

Increased Glycemic Variability Is Independently Associated With Length of Stay and Mortality in Noncritically Ill Hospitalized Patients

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OBJECTIVE—To investigate the association between glycemic variability (GV) and both length of stay (LOS) and 90-day mortality in noncritically ill hospitalized patients.

RESEARCH DESIGN AND METHODS—This study retrospectively analyzed 4,262 admissions to the general medicine or surgery services during a 2 year period. Patients with point-of-care glucose monitoring and a minimum of two glucose values per day on average were selected. GV was assessed by SD and coefficient of variation (CV). Data were analyzed with linear and logistic multivariate regression analysis in separate models for SD and CV. Analysis was performed with generalized estimating equations to adjust for correlation between multiple admissions in some individual cases.

RESULTS—After exclusions, 935 admissions comprised the sample. Results of adjusted analysis indicate that for every 10 mg/dL increase in SD and 10–percentage point increase in CV, LOS increased by 4.4 and 9.7%, respectively. Relative risk of death in 90 days also increased by 8% for every 10-mg/dL increase in SD. These associations were independent of age, race, service of care (medicine or surgery), previous diagnosis of diabetes, HbA_{1c}, BMI, the use of regular insulin as a sole regimen, mean glucose, and hypoglycemia occurrence during the hospitalization.

CONCLUSIONS—Our results indicate that increased GV during hospitalization is independently associated with longer LOS and increased mortality in noncritically ill patients. Prospective studies with continuous glucose monitoring are necessary to investigate this association thoroughly and to generate therapeutic strategies targeted at decreasing GV.

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Inpatient hyperglycemia is common, and it has been associated with increased morbidity and mortality in patients with and without diabetes (1–7). In the intensive care unit (ICU) setting, hypoglycemia has also been independently associated with a significant increase in mortality (8–10). Recently, a third metric of glucose control, known as glycemic variability (GV), has been proposed to be additionally implicated in the disease-associated process of dysglycemia (11).

GV refers to fluctuations of blood glucose values around the mean and has been posited as a novel marker for poor glycemic control (12,13). In vitro and human studies suggest that high GV leads to greater oxidative stress than does sustained hyperglycemia (14,15). Studies of ICU patients have consistently demonstrated that increased GV is independently associated with higher mortality (16–19). Notably, results from a large multicenter study concluded that GV was a stronger predictor of ICU mortality

than was mean glucose concentrations (20).

Although there is no consensus as to the best method to determine GV in hospitalized patients, the use of SD of glucose values has been well validated by previous ICU studies (16,20). Coefficient of variation (CV) has also been suggested as a strong independent index for measuring GV because it corrects for mean glucose levels (21,22).

Despite substantial scientific evidence from the ICU, no previous studies have investigated the association between GV and clinical outcomes in patients admitted to the general medical and surgical wards. The purpose of this study was therefore to investigate the association between GV and length of stay (LOS) and 90-day mortality in noncritically ill hospitalized patients. We hypothesize that increased GV in this setting is associated with increased LOS and mortality.

RESEARCH DESIGN AND METHODS

Study design and patient selection

We performed a retrospective cohort study that included patients admitted to the acute non-ICU medicine and surgery services of the Stratton Veterans Affairs Medical Center in Albany, NY, between January 2008 and January 2010.

Approval of the institutional review board was obtained. The initial query included all patient admissions with available blood glucose concentration from any of the admitting hospital services ($n = 4,262$).

Exclusion criteria applied to the study included the following: patients admitted to or transferred from the ICU and long-term care wards ($n = 1,624$); patient admissions with very long hospital stays (>60 days), to avoid patients not acutely ill ($n = 5$); patient admissions with no point-of-care glucose monitoring ($n = 1,456$); patient admissions with fewer than two glucose values per day of hospitalization on average ($n = 240$); and

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patient admissions with inconsistent date of death information ($n = 2$). Patients who were hospitalized more than once had each admission counted separately.

Data collection

Data were extracted from the VISN 2 Veterans Health Information Systems and Technology Architecture (VistA) and the Veterans Affairs Regional Data Warehouse (VARDW). Data from VistA were collected via a Mumps program routine and imported as a spreadsheet to Microsoft SQL Server Database. They were merged with the VARDW data by means of specific Structured Query Language queries.

Blood glucose concentrations were measured in capillary blood obtained by finger stick with a point-of-care device (ACCU-CHEK Inform system). We also made use of glucose determinations performed on venous blood in the central hospital laboratory. In an attempt to correct for false high or low readings, duplicates and glucose values that were followed by a confirmatory reading within 5 min were removed from the sample.

Outcome measures included LOS and mortality. LOS was calculated by the number of days from admission date to discharge or death date. Mortality was defined as in-hospital death or death within 90 days from discharge.

Glucose metrics and statistical analysis

Mean in-hospital glucose (MHG) was calculated from all glucose readings available during each individual hospitalization. In addition, to correct for variation in the number of readings each day, a mean patient-day glucose (MDG) was calculated as the average of daily mean glucose values during hospitalizations. Hypoglycemia was defined as any episode of blood glucose <70 mg/dL during the hospital stay.

We quantified GV with SD and CV for the data set of all available glucose readings for each admission. CV was defined as the ratio of SD to MHG, expressed as a percentage. Linear and modified Poisson regression analyses were used to assess associations between measures of GV and the two outcomes. The associations between GV and the outcome measures were assessed in separate models for SD and CV. Other variables assessed for potential confounding included age, race, sex, hospital service (medicine or

surgery), previous diagnosis of diabetes, glycosylated hemoglobin (HbA_{1c}) obtained within 3 months from admission, BMI, Charlson comorbidity index (CCI), hypoglycemia, MHG, MDG, and use of human regular insulin as the sole regimen for glycemic control during the hospitalization.

Analyses were performed with generalized estimating equations to adjust for correlation between multiple admissions in some cases. Log-transformed LOS and 90-day mortality were the dependent variables. A linear link and normal error structure were used for the LOS, and a logit link and binomial error structure were used for 90-day mortality.

A bivariate analysis was initially performed to identify significant associations between individual variables and the two outcome measures. Those variables for which $P \leq 0.1$ were subsequently included in multivariate models to assess whether the associations between SD (SD model) or CV (CV model) and LOS and mortality were independent of other variables. In the multivariate models, those variables with a level of statistical significance of $P < 0.05$ were subsequently retained through backward elimination.

To investigate the potential influence of hypoglycemia on the associations between GV and LOS and mortality, separate additional models that did not correct for hypoglycemia were created for CV and SD. Moreover, regression analyses were performed to assess the risk of hypoglycemia occurrence in those patient admissions with high CV and high SD of glucose. Subgroup analyses were also performed by SD and CV categories within patient admissions with adequate glycemic control (MHG 90–180 mg/dL) and those with significant hyperglycemia (MHG >180 mg/dL).

Because LOS was not normally distributed, it was log-transformed, and the results presented and interpreted accordingly. Statistical software STATA 11.0 was used for all analyses.

RESULTS

Subjects

After exclusion criteria were applied, the final sample consisted of 935 hospital admissions comprising 620 individual patients. Table 1 summarizes the characteristics of the study subjects and the results of bivariate analyses. The patient population was composed mainly of

elderly, white male subjects, most of whom were admitted to the acute medical service. Diabetes had been diagnosed in 801 patients (85.7%) before admission. Study patients had on average 3.56 ± 0.9 glucose readings per day. The mean LOS was 5.72 ± 6.37 days, and there were 120 deaths (12.83%) within 90 days of discharge.

Length of stay

Table 1 summarizes associations between the examined variables and LOS. Higher SD and CV of glucose were both significantly associated with longer LOS. LOS increased by 6.4% with each 10 mg/dL increment in SD of glucose (95% CI 4.4–8.3%, $P < 0.001$) and by 16.5% with each 10–percentage point increment in CV of glucose (12.1–20.9%, $P < 0.001$). In addition, LOS increased by 6.6% with each 10-year increment in age (1.3–12.0%, $P = 0.015$), and LOS of patients with hypoglycemia was 56.2% longer than that of those without (42.8–69.6%, $P < 0.001$). A lower BMI was also significantly associated with longer LOS. None of the other variables, including sex, race, previous diagnosis of diabetes, HbA_{1c} , service (medicine versus surgery), MDG, MHG, CCI, or the use of human regular insulin as a sole regimen, had a significant association with LOS.

Table 2 shows the adjusted associations between both GV measures and LOS after correction for age and hypoglycemia in separate models. In the SD model, the association between SD of glucose and LOS was reduced to 4.4% (95% CI 2.4–6.3%, $P < 0.001$), that of hypoglycemia decreased to 47.3% (33.3–61.2%, $P < 0.001$), and that of age decreased to 5.1% (0.2–10.1%, $P = 0.043$). In the SD model that did not correct for hypoglycemia, the associations of SD and age with LOS decreased slightly relative to the results of the bivariate analysis (5.9%, 0.8–11.0%, $P < 0.001$ vs. 6.3%, 4.3–8.2%, $P < 0.001$ respectively). In the CV model, the association between CV of glucose and LOS decreased to 9.7% (4.7–14.8%, $P < 0.001$) and that of hypoglycemia to 40.5% (24.7–56.3%, $P < 0.001$). Age no longer had a significant association with LOS in that model.

Mortality

In the bivariate analysis, age, a lower BMI, admission to the medical service, higher CCI, hypoglycemia, and both SD and CV of glucose were significantly associated with increased 90-day mortality (Table 1).

Table 1—Sample characteristics and bivariate analysis on LOS and 90-day mortality (n = 935)

Variable	Value	Change in LOS		90-Day mortality risk	
		% (95% CI)	P	RR (95% CI)	P
Age (years)†	69.8 ± 11.2	6.6 (1.3–12.0)	0.015*	1.59 (1.24–2.05)	<0.001*
Sex (male)	895 (95.7)	−4.4 (−32.2 to 23.5)	0.759	0.72 (0.34–1.54)	0.400
Race (white)‡	922 (89.8)	9.9 (−10.5 to 30.4)	0.340	1.08 (0.56–2.09)	0.811
PDD	801 (85.7)	−12.3 (−28.9 to 4.3)	0.146	1.17 (0.67–2.05)	0.579
HbA _{1c} (%)§	7.60 ± 1.9	1.7 (−1.4 to 4.8)	0.287	1.02 (0.91–1.14)	0.727
Surgical service	171 (18.2)	9.7 (−6.3 to 25.8)	0.235	0.28 (0.12–0.63)	0.002*
Medical service	764 (81.7)	Reference		Reference	
BMI (kg/m ²)	30.0 ± 7.9	−9.3 (−18.1 to −0.5)	0.038*	0.58 (0.43–0.80)	0.001*
HRI	99 (10.6)	2.8 (−5.9 to 11.5)	0.527	0.88 (0.62–1.23)	0.444
CCI					
0	353 (36.8)	Reference		Reference	
1	206 (24.5)	−10.7 (−26.4 to 5.0)	0.181	1.05 (0.60–1.87)	0.856
≥2	401 (41.8)	4.5 (−9.9 to 19)	0.537	1.72 (1.09–2.72)	0.020*
Hypoglycemia¶	228 (24.4)	56.2 (42.8–69.6)	<0.001*	1.73 (1.21–2.47)	0.002*
MHG (mg/dL)	182.4 ± 56.9	−0.06 (−0.16 to 0.03)	0.201	1.00 (1.00–1.00)	0.139
MDG (mg/dL)	182.6 ± 56.7	−0.1 (−0.2 to −0.004)	0.059	1.00 (1.00–1.00)	0.181
Glucose SD (mg/dL)#	57.9 ± 29.3	6.4 (4.4–8.3)	<0.001*	1.10 (1.04–1.16)	<0.001*
Glucose CV (%)**	31.9 ± 13.4	16.5 (12.1–20.9)	<0.001*	1.21 (1.07–1.35)	0.002*

Results are presented as mean ± SD or n (%) except as specified otherwise. HRI, human regular insulin (as sole regimen during hospitalization); PDD, previous diabetes diagnosis (before admission). * $P < 0.05$. †Per 10-year increment in age. ‡White race as compared with African American, Hispanic, Pacific Islander, and other unspecified. §Per each percentage point in HbA_{1c} 7.6% = 60 mmol/mol. ||Per every 10 kg/m² increment in BMI. ¶Hypoglycemia is defined as any documented in-hospital episode of glucose < 70 mg/dL, and effect is compared with subjects with no hypoglycemia. #Per 10 mg/dL increment in SD of glucose. **Per 10–percentage point increment in CV of glucose.

The risk of death within 90 days increased by 10% with each 10 mg/dL increment in SD of glucose (risk ratio [RR] 1.10 [95% CI 1.04–1.16], $P < 0.001$) and by 21% with each 10–percentage point increment in CV of glucose (RR 1.21 [1.07–1.35], $P = 0.002$). Variables without a significant association with mortality included sex, race, previous diagnosis of diabetes, HbA_{1c}, MHG, MDG, and regular insulin as sole in-hospital regimen.

After multivariate adjustment (Table 2), age, lower BMI, admission to the medical

service, and SD of glucose remained as independent predictors of 90-day mortality in the SD model. The risk of increased mortality in 90 days changed to 8% with every 10 mg/dL increment in SD of glucose (RR 1.08 [95% CI 1.02–1.14], $P = 0.005$). Although hypoglycemia no longer retained a significant association with increased mortality when introduced into the SD model, a small reduction of the association between SD and mortality was noted (RR 1.07 [1.01–1.13], $P = 0.022$). Similarly, in the CV

model that corrected for hypoglycemia, CV of glucose and hypoglycemia were no longer independent predictors of mortality, whereas age, BMI, and admission to the medical service remained significant predictors. In the CV model that corrected for age, BMI, and hospital service, but not for hypoglycemia, however, CV remained significantly associated with increased 90-day mortality, which rose by 14% with each 10–percentage point increment in CV of glucose (RR 1.14 [1.01–1.29], $P = 0.037$).

Table 2—Associations between GV (SD and CV) and LOS and 90-day mortality (adjusted)

Variable	Change in LOS (%)			90-Day mortality (RR [95% CI])			
	SD model†	SD model†‡	CV model§	SD model†	SD model†‡	CV model§	CV model‡§
GV	4.4 (2.4–6.3)	6.3 (4.3–8.2)	9.7 (4.7–14.8)	1.07 (1.01–1.13)	1.08 (1.02–1.14)	1.08 (0.93–1.24)*	1.14 (1.01–1.29)
Age	5.1 (0.2–10.1)	5.9 (0.8–11.0)	—	1.43 (1.12–1.82)	1.43 (1.12–1.83)	1.42 (1.11–1.82)	1.42 (1.11–1.82)
BMI¶	—	—	—	0.68 (0.50–0.93)	0.68 (0.50–0.92)	0.68 (0.50–0.93)	0.68 (0.50–0.93)
Service							
Medicine	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Surgery	—	—	—	0.37 (0.16–0.85)	0.36 (0.16–0.84)	0.35 (0.15–0.82)	0.35 (0.15–0.81)
Hypoglycemia							
Absent	Reference	—	Reference	—	—	Reference	—
Present#	47.3 (33.3–61.2)	—	40.5 (24.7–56.3)	1.36 (0.95–1.94)*	—	1.38 (0.92–2.05)*	—

* $P > 0.05$; for all other values, $P < 0.05$. †Per every 10 mg/dL increment of SD. ‡Not correcting for hypoglycemia. §Per every 10–percentage point increment of CV. ||Per every 10-year increment. ¶Per every 10 kg/m² increment in BMI. #Hypoglycemia is considered to be present with any documented in-hospital episode of glucose < 70 mg/dL.

Subgroup analyses

Analyses examining the association between both GV measures and hypoglycemia are presented in Table 3. The risk of hypoglycemia increased by 65% per every 10–percentage point increase in CV of glucose (RR 1.65 [95% CI 1.48–1.85], $P < 0.001$) and by 14% per every 10 mg/dL increase in SD of glucose (RR 1.14 [1.11–1.18], $P < 0.001$). In addition, the likelihood of hypoglycemia rose incrementally within each CV and SD tertile.

Figure 1 illustrates the associations between both SD and CV of glucose with mean LOS (days) and 90-day mortality (%) after stratification for MHG. Mean LOS and mortality rose incrementally with SD and CV. This trend was seen in patients with MHG suggestive of adequate glycemic control (90–180 mg/dL) as well as in those subjects with MHG consistent with significant hyperglycemia (≥ 180 mg/dL). Linear regression analyses showed that these trends were statistically significant for all series except for the 90-day mortality in the MHG ≥ 180 mg/dL group for both SD and CV.

CONCLUSIONS—Our study aimed to determine the associations between GV and both LOS and 90-day mortality in medicine and surgery patients in the non-ICU setting. We found a significant association between high GV and longer LOS and increased 90-day mortality. This association was not significantly influenced by age, race, service of care (medicine or surgery), a previous diagnosis of diabetes, HbA_{1c}, BMI, or the use of regular insulin as a sole regimen during the hospitalization. Furthermore, this association was noted to be independent both of

glycemic control (mean glucose) and of hypoglycemia.

Several previous studies have reported on the negative association found between increased GV and morbidity and mortality in critically ill patients, such as those with sepsis and congestive heart failure (16–19). Egi et al. (20) concluded from a large multicenter ICU study that GV was a stronger predictor of mortality than mean glucose levels. In agreement with these results, neither mean glucose during hospital stay nor mean patient-day glucose was directly associated with longer LOS or mortality in this study. Additionally, in accordance with the work of Krinsley (16) and Hermanides et al. (19), the added negative effects with increasing GV tertiles seen in our sample were evident in patients with adequate glycemic control as well as in those with significant hyperglycemia (Fig. 1).

The association between hypoglycemia and poor clinical outcomes in hospitalized patients has been well established (8–10,23,24). In this study, hypoglycemia was found to be significantly and independently associated with increased LOS. In addition, our results suggest that hypoglycemia has a modifying effect on the associations between GV and the examined outcomes, indicating that it is at least partially implicated in the causal pathway of GV and increased LOS and mortality. This influence seems to differ, however, according to which GV measure is used (SD or CV).

Although a noticeable attenuation in the association between SD and LOS was seen after adjustment for hypoglycemia (reduction from 6.3 to 4.4% increase in

LOS per every 10 mg/dL increment in SD), there was no significant change in the association between SD and mortality. Conversely, the associations between CV and both LOS and mortality were significantly affected after adjustment for hypoglycemia. The association with LOS was considerably diminished (reduction from 16.5 to 9.7% increase in LOS per every 10 percentage point increase in CV), and in the multivariate analyses for mortality both CV and hypoglycemia were rendered not significant when the two variables were simultaneously retained in the model (Table 2).

The CV has been proposed to be a strong predictor of, and closely related to, hypoglycemia (25). In our study, patient admissions with increased CV were significantly more likely to develop hypoglycemia than were those with increased SD (Table 3). Given that CV is directly proportional to SD and inversely proportional to mean glucose, hypoglycemia is expected to naturally occur in subjects with high SD and low mean (high CV). Thus, as suggested by our results, adjusting for hypoglycemia when using CV may not be methodologically appropriate and may lead to overadjustment. Alternatively, SD of glucose might be a better metric than CV when the potential effects of GV need to be separated from those of hypoglycemia.

Reports based on ICU patients have used other methods to assess more accurately patterns of GV over time, such as mean amplitude of glycemic excursions (MAGE) and mean absolute glucose rate of change (MAG) (19,22). Baghurst et al. (26) showed that as glucose values separate in time (>4 h between readings), the use of MAGE becomes less reliable than SD to estimate GV. Similarly, Harmsen et al. (27) found that using MAG to estimate GV accurately requires similar glucose measurement frequencies, which were not available in our sample.

Focusing on patients from general wards rather than ICU is an important strength of our study. We believe this provides a novel perspective of the implications that GV might have in this specific patient population. Despite this population being the largest in most hospitals, it has not been as studied in terms of glycemic control and GV. Another strong point of this study is that the mean number of daily glucose measurements used for analysis (3.56 ± 0.9) allowed enough data for accurate assessment

Table 3—Associations between GV (SD and CV) and hypoglycemia

Association	RR	P	95% CI
CV and hypoglycemia*			
CV†	1.65	<0.001	1.48–1.85
1st tertile†	Reference	Reference	Reference
2nd tertile †‡	10.40	<0.001	4.21–25.69
3rd tertile†‡	34.3	<0.001	14.29–82.37
SD and hypoglycemia*			
SD§	1.14	<0.001	1.11–1.18
1st tertile§	Reference	Reference	Reference
2nd tertile‡§	2.15	<0.001	1.46–3.18
3rd tertile‡§	3.98	<0.001	2.79–5.67

*Hypoglycemia is considered to be present with any documented in-hospital episode of glucose <70 mg/dL. †Per every 10 mg/dL increment of CV. ‡In comparison with 1st tertile. §Per every 10–percentage point increment of SD.

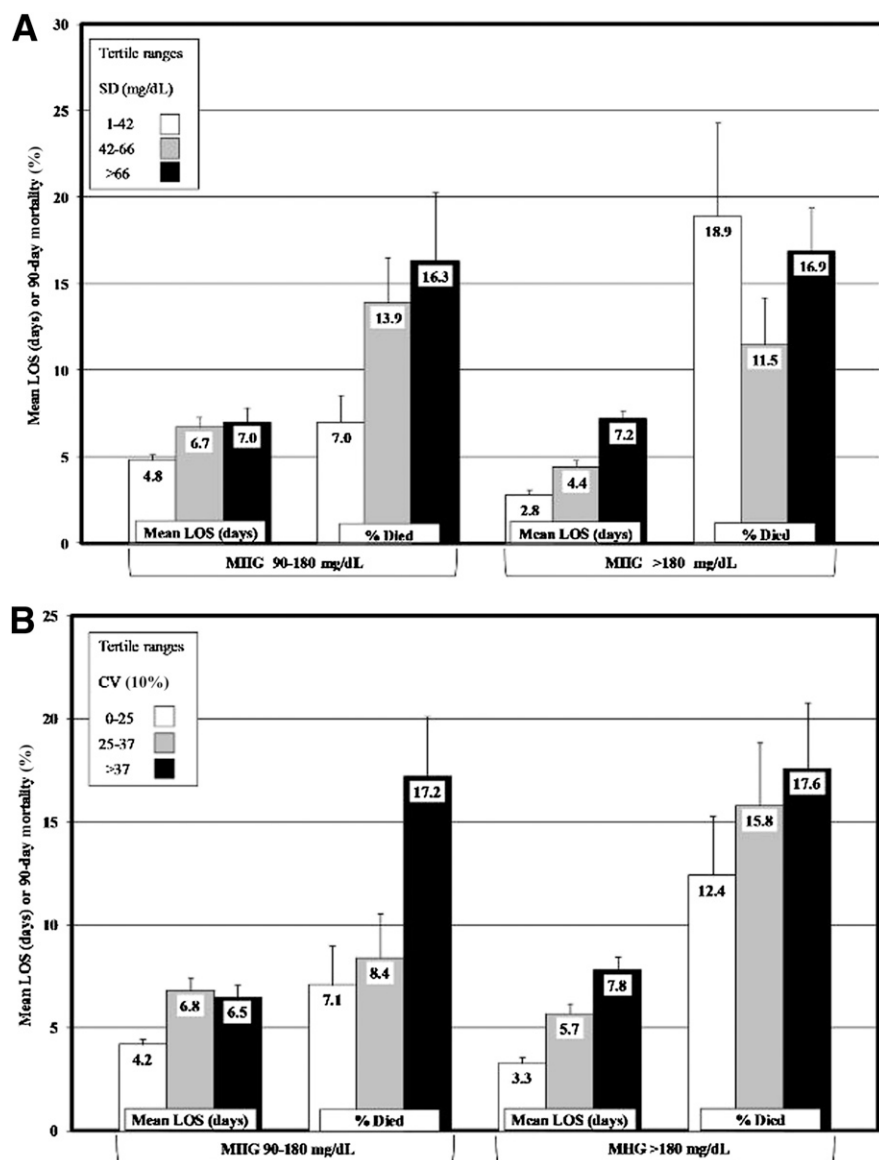


Figure 1—A: Mean LOS (days \pm SE) and 90-day mortality (% \pm SE) of increasing SD tertiles across two MHG categories (90–180 mg/dL and \geq 180 mg/dL). B: Mean LOS (days \pm SE) and 90-day mortality (% \pm SE) of increasing CV tertiles across two MHG categories (90–180 mg/dL and \geq 180 mg/dL). For linear trend, $P < 0.05$ for all series except the 90-day mortality in the MHG \geq 180 mg/dL group for SD ($P = 0.77$) and CV ($P = 0.24$).

of GV during the hospital stay. In addition, setting a relatively high limit for the hypoglycemia analyses (any episode <70 mg/dL), instead of only severe episodes (<40 mg/dL), supports the hypothesis that GV has a deleterious effect on LOS and mortality independent of the effect of hyperglycemia itself.

The possible mechanisms implicated in the pathophysiology of GV include an overproduction of reactive oxygen species through the same four pathways involved in the tissue-damaging effects of hyperglycemia (28). Quagliaro et al. (14) showed that endothelial adhesion

molecules activated during inflammation are increased in the presence of oscillating glucose levels versus stable high glucose. Endothelial function was also shown to be further impaired in rats who were exposed to oscillating levels of blood glucose when compared with those with persistent hyperglycemia (29). Monnier et al. (15) studied the effects of GV on oxidative stress in patients with diabetes. With the use of continuous glucose monitoring (CGM), they concluded that GV had a more specific triggering effect on oxidative stress than did chronic sustained hyperglycemia.

We acknowledge the following limitations in this study. The data were collected retrospectively, thus limiting the acquisition of records of factors such as nutritional status, fluids, certain medications (such as steroids), and time of administration of insulin, which may have influenced the assessed GV. Although the CCI was used to account for a range of coexisting medical conditions, other variables, such as smoking status or serum creatinine, were not included in the analyses.

The lack of glucose monitoring protocols with standardized frequency for patients in the general wards is probably the most important limitation of our study. As suggested by Hermanides et al. (19), there are added benefits from using indexes such as MAG to more accurately assess GV across time. Because of the heterogeneity of our glucose data, however, these indices could not be properly calculated. Thus, although the results of this study provide an estimate of overall GV during the hospital stay, these do not differentiate subjects with gradual glucose changes from those with acute swings.

In addition, because our study was performed in a single Veterans Affairs medical center, the sample consisted of mainly older white males, which precludes our results from generalization. Limitations inherent in the sample could also possibly explain the high rate of diabetes and the lack of a significant association between hyperglycemia and the measured outcomes found in this study. The inclusion criteria used in this study resulted in a sample in which most subjects had an important component of hyperglycemia (MHG 182.4 ± 56.9 mg/dL) and $>85\%$ admissions were of patients with a previous diagnosis of diabetes. It could be therefore speculated that in a more heterogeneous sample including a larger group of euglycemic subjects, hyperglycemia would have been significantly associated with worse outcomes.

Studies examining the possible causes of increased GV in hospitalized patients are not available to date. It has been suggested that sliding scale insulin therapy could be a factor that directly would lead to increased GV (30). In this study, however, we did not find an association between the use of human regular insulin as a sole regimen and higher GV. This could have been the result of lack of information regarding dosing, times of

administration of insulin, and nutritional status. In addition, in light of the lack of insulin protocols used in the facility for the studied dates, a potential association between the multiple combinations of other antidiabetic regimens and GV could not be explored.

Our results have important clinical implications. The increased LOS observed in the patients with higher GV may indicate a significant increase in morbidity and could directly affect the cost of care. Patients in the group of highest GV (SD >66 mg/dL and CV >37%) stayed an average of an additional 3 days in the hospital, with an estimated additional cost of \$7,500 U.S. in hospital expenses relative to those with low GV (SD < 42 mg/dL or CV <25%) (31). Moreover, high inpatient GV may be an underestimated factor associated with increased risk of death within 90 days from hospital discharge that should alert clinicians about high-risk patients.

Although analysis of SD and CV from four-point glucose profiles provides a measurable estimate of GV, studies comparing the quality of this information against data obtained from CGM are not available for noncritically ill hospitalized patients. For a better understanding of the association between GV and clinical outcomes in hospitalized patients, future prospective studies therefore should use CGM technology to allow more direct measurement of GV.

In conclusion, our results indicate that increased GV is independently associated with longer LOS and greater 90-day mortality in noncritically ill hospitalized patients. Prospective studies with CGM to investigate more fully the relationship between GV, mean glucose, and hypoglycemia and clinical outcomes in this patient population are necessary before new strategies for inpatient glycemic control can be recommended.

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C.E.M. designed the study, researched the data, and wrote the manuscript. K.-T.M. researched the data and wrote the manuscript. A.A. analyzed data and wrote the manuscript. R.J.T., J.C.-E., and G.E.U. contributed to critical review and edited the manuscript. C.E.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes

responsibility for the integrity of the data and the accuracy of the data analysis.

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