Uncovering the Predictive Value of Minimum Blood Glucose Through Statistical Analysis of a Large Clinical Dataset

Ying Zhang, MEng[1,2], Michael S. C. Hemond, PhD[2]
[1]MIT, Cambridge, MA; [2]Harvard Medical School, Boston, MA

Abstract

The clinical utility and risk of strict glycemic control during critical care have been under intense debate. This study aims to elucidate the relationship between glycemic status and patient outcome in an integrated database collected at a tertiary teaching hospital. Clinical data of 16,135 critically ill adult patients with blood glucose measurements were extracted. The lowest blood glucose levels were analyzed against patient outcome. Major findings are 1) mortality of non-diabetic patients who experience persistent hyperglycemia during intensive care rises with increasing hyperglycemia, 2) minimum blood glucose concentration within the 80-110 mg/dL range corresponds to the highest percentage of survival among patients receiving insulin, and 3) in-hospital mortality among patients receiving insulin increases as blood glucose concentration falls into the hypoglycemic range. These results suggest that glycemic status and patient outcome are closely associated and the lowest blood glucose concentration that each patient experiences predicts the patient's eventual outcome.

Introduction

The stress from critical illnesses induces both insulin resistance and unsuppressed gluconeogenesis, necessitating blood glucose monitoring in over 90% of the patients in the Intensive Care Unit (ICU). For decades, a moderate level of this stress-induced hyperglycemia was considered a beneficial compensatory mechanism, and the conventional insulin therapy for adults worked to maintain blood glucose levels in the 180-215 mg/dL range. Since 2001, however, a number of randomized, controlled clinical trials have demonstrated that strict control to the normoglycemic range of 80-110 mg/dL reduced both in-hospital mortality and morbidity for adult patients who were treated in the surgical ICU for more than five days and for those who were treated in the medical ICU for more than three days[1,2].

As ICUs implement more intense insulin therapy with a lower and narrower target range for blood glucose concentration, the risk for developing acute hypoglycemia among ICU patients also increases[3,4,5,6]. Achieving tighter glycemic control is made difficult because today's workload on ICU staff enables neither more frequent blood glucose measurements nor more timely adjustments to the anti-hyperglycemic therapy. Moreover, ICU patients often concurrently receive multiple drugs that may affect the distribution and metabolism of insulin. The variety of nutritional support during critical care also requires patient-specific adjustments to the existing insulin infusion protocols. Thus, it is no surprise that ICU patients' blood glucose concentration is often maintained within the target range for only a less-than-desirable fraction of the time[7].

Acute hypoglycemia might not be the sole consequence of excess exogenous insulin, but it is one of the first physiological "red flags" that signal adverse effects of anti-hyperglycemic therapy. Although almost all clinical trials of strict glycemic control in the ICU report an increase in the incidence rate of acute hypoglycemia among patients on intense insulin therapy, many of them stated that the observed hypoglycemic events did not cause immediate death or complications[1,2], while some trials were terminated due to concurrent increases in the rate of acute hypoglycemia and the number of serious adverse events[4]. Recently, the clinical value of strict glycemic control has also been subjected to debate and uncertainties[2,4,8,9]. A meta-analysis of 34 randomized trials completed by 2008 found that strict glycemic control among critically ill adult patients was not associated with significantly reduced in-hospital mortality or increased need for dialysis, and the association with reduced septicemia was limited to surgical ICU patients[5]. The most recent report from a large, international, randomized clinical trial showed that strict glycemic control, comparing to conventional insulin therapy, increased the absolute risk of death at 90 days by 2.6%[6].

This study, initiated independently in 2007, specifically aims to assess the relationship between glycemic status and patient outcome. Our results from categorical logistic regression showed that acute hypoglycemic events during intravenous insulin administration were associated with poor patient outcome in terms of in-hospital mortality. A central hypothesis since is that simple physiological

parameters that are readily available in the ICU, such as patients' minimum blood glucose concentration (MBGC), could help predict in-hospital mortality. It has been tested on real patient data in a comprehensive and integrated ICU database collected from a tertiary teaching hospital. The major findings from this study may be helpful to intensivists in providing better and safer patient care.

Method

This study examines real patient data in MIMIC II (Multiparameter Intelligent Monitoring in Intensive Care database II)[10], a comprehensive and integrated ICU database collected from the ICUs at Beth Israel Deaconess Medical Center, Boston, MA. This database includes continuous high resolution physiologic waveforms such as ECG, vital signs, monitoring alarms, therapeutic intervention profiles, laboratory results, fluid balance data, continuous IV medications, physician order entries, nursing progress notes, discharge summaries, and patient outcomes for over 17,242 patients. It contains blood glucose measurements for 16,144 of these patients; the size and diversity of this patient cohort make our findings more generalizable than those of similar studies elsewhere. All patient data have been collected, stored, and used for research purposes according to a protocol approved by the Institutional Review Board of Beth Israel Deaconess Medical Center and the Committee on the Use of Humans as Experimental Subjects of Massachusetts Institute of Technology.

MIMIC II is currently hosted on a secure central server as an ORACLE database. Using SQL queries, we identified all the patients in MIMIC II whose blood glucose levels were being monitored. We extracted their blood glucose measurements from laboratory results, continuous IV infusion data from medication records, anti-hyperglycemic treatment regimen from physician order entry, outcome (focusing on death vs. no death) from records of in-hospital death, history of diabetes from ICD9 codes, as well as age, gender, and length of ICU stay from patient census data. Of the 16,144 patients, 16,135 had clinically valid blood glucose measurements and formed the patient population for this study.

We first examined how blood glucose levels had changed over time in 3116 adult ICU patients who received insulin intravenously (the *IV insulin cohort*) and tracked IV insulin administration in correlation with the blood glucose data and the treatment protocol used. We then grouped these patients according to their lowest blood glucose concentration, highest blood glucose concentration, and average blood glucose concentration, in increments of 10 mg/dL. For each group, we found the number of patients who died during their hospital stay and the number of patients who were discharged or transferred to another care facility. Subsequently, we performed categorical logistic regression on blood glucose measurements and patient outcome data to obtain odds ratios of death for hypoglycemic patients. To analyze trends among patients with MBGC above 110 mg/dL, we used logistic regression to fit the group data to a single logistic regression line. We repeated the above analysis for patients who did not receive insulin intravenously but did receive insulin or insulin analogs subcutaneously according to physician-ordered sliding scale (the *SS insulin cohort*). We also performed the same analysis for patients who neither received IV insulin nor were prescribed subcutaneous insulin on a sliding scale (26 of these patients occasionally received insulin orally or subcutaneously with meals but were never being prescribed for anti-hyperglycemic therapy; nevertheless, to draw distinction based on treatment, we refer to this patient group as the *No insulin cohort*). We further stratified each of the three patient groups according to records of any prior history of diabetes mellitus. All patients with ICD9 codes for Type I diabetes, Type II diabetes, diabetic sequelae, or admission for diabetic ketoacidosis were considered to have a prior history of diabetes.

"Acute hypoglycemia" is widely used to describe a state with a sudden onset (i.e., within minutes or hours) of abnormally low blood glucose concentration. The actual threshold is still subject to debate. In this study, we define *acute hypoglycemia* as when the patient's blood glucose concentration drops below 60 mg/dL, and *severe hypoglycemia* as when the patient's blood glucose level drops below 40 mg/dL. Based on patients' MBGC, we divided each patient cohort into four categories: MBGC 1) not below 60 mg/dL; 2) between 50 mg/dL and 60 mg/dL; 3) between 40 mg/dL and 50 mg/dL; and 4) below 40 mg/dL.

Results

A total of 3116 patients received the insulin "Regular" via intravenous drip; 4034 patients received insulin or insulin analogs only subcutaneously according to physician-ordered sliding scale; and 8958 patients were not treated with IV insulin or SS insulin. Most blood glucose measurements were obtained by fingerstick test of whole blood; some data points came from the basic metabolic panel CHEM-7. When a patient was on IV

insulin, blood glucose was measured hourly, while subcutaneous administration of insulin required a blood glucose measurement every four hours. Patients in the No insulin cohort had comparatively less frequent measurements.

The mortality rates of the IV insulin cohort, the SS insulin cohort, and the No insulin cohort are 20.06%, 23.30%, and 12.09%, respectively. Patient outcomes for each glycemic category are summarized in Tables 1, 2, and 3. The median, mean, and standard deviation of age for the study population are 65.4, 63.3, and 17.6, respectively. The hospital patient census recorded gender for 12,254 of the 16,135 patients, with a female to male ratio of 0.78. Age and gender statistics do not appear to vary significantly among the three patient cohorts.

Exposure		No. of Patients	Mortality	LOS (days)
60≤ MBGC	D	878	12.53%	2.7
	ND	1234	18.23%	3.8
	C	2112	15.86%	3.2
50 ≤ MBGC < 60	D	255	14.90%	5.1
	ND	231	34.63%	9.8
	C	486	24.28%	6.6
40 ≤ MBGC < 50	D	134	23.13%	5.2
	ND	126	37.30%	14.0
	C	260	30.00%	9.3
MBGC < 40	D	151	26.49%	8.5
	ND	107	50.47%	17.0
	C	258	36.43%	11.6

Table 1. Patient outcome for the IV insulin cohort. "D" denotes prior history of diabetes, "ND" for no recorded history of diabetes, "C" for D and ND combined, and "LOS" for median length of ICU stay.

Exposure		No. of Patients	Mortality	LOS (days)
60≤ MBGC	D	1002	20.86%	2.0
	ND	2720	22.87%	2.9
	C	3722	22.33%	2.6
50 ≤ MBGC < 60	D	67	25.37%	2.9
	ND	97	37.11%	8.8
	C	164	32.32%	4.8
40 ≤ MBGC < 50	D	35	25.71%	2.9
	ND	37	40.54%	5.9
	C	72	3.33%	4.2
MBGC < 40	D	42	30.95%	3.1
	ND	34	55.88%	8.6
	C	76	42.11%	5.0

Table 2. Patient outcome for the SS insulin cohort. Notations are the same as in Table 1.

Exposure		No. of Patients	Mortality	LOS (days)
60≤ MBGC	D	436	21.10%	1.7
	ND	6435	13.60%	1.5
	C	6871	14.07%	1.6
50 ≤ MBGC < 60	D	17	41.18%	4.7
	ND	936	3.53%	2.5
	C	953	4.20%	2.6
40 ≤ MBGC < 50	D	14	14.29%	1.8
	ND	562	4.80%	5.7
	C	576	5.03%	5.6
MBGC < 40	D	17	58.82%	3.5
	ND	568	7.22%	9.1
	C	585	8.72%	8.8

Table 3. Patient outcome for the No insulin cohort. Notations are the same as in Table 1.

Results from decadal analysis of minimum blood glucose concentration and in-hospital mortality are presented in Figures 1, 2, and 3.

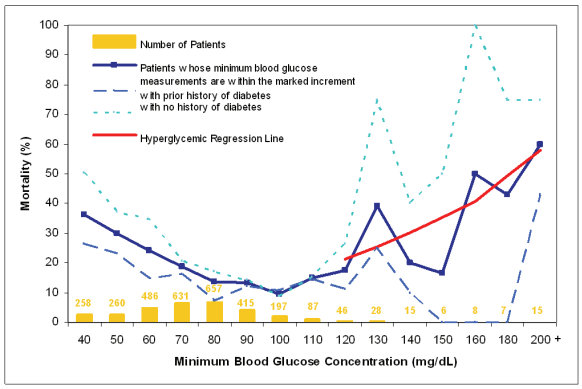

Figure 1. Mortality rate distributed according to patients' MBGC for the IV insulin cohort. The slope of the regression line differs from zero with p=0.004. The slope of the regression line for diabetic patients only (not drawn) is not significant.

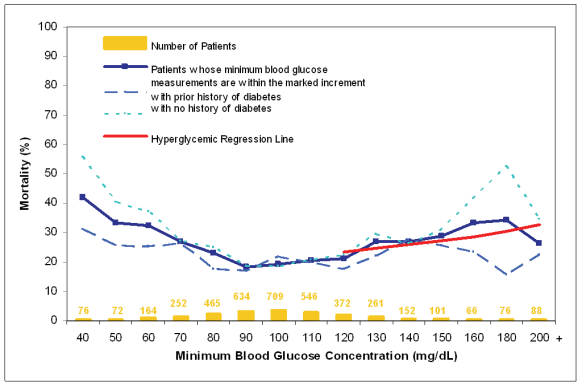

Figure 2. Mortality rate distributed according to patients' MBGC for the SS insulin cohort. The slope of the regression line differs from zero with p=0.032.

The slope of the regression line for diabetic patients only (not drawn) is not significant.

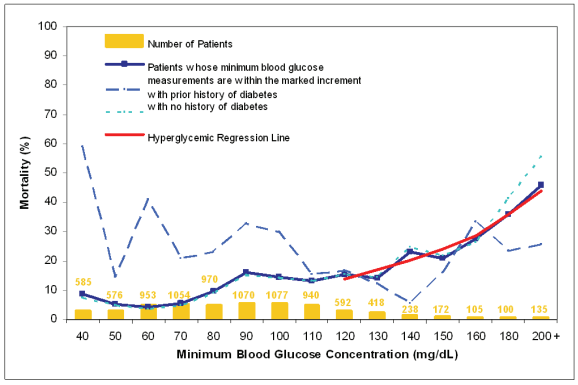

Figure 3. Mortality rate distributed according to patients' MBGC for the No insulin cohort. The slope of the regression line differs from zero with $p<0.001$; for diabetic patients only (not drawn), it differs from zero with $p=0.045$.

Categorical logistic regression analysis yields Table 4. Analysis of the maximum blood glucose concentration for each patient and that of the average concentration during the course of ICU stay did not yield patterns or trends. There is no correlation between a patient's minimum blood glucose concentration and the maximum blood glucose concentration. No pattern between the maximum-minimum pair of blood glucose measurements and patient outcome was observed.

Discussion

Results from the categorical logistic regression analysis (Table 4) indicate that minimum blood glucose levels below 60 mg/dL are associated ($p<0.05$) with higher odds for in-hospital death than those for the non-hypoglycemic group for all patients except those with prior history of diabetes and either received IV insulin with MBGC between 50-60 mg/dL, only subcutaneous insulin according to a sliding scale, or no anti-hyperglycemic treatment. The odds of death increase further for patients who experienced severe hypoglycemia: MBGC < 40mg/dL is associated ($p<0.05$) with the highest odds of death. Figures 1, 2, and 3 also illustrate that in-hospital mortality among patients receiving insulin increases as blood glucose concentration falls into the hypoglycemic range. The patient distributions over MBGC decades show that a bigger percentage of the IV insulin cohort have their MBGC in the hypoglycemic range than that of the SS insulin or No insulin cohorts, suggesting that IV insulin therapy does introduce higher risk of acute hypoglycemia.

MBGC (mg/dL)	Odds Ratio	*Z*	*p*-value	95% CI
IV insulin cohort with history of diabetes:				
<40	2.516	4.38	<.001	1.665-3.802
40-49	2.101	3.25	.001	1.342-3.291
50-59	1.223	0.99	.323	.821-1.821
IV insulin cohort with no history of diabetes:				
<40	4.569	7.34	<.001	3.046-6.854
40-49	2.667	4.95	<.001	1.808-3.936
50-59	2.376	5.52	<.001	1.748-3.230
SS insulin cohort with history of diabetes:				
<40	1.701	1.55	.121	.869-3.330
40-49	1.313	0.69	.490	.606-2.846
50-59	1.290	0.87	.382	.729-2.283
SS insulin cohort with no history of diabetes:				
<40	4.272	4.17	<.001	2.158-8.457
40-49	2.300	2.46	.014	1.186-4.460
50-59	1.991	3.20	.001	1.306-3.034
No insulin cohort with history of diabetes:				
<40	5.342	3.31	0.001	1.979-14.42
40-49	0.623	-0.61	0.541	.137-2.834
50-59	2.617	1.90	0.058	.970-7.064
No insulin cohort with no history of diabetes:				
<40	0.494	-4.24	<0.001	.357-.685
40-49	0.321	-5.67	<0.001	.216-.475
50-59	0.232	-8.07	<0.001	.163-.331

Table 4. Odds ratio of death from categorical logistic regression analysis, compared to the non-hypoglycemic (MBGC ≥ 60mg/dL) group**.**

Figures 1 and 2 show that for both diabetic and non-diabetic patients MBGC within the 80-110 mg/dL range corresponds to the highest percentage of survival among patients receiving insulin. Figure 3 reveals that, for the No insulin cohort, MBGC within the 130-150 mg/dL range corresponds to the highest percentage of survival among diabetic patients, while MBGC near the hypoglycemic range (50–70 mg/dL) corresponds to the highest survival rate for non-diabetic patients. These findings seem to support the concept of strict glycemic control (i.e., maintaining patients within the normoglycemic range) independent of prior history of diabetes.

The regression lines in Figures 1, 2, and 3 indicate that mortality increases with increasingly severe persistent hyperglycemia (i.e., a patient is persistently

hyperglycemic if his/her blood glucose levels are in the hyperglycemic range throughout the ICU stay). This trend is particularly evident among non-diabetic patients who experience persistent hyperglycemia during intensive care, in all three treatment cohorts. It provides another validation for the observation that persistent hyperglycemia during critical illnesses is associated with poor patient outcome.

It would be useful to stratify patients based on not only prior history of diabetes but also severity of illness. Unfortunately, the version of MIMIC II that has been released for research does not have all the physiological variables for calculating APACHE scores, SAPS, or APS for a significant portion of our patient population. Methods for estimating patient acuity have been developed, but they involve significant data interpolation and are limited to specific patient groups. Since this study focuses on clinical relationships in terms of association as opposed to causation, we decided to avoid introducing additional bias from normalizing our results with incomplete disease severity assessments.

While patients' length of stay in the ICU is not solely dictated by the severity of illness, based on empirical observations, sicker patients do tend to either expire soon after admission or require a long course of intensive care. Because of this dichotomy and the fact that a patient's length of stay is also influenced by a number of factors (e.g., patient's advance directive), we chose not to use length of stay as an indirect measure of patient's severity of illness; however, we take note that in all three treatment cohorts, MGBC is inversely correlated with length of stay (Tables 1, 2, and 3). Furthermore, non-diabetic patients have longer median length of stay and higher mortality compared to diabetic patients in the IV insulin and SS insulin cohorts. Table 3 shows that non-diabetic patients with MBGC below 50 mg/dL interestingly have not only higher survival rate but also longer length of stay comparing to the diabetic patients in the same category.

Conclusion

Large database such as MIMIC II provide rich resources for uncovering and verifying clinical trends. There are, however, concrete challenges with data extraction and analysis, as no large database is free of missing values and artifacts. This study has been a major exercise in utilizing a large dataset for clinical research. Its results are consistent with the hypothesis that both acute hypoglycemia and persistent hyperglycemia increase patient mortality in the ICU. With MBGC being a predictor of patient outcome, caregivers in the ICU may become more aware of patients' blood glucose levels and more selective of glycemic control strategies, through which the methods and findings in this study may help bring about safer, more effective blood glucose management for critically ill patients.

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