Effect of Glycemic Gap upon Mortality in Critically Ill Patients with Diabetes

Ran Lou1, Li Jiang1,* and Bo Zhu2

1Department of Critical Care Medicine, Xuanwu Hospital Capital Medical University. 45Changchun Street, Xicheng District, Beijing 100053, China. 2Department of Critical Care Medicine, Fu Xing Hospital, Capital Medical University. 20A Fuxingmenwai Street, Xicheng District, Beijing 100038, China.

*Correspondence: Li Jiang, Email: jianglipaper@sina.com

Abstract

Objectives: Hyperglycemia, hypoglycemia and blood glucose fluctuation are associated with the outcomes in critically ill patients, but target of blood glucose control is debatable especially in patients with diabetes regarding to the situation of blood glucose control before admission to ICU. This study is aimed to investigate the association between glycemic gap which is calculated as the mean blood glucose level during the first 7 days after admission to ICU minus the A1C-derived average glucose and outcomes of critically ill patients with diabetes.

Method: This study undertaken in two intensive care units (ICUs) with a total of 30 beds. Patients with diabetes expected to stay for more than 24hrs were enrolled, HbA1c was tested within 3 days after admission.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/JDI.13606

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and converted to the A1C-derived average glucose (ADAG) by the equation: ADAG = \[ \frac{ ( \text{HbA1c} \times 28.7 ) - 46.7 }{\sqrt{18}} \], arterial blood glucose measurements were fourth per day routinely during the first 7 days after admission, APACHE II score within first 24 hours, the mean blood glucose level (MGL), standard deviation (SD), and coefficient of variation (CV) during first 7 days were calculated for each person, \( \text{GAP}_{\text{adm}} \) and \( \text{GAP}_{\text{mean}} \) were calculated as admission blood glucose and MGL minus ADAG respectively, the incidence of moderate hypoglycemia (MH) and severe hypoglycemia (SH), total dosage of glucocorticoids and average daily dosage of insulin within 7 days, duration of renal replacement therapy (RRT), ventilator-free hours, and non-ICU stay days within 28 days were also collected. Patients enrolled were divided into survival group and nonsurvival group according to survival or not at 28-day and 1-year after admission, exploration of the relationship between parameters derived from blood glucose and mortality in critically ill patients enrolled were undergone.

**Results:** 502 patients were enrolled and divided into survival group (n=310) and nonsurvival group (n=192). It was shown that two groups had comparable level of HbA1c, the nonsurvivors had greater APACHE II, MGL, SD, CV, \( \text{GAP}_{\text{adm}} \), \( \text{GAP}_{\text{mean}} \), and higher hypoglycemia incidences. Less duration of ventilator-free, non-ICU stay, and longer duration of RRT were recorded in nonsurvival group, of whom received less carbohydrate intake, higher insulin daily dosage, and glucocorticoid dosage. \( \text{GAP}_{\text{mean}} \) had the greatest predictive power with AUC of 0.820 (95%CI: 0.781-0.850), the cut-off value was 3.60 mmol/L (sensitivity 78.2% and specificity 77.3%). Patients with low \( \text{GAP}_{\text{mean}} \) tended to survive longer than the high \( \text{GAP}_{\text{mean}} \) group 1 year after admission.

**Conclusion:** Glycemic GAP between the mean level of blood glucose within first 7 days after admission to ICU and A1C-derived average glucose was independently associated with 28-day mortality of critically ill patients with diabetes, the predictive power extended to 1 year. The incidence of hypoglycemia was associated with mortality either.

**Key words:** Glycemic gap; Critically ill patients; Diabetes; Hyperglycemia; Hypoglycemia; Variability of blood glucose; Glycosylated hemoglobin

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Background

Metabolism disturbance is commonplace in critically ill patients, hyperglycemia, and hypoglycemia are proved to be risk factors for adverse outcomes in the populations of acutely ill patients\textsuperscript{[1][2][3]}. Nevertheless, Paul E Marik suggests that hyperglycemia and insulin resistance might be preserved adaptive responsiveness and beneficial to patients suffered acute diseases\textsuperscript{[4][5]}. The association between occurrence of hypoglycemia and poor outcome is repeatedly presented\textsuperscript{[6]}, however, whether hypoglycemia including iatrogenic episode of hypoglycemia is by itself harmful or not remains unclear, especially corrected for baseline risk factors and duration of ICU stay\textsuperscript{[7]}. Besides, glycemic fluctuation might be much more harmful than both hyperglycemia and hypoglycemia\textsuperscript{[8][9]}, variability of blood glucose as the most used index is confirmed associated with mortality of critically ill patients in researches\textsuperscript{[10]}, which is controversial in some studies yet\textsuperscript{[11]}, because this association is more commonly proven in the non-DM cohort but not in the DM\textsuperscript{[12]}, so as the hyperglycamia\textsuperscript{[13]}

Acute hyperglycemia in patients with diabetes could result from acute physiological stress, a high baseline blood glucose, or both. Glycosylated hemoglobin (HbA1c) is applied to represent the premorbid glycaemia in the 3 months prior to intensive care unit(ICU) admission\textsuperscript{[14]} and is widely used to judge the adequacy of diabetes treatment and adjust therapy\textsuperscript{[15]}. Furthermore, the glycemic gap, difference between admission blood glucose and A1C-derived average glucose (ADAG) levels, which has been used to evaluate the disease severity, predict the outcomes and explore the relationship between stress induced hyperglycemia (SIH) and mortality in critically ill patients with diabetes. It is confirmed that glycemic gap can depress the impact of chronic hyperglycemia on the disease severity assessment in patients with diabetes and optimally improve the value of the assessment consequently\textsuperscript{[16]}

However, we found the top level of blood glucose occurred within first 7 days mostly in preliminary
experiment, which means the level of admission blood glucose could not reflect the severity of diseases and SIH precisely. The objective of this study is in order to identify whether GAP\textsubscript{mean} defined as difference which is between the mean blood glucose level within the first 7 days after admission to ICU and ADAG is independently associated with mortality of critically ill patients with diabetes or not and to evaluate the predictive power on outcomes comparing with GAP\textsubscript{adm}, the difference between the admission blood glucose and ADAG.

**Methods**

**Study Design and Setting**

We conducted a prospective observational cohort study of consecutive patients with type 2 diabetes admitted to general ICU between June 1, 2017 and May 31, 2020 in two general ICUs of two tertiary hospitals in Beijing with a total of 30 beds. The institutional review board for human investigation approved this study and waived the need for informed consent. The protocol was elaborately formulated by director, elaborately performed by all the staffs and closely supervised by a group of intensivists who were charged with this study.

**Cohort and Data Collection**

Adult patients admitted to our ICU during the 3-year period of the study, of those with diagnosis of type 2 diabetes (in accordance with 1999 WHO diagnostic criteria for type 2 diabetes) estimated to stay over 24 hours without oral feeding were enrolled regardless of whether insulin or oral antidiabetic agents were prescribed previously. Patients were excluded based on the following criteria: 1) an admission diagnosis of diabetic ketoacidosis or hyperosmolar hyperglycemic state, 2) treatment with corticosteroids or admitted to ICU within 3 months before admission, 3) patients or their representatives signed informed consent of withdrawing life-sustaining treatment within 28 days after the admission, 4) the level of HbA1c was not obtained and the number of blood glucose value obtained was no more than 3 during the period of study, 5) ICU stay was no more than 24 hours.
The medical records of enrolled patients were reviewed for the following data: age, sex, body mass index (BMI), whether received regular insulin therapy before admission, primary disorders, underlying comorbidities, APACHE II score within first 24 hours after admission, laboratory data including arterial blood glucose level during the first 7 days, and HbA1c levels measured within 24 hours after admission. Average daily amount of carbohydrate intake, average daily dosage of insulin (Novolin R) and total dosage of glucocorticoid (converted into dosage of Methylprednisolone) for the first 7 days were obtained.

Outcome indicators including duration of ventilator free hours, renal replacement therapy (RRT) and non-ICU length of stay during 28 days, survived or not at 28-day and 1-year and survival time after admission were recorded. Survival or not at 28-day was the primary endpoint, which was the criteria for patients were separated into different groups.

Data of Blood Glucose Level, HbA1c Value and Glycemic Gap

We tested arterial blood glucose level at least every 6 hours during first 7 days after admission to ICU for each patient using a blood-gas analyzer (GEM PRIMIER3000) equipped with current method. HbA1c in venous blood was detected within the first 24 hours by high-performance liquid chromatography.

Parameters including mean blood glucose level (MGL), standard deviation (SD), and coefficient of variation (CV) which was divided MGL by SD during first 7 days after admission were calculated based on measurements of blood glucose level for each patient. The incidence of moderate hypoglycemia (MH) defined as blood glucose level at range of 2.2-3.3mmol/L and severe hypoglycemia (SH) defined as blood glucose level lower than 2.2mmol/L were documented.

HbA1c levels were converted into A1C-derived average glucose (ADAG) to represent chronic average blood
glucose levels within 3 months before admission to ICU using the following equation: A1C-derived average glucose (ADAG) = [(HbA1c * 28.7) – 46.7] * 18^{-1[17]}. GAP_{adm} was calculated as admission blood glucose minus ADAG as follows: GAP_{adm} = [admission BG – ADAG], GAP_{mean} was calculated as MGL minus ADAG as follows GAP_{mean} = [MGL – ADAG].

Statistical Analysis
Consecutive data with normally distribution are expressed as mean± standard deviation and represented by quartiles in non-normally distributed data, categorical data are expressed as frequencies (percentage). Analyses were performed by the 2-tailed Student t test and the Chi-square test or Fisher exact test. The factors associated with mortality at 28-day were analyzed using binary logistic regression and receiver operating characteristic (ROC) curves were plotted to analyze the discernibility of the predictive parameters, the area under the ROC curve (AUC) and 95% confidence internal (CI) was calculated simultaneously to identify the relationship between the glycemic gap and 28-day mortality. Youden’s index was applied to ascertain the preponderant value of glycemic gap as an independently predictive factor of 28-day mortality. Survival analysis was shown as Kaplan-Meier survielve curve. Data analyzed using SPSS statistics, Version 24.0. Graphs were built using Medcalc, Version 19.6.1 and GraphPad Prism, Version 8.0. P value of <0.05 was considered statistically significant.

Results
Study Population and Baseline Characteristics
1867 patients were admitted to the two general ICUs during study period, 502 patients were enrolled, of which 192 (38.25%) died at 28-day after inclusion, based on which we separated patients into two groups, survival and nonsurvival (Figure 1). Blood glucose samples with number of 14552 in total and 28.99 per capita were collected. Nonsurvivors tended to be older and had higher APACHE II score comparing with survivors. The proportion of patients undergoing surgery in nonsurvivors was lower than that of survivors. There was no
statistically significant in sex, BMI, insulin therapy before admission between two groups. Nonsurvivors had higher rates of sepsis and postoperative care as main reason for admission and accompanied by cardiac and vascular disease and chronic renal disease (Table 1).

### Relevant Data of Blood Glucose Level

There were no significant differences in HbA1c value and ADAG between two groups, greater level of BG at admission, MGL, SD, and CV were found in nonsurvivors, the incidence of MH and SH were more common among nonsurvivors who had higher GAP\textsubscript{adm} and GAP\textsubscript{mean} (P < 0.05, Table 2).

Patients with different level of HbA1c—whether higher than 6.5mmol/L or not—were regarded as under different blood glucose control. Patients were divided into 4 groups with interquartile ranges of MGL, the distribution of GAP\textsubscript{mean} moved to higher level in nonsurvivors regardless of the level of HbA1c or ADAG (Figure 2.).

### Therapy and Outcome Data

Nonsurvivors received lower daily intake of carbohydrate and higher daily dosage of insulin (Novolin R) and accumulated dosage of glucocorticoid (converted into dosage of Methylprednisolone) during the first 7 days of admission.

Outcome indicators including ventilator-free hours and non-ICU stay days during 28 days were longer and duration of renal replacement therapy (RRT) shorter among survivors (P < 0.05, Table 3).

### Relative factors and predictors of 28-day Mortality

Variables related to the primary outcome were screened out during single factor analysis and binary logistic
regression analysis revealed the correlation between the indexes of age, APACHE II score, MH, SH, and GAP\textsubscript{mean} and mortality at 28-day (Table 4). Data showed consistent trend of MH and SH, the two indexes were combined to generate the index: \(MH/SH\); and the OR value was higher than other factors which meant the incidences of MH or SH doubled the risk of death.

The AUC of APACHE II, GAP\textsubscript{adm}, and GAP\textsubscript{mean} within first 7 days to predict the mortality of 28-day were plotted, AUC of GAP\textsubscript{mean} was the highest, which reflected the greater predictive power. The optimal cut-off value of GAP\textsubscript{mean} to predict 28-day mortality was 3.6mmol/L (sorted by Youden index), which provided a sensitivity and specificity of 78.2% and 77.3%. APACHE II incorporated with GAP\textsubscript{adm} were performed as well, of which AUC was not improved remarkably (Figure 3.).

**Survival Analysis**

The Kaplan-Meier survival curve shows that patients with GAP\textsubscript{mean} higher than 3.6mmol/L was associated with significantly shorter survival than patients with lower GAP\textsubscript{mean}, and the level of HbA1c does not make any difference to the survival at 1 year after admission (Figure 4.).

**Discussion**

Dysglycemia commonly happens in critically ill patients with and without a history of diabetes, hyperglycemia is one of the common manifestations, patients with the degree of hyperglycemia being associated with progressively worse outcome\cite{18}. We actually found that mean glucose level in nonsurvivors was higher than that in survivors, which was not an independent predictor for 28-day mortality. Some researchers have the opinion that whether a raised blood glucose concentration is independently associated with a poor prognosis or may indicate a more severe illness with an increased response to stress is disputable\cite{19}. These findings indicate that the absolute hyperglycemia is not directly associated with the mortality of critically ill patients with diabetes. Evidences showed the fact that hyperglycemia of critically ill patients could not totally attribute to
Researchers have concluded that admission hyperglycemia result from a combination of acute physiological stress or higher baseline blood glucose. SIH is presenting secondary to elevated level of counter-regulatory hormones (cortisol, catecholamines, glucagon, and growth hormone) and impaired response, which results in increased gluconeogenesis and decreased glycogenolysis. Moritoki et al. reported that in patients with critical illness-associated hyperglycemia (CIAH) and adequately controlled diabetes, acute hyperglycemia is associated with increased mortality, whereas in patients with insufficiently controlled diabetes it is not. Critically ill patients with elevated level of HbA1c seem to better tolerate hyperglycemia and large glucose fluctuations during compared with patients with normal level of HbA1c. Therefore, quantification of the level of chronic glycemia in the critically ill patients is helpful to confirm the severity of critical illness-associated dysglycemia. The level of HbA1c represents premorbid chronic hyperglycemia before the admission and is not affected by stress or fasting status, it is inconsiderable within-day and day-to-day variations. HbA1c thus can be regarded as a parameter for distinguishing SIH and diabetic hyperglycemia, further evidences show the difference between blood glucose level at admission and ADAG was associated with adverse outcomes.

Farid Fawzy believed that the elevated glycemic gap between admission blood glucose and previous glycemic level was associated with an increased ICU mortality, and the predictive power for the mortality of critically ill patients was improved effectively with APACHE II score incorporated. Meanwhile, stress hyperglycemia ratio, that is, fasting glucose concentration at admission divided by the ADAG was confirmed by Andrea Fabbri et al. was predictive of mortality following admission for sepsis, and may be used to refine prediction of an unfavorable outcome. Nevertheless, this study had witnessed the unparalleled predictive power of GAP_mean on 28-day mortality in the critically ill patients with diabetes comparing with other parameters, GAP_adm with smaller AUC than previous studies, despite improvement attributed to incorporation of APACHE II, the AUC was lower than 0.70 yet. The reasons might refer to diverse reactivities among individuals, severity and progression of the diseases, single point of blood glucose value could not reflect the
reality and variation of the diseases veritably and timely with numerous impacted factors and unforeseen circumstances, whereas the mean level of blood glucose during several days after admission to ICU might provide more comprehensive clinical information. This difference between the mean level of blood glucose after admission to ICU and level of chronic glycemia demonstrates the situation of the patients virtually, and sequentially shows the prominent predictive power for mortality of the critically ill patients enrolled, which persists till a year later.

Hypoglycemia is proved an independent predictor for mortality of critically ill patients with diabetes in this study, which is consistent with previous studies, and we do not find correlation with the amount of carbohydrate intake and dosage of insulin and glucocorticoid. Patients with diabetes tend to be tolerant of prolonged hyperglycemia and might be adaptive to wider and individualized range of blood glucose. In critically ill patients, chronic pre-morbid hyperglycemia increases the risk of hypoglycemia and modifies the association between acute hypoglycemia and mortality, the association between hypoglycemia and outcome is confounded by severity of illness, with sicker patients being more prone to spontaneous hypoglycemia, patients with poorly controlled diabetes as expressed by a high HbA1c level, appear more vulnerable to hypoglycemia, tight glucose control makes it worse with the use of insulin-providing medications. Hypoglycemia is confirmed repeatedly associated with ICU mortality regardless of whether the patients are diagnosed of diabetes, which may result in drastic fluctuation of blood glucose and induce more serious cellular impairment. That might be the reason why studies fail to replicate the benefit of tight glycemic control on ICU mortality. The conclusion above impels us to implement more rational and effective protocol to monitor and control the level of blood glucose to avoid or balance the two extremes which are uncontrolled hyperglycemia and over tightly controlled glucose. Therefore, hypoglycemia may indicate the severity of acute illnesses and it seems prudent to prevent longlasting hypoglycemia as much as possible by frequent and accurate blood glucose measurements and by use of a proper insulin protocol with safe and rational blood glucose range.
Limitations

There are limitations in the study. First, this is a study conducted in two general ICUs with a limited number of samples, the patients enrolled are admitted for medical diseases more than surgical diseases, thus selection bias may exist. Second, there remains controversy about strategy of controlling and target range of blood glucose. Insulin was administered through intravenous way continuously or subcutaneous way intermittently to achieve the target blood glucose level ranged from 8.0mmol/L to 10.0mmol/L, which might not be appropriate for the cohort. It is approved that long lasting hypoglycemia is associated with short term mortality in critically ill patients\cite{40}, but we do not assess the duration of hypoglycemia. Third, we did not exclusively analyze the impact on blood glucose the type of nutritional support or medication such as catecholamine, diuretic or antibiotics may have, level of lactic acid was not documented neither. Fourth, there is no consensus has been reached to point out the foremost tool for identifying the severity of critically ill patients\cite{41}. More studies are required to evaluate various scoring tools for predicting mortality in ICU, such as the sequential organ failure assessment (SOFA). Finaly, the detection method of HbA1c is not uniform in our country, which is the reason that HbA1c cannot be used as a diagnostic criterion and compared between different hospitals at present. It is necessary to standardize the testing method for HbA1c and carry out multi-center studies to increase sample size and balance the process of monitoring and controlling the level of blood glucose in the future, subgroup analysis of the effects of related medication and classifications of adverse outcome may be needed either.

Conclusions

In this study, an elevated glycemic gap between the mean blood glucose level in the first 7 days after admission to ICU and A1C-derived average glucose (ADAG) was independently associated with 28-day mortality in critically ill patients with diabetes, the predictive power on mortality was superior to $\text{GAP}_{\text{adm}}$ (the difference between the value of blood glucose at admission and ADAG) even incorporated with APACHE II score,
patients with lower GAP\textsubscript{mean} survived longer than patients with higher GAP\textsubscript{mean} 1 year after admission. Hypoglycemia is also an independent predictor for the mortality of critically ill patients with diabetes.

**Disclosure statement**

We declare there is no conflict of interest.

This research was approved by Fu Xing Hospital, Capital Medical University IRB with the approval notice number 2015FXHEC-KY012 on May 10, 2017.

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Figure 1. Flow chart of the study

Legend: 1867 patients were admitted to the two general ICUs during study period, 918 patients were diagnosed with diabetes, 276 patients were excluded, 502 patients were enrolled, of which 310 (61.75%) survived and 192 (38.25%) died at 28-day.
Figure 2. Frequency of GAP\textsubscript{mean} in survivors and nonsurvivors based on MGL categories
Legend: Patients were divided into 4 groups with interquartile ranges of MGL, the distribution of GAP\textsubscript{mean} moved to higher level in nonsurvivors regardless of the level of HbA\textsubscript{1c} or ADAG.

Figure 3. ROC curves for GAP and APACHE II score for predicting 28-day mortality
Legend: The AUC of GAP\textsubscript{mean} was the highest among that of other predictors for 28-day death. APACHE II incorporated with GAP\textsubscript{adm} were performed as well, of which AUC was not improved remarkably.

Figure 4. Kaplan-Meier survival curve of HbA\textsubscript{1c} and GAP\textsubscript{mean} at 1-year
Legend: The Kaplan-Meier survival curve shows that patients with GAP\textsubscript{mean} higher than 3.6mmol/L was associated with significantly shorter survival than patients with lower GAP\textsubscript{mean} at 1 year after admission, which is regardless of the level of HbA\textsubscript{1c}.

Table 1. Baseline Characteristics of the Diabetic ICU Survivors and Non-survivors

|                        | Survivors (n=310) | Nonsurvivors (n=192) | All Patients (n=502) | P-Value |
|------------------------|-------------------|----------------------|----------------------|---------|
| Sex (male),n (%)        | 184(59.4)         | 101(52.6)            | 285(56.8)            | 0.140   |
| Age (y)                | 79(68, 85)        | 83(77, 86.8)         | 81(71.8, 85.3)       | \( \geq 0.001^* \) |
| BMI (Kg/m\textsuperscript{2}) | 24.2(21.7, 26.1) | 23.9(21.5, 26.1)     | 24.2 (21.6, 26.1)    | 0.245   |
| APACHE II score        | 19(14, 24)        | 25.4±8.7             | 21(15, 27)           | \( \geq 0.001^* \) |
| Surgical patients, n(%)| 43(13.9)          | 15(7.8)              | 58(11.6)             | 0.044*  |
| Insulin therapy before ICU, n(%) | 133(42.9) | 86(44.8)             | 219(43.6)            | 0.711   |
| Reasons for ICU admission, n(%) |                   |                      |                      |         |
| Sepsis                 | 74(23.9)          | 83(43.2)             | 157(31.3)            | \( \geq 0.001^* \) |
| Thoracic or respiratory disease | 97(31.3)         | 45(23.4)             | 142(28.3)            | 0.066   |
| Cardiac and vascular disease | 59(19.0)         | 42(21.9)             | 101(20.1)            | 0.492   |
| Neurologic disease     | 20(6.5)           | 5(2.6)               | 25(6.5)              | 0.059   |
| Renal dysfunction      | 19(6.1)           | 8(4.2)               | 27(5.4)              | 0.418   |
| Patient comorbidities                        | Survivors (n=310) | Non-survivors (n=192) | All Patients (n=502) | P-Value |
|---------------------------------------------|-------------------|-----------------------|----------------------|---------|
| Gastrointestinal disease                    | 19(6.1)           | 6(3.1)                | 25(5.0)              | 0.146   |
| Postoperative care                          | 14(4.5)           | 2(1.0)                | 16(3.2)              | 0.036*  |
| Other                                       | 8(2.6)            | 1(0.5)                | 9(1.8)               | 0.163   |
| Respiratory disease                         | 63(20.3)          | 47(24.5)              | 110(21.9)            | 0.318   |
| Cardiac and vascular disease                | 272(87.7)         | 167(95.3)             | 390(90.6)            | 0.004*  |
| Cerebrovascular disease                     | 205(66.1)         | 113(58.9)             | 318(63.3)            | 0.106   |
| Chronic renal disease                       | 113(36.5)         | 91(47.4)              | 178(40.6)            | 0.019*  |
| Gastrointestinal disease                    | 20(6.5)           | 16(8.3)               | 36(7.2)              | 0.478   |
| Malignancy                                  | 64(20.6)          | 31(16.1)              | 95(18.9)             | 0.241   |

APACHE II scores: Acute Physiology and Chronic Health Evaluation II score

*P < 0.05

| Table 2. Relevant Data of Plasma Glucose Levels and GAP |
|--------------------------------------------------------|
| Survivors (n=310) | Nonsurvivors (n=192) | All Patients (n=502) | P-Value |
|-------------------|----------------------|----------------------|---------|
| **BG at admission (mmol/L)** | 10.2(7.7, 13.8) | 11.9(9.0, 15.0) | 10.8(8.2, 14.3) | 0.002* |
| **MGL (mmol/L)**   | 10.5 ± 3.1           | 12.7 ± 2.4           | 11.6(9.4, 13.3)    | √ 0.001* |
| **SD (mmol/L)**    | 2.6(1.9, 3.5)        | 3.9 ± 1.5            | 2.9(2.1, 4.1)      | √ 0.001* |
| **CV (%)**         | 25.7(20.3, 33.3)     | 30.7 ± 10.4          | 27.6(21.2, 34.9)   | √ 0.001* |
| **HbA1c (mmol/L)** | 6.9(6.1, 7.9)        | 7.0(6.2, 7.8)        | 6.9(6.2, 7.9)      | 0.763   |
| **ADAG (mmol/L)**  | 8.4(7.1, 10.0)       | 8.6(7.3, 9.8)        | 8.4(7.3, 10.0)     | 0.784   |
| **GAP<sub>adm</sub> (mmol/L)** | 1.8(-0.6, 4.4) | 3.3(0.9, 6.3)       | 2.3(-0.2, 5.3)     | √ 0.001* |
| **GAP<sub>mean</sub> (mmol/L)** | 2.4(-0.1, 3.5) | 4.2(3.7, 5.0)       | 3.3(1.2, 4.2)      | √ 0.001* |
MH, n(%)  14(4.5)  45(23.4)  59(11.8)  √ 0.001*
SH, n(%)  4(1.3)  21(10.9)  25(5.0)  √ 0.001*

BG: blood glucose, MGL: mean glucose level, ADAG: A1C-derived average glucose, GAP_{adm}: glycemic gap between blood glucose at admission and ADAG, GAP_{mean}: glycemic gap between MGL and ADAG, MH: moderate hypoglycemia, blood glucose: 2.2-3.3mmol/L, SH: severe hypoglycemia, blood glucose: <2.2mmol/L

*P < 0.05

Table 3. Therapy and Outcome Data

|                          | Survivors (n=310) | Nonsurvivors (n=192) | All Patients (n=502) | P-Value |
|--------------------------|-------------------|----------------------|----------------------|---------|
| Carbohydrate intake (Kcal/kg) | 150.2(132.4, 171.4) | 141.1(122.5, 162.2) | 145.6(127.9, 168.1) | 0.013* |
| Insulin daily dosage (u)  | 9.3(0, 34.3)      | 18.6(2.5, 34.3)      | 12.9(0, 34.3)        | 0.010* |
| Glucocorticoid dosage (mg)| 0(0, 66.7)        | 40(0, 198.3)         | 26.7(0, 106.7)       | √ 0.001* |
| Duration of ventilator-free (h) | 551(327.5, 652)   | 1(0, 43.5)           | 257.5(6, 590.3)      | √ 0.001* |
| Duration of RRT (h)       | 0(0,0)            | 0(0, 44)             | 0(0, 11.3)           | √ 0.001* |
| ICU-free days (d)         | 14(1, 21)         | 0(0,0)               | 0(1,17)              | √ 0.001* |

MV: mechanical ventilation, RRT: renal replacement therapy

*P < 0.05

Table 4. Predictors for mortality at 28-day

| Predictor  | OR (95%CI)    | P-Value |
|------------|---------------|---------|
| age        | 1.030(1.007-1.153) | 0.010*  |
| APACHE II score | 1.072(1.019-1.147) | √ 0.001* |
| MH/SH     | 2.075(1.862-2.243) | √ 0.001* |
| GAP_{mean} | 1.833(1.588-2.115) | √ 0.001* |
APACHE II scores: Acute Physiology and Chronic Health Evaluation II score, MGL: mean glucose level, ADAG: A1C-derived average glucose, GAP$_{mean}$: glycemic gap between MGL and ADAG, MH: moderate hypoglycemia, blood glucose: 2.2-3.3mmol/L, SH: severe hypoglycemia, blood glucose: <2.2mmol/L

*P < 0.05
Figure 1. Flow chart of the study
Figure 3. ROC curves for GAP and APACHE II score for predicting 28-day mortality

| Measure          | AUC  | 95% CI         |
|------------------|------|----------------|
| age              | 0.613| 0.564-0.663    |
| APACHE II        | 0.710| 0.663-0.757    |
| GAP<sub>adm</sub> | 0.601| 0.549-0.652    |
| GAP<sub>mean</sub> | 0.820| 0.781-0.860    |
| APACHE II+GAP<sub>adm</sub> | 0.716| 0.670-0.763    |
Figure 4. Kaplan-Meier survival curve of HbA1c and GAP mean at 1-year.