regular time points during hospitalisation for AP. Furthermore, all participants were followed up every 6 months over two years after hospital discharge. Glycated haemoglobin was measured at baseline and during follow-ups (in the same accredited laboratory using an assay certified by the National Glycohaemoglobin Standardisation Program and standardised to the Diabetes Control and Complications Trial reference assay), which was used to determine the glycaemia groups. We used HbA1c trajectories during follow-up as the study outcome (as opposed to merely the presence or absence of new-onset diabetes after AP based on a binary classification[17,25]), which offered an additional facet of robustness. This is important as ignoring the fact that the diabetes status of an individual may not only escalate but also de-escalate over time may lead to biased inferences.[26] We acknowledge though that all the patients who took the high-increasing HbA1c trajectory in the present study had new-onset diabetes (defined in line with the American Diabetes Association guidelines and the 2021 'DEP criteria'[17,25]). Also, we used a series of multinomial logistic regression analyses with adjustments for possible confounders (such as sex, age, and BMI) to obtain the most robust results.

The study found that all the four studied predictors had excellent accuracy (AUC >0.90) in predicting the high-increasing HbA1c trajectory (and new-onset diabetes after AP) during follow-up. Specifically, elevated levels of ABG, ARV, SD_{BG}, and GLI increased the odds of having progressively worsening hyperglycaemia between 2-fold and 13-fold. The ARV, SD_{BG}, and GLI findings were specific for the high-increasing HbA1c trajectory (as the same indices were not accurate in predicting the moderate-stable HbA1c trajectory), suggesting that these GV indices could potentially be clinically useful in predicting new-onset diabetes during follow-up. In addition, a sensitivity analysis showed that the above associations remained significant in individuals with non-necrotising AP alone, indicating that glucose fluctuations during hospitalisation for even mild AP (that comprises the majority of AP cases) is a useful predictor of future risk of new-onset diabetes after hospital discharge. This is particularly important as the routine parameters collected during hospitalisation for AP (such as common markers of inflammation, pancreatitis-related characteristics, lipid profile, liver panel, and anthropometrics) were not significant predictors of the high-increasing HbA1c trajectory in a previous study that emanated from the LACERTA project.[8]

Hyperglycaemia during myocardial infarction, stroke, and other acute and critical illnesses is a well-known phenomenon, which is mediated by a complex interplay of glucoregulatory hormones, inflammatory pathways, and neuroendocrine systems.[27] The metabolic response to stress was previously considered an essential adaptive response that subsides during recovery. However, a comprehensive 2017 systematic review and meta-analysis by the COSMOS group pooled data on 121,501 patients with acute and critical illnesses (without pre-existing diabetes) and showed that the prevalence of new-onset diabetes during follow-up escalates with the degree of in-hospital hyperglycaemia.[28] Further, several studies demonstrated

that GV is a stronger correlate of poor outcomes than degree of hyperglycaemia.[29,30] In the present study, wide excursions in glucose concentrations during hospitalisation for AP significantly increased the patients' odds of taking the high-increasing HbA1c trajectory (and having new-onset diabetes) within two years after hospital discharge. Specifically, the high-increasing glycaemia group showed the strongest association with GLI (OR = 13.7, p = 0.040), followed by SD_{BG} (OR = 3.36, p = 0.034) and ARV (OR = 2.83, p = 0.048) in the adjusted model. It is worth noting that patients without diabetes in two of the three trajectory groups (high-increasing and moderate-stable) had borderline impaired glucose tolerance (prediabetes) at baseline (HbA1c of 5.8% in the high-increasing group and HbA1c of 5.6% in the moderate-stable group). Taking into account that HbA1c values reflect glucose measurements over the previous 2–3 months and are not affected by short-term blood glucose fluctuations, significant associations between three indices of GV and the high-increasing group only (and not the moderate-stable group) suggest that individuals with a similar degree of early glucose derangements at baseline may differ in terms of GV. Acute fluctuations in blood glucose values lead to a less stable glucose homoeostasis and tip it over the edge in susceptible patients, thereby contributing to overt diabetes during follow-up. Our findings indicate that high GV during the early course of AP is important in distinguishing patients with impaired glucose intolerance (prediabetes) who will take the high-increasing glycaemic trajectory (develop new-onset diabetes) from those who will take the moderate-stable glycaemic trajectory (remain with prediabetes). Moreover, the fact that the above associations remained consistently significant in patients with non-necrotising AP further supports the paradigm that mechanisms other than extensive β-cell destruction are involved in the pathogenesis of new-onset diabetes after AP.[31–33]

One of the mechanisms underlying the development of new-onset diabetes in patients with in-hospital hyperglycaemia could relate to 'glycaemic memory'.[34] Hyperglycaemia increases oxidative stress and stimulates the production of reactive oxygen species, leading to overexpression of superoxides, activation of the protein-kinase C pathways, increased flux through the polyol pathway, and excessive production of advanced glycation end-products.[35] Moreover, hyperglycaemia-linked epigenetic changes (such as DNA methylation and histone diacylation) in the antioxidant and inflammatory genes exacerbates the systemic inflammatory response and insulin resistance.[36] Evidence from preclinical and clinical studies has shown that exposure to oscillating levels of glucose (as opposed to constant levels) increases oxidative stress, causing a more pronounced effect on endothelial dysfunction in both healthy and type 2 diabetes individuals.[37,38] Further, a positive correlation between GV indices and markers for oxidative stress (e.g., 8-iso-prostoglandin F2α) has been reported.[38,39] These findings reinforce 'the legacy effect' of glycaemic memory in diabetes, suggesting that imbalance of glucose metabolism during acute illnesses and the resulting persistent oxidative stress could increase an individual's risk of future hyperglycaemia.

It is important to note that, although all the four studied predictors consistently had an AUC >0.90 that signifies an overall very good prognostic accuracy,[40] their potential to be used in the clinic differs. Admission blood glucose, a simple single blood measurement that is routinely done upon admission of patients with AP, was a significant predictor (OR = 2.19) of the high-increasing HbA1c trajectory (and new-onset diabetes after AP). At the same time, it was also a significant predictor (OR = 1.46) of the moderate-stable HbA1c trajectory (and prediabetes during follow-up). In a *post hoc* analysis we found that, if ABG alone had been used, half of patients with new-onset diabetes after AP would have been missed. The above arguments suggest that, albeit ABG is a far easier measurement than ARV, SD_{BG}, and GLI, ABG alone cannot accurately identify people with AP who are at high risk of new-onset diabetes. The other studied predictors were more labour-intensive (required serial blood glucose measurements over three consecutive days of hospitalisation) but were associated specifically with the high-increasing HbA1c trajectory (and new-onset diabetes after AP). Standard $deviation_{BG}$ (AUC = 0.94, OR = 3.36) was a stronger predictor of the high-increasing HbA1c trajectory than ABG. It is arguably the most commonly used GV index in published studies, which measures the dispersion of blood glucose data. However, SD_{BG} is often hampered by the lack of normally distributed glucose profile and its numerical values may be similar in widely different glycaemic curves.[41] The accuracy of ARV (AUC = 0.94, OR = 2.82) was comparable with that of SD_{BG}. Given that ARV estimates the average of the differences in consecutive glucose readings, it appears to be a more accurate measure of GV than SD_{BG}. Glycaemic lability index, with an OR of 13.7 and AUC of 0.95, stood out as the most prescient predictor of the high-increasing HbA1c trajectory (and new-onset diabetes after AP) in the present study. Glycaemic lability index reflects the degree to which glucose concentrations vary over time[20] and serves as an effective measure of glycaemic instability. However, the downside of this index is the complexity of the calculation in a hospital environment, limiting its current use in routine clinical practice. A purposely designed GLI calculator may need to be developed to facilitate the use of this index in routine clinical practice. To the best of our knowledge, the available GV calculators (e.g., GlyCulator 2.0) do not measure GLI or are not sufficiently user-friendly (e.g., EasyGV) to be used in a busy hospital setting.

The study had several limitations that need to be acknowledged. First, the studied predictors were calculated using fasting blood glucose values taken once daily (at prespecified regular intervals) over the first 72 h of hospitalisation. Given that most of our study participants had mild AP and were discharged within 3–5 days and taking into account that the feeding regimen during the course of AP[42,43] may affect glucose concentrations, we elected to use fasting glucose concentrations (at least 8 h of fasting) obtained over first 72 h to ensure the number of glucose readings and the clinical conditions of participants at the time of measurements were comparable. Second, one could argue that the predominance of male participants in the high-increasing glycaemia group might have introduced a bias. However, several large scale population-based studies from different parts of the world have consistently demonstrated that men are more prone to the development of post-pancreatitis diabetes

mellitus than women.[25,44,45] Nevertheless, all our statistical analyses were adjusted for sex. Third, the number of participants in the high-increasing trajectory group was rather small. However, this represented an inevitable trade-off with a view to having a robust endpoint (i.e., trajectory over 2 years of follow-up) that is sensitive to dynamic changes in glycaemic status at several regular follow-ups (as opposed to the rigid status of the mere presence or absence of diabetes at a single follow-up).[46,47] Fourth, while patients with persistent organ failure (i.e., severe or critical AP) may have higher GV, the overwhelming majority of patients in the present study had mild or moderate severity of AP and none required ICU management. Whether our findings hold true in patients requiring ICU admission remains to be investigated in future studies. Last, while HbA1c is an acceptable means of diagnosing new-onset diabetes after AP, one could argue that the use of an oral glucose tolerance test could be more useful in this patient group.[48] Future studies may consider investigating the accuracy of GV indices in predicting new-onset diabetes diagnosed based on an oral glucose tolerance test.

In conclusion, GV during hospitalisation for AP was associated with at least two-times higher risk of consistently worsening HbA1c pattern (and new-onset diabetes) during follow-up in previously non-diabetic individuals. Glycaemic lability index had the best accuracy in predicting the high-increasing HbA1c trajectory. Identifying increased GV during hospitalisation for AP holds considerable potential as a reasonably straightforward approach to identifying high-risk individuals for developing new-onset diabetes after AP.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Study concept and design: Maxim S. Petrov. Acquisition of data: Sakina H. Bharmal, Jaelim Cho, Juyeon Ko. Statistical analysis: Jaelim Cho. Interpretation of data: Sakina H. Bharmal and Jaelim Cho. Drafting the manuscript: SHB. Critical revision of the manuscript: Jaelim Cho, Juyeon Ko, and Maxim S. Petrov. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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SUPPORTING INFORMATION

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