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Glycemic variability and mortality in patients hospitalized in general surgery wards

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ABSTRACT

Background: Glucose variability is common among hospitalized patients, but the prognostic implications among patients hospitalized in surgical wards are unknown. The objective of this study was to investigate the association between glucose variability, length of stay, and mortality.

Methods: Historical prospectively collected data of patients ≥18 years of age, hospitalized in general surgery wards between January 2011 and December 2017. Glucose variability was assessed by coefficient of variance and standard deviation of glucose values during hospitalization. The main outcomes were length of stay and 30-day and end-of-follow-up mortality.

Results: The cohort included 8,894 patients (mean age 63 ± 19 years, 48% male, mean follow-up 3.0 ± 1.8 years). A total of 2,012 (23%) patients had diabetes mellitus. The mean length of stay was longer with a higher coefficient of variance or standard deviation in patients without and with diabetes mellitus. The 30-day mortality was 6%, associated with a higher versus a lower coefficient of variance (9% vs 3%) and standard deviation (9% vs 3%) in patients without diabetes mellitus and with diabetes mellitus (9% vs 5%; 8% vs 5%, respectively). Mortality at the end of follow-up was increased in patients without diabetes mellitus with a higher coefficient of variance (27% vs 18%) and standard deviation (29% vs 17%) and in patients with diabetes mellitus (33% vs 24% and 32% vs 21%, respectively). Multivariate analysis indicated an increased risk for 30-day and end-of-follow-up mortality, in both groups. Adjustment for glucocorticoid treatment or hypoglycemia did not affect the results. In patients with a high or low coefficient of variance, mortality was higher with median glucose levels during hospitalization ≥180 mg/dl, compared with <180 mg/dl.

Conclusion: In patients with and without diabetes mellitus hospitalized in general surgery wards, increased glucose variability is associated with longer hospitalization and increased short-term and long-term mortality.

Introduction

Increased glucose variability (GV), which relates to the changes in blood glucose levels, has been associated with prolonged length of hospital stay and mortality in patients with and without diabetes mellitus (DM).[1–6] As patients with similar glycated hemoglobin can have marked differences in their glycemic profile, low GV has been suggested as a possible treatment goal.[1,2,5,7]

Most studies on GV and mortality have focused on mixed surgical and medical patients[4] or intensive care unit patients.[7–14] However, data regarding the prognostic importance of GV among patients hospitalized in general surgery wards are lacking. We have reported elsewhere that, for patients hospitalized in medical wards, high GV was associated with increased short-term and long-term mortality among patients with and without having had a diagnosis of DM.[2]

Although there are several methods to quantify GV, the simplest ones are the calculation of the standard deviation (SD) or the

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coefficient of variation (CV) of glucose values.[15] CV is the ratio of the standard deviation to the mean and is expressed as a percentage. Because the SD of glucose is highly correlated with the mean glucose, CV is considered an accurate and simple method to assess GV.[15–17]

Our institution has an established protocol for the management of in-hospital hyperglycemia in patients with and without a pre-existing diagnosis of DM, which is in line with the Endocrine Society guidelines.[18] The target blood glucose levels during hospitalization are 71–180 mg/dL. The recommended treatment for in-hospital hyperglycemia is with insulin, whether basal insulin only or a basal-bolus regimen. The insulin regimen will be adjusted daily and will include a correction factor in addition to the bolus dose. A sliding-scale insulin regimen is to be avoided. For patients with uncontrolled DM and blood glucose levels >180 mg/dL on 2 occasions, it is recommended to adjust insulin based on the following: (1) In patients who are fasting, basal insulin only is usually recommended; however, short-acting insulin will be used if needed. In patients who are not fasting, basal insulin is recommended in combination with bolus insulin with meals. In a small minority of young and stable patients who had been on oral medical treatment for DM and have no contraindications, this regimen will be continued. In those with hyperglycemia, but with no earlier diagnosis of DM, the basal-bolus insulin regimen is recommended as long as there is evidence for hyperglycemia.

On the basis of our study of GV in patients hospitalized to medical wards, in this study we aimed to investigate the association between GV, as assessed by the CV and SD of glucose measurements during admission, and the length of admission and all-cause mortality among patients admitted to general surgery wards.

Methods

The study was conducted at a large 1,300-bed university-affiliated tertiary medical center. The vast majority of admissions to the 4 general surgery wards are through an emergency department. All patient data are recorded in electronic medical charts (based on the same database platform used in community primary care facilities). Deaths are entered into the hospital's mortality database, which is updated according to the population registry of the Ministry of the Interior. The study was approved by the Rabin Medical Center's Institutional Review Board (Petach Tikva, Israel). Consent was obtained from each patient after a full explanation of the purpose and nature of all the procedures used.

For the present study, historical prospectively collected observational data were extracted from the medical records of all patients admitted for any cause to the hospital's general surgery wards between January 1, 2011, and December 31, 2017. Mortality data were obtained up to April 1, 2018. Self-reported data regarding alcohol use, smoking, and body mass index (BMI), as well as comorbidities, were collected from the database.

DM was defined as having had a diagnosis of DM coded in the medical records or use of any oral hypoglycemic agent, glucagon-like peptide 1 (GLP-1) receptor agonist, sodium-glucose cotransporter-2 inhibitor, or insulin at time of admission.

Blood glucose values were based on point-of-care bedside measurements in capillary blood, as well as serum glucose levels in venous samples.

We excluded patient admissions with very long hospital stays (>60 days) to focus on acutely ill patients. We also excluded patients with type 1 DM, and patients with fewer than 3 glucose measurement during hospitalization. In patients with multiple admissions, the first hospital stay was analyzed, and we collected data regarding readmissions.

We collected all glucose readings for each patient and calculated CV and SD. CV was defined as the ratio of SD to mean glucose values during hospitalization, expressed as percentage.We calculated the median CV and SD for the entire cohort (including patients with and without DM), and according to the median GV indices, the comparisons between patients with the high and low values of CV or SD were conducted.

Outcome measures included length of admission, readmissions, 30-day mortality, and mortality at the end of follow-up according to CV and SD. Furthermore, we analyzed the data based on in-hospital hypoglycemia and median glucose values during hospitalization, aiming to investigate the importance of GV independent of hypoglycemia or hyperglycemia.

Statistical analysis

The statistical analysis for this report was generated using SAS software, v 9.4 (SAS Institute, Cary, NC).

Continuous variables were presented by mean ± SD, categorical variables were presented by (*N*, %). The *t* test was used to compare continuous variables between patients with DM and without DM and χ^2 (for more than two groups) or the Fisher exact (for two groups) tests were used to compare the value of categorical variables between these groups.

The association between covariates and 30-day mortality was assessed by logistic regression. We have also weighted the data, using the inverse propensity score method, where the propensity score for CV or SD above the median was calculated as a function of the baseline variables, including age, gender, and comorbidities, using logistic regression. The analysis of study outcomes was performed on the Inverse Propensity Score Weighted database. Overall survival was assessed by Kaplan-Meier survival analysis, with the log-rank test.

The Cox proportional hazards model was used to assess overall survival, adjusted for age, gender, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, and in-hospital hypoglycemia. Two-sided *P* values <.05 were considered statistically significant. No imputation for missing data was done because missing at random cannot be assumed. Cox proportional hazard and Fine and Gray's competing risk model was used to evaluate the interaction between glycemic variability, readmissions, and mortality.

Results

Study cohort

A total of 42,188 admissions to the 4 general surgery wards occurred during the study period. After exclusion of repeat admissions (12,198 admissions), patients with fewer than 3 glucose measurements during the hospitalization (20,998 patients), those hospitalized for >60 days (54 patients), and patients with type 1 DM (44 patients), the final study cohort consisted of 8,894 patients (Fig 1). This cohort included 4,231 men (48%), mean age of the patients at admission was 63 years (SD 19), and 2,012 patients (23%) had a pre-existing diagnosis of type 2 DM (Table I).

The median number of blood glucose measurements was 5, and the mean number of glucose measurements was mildly greater in patients with DM, compared with patients without DM (7.1 ± 9 vs 6.7 ± 8, $P = .035$; Table I). The median CV was 21 ± 13% in the total cohort, with a median CV of 24 ± 14% and 20 ± 13% in patients with and without DM, respectively ($P < .001$). The respective median SD were 24 ± 27 in the total cohort,

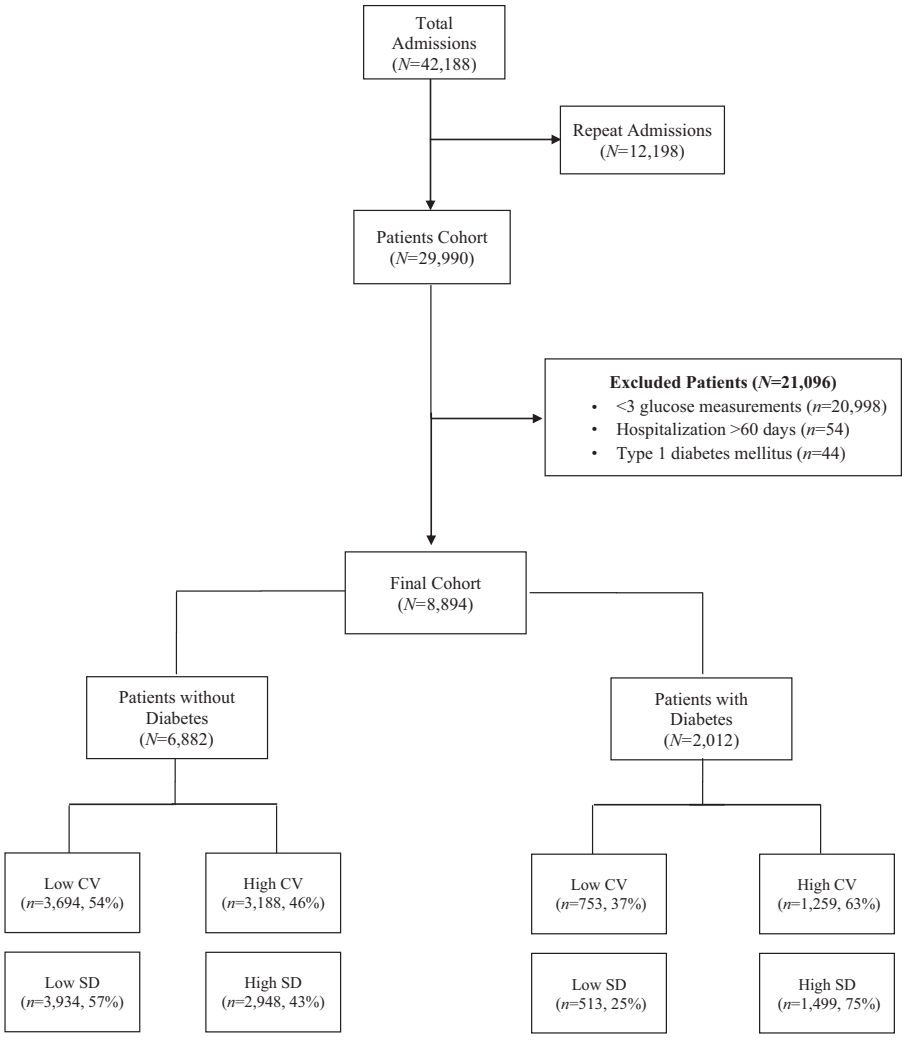

Fig 1. Flow diagram of exclusion criteria for final analysis profile. The records of all patients 18 years of age or older admitted for any cause to the Rabin Medical Center's general surgery wards between January 2011 and December 2017 were screened as described in this report.

and 38 ± 33 and 22 ± 23 mg/dL in patients with and without DM, respectively ($P < .001$).

The CV groups were divided as follows: low CV: ≤21%, high CV: >21%. Most patients with DM were in the high CV group (63%, 1,259/2,012), and most patients without DM were in the low CV group (54%, 2,501/6,882; Table II).

The SD groups were divided as follows: low SD: ≤24 mg/dL, high SD: >24 mg/dL. Most patients with DM were in the high SD group (75%, 1,499/2,012), and most patients without DM were in the low SD group (57%, 3,934/6,882; Table III).

The median glucose levels during hospitalization in patients with DM were 135 ± 48 mg/dl and 165 ± 55 mg/dl in those with low and high CV, respectively. In patients without DM, the respective median glucose levels were 98 ± 21 mg/dl and 117 ± 34 mg/dl (Table II). The median glucose levels according to SD groups in patients with DM were 117 ± 37 mg/dl and 145 ± 51 mg/dl, and in patients without DM 96 ± 17 mg/dl and 103 ± 32 mg/dl, respectively (Table III).

Rates of hypertension, ischemic heart disease, congestive heart failure, cerebrovascular disease, malignancy, and chronic renal failure were considerably higher in the group of patients with DM, compared with patients without DM. The characteristics of the patients by group are presented in Table I.

Length of hospitalization

The mean length of stay (LOS) was 8 ± 7 days, with similar LOS in patients without DM (8 ± 7 days) and patients with DM (8 ± 7 days, $P = .11$).

Higher SD and CV of glucose were both significantly associated with longer length of hospital stay in both patients with and without DM. There was a significant association between CV of glucose and LOS ($P < .0001$), and mean LOS was longer with a higher CV of glucose in patients without DM (9 ± 8 vs 7 ± 6 days) and in patients with DM (9 ± 8 vs 7 ± 5 days) (Table II). Increased SD was also associated with longer hospital stay in patients without DM (9 ± 8 vs 7 ± 6 days) and in patients with DM (9 ± 8 vs 7 ± 5 days; all $P < .001$; Table III).

Hypoglycemia

During the hospitalization 13% of the patients (1,119/8,894 patients) had at least 1 glucose value lower than 70 mg/dl, including 14% of patients without DM (958/6,882 patients) and 8% of patients with DM (161/2,012 patients). Hypoglycemia was more common in patients in the high CV group (24% and 12% in patients without and with DM, respectively), compared with low CV (5% and 2%,

Table I
Baseline characteristics and comorbidites of patients with and without DM*

	Patients without diabetes (n = 6,882)	Patients with diabetes (n = 2,012)
Patient characteristics		
Age, mean (years) (median)	61 ± 20 (64)	69 ± 13 (70)*
Men, n (%)	3,284 (48%)	947 (47%)
Smoking (%)	1,015 (21%)	218 (17%)*
Alcohol (%)	154 (3%)	15 (1%)*
BMI, median	26	28*
Glucocorticoid in hospital	347 (5%)	116 (6%)
Comorbidities, n (%)		
Malignancy	344 (5%)	126 (6%)*
Hypertension	1,636 (24%)	1,147 (57%)*
Ischemic heart disease	434 (6%)	365 (18%)*
Congestive heart failure	170 (3%)	140 (7%)*
Chronic renal failure	137 (2%)	99 (5%)*
Cerebrovascular disease	181 (3%)	154 (8%)*
Glucose variability		
Blood glucose measurements, mean ± SD (median)	6.7 ± 8 (5)	7.1 ± 9 (5)*
CV, median ± SD	20 ± 13 (%)	24 ± 14 (%)*
SD, median ± SD	22 ± 23	38 ± 33*

* $P < .05$.

respectively). Similarly, hypoglycemia was more common in patients in the high SD of glucose (20% and 10% in patients without and with DM, respectively), compared with the low SD (10% and 4%, respectively).

Significant hypoglycemia, defined as a glucose value ≤54 mg/dl, was 3% among patients without DM (196/6,882 patients), and 3% of those with DM (53/2,012 patients). Significant hypoglycemia was more common in patients in the high CV group (6% and 4% in patients without and with DM, respectively), compared with low CV (0.3% and 0.1%, respectively). Similarly, significant hypoglycemia was more common in patients in the high SD of glucose (5% and 3% in patients without and with DM, respectively), compared with the low SD (1% and 0.4%, respectively).

Readmissions

During the long-term follow-up, 3,110 patients (34%) were readmitted for any cause, including 734 patients (37%) with DM and 2,376 patients (35%) without DM. The readmission risk was not significantly different between patients with high compared with low glycemic variability, with and without DM (Tables II and III).

Other than the median LOS of the index admission, that was significantly longer in patients that were readmitted during the follow-up, there was no difference between those who were readmitted and those with no further readmission during the follow-up in comorbidities, age, gender, BMI, alcohol, smoking, use of glucocorticoid or hypoglycemia during hospitalization. With a competing risk model for readmission and mortality, there was no significant association between CV or SD rates of readmissions in patients with DM or in patients without DM (Tables II and III).

Mortality

Complete follow-up data were available for all patients, with follow-up of up to 7.1 years (mean follow-up 3.0 ± 1.8 years).

30-day mortality

Overall 30-day mortality was 6% (548/8,894), including 6% of patients without DM (399/6,882 patients) and 7% of patients with DM (149/2,012 patients).

Among patients with and without DM, there was a significant association between CV of glucose and 30-day mortality ($P < .05$). High CV was associated with increased 30-day mortality in patients without DM (high CV versus low CV, 9% vs 3%, odds ratio [OR] = 2.7, 95% confidence interval [CI] [2.1,3.3]), and in patients with DM (high CV versus low CV, 9% vs 5%, OR = 1.8, 95% CI [1.2,2.6]). After adjustment for age, gender, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, and in-hospital hypoglycemia, respective adjusted odds ratios were 1.6 (1.2–2.3) in patients without DM, and 2.6 (1.3–5.0) in patients with DM (Table II, Model 2). Adjustment for in-hospital significant

Table II
Mortality and length of stay according to glucose variability according to CV in patients with diabetes and without diabetes

Coefficient of variance					
		Patients without DM		Patients with DM	
		Low CV (n = 3,694)	High CV (n = 3,188)	Low CV (n = 753)	High CV (n = 1,259)
Length of stay, days, mean (median)		7 ± 6 (6)	9 ± 8 (7)	7 ± 5 (6)	9 ± 8 (7)
Median glucose, mg/dl		98 ± 21	117 ± 34	135 ± 48	165 ± 55
Glucocorticoid treatment, n (%)		159 (4%)	188 (6%)	36 (5%)	80 (6%)
Readmissions, n (%)		1,247 (34%)	1,129 (36%)	269 (36%)	465 (37%)
Competing risk for readmissions (hazard ratio)	Model 1*	—	1.1 (0.98–1.2)	—	1.1 (0.91–1.2)
	Model 2†	—	1.0 (0.92–1.2)	—	1.0 (0.85–1.3)
	Model 3‡	—	1.1 (0.95–1.2)	—	1.1 (0.87–1.3)
30-day mortality		126 (3%)	273 (9%)	38 (5%)	111 (9%)
30-day mortality (odds ratio)	Model 1*	—	2.7 (2.1–3.3)	—	1.8 (1.2–2.6)
	Model 2†	—	1.6 (1.2–2.3)	—	2.6 (1.3–5.0)
	Model 3‡	—	1.8 (1.3–2.5)	—	3.0 (1.5–5.8)
	Model 4§	—	1.7 (1.2–2.3)	—	2.6 (1.3–5.0)
Mortality at the end of follow-up		659 (18%)	853 (27%)	178 (24%)	415 (33%)
Mortality at the end of follow-up (hazard ratio)	Model 1*	—	1.6 (1.4–1.8)	—	1.5 (1.3–1.8)
	Model 2†	—	1.2 (1.1–1.4)	—	1.5 (1.2–2.0)
	Model 3‡	—	1.3 (1.1–1.4)	—	1.6 (1.3–2.1)
	Model 4§	—	1.2 (1.1–1.4)	—	1.5 (1.2–2.0)

* Model 1: Comparison with low glycemic variability, unadjusted model.
† Model 2: Comparison with low glycemic variability, adjustment for age, gender, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, and in-hospital hypoglycemia (< 70 mg/dl).
‡ Model 3: Comparison with low glycemic variability, adjustment for age, gender, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, and in-hospital significant hypoglycemia (≤ 54 mg/dl).
§ Model 4: Model 2 + adjustment for glucocorticoid treatment during hospitalization.

Table III
Mortality and length of stay according to glucose variability according to SD in patients with DM and without DM

Coefficient of variance					
		Patients without DM		Patients with DM	
		Low SD (n = 3,934)	High SD (n = 2,948)	Low SD (n = 513)	High SD (n = 1,499)
Length of stay, days, mean (median)		7 ± 6 (6)	9 ± 8 (7)	7 ± 5 (6)	9 ± 8 (7)
Median glucose, mg/dl		96 ± 17	103 ± 32	117 ± 37	145 ± 51
Glucocorticoid treatment, *n* (%)		170 (4%)	177 (6%)	28 (5%)	88 (6%)
Readmissions, *n* (%)		1,327 (34%)	1,049 (36%)	177 (35%)	557 (37%)
Competing risk for readmissions (hazard ratio)	Model 1*	—	1.1 (0.98–1.2)	—	1.1 (0.94–1.3)
	Model 2†	—	1.0 (0.94–1.2)	—	1.2 (0.92–1.5)
	Model 3‡	—	1.1 (0.95–1.2)	—	1.2 (0.93–1.5)
30-day mortality		136 (3%)	263 (9%)	27 (5%)	122 (8%)
30-day mortality (odds ratio)	—	2.7 (2.2–3.4)	—	1.6 (1.1–2.4)	1.8 (1.2–2.6)
	—	1.7 (1.3–2.3)	—	2.0 (1.0–4.4)	2.6 (1.3–5.0)
	—	1.8 (1.3–2.5)	—	2.3 (1.1–4.9)	3.0 (1.5–5.8)
	—	1.7 (1.2–2.3)	—	2.6 (1.3–5.0)	2.6 (1.3–5.0)
Mortality at the end of follow-up		665 (17%)	847 (29%)	110 (21%)	483 (32%)
Mortality at the end of follow-up (hazard ratio)	—	1.8 (1.6–2.0)	—	1.6 (1.3–2.0)	1.5 (1.3–1.8)
	—	1.3 (1.2–1.5)	—	1.7 (1.2–2.4)	1.5 (1.2–2.0)
	—	1.3 (1.2–1.5)	—	1.8 (1.3–2.5)	1.6 (1.3–2.1)
	—	1.3 (1.2–1.5)	—	1.7 (1.2–2.4)	1.5 (1.2–2.0)

* Model 1: Comparison with low glycemic variability, unadjusted model.
† Model 2: Comparison with low glycemic variability, adjustment for age, gender, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, and in-hospital hypoglycemia (< 70 mg/dl).
‡ Model 3: Comparison with low glycemic variability, adjustment for age, gender, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, and in-hospital significant hypoglycemia (≤ 54 mg/dl).

hypoglycemia, instead of in-hospital hypoglycemia, indicated adjusted odds ratios of 1.8 (1.3–2.5) and 3.0 (1.5–5.8) in those without and with DM, respectively (Table II, Model 3).

Similarly, among patients with and without DM, there was a significant association between SD of glucose and 30-day mortality ($P < .0001$). High SD of glucose was associated with increased 30-day mortality in patients without DM (high SD versus low SD, 9% vs 3%, OR = 2.7, 95% CI [2.2,3.4]), and in patients with DM (high SD versus low SD, 8% vs 5%, OR = 1.6, 95% CI [1.1,2.4]). After adjustment for study variables, respective adjusted odds ratios were 1.7 (1.3–2.3) in patients without DM, and 2.0 (1.0–4.4) in patients with DM. (Table III, Model 2). Adjustment for in-hospital significant hypoglycemia, instead of in-hospital hypoglycemia, indicated adjusted odds ratios of 1.8 (1.3–2.5) and 2.3 (1.1–4.9) in those without and with DM, respectively (Table III, Model 3).

According to the receiver operating characteristics analysis, the optimal cutoff value for predicting 30-day mortality were CV of 21.7 (area under the curve = 0.65), with sensitivity of 67%, specificity of 55%, positive predictive value of 89%, and negative predictive value of 96%. The optimal SD cutoff value for predicting 30-day mortality was 26.6 (area under the curve = 0.66), with sensitivity of 66%, specificity of 57%, positive predictive value of 92%, and negative predictive value of 96%.

We have also weighted the data, using the inverse propensity score method, where the propensity score for CV above the median, was calculated as a function of baseline variables using logistic regression, supporting the statistical significance of high CV for 30-day mortality risk (hazard ratio [HR]) among patients with (HR = 1.6, 95% CI, 1.2–2.3) and without DM (HR = 1.8, 95% CI, 1.5–2.1). The propensity score for SD above the median also supported the significance of SD for mortality risk among those with (HR = 1.6, 95% CI, 1.1–2.4) and without DM (HR = 2.7, 95% CI, 2.2–3.4).

Mortality at the end of follow-up

Overall mortality rate for the entire cohort at the end of follow-up was 24% (2,105/8,894), including 22% of patients without DM (1,512/6,882 patients) and 29% of patients with DM (593/2,012 patients).

Exploratory laparotomy (6%) was the most common surgical procedure in the group of patients who died during the long-term follow-up, and the second most common procedure (3%) among those who survived. The other common procedure among those who died during the follow-up included total esophagectomy (3%). Among those who survived, the most common procedure included laparoscopic cholecystectomy (4%). The mortality risk at the end of follow-up was significantly high among patients with a diagnosis of congestive heart failure (61% mortality), and/or chronic renal failure (50% mortality). The mortality risk was even higher in those patients with high CV. For example, congestive heart failure was associated with a 65% mortality risk in patients with high CV, compared with a 56% mortality risk in those with low CV (Table IV).

High CV of glucose was associated with increased mortality at the end of follow-up in patients without DM (high CV versus low CV, 27% vs 18%, HR = 1.6, 95% CI [1.4,1.8]), and in patients with DM (high CV versus low CV, 33% vs 24%, HR = 1.5, 95% CI [1.3,1.8]). After adjustment for study variables, respective adjusted hazard ratios were 1.2 (1.1–1.4) in patients without DM, and 1.5 (1.2–2.0) in patients with DM (Table II, Model 2). Adjustment for significant hypoglycemia indicated adjusted odds ratios of 1.3 (1.1–1.4) and 1.6 (1.3–2.1) in those without and with DM, respectively (Table II, Model 3).

High SD of glucose was associated with increased mortality at the end of follow-up in patients without DM (high SD versus low SD, 29% vs 17%, HR = 1.8, 95% CI [1.6,2.0]), and in patients with DM (high SD versus low SD, 32% vs 21%, HR = 1.6, 95% CI [1.3,2.0]). After adjustment, respective adjusted hazard ratios were 1.3 (1.2–1.5) in patients without DM, and 1.7 (1.2–2.4) in patients with DM (Table III, Model 2). Adjustment for in-hospital significant hypoglycemia indicated adjusted hazard ratios of 1.3 (1.2–1.5) and 1.8 (1.3–2.5) in those without and with DM, respectively (Table III, Model 3).

The Kaplan-Meier curves depicted better survival with low GV compared to high GV according to either CV (Fig 2, *A*) or SD (Fig 2, *B*).

Propensity score analysis supported the statistical significance of CV for mortality risk among patients with (HR = 1.4, 95% CI, 1.2–1.6) and without DM (HR = 1.2, 95% CI, 1.1–1.3).

Table IV
Mortality according to comorbidities and glucose variability*

	Patients, *n*	Mortality, *n*, %	High CV, *n* (%)	Mortality with high CV, *n*, %	Low CV, *n* (%)	Mortality with low CV, *n*, %
Malignancy	470	166 (35%)	259 (55%)	106 (41%)	211 (45%)	60 (28%)
Hypertension	2783	928 (33%)	1,565 (56%)	579 (37%)	1,218 (44%)	349 (29%)
Ischemic heart disease	799	320 (40%)	457 (57%)	201 (44%)	342 (43%)	119 (35%)
Congestive heart failure	310	188 (61%)	172 (55%)	111 (65%)	138 (45%)	77 (56%)
Chronic renal failure	236	118 (50%)	137 (58%)	84 (61%)	99 (42%)	48 (48%)
Cerebrovascular disease	335	135 (40%)	195 (58%)	73 (37%)	140 (42%)	51 (36%)

CV, coefficient of variance.
* Mortality risk at the end of follow-up according to major comorbidities and high, compared with low CV.

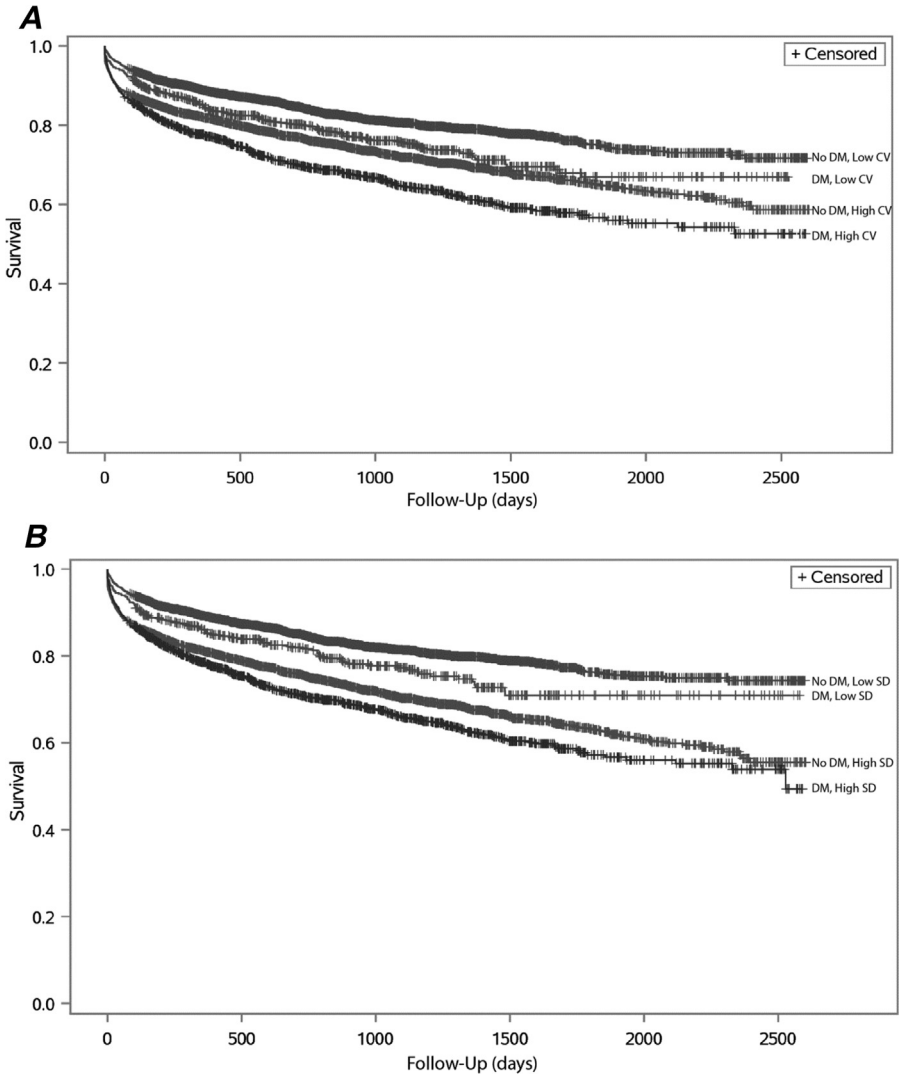

Fig 2. Kaplan-Meier analysis of patients after discharge. Patient survival was analyzed as time until death. Observations were censored at the end of follow-up ($P < .05$). (*A*) According to CV, and (*B*) according to SD, in patients without DM and with DM.

Similarly, propensity score for SD above the median also supported the significance of SD for mortality risk among those with (HR = 1.6, 95% CI, 1.3–2.0) and without DM (HR = 1.8, 95% CI, 1.6–2.0).

Glucocorticoid treatment

During hospitalization 5% of the patients (463/8,894 patients) in the cohort were treated with glucocorticoids, including 5% of patients without DM (347/6,882 patients), and 6% of patients with DM (116/2,012 patients). Although glucocorticoid treatment was more prevalent in patients with high CV or SD, in patients with or without DM, further adjustment of the model to glucocorticoid treatment during hospitalization had no significant impact on the results (Table II, Model 4).

Median glucose during hospitalization

We analyzed the data according to median glucose levels during hospitalization, classifying the median levels to the normal range

for hospitalized patients (70–180 mg/dl) and high median glucose levels (>180 mg/dl).

Among patients with high median glucose levels during hospitalization, high compared with low CV was associated with increased 30-day mortality risk, whether the patients had DM (14% vs 6%) or not (22% vs 11%). This pattern was similar with normal median glucose levels, both in patients with (8% vs 5%) and without DM (8% vs 3%).

As for mortality at the end of follow-up, in patients with high median glucose levels, mortality risk was greater with high versus low CV in patients with DM (38% vs 29%), but not in those without pre-existing DM (45% vs 46%). However, in those with normal median glucose levels, high CV was associated with increased mortality risk compared with low CV, whether the patient had DM (32% vs 23%) or not (26% vs 18%).

Discussion

This study suggests an increased short-term and long-term mortality risk in patients hospitalized in general surgery wards with increased GV, with and without having had a diagnosis of DM. Increased GV was also associated with longer length of hospitalization, but there was no association with risk for readmission during the long-term follow-up.

Our study included a large cohort of patients with the evaluation of long-term mortality, which focused on patients admitted to general surgery wards, unlike most studies on GV and mortality that focused on intensive care unit patients[7–14] or mixed surgical and medical patients.[4]

After adjustment for age, gender, smoking, alcohol, BMI, and comorbidities, as well as hypoglycemia during the hospital stay, the results in patients with and without DM indicated longer length of admission in patients with increased GV. Similar to our earlier study of GV that focused on patients admitted to medical wards[2] and similar to the results of Mendez et al,[4] this study indicated that higher GV was associated with approximately 2-day increase of hospital stay, compared with lower GV. Compared with low GV, increased GV was associated with a three-fold increase of 30-day mortality GV (9% vs 3%) in patients without DM, and almost a two-fold increase in those with DM. Analysis of mortality at the end of follow-up, with follow-up of up to 7 years, demonstrated a 1.5-fold and 1.7-fold increase in mortality with high versus low CV (27% vs 18%) or SD (29% vs 17%) in patients without DM. In patients with DM, there was a 1.4-fold and 1.5-fold increase in mortality risk with high versus low CV (33% vs 24%) or SD (32% vs 21%).

As hypoglycemia during hospitalization has been shown to be associated with increased mortality[19–28] and is therefore a possible explanation for increased mortality in patients with increased GV, our data were adjusted for hypoglycemia during the hospitalization. Unsurprisingly, in-hospital hypoglycemia was more common in those with high GV, because in these patients it is reasonable to believe that fluctuations of glucose levels, with hypoglycemia and hyperglycemia, contributed to the high variability. However, it is interesting that in-hospital hypoglycemia was more common in patients without DM, compared with those with DM. This finding is in contrast with our earlier study in patients hospitalized in medical wards, and a possible explanation may be that, frequently, patients in surgical wards are required to fast and that may lead to mild hypoglycemia in those with normal glucose homeostasis. On the other hand, it is quite common to hold glucose-lowering medications during hospitalization, especially while fasting, thus glucose levels will usually increase and hypoglycemia will be less frequent among those with pre-existing DM. When we investigated significant hypoglycemia, defined according to the American Diabetes Association as glucose values $\leq$54 mg/dl, the rates of significant hypoglycemia were similar in patients with and without DM. Of note, adjustment to in-hospital hypoglycemia or in-hospital significant hypoglycemia indicated similar mortality risks.

Hyperglycemia has also been reported to be associated with adverse outcomes in surgical patients.[29–32] Because our study focused on the glycemic variability and not hyperglycemia per se, we also analyzed the data according to median glucose levels, proving that, in patients with and without DM, whether CV was high or low, short-term and long-term mortality risk was higher with glucose levels $\geq$180 mg/dl, compared with median glucose levels <180 mg/dl. Median glucose level of 180 mg/dl was chosen as a cut point in accordance with the American Diabetes Association guidelines' definition of the glucose level requiring medical intervention during hospitalization.[33]

As glucocorticoid treatment may have a significant impact on glucose levels and GV, we also retrieved data regarding treatment during hospitalization and added another model, aimed to analyze the impact of GV adjusted further to glucocorticoid treatment, with no significant change in the calculated odds and hazard ratios.

Other studies have suggested that, in surgical patients with and without DM, increased preoperative or postoperative glucose levels are associated with morbidity and mortality.[29–35] However, although these studies reported mostly the importance of hyperglycemia, our study is the first to investigate the short-term and long-term importance of glycemic variability in a large cohort of patients hospitalized in general surgery wards.

The mechanism of the increased mortality risk in patients with increased GV is probably a multifactorial one. Fluctutations in glucose levels may result in impaired endothelial function,[36,37] increased reactive oxygen species,[5,38,39] or activation of platelet aggregation.[39,40] Changes in glucose levels during hospitalizaiton may be secondary to changes in the patients' condition, or secondary to medical intervention, such as treatment with glucocorticoid or insulin. One of the interesting findings in our study is the high mortality risk with high GV in patients without DM. The mortality risk in this group was quite similar to the risk found in those with DM and high GV (29% vs 32%, respectively). This may be the result of undiagnosed DM, a well-known issue, as according to the The Centers for Disease Control and Prevention, about one-quarter of patients with diabetes have undiagnosed DM.[41] It is possible that as these patients were not diagnosed, they did not receive treatment for DM, which might put them at risk for DM complications, morbidity, and mortality. However, it is also possible that GV is merely a marker of poor health status, with swings in blood glucose levels in accordance with changes in the renal, adrenal, or liver dysfunction. However, Takeishi et al[42] investigated the association between glycemic control, reactive inflammatory biomarkers, and vital signs, and showed that glycemic variability has an independent effect. Their study indicated GV is associated with increased mortality in nonintensive care unit patients, with no association between reactive inflammatory biomarkers or vital signs with mortality. In our study, we have shown that, with a given major comrobidity, such as congestive heart failure, the mortality risk is higher with incresed GV, compared with low GV. We believe that avoiding glycemic instability and glucose swings is a reasonable goal of glycemic control during hospitalization.

Approaches to reduce GV may include pharmacologic and nonpharmacolgoic options. Nutritional consultation and continuous glucose monitoring may assist in adjusting treatment to better control glucoe levels and may reduce GV, as shown in the DIAMOND trial.[43] Several studies have investigated the effects of different treatment regimens on GV.[44–47] These may suggest that a combination of basal insulin with incretin mimetic (GLP-1 receptor agonists) can reduce GV, without increasing the risk of hypoglycemia. The FLAT-SUGAR trial,[44] a 26-week study comparing the

basal-bolus insulin regimen with a combination of basal insulin and short-acting GLP-1 receptor agonist, exenatide, reported reduced short-term GV. The AWARD-4 substudy reported significantly decreaed GV with combination of once-a-week GLP-1 receptor agonist, dulaglutide, and bolus insulin, compared with the basal-bolus insulin regimen.[45] The introduction of ultra-long–acting insulins, such as insulin degludec and insuline glargine 300U/ml, may assist the efforts to reduce GV.[47] King et al[46] reported an improvement in GV with a fixed-ratio combination of ultra-long–acting insulin, degludec, with GLP-1 receptor agonist, liraglutide, compared with either drug alone.

The retrospective design of the study is one of its major limitations. In addition, it should be considered that patients with a history of abnormal glucose levels, whether hypoglycemia or hyperglycemia, have a greater chance of having their blood glucose measured more often, with a higher probability of detecting an increased variability. Glucometers are the most frequent method for blood glucose monitoring of hospitalized patients with DM. However, in patients without DM, the use of glucometers is infrequent, and many abnormal blood-glucose measurements are identified incidentally in routine blood work. In our institution, serum glucose levels are usually included in the routine blood works for hospitalized patients with and without DM. For that reason, the glucose measurements in our study were based on both venous blood glucose and bedside glucometers. It should be noted that with abnormally high blood-glucose or low blood-glucose reading using bedside glucometers, most patients are treated immediately, and venous blood samples may be obtained only later. One more limitation relates to the fact that we have no documentation of the timing of glucose measurement with relation to meal and whether there was any difference between fasting or postprandial measurements.

This is the first large study to investigate the importance of glycemic variability in patients admitted solely to general surgery wards, with long-term follow-up. In addition, our data represent real-life experience, as opposed to prospective randomized-controlled studies in which patients undergo intensive monitoring and treatment adjustments. We have focused on patients with at least 3 glucose measurements during hospitalization, to provide a better estimation of GV.

In conclusion, our findings suggest that increased GV, whether in patients with or without pre-existing DM, is associated with longer length of hospitalization and increased short-term and long-term mortality risk among patients hospitalized in general surgery wards. A high GV must alert physicians to the potential increased mortality risk of the patients. Although our study does not prove that correction of high short-term GV can reduce mortality risk, it does emphasize that high GV should probably be avoided in hospitalized patients. Interventional trials are needed to investigate the impact of minimizing GV on morbidity and mortality.

Disclosure

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