ORIGINAL ARTICLE

Association of Glycemic Variability with Outcomes in Non-diabetic Sepsis Patients: A Prospective Observational Study

Prithiviraaj Prakash[1], Prayas Sethi[2], Naval Vikram[3], Maroof Khan[4], Yashdeep Gupta[5], Ranveer S Jadon[6], Arvind Kumar[7], Ved P Meena[8], Naveet Wig[9]

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Abstract

Background: Glycemic variability (GV) is the third domain of sepsis-induced dysglycemia, after hyperglycemia and hypoglycemia, potentially leading to adverse outcomes. This study analyzed the association of GV with in-hospital mortality and length of stay (LOS) in non-diabetic sepsis patients.

Materials and methods: In this prospective observational study, non-diabetic sepsis patients were followed till day 14 of hospital stay, and blood glucose levels were assessed by finger-prick method (seven times per day) daily; clinico-laboratory and GV parameters [standard deviation (SD), coefficient of variation (CV), mean amplitude of glycemic excursion (MAGE)] were assessed on days 1, 3, 5, 7, 10, and 14 of admission.

Results: Two hundred thirteen patients were screened and 80 (mean age 45.6 ± 15.37 years; 50% men) were included in the final analysis. Patients with in-hospital mortality had significantly higher GV when compared to patients without in-hospital mortality [SD: 37.57 vs 25.21, adjusted odds ratio (aOR) 1.13, 95% confidence interval (CI) 1.02–1.24, $p = 0.013$; CV: 24.91 vs 16.88, aOR 1.19, 95% CI: 1.03–1.38, $p = 0.016$; MAGE: 73.13 vs 48.03, aOR 1.05, 95% CI: 1.01–1.11, $p = 0.014$], independent of illness severity (APACHE II), mean blood glucose and hypoglycemia on multivariate regression analysis. There was no significant correlation between GV and LOS. Multivariate analysis showed a significant independent association between CV and ventilator requirement (aOR 1.15, 95% CI: 1.03–1.29, $p = 0.017$) and between SD and need for renal replacement therapy (aOR 1.04, 95% CI: 1–1.09, $p = 0.044$).

Conclusion: This study demonstrated that GV is independently associated with increased in-hospital mortality in non-diabetic sepsis patients. Further studies are required to investigate whether targeting lower GV in septic patients would translate to better outcomes.

Clinical significance: Glycemic variability in sepsis is controversial, with discordant results and a paucity of studies on the Indian population in the literature. Despite blood sugar monitoring being routinely done in sepsis patients, GV is rarely measured and the results of our study indicate that it may be worthwhile to estimate GV in sepsis. This may aid in identifying a subset of patients with increased mortality risk, who may benefit from intensive glucose monitoring and modification of insulin regimen.

Keywords: Glycemic variability, Mortality, Non-diabetes, Sepsis.

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Highlights

- Glycemic variability was associated with high in-hospital mortality in non-diabetic sepsis patients.
- This association between GV and in-hospital mortality was independent of illness severity, mean blood glucose, and hypoglycemia.
- Coefficient of variation and standard deviation had significant independent associations with ventilator requirement and need for renal replacement therapy, respectively.

Introduction

Sepsis is one of the major causes of mortality worldwide and is the leading cause of intensive care unit (ICU) mortality.[1] Globally in 2017, the incidence and mortality of sepsis was 48.9 million and 11 million deaths, respectively.[2] In a study conducted by Hammond et al.[3] the point prevalence of sepsis in the Indian ICU setting was 56.4% with a 30-day mortality of 27.6%.

Sepsis is known to cause stress hyperglycemia (SH), occurring due to a complex interplay of sympathoadrenal and hypothalamic-pituitary axes with increased release of pro-inflammatory cytokines and counter-regulatory hormones. Persistent hyperglycemia is associated with poor outcomes;[4] however, SH is an evolutionarily preserved adaptive response, facilitating a higher blood glucose diffusion gradient that increases glucose uptake in conditions of maldistributed microvascular flow like sepsis[5] and recently there

[1–3,6–9]Department of Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India

[4]Department of Biostatistics, All India Institute of Medical Sciences (AIIMS), New Delhi, India

[5]Department of Endocrinology, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Corresponding Author: Prayas Sethi, Department of Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India, Phone: +91 9599544679, e-mail: prayassethi82@gmail.com

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is increasing evidence to show that iatrogenic efforts to interfere with stress hyperglycemia may have adverse clinical outcomes. "NICE SUGAR" trial reported tight glycemic control (81–108 mg/dL) to be deleterious with increased 90-day mortality, resulting in subsequent glucose management guidelines favoring a more conservative approach of blood glucose management (140–180 mg/dL) in critically ill patients.[6]

Hypoglycemia (blood glucose <70 mg/dL) is associated with higher mortality in sepsis[7] and has been attributed to depleted glycogen stores, inhibition of the corticosteroid response to stress, impaired gluconeogenesis, and increased peripheral glucose utilization.[8] Bagshaw et al.[9] showed that hyperglycemic and hypoglycemic sepsis patients have higher mortality than normoglycemic patients, demonstrating a "U or J" shaped relationship between mortality and blood glucose levels.

Glycemic variability (GV) is the measurement of the fluctuation of glucose homeostasis parameters over a given interval of time. It has recently been considered the third domain of sepsis-induced dysglycemia, apart from hyperglycemia and hypoglycemia.[10] Analysis of the Leuven database by Meyfroidt et al.[11] found that GV in ICU patients was significantly associated with increased mortality, regardless of blood glucose level. Chao et al.[10] reported a significant correlation between GV at ICU admission and 30-day mortality in sepsis, especially among non-diabetic patients, postulating that diabetic septic patients may have better tolerance to GV.

In our study, we evaluated the association of GV with in-hospital mortality, length of stay (LOS), and other adverse events in non-diabetic sepsis patients. There is only one previous retrospective study in the Indian setting on dysglycemia in critically ill patients[12] and most of the foreign studies are retrospective. Our prospective observational study thus aimed to shed some clarity on this elusive subject matter of dysglycemia in sepsis which has discordant results in literature.

Materials and Methods

This prospective observational study was conducted in the Medicine ICU and Medicine ward of a tertiary care hospital in Northern India between July 2022 and March 2024. 213 sepsis patients [fulfilling SEPSIS 3 criteria (1)] between 18 and 70 years of age were screened within 48 hours of hospital admission. The analysis excluded 87 patients with pre-existing diabetes mellitus, 22 patients who died within 72 hours of admission, 13 patients with end-stage renal disease, eight patients with decompensated chronic liver disease, and three patients with intracranial hemorrhage. 80 non-diabetic sepsis patients were finally included in the analysis. The institutional review board (Ethical Committee) approved the study (IECPG-672/25.08.2022) and written informed consent was obtained from each of the study participants.

Patients were followed up till day 14 of the hospital stay. Demographic details were obtained at recruitment and patients' clinical (history, examination, focus of sepsis, organ dysfunction, acute physiology, and chronic health evaluation II score (APACHE II), sequential organ failure assessment score (SOFA), septic shock, hydrocortisone use, bleeding manifestations) and laboratory parameters (complete hemogram, kidney and liver function tests and inflammatory markers) were meticulously followed up on days 1, 3, 5, 7, 10, and 14 of hospital stay. Blood glucose levels were assessed daily (seven times per day) by finger prick capillary blood glucose measurement. A glycemic target of 140–180 mg/dL was applied and the type and route of administration of insulin was left to the discretion of the treating physician.

Table 1: Cut-off levels for 3 groups of GV

GV parameter	*Groups*	*Cut-off level*
SD (mg/dL)	1 (n = 20) (low)	12.13–22.5
	2 (n = 40) (moderate)	22.6–44
	3 (n = 20) (high)	44.1–85
CV	1 (n = 20) (low)	9.1–15.5
	2 (n = 40) (moderate)	15.6–26.2
	3 (n = 20) (high)	26.3–49
MAGE (mg/dL)	1 (n = 20) (low)	21.5–43.73
	2 (n = 40) (moderate)	43.74–84.9
	3 (n = 20) (high)	85–168

CV, coefficient of variation; GV, glycemic variability; MAGE, mean amplitude of glycemic excursion; mg/dL, milligram/deciliter;

Glycemic variability was assessed using standard deviation (SD), coefficient of variation (CV), and mean amplitude of glycemic excursion (MAGE). SD describes the dispersion of all glucose values in a timeframe relative to the mean glucose value in that timeframe and was calculated daily using the formula, $SD = \sqrt{\sum(x - x_1)^2/k - 1}$ (x–glucose level, x_1–mean glucose level of that day, k–number of observations of glucose on that day).[13] Coefficient of variation is the normalized measure of dispersion (corrected for mean glucose), obtained by dividing SD by mean glucose ($CV = SD/x_1$), and was assessed daily.[13] Mean amplitude of glycemic is the mean of clinically relevant glycemic excursions (>1 SD of glucose mean) from consecutive glucose peak to nadir and vice versa[13] and was calculated for every two days (utilizing 14 glucose readings) till day 14 of hospital stay. Total units of insulin used/day and number of hypoglycemic events (glucose ≤70 mg/dL) were assessed daily.

The main outcomes studied were in-hospital mortality and LOS (data on in-hospital mortality and LOS beyond day 14 of hospital stay were obtained from electronic medical records). Analysis was also done to study the association between GV and adverse events like hospital-acquired infection (HAI), hypoglycemia, ventilator requirement, need for renal replacement therapy (RRT), septic shock, and hydrocortisone use. Patients were also categorized into three groups, namely low, moderate, and high GV [<25th percentile (n = 20), 25th–75th percentile (n = 40), and >75th percentile (n = 20), respectively] (cut-off levels shown in Table 1) and association with clinical outcomes and adverse events were assessed among the three groups.

Statistical Analysis

Data analysis was done using the STATA 18.0, College Station, Texas, USA, by trained personnel. Categorical variables are presented as frequency and percentages whereas continuous variables are reported as mean/SD or median (with interquartile range) according to the normality of data distribution. Chi-square/Fisher's exact test was used to establish an association between qualitative variables, while the Student's t-test/Wilcoxon signed-rank test was used for quantitative variables. Correlation between continuous variables was done using the Spearman correlation test. Multivariate regression analysis was done to evaluate the independent association between glycemic variability and clinical outcomes. Kaplan–Meier survival analysis curve with log-rank test was used to compare time to mortality between three groups of GV. The receiver operating characteristic curve (ROC curve) was used to find the cut-off of GV values to predict in-hospital

mortality. For all tests, *p*-value <0.05 was considered statistically significant.

Results

The mean age of the study population was 45.6 years, with an equal number of male and female patients. The predominant foci of sepsis were the lungs (38.75%) and kidneys (35%). Mean APACHE II and SOFA scores at admission were 20.8 and 10.7, respectively (Table 2). During the study period, 65% of patients had septic shock, 53.75% required ventilator support, 36.25% required RRT, 31.25% had at least one hypoglycemic event and 34 patients received hydrocortisone. In-hospital mortality occurred in 35 patients (43.75%), 44 patients survived and 1 patient was discharged against medical advice and the median length of stay was 15 days [interquartile range respectively (IQR), 10–23.5)]. 21 patients (26.25%) developed hospital-acquired infection (HAI) during the study, ventilator-associated pneumonia (VAP) being the most common HAI (71%).

Our study revealed a significant association between GV and in-hospital mortality; patients with in-hospital mortality had significantly higher GV compared to patients without in-hospital mortality (SD: 37.57 vs 25.21, CV: 24.91 vs 16.88, MAGE: 73.13 vs 48.03; $p < 0.0001$ in all). This association between GV and in-hospital mortality remained significant even after adjusting for age, APACHE II, creatinine, mean blood glucose, and hypoglycemia on multivariate analysis [SD: adjusted odds ratio (aOR) 1.13, 95% confidence interval (CI) 1.02–1.24, $p = 0.013$; CV: aOR 1.19, 95% CI: 1.03–1.38, $p = 0.016$; MAGE: aOR 1.05, 95% CI: 1.01–1.11, $p = 0.014$] (Table 3). A significant correlation was absent between GV and length of stay (LOS) (Table 4).

There was a significant independent association between CV and ventilator requirement (aOR 1.15, 95% CI: 1.03–1.29, $p = 0.017$) and between SD and need for RRT (aOR 1.04, 95% CI: 1–1.09, $p = 0.044$) after multivariate analyses (adjusting for age and APACHE II score). Septic shock, hydrocortisone use, and development of HAI were significantly associated with GV on univariate analyses, but this association was lost after adjusting for illness severity (APACHE II score) and age (Table 3). Our study also demonstrated a significantly

Table 2: Baseline characteristics of the study population

Parameter	*Baseline data (N = 80)*
Age (mean ± SD) (years)	45.6 ± 15.37
Male [*N* (%)]	40 (50)
Focus of sepsis [*N* (%)]	
(i) Lung	31 (38.7)
(ii) Kidney	28 (35)
(iii) Soft tissue	10 (12.5)
(iv) Abdomen	9 (11.2)
(v) CNS	8 (10)
(vi) Others	6 (7.5)
APACHE II [mean ± SD]	20.85 ± 5.28
SOFA [mean ± SD]	10.73 ± 5
TLC [median (min, max)] ($\times 10^3/\mu L$)	15.79 (0.5–60)
Neutrophil [mean ± SD] (%)	82.97 ± 12.48
Platelet count [median (min, max)] ($\times 10^3/\mu L$)	159.5 (20–867)
Creatinine [median (min, max)] (mg/dL)	2.8 (0.4–15)
Total bilirubin [median (min, max)] (mg/dL)	0.9 (0.19–12.7)
ALT [median (min, max)] (U/L)	29 (6–1034)
MBG [median (min, max)] (mg/dL)	152.06 (113–327.42)
SD [median (min, max)] (mg/dL)	38.05 (13.19–152.65)
CV [median (min, max)]	23.47 (6.49–68.83)
MAGE [median (min, max)] (mg/dL)	71.08 (21.4–212)
Insulin given [median (min, max)] (units)	0 (0–24)
Hypoglycemic events (atleast one) [*N* (%)]	6 (7.5)
Septic shock [*N* (%)]	42 (52.5)
Ventilator requirement [*N* (%)]	23 (28.7)
Hydrocortisone use [*N* (%)]	18 (22.5)
Bleeding manifestation [*N* (%)]	4 (5)
Transaminitis (ALT > 70 U/L) [*N* (%)]	12 (15)

ALT, alanine aminotransferase; APACHE, acute physiology and chronic health evaluation; CNS, central nervous system; CV, coefficient of variation; min, minimum; max, maximum; MBG, mean blood glucose; *N*, number; SD, standard deviation; SOFA, sequential organ failure assessment; TLC, total leukocyte count; µL, microliter; mg/dL, milligram/deciliter; U/L, units/liter

Table 3: Association of glycemic variability with in-hospital mortality and adverse events (univariate and multivariate logistic regression analysis)

	In-hospital mortality				
GV parameter	*Absent (N = 44)*	*Present (N = 35)*	*p-value*	*Adj p-value*	*aOR (95% CI)*
SD	25.21 (12.13, 55.6)	37.57 (16.96, 66.93)	0.0000*	0.013#	1.13 (1.02–1.24)
CV	16.88 (9.1, 35.75)	24.91 (13.14, 37.05)	0.0000*	0.016#	1.19 (1.03–1.38)
MAGE	48.03 (21.52, 103.18)	73.13 (32.48, 123.3)	0.0000*	0.014#	1.05 (1.01–1.11)
	Ventilator requirement				
	Absent (N = 37)	*Present (N = 43)*	*p-value*	*Adj p-value*	*aOR (95% CI)*
SD	25.76 (12.13, 48.85)	37.49 (14.54, 84.84)	0.0005*	0.085	1.05 (0.99–1.1)
CV	16.9 (9.1, 30.06)	24.54 (11.35, 48.86)	0.0000*	0.017#	1.15 (1.03–1.29)
MAGE	48.86 (21.52, 97.44)	73.03 (27.61, 167.36)	0.0003*	0.127	1.02 (0.99–1.05)
	Renal replacement therapy				
	Absent (N = 51)	*Present (N = 29)*	*p-value*	*Adj p-value*	*aOR (95% CI)*
SD	26.8 (12.13, 84.84)	38.8 (14.6, 66.9)	0.001*	0.044#	1.04 (1–1.09)
CV	17.98 (9.1, 48.8)	25.18 (12.32, 35.75)	0.002*	0.128	1.07 (0.98–1.16)
MAGE	52.15 (21.5, 167.3)	82.91 (26.2, 123.3)	0.001*	0.061	1.02 (1–1.04)

(Contd...)

Table 3: *(Contd...)*

	Hospital acquired infection				
GV parameter	*Absent (N = 59)*	*Present (N = 21)*	*p-value*	*Adj p-value*	*aOR (95% CI)*
SD	26.8 (12.1, 84.8)	37.5 (25.8, 66.9)	0.004*	0.243	1.03 (0.98–1.07)
CV	18.1 (9.1, 48.86)	25.18 (16.87, 35.4)	0.001*	0.331	1.05 (0.96–1.14)
MAGE	54.5 (21.5, 167.3)	73.1 (45.1, 123.3)	0.002*	0.184	1.02 (0.99–1.04)
	Hypoglycemia (atleast one event)				
	Absent (N = 55)	*Present (N = 25)*	*p-value*	*Adj p-value*	*aOR (95% CI)*
SD	25.8 (12.13, 65.1)	39.2 (25.8, 84.84)	<0.001*	0.033#	1.06 (1–1.11)
CV	17.4 (9.1, 35.7)	26.37 (18.42, 48.8)	<0.001*	0.003#	1.21 (1.07–1.37)
MAGE	49.97 (21.5, 115.1)	82.9 (45.1, 167.3)	<0.001*	0.02#	1.03 (1–1.06)
	Septic shock				
	Absent (N = 28)	*Present (N = 52)*	*p-value*	*Adj p-value*	*aOR (95% CI)*
SD	23.98 (14.54, 48.85)	34.64 (12.13, 84.84)	0.0001*	0.145	1.04 (0.99–1.1)
CV	16.48 (11.94, 28.68)	23.92 (9.1, 48.86)	0.0001*	0.085	1.11 (0.99–1.24)
MAGE	45.01 (26.22, 93.88)	72.14 (21.52, 167.36)	0.0001*	0.063	1.86 (1–1.06)
	Hydrocortisone use				
	Absent (N = 46)	*Present (N = 34)*	*p-value*	*Adj p-value*	*aOR (95% CI)*
SD	25.81(12.13, 66.93)	38.21 (15.43, 84.84)	0.0013*	0.979	1 (0.94–1.06)
CV	17.62 (9.1, 35.71)	23.92 (11.35, 48.86)	0.0020*	0.525	0.96 (0.85–1.08)
MAGE	49.41 (21.52, 123.3)	73.08 (28.22, 167.36)	0.0011*	0.995	1 (0.97–1.03)

Adj, adjusted; aOR, adjusted odds ratio; CI, confidence interval; CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; *N*, number; SD, standard deviation; Values are represented as Median (minimum, maximum); Two-sample Wilcoxon rank-sum (Mann–Whitney) test was used. *Significant on univariate analysis. #Significant after multivariate analysis

Table 4: Association of GV with LOS and adverse events

GV parameter	*LOS*	*APACHE-II*	*SOFA*	*Creatinine*	*ALT*
SD	0.10 (0.35)	0.545 (0.00)	0.273 (0.014)	0.4897 (0.000)	–0.028 (0.799)
CV	0.16 (0.13)	0.568 (0.00)	0.273 (0.014)	0.4855 (0.000)	–0.107 (0.340)
MAGE	0.11 (0.32)	0.548 (0.00)	0.299 (0.007)	0.4811 (0.000)	–0.038 (0.737)

CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; SD, standard deviation; Spearman correlation test was used; values are represented as Rho (*p*-value)

high positive correlation between GV (SD, CV, and MAGE) illness severity (APACHE II, SOFA scores) and creatinine level (Table 4).

Analysis was also done after dividing patients into three groups (low, moderate, and high GV) (Table 1). Patients with high GV had significantly increased in-hospital mortality compared to patients with moderate and low GV (high vs moderate vs low; SD: 65 vs 52.5 vs 5%, $p < 0.0001$; CV: 70 vs 50 vs 5%, $p < 0.0001$; MAGE 70 vs 47.5 vs 10%, $p < 0.0001$) (Table 5). Similarly, patients with high GV (SD, CV, and MAGE) had increased ventilator requirement, need for RRT, HAI, hypoglycemia (at least one event), septic shock, and hydrocortisone use compared to the other two groups. There was no significant difference in LOS among the three groups (Table 5).

The Kaplan–Meier survival curve (log-rank test) showed a statistically significant difference in time to mortality between high and moderate GV (SD: $p = 0.002$; CV: $p = 0.0227$; MAGE: $p = 0.001$) (Figs 1 to 3). Receiver operating characteristic (ROC) analyses on SD, CV, and MAGE were done to assess their diagnostic accuracy for predicting in-hospital mortality (Fig. 4). Coefficient of variation had the highest area under the curve (AUC) (0.8114) among the three GV parameters, with sensitivity and specificity of 80 and 75%, respectively for predicting in-hospital mortality at an optimal cut-off of 20.31 (Table 6).

Twenty-five patients in our study cohort had at least one hypoglycemic event (glucose <70 mg/dL) and the in-hospital mortality rate in these patients was 87.5% compared to 25.45% in patients without hypoglycemia ($p < 0.0001$). Since hypoglycemia had a significant association with in-hospital mortality, we studied the association of GV with in-hospital mortality after excluding patients with hypoglycemia (at least one event). In a cohort of 55 patients (after excluding patients with hypoglycemia), SD and CV still had a significant association with in-hospital mortality (SD: aOR 1.13, 95% CI: 1–1.27, $p = 0.046$; CV: aOR 1.17, 95% CI: 1–1.37, $p = 0.05$) on multivariate analysis (Table 7).

Discussion

This prospective observational study, the first of its kind in the Indian population demonstrated a significant association between GV and in-hospital mortality, independent of illness severity, hypoglycemia, and mean blood glucose. Increased glycemic variability in sepsis is likely due to metabolic instability, resulting from the combined effects of stress hyperglycemia (SH) and hypoglycemia.[14] Increased GV in sepsis could also be attributed to variability in insulin sensitivity as proposed by Rivas and Nugent.[15]

Among the multiple retrospective studies assessing glycemic variability in critically ill patients, few have been done exclusively in sepsis patients. Previous studies have used SD, CV, MAGE, and glycemic liability index (GLI) for assessing GV in sepsis patients.[16]

Table 5: Comparison of in-hospital mortality, LOS, and adverse events among three groups of GV

GV parameter	*Clinical variable*	*Group I (low) (N = 20)*	*Group II (moderate) (N = 40)*	*Group III (high) (N = 20)*	*p-value*
SD	In-hospital mortality	1 (5)	21 (52.5)	13 (65)	0.000*
	HAI	0 (0)	13 (32.5)	8 (40)	0.002*
	Shock	7 (35)	28 (70)	17 (85)	0.004*
	Ventilator requirement	4 (20)	24 (60)	15 (75)	0.001*
	Renal replacement therapy	3 (15)	13 (32.5)	13 (65)	0.004*
	Hypoglycemia	0 (0)	15 (37.5)	10 (50)	0.001*
	Hydrocortisone use	3 (15)	20 (50)	11 (55)	0.015*
	LOS [median (min, max)]	12 (6.71)	18 (5.80)	11.5 (7.50)	0.0178
CV	In-hospital mortality	1 (5)	20 (50)	14 (70)	0.000*
	HAI	0 (0)	14 (35)	7 (35)	0.003*
	Shock	4 (20)	23 (57.5)	16 (80)	0.001*
	Ventilator requirement	0 (0)	16 (40)	14 (70)	0.000*
	Renal replacement therapy	3 (15)	16 (40)	10 (50)	0.055
	Hypoglycemia	0 (0)	12 (30)	13 (65)	<0.001*
	Hydrocortisone use	3 (15)	19 (47.5)	12 (60)	0.011*
	LOS [median (min, max)]	12 (6.71)	15.5 (7.80)	18 (5.52)	0.1590
MAGE	In-hospital mortality	2 (10)	19 (47.5)	14 (70)	0.000*
	HAI	0 (0)	13 (32.5)	8 (40)	0.002*
	Shock	8 (40)	25 (62.5)	19 (95)	0.001*
	Ventilator requirement	6 (30)	20 (50)	17 (85)	0.002*
	Renal replacement therapy	2 (10)	14 (35)	13 (65)	0.001*
	Hypoglycemia	0 (0)	14 (35)	11 (55)	0.001*
	Hydrocortisone use	4 (20)	17 (42.5)	13 (65)	0.016*
	LOS [median (min, max)]	12 (6.71)	18 (5.80)	13 (7.50)	0.1084

Values are represented as frequency (percentage); All analyses (except LOS) were done using Chi-square/Fischer's exact *t*-test; Kruskal–Wallis equality of populations rank test was used for LOS analysis. CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; SD, standard deviation. *Significant

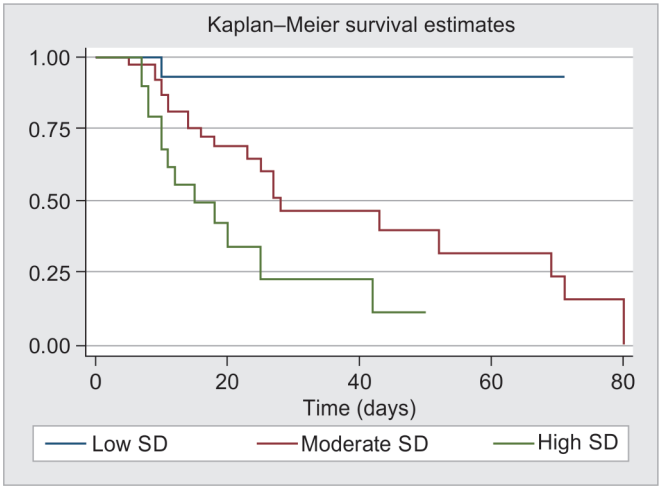

Fig. 1: Kaplan–Meier survival analysis for three groups of SD
SD, standard deviation

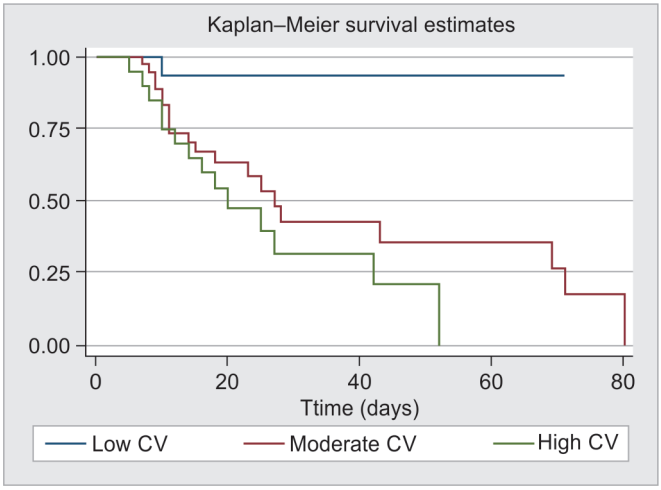

Fig. 2: Kaplan–Meier survival analysis for three groups of CV
CV, coefficient of variation

Ali et al.[17] demonstrated a significant association between GV [MAGE, SD, and glycemic liability index (GLI)] and hospital mortality ($p < 0.001$ in all cases) in sepsis patients. In a retrospective cohort study by Chao et al.[10] on 452 sepsis patients in the ICU setting, there was a significant association between the GV on day 1 of ICU admission (MAGE, CV) with 30-day mortality ($p = 0.018$). Interestingly, this association remained strong in non-diabetic patients ($p = 0.035$), unlike the diabetic group ($p = 0.254$) even though diabetic patients had higher GV, hypothesizing that diabetic septic patients may tolerate GV better than non-diabetics. A similar positive association between GV and mortality was obtained in studies by Atamna et al.,[18] Liu et al.,[14] Lu et al.,[19] and Yao et al.[16]

The only Indian study on GV in critically ill patients, a retrospective review of 2208 ICU patients by Todi et al.,[12] showed a significant association between GV (SD, GLI) ($p < 0.001$) and ICU mortality, independent of hypoglycemia.

After an extensive literature search, we were able to find only three prospective studies on GV in critically ill patients. Furushima et al.,[20] reported a significant independent association between MAGE and 90-day all-cause mortality, 90-day ICU-free days, and urinary isoprostaglandin F2α on multivariate analysis among 40 ICU patients. Dong et al.,[21] reported that raised GV was highly associated with poor prognosis, with even more predictive power than hyperglycemia/ hypoglycemia in 780 pediatric ICU patients. In addition to the correlation between SD and ICU, hospital mortality (higher in patients with SD>20 mg/dL), Waeschle et al.,[22] were able to demonstrate a significant association between SD and critical hypoglycemia in septic shock patients ($p = 0.0197$).

In a recent meta-analysis by Li et al.,[23] which included 10 studies with 4296 septic patients, pooled results showed that septic patients with higher GV had significantly higher mortality compared with patients with lower GV ($p < 0.001$ for SD, CV, MAGE, and GLI), with multivariate analyses in eight studies adjusting for variables like age, sex, APACHE II and SOFA scores.

Our study population was categorized into three groups namely, low, moderate, and high GV (<25th percentile, 25th–75th percentile, and >75th percentile, respectively), similar to Lu et al.,[19] with almost similar cut-offs. This study demonstrated a significant difference in time to mortality between the three groups (Figs 1 to 3) with *p*-values of 0.002, 0.0227, and 0.001 for SD, CV, and MAGE, respectively. Similarly, in a retrospective study of 1485 hospitalized patients with bacterial infections by Atamna et al.,[18] CVs of glucose levels were divided into tertiles; however, no significant association between GV and LOS was reported. Higher bacteremia rates were present in the upper CV tertile compared with the lower one (6 vs 2%, $p = 0.007$); 30-day mortality was significantly increased in the mid and upper CV tertiles compared with the lower tertile (13 vs 5%, $p = 0.005$; and 40 vs 5%, $p = 0.002$, respectively). Very few studies have compared the GV parameters for their efficacy in predicting mortality. AUC for the ROC curve was maximum for CV (0.8114) in our study compared to SD and MAGE. Glycemic liability index had the highest AUC (ROC curve) in studies conducted by Ali et al.,[17] (MAGE, SD, and GLI) and Liu et al.,[14] (SD, CV, GLI) whereas mean absolute glucose (MAG) had the highest AUC in the study by Dong et al.,[21] for predicting mortality.

From the results of our study, complimented by similar results in multiple previous studies it seems clear that GV is an independent predictor of mortality in sepsis, implicating a potential role for routine incorporation of GV evaluation in sepsis patients for better risk stratification. In our study, SD, CV, and MAGE > 57.98, >37.05, and >105.11 respectively had 100% specificity for predicting in-hospital mortality, which could serve as cut-offs in clinical practice warranting more intensive glycemic monitoring and control to prevent dire outcomes. An even more pressing question left to be answered is whether targeting lower GV in sepsis patients could improve prognosis. Leng et al.,[24] showed that minimized glycemic fluctuation was associated with decreased severity and mortality in COVID-19 patients. Almagthali et al.,[25] studied the impact of insulin infusion therapy vs insulin sliding scale on GV in 80 critically ill patients and explored its impact on clinical outcomes. Patients randomized to the infusion therapy group had significantly lower GV ($p = 0.01$) and had lower rates of hypoglycemia (6.5 vs 2.77%).

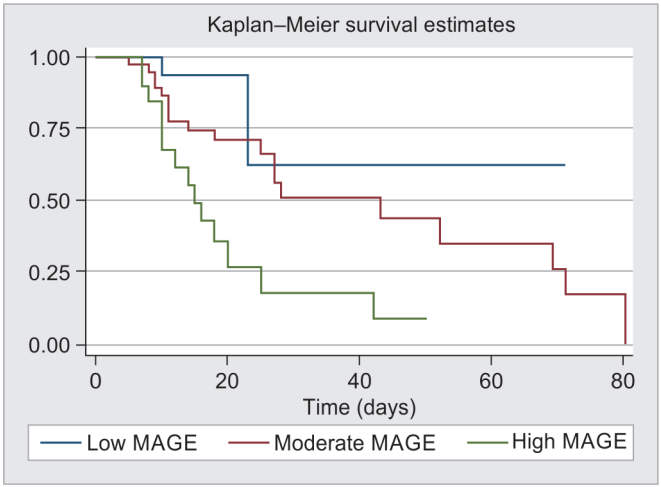

Fig. 3: Kaplan–Meier survival analysis for three groups of MAGE

MAGE, mean amplitude of glycemic excursion

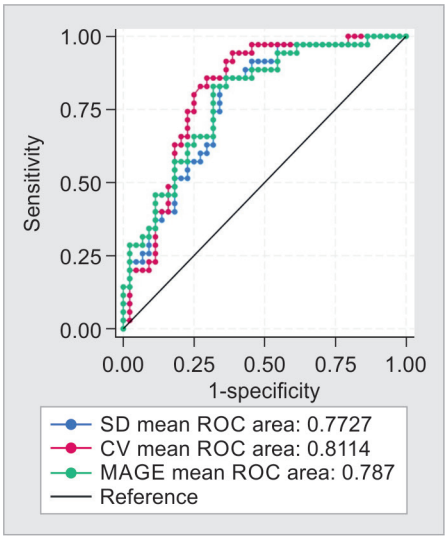

Fig. 4: ROC curves for SD, CV, and MAGE

CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion ROC, receiver operating characteristic; SD, standard deviation

Table 6: Receiver operating characteristic generation table for the cut-off value of SD, CV, and MAGE for predicting in-hospital mortality

Glycemic parameter	*Sensitivity*	*Specificity*	*Correctly classified*	*LR+*	*LR–*	*PPV*	*NPV*	*Cut off value*
SD	82.86%	65.91%	73.42%	2.43	0.26	65.2%	82.3%	29.58
CV	80%	75%	77.22%	3.20	0.27	70.7%	82.1%	20.31
MAGE	82.86%	68.18%	74.68%	2.60	0.25	65.9%	83.3%	55.4

CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; NPV, negative predictive value; SD, standard deviation; LR+, positive likelihood ratio; LR–, negative likelihood ratio; PPV, positive predictive value

Table 7: Association between GV and in-hospital mortality, LOS, and adverse events (after excluding hypoglycemia)

	In-hospital mortality				
GV parameter	*Absent (N = 41)*	*Present (N = 14)*	*p-value*	*Adj p-value*	*aOR (95% CI)*
SD	24.3 (12.1, 55.6)	32.6 (16.9, 65.1)	0.003*	0.046#	1.13 (1–1.27)
CV	16.1 (9.1, 35.8)	22.9 (13.1, 32.4)	0.001*	0.05#	1.17 (1–1.37)
MAGE	46.02 (21.5, 103.1)	66.6 (32.4, 115.1)	0.003*	0.092	1.05 (0.99–1.1)

Values are represented as median (minimum, maximum); A two-sample Wilcoxon rank-sum (Mann–Whitney) test was used. Adj, adjusted; aOR, adjusted odds ratio; CI, confidence interval; CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; *N*, number; SD, standard deviation. *Significant on univariate analysis; #Significant after multivariate analysis

However, there was no significant difference in LOS in ICU and ICU mortality between the two groups. Further prospective studies with larger study populations are required in sepsis patients to assess the possible role of treating GV as a therapeutic target.

The exact pathophysiological basis behind worse outcomes in patients with higher GV is yet to be determined and is likely multi-factorial.[14] Both stress hyperglycemia and hypoglycemia are associated with higher mortality in sepsis and patients with higher GV are likely to suffer the brunt of both these processes. Activation of oxidative stress with high GV, as suggested by the association of GV with higher urinary 8-isoprostaglandin F2α (a marker of oxidative stress) has also been implicated to play a key role in the exacerbation of sepsis. A possible link between GV and end-organ damage through endothelial dysfunction has also been postulated.[26,27]

Our study showed no significant association between GV and LOS, similar to the results of Atamna et al.,[18] Akirov et al.,[28] reported longer LOS in patients with higher GV (CV, SD) ($p < 0.001$). A possible explanation for this discrepancy could be that Akirov et al.,[28] studied GV in hospitalized patients in general, in contrast to our study which had a sicker cohort of patients with LOS possibly being influenced by high mortality rate.

In our study, patients with ventilator requirement had significantly higher GV (CV: aOR 1.15, 95% CI: 1.03–1.29, $p = 0.017$) than those without ventilator requirement, even after adjustment for illness severity in multivariate analysis. Since there is no biologically plausible explanation for the association between GV and ventilator requirement, it could be due to the confounding effects of sedation either directly (effect of sedating agents on glucose metabolism) or indirectly (due to altered sensorium leading to decreased hypoglycemic awareness).[29] The significant independent association between GV and the need for RRT (SD: aOR 1.04, 95% CI: 1–1.09, $p = 0.044$) in our study, was similar to the results by Ali et al.,[17] who also showed a higher rate of AKI (68%) in patients with GLI above cohort median compared to 47% below cohort median ($p < 0.001$). Increased need for RRT in patients with higher GV may be due to hyperglycemia-induced renal mitochondrial swelling and enhanced oxidative stress.[30]

Fifty-two patients had septic shock in our study and these patients had significantly higher GV than those without shock on univariate analysis, but after adjusting for illness severity (APACHE II) on multivariate analysis, this significance was lost. Waeschle et al.,[22] conducted a prospective study in 191 patients (sepsis, severe sepsis, and septic shock) to study the impact of sepsis severity on GV and hypoglycemia. They reported a positive association between disease severity and GV, with all patients in the severe sepsis and septic shock group having SD >20 mg/dL, and also reported a significant association of SD with critical hypoglycemia, particularly for septic shock patients ($p = 0.0197$). Thirty-four patients with septic shock had received hydrocortisone and sub-group analysis to study the effect of hydrocortisone use on GV did not show significance on multivariate analysis after adjusting for illness severity (APACHE II). Similarly, the association between GV and HAI was lost after accounting for illness severity. These findings further highlight that the association of shock, hydrocortisone use, and HAI with GV was attributable to illness severity and not due to the inherent effects of shock/hydrocortisone/HAI on GV.

Hypoglycemia was significantly associated with in-hospital mortality ($p < 0.0001$) in our study. The association between hypoglycemia and mortality in sepsis is well known, attributed mainly to the blunted physiological response to hypoglycemia in critically ill patients, neuroglycopenia, and excitotoxicity due to glutamate.[31] The relative risk of mortality for hypoglycemia in the VISEP study was 3.3 and even a single hypoglycemic event during a hospital stay was an independent risk factor for mortality (OR 2.98), as shown by Park et al.[32,33] We also observed a significant independent association between hypoglycemia and GV ($p = 0.033$, 0.003, and 0.02 for SD, CV, and MAGE, respectively). This brings us to the dilemma of whether the significant association between GV and in-hospital mortality could be attributed to hypoglycemia alone or whether GV had an independent association with mortality. To decipher these queries, a multivariate regression analysis was conducted, which elicited a significant independent association between GV and in-hospital mortality even after adjusting for illness severity (APACHE II) and hypoglycemia. We were also able to establish a significant association between GV and in-hospital mortality in a separate analysis, after excluding patients with hypoglycemia (at least one glucose value <70 mg/dL during the study).

This study had some limitations, such as the small sample size and that it was conducted in a single center. Our study did not utilize continuous glucose monitoring (CGM), which could be a better tool for GV estimation. In addition, consideration of dietary factors and standardization of insulin regimen were not performed in our study.

Conclusion

Glycemic variability (SD, CV, and MAGE) is associated with increased in-hospital mortality in non-diabetic sepsis patients. This association was independent of illness severity, mean blood glucose, and hypoglycemia. There was no significant association between GV and LOS. There are no randomized control trials at present, to specifically explore the therapeutic benefit of achieving lower glycemic variability in sepsis patients, which may be addressed in future trials.

Clinical Significance

Glycemic variability in sepsis is controversial, with discordant results and a paucity of studies in the Indian population in literature. Despite blood sugar monitoring being routinely done in sepsis

patients, GV is rarely measured and the results of our study indicate that it may be worthwhile to estimate GV in sepsis. This may aid in identifying a subset of patients with increased mortality risk, who may benefit from intensive glucose monitoring and modification of insulin regimen.

Orcid

Prithiviraaj Prakash https://orcid.org/0000-0002-8155-8158
Prayas Sethi https://orcid.org/0000-0001-8525-8374
Naval Vikram https://orcid.org/0000-0002-6202-576X
Maroof Khan https://orcid.org/0000-0001-9449-6518
Yashdeep Gupta https://orcid.org/0000-0002-4345-717X
Ranveer S Jadon https://orcid.org/0000-0002-3269-2174
Arvind Kumar https://orcid.org/0000-0002-9229-1081
Ved P Meena https://orcid.org/0000-0003-2537-8125
Naveet Wig https://orcid.org/0000-0002-6603-601X

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