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ORIGINAL RESEARCH

Mean Blood Glucose Level During ICU Hospitalization is a Strong Predictor of the Mortality of COVID-19

Jie Hu[1,2,*], Lin Ouyang[3,*], Jinxiu Li[1], Xia Li[2], Yanjun Zhong[1], Can Hou[2]

[1]Critical Care Medicine Center, The Second Xiangya Hospital, Central South University, Changsha, People's Republic of China; [2]National Clinical Research Center for Metabolic Diseases, Department of Metabolism and Endocrinology, Key Laboratory Diseases Immunology, Ministry of Education, The Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China; [3]Department of Critical Care Medicine Center, Guilin Hospital of the Second Xiangya Hospital, The Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Can Hou, National Clinical Research Center for Metabolic Diseases, Department of Metabolism and Endocrinology, Key Laboratory Diseases Immunology, Ministry of Education, The Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China, Email houcan84@csu.edu.cn; Yanjun Zhong, Critical Care Medicine Center, The Second Xiangya Hospital, Center South University, Changsha, People's Republic of China, Email zhongyanjun@csu.edu.cn

Objective: To investigate the potential prognostic value of mean blood glucose (MBG) in hospital for prognosis of COVID-19 adult patients in the intensive unit care unit (ICU).

Methods: A single-site and retrospective study enrolled 107 patients diagnosed as COVID-19 from department of critical care medicine in the Second Xiangya Hospital between October 2022 and June 2023. Demographic information including glucose during ICU hospitalization, comorbidity, clinical data, types of medications and treatment, and clinical outcome were collected. The multivariate logistic and cox regression was used to explore the relationship between blood glucose changes and clinical outcomes of COVID-19 during ICU stay.

Results: In total, 107 adult patients confirmed with COVID-19 were included. Multivariate logistic regression results showed an increase in MBG was associated with ICU mortality rate. Compared with normal glucose group (MBG <= 7.8 mmol/L), the risk of ICU mortality, 7-day mortality and 28-day mortality from COVID-19 were significantly increased in high glucose group (MBG >7.8mmol/L).

Conclusion: MBG level during ICU hospitalization was strongly correlated to all-cause mortality and co-infection in COVID-19 patients. These findings further emphasize the importance of overall glucose management in severe cases of COVID-19.

Keywords: mean blood glucose, intensive care medicine, ICU mortality, COVID-19

Introduction

Critically ill patients often have glucose dysfunction due to complex factors such as glucagon, adipokines and insulin resistance, manifested as stress hyperglycemia, hypoglycemia and high glucose variability.[1] During the COVID-19 pandemic, a number of studies found that COVID-19 infection can cause glucose abnormalities.[2,3] Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection reduced insulin sensitivity by damaging pancreatic beta cell, on the other hand, increased insulin resistance due to inflammatory cytokines release, thereby aggravating organ dysfunction of patients.[4] In addition, Emmanuelle et al in 2021 reported increased susceptibility to SARS-CoV-2 in type 2 diabetes patients,[5] while Zhu et al published in Cell Metabolism concluded that the survival rate with good glucose control was higher than with poor control of COVID-19 patients staying in ICU with diabetes.[6] Recently, a cohort study illustrated that enhanced prehospital glucose levels increased the risk of 30-day mortality of COVID-19 patients.[7]

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As COVID-19 patients hospitalized in intensive care units (ICU), there were some reports found that inpatient blood glucose was strongly associated with ICU mortality.[8,9] Another research reported that higher glucose variability within 24 hours of patients enrolled to ICU was significantly associated with the 30-days ICU mortality. However, the relationship between the average blood glucose level during ICU stay and ICU mortality has still not been reported. Our study primarily explored the potential relationship between average blood glucose during ICU hospitalization and the mortality of COVID-19 patients admitted to ICU, so as further to explore the new paradigm of glucose management in critical ill patients.

Methods

Research Design and Participants

126 patients were admitted to the Department of Critical Care Medicine of the Second Xiangya Hospital of Central South University with confirmed COVID-19 diagnosis from October 2022 to June 2023, and all patients diagnosed according to the criteria of the "Novel Coronavirus Pneumonia Diagnostic and Treatment Program (Trial Ninth Edition)" formulated by the General Office of the National Health Commission. All patients were positive for novel coronavirus nucleic acid test (RT-PCR). The research was approved by the institutional review board of our institution. 9 patients were excluded according to the exclusion criteria as: ICU stay <24 hours and pregnant patients. The main endpoint was referral to death or a general ward. Glucose grouping criteria: normal glucose group: mean glucose ≤7.8 mmol/L, high glucose group: mean glucose >7.8 mmol/L.

Ethics

This study was approved by Clinical Research Ethics Committee of the Second Xiangya Hospital, Central South university. t was conducted according to the principles of the Declaration of Helsinki. Meanwhile, this study obtained informed consent from all patients.

Data Collection

Relevant indicators were collected for all patients including (1) age, gender, underlying disease, comorbidity (sepsis, acute hepatic insufficiency, acute renal insufficiency, hypoproteinemia, and secondary infections), site of infection and bacterial category, use of mechanical ventilation (MV) and duration of ventilator use, use of continuous renal replacement therapy (CRRT), white blood cell count at admission, neutrophil ratio, lymphocyte count, insulin use, norepinephrine use, hospital expenses, and clinical outcomes. (2) All blood glucose measurements after admission.

Statistical Analysis

Methods Statistical analysis was performed using SPSS 25.0 software, and all measures were tested for normality. Measures obeying normal distribution were expressed as mean ± SD, and those not obeying normal distribution were expressed as median (inter quartile spacing). All categorical information were described as frequencies (percentages). Logistic regression models were used to analyze the relationship between covariance and outcome indicators, and differences at $p<0.05$ were considered statistically significant.

Results

Baseline Characteristics of COVID-19 Survival and Non-Survival Patients

A total of 107 patients were eventually included in the study, 57 of whom died in hospital. In the survival group, the mean age was 64±17 years, and 60.0% were male. 84.3% of patients who survived had comorbidities, with a predominance of diabetes (18, 36.0%), hypertension (32, 64.0%), cardiovascular disease (17, 33.3%), cerebrovascular disease (8, 16.0%), renal disease (11, 22.0%), and immunodeficiency (9, 18.0%). The mean age of the non-survival patients was 71±14 years, and 22.8% were male. 87.5% patients had comorbidities with a proportion of diabetes (22, 38.6%), hypertension (31, 54.4%), cardiovascular disease (21, 36.8%) and cerebrovascular disease (19, 33.3%). Compared with the survival group, patients in the non-survival group were significantly older ($p=0.017$) and had

Table 1 Clinical Characteristic and Laboratory Findings of Patients with COVID-19

Features	Survivor (n=50)	Non-Survivors (n=57)	p value
Demographic features			
Age	64 (17)	71 (14)	0.017
Gender			0.055
Female (N, %)	20 (40.0)	44 (77.2)	
Male (N, %)	30 (60.0)	13 (22.8)	
Comorbidities (N, %)			
Diabetes	18 (36.0)	22 (38.6)	0.782
Hypertension	32 (64.0)	31 (54.4)	0.313
COPD	0 (0.0)	8 (14.0)	0.007
Immunosuppression	9 (18.0)	8 (14.0)	0.576
Renal disease	11 (22.0)	12 (21.1)	0.905
Cerebrovascular disease	8 (16.0)	19 (33.3)	0.039
Cardiovascular disease	17 (33.3)	21 (36.8)	0.759
Laboratory Results at admission			
White blood cell count (10^9/L)	10.7 (7.6)	10.9 (9.5)	0.418
Neutrophils (10^9/L)	7.2 (5.6)	9.0 (8.4)	0.753
Lymphocytes (10^9/L)	1.3 (0.6)	0.5 (0.6)	0.055
Platelets (10^9/L)	206 (94)	190 (100)	0.555
Alanine aminotransferase (U/L)	22.8 (17.4)	23.6 (19.8)	0.759
Aspartate aminotransferase (U/L)	30.6 (36.2)	34.2 (31.8)	0.559
Creatine (umol/L)	98.5 (76.6)	101 (183.5)	0.392
PCT (ng/mL)	0.85 (4.47)	1.39 (7.52)	0.384
IL-6 (pg/mL)	174.5 (732.5)	65.9 (198.3)	0.331
S-CRP (pg/mL)	135.3 (94.0)	121.9 (90.5)	0.418

Abbreviations: COPD, chronic obstructive pulmonary disease; PCT, procalcitonin; S-CRP, high-sensitive C-reactive protein; IL-6, Interleukin 6.

significantly higher proportions of cerebrovascular disease, and chronic obstructive pulmonary disease (COPD) (p=0.039 and p=0.007) (Table 1).

There was no significant difference in laboratory findings between the two groups including white blood cell count, neutrophils, lymphocytes, platelets, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine, procalcitonin (PCT), high-sensitive C-reactive protein (hS-CRP) and interleukin 6 (IL-6) (Table 1).

Non-Survived COVID-19 Patients Had Higher Levels of Average Blood Glucose

Mean blood glucose was significantly higher in the non-survival group than in the survival group (p=0.002). Further comparisons showed no statistically significant differences in the standard deviation of blood glucose, glycemia variability, and maximum blood glucose fluctuation between the two groups (Table 2).

Table 2 Glucose Variability in Two Study Groups of COVID-19 Patients Admitted to ICU

Glucose Index	Survivors (n=50)	Non-Survivors (n=57)	*p* value
MBG	9.1 (2.0)	10.2 (1.7)	0.002
GluCV	21.8 (8.6)	22.7 (10.0)	0.430
GluSD	2.1 (1.2)	2.4 (1.4)	0.074
LAGE	10.4 (5.9)	11.1 (4.0)	0.509

Abbreviations: MBG, Mean blood glucose; GluCV, glucose variation coefficient; LAGE, largest amplitude of glycemic excursion.

Comparison of Average Blood Glucose-Related Indicators at Different Levels

According to the blood glucose grading criteria of average blood glucose, patients were divided into two groups which were the normal glucose group (22 cases mean blood glucose ≤7.8 mmol/L), the high glucose group (85 cases, mean blood glucose >7.8 mmol/L). There were significantly differences in the percentage of diabetes, hypertension, multiple organ failure mechanical ventilation, and insulin use between two groups (p=0.002, p=0.016, p=0.0.016, p<0.001 and p<0.001, respectively) (Table 3).

Average Blood Glucose Was Significantly Associated with in-Hospital Mortality

The survival curves demonstrated the strong association between mean glucose level in ICU stay and ICU mortality (Figure 1A), 7-day mortality (Figure 1B) and 28-day mortality (Figure 1C). Multivariate Cox analysis showed that, compared to the normal glucose group, the high glucose group had an increased risk of ICU mortality (5.9, 1.7–20.5, p=0.005), 7-day (5.0, 1.3–18.4, p=0.016) and 28-day mortality (5.0, 1.5–11.2, p=0.007) (Table 4).

Discussions

The single-center and retrospective cohort study was conducted in both COVID-19 diabetics and non-diabetic patients to determine the relationship between hospitalized mean blood glucose and the mortality of ICU staying. Different from previous studies,[6–13] fasting glucose level and a history of diabetes were not prognostic factors of the COVID-19 mortality in our study. Our study found that high mean glucose level increased the risk of in-hospital mortality of COVID-19 (Figure 1 and Table 4). There was a significant difference in mean blood glucose level of survivors compared patients who died. However, no difference was found in glucose variation coefficient glucose standard deviation and largest amplitude of glycemic excursion (LAGE).

Table 3 Features and Clinical Findings in Different Mean Blood Glucose Group

Features	Normal Glucose (<=7.8) (n=22)	High Glucose (>7.8) (n=85)	*p* value
Demographic features			
Age	63 (21)	71 (19)	0.105
Gender			0.251
Female (N, %)	9 (40.9)	13 (28.2)	
Male (N, %)	24 (59.1)	61 (71.8)	
Comorbidity (N, %)			
Diabetes	2 (9.1)	38 (44.7)	0.002
Hypertension	8 (36.4)	55 (64.7)	0.016
COPD	0 (0)	8 (9.4)	0.135
Chronic liver disease	2 (9.1)	4 (4.7)	0.426
Immunosuppression	4 (18.2)	13 (15.3)	0.741
Renal disease	4 (18.2)	19 (22.4)	0.671
Cerebrovascular disease	7 (31.8)	20 (23.5)	0.425
Cardiovascular disease	7 (32.3)	31 (37.6)	0.684
Sepsis	8 (36.4)	46 (51.4)	0.098
Multiple organ failure	17 (77.3)	80 (94.1)	0.016
Secondary infection	15 (68.2)	38 (67.9)	0.153
Bacterial infection	12 (54.5)	58 (68.2)	0.229
Fungal infection	0 (0)	12 (14.1)	0.061
Curing			
RRT	8 (36.4)	32 (38.6)	0.851
MV	7 (31.8)	65 (76.5)	0.000
Insulin	2 (9.1)	62 (72.9)	0.000

Abbreviations: COPD, chronic obstructive pulmonary disease; RRT, renal replacement therapy; MV, mechanical ventilation.

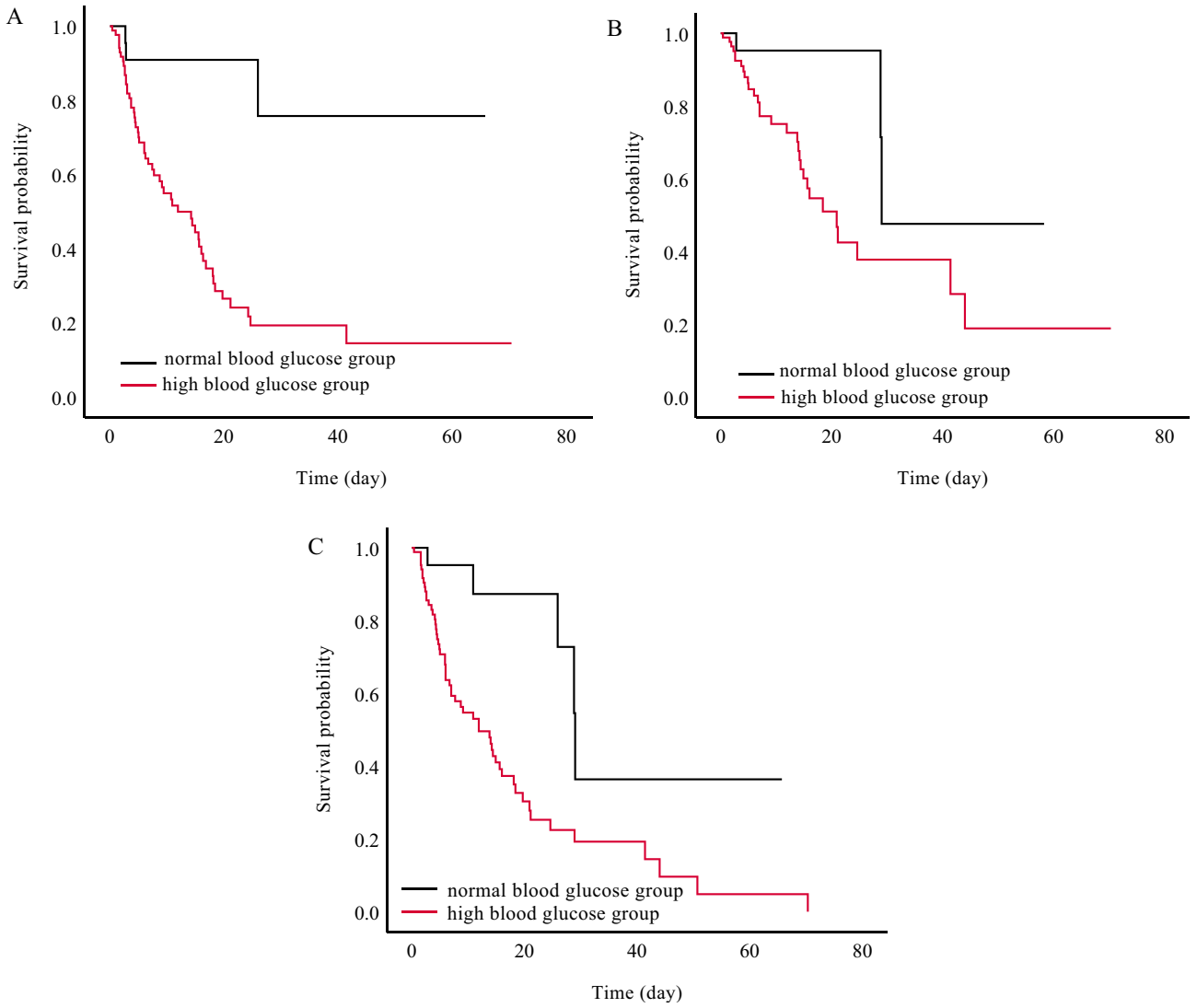

Figure 1 Legend Survival Curves for (**A**) ICU mortality, (**B**) 7-day mortality and (**C**) 28-day mortality among different mean blood glucose group. Black, normal blood glucose group; Red, high blood glucose group.

Previous research has illustrated that intensive glycemic control played a crucial effect on prognosis of the critically ill.[14–16] Poor glycemic control extremely increased ICU mortality, potential infection and the time of mechanical ventilation and hospitalization.[16] Lu et al reported that in terms of sepsis patients, as increasing of mean blood glucose and glycemic variation coefficient, the all-cause mortality enhanced.[17] On the other hand, diabetes and higher blood glucose at admission increased the 30-days mortality of acute myocardial infarction complicated by cardiogenic shock.

Fortunately, glycemic disorder can be well controlled by standard and individual treatment. A landmark trial in 2001 found that intensive insulin treatment can maintain at or below 110mg/dL, which can reduce the ICU mortality and related morbidity of severely ill patients.[18,19] A 2008 report found intensive insulin therapy reduced the length of ICU stay by 3 days.[20] A meta-analysis including NICE-SUGAR data in 2009 reported that sustain insulin admission significantly increased the risk of hypoglycemia but not ICU mortality.[21] Subsequently studies have illustrated that strictly glycemic control by insulin therapy increased the risk of hypoglycemia and mortality.[22,23] These finding prompted us to explore new therapeutic methods of glucose control. Recently, some studies of continuous glucose monitoring in ICU may be possible and potential benefit to patients of ICU admission.[24–26]

The study still has some limitations. First, this was a single-center retrospective study, which has location and time specific limitations in terms of general acceptability across different demographic and regional context. Second, the

Table 4 Multiple Analysis for the Association Between Candidate Risk Factors and Outcomes of ICU Mortality, 7-Day Mortality and 28-Day Mortality

Variables	ICU Mortality		7-Day Mortality		28-Day Mortality	
	Adjust HR (95% CI)	p	Adjust HR (95% CI)	p	Adjust HR (95% CI)	p
Age	1.0 (0.97–1.01)	0.700	1.00 (0.97–1.03)	0.923	1.01 (0.98–1.03)	0.603
Sex	0 77 (0.40–1.50)	0.445	1.77 (0.83–3.76)	0.139	1.17 (0.65–2.10)	0.611
Diabetes	0.67 (0.36–1.19)	0.166	0.28 (1.11–0.75)	0.011	0.62 (0.36–1.14)	0.126
Cardiovascular disease	1.70 (0.86–3.35)	0.124	1.38 (0.58–3.60)	0.514	1.78 (0.92–3.46)	0.087
Hypertension	0.63 (0.33–1.21)	0.164	1.34 (0.50–3.59)	0.556	0.87 (0.45–1.69)	0.690
COPD	2.50 (1.02–6.12)	0.046	0.94 (0.11–7.84)	0.952	1.92 (0.62–6.00)	0.259
Sepsis	1.72 (0.92–3.23)	0.103	2.20 (0.84–5.76)	0.109	1.00 (0.53–1.89)	0.991
MV	2.24 (0.85–5.88)	0.103	1.56 (0.48–5.04)	0.458	1.40 (0.64–3.07)	0.400
Glucose						
<=7.8	Reference		Reference		Reference	
>7.8	5.9 (1.7–20.5)	0.005	5.0 (1.3–18.4)	0.016	5.0 (1.5–11.2)	0.007

Abbreviations: HR, hazard ratio; CI, confidence interval; COPD, chronic pulmonary disease; MV, mechanical ventilation.

sample size was too small to be powered to answer specific clinical questions. Third, the diagnosis of diabetes of patients were identified through past medical record while their hemoglobin A1c level was not obtained. Forth, heavy workload in ICU and instrumental measurement error may have influenced accuracy of some parameters. Despite these involved limitations, we assessed the predictive value of mean blood glucose level in COVID-19 patients in ICU stay. We believe that this information will be found particularly helpful for clinical workers to treat severe COVID-19, and even be applied to other critical illness.

In conclusion, among severe COVID-19 patients with or without diabetes enrolled in ICU, increased mortality of ICU was strongly associated with higher mean blood glucose during ICU stay. Because of the impact of average blood glucose changes on the prognosis of COVID-19, enhanced continuous glucose monitoring and insulin treatment are crucial to prognosis of critical COVID-19.

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Disclosure

The authors report no conflicts of interest in this work.

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