

Association of Blood Glucose Variability with Sepsis-Related Disseminated Intravascular Coagulation Morbidity and Mortality

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Purpose: Sepsis-related disseminated intravascular coagulation (DIC) is closely associated with poor prognosis and high mortality. Higher blood glucose (BG) variability indicates an increased risk of mortality in sepsis; however, its relationship with sepsis-related DIC has not been investigated. This study aimed to determine the association between glucose variability and sepsis-related DIC.

Patients and Methods: Patients with sepsis admitted to the intensive care unit were enrolled between October 2017 and January 2021. Baseline data and BG records from the first 72 h were collected. We calculated the glucose liability index (GLI), largest amplitude of glucose excursion, BG standard deviation, and coefficient of variation on days 1 and 3. The relationship between GLI and morbidity of sepsis-related DIC was explored using a competing risk model. In subgroup analysis, we divided patients with and without diabetes into three groups according to the BG range.

Results: Of the 238 patients enrolled, 28.2% developed DIC during hospitalization (n=67). GLI on day 3 was found to have the closest relationship with DIC incidence as it has the largest area under the ROC curve and the highest associated odds ratio of death per unit change (GLI3-day: AUC=0.891 OR=1.84), also independently increased the occurrence of DIC after adjusting for the competing risk of death (sub-distribution hazard ratios=1.866, p<0.01). In subgroup analysis, patients with diabetes had worse outcomes under hypoglycemia than under hyperglycemia. Patients without diabetes having stable BG had the best outcomes.

Conclusion: Our study suggested that a higher GLI in patients with sepsis at 72 h was independently associated with an increased risk of sepsis-related DIC, which was not associated with pre-existing diabetes.

Keywords: blood disorder, glycemic variability, hypoglycemia, sepsis

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.¹ This encompasses exaggerated inflammatory, immunosuppressive, vascular leaking, and coagulative processes.² Although the activation of coagulation in patients with sepsis is considered the fundamental host response against infection,³ over-activation can be harmful.⁴ Severe consumptive coagulopathy, termed disseminated intravascular coagulation (DIC), is associated with organ dysfunction and hemorrhage and directly increases the mortality rate of patients with sepsis.⁵

Sepsis-related DIC is a fatal complication of sepsis and is closely associated with organ dysfunction and hemorrhage. A large, multicenter, prospective validation study showed that the mortality of patients with sepsis having DIC was 38.4%, which was almost twofold higher than that of those without DIC.⁶ Moreover, subgroup analyses of large studies showed a higher incidence of DIC and increased mortality rate in patients with severe sepsis when they did not receive

timely activated protein C or antithrombin treatments.^{7,8} Therefore, earlier diagnosis and appropriate treatment are crucial in the management of patients with sepsis.

Stress hyperglycemia with insulin resistance is common in critically ill patients,^{9,10} and controlling blood glucose (BG) is critical in the intensive care unit (ICU) treatment of patients with sepsis.^{11–14} However, as several large multicenter studies on intensive insulin therapy failed to demonstrate higher survival rates from strictly controlling BG levels,^{15–19} especially large amount of evidence suggests that BG variability gets more strong association with worse prognosis than simple BG measurements in the critically ill patient population,²⁰ so the BG variability is gaining more attention nowadays.^{21–25}

The metrics of BG variability (GV), including HbA1c,²⁵ standard deviation (SD),^{26,27} mean amplitude of glucose excursions (MAGE),^{27–30} and glycemic lability index (GLI)^{31,32} are associated with an increased risk of mortality in critically ill patients.^{26,30,33,34} Moreover, a retrospective cohort study reported that low variability had a protective effect, even in cases of hyperglycemia.³⁴

Furthermore, GV has been thought to be closely associated with endothelial dysfunction in vivo.³⁵ In vitro studies have shown that acute fluctuations in glucose can induce endothelial cell damage. Epitheliopathy plays a critical role in the pathogenesis of sepsis,³⁶ including the aberrant activation of intravascular coagulation, which may lead to sepsis-related DIC.

Although the association between GV and sepsis has been broadly studied, the relationship between GV and sepsis-related DIC has not yet been identified. This study aimed to explore the internal relevance of GV and sepsis-related DIC in the ICU setting.

Materials and Methods

Study Design and Data Collection

We recorded data on comorbidities, prothrombin time, activated partial thromboplastin time (APTT), D-dimer, fibrinogen level, and platelet count and then calculated the points according to the Chinese Society of Thrombosis and Haemostasis Scoring System for DIC (CDSS).^{37,38} Subsequently, the patients were divided into “survivor” or “non-survivor” groups based on whether they were alive at 28 days after admission.

We collected all recorded BG values and recorded the time points within the first 72 h. We then performed calculations for later analysis (see BG measures).

Patient Enrolment in the ICU Setting

This was a retrospective, exploratory study based on a review of the medical records of adult intensive care patients at two highly complex, public, tertiary hospitals (Xinhua Hospital, affiliated with the Shanghai Jiao Tong University School of Medicine, and the Shanghai Tenth People’s Hospital, affiliated with Tongji University School of Medicine, Shanghai, China). These ICUs have capacities of 13 and 23 critical care beds, respectively. Patients admitted to the ICUs were treated per the glucose regulation protocol, in which insulin is commonly used for glucose control to maintain targets of 80–180 mg/dL (4.4–10 mmol/L).³⁹ In the event of hypoglycemia, 40 mL of 50% glucose solution (GS) was injected, followed by a 10% GS intravenous drip, and the BG was re-tested after 1 h.

Adult patients diagnosed with sepsis and/or septic shock, admitted to the ICU between October, 2017, and January, 2021, were screened for eligibility according to the following criteria: (1) age ≥ 18 years; (2) sequential organ failure assessment (SOFA) score ≥ 2 points within 24 h of admission; (3) hospital stay ≥ 3 days; and (4) routine BG monitoring every 2–6 h in the ICU.

Patients with the following criteria were excluded: (1) discharged or died within 3 days of admission; (2) fewer than four records of BG per day within a 72-h period; and (3) concurrent tumors, pregnancy, blood diseases, active bleeding, or anemia.

BG Measures

In both ICUs, routine BG measures applied every 2–6 h depending on patients’ condition. It was assured that patients all got > 4 times measures in recording days.

We screened all patients and collected the values and time points of glucose records within 72 h of admission.

Glucose Liability Index (GLI)

The GLI was one of the most significant indexes for assessing glucose variability in this study. It is calculated as the squared difference between consecutive glucose measurements per unit of actual time (Δh) between those records: $GLI = \Sigma[\{\Delta\text{glucose (mmol/L)}\}^2 \cdot \Delta h^{-1}] \cdot (\text{per se})$.^{40–43}

Largest Amplitude of Glucose Excursion (LAGE)

This index stands for the glucose excursion for a certain duration, calculated as $LAGE = Glu_{\max} - Glu_{\min}$. We calculated $LAGE_{\text{day1}}$ and $LAGE_{3\text{-days}}$ separately.

Additionally, we calculated the mean glucose values.

All indexes were calculated separately for day 1 and 3-day (“3-day” means 3 days’ data together), which either gives the earliest information about patients’ disease baseline or offers the clinicians the patients’ blood glucose change pattern under certain treatment in early period in ICU.

Definitions

Diabetes

Diabetes was diagnosed based on the standards of the American Diabetes Association.^{40–43}

Sepsis and Septic Shock

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction was defined by an increase in the SOFA score by ≥ 2 points. Septic shock is a type of sepsis characterized by profound circulatory, cellular, and metabolic abnormalities associated with a greater risk of mortality than sepsis alone.

Sepsis Related DIC

We defined sepsis related DIC based on the criteria of CDSS previously described elsewhere (details given in [Supplementary Material Table 1](#)).³⁸

In summary, CDSS score was counted by clinicians or trained nurses, including underlying disease, clinical manifestation, and laboratory examination. The score has been counted twice a day separately in morning and night shift in enrolled sepsis patients, and If the score was >7 points, the septic patient would be defined as having sepsis related DIC.

Statistical Analyses

We used mean \pm SD or median and interquartile range to describe continuous variables with the variable distribution. Counts and percentages are used to describe categorical variables. In comparison between the two groups, the Student’s *t*-test or Wilcoxon rank-sum test and χ^2 test or Fisher’s exact test were used for continuous and categorical variables, respectively. For comparisons among three or more subgroups, we performed a one-way analysis of variance or Kruskal–Wallis (*H*-test) depending on variable distribution.

The receiver operating characteristic (ROC) curve was plotted as sensitivity versus 1-specificity values. The area under the curve (AUC) was calculated from the ROC curve. AUC has been used in the research as one of the references to select a better “predictor” with higher association with sepsis related DIC occurrence from multiple GVs.

Sepsis-related DIC occurrence and 90-day mortality were set as the primary and secondary endpoints, respectively. We considered death before DIC diagnosis as a competing risk factor for DIC morbidity. We used the competing risk model (Fine and Gray model) that assessed the factors influencing DIC morbidity independently after adjusting for competing risk. Combined with clinical reality, univariate logistic regression results, together with the results of the Student’s *t*-test and χ^2 test, were used to determine the factors included in the competing risk model. We reported the sub-distribution hazard ratios (sHRs) of the competing risk regression covariates with corresponding 95% confidence intervals.

Furthermore, in subgroup analysis, we explored the differences in sepsis-related DIC occurrence rates within groups that achieved the moderate target glucose range of 70–180 mg/dL (4–10 mmol/L)¹⁹ to determine if moderate control will benefit patients with sepsis having DIC. We divided patients with and without diabetes into three groups according to their BG range

within 72 h as the low BG group (low blood glucose [LBG], minimum BG \leq 72 mg/dL [4 mmol/L], n=11), moderate BG group (MBG, minimum BG \geq 72 mg/dL [4 mmol/L], \leq 180 mg/dL [10 mmol/L], n=64), and high BG group (HBG, maximum BG \geq 180 mg/dL [10 mmol/L], n=163). Moreover, we divided patients within LBG into two subgroups, in which diabetic patients were included in group 1 (LBG1), and non-diabetic patients were enrolled in group 2 (LBG2).

Analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Sample size calculation was performed using G*power (version 3.1.9.7 for Windows 10, Franz Faul, University of Kiel, Kiel, Germany). Competing risk analysis was performed in R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) using the “cmprsk” package³⁸ by following the steps mentioned on the website and the document downloaded from the official website.⁴⁴ Statistical significance was defined as a two-sided *p*-value of <0.05 .

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline has been used to construct our methodological design.⁴⁵

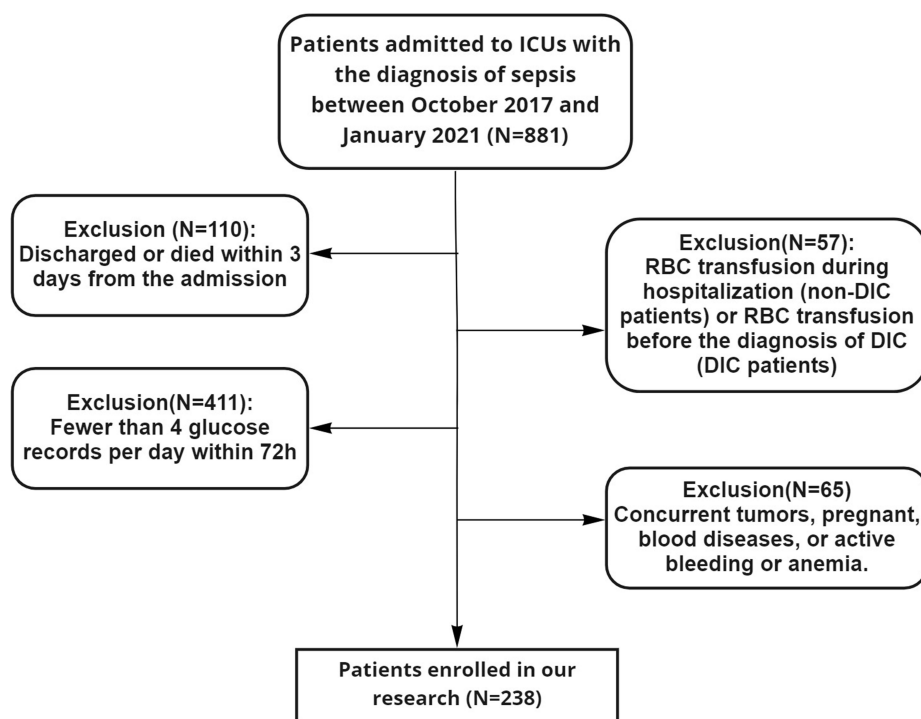
Results

Baseline of Enrolled Patients

Between October 2017, and January 2021, 881 patients were screened for this study. Finally, a total of 238 patients (143 men [60.1%]) were enrolled (Figure 1). The average age was 69.9 years and the average SOFA score at admission was 5.0 with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 17.1. Respiratory tract infection was the main cause of sepsis in most patients (n=96, 40.3%), followed by abdominal infection, urinary tract infection, and soft tissue infection. Within the group, 67 patients (28.2%) developed DIC (CDSS) during hospitalization and 80 (33.6%) were identified as having MODS during admission, whereas 88 (37%) died within 90 days after admission. Detailed baseline characteristics are shown in Table 1.

GV

As mentioned previously, we calculated several GV variables. Based on previous research,⁴⁶ we explored the relationship between different expressions of GV and DIC occurrence using the univariate logistic regression model and receiver



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Figure 1 Enrollment strategy of the study.

Table 1 Patient Characteristics

Variables	Total Population (N=238) Mean ± SD/Median (IQR)	DIC Group (N=67)	Non-DIC Group (N=171)
Baseline admission			
Sex (male), n (%)	143 (60.1%)	38 (56.7%)	105 (61.4%)
Age	69.9±12.6	70.7±12.1	69.5±12.8
SOFA (admission)*,	5.0 (5.0)	8.0 (5.0) [#]	4.0 (4.0)
SOFA (discharge or die)*	2.0 (9.0)	12.0 (13.0) [#]	1.0 (3.0)
APACHE II (admission)	17.1±7.4	20.7±7.9 [#]	15.7±6.6
APACHE II (discharge or die)*	11.5 (12.0)	22.0 (17.0) [#]	10.0 (6.0)
Possible infection site			
Respiratory tract	96 (40.3%)	/	/
Urinary tract	58 (24.4%)	/	/
Abdomen	74 (31.1%)	/	/
Soft tissue	9 (3.8%)	/	/
Other	1 (0.4%)	/	/
Underlying diseases			
AF n (%)	37 (15.5%)	26 (15.2%)	11 (16.4%)
DVT n (%)	2 (0.8%)	2 (100%) [#]	0 (0%)
COPD n (%)	9 (3.8%)	3 (4.5%)	6 (3.5%)
Diabetes n (%)	85 (35.7%)	62 (36.3%)	23 (34.3%)
Hypertension n (%)	125 (52.5%)	31 (46.3%)	94 (55.0%)
Laboratory^c			
Procalcitonin* (ng/mL)	10.4 (44.0)	21.6 (98.7) [#]	7.7 (35.3)
C-reactive protein (mg/L)	127.9±65.1	146.7±63.0 [#]	120.5±64.6
NT-proBNP* (ng/mL)	2185 (6928.2)	3822 (13766.5)	1711 (5231.0)
Neutrophil (%) [*]	88.5 (12.2)	89.9 (8.3)	87.0 (12.5)
White blood cell count* (10 ⁹ /L)	12.5 (11.1)	13.9 (14.6)	12.0 (10.6)
Platelet (10 ⁹ /L)	143.6±95.7	81.1±67.9 [#]	168.1±94.0
MODS n (%)	80 (33.6%)	46 (68.7%) [#]	34 (19.9%)
Shock n (%)	104 (43.7%)	53(79.1%) [#]	51 (29.8%)
Mortality (within 28 days) n (%)	82 (34.5%)	43 (64.2%) [#]	39 (22.8%)
Total Mortality n (%)	88 (37.0%)	46 (68.7%) [#]	42 (24.6%)
Hospitalization time (day)	15.4±8.8	17.5±12.3 [#]	14.7±6.9
DIC (CDSS)	67 (28.2%)	/	/
DIC time (day) ^d	/	6.9±6.5	/
Blood glucose related			
Day 1 glucose mean	9.7±3.6	10.7±3.8 [#]	9.3±3.5
SD _{day1}	1.8±1.4	3.3±1.6	1.3±0.9
CV _{day1}	0.2±0.1	0.3±0.1	0.1±0.01
LAGE _{day1}	4.3±3.4	7.8±3.7 [#]	2.9±2.0
GLI _{day1} ((mmol/l) ² /h/per se)	2.3±4.1	5.0±5.2 [#]	1.2±2.9
3-Day glucose mean	9.5±2.9	10.8±3.0 [#]	9.0±2.7
SD _{3-day}	2.4±1.3	3.6±1.3	1.9±1.0
CV _{3-day}	0.2±0.1	0.3±0.1	0.2±0.1
LAGE _{3-day}	7.7±4.4	11.9±4.5 [#]	6.1±3.1
GLI _{3-day} ((mmol/l) ² /h/per se)	3.8±5.1	5.7±4.4 [#]	3.0±5.1

Notes: *Means the variable is not normally distributed. We report the description with median and interquartile range (interquartile range) and analyzed the difference between groups with Wilcoxon rank-sum test and Fisher's exact test for continuous variable and categorical variables, respectively. [#]Means that there are significant differences ($p < 0.05$) compared with the non-DIC group. ^cLaboratory data refer to the results of routine blood tests conducted within 24 h of admission. ^d"DIC time" means the day when patients were diagnosed with DIC.

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CV, coefficient of variation; DVT, deep vein thrombosis; GLI, glucose liability index; HF, heart failure; LAGE, largest amplitude of glucose excursion; MODS, multiple organ dysfunction syndrome; SD, standard deviation.

Table 2 Determination of Glucose Variability

Glucose Variability Term	Univariate Logistic Regression		ROC of the Variable and DIC Occurrence	
	OR (95% CI)	p	AUC	95% CI
Day 1 glucose mean	1.11 (1.02, 1.20)	0.01	0.629	0.55–0.70
SD _{day1}	3.86 (2.67, 5.60)	<0.001	0.851	0.81–0.90
CV _{day1}	1185750 (29715.46, 47315560.58)	<0.001	0.711	0.61–0.76
LAGE _{day1}	1.39 (1.23, 1.58)	<0.001	0.868	0.82–0.92
GLI _{day1} ^a	1.51 (1.38, 1.79)	<0.001	0.887	0.84–0.93
3-Day glucose mean	1.23 (1.12, 1.36)	<0.001	0.702	0.63–0.77
SD _{3-day}	3.36 (2.40, 4.73)	<0.001	0.870	0.82–0.92
CV _{3-day}	48609003 (388252.96, 6085813656)	<0.001	0.860	0.81–0.91
LAGE _{3-day}	1.11 (1.04, 1.17)	0.001	0.795	0.74–0.85
GLI _{3-day} ^a	1.84 (1.75, 1.91)	<0.001	0.891	0.84–0.94

Note: ^aThe unit of GLI is (mmol/l)²/h/per sec.

Abbreviations: AUC, area under the ROC curve; CV, coefficient of variation; GLI, glucose liability index; LAGE, largest amplitude of glucose excursion; ROC, receiver operating characteristic; SD, standard deviation.

operating characteristic (ROC) curve (Table 2). We found that the GLI_{3-day} had the largest area under the ROC curve (AUC) and the highest associated odds ratio (OR) of death per unit change (GLI_{3-day}: AUC=0.891 OR=1.84), suggesting that GLI_{3-day} is the most ideal variable for use in subsequent analyses.

Fine and Gray Model Related to DIC Morbidity

We considered death before DIC diagnosis as a competing risk for DIC morbidity.

Univariate logistic regression results are shown in Table 3. We took the results of the logistic regression and cox risk model (not given in the manuscript), together with clinical reality and the comparison between groups previously performed in another study,³⁸ those relevant risk factors in the risk competition model has been decided (Table 3).

Table 3 The Results of Univariate Results and Multivariable Competing Risk Model

Variables	Univariate Logistic Regression			Competing Risk Model (Fine and Gray Model)		
	Wald	OR (95% CI)	p value	z value	Multivariable sHR (97.5% CI) ^{b,c}	p value
Age	0.46	1.008 (0.985–1.031)	0.498	/	/	/
Sex (Female)	0.44	1.214 (0.685–2.153)	0.507	2.428	0.418 (0.206–0.845)	<0.05
SOFA (admission)	27.41	1.248 (1.149–1.356)	<0.01	1.28	1.063 (0.968–1.167)	0.2
APACHE II admission	19.66	1.099 (1.054–1.145)	<0.01	0.771	0.986 (0.951–1.022)	0.44
Procalcitonin (ng/mL) ^a	14.14	1.015 (1.007–1.023)	<0.01	0.565	1.001 (0.997–1.006)	0.57
C-reactive protein (mg/L) ^a	7.56	1.007 (1.002–1.011)	<0.01	2.45	1.005 (1.001–1.009)	<0.01
White blood cell count (10 ⁹ /L) ^a	1.18	1.009 (0.993–1.026)	0.277	/	/	/
Platelet (10 ⁹ /L) ^a	34.59	0.982 (0.976–0.988)	<0.01	7.427	0.973 (0.96–0.988)	<0.01
Shock	39.11	8.152 (4.224–15.735)	<0.01	2.123	2.14 (1.06–4.318)	<0.05
MODS	44.71	8.826 (4.662–16.711)	<0.01	0.893	1.289 (0.739–2.248)	0.37
Diabetes	0.08	0.919 (0.508–1.663)	0.78	1.206	1.414 (0.805–2.481)	0.23
DVT	0.00	/	0.999	/	/	/
Day 1 glucose mean	6.57	1.106 (1.024–1.195)	<0.05	/	/	/
3-Day glucose mean	17.21	1.232 (1.116–1.36)	<0.01	/	/	/
GLI _{3-day} ((mmol/l) ² /h/per se)	49.95	1.505 (1.344–1.685)	<0.01	4.865	1.866 (1.41–2.47)	<0.01

Notes: ^aLaboratory data refer to the results of routine blood tests conducted within 24 h of admission. ^bThe sHR (0.418) of “sex (female)” is the ratio compared to male (ratio of man=1), which means men are 2.39 times more likely to get DIC than women, for instance. ^cThe sHRs of “shock”, “MODS”, “diabetes” and “DVT” are the ratios compared to non-disease group (eg ratio of non-shock=1).

Abbreviations: DVT, deep vein thrombosis; GLI, glucose liability index; MODS, multiple-organ dysfunction syndrome; sHRs, sub-distribution hazard.

After adjusting for sex (female), SOFA on admission, APACHE II on admission, procalcitonin (PCT), C-reactive protein (CRP), platelet count, shock, multiple-organ dysfunction syndrome (MODS), diabetes, and $GLI_{3\text{-day}}$, we found that male sex (sHR=2.39, $p<0.05$), CRP (sHR=1.005, $p<0.01$), shock (sHR=2.140, $p<0.05$), platelet count (sHR=0.973, $p<0.01$), and $GLI_{3\text{-day}}$ (sHR=1.866, $p<0.01$) were the factors which strongly and independently influenced DIC occurrence in patients with sepsis.

Different Outcomes of Patients With and Without Diabetes

In subgroup analysis, we found that the MBG group (n=64) had the most stable BG and a significantly lower DIC occurrence rate (3.1%, $p<0.01$) (Supplemental Material 1). The MBG group had the best outcomes among the three groups, indicating that achieving a moderate BG target (72–180 mg/dL) may be advantageous to patients with sepsis.

Patients with diabetes were more likely to have abnormal BG (Supplemental Material 1), as only 12.5% of patients with diabetes had MBG; however, 54.5% had LBG and 43.6% had HBG ($p<0.01$). We then divided the patients into groups based on whether they had diabetes or not for further analysis (Table 4).

There were 85 patients with diabetes, 6 with LBG1, 8 with MBG1, and 71 with HBG1. LBG1 had higher scores when discharged, including SOFA and APACHE II ($p<0.05$), suggesting that the occurrence of hypoglycemia leads to worse outcomes in patients with sepsis having diabetes. Strikingly, all patients in the LBG1 group died within 28 days, 83.3% in the LBG1 group developed DIC (n=5), and DIC occurrence and mortality were significantly higher in the LBG1 group than in the other groups ($p<0.05$). In contrast, the MBG1 group had the lowest DIC occurrence (n=0, 0%) and mortality rates (n=2, 25%) and achieved the most stable BG during the first 72 h ($p<0.05$).

Table 4 The Outcomes Comparison Among Different Blood Glucose Level Groups in Diabetic Patients and Non-Diabetic Patients

Variables	Diabetic Patients ^b			Non-Diabetic Patients ^b		
	LBG1 (n=6)	MBG1 (n=8)	HBG1 (n=71)	LBG2 (n=5)	MBG2 (n=56)	HBG2 (n=92)
SOFA (admission)*, ^a	7 (3)	4.5 (7)	5 (4)	3 (4)	4 (5) ⁺	6 (6)
SOFA (discharge or die)*	13.5 (14)	1.5 (5)	2(9)	4 (8)	1 (2) ⁺	3.5 (12)
APACHE II (admission)*	27 (17) ⁺	14.5 (8)	16 (9)	14 (8)	15 (7) ⁺	18.5 (12)
APACHE II (discharge or die)*, ^d	29 (36) ^{##}	12 (5)	12 (12)	14 (11)	9.5 (6) ⁺	13 (17)
MODS n (%)	3 (50%)	1 (12.5%)	22 (31.0%)	1 (20%)	8 (14.3%) ⁺	45 (48.9%)
Shock n (%)	3 (50%)	1(12.5%)	29 (40.8%)	3 (60%) [#]	13 (23.2%) ⁺	55 (59.8%)
Mortality (within 28 days) n (%)	6 (100%) ^{##}	2 (25%)	24 (33.8%)	4 (80%) [#]	7 (12.5%) ⁺	49 (42.4%)
Total Mortality n (%)	6 (100%) ^{##}	2 (25%)	25 (35.2%)	4 (80%) ^{##}	8 (14.3%) ⁺	43 (46.7%)
Hospitalization time (day)*	19 (25)	13.5 (6)	13(8)	10(11)	13.5(8)	16(11)
DIC (CDSS) n (%)	5 (83.3%) ^{##}	0(0.0%) ⁺	18 (25.4%)	3 (60%) [#]	2 (3.6%) ⁺	39 (42.4%)
DIC time (day) ^c	7±6.21	/	6.89±5.422	8±5.57	2±0	7.13±7.30
Blood glucose related						
Day 1 glucose mean	7.71±3.14 ⁺	7.40±1.0 ⁺	12.47±4.04	6.00±1.87 ⁺	6.87±1.15 ⁺	9.72±2.71
LAGE _{day1}	7±4.74 ^{##}	2.3±0.78 ⁺	5.18±3.62	6.48±4.53 [#]	1.73±1.07 ⁺	5.02±3.35
GLI_{day1} ((mmol/l) ² /h/per se)*	1.33 (5.14)	0.30 (0.38) ⁺	1.47 (3.02)	1.43 (5.76) [#]	0.22 (0.56) ⁺	1.11 (2.51)
3-Day glucose mean	7.56±2.14 ⁺	7.41±0.81 ⁺	12.02±3.01	7.42±1.56 ⁺	6.75±0.85 ⁺	9.68±2.05
LAGE _{3-day}	9.18±4.52 [#]	4.16±0.67 ⁺	9.40±3.82	11.88±7.60 [#]	3.63±1.25 ⁺	8.88±4.34
$GLI_{3\text{-day}}$ ((mmol/l) ² /h/per se)*	2.76 (4.00) [#]	1.00 (0.70) ⁺	3.08 (6.70)	2.47 (15.27) [#]	0.48 (0.67) ⁺	2.54 (4.24)

Notes: 1. *Means the variable is not normally distributed. We report the description with median and interquartile range (interquartile range), and analyze the difference between groups with Kruskal–Wallis (*H*-test); the normally distributed variables are reported with mean±SD. 2. Grouping: LBG: low blood glucose group, minimum BG ≤ 72 mg/dL [4 mmol/L]; MBG: moderate BG group, minimum BG ≥ 72 mg/dL [4 mmol/L], ≤180 mg/dL [10 mmol/L]; HBG: high BG group, maximum BG ≥ 180 mg/dL [10 mmol/L]. While diabetic patients were included in group 1 (LBG1, MBG1, HBG1), and non-diabetic patients were enrolled in group 2 (LBG2, MBG2, HBG2). 3. "DIC time" means the day when patients were diagnosed with DIC. 4. [#]Means that there are significant differences when compared with MBG, ⁺Means that there are significant differences when compared with HBG. A two-sided p-value <0.05 was considered statistically significant.

Abbreviations: AF, atrial fibrillation; BG, blood glucose; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; GLI, Glucose liability index; HF, heart failure; LAGE, largest amplitude of glucose excursion; MODS, multiple organ dysfunction syndrome; SD, standard deviation.

Although the HBG group had the highest BG variability, they did not appear to have the highest mortality and DIC occurrence or a higher SOFA score when discharged.

For the group without diabetes, the MBG2 group had a significantly lower incidence of MODS (14.3%) and shock (23.2%) than the HBG2 group (48.9% versus 59.8%). Moreover, the MBG2 group had the fewest patient deaths within the 90-day period and the number of patients who developed DIC during hospitalization. However, both LBG2 and HBG2 groups had high MODS and shock morbidities and higher mortality and DIC occurrence rates than MBG; however, no significant differences were observed between the groups.

Discussion

This study explored the association between GV and sepsis-related DIC in patients in the ICU. We noted that $GLI_{3\text{-day}}$ was the most sensitive predictor of sepsis-related DIC and independently influenced DIC morbidity. Further, we found that hypoglycemic episodes in patients with diabetes having sepsis were associated with a higher DIC occurrence rate and 90-day mortality. Patients who maintained moderate BG for 72 h achieved better outcomes, including significantly lower DIC morbidity and 90-day mortality. We observed that patients with the lowest glycemic variability had the lowest DIC occurrence. Our study indicated that the GLI of patients with sepsis potentially predicts sepsis-related DIC, notably BG at the 72nd hour.

Here, 238 patients were enrolled, and 72-h BG records of 3195 were included in our final analysis. In our cohort, after applying the CDSS scoring system to define DIC, DIC incidence and total 90-day mortality rate were 28.2% and 37.0%, respectively, which is similar to previous rates.^{7,47}

Several GVs were calculated based on our data set, including glucose mean, GLI, and LAGE (see BG measures). We demonstrated that $GLI_{3\text{-day}}$ was the most sensitive predictor of the incidence of sepsis-related DIC and independently influenced DIC morbidity after adjusting for sex, SOFA on admission, APACHE II on admission, PCT, CRP, platelet count, shock, diabetes, and MODS.

Although DIC is considered a late complication of sepsis, coagulation dysfunction occurs throughout the pathological process of sepsis, as confirmed by various studies.^{47–49} Therefore, timely monitoring of various indicators of DIC is of great significance for its prompt treatment and management and may help to improve the prognosis and survival of patients.^{50,51}

The GLI is an index based on the change of glucose level over time, more so for prolonged periods.^{43,52} Frequent testing may result in a slightly higher GLI without immensely skewing the values. Researchers may obtain a relatively high MAGE after testing for several days. Additionally, GLI takes advantage of the inclusion of time and rate of change in its calculation, which may lead to a better association with DIC occurrence than CV, SD, and LAGE. Moreover, GLI was developed to describe the variability in patients with diabetes who underwent over four examinations per day,⁴³ analogous to an actual ICU setting.

Recent decades have demonstrated a difference in the relationship between diabetes and sepsis outcomes. Some studies have shown that diabetes is associated with increased mortality in patients with sepsis,^{53,54} whereas others have suggested a neutral or even decreased risk.^{54–57}

Here, diabetes was not associated with DIC occurrence and 90-day mortality; however, we found that patients with diabetes were more likely to develop dysglycemia within 72 h.

Further subgroup analysis showed that clinicians should focus on hypoglycemic episodes in patients with diabetes having sepsis since it was associated with a higher DIC occurrence rate and 90-day mortality. Hypoglycemia was reported as a predictor of poor outcomes in patients with sepsis and is closely associated with ICU and hospital mortality.^{58–61} This may be exaggerated in patients with diabetes having sepsis. However, hyperglycemia was not associated with more complications and worse outcomes in patients with diabetes having sepsis, which may be the result of high mean BG tolerance in the diabetes group.^{62,63}

In contrast, in the group with sepsis not having diabetes, no differences were observed between the outcomes of the HBG2 and LBG2 groups. Notably, patients who maintained moderate BG for 72 h achieved better outcomes, including significantly lower DIC morbidity and 90-day mortality. Regardless of the presence of diabetes, the MBG group had

significantly better outcomes. In particular, the MBG group had the lowest GLI, indicating the potential of low GLI as a predictor of favorable outcomes.

High BG variation is associated with an increased risk of mortality in critically ill patients. A novel finding of our study is that variable BG increased the morbidity of sepsis-related DIC even after adjusting for the competing risk of death. This may be due to the endothelial dysfunction because of high glycemic variability. Dysglycemia and high glucose variability are related to compromised endothelial function and injured endothelial cells in patients with type I and II diabetes, as well as in patients with coronary artery disease.^{64–66} Endothelial cells play a key role in maintaining intravascular patency,⁶⁷ thus, disrupted endothelial homeostasis in septic conditions may play a fundamental role in the pathogenesis of sepsis-related DIC (36) and contribute to the high glycemic variability. Similarly, we observed that patients with the lowest glycemic variability had the lowest DIC occurrence.

Our study indicated that the GLI of patients with sepsis may have the potential to predict sepsis-related DIC. Therefore, patients with unstable BG during hospitalization should be closely monitored for DIC. However, this study had some limitations. First, as an observational study, we lack a unified BG management protocol with a strict BG target for all patients, so there might rise a problem on detection bias. However, ICUs involved in our research followed certain routine measure for BG so >90% enrolled patients got 4–6 records/day, which gave a less possibility for the bias among patients. An estimated range of BG levels for the patients with sepsis was recommended; however, the target BG was dependent on the patient's clinical status. The administration of insulin injections was the mainstay of controlling BG levels when BG was >180 mg/dL, similar to the recommendations of the surviving sepsis campaign.⁶⁸ However, we were not able to follow a detailed management protocol for every patient. Second, we were unable to address the underlying mechanism of this disease. Moreover, limited by the facility and setting, we were not able to apply continuous glucose monitoring for our patients; therefore, some information may have been missed during our research period. These limitations should be considered in future studies.

Conclusion

Our study indicated that a higher 72-h GLI in patients with sepsis was independently associated with an increased risk of sepsis-related DIC that was not associated with pre-existing diabetes. Therefore, healthcare workers who manage patients with sepsis could pay more attention to closely monitor BG levels, especially during the 72nd hour, which might give extra information about the septic patients' condition changes.

Abbreviations

AF, atrial fibrillation; APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; AUC, area under the ROC curve; BG, blood glucose; CDSS, clinical decision support system; COPD, chronic obstructive pulmonary disease; CV, coefficient of variation; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GLI, glucose liability index; GS, glucose solution; GV, glycemic variability; HBG, high blood glucose; HF, heart failure; HR, hazard ratios; ICU, intensive care unit; LAGE, largest amplitude of glucose excursion; LBG, low blood glucose; MAGE, mean amplitude of glucose excursions; MBG, mean blood glucose; MBG, moderate BG Group; MODS, multiple organ dysfunction syndrome; OR, odds ratio; ROC, receiver operating characteristic; SD, standard deviation; sHRs, sub-distribution hazard ratios; SOFA, sequential organ failure assessment.

Data Sharing Statement

Data of the manuscript are not sharing online. Please contact correspondence authors to obtain data if necessary.

Ethics Approval and Consent to Participate

This study was approved by the Shanghai Tenth People's Hospital, which is affiliated with the Tongji University School of Medicine (SHSY-IEC-5.0/22K84/P01) and the Xinhua Hospital, which is affiliated with the Shanghai Jiao Tong University School of Medicine (No. XHEC-D-2022-032). The requirement for informed consent was waived owing to the retrospective nature of the study design.

Consent for Publication

The study was conducted from October 2017 to January 2021. All patients enrolled in this study have signed the written informed consent, which permits the researchers to engage in research use of identifiable biospecimens and identifiable data during the peri-operative period and future follow-up without the requirement to obtain additional consent for the future storage, maintenance, or research use, so long as the future activities are within the scope of the broad consent. Patients' data used in the manuscript are maintained with confidentiality. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Dan Liu and YiWen Fan contributed the same to the manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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