Glycemic Variability is Independently Associated with Poor Prognosis in Main PICU Centers in Southwest China

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Abstract

Background: Glucose variability (GV) is one of the common complications in critically ill patients, and studies investigating the role of GV in the prognosis of pediatric patients are scarce in China. And there is no consensus on the measurement of GV. Thus, this study took a prospective, multi-center cohort observational study to identify the 'best' index of variability in non-diabetic critically ill children and to confirm whether GV is associated with unfavorable outcomes and whether this association persists after control of hypoglycemia and hyperglycemia.

Materials and Methods: Four GV indices were chosen and calculated in our study, namely, mean absolute glucose (MAG), standard deviation (SD), glycemic lability index (GLI), and another metric-average consecutive absolute change percentage (ACACP), which can be used in the real-time clinical decision. The primary outcome was 28-day mortality. Multivariate Cox regression analysis was used to identify the potential predictors for the outcome. And the area under the curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated to assess the predictability of dysglycemia (glucose variability and hypo/hyperglycemia) on the unfavorable outcome.

Results: Of the total of 780 participants, 12.4% (n=97) died within 28 days after PICU admission. There were statistical differences in terms of four GV indices (SD, GLI, MAG, and ACACP) between survivors and non-survivors, in which MAG obtained the largest area under the curve and showed a strong connection to ICU mortality independently. Subsequent addition of MAG to the multivariate Cox model for hyperglycemia resulted in further quantitative evolution of the model statistics (AUC 0.651 to 0.681, $P=0.001$; IDI: 0.017, $P=0.044$; NRI:0.224, $P=0.186$). And the impact of hyperglycemia (adjusted HR1.419, 95% CI 0.815-2.471, $p=0.216$) on outcome was attenuated and no longer statistically relevant after adjustment for MAG (adjusted HR 2.455, 95%CI 1.411-4.270, $p=0.001$).

Conclusions: GV is closely associated with unfavorable outcomes, and may be a more powerful negative predictor of outcome than hypoglycemia and hyperglycemia. These findings emphasize the crucial role of GV in PICU children. GV index that contains information such as time, rate of change, etc. is the focus of future research. MAG may be a good choice.

Trial registration: Chinese clinical registration (ChiCTR), ChiCTR2000030846. Registered 15 March 2020, <https://www.chictr.org.cn/showproj.aspx?proj=50760>.

1 Background

Glucose management is an important element of intensive care management. In general, glucose dysregulation is related to regrettable outcomes in the critically ill, as one of the multi-system complications (1). A few professors have explored the effectiveness of glucose levels on the prognosis with different glucose management protocols, but the results are contradictory, especially concerning whether controlling glucose tightly actually improves clinical prognosis (2,3). Increased glycemic variability (GV) augments the risk of poor outcome may explain this inconsistency (4).

In 2006, Egi et al (5) demonstrated that GV was closely related to poor outcomes in critically ill adults for the first time. In recent years, a growing number of studies have confirmed that GV is connected to unfavorable outcomes in critically ill adults independently, regardless of its definition (6-10). However, fewer studies that explored the impact of GV on negative prognosis have focused on pediatric populations, compared to the adult, and most of the

previous researches (11,12) were retrospectively conducted in a single center. Thus, the affiliation between adverse prognosis and GV in pediatrics warrants prospective investigation in multicenter. Subsequently, we conducted this study with a prospective analysis of a pediatric cohort to address this clinical issue.

GV, also known as glucose fluctuation, represents the fluctuation of glucose levels over time and refers to a non-stationary state in which glucose levels fluctuate between their high and low values, including the speed, magnitude, and frequency. A few glucose variability metrics were reported to correlate with a worse outcome in the critically ill, such as standard deviation (7,8,13), coefficient of variation (7,13,14), mean amplitude of glycemic excursion (7,13,15), mean absolute glucose (13,16), glycemic lability index (15) and so on. These measurements differ in the requirements for calculations, such as the considerations of the frequency or the time interval between glucose measurements. Nevertheless, there is currently no consensus on the definition of GV and the 'best' index.

Our retrospective study (17) also demonstrated that GV is associated with unfavorable outcomes independently. In addition, hyperglycemia and hypoglycemia are indications of poor outcomes among pediatric patients (11,18-20). We have, therefore, prospectively studied if the correlation between GV and poor prognosis remained after controlling for hyperglycemia and hypoglycemia. This research was attempted to broaden the understanding of how GV, as well as hypoglycemia and hyperglycemia, are associated with adverse clinical outcomes for the children admitted to PICUs and to pick up a better understanding of glucose management.

2 Materials And Methods

2.1 Study Design and Quality Control

This was a prospective, multi-center, observational study conducted between January 1th, 2020, to December 31st, 2020. The participants were derived from five PICUs, which belong to tertiary A hospitals in southwest China and represent the top intensive care centers, providing top-tier medical care to the majority of critically ill children in these regions.

Before beginning the survey, we provided professional training for data loggers in each research PICU, including project objectives, research progress, and data collection. Multi-center data collection was performed by recorders according to strict definition. After collection and entry, the data were sent to a central repository where they were corrected for any suspicious errors or missing values by the coordinator and physicians in charge before acceptance.

The sample size of 665 can produce 90% power at the 5% level of significance when we took into account a 20% lost-to-review rate, which was calculated based on the primary outcome—28-day mortality in PICU, with cohort study analysis, using estimated ICU mortality of 10% and risk ratio of 2 as calculated from the literature (21,22).

2.2 Inclusion and Exclusion Criteria

All critically ill children aged 36 weeks (corrected gestational age) to 16 years, and receiving vasoactive drug support for hypotension or ventilatory support for respiratory failure, were considered as potential subjects. Exclusion criteria included children (1) who had a PICU stay of less than 24hours, or (2) the children who were diagnosed with diabetes mellitus or inborn errors of metabolism, or (3) had utilized glucocorticoids, or total

parenteral nutrition (TPN) treatment during 3 days after PICU admission. (4) Readmissions to PICU were also excluded.

2.3 Data collection

Data were manually entered into the EpiData program, version 3.1. For each patient, demographic data (age, sex, nutritional status), clinical treatments (vasoactive and glucose infusions, mechanical ventilation, and other adjuvant therapies), and prognosis (28-day mortality, multi-organ dysfunction syndrome, length of PICU stay) were recorded. The follow-up for each patient, admitted to our PICUs, was performed and recorded by the nurse one month after discharge utilizing telephone interviews (the questionnaire is shown on Supplementary Material). And we chose The Pediatric Index of Mortality–2 (PIM2) score (23) to estimate the severity of the illness at admission to the PICUs. The index that ascertained nutritional status as the “z” score for weight/height (5 years old) or BMI (>5 years old) for age using the Epi-Info software. Overweight was defined as BMI for age $>+2$ SD and wasting was <-2 SD.

2.4 Blood Glucose Indices

We collected all blood glucose values for the first 72hs after admission. The PICU children experienced examining for blood gases at least twice a day according to daily treatment. Consequently, no additional blood specimen was done for the study purpose alone. The specimens were mainly from arterial blood but also included venous and capillary blood sources.

In each patient, we calculated the following metrics according to all the available glucose values: the average glucose (Mean), standard deviation (SD), Glycemic lability index ($GLI = \sum (\Delta BG^2 / \Delta h) / d$, (mmol/L)²/h/d) (7), and mean absolute glucose ($MAG = \sum |X_i - X_{i-1}| / \Delta \text{time}$, mmol/L/h) (16). Besides, average consecutive absolute change percentage ($ACACP = 1/(n_i - 1) \sum |X_i - X_{i-1}| / X_i$) (24) was introduced, an index can be used in the real-time clinical decision conveniently. The glucose measurement on admission (Adm) was the first glucose value after ICU admission. We chose to define hypoglycemia as glucose value ≤ 3.6 mmol/L and hyperglycemia cutoff values of 8.3 mmol/L based on both adult and pediatric studies. (11,25)

2.5 Blood glucose management

As per the existing unit policy, stop glucose infusion when glucose value exceeds 15mmol/L and actively deal with the primary disease (26). Then we can observe for one hour. If there was no downward trend (glucose descend less than 4mmol/L/h), we can infusion insulin (0.05–0.1U/kg), and Insulin was stopped if BG was <10 mmol/L (27,28).

2.6 Statistical Analysis

Description of the baseline variables: categorical variables were described by n (%) and continuous variables without normal distribution was described by the median (IQR). Comparisons between the two groups: the Wilcoxon rank-sum test was used for continuous variables without normal distribution, while the Chi-square test was used for categorical variables. We used receiver operating characteristic (ROC) curve analysis to compare the predictive power of different indicators of glucose variability for the primary outcome. The glucose variability index with the largest AUC was also converted to a categorical variable based on the cut-off value for subsequent analysis. The

glucose variability index and hypo/hyperglycemia were gradually substituted into a multivariate Cox regression model adjusted for confounders with a significance level of $P \leq 0.10$ to prevent the exclusion of significant variables from the regression model. Results were expressed as HR (95% CI). The overall predictive accuracy of the model was also quantified using the area under the ROC curve (AUC). In addition, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses (29) were performed to assess glucose variability and hypoglycemia/hyperglycemia predictive power. Depending on the type of outcome variable, multivariable logistic regression or linear regression would also be used to assess the impact of glucose variability on other outcome indicators (e.g., ICU-free days or ventilator-free days to day 28, and multiple organ dysfunction syndromes). A value of $P < 0.05$ for a two-sided test is considered statistically significant. Statistical analyses were performed using R, version 4.0.0.

3 Results

We consecutively monitored a total of 2,725 patients in the five participating units during the study period, of which 780 patients met the nadir criteria for entry into the study. The flow chart of case screening is shown in Figure 1.

In all, 97 (12.4%) of 780 participants died within 28-day after PICU admission. Based on the primary endpoint (28-day mortality), participants were divided into survival and non-survival groups. A total of 9,142 glucose values were collected, of which 65.9% were from arterial blood gas analysis, 3.4% from venous blood, and 30.7% from capillary blood, and with a median frequency of 11 (IQR: 8.25-14) glucose monitoring per patient. Demographic information, clinical features, and the severity of the disease between the survival and non-survival group are detailed in Table 1.

Table 2 illustrates the comparative differences in glucose metrics between the survival and non-survival groups, and it can be seen that all glucose metrics were significantly lower in the survival group than in the non-survivors ($P < 0.05$ for all).

The areas under the ROC curves were shown in Table 3, which were plotted to evaluate the abilities of glucose metrics and PIM2 score in predicting 28-day PICU mortality. These results show that most measures of variability moderately correlate to PICU 28-day mortality in a statistically significant manner ($AUC > 0.700$, $P < 0.05$). However, MAG ($AUC: 0.762$, $95\%CI: 0.705-0.819$, $P < 0.001$) has the largest areas than other glucose variability indices in the prediction of PICU 28-day mortality. And MAG has significantly better discrimination of PICU 28-day mortality than other metrics ($p < 0.05$). Therefore, we used MAG to represent GV and to explore the impact on adverse outcomes. Additionally, we utilized an optimal cut-off value of 28-day mortality prediction respectively.

We sequentially included the baseline variables in the COX regression model with $P \leq 0.1$ in Table 1, followed by hypoglycemia, and then MAG. The results of the multivariate regression model showed that hypoglycemia was not relevant to 28-day mortality (Table 4, Model 2) after adjusting for significant confounders. However, GV represented by MAG (adjusted HR 2.795, $95\%CI$ 1.687-4.632, $P < 0.001$) was still related to PICU mortality after adjustment for hypoglycemia (Table 4, model 3). And the addition of MAG to the model for hypoglycemia led to further quantitative evolution of the model statistics (AUC : from 0.616 to 0.668, $P < 0.001$; IDI : 0.030, $P = 0.006$; NRI : 0.325, $P = 0.022$). There was no interaction between MAG and hypoglycemia.

We constructed the same model described above by replacing hypoglycemia with hyperglycemia. After adjustment for confounding factors, patients with hyperglycemia experienced increased rates of 28-day mortality (adjusted HR in hyperglycemia: 2.026; $95\%CI$: 1.240-3.310; $P = 0.005$) (Table 5, model 2). Subsequent addition of MAG to the model for hyperglycemia resulted in an early incremental improvement in model statistics (AUC : from 0.651 to

0.681, $P=0.001$; IDI: 0.017, $P=0.044$; NRI: 0.224, $P=0.186$). And after adjusting for MAG (adjusted HR 2.455, 95% CI 1.411-4.270, $P=0.001$), the effect of hyperglycemia (adjusted HR 1.419, 95% CI 0.815-2.471, $P=0.216$) (Table 5, model 3) on the adverse outcome was attenuated and not statistically relevant anymore. In the final model, MAG had a greater prognostic contribution than hyperglycemia (c^2 -df (30): 9.115 and 0.528 for MAG and hyperglycemia, respectively).

However, the interaction between hyperglycemia and MAG was detected with statistical significance ($p=0.016$). We used Cochran's and Mantel-Haenszel's statistics to further explore the relationship between hyperglycemia, MAG, and mortality (Figure 2). Higher mortality in the high GV group than low GV group ($P<0.001$), regardless of the presence of hyperglycemia. Test of Homogeneity of Odds Ratio showed $P=0.022$, so after stratifying by MAG, in the low GV group, hyperglycemia was relevant to PICU mortality (OR=2.910, 95% CI 1.513-5.596, $P=0.001$). While in the high GV group, hyperglycemia did not affect mortality (OR: 0.846, 95% CI:0.363-1.974, $P=0.699$). This means that hyperglycemia patients will have different mortality rates depending on the MAG. In contrast, in the high GV group, hyperglycemia no longer played a role in the occurrence of mortality events. The results supported the possibility that GV may be a stronger predictor of 28-day mortality than hyperglycemia.

Table 6 shows the effect of blood fluctuations on ICU-free day to day 28, mechanical ventilation-free day to day 28, and the incidence of multi-organ dysfunction syndrome. The results showed that the median ICU-free days in the high variability group were lower than that of the lower group (15 (0.0 to 22.9) vs22 (15.1-24.5), $P=0.001$). And the similar results were observed in the ventilator-free days (21.5 (0.0-26.1) vs25.7 (21.0-28.0), $P<0.001$). The incidence of MODs was significantly higher in the high-GV group than in the low-GV group (62.9% vs29.5%, $P<0.001$).

4 Discussion

In our impression, this is the first multicenter prospective study of pediatric dysglycemia (including hypoglycemia, hyperglycemia, and glucose variability) conducted in Southwest China that attempts to establish an association between dysglycemia and 28-day mortality in PICUs. We observed several important relationships. Firstly, GV was independently associated with the unfavorable outcome, and it may play a more predictive role in PICU mortality than hyperglycemia and hypoglycemia. These findings above emphasize the important role of glucose variability in children admitted to PICU. Secondly, MAG may be a dominant index reflecting glucose fluctuations, which considered speed and magnitude of change, and the time series among glucose values.

The strong relationship between increasing GV and poor prognosis has been consistently reported in adult patients (6-10,31). Fewer researches have been done on pediatrics, but similar insights have been obtained. In 2006, Wintergerst KA et al (11) retrospectively observed in 1094 PICU admissions in a single center that increased GV was related to increased hospitalization stay and mortality rates, but ignoring severity of the disease. Hirshberg E and his colleagues (22) performed a retrospective study of 863 nondiabetic PICU children during one year period and found that the incidence of glucose fluctuations (defined by having both hyperglycemia and hypoglycemia) was 6.8%, and glucose fluctuations were still associated with high mortality after adjusting for PRISM score. In another retrospective cohort of 101 critically ill children, researchers found that increased GV accompanied by increased mortality (12). Similarly, Bhutia TD et al (21) prospectively observed 170 critically ill children and found that GV was related to multi-organ dysfunction. Pinchefsky EF et al (32) found that GV also was independently relevant to deterioration in brain function in neonates with encephalopathy. Although these studies involve children in a single clinical setting, they add to the evidence that GV is associated with adverse outcomes. In our series, we further prospectively investigated the relationship between GV and deleterious effects in multicenter, and similar results

were reported in our findings, that GV was associated with mortality, MODs, and ventilator/ICU-free days, which confirmed the strong predictor role of GV in PICU children. This association may be attributed to oscillatory glucose induction that exacerbates oxidative stress, promotes inflammatory responses, and regulates ROS-mediated NF κ B/RAGE activation, resulting in Endothelial cells injury (33-35). Taken together, the above results emphasize the dangerous role of GV in critically ill patients. Management of GV may need to be added to glucose management regimens.

Our data are also complementary to findings from observational studies that evaluated associations between hypo/hyperglycemia and glucose variability during critical illness and mortality. The results of our study suggested that GV may be a more powerful independent risk factor with mortality in PICU patients than hyperglycemia and hypoglycemia. Consistent with our findings, Bagshaw et al (36) found that glucose fluctuation, defined as having both hypoglycemia and hyperglycemia, was relevant to a larger odds ratio of ICU (1.5 vs 1.2 vs 1.0, $P<0.05$) and hospital (1.4 vs 1.2 vs 1.0, $P<0.05$) mortality, compared to hypoglycemia only or neither. And several in vitro or animal experiments (37-39) have demonstrated that oscillating glucose aggravated oxidative stress than persistent hyperglycemia, resulting in accelerating cell injury and apoptosis. Quagliaro et al (37) demonstrated that in umbilical vein cells, the levels of protein kinase C- β were increased in the rapid glucose fluctuation group compared to the sustained hyperglycemia group.

From the perspective of clinical treatment, a single blood glucose value is susceptible to various factors such as medication, diet, and stress status. Therefore, hyperglycemia or hypoglycemia reflected by a single value may not accurately reflect the metabolic status of critically ill patients. On the contrary, GV is calculated by a few glucose values and may reveal dynamic glucose changes. Maybe it's one of the explanations that glucose fluctuation may be a stronger predictor of mortality than hyperglycemia and hypoglycemia to some extent. It is therefore recommended that GV should be included as an important predictor in future studies of prognostic models in critically ill patients and clinicians should pay more attention to dynamic fluctuations than single glucose value.

Different from the previous study, which only took a single index that defined the GV, our study selected four indicators (SD, GLI, MAG, and ACACP). And the results showed most GV indicators had a moderate predicted value for the mortality of PICU children ($AUC>0.7$, $P<0.05$). Among the four indices, MAG obtained the largest AUC and was found to be a better reflection of GV than SD. Hermanides's study (16) illustrated that the glucose profile demonstrated different MAG even in the presence of the same SD value, and MAG was superior to SD in the terms of predicting mortality. Variability should be considered the Speed and magnitude of change, and the time interval between glucose measurements, MAG did, but SD did not. Our retrospective study (17) found that GLI, a variability indicator that also takes arrangement of estimations and time into consideration, had a better predictive power for PICU mortality compared to SD, CV, and MAGE ($AUC: 0.626$ vs $0.601, 0.599, 0.573$). Combined previous studies (7,15) and our results, we should choose the GV index which considered the range, speed, time series, MAG, or GLI may be a good choice. Given the clinical practicality, we have introduced ACACP as a GV indicator and it is simple to transfer into a treatment protocol (24). Because this index focused on the comparison of changes between subsequent blood glucose values. Although the AUC of ACACP was smaller than MAG in our data set, its unique calculation and clinical significance suggest that GV metrics should reflect the change from one value to the next and guide clinical management to minimize this change, thereby facilitating glycemic management and improving prognosis in clinical practice. Finding indicators that contain information such as time series, rate, and range of change, and are convenient for clinical application is a potential, practical target for future treatment.

The multicenter, prospective design is a major strength of this study, particularly the choice to assess four GV indices in a large cohort of unselected PICU children and to explore their relationship with adverse outcomes. The results have stronger applicability than those of single-center studies. In addition, GV in the early stages may reflect a physiological stress response; and as treatment duration increases, it may be influenced by many factors related to treatment, including nutritional intake and drug usage (40). In the present study, GV metrics' calculations included the first 72 hours of glucose values and excluded children using glucocorticoids or total parenteral nutrition, reducing the impact of medical management. Thus, GV in our study may provide a prior prediction of mortality.

Our study does have its limitations. First, there may be ascertainment bias as patients with abnormal blood glucose levels may have more frequent measurements, whereas patients with normal blood glucose do not measure as frequently. As a result, we may miss the record of hyperglycemia or hypoglycemia in some patients. Ideally, continuous glucose monitoring should be performed at predetermined time points; however, this will increase the amount of blood sampled and suffering from young children. Advances in CGM technology will facilitate the management or monitoring of early GV in critically ill children. We suggest that future studies exploring optimal glycemic control strategies for patients with high GV should make full use of CGM techniques. Secondly, our glucose measurements were obtained from different blood specimens, the homogeneity can't be ensured. Finally, our study cannot conclude causality because the results of observational studies can only assume an association.

5 Conclusion

Our results endorse and expand on previous literature findings by showing that fluctuation in blood glucose control affects clinical prognosis negatively in PICU children, and GV may be more strongly associated with mortality outcomes, compared to hypoglycemia and hyperglycemia. Clinicians in the PICUs should pay more attention to glucose variability. MAG may be the dominant indicator of glucose variability which contains information on the speed and magnitude of blood glucose changes. These results emphasize the importance of monitoring GV in PICU children, such as the usage of the CGM system. Exploring the mechanisms of GV and optimizing personal glycemic management in PICU is the focus of future research to minimize the potential risk of healthcare-acquired events.

Abbreviations

ACACP: Average consecutive absolute change percentage; Adm: Blood glucose concentration at admission; AUC: Area under the curve; BAZ: Body mass index for age Z score; BMI: Body mass index; CPR: Cardiopulmonary resuscitation; CRRT: Continuous renal replacement therapy; GIR: Glucose infusion rate; GLI: Glycemic lability index; HR: Hazard Ratio; MAG: Mean absolute glucose; Mean: Average blood glucose; MODS: Multiorgan dysfunction; MV: Mechanical ventilation; PICU: Pediatric intensive care unit; ROC: The receiver operating characteristic; SD: Standard deviation; TGC: Tight glycemic control; PIM2: Pediatric index of mortality score II; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; +PV: Positive predictive value; -PV: Negative predictive value.

Declarations

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Author Contributions

JL: study design and project management, supervision; MLD and WJL: conceptualization and design of forms, data management and quality control, writing and editing; JL, BH, YBZ, GYZ, JYJ, and HMF: project implementation organization and management, data quality control; MLD and YTL: statistical analysis and documentation; MLD, WJL, FYL, JC, LD, DXX and KY: recruitment of participants and documentation of data. All authors contributed to this article and approved the submitted version.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

The study protocol was approved by the ethical committee of Children's Hospital of Chongqing Medical University (File No. 2019,37) and the clinical trial registration was completed (ChiCTR2000030846).

Consent for publication

Not applicable.

Conflict of Interest

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tables

Table 1

The comparison of baseline variables between survivors and non-survivors[M(P25-P75) n(%)]

	All(n=780)	Survivors(n=683)	Non-survivors(n=97)	χ^2/Z	P value
Age group/n (%)					
<3ys	542(69.5)	483(70.7)	59(60.8)		
3ys to <16ys	238(30.5)	200(29.3)	38(39.2)	3.920	0.059
Male/n (%)	464(59.5)	404(59.2)	60(61.9)	0.258	0.659
Medical/n (%)	600(76.9)	522(76.4)	78(80.4)	0.760	0.441
BMZ/ n (%)					
<-2	173(22.2)	149(21.8)	24(24.7)		
-2~2	551(70.6)	481(70.4)	70(72.2)		
>2	56(7.2)	53(7.8)	3(3.1)	2.941	0.232
MV/ n (%)	588(75.4)	495(72.5)	93(95.9)	25.068	<0.001
CRRT/ n (%)	51(6.5)	29(4.2)	22(22.7)	47.233	<0.001
CPR/ n (%)	26(3.3)	11(1.6)	15(15.5)	-	<0.001
Vasoactive drug/n (%)	182(23.3)	126(18.4)	56(57.7)	73.273	<0.001
Insulin/ n (%)	27(3.5)	10(1.5)	17(17.5)	-	<0.001
GIR	0.7(0.4,1.2)	0.6(0.3,1.1)	1.0(0.5,1.7)	-4.793	<0.001
PIM2 score	-2.6(-3.3, -1.9)	-2.6(-3.5, -2.1)	-1.4(-2.6, 1.9)	-7.240	<0.001

Table 2

The comparison of glucose metrics between survivors and non-survivors[M(P25-P75) n(%)]

Metrics	All(n=780)	Survivors (n=683)	Non-survivors (n=97)	χ^2/Z	P value
Adm	5.9(5.1,7.2)	5.8(5.0,7.1)	6.6(5.2,9.6)	-3.094	0.002
Mean	5.8(5.4,6.4)	5.8(5.4,6.3)	6.2(5.3,7.9)	-2.878	0.004
Hyperglycemia/n (%)	289(37.1)	224(32.8)	65(67.0)	42.630	<0.001
Hypoglycemia/n (%)	155(19.9)	119(17.4)	36(37.1)	20.681	<0.001
SD	1.0(0.7,1.5)	0.9(0.7,1.4)	1.6(1.1,3.0)	-7.279	<0.001
GLI	1.6(0.6,4.4)	1.4(0.6,3.6)	6.1(1.7,43.6)	-7.316	<0.001
MAG	0.2(0.1,0.3)	0.1(0.1,0.2)	0.3(0.2,0.8)	-8.360	<0.001
ACACP (%)	16.9(12.8,23.0)	16.5(12.5,22.2)	22.3(16.4,32.6)	-5.788	<0.001

Table 3

Receiver operating characteristic curves for mortality on critically ill children

	AUC (95%CI)	Cutoff value (sensitivity/specificity, %)	P	+LR	-LR	+PV	-PV
Adm	0.597(0.530,0.664)	6.70(48.45, 71.89)	0.002	1.72	0.72	19.7	90.8
PIM2	0.727(0.668,0.786)	-1.88(56.70,81.55)	<0.001	3.07	0.53	30.4	93.0
Mean	0.590(0.518,0.662)	7.03(32.99,90.48)	0.004	3.47	0.74	33.0	90.5
SD	0.728(0.671,0.785)	1.11(75.26,62.23)	<0.001	1.99	0.40	22.1	94.7
GLI	0.729(0.670,0.789)	4.37(57.73,79.65)	<0.001	2.84	0.53	28.7	93.0
MAG	0.762(0.705,0.819)	0.27(59.79,82.58)	<0.001	3.43	0.49	32.8	93.5
ACACP	0.681(0.621,0.742)	24.20(47.42,81.55)	<0.001	2.57	0.64	26.7	91.6

Table 4

Multivariable COX regression: associations of hypoglycemia and MAG With 28-day mortality

Sequential Models for 28-day Mortality	Main Variables	HR (95%CI)	<i>P</i> <i>value</i>	Model Statistics		
				Likelihood Ratio	<i>p</i> ‡ <i>value</i>	AUC (95%CI)
Multivariable model 1:	Mean	1.049	0.443	290.04	-	0.607
		(0.928,1.187)				(0.541,0.674)
Multivariable model 2: model1+hypoglycemia	Mean	1.065	0.313	296.739	0.168	0.616
		(0.942,1.205)				(0.552,0.681)
	Hypoglycemia	1.415	0.162			
		(0.870,2.300)				
Multivariable model3: model2+MAG	Mean	0.974	0.689	304.543	<0.001	0.668
		(0.853,1.112)				(0.608,0.729)
	Hypoglycemia	1.195	0.472			
		(0.735,1.942)				
	MAG	2.795	<0.001			
		(1.687,4.632)				

Note: Model 1: adjusted for confounders with a significance level of P£0.10 from Table1, including PIM2 score, Mean, and so on. Model 2: adjusted for factors as in model 1, and hypoglycemia. Model 3: adjusted for factors as in model 2, and MAG. ‡For likelihood ratio test between sequential models; the P-value is for comparison of the multivariable model to the previous model.

Table 5

Multivariable COX regression: associations of hyperglycemia and MAG With 28-day mortality

Sequential Models for 28-day mortality	Main Variables	HR (95%CI)	<i>P</i> <i>value</i>	Model Statistics		
				Likelihood Ratio Chi-Square	<i>P</i> ‡ <i>value</i>	AUC
Multivariable model 1:	Mean	1.049 (0.928,1.187)	0.443	290.04	-	0.607 (0.541,0.674)
Multivariable model 2: model1+hyperglycemia	Mean	0.980 (0.860,1.117)	0.765	290.155	0.005	0.651 (0.590,0.712)
	hyperglycemia	2.026 (1.240,3.310)	0.005			
Multivariable model 3: model2+MAG	Mean	0.942 (0.824,1.075)	0.385	303.479	0.001	0.681 (0.622,0.739)
	hyperglycemia	1.419 (0.815,2.471)	0.216			
	MAG	2.455 (1.411,4.270)	0.001			

Note Model 1: adjusted for confounders with a significance level of $P \leq 0.10$ from Table1, including PIM2 score, Mean, and so on. Model 2: adjusted for factors as in model 1, and hyperglycemia. Model 3: adjusted for factors as in model 2, and MAG. ‡For likelihood ratio test between sequential models; the P-value is for comparison of the multivariable model to the previous model.

Table 6

Effect of Glucose variability on 28-day ICU-free days, 28-day ventilator-free days, and multiorgan dysfunction syndrome [M(IQR)/n (%)]

	MAG $\geq$ mmol/l		<i>P</i> value
	<0.27	≥ 0.27	
28-day ICU-free days	22.0(15.1,24.5)	15(0.0,22.9)	0.001
28-day ventilator-free days	25.7(21.0,28.0)	21.5(0.0,26.1)	<0.001
Multiorgan dysfunction syndrome	176(29.1)	110(62.9)	<0.001

Note: adjusted for factors with a significance level of $P \leq 0.10$ from Table1.

Figures

Figure 1

Flowchart Illustrating the Inclusion and Exclusion of Participants for the Study

Figure 2

Mortality for hyperglycemia and glucose variability

Supplementary Files

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