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Blood Glucose Variability Measures: Going Beyond Traditional Methods

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Blood Glucose Variability Measures: Going Beyond Traditional Methods

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Blood Glucose Variability Measures: Going Beyond Traditional Methods

By: Michael Kelleman

BACKGROUND: The establishment of a formal and effective method to characterize glucose variability is a crucial step in the advancement of reducing morbidity and mortality, especially in critically ill patients in the intensive care unit (ICU). Previous studies have used measures that are unable to account for correlation between blood glucose measurements. We sought to provide a standardized method of data analysis from a glucose management protocol in hospitalized patients that is more appropriate for these repeated measures.

METHODOLOGY: Our study population consisted of 153 pediatric patients from two pediatric intensive care units (PICU): Children's Healthcare of Atlanta (CHOA) in Atlanta, GA and James Whitcomb Riley Hospital for Children in Indianapolis, IN. Baseline severity of illness scores (PELOD) were calculated at the time of admission and on day 6. Blood glucose measurements were collected throughout their hospitalization and PICU (length of stay) LOS and hospital LOS were recorded. We performed GEE analysis on blood glucose variability measures to determine the association with mortality. Additionally, we performed mixed linear model analysis on blood glucose variability measures to determine the association with PICU LOS, hospital LOS and change in PELOD scores.

RESULTS: We observed increased hospital and PICU LOS with increasing maximal glucose levels and decreased hospital and PICU LOS with increasing minimal glucose levels. No glucose variability measures were found to be associated with mortality either independently or in a GEE model. Standard deviation (SD) and glucose variability index were not found to be significantly associated with PICU or hospital LOS while coefficient of variation CV was found to be significantly associated with both PICU of hospital LOS. CV and was also significantly associated with change in PELOD after controlling for baseline severity of illness while SD and glucose variability index were not significantly associated with changed in PELOD.

DISCUSSION: These results are consistent with previous studies while we introduced a novel way to analyze blood glucose measurement from critically ill pediatric patients in the PICU. Further research on glucose variability and repeated measure analysis should consider incorporating other characteristics of variability measured using area under the curves AUC applied to glucose versus time.

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Chapter I

Introduction

Background

The pediatric intensive care unit (PICU) cares for both surgical and medical (non-surgical) pediatric patients and, due to the nature of the critical illness, many experience episodes of hyperglycemia. Treating the condition of hyperglycemia with insulin to return the patient to a state of normoglycemia has an impending side effect of hypoglycemia. Potential consequences of these conditions include increased morbidity, mortality and length of stay (LOS) in both the hospital and PICU [1]. Increased LOS in the hospital and PICU have been associated with increased mortality from such conditions as acute renal failure, infection, and sepsis.

There are two main clinical practices for handling the potentially serious issues of hyperglycemia and hypoglycemia: (1) apply a clinical protocol in blood glucose testing and treat via insulin if the glucose levels are greater than the upper limit of a particular acceptable range, say 80-140 mg/dL, and (2) having no window and allowing glucose levels to vary naturally. The former can be difficult to manage for many reasons such as the reliance of such protocol on nursing staff, failure to comply with the clinical protocols, and the nature of the critically ill patient. Among the risks of administering insulin are seizures, hypoglycemia and death. Additionally, having no clearly defined target range of normal values may allow glucose levels to reach such a high level that the risks of morbidity and mortality are increased. In terms of public policy, the protocol in

adult ICU population is becoming more relaxed to allow for greater glucose variability [2], but little research has been conducted in pediatric patients.

Problem Statement

It is not known whether it's better to institute glycemic control within a window of normal values therefore restricting the blood glucose variability or having no window and let blood glucose levels vary if they need to vary [3]. Previous studies have used clinician's knowledge and previous experience about glucose management of pediatric patients in the PICU. Since there are no agreed upon defined ranges for hyperglycemia or hypoglycemia in pediatric patients, a standardized plan of action for addressing these conditions has mostly been the responsibility of the attending physicians. Many glucose management protocols attempt to restrict glucose levels to be within 80-220 mg/dL [4].

The critically ill patient's blood glucose can be tested hundreds of times during their ICU stay. There have been previous reports which have studied the variability of blood glucose in the ICU. However, since these studies have been treating measurements as independent, without accounting for within-patient correlation, they have not been properly accounting for previous measurements available across time. The presence of within-patient correlation violates the assumptions of most statistical estimates (eg. standard deviation) since patients' glucose levels at one time may be related to previous measurements. Ignoring within-patient correlation may lead to incorrect estimates, standard errors, hypothesis tests and most importantly, incorrect interpretations and conclusions.

While there haven't been many studies investigating glucose variability, there is an extensive literature on heart rate variability and recommended practices to measure and manage this variability. Heart rate variability calculations are considered an informative method in determining glucose variability since there are similarities in the cyclical nature of heart rate and glucose as well as the frequency in which these data are collected.

Purpose Statement

The objective of this paper is to introduce a statistical analysis of glucose variability data from pediatric hospitalizations that include the within-patient correlation at each measured time point. This paper will show how the results compare to previous reports of glucose-induced outcomes that excluded the assumption that each measured time point was dependent on previous time points. The approach allows standardization of data analysis from glucose management protocol in hospitalized patients. Relationships between different measures of blood glucose variability and clinical outcome will also be assessed. Due to the rarity of mortality in the patient population, we are also interested in examining the association of different measures of glucose variability with LOS in the PICU, total (hospital) LOS, change in PELOD score from baseline to day 6.

Significance Statement

The aim of this paper may provide clinicians and researchers with support for a more standardized approach to analyze data from glucose management protocols for the reduction in mortality and morbidity of surgical and medical pediatric patients in the

hospital and PICU. These reductions are measured by decreased instances of death and decreased LOS in the PICU and/or hospital.

Assumptions

In these datasets, some patients experience more than one hospitalization. We considered each hospitalization to be independent. We believe that there was little if any glucose profile correlation between separate hospitalizations for the same patient. Additionally, due to the variety of sources that were used to collect glucose data, such as glucose strips, point-of-care devices, and laboratory derived values, we did not account for potential differences in these devices. We assumed that each of these sources were well-calibrated and comparable with each other.

Definition of Terms

AUC = Area under the curve in a chart of measurement time versus blood glucose levels. This calculation is used as a relative measure of glycemic control.

Pediatric = Children aged 0 until 21 years of age

Glycemic control = Medical term referring to the typical levels of blood glucose in a healthy person.

Hyperglycemia = Condition in which an excessive amount of glucose circulates in the blood plasma. In this study > 140 mg/dL plasma glucose is considered mildly hyperglycemic, > 180 mg/dL plasma glucose is considered moderately hyperglycemic and > 200 mg/dL plasma glucose is considered severely hyperglycemic.

Hypoglycemia = Condition in which a diminished amount of glucose circulates in the blood plasma. In this study < 80 mg/dL plasma glucose is considered less than normoglycemic, < 70 mg/dL plasma glucose is considered moderately hypoglycemic, and < 40 mg/dL plasma glucose is considered severely hypoglycemic.

Length of stay (LOS) = Duration of hospitalization for a patient in hospital; total (hospital) LOS includes period of time spent in PICU.

Normoglycemia = Within range, “normal” glycemic range

Chapter II

Literature Review

Introduction

The establishment of a formal and effective method to characterize glucose variability is a crucial step in reducing morbidity and mortality, especially in critically ill patients in the ICU. This research examines the various methods to measure glucose variability and whether a more appropriate method could be substituted for previous measures of glucose variability. We will be drawing our experience from studies that calculated glucose variability to examine its relationship to mortality as well as studies that performed similar variability calculations using heart rate measurement data.

Many glucose measurements of critically ill patients are performed through the use of point-of-care (POC) capillary fingerstick glucose assessments as well as through routine central laboratory analysis of venous or arterial samples using standard hospital blood collection protocols [4]. There are several methods to calculate glucose variability, but there is yet to be an established standard procedure. Two commonly reported and easy measures of glucose variability are the standard deviation (SD) of all glucose measurements per patient and the coefficient of variation (CV). Typical calculations of the SD assume independent observations; however, repeated blood samples from hospitalized patients are likely correlated within patient. Even so, SD is a convenient measure to calculate and can be valuable. The CV calculation also can be a useful measure since it is a normalized summary of the distribution and illustrates the relative extent of the variability as a percentage of the mean. Another measure that was

introduced by Schlichtkrull et al in 1964, called the M-Value, is an index attempting to indicate the lack of efficacy of the treatment of diabetes in an individual patient [5]. This measure has been modified to allow for different "ideal" glucose values between investigators and is now referred to the adjusted M-Value [6]. It is a measure of the stability of the glucose deviations compared to an ideal glucose value, generally 80-100 mg/dL. The adjusted M-Value is zero for healthy controls and increases for patients with higher glucose variability and high mean glucose. As a result, this measure is unable to distinguish between patients with either high mean glucose or those with high glucose variability/poor glycemic control.

While many studies use POC protocols or standard laboratory analysis to determine plasma glucose levels, there are a number of studies that utilize continuous glucose monitoring (CGM) collection devices to provide real-time measurements of glucose levels. With these devices, glucose can be sampled from 1 minute to 1 hour intervals and data can be stored for up to 72 hours to be downloaded to a computer to view and track a patient's glucose control [7, 8]. For CGM data, there have been additional measures for glucose variability that take advantage of the standardized intervals between glucose measurements. The mean amplitude of glycemic excursions (MAGE) was introduced by Service *et al.* in 1970 and was developed using hourly blood glucose sampling for 48 hours but has been under scrutiny since it ignores glucose values less than 1 SD [6, 9]. Lastly, a measure that is calculated as the SD of the summed differences between a current observation and an observation *n* hours previously, called continuous overlapping net glycemic action (CONGA-*n*) was proposed by McDonnell *et al.* [10]. Due to the many possible values of *n*, it is not yet known which CONGA-*n*

values are preferable [6]. Figure 1 displays the various variability measures, their formulas, and a few of the distinguishing features that each possess.

Glucose Variability

Proposed methods of measuring glucose variability have led to promising results in different studies and populations. Two different groups conducted retrospective analyses of glucose variability as a predictor of mortality while hospitalized in the adult ICU [1, 11]. Both groups concluded that using the SD of glucose within each patient was a significant predictor of mortality in critically ill patients independent of APACHE II scores, a measure of severity of illness. Egi *et al.* performed a further subgroup analysis based on SD of diabetic patients in the ICU and found that the glucose variability and mortality relationship was not present [11]. Due to the nature of these studies each had differing glucose management protocols. Egi *et al.* did not define a target window for glycemic control while Krinsley's study began without a window, but then collected data for the last four years of their 8-year study within a relatively tight glycemic target window of 80 mg dL to 140 mg/dL [1, 11]. In a diabetic subgroup, they may have not had sufficient power to detect a difference and it is reasonable to assume that the diabetic population is not necessarily like every other critically ill non-diabetic patient.

In critically ill patients, particularly those admitted to the cardiac ICU, mortality may be largely attributable to underlying factors that are difficult to standardize such as anatomical defects and/or surgical expertise. Using a two-center, randomized trial of critically ill children (n=980), Agus *et al.* showed that using a tight glycemic control protocol of 80 mg/dL to 110 mg/dL did not change the rate of health care-associated

infections, LOS in the cardiac ICU, or mortality [3]. Although the authors implemented an explicit insulin-dosing algorithm to minimize hypoglycemia, they were unsuccessful in showing any significant benefit of a tight glycemic control in critically ill children who had undergone cardiac surgery. As a consequence of using a tight glycemic control protocol, the investigators minimized glucose variability within patients but were unable to show an association with improved outcome [3]. However, in a retrospective study of non-diabetic patients in PICU (n = 1038), glucose variability was found to be associated with mortality and increased LOS [12], where. The glucose variability index in this study was calculated as the mean of the absolute difference of sequential glucose values divided by the difference in collection time [12].

The previous glucose variability studies mentioned do not account for within-patient correlation and instead treat each glucose measurement in a patient as an independent event. In reality, each data set contains repeated differences of subsequent glucose measurements that include many intervals. Ignoring this correlation may lead to incorrect estimates and, more importantly, incorrect conclusions. With the increasing use of CGM devices to monitor and evaluate glucose management of patients, investigators have explored alternative methods for measuring glucose variability that account for within-patient correlation. Breton and Kovatchev applied classical time-series techniques to CGM data in order to propose the use of an autoregressive moving average model to account for the time dependence of consecutive sensor errors. These investigators found that consecutive sensor errors were highly interdependent and they developed a computer simulation of sensor errors that found no significant difference between observed and simulated distribution of sensor errors ($p > 0.46$) [13].

Rodbard published a review of numerous glucose variability measurements from CGM data and determined the correlation between each of these various measures of variability. The data analyzed was collected over many days and the author focused on measures related to SD since there are linear relationships between SD and CV, MAGE and CONGA-*n*. Additionally, total glucose variability was partitioned into two parts: the variability within day and the variability between day (mean daily glucose and between glucose values obtained at same time of day for sequential days). The author provided the range of approaches available for measuring glucose variability and produced a schema for researchers to follow for characterizing glucose variability [14].

Of the two main methods of glucose measurements, POC assessments are more convenient to perform, less expensive and, presumably, as accurate as CGM devices [7]. As a result, many glucose measurements are routinely collected by POC and the timing of these measurements is highly variable since they depend on factors such as scheduling of nurses, laboratory personnel and priority of testing procedure. Due to the non-standard difference in time between measurements it is difficult to propose a standardized procedure to measure glucose variability across all data collection protocols.

Heart Rate Variability

When patients are hospitalized, whether on the floor or in the ICU, a very commonly collected measurement is heart rate through the use of electrocardiogram (ECG) machines. Similar to blood glucose levels, heart rate is rarely constant throughout hospitalization and can fluctuate during a patient's stay. Heart rate variability is a description of the oscillation in consecutive heart beats and there are also various

methods to quantify heart rate variability [15, 16]. Time domain methods are used to measure either the heart rate at any point in time or the intervals between successive normal heart beats. These methods include statistical measures (e.g. SD) and geometrical measures (e.g. patterns of interval durations) that can be used only from recordings of the same duration. Frequency domain methods use power spectral analysis from short-term recordings (e.g. 2 to 5 minute) and long-term recordings (e.g. entire 24-hour period) to examine very low frequency (VLF), low frequency (LF), and high frequency (HF) components. Time and frequency domains methods over a 24-hour period have been found to be strongly correlated [15].

Camm et al. and Indic et al.used an autoregressive correlation structure in modeling heart rate variability since they believed that heart rate observations were most similar for observations closer in time than observations farther apart in time [15, 17]. We will use some of these ideas and concepts to address appropriate measures of glucose variability in critically ill pediatric patients.

Chapter III

Methodology

Study Population and Measurements

This study was conducted in a pediatric patient population from Children's Healthcare of Atlanta (CHOA) in Atlanta, GA and James Whitcomb Riley Hospital for Children (Riley) in Indianapolis, IN. Pediatric patients were randomized to either a strict or conservative glucose management protocol. At admission to either PICU or CICU, baseline characteristics such as weight (kg), age (years), gender, and Pediatric Logistic Organ Dysfunction (PELOD) Scores were determined and recorded.

Two methods for measuring glucose levels were used; whole-blood glucose levels were measured with point-of-care devices and plasma glucose levels were measured in the hospital clinical laboratory. All glucose values were reported as plasma equivalents. For each patient, the mean glucose level was calculated as the mean of all glucose measurements; the minimal glucose level was the lowest observed glucose measurement and the maximal glucose level was the highest observed glucose measurement for the entire PICU admission. The date and time of each blood glucose measurement was also recorded. The glucose variability index was calculated for each patient having ≥ 3 plasma glucose measurements by dividing the absolute difference of sequential glucose values by the difference in collection time in hours $+ 0.01$. The mean of these ratios for each subject forms the variability index [12]. Glucose variability measures of SD, CV and the glucose variability index were calculated for each patient. The median, median absolute deviations (MAD), and mean of each glucose variability measure were

calculated and stratified by hospital. The glucose variability index was divided into quintiles for analysis.

There is no standard definition of hypoglycemia in clinically ill, non-diabetic patients since it can vary by the age and fasting state of the patient. As such, we chose to use cutoffs of blood glucose concentrations at < 40 mg/dL to indicate severe hypoglycemia, < 70 mg/dL to indicate moderate hypoglycemia, and < 80 mg/dL to indicate mild hypoglycemia. Similarly, there are no specific criteria defining hyperglycemia in our pediatric population. We chose cutoffs of blood glucose concentration at > 140 mg/dL to indicate mild hyperglycemia, > 180 mg/dL to indicate moderate hyperglycemia, and > 200 mg/dL to indicate severe hyperglycemia.

Mean, maximum, and minimum glucose measurements for a patient during their entire hospitalization were calculated and tabulated. The maximum and minimum glucose values for all patients were divided into quintiles. Analysis of the data according to quintiles removed any bias associated with the choice of arbitrary cutoff values defining hyperglycemia and hypoglycemia while allowing categorizing of the glucose variability index.

PELOD scores were calculated at the time of admission to the PICU. For the PELOD score, six organ systems (neurologic, cardiovascular, renal, respiratory, hematologic and hepatic) are considered, each with up to 3 variables (total 12 variables). Each component is assigned points (0, 1, 10 or 20) based on the level of severity. For our study, we chose to categorize PELOD scores as low (< 10), medium ($10 - 19$), and high

(≥ 20), as in a previous report examining PELOD scores and survival in critically ill pediatric patients [18].

Analysis

Data analysis was performed with SAS Software version 9.3 (SAS Institute, Cary, NC) and R Software version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). Since many of the measures were not distributed normally, medians and MAD were reported and frequencies were calculated for binary variables. When two variables were both ordinal (e.g., LOS versus maximal glucose level quintile), significance was calculated with the nonparametric Wilcoxon rank-sum test. When quintiles were assessed, all 5 levels were used. The strength of association between two ranked variables was calculated with Spearman's rank-order correlation. For PELOD categories, all 3 levels were used. When a variable was nominal (e.g., death or glucose level above or below a certain cutoff value), significance was calculated with Pearson's χ^2 test or an exact test if the expected number of deaths in a category was < 5. Obtaining $p < 0.05$ was considered a statistically significant result.

Generalized estimating equations (GEE) were used to assess the association of blood glucose variability measures with mortality. PROC GENMOD was used to determine the correlation matrix for the first 15 blood glucose variability measures and mortality in patients whom had at least 15 measurements, while controlling for baseline severity of illness. A model was fit treating PELOD scores as continuous and a model was fit treating PELOD scores as categorical (low, medium, high). We assumed an autoregressive correlation structure to describe the within patient blood glucose

variability. An autoregressive correlation structure indicates that two observations taken close in time (or space) within an individual tend to be more highly correlated than two observations taken far apart in time from the same individual.

Since hospital and PICU LOS was skewed to the right, LOS was log-transformed to follow a more normal distribution. A mixed linear model (MLM) approach was used to account for correlation in blood glucose within patients. PROC MIXED was used to examine the association of blood glucose variability measures and patient LOS in hospital and PICU. We also examined the association of blood glucose variability measures and change in PELOD scores from baseline to day 6. We assumed an autoregressive covariance structure to describe the within patient blood glucose variability. An autoregressive covariance structure indicates that two observations taken close in time (or space) within an individual tend to be more highly correlated than two observations taken far apart in time from the same individual.

Chapter IV

Results

Patient Demographics

Among the 153 pediatric patients included in the analyses, there were 77 females (50.3%) and 76 males (49.7%), ranging in age from 1 days to 20.5 years (median age: 2.7 years; MAD age: 2.3 years) (Table 1). Most of the pediatric patients (79.1%) were admitted to the CICU compared to the PICU (20.9%). For the total study population, the median PICU LOS was 2 days (MAD PICU LOS: 1 day), and the median total hospital LOS was 5 days (MAD hospital LOS: 2 days). A total of 8 of the 153 pediatric patients (5.2%) died during the study period (Table 1).

Glucose Variability Measures

During the study period, 153 pediatric patients had 7,036 glucose measurements performed (median number of glucose measurements per pediatric patient: 26; MAD of glucose measurements per pediatric patient: 7; mean number of glucose measurements per pediatric patient: 46.0; SD of glucose measurements per pediatric patient: 63.0). Table 2 shows the different glucose variability measures calculated for this study. There were no significant differences with regard to either SD or CV between Riley and CHOA pediatric patients. The glucose variability index differed significantly in terms of both the median glucose variability index ($p < 0.001$) and mean glucose variability index ($p < 0.001$) between Riley (median = 12.0, MAD = 6.2, mean = 16.3) and CHOA (median = 29.0, MAD = 9.3, mean = 32.4) pediatric patients.

Hyperglycemia and Hypoglycemia

Table 3 shows the glucose ranges and glucose cutoff values according to PICU LOS, hospital LOS and mortality. All subjects included within a glucose range were calculated using mean glucose values; all subjects included within a < glucose cutoff value were calculated using minimum glucose values; all subjects within a > glucose cutoff value were calculated using maximum glucose values. Many patients achieved "normal" mean glucose levels (56.9%) between 80 mg/dL to 140 mg/dL and almost all patients (92.2%) had mean glucose levels between 70 mg/dL and 180 mg/dL (Table 3). Also, many patients (83.7%) experienced at least one episode of moderate hyperglycemia (blood glucose value > 180 mg/dL). Additionally, 111 patients experienced at least one episode of severe hyperglycemia (blood glucose value > 200 mg/dL). Conversely, the majority of patients (53.6%) experienced at least one episode falling below the lower end of normoglycemia (blood glucose value < 80 mg/dL). Thirty five patients (22.9%) experienced at least one episode of moderate hypoglycemia (blood glucose value < 70 mg/dL) while only 1 patient experienced severe hypoglycemia (blood glucose value < 40 mg/dL). All patients ($n = 8$) who had died in the ICU experienced at least one episode of moderate hyperglycemia (blood glucose value > 180 mg/dL) and at least one episode falling below the lower end of normoglycemia (blood glucose value < 80 mg/dL).

Maximal Glucose, Minimal Glucose, and Glucose Variability Index Quintiles

The maximum glucose values, minimum glucose values and glucose variability index values for all patients were divided into quintiles. Analysis of the data according to quintiles removed any bias associated with the arbitrary cutoff values defining

hyperglycemia and hypoglycemia while allowing categorization of the glucose variability index. There was a significant association between maximal glucose level quintiles and LOS in both the PICU ($p = 0.001$) and the hospital ($p = 0.028$). Spearman rank-order correlation test also showed a significant association between maximal glucose level quintiles and PICU LOS ($\rho = 0.315, p < 0.001$) maximal glucose level quintiles and hospital LOS ($\rho = 0.221, p = 0.006$). The median PICU LOS increased from 4 days to 10 days and the median hospital LOS increased from 2 days to 5.5 days from the lowest to the highest maximal glucose levels. There was also a significant association between minimal glucose level quintiles and LOS in both the PICU ($p < 0.001$) and the hospital ($p < 0.001$). Spearman rank-order correlation test also showed a significant association between minimal glucose level quintiles and PICU LOS ($\rho = -0.421, p < 0.001$) minimal glucose level quintiles and hospital LOS ($\rho = -0.443, p < 0.001$). The median PICU LOS decreased from 10 days to 3 days and the median hospital LOS decreased from 6 days to 1 day from the lowest to the highest maximal glucose levels (Table 4). Neither the maximum or minimum glucose level quintiles were significantly associated with mortality.

To obtain an estimate of the effects of glucose variability on LOS in PICU or hospital and mortality rate, patients were divided into quintiles based on their individual glucose variability index (Table 4). While the glucose variability index was not significantly associated with increased mortality, it was significantly associated with both PICU LOS ($p = 0.012$) and hospital LOS ($p = 0.014$). Spearman rank-order correlation test also showed a significant association between PICU LOS and glucose variability index quintiles ($\rho = -0.184, p = 0.023$) and hospital LOS and glucose variability index

quintiles ($\rho = -0.197, p = 0.015$). The patients with the lowest glucose variability indices had the highest PICU LOS and the highest hospital LOS and the patients with the highest glucose variability indices had the lowest PICU LOS and lowest hospital LOS. The median PICU decreased 7 days to 2 days and the median hospital LOS decreased from 9.5 days to 4 days from the lowest to highest glucose variability indices.

Modeling Results

Patients with at least 15 glucose measurements were used for GEE modeling ($n = 147$). Blood glucose values were not predictive of mortality while controlling for baseline severity of illness (continuous and categorical) suggesting actual blood glucose values are not an important indicator of mortality. SD, CV, and the glucose variability index of blood glucose were not significant predictors of mortality while controlling for baseline severity of illness (continuous and categorical).

All patients were used for MLM modeling ($n = 153$). Glucose variability measures were analyzed as single predictors and were adjusted by baseline severity illness (continuous and categorical = low, medium, high). SD was not a significant predictor of PICU or hospital LOS while controlling for baseline severity of illness (continuous and categorical). SD was found to be a significant predictor of change in PELOD score (p =0.0269) and CV was found to be a significant predictor of PICU LOS after controlling for baseline severity of illness (continuous, p =0.0009; categorical, $p = 0.0007$). CV was also a significant predictor of hospital LOS after controlling for baseline severity of illness (continuous, p =0.0071; categorical, $p = 0.0071$). CV was found to be a significant predictor of change in PELOD score (p =0.0376) but not a significant

predictor after controlling for baseline severity of illness (continuous and categorical). Glucose variability index was not a significant predictor of PICU LOS, hospital LOS or change in PELOD score while controlling for baseline severity of illness (continuous and categorical).

Chapter V

Discussion

Summary of Study/Strengths & Limitations

This study used previously determined measures of glucose variability to examine potential associations between: (1) glucose variability measures and mortality, (2) glucose variability measures and LOS in both the hospital and PICU, and (3) glucose variability measures and change in PELOD scores. Analysis of the data according to quintiles reduced bias associated with the arbitrary cutoff values defining hyperglycemia and hypoglycemia while allowing categorization of the glucose variability index. We observed significantly increased hospital and PICU LOS with increasing maximal glucose levels and significantly decreased hospital and PICU LOS with increasing minimal glucose levels. No glucose variability measures were found to be associated with mortality either independently or in a GEE model. SD and glucose variability index were not found to be significantly associated with PICU or hospital LOS while CV was found to be significantly associated with both PICU of hospital LOS. CV was also significantly associated with change in PELOD after controlling for baseline severity of illness while SD and glucose variability index were not significantly associated with changed in PELOD.

There were a number of limitations that were beyond the control of the investigators. Since patients were enrolled in the PICU and treated by their needs, the number of glucose measurements per pediatric patient during their PICU stay ranged from 3 to 565 with a median of 26 and MAD of 7 measurements per pediatric patient

(mean = 46.0, SD = 63.0). The number of days each pediatric patient had their glucose measured, both in hospital and PICU, ranged from 1 to 236 days with a median of 5 and MAD of 2 days of glucose measured per patient (mean = 11.0, SD = 23.4). Additionally, the number of measurements per patient per day ranged from 0.6 to 16.3 with a median of 6.3 and MAD of 1.5 measurement per patient per day (mean = 6.2, SD = 2.5). As a result, pediatric patients that had more measurements per day may have been more closely supervised by nursing staff than patients who did not have as many measurements per day. The time between measurements was not standardized and could contribute to the lack of consistent correlation in blood glucose measurements and mortality.

Glucose measurements were performed using two different sources and the validity and calibration control of using both of these methods on the same patients is not known. This is typical in critical care centers as blood measurements are usually performed with readily available testing methods and recorded [4, 19]. For our outcome of mortality, we do not specify a cause of death; it could be directly related to glucose variability but may be related to other conditions such as hospital acquired infections or a more systemic cause like multiple organ failure.

Mis-specification of the correlation or covariance structure used in our analyses could drastically affect our results. We performed the same analyses using an exchangeable correlation structure that assumes every observation within an individual is equally correlated with every other observation from that individual. We obtained similar results using both exchangeable and autoregressive structures and felt it more appropriate to use an autoregressive structure for glucose variability modeling based on previous heart rate variability studies [15, 17].

Conclusions

We observed significantly increased hospital and PICU LOS with increasing maximal glucose levels and significantly decreased hospital and PICU LOS with increasing minimal glucose levels. These results are consistent with previous studies while we introduced a novel way to analyze blood glucose measurement from critically ill pediatric patients in the PICU by including the within-patient correlation at each measured time point in our analysis [12, 20].

Surprisingly, we did not find a significant association between glucose variability index and mortality. This is likely due to low statistical power from only 8 deaths in the population of 153 patients. Of note is that CHOA patients had higher median, MAD and mean glucose variability index values than Riley patients, yet there were a higher proportion of deaths in Riley patients than CHOA patients (16.7% mortality vs. 3.1% mortality; $p < 0.001$). While a higher proportion of cardiac PICU patients died than general PICU patients (18.8% mortality vs. 1.7% mortality; $p < 0.001$), CHOA and Riley each had 1 cardiac PICU and 3 general PICU patients. There were no significant differences in baseline severity of illness between Riley and CHOA ($p = 0.1750$).

Future Research

In addition to these glucose variability measures and using appropriate statistical methods like GEE and MLM to analyze correlated data, it may worthwhile to incorporate aspects of area under the curve (AUC) techniques in developing appropriate methods of measuring glucose variability (Figure 2). While AUC is generally used as an indirect measure of glucose variability, there may be important characteristics of glucose

variability that are not fully captured in the measures used in this study. For example, there is software available to calculate not only the AUC of glucose measurements but also the percentage of time spent within or outside a target range. While many studies focus on the number of measurements that are within or outside a target, incorporating a time-dependent measurement may be informative in reducing LOS and mortality in patients in the ICU.

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Appendix

Figures and Tables

Figure 1. Formulas Used in Describing Glucose Variability

Table 1. Pediatric Demographics

Table 2. Pediatric Glucose Variability Measures by Hospital

Table 3. LOS and Mortality Rates According to Glucose Ranges and Glucose Cutoff Values

Table 4. LOS and Mortality Rates According to Glucose and Glucose Variability Quintiles

Figure 2. Example AUC Chart

Figure 1. Formulas Used in Describing Glucose Variability (adapted from [6])

Variability measure	Formula	Explanation of symbols	Discriminating feature
SD	$\sqrt{\frac{\sum_{i=1}^{k}(x_i - \bar{x})^2}{k-1}}$	x_i = individual observation $\bar{x}$ = mean of observations k = number of observations	Easy to determine, extensively used
CV	$\frac{s}{\bar{x}}$	s = standard deviation	Easy to determine, SD corrected for mean
Adjusted M-value	$M_{GR} + M_W$ where $M_G = \frac{\sum_{i=t_1}^{t_k}\left\|\log_{10}\frac{GR_t}{IGV}\right\|^3}{k}$ and $M_W = \frac{G_{max} - G_{min}}{20}$	M_{GR} = M-value for glucose readings M_W = correction factor for $k < 24$ GR_t = glucose reading at time t IGV = ideal glucose value t_i = time in minutes after start of observations of the i^{th} observation G_{max} = maximum glucose reading G_{min} = minimum glucose reading	Not a pure variability measure
MAGE	$\sum \frac{\lambda}{n}$ if $\lambda > \nu$	λ = each blood glucose increase or decrease (nadir-peak or peak nadir) n = number of observations ν = 1 SD of mean glucose for 24-hr period	Used most extensively
CONGA-n	$\sqrt{\frac{\sum_{i=t_1}^{t_{k^*}}(D_t - \overline{D})^2}{k^* - 1}}$ where $D_t = GR_t - GR_{t-m}$ and $\overline{D} = \frac{\sum_{i=t_1}^{t_{k^*}} D_t}{k^*}$	k^* = number of observations where there is an observation $n \times 60$ minutes ago $m = n \times 60$ D_t = difference between glucose reading at time t and t minus n hours ago	Specifically developed for CGM

SD = standard deviation; CV = coefficient of variation; MAGE = mean amplitude of glycemic excursions; CONGA = continuous overall net glycemic action; CGM = continuous glucose monitoring. Units are in mmol/L or mg/dL depending on the unit of glucose values measured. To convert glucose values from mmol/L to mg/dL divide by 0.0555

Table 1. Pediatric Demographics

	No (%)	Age at Admission, Median (MAD), y	Weight, Median (MAD), kg	PICU LOS, Median (MAD), d	Total LOS, Median (MAD), d	Duration of Vasopressor Drugs, Median (MAD), d	Duration of Ventilation, Median (MAD), d	Deaths, n (%)
All Patients Admissions	153 (100.0)	2.7 (2.3)	12.1 (6.1)	2 (1)	5 (2)	2 (1)	1 (1)	8 (5.2)
Randomization Group								
Strict	78 (51.0)	2.9 (2.6)	11.9 (5.8)	2 (1)	6 (3)	1 (0)	1 (1)	5 (6.4)
Conservative	75 (49.0)	2.6 (2.2)	12.3 (6.3)	2 (1)	4.5 (2)	2 (1)	1 (1)	3 (4.0)
Gender								
Female	77 (50.3)	2.3 (1.9)	11.3 (5.3)	2 (1)	5 (2)	2 (1)	1 (0)	1 (1.3)[a]
Male	76 (49.7)	3.1 (2.8)	13.5 (7.3)	2 (1)	7 (4)	2 (1)	1 (1)	7 (9.2)[a]
Hospital								
Riley	24 (15.7)	1.4 (1.0)	8.2 (2.7)	7 (4)[a]	9 (4)[a]	5 (3)	2.5 (2.5)	4 (16.7)[a]
CHOA	129 (84.3)	3.1 (2.8)	12.7 (6.7)	2 (1)[a]	5 (2)[a]	1 (0)	1 (0)	4 (3.1)[a]
ICU Patient Type								
Cardiac	121 (79.1)	2.3 (1.9)	11.4 (5.4)	2 (1)[a]	4.5 (1.5)[a]	1 (0)	1 (0)	2 (1.7)[a]
General	32 (20.9)	4.6 (3.3)	14.1 (7.4)	9 (5.5)[a]	14 (9.5)[a]	7 (3)	2 (2)	6 (18.8)[a]
PELOD Score								
Low (< 10)	54 (35.3)	2.2 (1.8)	12.1 (5.7)	2 (1)	5 (2)	1 (0.5)	1 (0)	1 (1.9)
Med (10 - 19)	41 (26.8)	1.9 (1.5)	9.7 (3.7)	2 (1)	6 (3)	2 (1)	1 (1)	1 (2.4)
High (≥ 20)	58 (37.9)	5.8 (5.1)	13.1 (8.5)	2 (1)	5 (2)	2 (1)	1 (1)	6 (10.3)

[a]Indicates $p < 0.05$

Table 2. Pediatric Glucose Variability Measures by Hospital

	Riley, Median (MAD)	Riley, Mean	CHOA, Median (MAD)	CHOA, Mean	All Patient Admissions, Median (MAD)	All Patient Admissions, Mean
Patient Admissions, n (%)	24 (15.7)	24 (15.7)	129 (84.3)	129 (84.3)	153 (100.0)	153 (100.0)
Variability Measure						
SD	40.7 (8.9)	40.6	37.7 (8.6)	43.1	38.6 (9.0)	42.7
CV	0.30 (0.07)	0.31	0.28 (0.05)	0.30	0.29 (0.06)	0.30
Glucose Variability Index	12.0 (6.2)[a]	16.3[b]	29.0 (9.3)[a]	32.4[b]	26.8 (9.2)	29.8

[a,b]Indicates $p < 0.05$

Table 3. LOS and Mortality Rates According to Glucose Ranges and Glucose Cutoff Values

Glucose Range, mg/dL	Glucose Cutoff, mg/dL	No.	PICU LOS, Median (MAD), d	Total LOS, Median (MAD), d	Duration of Vasopressor Drugs, Median (MAD), d	Duration of Ventilation, Median (MAD), d	Deaths According to Glucose Cutoff Value, n (%)
80-140		87 (56.9)	3 (2)	8 (5)	2 (1)	1 (1)	5 (5.7)
	< 80	82 (53.6)	4 (3)	8 (4)	2 (1)	1.5 (1)	5 (6.1)
	> 140	153 (100.0)	2 (1)	5 (2)	2 (1)	1 (1)	8 (5.2)
80-110		6 (3.9)	5 (2.5)	10 (2.5)	3.5 (2)	2 (1)	1 (16.7)
	> 110	153 (100.0)	2 (1)	5 (2)	2 (1)	1 (1)	8 (5.2)
40-200		151 (98.7)	2 (1)	5.5 (2.5)	2 (1)	1 (1)	7 (4.6)
	< 40	1 (0.7)	60 (0)	60 (0)	13 (0)	7 (0)	0 (0.0)
	> 200	111 (72.5)	2 (1)	6.5 (3.5)	2 (1)	1 (1)	7 (6.3)
70-150		116 (75.8)	2 (1)	6 (3)	2 (1)	1 (1)	6 (5.2)
	< 70	35 (22.9)	6 (5)	9 (5)	4 (3)	2 (1.5)	3 (8.6)
	> 150	151 (98.7)	2 (1)	5.5 (2.5)	2 (1)	1 (1)	8 (5.3)
70-180		141 (92.2)	2 (1)	6 (3)	2 (1)	1 (1)	7 (5.0)
	> 180	128 (83.7)	2 (1)	6 (3)	2 (1)	1 (1)	8 (6.3)

All ranges were calculated using mean glucose values

All < cutoffs were calculated using minimum glucose values

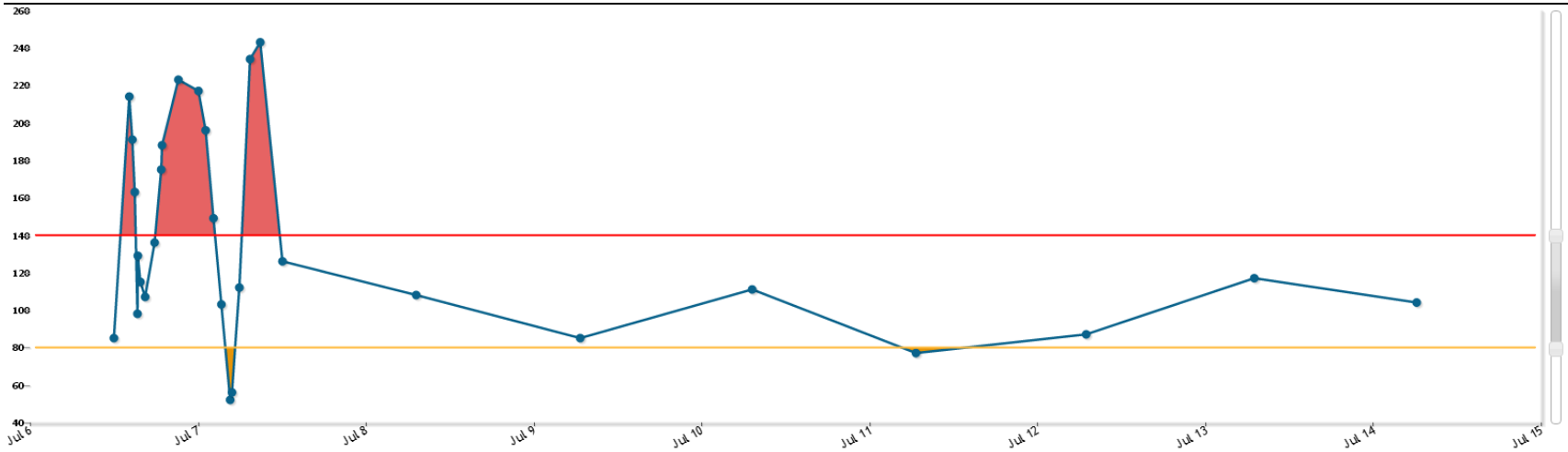
All > cutoffs were calculated using maximum glucose values

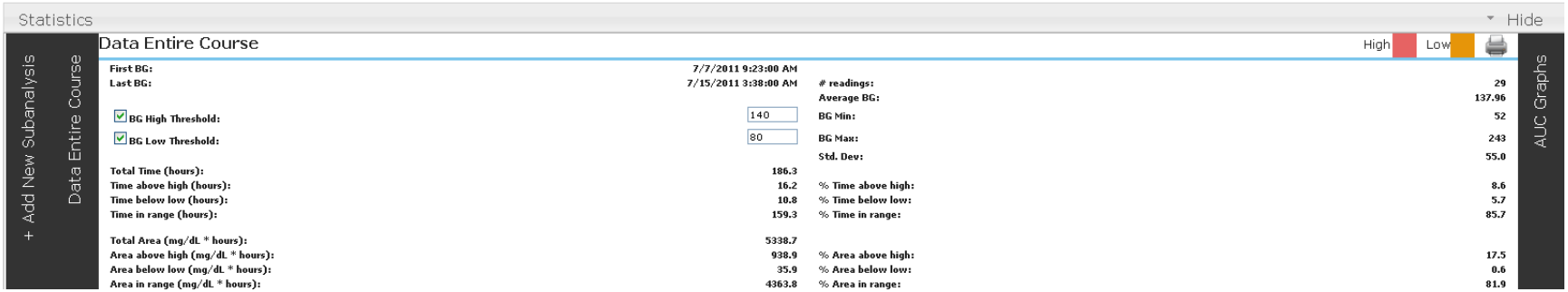
Table 4. LOS and Mortality Rates According to Glucose and Glucose Variability Index Quintiles

	Glucose Range, mg/dL	No.	PICU LOS, Median (MAD), d	Total LOS, Median (MAD), d	Duration of Vasopressor Drugs, Median (MAD), d	Duration of Ventilation, Median (MAD), d	Deaths According to Quintile, n (%)
Maximal glucose level quintile							
1	145-184	30	2 (1)[a]	4 (1)[a]	1 (0)	1 (0)	1 (3.3)
2	185-218	31	1 (0)[a]	5 (2)[a]	1 (0)	1 (0)	1 (3.2)
3	220-247	31	2 (1)[a]	6 (3)[a]	1 (1)	1 (1)	1 (3.2)
4	249-307	29	2 (1)[a]	4 (2)[a]	1 (1)	1 (1)	2 (6.9)
5	309-881	32	5.5 (4.5)[a]	10 (7)[a]	4 (3)	3 (2)	3 (9.4)
Minimal glucose level quintile							
1	29-67	30	6 (4.5)[a]	10 (4)[a]	4.5 (3.5)	3 (2)	3 (10.0)
2	68-75	28	3 (2)[a]	5 (2)[a]	2 (1)	1 (1)	1 (3.6)
3	76-83	34	2 (1)[a]	6.5 (3)[a]	1.5 (0.5)	1 (1)	1 (2.9)
4	84-90	30	1 (0)[a]	4.5 (1.5)[a]	1 (0)	1 (0)	2 (6.7)
5	91-217	31	1 (0)[a]	3 (1)[a]	1 (0)	1 (0)	1 (3.2)
Glucose variability index quintile							
1	1.64-15.39	31	7 (6)[a]	9.5 (5.5)[a]	5 (3.5)	1 (1)	2 (6.5)
2	15.88-23.82	30	2 (1)[a]	4.5 (1.5)[a]	1 (0))	1 (0))	2 (6.7)
3	23.97-29.75	31	2 (1)[a]	5 (2)[a]	1 (0)	1 (0.5)	2 (6.5)
4	30.63-39.69	30	2 (1)[a]	5.5 (2.5)[a]	2 (1)	2 (1)	0 (0.0)
5	39.94-204.44	31	2 (1)[a]	4 (1)[a]	1 (0)	1 (0)	2 (6.5)

[a]Indicates $p < 0.05$ Analyses of LOS and individual quintiles were performed with the nonparametric Wilcoxon rank-sum test.

Figure 2. Example AUC Chart [21]





HT = High Threshold of Target Range; LT = Low Threshold of Target Range
Time Calculations: Total Time (hours), Time above HT (hours and %), Time below LT (hours and %), Time in Range (hours and %)
Area Calculations: Total Area (mg/dL × hours), Area above HT (mg/dL × hours and %), Area below LT (mg/dL × hours and %), Area in Range (mg/dL × hours and %)