High Glucose Variability Increases Mortality Risk in Hospitalized Patients

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Context: Glucose variability (GV) is common among hospitalized patients, but the prognostic implications are not understood.

Objective: Investigate the association between GV, hospital length of stay (LOS), and mortality.

Methods: GV was assessed by coefficient of variance (CV) and standard deviation (SD) of glucose values during hospitalization.

Setting: Historical prospectively collected data of patients hospitalized between January 2011 and December 2013.

Patients: Patients ≥18 years old.

Main outcome: LOS, and in-hospital and mortality at end of follow-up.

Results: The cohort included 20,303 patients (mean age ± SD, 70 ± 17 years; 51% men; median follow-up, 1022 days), of whom 8565 patients (42%) had diabetes mellitus (DM). Mean LOS was longer with higher CV or SD tertiles in patients without and with DM. In-hospital mortality was 8.2%, associated with higher tertiles of CV (4%, 10%, 19%) and SD (4%, 11%, 21%) in patients without DM and with DM (3%, 5%, 10%; and 2%, 4%, 9%, respectively). Mortality at the end of follow-up was increased in patients without DM with higher CV (28%, 42%, 55%) and SD (28%, 44%, 57%) tertiles and in patients with DM (26%, 35%, 45%; and 25%, 34%, 44%, respectively). Multivariate analysis indicated increased risk for in-hospital and end of follow-up mortality, in both groups. Adjustment for glucocorticoid treatment or hypoglycemia did not affect the results. Glucose levels during hospitalization and GV were two independent factors affecting LOS and in-hospital mortality. In each CV tertile, mortality was higher with median glucose ≥180 mg/dL, compared with <180 mg/dL.

Conclusions: In hospitalized patients with and without DM, increased GV is associated with longer hospitalization and increased short- and long-term mortality. (***J Clin Endocrinol Metab*** **102: 2230–2241, 2017)**

Studies have reported that inpatient hyperglycemia and hypoglycemia are associated with several complications, including longer hospital stay and mortality in patients with and without diabetes mellitus (DM) (1–13). Glucose variability (GV) relates to the blood glucose fluctuations, and patients with similar mean glucose or hemoglobin A1c values can have different daily glucose profiles (14). GV may serve as a marker for poor glycemic control and increased risk for complications, including prolonged admission and mortality (15, 16).

Currently, there are four known mechanisms of hyperglycemia-induced tissue damage: the polyol pathway,

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Abbreviations: BMI, body mass index; CI, confidence interval; CV, coefficient of variance; DM, diabetes mellitus; GV, glucose variability; HR, hazard ratio; LOS, length of stay; OR, odds ratio; SD, standard deviation.

the hexosamine pathway, protein kinase C activation, and formation of advanced glycation end products. Brownlee *et al.* (17, 18) suggested that high GV and increased production of mitochondrial reactive oxygen species by hyperglycemia are major causes of the complications associated with DM. These may underlie the glycemic memory phenomenon, a term coined after the results of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications follow-up (19–21), which demonstrated that the speed of progression of diabetic retinopathy is dictated by the level of glycemic control early in the disease process (17, 22).

There are several methods to quantify GV, but no method is considered the gold standard. The simplest methods are calculation of the standard deviation (SD) of glucose values; the other is coefficient of variation (CV) (14). CV is the ratio of the SD to the mean and is expressed as a percentage. Because the SD of glucose is highly correlated with the mean glucose level, CV is considered an accurate and simple method to assess GV (14, 23, 24). A recent meta-analysis of 12 studies concluded that different measures of GV are associated with mortality in critically ill patients (25).

In contrast with the substantial evidence in patients admitted to intensive care units, there are scarce data with inherent limitations regarding noncritically ill patients admitted to medical wards (15, 26). In this study, the association between GV, assessed by the CV and SD of glucose measurements during admission, and the hospital length of stay (LOS) and all-cause mortality was evaluated among a large cohort of hospitalized patients. Furthermore, an aim of the study was to determine if GV has any added value to median glucose levels during hospitalization.

Methods

The study was conducted at a large, 1300-bed, university-affiliated tertiary medical center. Most admissions to the 10 medical 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 hospital's institutional review board.

Historical, prospectively collected observational data were extracted from the medical records of all patients admitted for any cause to the hospital's medical wards between 1 January 2011 and 31 December 2013. Mortality data were obtained up to 1 June 2015. Self-reported data regarding alcohol use, smoking, and body mass index (BMI), as well as comorbidities, were also collected from the database.

DM was defined as a previous diagnosis of DM coded in the medical records or use of any oral hypoglycemic agent, glucagon-like peptide 1 agonist, 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 admission with very long hospital stays (*i.e.*, >60 days) to focus on acutely ill patients. We also excluded patients with fewer than three glucose measurements during hospitalization. For patients with multiple admissions, only the first hospital stay was analyzed.

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 a percentage. We calculated the CV tertiles for the entire cohort, including patients with and without DM. Furthermore, we calculated SD tertiles and classified the patients accordingly. Because the SD of glucose is highly correlated with the mean glucose level, CV is considered an accurate and simple method to assess GV.

Outcome measures included LOS, in-hospital mortality, and mortality at the end of follow-up according to CV and SD. Furthermore, we analyzed the interaction between CV and SD with median glucose values during hospitalization, aiming to investigate the importance of GV independent of median glucose levels.

Statistical analysis

The statistical analysis for this study was generated using SAS Software, version 9.4 (SAS Institute). Continuous variables are presented as mean ± SD; categorical variables are presented as number (%). 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 Fisher exact (for two groups) tests were used to compare the value of categorical variables between these groups.

The association between covariates and in-hospital mortality was assessed by logistic regression. 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, sex, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, and chronic renal failure. Two-sided P values < 0.05 were considered statistically significant. We had complete data for all the study variables, other than alcohol and smoking. No imputation for missing data were done because missing at random cannot be assumed.

Results

Study cohort

There were 73,796 admissions to the 10 medical wards during the study period. After exclusion of repeated admissions (n = 40,121 admissions), fewer than three glucose measurements during the hospitalization (n = 13,320 patients), and patients hospitalized for >60 days (n = 52 patients), the final study cohort consisted of 20,303 patients (Fig. 1). Of these, 10,451 (51%) were male and the mean age was 70 ± 17 years at admission; and 8565 (42%) had DM (Table 1).

The median number of blood glucose measurements was five; this was higher in patients with DM compared

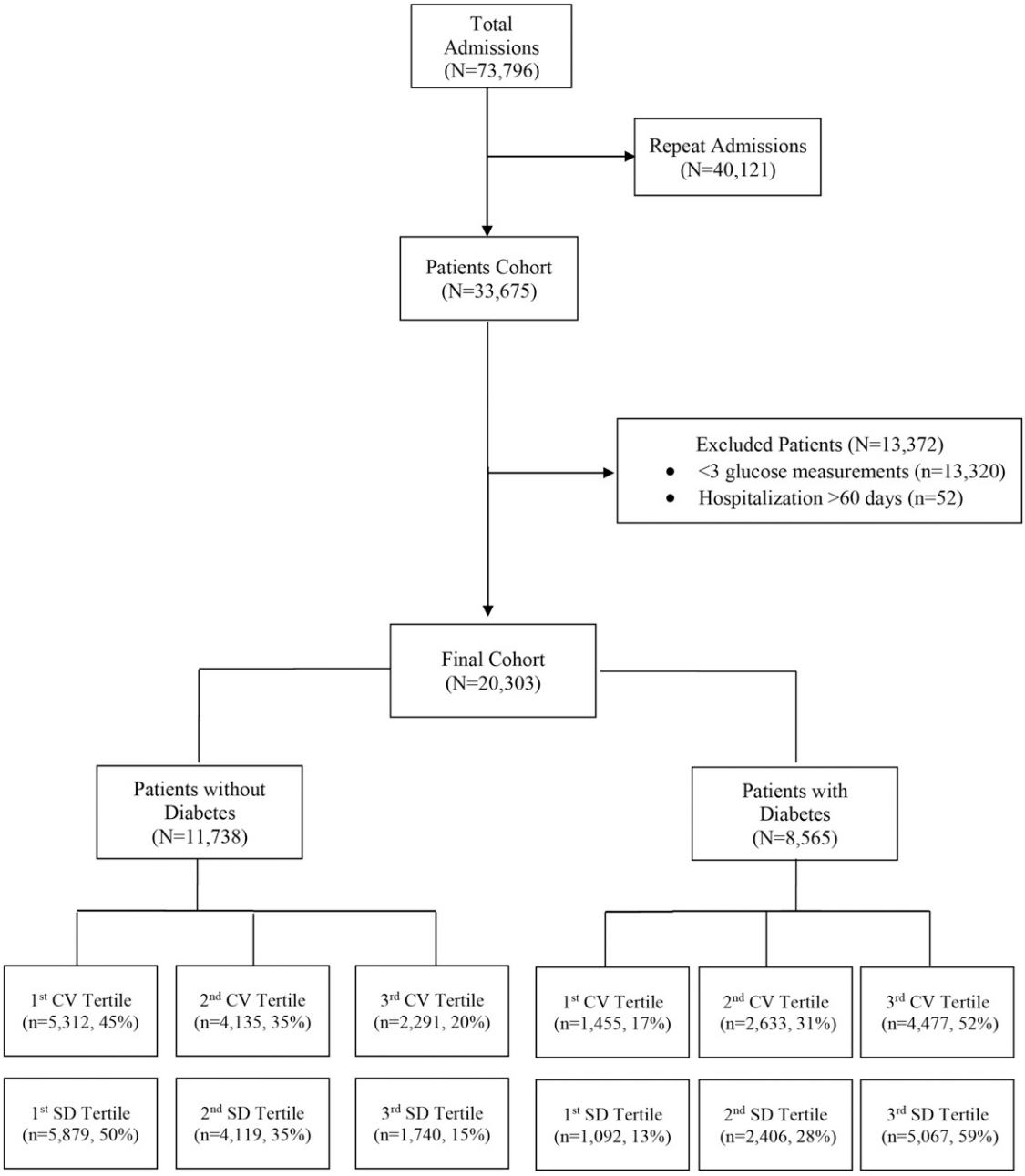

Figure 1. Flow diagram of exclusion criteria for final analysis profile. The records of all patients ≥18 years old who were admitted to the Rabin Medical Center's medical wards between January 2011 and December 2013 were screened as described in the text.

with patients without DM (9 ± 19 vs 4 ± 9; $P < 0.001$; Table 1). The median CV was 20% ± 14% in the total cohort, with a median CV of 27% ± 14%, and was 16% ± 12% in patients with and without DM, respectively ($P < 0.001$). The respective median SDs were 25 ± 32 mg/dL in the total cohort, and 45 ± 35 mg/dL and 17 ± 22 mg/dL in patients with and without DM, respectively ($P < 0.001$).

The CV tertiles were divided as follows: first tertile, <15%; second tertile, 15% to 26%; and third tertile, >26%. Most patients with DM were in the third CV tertile (52%; 4477 of 8565 patients), whereas most patients without DM were in the first CV tertile (45%; 5312 of 11,738 patients) or the second tertile (35%; 4135 of 11,738 patients). Most patients in the first and second tertiles did not have DM [79% (5,312 of 6,767 patients) and 61% (4135 of 6768 patients), respectively], but most patients in the third tertile had DM (66%; 4477 or 6768 patients; Table 2).

The SD tertiles were divided as follows: first tertile, ≤17 mg/dL; second tertile, 18 to 37 mg/dL, and third tertile, ≥38 mg/dL. Most patients with DM were in the third SD tertile (59%; 5067 of 8565 patients), whereas most patients without DM were in the first SD tertile (50%; 5879 of 11,738 patients). Most patients in

Table 1. Baseline Characteristics and Comorbidities of Patients With and Without DM

	Patients Without DM (n = 11,738)	Patients With DM (n = 8565)
Patient characteristics		
Age, mean ± SD (median), y	68 ± 19 (73)	72 ± 13 (74)[a]
Men	5901 (50)	4550 (53)[a]
Smoking	1669 (16)	967 (13)[a]
Alcohol	243 (2)	97 (1)[a]
BMI, median. kg/m^2	25	28
Glucocorticoid given in hospital	2523 (21)	1494 (17)
Comorbidities		
Malignancy	2017 (17)	1245 (15)[a]
Hypertension	4911 (42)	5799 (68)[a]
Ischemic heart disease	2322 (20)	3072 (36)[a]
Congestive heart failure	1225 (10)	1373 (16)[a]
Chronic renal failure	1033 (9)	1382 (16)[a]
Cerebrovascular disease	1036 (9)	1224 (14)[a]
GV		
Blood glucose measurements, mean ± SD (median)	7 ± 9 (4)	15 ± 19 (9)[a]
CV, median ± SD	16 ± 12	27 ± 14[a]
SD, median ± SD	17 ± 22	45 ± 35[a]

Data given as no. (%) unless otherwise indicated.

[a] $P < 0.05$.

the first and second tertiles did not have DM [84% (5879 of 6971 patients) and 63% (4119 of 6525 patients), respectively], whereas most patients in the third SD tertile had DM (74%; 5067 of 6807 patients; Table 3).

The median glucose levels during hospitalization in patients with DM were as follows: 135 ± 52 mg/dL, 150 ± 58 mg/dL, and 170 ± 65 mg/dL in the first, second, and third CV tertiles, respectively. In patients without DM, the respective median glucose levels were 103 ± 20 mg/dL, 110 ± 31 mg/dL, and 119 ± 55 mg/dL. The median glucose levels according to SD tertile in patients with DM were 122 ± 32 mg/dL, 136 ± 37 mg/dL, and 184 ± 65 mg/dL, and in patients without DM (101 ± 16 mg/dL, 112 ± 24 mg/dL, and 137 ± 62 mg/dL, respectively; Table 3).

Rates of hypertension, ischemic heart disease, congestive heart failure, cerebrovascular disease, 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 shown in Table 1.

Because there was a statistically significant interaction between DM, CV tertile and LOS, as well as between DM, CV tertile, and mortality (in-hospital and at end of follow-up), we analyzed the data separately in patients with DM and patients without DM.

LOS

The mean LOS was 7 ± 6 days, with longer LOS in patients without DM (7 ± 6 days) compared with patients with DM (6 ± 6 days; $P < 0.001$).

Higher SD and CV of glucose were both significantly associated with longer LOS in both patients with and without DM. There was a significant interaction between CV of glucose and LOS ($P < 0.0001$), and mean LOS was longer with higher CV tertiles of glucose in patients without DM (6 ± 5, 8 ± 7, and 9 ± 8 days, respectively) and in patients with DM (4 ± 3, 5 ± 5, and 7 ± 7 days, respectively). Increased SD tertile was also associated with longer LOS in patients without DM (6 ± 5, 8 ± 7, and 8 ± 8 days, respectively) and in patients with DM (4 ± 3, 5 ± 5, and 7 ± 7 days, respectively; Table 3).

In patients with DM, the LOS was 3.2 days longer in the third CV tertile and 1.4 days longer in the second CV tertile compared with patients in the first tertile. In the group of patients without DM, LOS was 2.7 and 1.8 days longer, respectively, in the third and second tertiles.

In patients with DM, LOS was 2.8 days longer in the third SD tertile and 1.4 days longer in the second SD tertile compared with patients in the first tertile. Similarly, in the group of patients without DM, LOS for the third and second tertiles was 2.5 and 1.8 days longer, respectively.

Mortality

Complete follow-up data at 12 months were available for all patients, with the first patient censored after 1.4 years. Median follow-up time was 1022 days for the entire cohort.

In-hospital mortality

Overall in-hospital mortality was 8.2% (1666 of 20,303 patients), including 9% of patients without DM (1058 of 11,738 patients) and 7.1% of patients with DM (608 of 8565 patients).

Higher CV tertile was associated with increased in-hospital mortality in patients without DM [second tertile vs first tertile: 10% vs 4%, odds ratio (OR), 2.3 (95% confidence interval [CI], 2.0 to 2.7); third tertile vs first tertile: 19% vs 4%, OR, 5.1 (95% CI, 4.3 to 6.0)], and in patients with DM [second tertile vs first tertile: 5% vs 3%, OR, 1.5 (95% CI, 1.1 to 2.1); third tertile vs first tertile: 10% vs 3%, OR, 3.1 (95% CI, 2.3 to 4.2)]. After adjustment for age, sex, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, and chronic renal failure,

Table 2. Mortality and LOS According to GV by CV Tertiles in Patients With and Without DM

		Patients Without DM			Patients With DM		
	Statistical Analysis	First Tertile (n = 5312)	Second Tertile (n = 4135)	Third Tertile (n = 2291)	First Tertile (n = 1455)	Second Tertile (n = 2633)	Third Tertile (n = 4477)
LOS, mean ± SD (median), d		6 ± 5 (5)	8 ± 7 (5)	9 ± 8 (6)	4 ± 3 (3)	5 ± 5 (4)	7 ± 7 (5)
Glucose level, median ± SD, mg/dL		103 ± 20	110 ± 31	119 ± 55	135 ± 52	150 ± 58	170 ± 65
In-hospital mortality, No. (%)		232 (4)	394 (10)	432 (19)	48 (3)	128 (5)	432 (10)
OR (95% CI)	Model 1[a]	—	2.3 (2.0–2.7)	5.1 (4.3–6.0)	—	1.5 (1.1–2.1)	3.1 (2.3–4.2)
	Model 2[b]	—	2.2 (1.7–2.9)	4.8 (3.7–6.2)	—	1.7 (1.0–2.9)	3.1 (1.9–4.9)
	Model 3[c]	—	2.0 (1.6–2.6)	4.1 (3.2–5.3)	—	1.7 (1.0–2.8)	2.7 (1.7–4.4)
	Model 4[d]	—	2.1 (1.6–2.7)	3.8 (2.9–5.0)	—	1.7 (1.0–2.8)	2.3 (1.4–3.7)
Mortality at the end of follow-up, No. (%)		1495 (28)	1735 (42)	1251 (55)	383 (26)	916 (35)	2033 (45)
HR (95% CI)	Model 1[a]	—	1.7 (1.5–1.8)	2.4 (2.3–2.6)	—	1.4 (1.2–1.6)	2.0 (1.8–2.2)
	Model 2[b]	—	1.5 (1.4–1.7)	2.3 (2.0–2.5)	—	1.4 (1.2–1.6)	1.9 (1.6–2.3)
	Model 3[c]	—	1.4 (1.3–1.6)	2.1 (1.8–2.3)	—	1.3 (1.1–1.6)	1.8 (1.5–2.1)
	Model 4[d]	—	1.4 (1.3–1.6)	2.0 (1.8–2.2)	—	1.3 (1.1–1.6)	1.7 (1.4–2.0)

Abbreviation: —, reference group.

[a]Model 1: Comparison with first tertile, unadjusted model.

[b]Model 2: Comparison with first tertile, adjustment for age, sex, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, and chronic renal failure.

[c]Model 3: Model 2 plus adjustment for glucocorticoid treatment during hospitalization.

[d]Model 4: Model 2 plus adjustment for hypoglycemia during the hospitalization.

respective adjusted ORs were 2.2 (95% CI, 1.7 to 2.9) and 4.8 (95% CI, 3.7 to 6.2) in patients without DM, and 1.7 (95% CI, 1.0 to 2.9), and 3.1 (95% CI, 1.9 to 4.9) in patients with DM (Table 2, model 2).

Higher SD tertile was associated with increased in-hospital mortality in patients without DM [second tertile vs first tertile: 11% vs 4%, OR, 3.0 (95% CI, 2.5 to 3.5); third tertile vs first tertile: 21% vs 4%, OR, 6.4 (95% CI, 5.4 to 7.6)], and in patients with DM [second tertile vs first tertile: 4% vs 2%, OR, 2.1 (95% CI, 1.3 to 3.2); third tertile vs first tertile: 9% vs 2%, OR, 4.6 (95% CI, 3.1 to 7.0)]. After adjustment for study variables, respective adjusted ORs were 2.8 (95% CI, 2.2 to 3.7) and 6.4 (95% CI, 4.9 to 8.4) in patients without DM, and 1.8 (95% CI, 1.0 to 3.4), and 3.8 (95% CI, 2.1 to 6.8) in patients with DM (Table 2, model 2).

Table 3. Mortality and LOS According to GV by SD Tertiles in Patients With and Without DM

		Patients Without DM			Patients With DM		
		First Tertile (n = 5879)	Second Tertile (n = 4119)	Third Tertile (n = 1740)	First Tertile (n = 1092)	Second Tertile (n = 2406)	Third Tertile (n = 5067)
LOS, mean ± SD (median), d		6 ± 5 (5)	8 ± 7 (6)	8 ± 8 (6)	4 ± 3 (3)	5 ± 5 (4)	7 ± 7 (5)
Glucose level, median ± SD, mg/dL		101 ± 16	112 ± 24	137 ± 62	122 ± 32	136 ± 37	184 ± 65
In-hospital mortality, No. (%)		235 (4)	457 (11)	366 (21)	24 (2)	106 (4)	478 (9)
OR (95% CI)	Model 1[a]	—	3.0 (2.5–3.5)	6.4 (5.4–7.6)	—	2.1 (1.3–3.2)	4.6 (3.1–7.0)
	Model 2[b]	—	2.8 (2.2–3.7)	6.4 (4.9–8.4)	—	1.8 (1.0–3.4)	3.8 (2.1–6.8)
	Model 3[c]	—	2.6 (2.0–3.4)	5.4 (4.1–7.2)	—	1.8 (1.0–3.3)	3.4 (1.9–6.0)
	Model 4[d]	—	2.7 (2.1–3.4)	5.5 (4.1–7.2)	—	1.7 (1.0–3.2)	3.0 (1.7–5.5)
Mortality at the end of follow-up, No. (%)		1670 (28)	1815 (44)	996 (57)	278 (25)	822 (34)	2232 (44)
HR (95% CI)	Model 1[a]	—	1.7 (1.6–1.9)	2.6 (2.4–2.8)	—	1.4 (1.2–1.6)	2.0 (1.7–2.2)
	Model 2[b]	—	1.5 (1.4–1.7)	2.5 (2.3–2.9)	—	1.4 (1.2–1.8)	2.0 (1.7–2.4)
	Model 3[c]	—	1.5 (1.3–1.6)	2.3 (2.0–2.6)	—	1.4 (1.2–1.7)	1.9 (1.6–2.3)
	Model 4[d]	—	1.5 (1.3–1.6)	2.3 (2.0–2.6)	—	1.4 (1.1–1.7)	1.8 (1.5–2.1)

Abbreviation: —, reference group.

[a]Model 1: Comparison with first tertile, unadjusted model.

[b]Model 2: Comparison with first tertile, adjustment for age, sex, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, and chronic renal failure.

[c]Model 3: Model 2 plus adjustment for glucocorticoid treatment during hospitalization.

[d]Model 4: Model 2 plus adjustment for hypoglycemia during the hospitalization.

Mortality at the end of follow-up

Overall mortality rate for the entire cohort at the end of follow-up was 38.5% (7813 of 20,303 patients), including 38% of patients without DM (4481 of 11,738 patients) and 39% of patients with DM (3332 of 8565 patients).

Higher CV tertile was associated with increased mortality at the end of follow-up in patients without DM [second tertile vs first tertile: 42% vs 28%, hazard ratio (HR), 1.7 (95% CI, 1.5 to 1.8); third tertile vs first tertile: 55% vs 28%, HR, 2.4 (95% CI, 2.3 to 2.6)], and in patients with DM [second tertile vs first tertile: 35% vs 26%, HR, 1.4 (95% CI, 1.2 to 1.6); third tertile vs first tertile: 45% vs 26%, HR, 2.0 (95% CI, 1.8 to 2.2)]. After adjustment for study variables, respective adjusted HRs were 1.5 (95% CI, 1.4 to 1.7) and 2.3 (95% CI, 2.0 to 2.5) in patients without DM, and 1.4 (95% CI, 1.2 to 1.6), and 1.9 (95% CI, 1.6 to 2.3) in patients with DM (Table 2).

Higher SD tertile was associated with increased mortality at the end of follow-up in patients without DM [second tertile vs first tertile: 44% vs 28%, HR, 1.7 (95% CI, 1.6 to 1.9); third tertile vs first tertile: 57% vs 28%, HR, 2.6 (95% CI, 2.4 to 2.8)], and in patients with DM [second tertile vs first tertile: 34% vs 25%, HR, 1.4 (95% CI, 1.2 to 1.6); third tertile vs first tertile: 44% vs 25%, HR, 2.0 (95% CI, 1.7 and 2.2)]. After adjustment, respective adjusted HRs were 1.5 (95% CI, 1.4 to 1.7) and 2.5 (95% CI, 2.3 to 2.9) in patients without DM, and 1.4 (95% CI, 1.2 to 1.8) and 2.0 (95% CI, 1.7 to 2.4) in patients with DM (Table 2).

The Kaplan-Meier curves depicted better survival with low GV compared with high GV according to either CV [Fig. 2(a)] or SD [Fig. 2(b)] tertiles.

Glucocorticoid treatment

During hospitalization, 20% of the patients in the cohort were treated with glucocorticoids, including 21% of patients without DM (2523 of 11,738 patients) and 17% of patients with DM (1494 of 8565 patients). Although glucocorticoid treatment was more prevalent in patients in the third CV or SD tertiles in patients with or without DM, further adjustment of the model to glucocorticoid treatment during hospitalization had no significant impact on the results (Table 2, model 3).

Hypoglycemia

During hospitalization, 12% of patients had at least one glucose value <70 mg/dL, including 9% of patients without DM (1085 of 11,738 patients) and 16% of patients with DM (1392 of 8565 patients). Hypoglycemia was more common in patients in the third CV tertile (27% and 29% in patients without and with DM, respectively), compared with the first CV tertile (2% and 1%, respectively). Similarly, hypoglycemia was more common in patients in the third SD tertile (20% and 24% in patients without and with DM, respectively), compared with the first SD tertile (4% and 3%, respectively). However, in patients with and those without DM, further adjustment of the model to hypoglycemia during the hospitalization had no significant impact on the results (Table 2, model 4).

Type of DM and treatment

Data on DM type were available for 8052 of the 8565 patients with DM: 76 (0.9%) had type 1 and 7976 (93%) had type 2 DM. In the remainder, type 2 DM was likely in most cases but this could not be confirmed. Analysis limited to patients with confirmed type 2 DM indicated similar patterns: Higher CV tertile was associated with increased in-hospital mortality [second tertile vs first tertile: OR, 1.7 (95% CI, 1.3 to 2.2); third tertile vs first tertile: OR, 2.6 (95% CI, 2.0 and 3.3)]. After adjustment for study variables, respective adjusted ORs were 1.6 (95% CI, 1.0 to 2.3) and 2.6 (95% CI, 1.8 to 3.9). Compared with patients in the first CV tertile, the adjusted HRs for mortality at the end of follow-up were 1.3 (95% CI, 1.1 to 1.5) and 1.8 (95% CI, 1.6 to 2.1) in patients in the second and third CV tertiles, respectively.

Due to the small number of patients with type 1 DM, we did not analyze the data specifically in this population.

Of the 7976 patients with type 2 DM, 3387 (42%) were treated with insulin, with or without additional oral medication, 3376 (42%) were treated with a noninsulin medication, and the rest (15%) did not receive drug treatment for DM.

Although most insulin-treated patients were in the third tertile (n = 1883 patients; 56%) or in the second CV tertile (n = 1115 patients; 33%), most of the patients treated with a noninsulin medication (50%) and those with no drug treatment for DM were in the first CV tertile (49%; Table 4). Analysis of the association of GV with mortality according to treatment of DM indicated increased in-hospital and long-term mortality in insulin-treated patients in the third CV tertile, compared with those in the first tertile. In patients treated with a noninsulin drug, increased mortality with increased GV was evident only at the end of follow-up, with no significant difference for in-hospital mortality. In patients with DM who received no drug treatment, there was a threefold and 1.5-fold increase in in-hospital and long-term mortality, respectively, in patients in the third CV tertile (Table 4).

Median glucose level during hospitalization

The Cox model showed no interaction between median glucose levels, LOS, and CV or SD tertiles (Tables 4 and 5). Furthermore, there was no interaction between

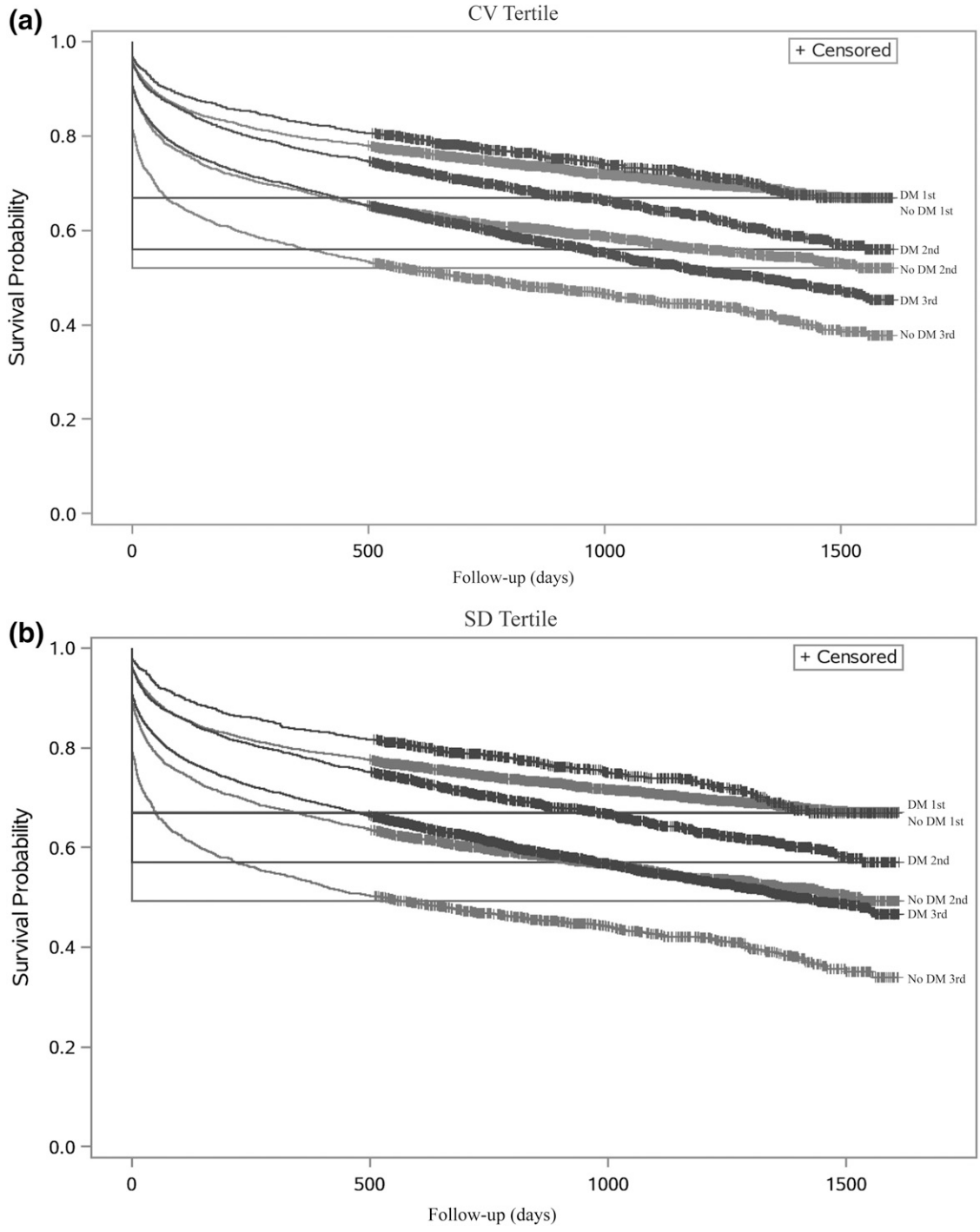

Figure 2. Kaplan-Meier analysis of patients following discharge (a) according to CV tertile, and (b) according to SD tertile in patients without DM and with DM. Patient survival analyzed as time until death; observations were censored at the end of follow-up ($P < 0.05$).

median glucose levels, in-hospital mortality, and CV or SD tertiles. However, because the Cox proportional hazards model indicated an interaction between median glucose levels, CV tertile, and mortality at the end of follow-up ($P < 0.05$), we analyzed the data according to median glucose levels. In patients without DM, in each CV tertile, mortality risk was higher with median glucose levels >180 mg/dL (50%, 61%, and 59% in first, second and third tertiles, respectively), compared with median glucose levels between 70 and 180 mg/dL (28%, 41%, and 54%, respectively). In patients with DM, the difference in mortality according to median glucose levels was less significant with median glucose >180 mg/dL (33%, 36%, and 49% in the first, second, and third tertiles, respectively) compared with lower levels (25%, 34%, and 43% mortality rates, respectively).

Table 4. Mortality According to GV, by CV Tertiles[a]

		Insulin Treatment		
		First CV Tertile (n = 389)	**Second CV Tertile (n = 1115)**	**Third CV Tertile (n = 1883)**
In-hospital mortality, No. (%)		18 (5)	110 (10)	231 (12)
OR (95% CI)	Model 1[b]	—	3.0 (1.8–4.9)	3.0 (1.8–4.9)
	Model 2[c]	—	2.9 (1.3–6.5)	2.9 (1.3–6.5)
Mortality at the end of follow-up, No. (%)		135 (35)	477 (43)	903 (48)
HR (95% CI)	Model 1[b]	—	1.6 (1.3–1.9)	1.6 (1.3–1.9)
	Model 2[c]	—	1.8 (1.4–2.3)	1.8 (1.4–2.3)
Noninsulin drug treatment				
		First CV Tertile (n = 1676)	Second CV Tertile (n = 1132)	Third CV Tertile (n = 568)
In-hospital mortality, No. (%)		52 (3)	46 (4)	26 (5)
OR (95% CI)	Model 1[b]	—	1.5 (0.9–2.4)	1.5 (0.9–2.4)
	Model 2[c]	—	1.2 (0.6–2.7)	1.2 (0.6–2.7)
Mortality at the end of follow-up, No. (%)		424 (25)	345 (31)	240 (42)
HR (95% CI)	Model 1[b]	—	1.8 (1.5–2.1)	1.8 (1.5–2.1)
	Model 2[c]	—	1.6 (1.3–1.9)	1.6 (1.3–1.9)
No drug treatment				
		First CV Tertile (n = 593)	Second CV Tertile (n = 412)	Third CV Tertile (n = 208)
In-hospital mortality, No. (%)		27 (5)	27 (7)	29 (14)
OR (95% CI)	Model 1[b]	—	1.4 (0.8–2.5)	3.2 (1.8–5.6)
	Model 2[c]	—	1.8 (0.7–4.4)	3.1 (1.1–8.2)
Mortality at the end of follow-up, No. (%)		228 (39)	206 (50)	112 (54)
HR (95% CI)	Model 1[b]	—	1.4 (1.2–1.7)	1.5 (1.2–1.9)
	Model 2[c]	—	1.4 (1.1–1.9)	1.5 (1.0–2.1)

Abbreviation: —, no data.

[a]Mortality according to drug treatment of type 2 DM: insulin treatment, noninsulin drug treatment, and no drug treatment, according to CV tertiles.

[b]Model 1: Comparison with first tertile, unadjusted model.

[c]Model 2: Comparison with first tertile, adjustment for age, sex, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, and chronic renal failure.

Interestingly, in patients without DM, mortality risk was similar with median glucose levels >180 mg/dL in patients in the second and third CV tertiles. However, in patients with DM, mortality risk was highest in patients in the third CV tertile, independent of median glucose values, with higher mortality in those with median glucose values >180 mg/dL in that tertile.

The adjusted HRs with higher median glucose compared glucose values <180 mg/dL in first, second, and third CV tertiles were 2.3 (95% CI, 1.3 to 4.0), 2.1 (95% CI, 1.5 to 2.8), and 1.6 (95% CI, 1.3 to 2.0) in patients without DM, and 1.7 (95% CI, 1.2 to 2.4), 1.0 (95% CI, 0.8 to 1.2), and 1.3 (95% CI, 1.2 to 1.5), respectively, in patients with DM.

Median glucose values <70 mg/dL were very uncommon; therefore, we did not analyze the results separately in that group.

Discussion

This study suggests an increased in-patient and post-admission mortality risk in hospitalized patients with increased GV, with and without a prior diagnosis of DM. Increased GV was also associated with longer LOS.

Unlike the Mendez *et al.* (15) study with a smaller cohort (<1000 patients), our study showed an interaction between DM and GV with LOS and mortality (*i.e.*, GV had a different impact on patients with DM and patients without DM); therefore, we analyzed the data separately in these two subgroups. Whereas most previous studies on GV and mortality focused on patients in the intensive care unit (27–34) or mixed surgical and medical patients (15), our study focused on patients admitted to medical wards. Furthermore, we included a large cohort of patients with evaluation of long-term mortality.

After adjustment for age, sex, smoking, alcohol, BMI, and comorbidities, the results in patients with and without DM indicated longer LOS in patients with increased GV. Like Mendez *et al.* (15), our data indicate that compared with low GV, higher GV was associated with an increase of 1.5 to 2 days of hospitalization in those with moderate GV, and 2.5 to 3 days in those with the most pronounced GV. Compared with low GV, increased GV was associated with a more than twofold increase in in-hospital mortality with moderate GV (10% vs 4%), and fivefold increase with marked GV (19% vs 4%) in patients without DM. In patients with DM, there

Table 5. Mortality According to GV and Treatment, by SD Tertiles[a]

		Insulin Treatment		
		First SD Tertile (n = 248)	**Second SD Tertile (n = 1004)**	**Third SD Tertile (n = 2135)**
In-hospital mortality, No. (%)		8 (3)	71 (7)	280 (13)
OR (95% CI)	Model 1[b]	—	2.1 (1.0–4.4)	3.6 (1.7–7.4)
	Model 2[c]	—	1.0 (0.4–2.6)	2.0 (0.8–4.8)
Mortality at the end of follow-up, No. (%)		85 (34)	402 (40)	1,028 (48)
HR (95% CI)	Model 1[b]	—	1.2 (1.0–1.5)	1.5 (1.2–1.9)
	Model 2[c]	—	0.9 (0.7–1.3)	1.2 (0.9–1.6)
Noninsulin drug treatment				
		First SD Tertile (n = 1734)	Second SD Tertile (n = 1263)	Third SD Tertile (n = 379)
In-hospital mortality, No. (%)		52 (3)	52 (4)	20 (5)
OR (95% CI)	Model 1[b]	—	1.2 (0.8–1.8)	1.3 (0.7–2.2)
	Model 2[c]	—	0.8 (0.4–1.5)	0.9 (0.4–2.2)
Mortality at the end of follow-up, No. (%)		453 (26)	402 (32)	154 (41)
HR (95% CI)	Model 1[b]	—	1.3 (1.1–1.4)	1.7 (1.4–2.0)
	Model 2[c]	—	1.1 (0.9–1.4)	1.7 (1.3–2.2)
No drug treatment				
		First SD Tertile (n = 677)	Second SD Tertile (n = 394)	Third SD Tertile (n = 142)
In-hospital mortality, No. (%)		33 (5)	35 (9)	15 (11)
OR (95% CI)	Model 1[b]	—	1.8 (1.1–3.0)	1.9 (0.9–3.9)
	Model 2[c]	—	0.9 (0.4–2.2)	2.0 (0.7–6.1)
Mortality at the end of follow-up, No. (%)		273 (40)	206 (52)	67 (47)
HR (95% CI)	Model 1[b]	—	1.4 (1.2–1.7)	1.2 (0.9–1.5)
	Model 2[c]	—	1.1 (0.8–1.5)	1.2 (0.8–1.9)

Abbreviation: —, no data.

[a]Mortality according to drug treatment of type 2 DM: insulin treatment, noninsulin drug treatment, and no drug treatment according to SD tertiles.

[b]Model 1: Comparison with first tertile, unadjusted model.

[c]Model 2: Comparison with first tertile, adjustment for age, sex, smoking, alcohol, BMI, hypertension, malignancy, ischemic heart disease, congestive heart failure, cerebrovascular disease, and chronic renal failure.

was a 1.7-fold and 3-fold increase with moderate (5% vs 3%) and marked (10% vs 3%) GV, respectively. Analysis of mortality at the end of follow-up, with median follow-up of ~3 years, demonstrated a 1.5- and 2.3-fold increase in mortality with moderate (42% vs 28%) and marked (55% vs 28%) GV in patients without DM, and a 1.4 (35% vs 26%) and almost twofold (45% vs 26%) increase in those with DM.

Because glucocorticoid treatment may have a significant impact on glucose levels and GV, we also retrieved data regarding treatment during hospitalization. Glucocorticoid treatment was more prevalent in patients with higher CV tertiles, with and without pre-existing DM. For that reason, we added another model, aimed at analyzing the impact of GV adjusted further to glucocorticoid treatment, with no significant change in the calculated ORs and HRs.

Previous studies suggested that hypoglycemia during hospitalization is associated with increased mortality and, therefore, is a possible explanation for increased mortality in patients with increased GV (4–13). Expectedly, our data show that hypoglycemia was more common in patients with increased GV; nevertheless, adjustment to hypoglycemia during the hospitalization had no significant impact on the calculated risk for in-hospital and end of follow-up mortality.

As has been suggested, higher mortality rates in patients with increased GV may stem from an increase in reactive oxygen species (17, 35). Fluctuations in glucose levels may impair endothelial function, as shown in a previous study reporting increased damage to endothelial tissue in rats with oscillating glucose levels compared with persistent hyperglycemia (36, 37). Monnier *et al.* (35) concluded that GV had a more specific triggering effect on oxidative stress than did sustained chronic hyperglycemia—an observation that was consistent with a previous study (38) indicating that platelet aggregation can be activated during insulin-induced hypoglycemia in patients with type 1 DM.

GV may be induced by an intervention, such as insulin or glucocorticoid treatment during hospitalization, or it may appear random, due to changes in the patient's condition. It is possible that GV is merely a marker of poor health status, with swings in blood glucose levels in accordance with changes in renal, adrenal, or liver dysfunction. However, when Takeishi *et al.* (26) investigated the association between glycemic control, reactive inflammatory biomarkers, and vital signs, they concluded

that GV was associated with increased mortality in patients not in the intensive care unit, but there was no association between reactive inflammatory biomarkers or vital signs with mortality, pointing to an independent effect of variations in glucose levels. We believe that avoiding glycemic instability and glucose swings may be another goal of glycemic control during hospitalization. As for the recommended GV, in this study, CVs <15% or SDs ≤17 mg/dL were associated with the best prognosis. Our findings demonstrate the practicality of using commonly available bedside glucose measurements without requiring continuous glucose monitoring for measuring mean amplitude of glycemic excursion or insulin clamp studies to determine the impact of GV on outcome. These results confirm and are consistent with other papers showing the clinical importance of limiting GV, which has been associated with changes in free radical production (16, 35).

In our cohort, insulin treatment was associated with increased GV, because most of these patients were in the third CV tertile. On the other hand, most patients with noninsulin drug treatment or with no drug treatment of DM were in the first CV tertile. These findings are not surprising for several reasons. First, diet, which is cited as the first-line treatment of DM and was the main treatment in those with no drug treatment of DM in this study, may have an impact on GV. Carbohydrates with low glucose indices, and fiber, which reduces the absorption of sugars, may limit GV (39, 40). Second, several medications for DM have demonstrated a possible impact on glucose swings in patients with type 2 DM, including acarbose (41), dipeptidyl-peptidase 4 inhibitors (42) and glucagon-like peptide 1 analogs (43). As for insulin treatment, it is important to note that during the study, the main basal insulin drugs were insulin glargine U100 and insulin detemir; thus, it is possible that with the new basal insulins, such as insulin tregludec or insulin glargine U300, GV will be reduced.

Because there was no interaction between median glucose levels, GV, LOS, or in-hospital mortality, we conclude that median glucose levels during hospitalization and GV are two independent factors affecting the LOS and in-hospital mortality. However, because there was an interaction between median glucose levels, CV tertile, and mortality at the end of follow-up, we analyzed the data according to median glucose levels. A 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 (44). In patients with DM and in patients without DM, in each CV tertile, mortality risk was higher with glucose levels ≥180 mg/dL compared with median glucose levels <180 mg/dL. The increase in mortality with higher levels was most evident in patients without DM. Furthermore, in both patients with and without DM, the increase in mortality with higher median glucose levels was more pronounced in the first CV tertile and least significant in those in the third tertile.

The in-hospital mortality in our patients without DM, compared with patients with DM, was higher (9% vs 7%). A possible explanation is a lower threshold for hospitalization of patients with DM and milder disease, compared with patients without DM. Alternatively, this mortality difference may stem from the higher malignancy rate in patients hospitalized without DM (17% vs 15%; Table 1). Nevertheless, long-term mortality was not different among the two patient populations.

Our study has several limitations. First, the retrospective design of the study based data regarding comorbidities solely on the medical records and based smoking and alcohol use on self-report. Another limitation is that patients with a history of hyperglycemia or hypoglycemia have a greater chance of having their blood glucose measured more often, with a higher probability of detecting an increased GV. GV was based on venous blood glucose samples and bedside glucometers. Glucose monitoring during hospitalization is the standard of care for patients with DM, thus allowing identification of normal and abnormal glucose levels. However, because the use of bedside glucometers is not as common in patients without DM and many abnormal blood glucose measurements are identified incidentally in a routine blood work, we based our findings on this measurement as well. It should be noted that with abnormally high or low blood glucose readings using bedside glucometers, most patients are treated immediately, and venous blood sample may be obtained only later. Another limitation regarding glucose measurements relates to the fact that we have no documentation of the timing of glucose measurement relative to meals; hence, we could not perform a separate analysis of fasting or postprandial glucose measurements.

The major strengths of our study are the large cohort of patients admitted solely to medical wards, as well as long-term follow-up, representing real-life experience as opposed to prospective, randomized controlled studies in which patients undergo intensive monitoring and treatment adjustments. Nevertheless, we excluded patients with fewer than three glucose measurements during hospitalization and the number of glucose measurements during hospitalization was high, thus supporting an accurate estimation of GV.

In conclusion, our findings suggest that increased GV, whether in patients with or without pre-existing DM, is associated with longer LOS and increased short- and long-term mortality risk. Mortality risk was higher in

patients with increased GV and high median glucose values during the hospitalization, with more significant differences in patients without DM, compared with patients with DM. Randomized controlled interventional trials are needed to investigate the impact of minimizing GV on morbidity and mortality.

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