Journal of Diabetes Science and Technology
Volume 5, Issue 5, September 2011

ORIGINAL ARTICLE

Average Daily Risk Range as a Measure of Glycemic Risk Is Associated with Mortality in the Intensive Care Unit: A Retrospective Study in a Burn Intensive Care Unit

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Abstract

Background:

Although tight glycemic control has been associated with improved outcomes in the intensive care unit (ICU), glycemic variability may be the influential factor in mortality. The main goal of the study was to relate blood glucose (BG) variability of burn ICU patients to outcomes using a sensitive measure of glycemic variability, the average daily risk range (ADRR).

Method:

Data from patients admitted to a burn ICU were used. Patients were matched by total body surface area (TBSA) and injury severity score (ISS) to test whether increased BG variability measured by ADRR was associated with higher mortality risk and whether we could identify ADRR-based classifications associated with the degree of risk.

Results:

Four ADRR classifications were identified: low risk, medium-low, medium-high, and high. Mortality progressively increased from 25% in the low-risk group to over 60% in the high-risk group ($p < .001$). In a *post hoc* analysis, age also contributed to outcome. Younger (age < 43 years) survivors and nonsurvivors matched by TBSA and ISS had no significant difference in age, mean BG or standard deviation of BG; however, nonsurvivors had higher ADRR ($p < .01$).

Conclusions:

Independent of injury severity, glycemic variability measured by the ADRR was significantly associated with mortality in the ICU. When age was considered, ADRR was the only measure of glycemia significantly associated with mortality in younger patients with burns.

J Diabetes Sci Technol 2011;5(5):1087-1098

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Abbreviations: (ADRR) average daily risk range, (BG) blood glucose, (FAC) single factor, (GV) glucose variability, (ICU) intensive care unit, (ISS) injury severity score, (POC) point of care, (SD) standard deviation, (TBSA) total body surface area

Keywords: average daily risk range, burn, critical illness, glucose control, glucose variability, glycemic risk

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Introduction

The benefits of insulin-driven glucose control in the intensive care unit (ICU) have been increasingly recognized.[1–4] However, factors involved with glycemic dysregulation and their contributions to poor outcomes are incompletely understood. In burns, hyperglycemia has been linked to infections, reduced healing, immune abnormalities, increased catabolism, and higher mortality,[5–10] while benefits secondary to undergoing intensive insulin therapy have been demonstrated. Additionally, the magnitude and number of glycemic excursions out of a target range has been linked to mortality in critically ill patients.[11] While the benefits of glucose control may be derived from decreased glucose variability (GV) and not solely on decreased mean glucose levels,[12] this notion is under debate.[13] Glycemic regulation and relevant outcomes using a measure that will more accurately represent GV needs to be duly studied.

The average daily risk range (ADRR) was introduced as a sensitive measure of GV.[14] In patients with diabetes (types 1 and 2), compared with other glycemic measures, ADRR demonstrated its superiority in sensitivity by predicting both future hypoglycemic and hyperglycemic episodes.[14] Intensive care unit and diabetic patients exhibit similarities in terms of poor glycemic control. Moreover, much like what is seen in the outpatient diabetic population, both hyperglycemia and hypoglycemia can result in negative outcomes in the ICU. Hence, ADRR is an excellent candidate to assess GV in the ICU, as it is sensitive to both low and high glucose excursions.

This study tested whether ADRR as a measure of GV over the first week (8 days) of admission to a burn ICU could be used to identify patients with unfavorable outcomes.

Methods

Study Database

Following approval from the Brooke Army Medical Center Institutional Review Board, patients admitted to the burn ICU at the U.S. Army Institute of Surgical Research in Fort Sam, Houston, Texas, between January 2002 and December 2008 were enrolled in our retrospective study. The U.S. Army Institute of Surgical Research burn center provides care to a mixed population of civilian and military patients who have similar outcomes after adjustments for age and injury severity.[15] The study database included arterial blood glucose (BG) measurements for the first 8 days of hospitalization. Since three is the minimum number of measurements for computation of ADRR,[14] we used only subjects who had at least 1 day in the ICU with three BG measurements (**Figure 1A**). In analyses comparing patients matched by the severity of their injury, only part of the survivors were included (see Initial Comparison; **Figure 1B**). From these survivors and nonsurvivors, we have chosen subgroups for a separate analysis that compares patients matched by the severity of their injury and who had only 20 days in the ICU (see 20 ICU days; **Figure 1C**).

Clinical Parameters

Data collected included age, gender, size of burn [total body surface area (TBSA)], injury severity score (ISS), presence of inhalation injury, and preexistence of diabetes. Blood glucose values in the database were both point-of-care (POC) glucometer (SureStep™ Flexx, LifeScan, Milpitas, CA) and hospital laboratory readings. Point-of-care values are corrected for error associated with anemic blood.[16,17]

Glycemic Risk Measures

We computed ADRR as a measure of GV for each subject (see **Appendix**). Computation of ADRR is similar to computing average daily BG range, but BG data are converted into risk values. ADRR is sensitive to both low and high excursions as it progressively penalizes deviations in both directions. The ADRR was previously developed with data from diabetes patients, and 112.5 mg/dl was selected as the center of the scale of GV risk; consequently, 112.5 mg/dl has a risk value of zero and deviations in either direction increase the risk value. Additionally, two standard measures of glycemia were calculated: mean (BG_{mean}) and standard deviation (SD; BG_{SD}) of BG.

Initial Comparison

First we compared survivors with nonsurvivors (**Figure 1A**) with respect to TBSA, ISS, age, BG_{mean}, BG_{SD}, and ADRR. Because we did not limit our study group in regard to size of burn, it was expected that severity of the injury would influence our findings. A binary logistic regression analysis in younger (<65 years of age) subjects confirmed that both TBSA and ISS are significantly associated with mortality. Therefore, survivors and nonsurvivors were later matched by both TBSA and ISS (**Figure 1B**).

Factor Analysis for Group Matching

A principal component factor analysis was used to extract from the two variables TBSA and ISS a single factor (FAC) accounting for most of the variance in TBSA and ISS. A group of survivors (live) were then chosen to match the group of all nonsurvivors (died) with respect to the initial injury. A threshold was identified for which the two groups had similar TBSA and ISS values. In particular, FAC varied from -1.33 up to 3.992, where the higher values corresponded to greater percentage TBSA burn and ISS. Starting from a FAC of -1 and increasing by steps of 0.2, we determined the value of FAC (0.2), such that, if we chose only survivors with FAC above this value, the selected group of survivals will not differ from the nonsurvivals with respect to TBSA and ISS. We selected only survivors with FAC higher than the highest cutoff point for which the two groups were not different with respect to TBSA and ISS (**Figure 1B**). Matched groups were then compared to determine differences in glycemic measures.

Identifying Degrees of Glycemic Variability Risk

Next, injury-severity-matched groups were combined to identify four risk groups based on ADRR quartiles. Quartile ranges were bracketed and classified from the lowest quartile to the highest as low, medium-low, medium-high, and high risk, respectively. The four risk groups were representative of four degrees of glycemic risk. Comparisons were made across the four risk groups.

Twenty Intensive Care Unit Days

The relationship of ADRR to outcome was expected to strengthen if survival status was assessed within a decreased period of time between glycemic assessments in the ICU and condition at discharge (recovery versus death). To verify this notion, we restricted the length of time we would assess subject outcomes. Our glycemic assessments were for the first week of ICU admission, and thus we limited our subsequent analysis to a subgroup of subjects that had either discharged favorably

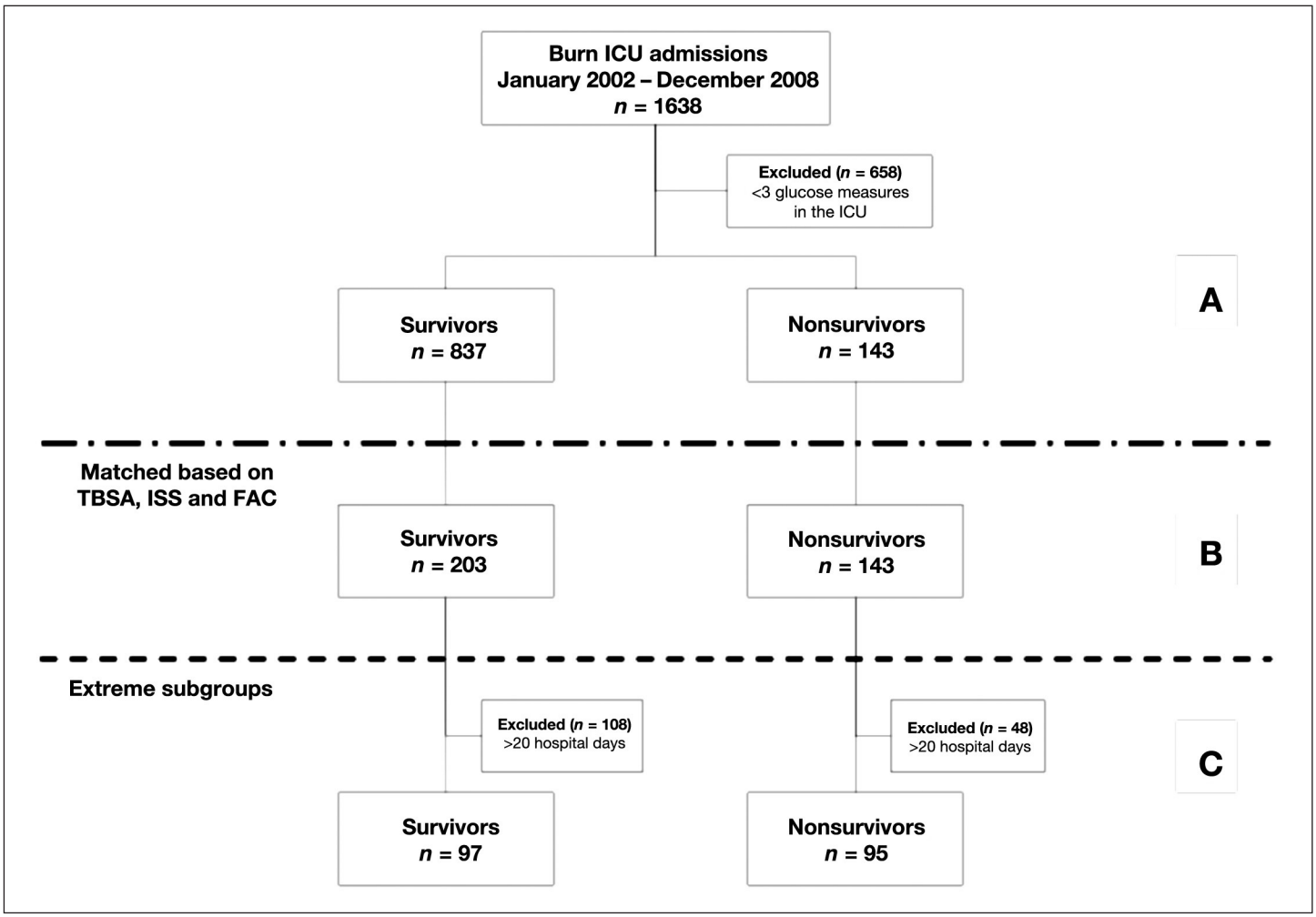

Figure 1. Database manipulation and identification of the main groups used in the analysis.

from the ICU or died before day 20 of hospitalization. The choice of the 20-day period was also directed by the goal to have groups that were of the same size to facilitate interpretation of the data. Thus two subgroups of similar size and injury severity were selected as survivors (n = 97) and nonsurvivors (n = 95; **Figure 1C**). Similar analyses as before were performed to confirm the relationship between the degree of glycemic variability and outcome.

Analysis with Age

Since age appeared to be a factor that also contributed to outcome in combination with ADRR, we proceeded to investigate whether there was an age limit under which outcome was no longer influenced by age. An age limit was determined by successive binary logistic regression models, where age was a covariate and mortality the dependent variable. Subjects were binned into age groups, and cross-tabulation analysis for mortality was performed for verification.

Once the age limit was defined, we selected a subgroup of all nonsurvivors of age under this limit. A subgroup of survivors was chosen from the live group with age under the determined limit to have the same number of subjects. In an effort to match the nonsurvivors by injury severity, we selected the survivors with the highest FAC. An analysis then confirmed that the subgroups have similar severity of the injury and age but different GV.

To further confirm significance of association, the initial 980 subjects were split into two groups of <43 and ≥43 years of age, and the association between ADRR and outcome were evaluated in each group.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 (College Station, TX). Group comparisons were performed by an independent sample t test or by one-way analysis of variance as appropriate for continuous variables or by binary logistic regression for discrete variables. Analysis of categorical data and mortality risk was done by cross tabulation and significance determined by χ^2.

Results

Out of 1638 patients admitted to the burn ICU within the study period, 980 were in the ICU for at least 1 day with a minimum of three glucose measurements (**Figure 1A**). These patients were predominantly males (82%) averaging 41 ± 19.5 years of age with severe injuries (TBSA of 27 ± 21.8; ISS of 17 ± 14.2) and mortality rate of 14.6% (143/837). Eleven percent (106/980) had preexisting diabetes.

Initial Comparison

After ADRR was computed using BG measurements from the first week of admission, we compared survivors (n = 837) to nonsurvivors (n = 143) in regard to age, TBSA, ISS, BG_{mean}, BG_{SD}, and ADRR (**Table 1**). This analysis identified survivors and nonsurvivors to differ in all of the previously mentioned parameters with the exception of BG_{mean}. Hence factors associated with mortality include age, severity of injury, glucose variance, and ADRR. We note the better association of ADRR with mortality as compared with standard measures of glycemia, as evident by the computed values of the statistical test. In a binary logistic regression analysis, where TBSA and ISS (correlated with r = 0.66) were covariates and mortality was the dependent variable, both TBSA and ISS were significantly ($p < .001$ and $p = .001$, respectively) associated with mortality in patients less than 65 years of age. The regression correctly classified 75% of the survivors and nonsurvivors.

Groups Matched by Single Factor

Therefore, to estimate the independent contribution of GV on outcome in the burn ICU, we compared glycemic measures between groups matched with respect to the severity of their injuries. To this end, we performed a factor analysis to inclusively account for injury severity using both TBSA and ISS. Identification of a FAC behind the metrics of injury severity allowed groups to be matched based on similar injury scores. Using the restriction FAC > 0.2 (Methods), a subgroup of survivors (n = 203) were matched to the nonsurvivors (n = 143; **Figure 1B**). The resultant live and died groups were of similar injury severities with respect to TBSA (p = .33) and ISS (p = .11). The two groups were also not different with respect to incidence of inhalation injury, but survivors had less prevalence of preexisting diabetes (**Table 2**). When glycemic assessments were compared, all risk measures were higher in the nonsurvivors (ADRR being the most significant, as evident by the value of the test; **Table 2**).

Degrees of Glycemic Variability Risk

Subsequently, survivors (n = 203) and nonsurvivors (n = 143) were used to bracket ADRR values into quartiles to identify degrees of risk. Four ADRR groups were identified as low (ADRR < 6.36; n = 86), medium-low (6.36 < ADRR < 10.31; n = 87), medium-high (10.31 < ADRR < 16.13; n = 87), and high risk (ADRR > 16.13;

Table 1.
Comparison between Survivors and Nonsurvivors with Respect to the Severity of the Injury, Age, and Measures of Glycemia Control

Group statistics							Levene's test for equality of variances		*t* test	
	Survive	*N*	Mean	SD	Standard error of the mean	Equal variances assumed	*F* distribution	Significance	*t*	Significance (two tailed)
TBSA	Yes	799	23.13	18.744	0.663	yes	60.561	0.000	-12.543	0;.000
	No	138	46.51	27.259	2.320	no			-9.687	0.000
ISS	Yes	720	14.79	12.136	0.452	yes	32.157	0.000	-9.860	0.000
	No	140	27.08	19.045	1.610	no			-7.352	0.000
Age	Yes	837	39.33	18.695	0.646	yes	10.189	0.001	-5.447	0.000
	No	143	48.81	22.109	1.849	no			-4.839	0.000
BG_{mean}	Yes	837	126.8	26.7	0.92171	yes	13.827	0.000	-2.116	0.035
	No	143	132.2	37.1	3.10061	no			-1.682	0.094
BG_{SD}	Yes	837	28.8633	17.29	0.59764	yes	4.371	0.037	-5.558	0.000
	No	143	37.9290	21.86	1.82790	no			-4.714	0.000
ADRR	Yes	823	8.6216	9.045	0.31530	yes	16.999	0.000	-8.351	0.000
	No	143	15.9859	13.02	1.08876	no			-6.497	0.000

Table 2.
Comparison between the Live and Died Groups and with Respect to Demographics, Severity of the Injury, and Preexisting Diabetes

	Live *n* = 203 mean ± SD (median; 95% confidence interval)	Died *n* = 143 mean ± SD (median; 95% confidence interval)	*p* value (*t*)
Demographics			
Gender (% male)	92%	69%	$p < .0001$
Age	30 ± 11.9 (25; 28.3–31.6)	49 ± 22.1 (45; 45.2–52.5)	$p < .0001$
Preexisting diabetes (% yes)	4%	16%	$p < .0001$
Initial condition			
TBSA	44 ± 15.6 (40; 41.9–46.2)	47 ± 27.1 (50; 42.3–51.4)	NS
ISS	30 ± 8.3 (26; 29.2–31.5)	29 ± 18.2 (25; 26.0–32.3)	NS
Inhalation injury (% yes)	33%	43%	NS
BG risk measures			
BG_{mean}	123 ± 19.4 (121; 120.2–125.6)	132 ± 37.9 (121; 126.1–138.6)	$p = .005$ ($t = -2.852$)
BG_{SD}	30 ± 13.8 (27; 28.0–31.8)	38 ± 21.6 (32; 34.3–41.5)	$p < .0001$ ($t = -3.918$)
ADRR	11 ± 7.8 (9; 9.4–11.7)	16 ± 13.0 (12; 13.8–18.1)	$p < .0001$ ($t = -4.431$)

NS, not significant.

n = 86). Mortality rates increased progressively from 25% in the low-risk group to 60% in the high-risk group ($p < .001$; **Table 3** and **Figure 2**).

While the groups were similar in regard to injury severity (TBSA, ISS, and FAC), they did, however, differ on other parameters (**Table 3**). The low group had the lowest incidence of inhalation injury ($p = .034$). Differences in the average minimal and maximal glucose levels suggest that variability in both the lower and higher end of glycemic extremes contribute to the GV risk. In addition, the high-risk group had older subjects with a higher mean glucose

Table 3.
Comparisons between the ADRR-Based Risk Groups with Respect to Demographics, Severity of the Injury, Preexisting Diabetes, and Measures of Glycemic Control

	Low n = 86 mean ± SD (median; 95% confidence interval)	Medium-low n = 87 mean ± SD (median; 95% confidence interval)	Medium-high n = 87 mean ± SD (median; 95% confidence interval)	High n = 86 mean ± SD (median; 95% confidence interval)	p value
Demographics					
Gender (% male)	90%	79%	87%	76%	$p < .04$
Age	32 ± 16.3 (24; 28-35)	38 ± 21.1 (29; 33.4-42.4)	36 ± 17.0 (30; 32-39.5)	46 ± 19.7 (46; 41.5-50.0)	$p < .0001$
Preexisting diabetes (% yes)	2%	0%	5%	30%	$p < .0001$
Initial condition					
TBSA	42 ± 19.6 (40; 38.0–46.6)	43 ± 20.1 (40; 38.8–46.6)	45 ± 20.1 (45; 41.2–49.8)	50 ± 23.5 (48; 44.8–54.9)	NS
ISS	29 ± 12.4 (25; 26.3–31.8)	30 ± 12.0 (29; 27.4–32.7)	30 ± 11.3 (29; 27.7–32.5)	30 ± 16.3 (25; 26.7–34.0)	NS
Inhalation injury (% yes)	25%	45%	43%	36%	$p < .04$
BG risk measures					
BG_{mean}	119 ± 11.7 (118; 116.9–122.0)	122 ± 17.2 (117; 117.1–125.5)	121 ± 19.6 (117; 117.1–125.5)	145 ± 46.0 (130; 135.1–154.8)	$p < .0001$
BG_{SD}	22 ± 7.0 (21; 20.3–23.3)	27 ± 6.4 (26; 26.1–28.8)	32 ± 10.3 (29; 29.7–34.1)	52 ± 24.0 (45; 46.7–57.0)	$p < .0001$
Mortality	26%	36%	44%	60%	$p < .0001$

NS, not significant.

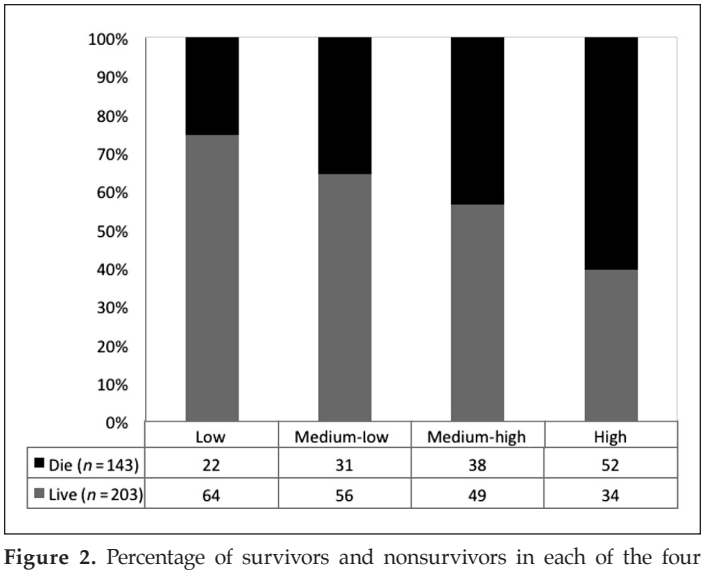

Figure 2. Percentage of survivors and nonsurvivors in each of the four glycemic variability risk groups.

level and the highest percentage of diabetes patients (30%). Since the high-risk group appeared to differ to a greater extent with respect to age and average glucose, additional analysis was performed excluding the high-risk group. The remaining three groups (low, medium-low, and medium-high) were similar in age (p = .07) and mean glucose levels (p = .70). The analysis confirmed a significant (p = .04) association between ADRR and mortality in these three groups.

Final Disposition by Day 20

Two new subgroups were identified in an effort to further investigate the association between ADRR and mortality within a timeframe of close relevance to the first week of glycemic measures (**Figure 1C**). Subjects who had a hospital stay of more than 20 days were excluded. We compared subjects who were either discharged (n = 97) or died (n = 95) within the first 20 days of hospital stay. Though these two subgroups differed in its demographics (age and sex), preexisting diabetes, and presence of inhalation injury (this last metric was in fact higher in survivors), they did not differ in severity of injury (TBSA and ISS; **Table 4**).

Next, when using previously determined risk classifications to compare the four risk groups, the relationship between mortality and ADRR-based risk strengthened (mortality rates progressively increased from 25% to 74%;

Table 4.
Comparison between the Live and Died Subgroups of Patients with Intensive Care Unit Days <20 with Respect to Demographics, Severity of the Injury, and Preexisting Diabetes

	Live n = 97 mean ± SD (median; 95% confidence interval)	Died n = 95 mean ± SD (median; 95% confidence interval)	*p* value (*t*)
Demographics			
Gender (% male)	93%	61%	$p < .0001$
Age	30 ± 12.3 (26; 27.8–32.7)	52 ± 22.1 (47; 47.7–56.8)	$p < .0001$
Preexisting diabetes (% yes)	4%	18%	$p < .01$
Initial condition			
TBSA	39 ± 13.0 (36; 36.2–41.4)	45 ± 27.5 (41; 39.1–50.6)	NS
ISS	28 ± 8.2 (25; 21–29)	28 ± 18.6 (25; 24–33)	NS
Inhalation injury (% yes)	22%	41%	$p < .005$
BG risk measures			
BG_{mean}	124 ± 21.8 (121; 120.0–128.8)	139 ± 44.0 (123; 129.6–147.6)	$p = .003$ ($t = -2.997$)
BG_{SD}	30 ± 16.2 (26; 27.0–33.5)	41 ± 24.8 (34; 36.3–46.4)	$p < .0001$ ($t = -3.695$)
ADRR	10 ± 9.0 (7; 8.0–11.6)	17 ± 14.3 (13; 13.8–19.6)	$p < .0001$ ($t = -4.009$)

NS, not significant.

$p < .001$; **Figure 3**). Again, we note the clearer association of ADRR with mortality versus the standard measures of glycemia.

Contributions of Age

Further, we determined that, for subjects younger than 43 years, age no longer contributed to mortality. To this end, we performed a binary logistic regression with age as a covariate. Then, the age limit was progressively lowered until age was no longer significant. Specifically, when the age limit was <44 years, age was still a significant predictor ($p = .03$); however, when the limit was age <43 years, significance was lost ($p = .08$). As a confirmation, we performed a separate analysis on the combined population (survivors and nonsurvivors). The combined population was divided by age into 12 groups of similar size. A cross tabulation was performed to classify subjects by survival status (**Table 5**). An increase of more than 17 points in mortality rate occurs between age groups "37–43" and "44–47". Despite an initial relationship across age groups and survival status ($p < .001$), significance was lost when groups (age ≥ 44 years) were excluded.

As an additional confirmation of the age limit, all subjects age < 43 years ($n = 580$) and age ≥ 43 years ($n = 400$) were considered (without being matched by TBSA and ISS) and compared based on survival status. Survivors and nonsurvivors in the age < 43 years group did not differ in age; on the contrary, the age ≥ 43 years group did ($p < .05$). In comparison with survivors, nonsurvivors had higher injury severity, BG_{SD}, and ADRR in both age groups. However, in each age group, BG_{mean} of survivors versus nonsurvivors was not different.

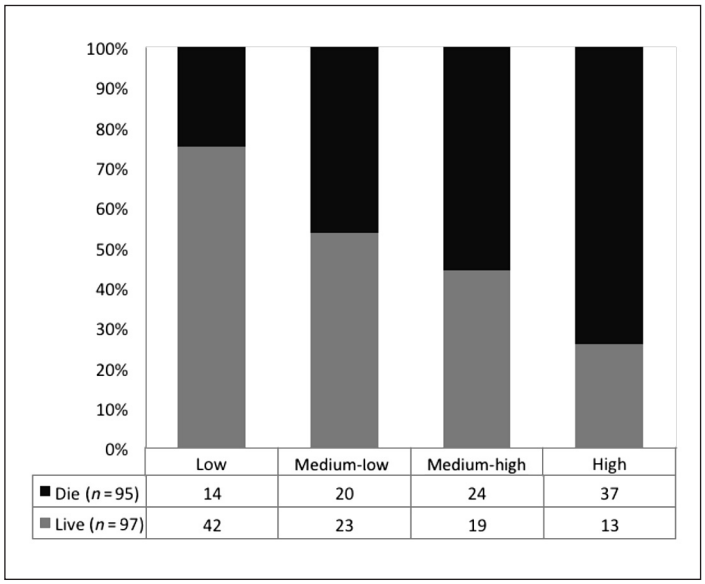

Figure 3. Percentage of survivors and nonsurvivors with less than 20 ICU day stays in each of the four glycemic variability risk groups.

Table 5.
Cross Tabulation of Age Groups by Mortality in Patients Who Were Matched by TBSA and ISS

Age Group Mortality Cross Tabulation					
			Live	Died	Total
Age group	≤20	Count	30	6	36
		% within age group	83.3%	16.7%	100.0%
	21	Count	21	9	30
		% within age group	70.0%	30.0%	100.0%
	22	Count	20	5	25
		% within age group	80.0%	20.0%	100.0%
	23–24	Count	27	10	37
		% within age group	73.0%	27.0%	100.0%
	25–27	Count	20	5	25
		% within age group	80.0%	20.0%	100.0%
	28–31	Count	19	8	27
		% within age group	70.4%	29.6%	100.0%
	32–36	Count	19	3	22
		% within age group	86.4%	13.6%	100.0%
	37–43	Count	16	15	31
		% within age group	51.6%	48.4%	100.0%
	44–47	Count	10	19	29
		% within age group	34.5%	65.5%	100.0%
	48–55	Count	10	16	26
		% within age group	38.5%	61.5%	100.0%
	56–74	Count	11	19	30
		% within age group	36.7%	63.3%	100.0%
	≥75	Count	0	28	28
		% within age group	0.0%	100.0%	100.0%
Total		Count	203	143	346
		% within age group	58.7%	41.3%	100.0%

Testing our findings, we selected two subgroups of survivors and nonsurvivors younger than 43 years of age that were equivalent in number and injury severity. Younger survivors were additionally restricted to have a high injury score (FAC > 1.12) in order to have groups of the same size (n = 58). The only parameter that differed between groups was ADRR (p = .01), which supported the association between ADRR and mortality.

Discussion

Glycemic control with intensive insulin treatment that results in minimal BG variability has been associated with reduced mortality in the burn ICU.[11] Here we extended these findings with ADRR—a more sensitive measure of GV—in a retrospective analysis of data from patients admitted to a burn center.

As expected, a significant predictor of mortality in the burn ICU was burn size (TBSA, representative of burn only). For the majority of the population (<65 years of age; ~90% of subjects) injury severity (ISS, representative of concomitant trauma) was also significantly associated with mortality. Of the investigated glycemic measures (ADRR, BG_{mean}, and BG_{SD}), ADRR was the most significant predictor of mortality (**Table 1**). Therefore, we chose groups of survivors and nonsurvivors matched by TBSA and ISS and then analyzed their GV—assessed by ADRR.

All nonsurvivors were included in the died group (n = 143) and were compared with a group of survivors (n = 203) matched by TBSA and ISS. The matching involved a factor analysis to determine a FAC accounting for the influence of both TBSA and ISS.

Since ADRR was the glycemic measure in which the two groups most significantly differed (**Table 2**), we stratified patients into groups by level of ADRR. Four GV risk groups were identified based on the ADRR quartiles, low, medium-low, medium-high, and high, which remained fixed for the rest of the data analysis. Lower ADRR was clearly associated with lower mortality ($p < .001$), and the risk of dying increased from 25% to 60% in the highest risk group (**Table 3** and **Figure 2**). The results suggest that variability at both ends of glycemic extremes contribute to the GV risk. The highest risk group was also associated with higher BG_{mean}, age, and incidence of diabetes. However, the first three risk groups were not different with respect to these parameters but still allowed for a significant classification for mortality risk, thereby emphasizing the strong relationship of GV to mortality.

For good reason, it was expected to find high glycemic variability in diabetic subjects. Interestingly, Krinsley[18] has reported no independent association in regard to mortality and glycemic variability observed in critically ill patients with diabetes. Another study also confirmed the limited influence preexisting diabetes has on various clinical outcomes of patients in a burn ICU.[19] Although diabetes patients are observed to be hyperglycemic from the time of admission and have greater glycemic variability, increased mortality was not identified. Thus, even though our highest risk group has the highest percentage of diabetes patients, we do not feel that diabetes is a significant factor that influences higher mortality rates.

We next tested the notion that the relationship of ADRR to outcome will strengthen if a decreased period of time between glycemic assessments and condition at discharge was considered. The rationale for this choice also stemmed from the expectation that, by restricting the ICU days, we are not taking into account survivors at higher risk and nonsurvivors at lower risk. This would exclude those who were high risk with long length of stay and those who were low risk but became high risk due to complications and died. We thus considered two extreme groups of survivors (subgroup of live group) and nonsurvivors (subgroup of died group) who had less than 20 ICU days, i.e., were discharged or died within 20 days. These groups were also of a similar size due to the length of the chosen ICU length-of-stay period (20 days). It was thus expected that, in these extreme groups, the association between mortality and GV would be even more apparent (due to the exclusion of those who were high risk with long length of stay and those who were low risk but became high risk due to complications and died), which was confirmed in the three-fold difference in the risks between the low- and high-risk groups (**Figure 3**; compare also **Figure 2** and **Figure 3**). The chosen period of 20 days is not the typical hospital mortality timeframe seen in the literature (normally 28 or 90 days is used). This choice was made to verify the expected performance of the ADRR used as a prognostic tool in a period of approximately 3 weeks and to guarantee an almost equal size of the resulting two groups of survivors and nonsurvivors. We note that, when the same analysis was performed with a cutoff of 28 days instead of 20 days, the results were similar (not shown).

The age of the patient was linked to mortality, but the association disappeared when only younger patients were considered (age < 43). Survivors matched to nonsurvivors by TBSA, ISS, and group size in comparison did not differ by age, BG_{mean}, or BG_{SD}. On the other hand, the ADRR of the nonsurvivors was higher (p = .01), which established a link between GV and mortality in the younger population independent of other factors. The separate contribution of age and ADRR as two different predictors of mortality was also supported by the fact that, even though the four GV risk groups were different in age, the medium-low-risk group had a higher average age than the medium-high-risk group, and the first three risk groups were not different in this parameter (see Degrees of Glycemic Variability Risk).

As was already pointed out, it is evident from the results in **Tables 1**, **2**, and **4** that ADRR was consistently better associated with mortality than other traditional measures of glycemia, such as BG_{mean} or BG_{SD} in our patient population. The ADRR produced results in line with the previously reported association between GV measured by the proportion of glycemic excursions outside a target range (80–110 mg/dl) and mortality.[11] Both metrics considered the risks of excursions with respect to a fixed glucose value or range. However, ADRR offered an additional advantage, as it was sensitive to the magnitude of BG variations, as it loads progressively higher, rather than fixed, values to larger excursions. In the current sample, ADRR performed better than the range-based metric proposed,[11] which, even though distinguishing between all four ADRR risk groups, did not find differences between the first three risk groups and in younger

patients (age < 43) and did not separate the live and died groups. Other range-based metrics sensitive to the magnitude of BG variations were also associated with mortality in the ICU.[20,21] Therefore using risk-based rather than range-based GV metrics may provide a more sensitive measure to assessing the patient's condition.

The current retrospective study has limitations. First, no causality can be proposed between the ADRR risk and mortality. Second, the ADRR has been developed to quantify glycemic risk in diabetes and measure deviations from 112.5 mg/dl. We would expect that this measure could be optimized to reflect better the characteristics of the ICU patient. Finally, in this study, the impact of the specific insulin treatment, infection rate, medication regimen, or whether the patient had inhalation injury was not taken into account. The primary focus is to examine whether the ADRR could be used appropriately in a different population (burn ICU patients) other than the outpatients with diabetes for which it was originally developed and to identify associated outcomes with the ADRR values. Thus, at this point, the results from this study are limited to our patients. Further research is needed to assess the applicability of ADRR in other ICU patient populations and possibly to link ADRR to outcomes other than mortality (e.g., organ failure). In terms of clinical application, the increased GV assessed by the ADRR may be representative of physiologic instability in which patients are having difficulty in responding and adapting to the injury and ultimately in disruption in glucose homeostasis. In this regard, the GV risk can be computed daily as an estimate of the current patient's condition.

Conclusions

In burn ICU patients, lower blood GV is associated with lower mortality independently of the severity of the injury. Patient age is also associated with mortality, but in a younger population (age < 43), age was no longer a significant factor and GV quantified by the ADRR was the only measure of glycemic variability significantly associated with mortality.

Funding:

The study was funded by a grant to the University of Virginia from The University of Texas Health Science Center at San Antonio (subaward 128542/125762; prime award W81XWH-07-1-0717; agency: U.S. Army Medical Research Acquisition Activity), the National Institutes of Health Grants 1 R01 GM063120-04 and R01 DK082805 and the Technologies for Metabolic Monitoring/Julia Weaver Fund, a congressionally directed program jointly managed by the U.S. Army Medical Research and Materiel Command, the National Institutes of Health, the National Aeronautics and Space Administration, the Juvenile Diabetes Research Foundation, and Combat Casualty Care Division U.S. Army Medical Research and Materiel Command.

Disclosures:

The views and opinions expressed in this article are those of the authors and do not reflect the official policy or position of the Army Medical Department, the Department of the Army, the Department of Defense, or the United States government. The ADRR is the subject of a 2005 patent application and constitutes intellectual property held by the University of Virginia Patent Foundation.

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Appendix

The ADRR is computed as follows. x_1^i, x_2^i, ... , $x_{n^i}^i$ are all n^i BG readings in day i: i = 1, 2, ... , M. Since the BG scale is asymmetric, calculation of ADRR uses our data transformation that normalizes the BG scale[14]: $f(BG) = 1.509[(\ln BG)^{1.084} - 5.381]$ for BG measured in mg/dl. Then BG readings are converted into risk values: $r(BG) = 10f(BG)^2$.

$$\begin{cases} rl(BG) = r(BG) & \text{if} \quad f(BG) < 0 \quad \text{and} \quad 0 \quad \text{otherwise (left branch)} \\ rh(BG) = r(BG) & \text{if} \quad f(BG) > 0 \quad \text{and} \quad 0 \quad \text{otherwise (right branch)} \end{cases}$$

Finally, ADRR is computed as the average of the risk range per day:

$$ADRR = \frac{1}{M} \sum_{i=1}^{M} (LR^i + HR^i) ,$$

where $LR^i = \max[rl(x_1^i), \ldots , rl(x_{n^i}^i)]$ and $HR^i = \max[rh(x_1^i), \ldots , rh(x_{n^i}^i)]$ for ICU day i: i = 1, 2, ... ,M.