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Association of Stress Hyperglycemia with Mortality and Clinical Outcomes in Critically Ill children: A Cross-Sectional Study

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ABSTRACT

Background and Objective: Hyperglycemia is a recognized response to acute stress in critically ill patients, arising from complex hormonal, inflammatory, and metabolic changes. Stress hyperglycemia (SH) frequently occurs in pediatric intensive care and is associated with increased morbidity and mortality. This study aimed to evaluate the association between SH and clinical outcomes in critically ill pediatric patients.

Methods: A cross-sectional study was conducted over one year in the Pediatric Intensive Care Unit (PICU) of the Government Medical College Jammu. Non-diabetic, critically ill children aged 1 month to 17 years requiring PICU care for at least 24 hours were included. Blood glucose levels were measured at admission and every 12 hours, with SH defined as blood glucose >140 mg/dL. Statistical analyses included t-tests, Chi-Square tests, ROC curve analysis, and multivariate logistic regression.

Findings: Of 204 children, 129 (63.24%) were hyperglycemic, with a median onset on the first day and a median duration of 2 days. Hyperglycemic patients had significantly higher median glucose levels at admission (141 mg/dL vs. 95 mg/dL) and peak glucose levels (211 mg/dL vs. 122 mg/dL) compared to non-hyperglycemic patients (P<0.0001). SH was associated with higher mortality (54.26% vs. 22.67%, P<0.0001), longer ventilator use (72.87% vs. 40%), and increased vasoactive support (76.74% vs. 41.33%). Peak glucose >177 mg/dL moderately predicted mortality (AUC 0.701).

Conclusion: SH is a significant marker of severity in critically ill pediatric patients, correlating with increased mortality and longer PICU stays. Future studies are needed to refine glycemic control strategies.

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Introduction

Stress hyperglycemia (SH) has been defined as hyperglycemia that is occurring in critically ill patients, who have not been previously diagnosed to have diabetes mellitus (DM).The American Diabetes Association (ADA,2022) guidelines described SH as having a random glucose level greater than 140 mg/dL at any given time in hospitalized patients [1]. Hyperglycemia is a well-recognized response to acute stress in critically ill patients, resulting from the complex interplay of hormonal, inflammatory, and metabolic changes. In pediatric intensive care settings, SH is frequently observed and has been associated with adverse outcomes, including increased morbidity and mortality [2]. Despite its prevalence, the precise role of hyperglycemia as an independent predictor of mortality in critically ill children remains debated.

Existing literature shows considerable heterogeneity in the definition of SH, timing of glucose measurement, and reported outcome associations, leading to inconsistent conclusions. Moreover, most available evidence is derived from adult studies, while pediatric data—especially from Indian PICU settings—are limited. There is also a lack of consensus regarding clinically relevant glucose thresholds that predict adverse outcomes in children. Therefore this study aimed to evaluate the association between SH and clinical outcomes, particularly mortality, in critically ill pediatric patients. By analyzing the timing, duration, and intensity of hyperglycemia, as well as its correlation with interventions such as invasive ventilation and vasoactive support, this study contributes to the existing body of knowledge and provides evidence for refining glycemic control strategies in pediatric critical care.

Methods

This prospective observational study was conducted over 1 year (Nov 2020 - Oct 2021) in the 8-bed pediatric intensive care unit (PICU) at Shri Maharaja Gulab Singh Hospital, Jammu. The PICU has an annual admission rate of 300-400 children.

Inclusion and Exclusion Criteria

Non-diabetic children aged 1 month to 17 years, with a PICU stay of at least 24 hours, requiring assisted ventilation or vasoactive infusion for at least 24 hours, and not on long-term steroids were included in the study. Exclusions included children under 1 month or over 17 years, those with a PICU stay under 24 hours, those who left against medical advice, those on long-term steroids, or those with known diabetes.

Sample Size

A previous study by Patki VK et al [3] reported a prevalence of SH of 69.3% among critically ill children. Taking this prevalence as a reference, the minimum required sample size was calculated using a margin of error of 6.5% and a 95% confidence level. Based on this calculation, the minimum sample size required was 194 patients. To further reduce the margin of error and improve the precision of estimates, a total of 204 patients were included in the study.

The sample size was calculated using the following formula: $N \geq (p(1-p))/(ME/z_{\alpha})^2$ where p represents the expected prevalence, ME denotes the margin of error, and Zα is the standard normal deviate corresponding to a two-sided alpha error of 5% (Z=1.96).

Out of 204 enrolled critically ill children, 86 were excluded. Data included demographic details, clinical history, treatment requirements, and blood glucose levels monitored at admission and every 12 hours. Hyperglycemia was defined as blood glucose >140 mg/dl (ADA guidelines) [1]. Bed-side glucometer was used for analysis of capillary blood glucose level.

All patients admitted to the Pediatric Intensive Care Unit (PICU) received isotonic saline with 5% dextrose as maintenance fluids. For fluid resuscitation in cases of hypovolemia, either Ringer's lactate or isotonic saline was administered, based on clinical indications.

Nutritional status of each patient was evaluated at admission using anthropometric measurements, including weight-for-age, weight-for-height, and BMI, which were interpreted as percentiles according to standard growth charts (WHO and IAP growth charts for ages upto 5 years and greater than 5 years respectively. Nutritional support was provided as per standard PICU protocol. Hemodynamically stable patients received enteral

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feeds, while critically unstable patients were kept NPO until clinical improvement.

Anthropometric Assessment

Weight was measured using a calibrated electronic weighing scale with the child minimally clothed and recorded to the nearest 0.1 kg. Length (for children <2 years) was measured in the supine position using an infantometer, while standing height (for children ≥2 years) was measured using a stadiometer to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). BMI-for-age Z-scores were derived using World Health Organization (WHO) growth standards. Severe malnutrition was defined as a BMI-for-age Z-score<−3 standard deviations (SD) for children ≥5 years, and for children <5 years as weight-for-height/length Z-score<−3 SD, or the presence of bilateral pitting edema, in accordance with WHO criteria.

Timing of hyperglycemia was defined as the first occurrence of blood glucose >140 mg/dL relative to PICU admission. Duration of hyperglycemia referred to the period during which blood glucose levels remained >140 mg/dL. The peak blood glucose level was defined as the highest recorded glucose value during the PICU stay, while the mean blood glucose level represented the average of all glucose measurements obtained during the PICU stay. Ventilator days were defined as the duration from endotracheal intubation to extubation, and ventilator-free days were calculated as the number of days in the PICU excluding ventilator days.

Outcome Measures

Patients were categorized into hyperglycemic and non-hyperglycemic groups based on blood glucose levels at admission and during the PICU stay. The primary outcome was in-PICU mortality, defined as death occurring during the PICU stay. Secondary outcomes included the requirement for mechanical ventilation, need for vasoactive or inotropic support, length of PICU stay, ventilator days, and ventilator-free days. All outcome variables were predefined prior to analysis and prospectively recorded during the PICU stay.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were assessed for normality using the Shapiro–Wilk test prior to analysis. Variables with a normal distribution were summarized as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median with interquartile range (IQR). Comparisons of continuous variables between groups were performed using the independent t-test for normally distributed data, while appropriate non-parametric tests were used for skewed data. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Receiver operating characteristic (ROC) curve analysis was used to assess the predictive ability of peak blood glucose levels and duration of hyperglycemia for mortality. Multivariate logistic regression analysis was performed to identify independent predictors of mortality. A p value <0.05 was considered statistically significant.

Data entry was done in Microsoft Excel and analyzed using SPSS software (version 21.0). A p-value <0.05 was considered statistically significant.

Results

The study included 204 critically ill children, with a median age of 4 years and a median weight of 17 kg. Males constituted 53% of the study population. None of the enrolled children were classified as severely malnourished. On the nutritional assessment ,7% of patients had anthropometric indices between the 3rd and 25th percentiles, indicating mild-to-moderate malnutrition, while 35% were between the 25th and 50th percentiles, reflecting lower-normal nutritional status. The majority of patients (55%) were between the 50th and 90th percentiles, representing average-to-good nutritional status, and (3%) were above the 90th percentile, suggesting overweight or obesity.

The median blood glucose at PICU admission was 116 mg/dL, with a peak median of 162 mg/dL during the stay (Table 1). Two-thirds of patients (63.2%, 129/204) developed hyperglycemia, with a median onset on day 1 and median duration of 2 days. Hyperglycemic patients had significantly higher

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median admission glucose (141 vs. 95 mg/dL), median glucose during PICU stay (135 vs. 98 mg/dL), and peak glucose levels (211 vs. 122 mg/dL) compared to non-hyperglycemic patients (P < 0.0001) (Table 1).

The distribution of admission diagnoses differed significantly between hyperglycemic and non-hyperglycemic patients (table 1, 2). Central nervous system (CNS) disorders were more common in the hyperglycemic group than in the non-hyperglycemic group (33.3% vs. 14.7%). The proportion of respiratory illnesses was comparable between the two groups, while septicemia and animal bite cases were more frequent among non-hyperglycemic patients. Overall, admission diagnosis was significantly associated with glycemic status (P=0.0048) (table 1, 2).

Nearly Three-fourths (72.87%) of hyperglycemic patients required invasive ventilation compared to 40% of non-hyperglycemic patients (P<0.0001) (table 1). Hyperglycemic patients also required longer durations of assisted ventilation and more frequent vasoactive or inotropic support (76.74% vs. 41.33%, P<0.0001) (table 1). In addition, the median length of PICU stay was significant lower in the hyperglycemic group (5 days vs. 3 days, P<0.0001) (table 1) and mortality was significantly higher among hyperglycemic patients (54.26% vs. 22.67%, P<0.0001) (table 1).

Clinical outcomes differed significantly between hyperglycemic and non-hyperglycemic patients (Table 1). Mortality was higher in the hyperglycemic group compared with the non-hyperglycemic group (54.26% vs. 22.67%), while step-down from the PICU was more frequent among non-hyperglycemic patients (77.33% vs. 45.74%). Overall outcome distribution was significantly associated with glycemic status (P < 0.0001) (table 1).

On ROC analysis, peak blood glucose demonstrated moderate ability to predict mortality, with an AUC of 0.701 (95% CI: 0.633–0.763; P < 0.0001), and an optimal cut-off value of >177 mg/dL (Table 3, Figure 1). In contrast, duration of hyperglycemia showed poor discriminatory power for mortality prediction (AUC 0.506; P = 0.91) (Table 3, Figure 2).

Non-survivors had significantly higher median and peak blood glucose levels compared with survivors (P<0.0001). On receiver operating characteristic analysis, peak blood glucose demonstrated moderate ability to predict mortality, with an AUC of 0.701 (95% CI: 0.633–0.763; P<0.0001) and an optimal cut-off value of >177 mg/dL (Table 2, Figure 1). In contrast, duration of hyperglycemia showed poor discriminatory power for mortality prediction (AUC 0.506; P=0.91) (Table 3, Figure 2).

On multivariate logistic regression analysis, fewer ventilator-free days were independently associated with increased mortality (aOR 0.504; 95% CI: 0.353–0.719; P=0.0005). An increasing number of vasoactive agents was also associated with higher mortality risk (aOR 3.039; 95% CI: 1.189–7.770; P=0.020). Male sex was independently associated with mortality (aOR 4.763; 95% CI: 1.414–16.044; P=0.012). Hyperglycemia was not an independent predictor of mortality after adjustment for confounding variables (Table 4).

Discussion

This study demonstrates a significant association between SH and adverse clinical outcomes in critically ill pediatric patients. Children with hyperglycemia had higher mortality, longer PICU stays, and a greater need for invasive ventilation and vasoactive support, suggesting that SH reflects underlying illness severity rather than acting as an independent causal factor.

The predominance of hyperglycemia among patients with CNS disorders in our cohort is consistent with findings reported by Patki et al. and Yung et al., who also observed a higher prevalence of SH in children with CNS infections, trauma, and seizures. Neuroendocrine activation, increased catecholamine release, and hypothalamic–pituitary–adrenal axis stimulation during CNS injury are well-recognized mechanisms contributing to glucose dysregulation. Similar associations have been reported in adult neurocritical care studies, reinforcing the biological plausibility of this finding [3, 4].

Respiratory illnesses constituted the second most common diagnostic category associated with hyperglycemia in our study, comparable to observations by Faustino and Apkon, who reported increased hyperglycemia among mechanically ventilated pediatric patients with severe pneumonia and ARDS [5].

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Table 1. Comparison of glycemic parameters, clinical characteristics, management, and outcomes between hyperglycemic and non-hyperglycemic patients

Variables		Hyperglycemic (n=129)	Non-hyperglycemic (n=75)	P-value
Glycemic parameters, median (IQR), mg/dL	Blood glucose at admission	141 (102–178)	95 (87.5–116)	<0.0001[π]
	Median blood glucose	135 (117–157)	98 (94–104)	
	Peak blood glucose	211 (170–262)	122 (113.5–129)	
Admission diagnosis, n (%)	Respiratory disorders	32 (24.81)	20 (26.67)	0.0048[*]
	CNS disorders	43 (33.33)	11 (14.67)	
	Gastrointestinal disorders	21 (16.28)	13 (17.33)	
	Septicemia	8 (6.20)	10 (13.33)	
	Others	25 (19.38)	21 (28.00)	
Assisted ventilation, n (%)	No respiratory support	1 (0.78)	0 (0.00)	<0.0001[*]
	HHHFNC	6 (4.65)	13 (17.33)	
	Non-rebreather mask	28 (21.71)	32 (42.67)	
	Invasive ventilation	94 (72.87)	30 (40.00)	
Vasoactive infusion, n (%)	Yes	99 (76.74)	31 (41.33)	<0.0001[#]
	No	30 (23.26)	44 (58.67)	
Length of stay (days)	Mean ± SD	6.25 ± 5.55	3.69 ± 2.37	<0.0001[π]
	Median (IQR)	5 (3–7)	3 (2–4)	
	Range	2–36	1–16	
Clinical outcomes, n (%)	Discharge	0 (0.00)	1 (1.33)	<0.0001[#]
	Step-down	59 (45.74)	58 (77.33)	
	Expired	70 (54.26)	17 (22.67)	

■ Values are presented as median (interquartile range), mean ± standard deviation, or frequency (percentage), as appropriate. P-values represent comparisons between hyperglycemic and non-hyperglycemic groups.

■ Abbreviations: CNS, central nervous system; HHHFNC, heated humidified high-flow nasal cannula; IQR, interquartile range; SD, standard deviation.

[π]independent t-test, [#]chi-square test, [*]Fisher's exact test

Table 2: Distribution of admission diagnosis of enrolled patients

Admission diagnosis	Frequency	Percentage
CNS disorders	54	26.47%
Respiratory disorders	52	25.49%
Gastrointestinal disorders	34	16.66%
Septicemia	18	8.82%
Animal Bite	15	7.35%
Haemato-oncology	7	3.43%
Undifferentiated fever	5	2.45%
Poisoning	4	1.96%
Cardio vascular disorders	4	1.96%
Others*	11	5.39%
Total	204	100.00%

* Others include musculoskeletal, renal, skin, burn injury, trauma, and genitourinary disorders.

Table 3. ROC analysis for predicting mortality

Parameter	Peak blood glucose(mg/dL)	Duration of hyperglycemia (days)
Area under the ROC curve (AUC)	0.701	0.506
Standard Error	0.038	0.0508
95% Confidence interval	0.633 to 0.763	0.416 to 0.595
P value	<0.0001	0.9108
Optimal Cut off Value	>177	≤4
Sensitivity (95% CI)	64.37% (53.4-74.4%)	90 % (80.5-95.9%)
Specificity (95% CI)	70.09 % (60.9-78.2%)	20.34 % (11.0-32.8%)
Positive Predictive Value (PPV)	61.5 % (50.8-71.6%)	57.3 % (47.5-66.7%)
Negative Predictive Value NPV	72.6 % (63.4-80.5%)	63.2 % (38.4-83.7%)
Diagnostic accuracy	67.65%	58.14%

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Table 4. Multivariate Logistic Regression Analysis for Independent Predictors of in-PICU Mortality

Variables	95 % confidence Interval	P value	Adjusted Odds ratio (aOR)
Mean blood glucose(mg/dL)	0.985-1.022	0.715	1.003
Peak blood glucose(mg/dL)	0.984-1.009	0.614	0.997
Ventilator free days	0.353-0.719	0.0005	0.504
Number of vasoactives	1.189-7.770	0.020	3.039
Male Gender	1.414-16.044	0.012	4.763
Hyperglycemia (yes Vs No)	0.656–12.530	0.161	2.868

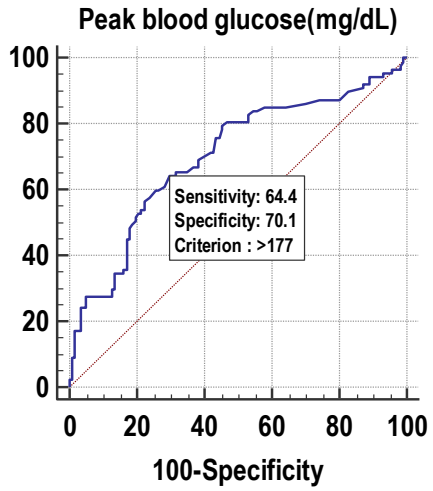


Figure 1: Receiver operating characteristic curve of peak blood glucose for predicting mortality

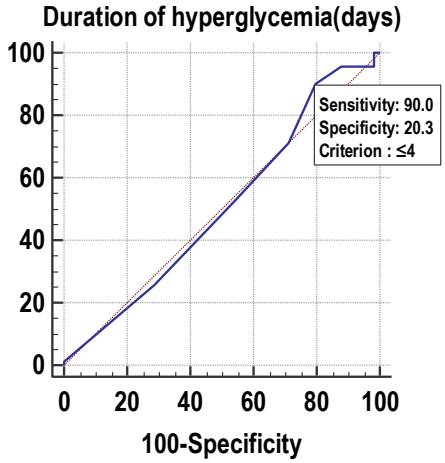


Figure 2: Receiver operating characteristic curve of duration of hyperglycemia for predicting mortality

Inflammatory cytokines, corticosteroid release, and ventilator-associated stress may collectively contribute to insulin resistance and elevated glucose levels in these patients. However, some studies have reported sepsis as the predominant diagnosis associated with hyperglycemia, a discrepancy that may reflect differences in case mix, admission diagnoses, and referral patterns across centers [6].

Our ROC analysis demonstrated that peak blood glucose had a moderate ability to predict mortality (AUC 0.701), which is comparable to findings from Srinivasan et al. and Wintergerst et al., who reported AUC values ranging from 0.65 to 0.75 [7, 8]. In contrast, the duration of hyperglycemia showed poor discriminatory value in our study, differing from some adult studies where prolonged hyperglycemia was associated with worse outcomes [9]. This discrepancy may be due to differences in pediatric metabolic adaptation, early intervention, or variability in glucose monitoring frequency.

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An important observation in our cohort was the trend toward normalization of blood glucose levels among survivors. Similar trends have been described by Faustino et al., who emphasized that glycemic variability and recovery may be more prognostically relevant than isolated glucose values. This supports the concept that SH is a dynamic response and that resolution of hyperglycemia may indicate recovery from the acute stress response [5].

Multivariate analysis revealed that hyperglycemia was not an independent predictor of mortality after adjustment for ventilator-free days and vasoactive support, aligning with several pediatric studies that identified illness severity markers as stronger predictors of outcome [10, 11]. In contrast, some studies have reported hyperglycemia as an independent risk factor, possibly due to differences in glucose thresholds, exclusion criteria, or statistical adjustment for confounders [12].

In the present study, hyperglycemic patients required invasive mechanical ventilation and vasoactive or inotropic support more frequently than non-hyperglycemic patients, reflecting greater illness severity. Similar associations have been reported by Wintergerst et al. and Faustino et al., who demonstrated that SH in critically ill children is strongly linked to increased need for mechanical ventilation and hemodynamic support. These interventions themselves are markers of severe physiological stress, systemic inflammation, and organ dysfunction, all of which contribute to insulin resistance and increased hepatic glucose production [5, 8]. In our multivariate analysis, ventilator-free days and the number of vasoactive agents emerged as independent predictors of mortality, whereas hyperglycemia lost statistical significance, suggesting that elevated blood glucose levels may act as a surrogate marker of disease severity rather than a direct mediator of poor outcomes. Differences across studies regarding the independent effect of hyperglycemia may be related to variations in case mix, timing of glucose measurement, thresholds used to define hyperglycemia, and adjustment for illness severity.

Current guidelines from the American Diabetes Association and critical care societies recommend maintaining blood glucose levels between 140 and 180 mg/dL in critically ill patients to balance the risks of hyperglycemia and hypoglycemia [1]. Our findings support these recommendations, as peak glucose levels above 177 mg/dL were associated with worse outcomes, while aggressive glucose lowering was not evaluated in this study.

Future research should focus on multicenter prospective studies to validate optimal glucose thresholds in different pediatric subgroups, examine the prognostic significance of glycemic trajectories, and assess the impact of nutritional strategies and fluid composition on SH. Interventional trials evaluating tailored glycemic control strategies in high-risk pediatric populations are also warranted.

Future studies should focus on multicenter trials to improve the generalizability of findings and provide larger sample sizes for detecting subtle effects. Longitudinal research is needed to explore the impact of glycemic trajectories over time and to clarify the mechanisms by which hyperglycemia influences clinical outcomes, particularly regarding the central nervous and immune systems. Additionally, the role of nutritional status and intravenous fluids on glucose metabolism warrants further investigation. Randomized controlled trials comparing different glycemic control strategies, including insulin therapy versus conservative management, are essential to identify approaches that may reduce harm and improve outcomes in critically ill children.

Limitations

This study has several limitations. As, it was conducted in a single Pediatric Intensive Care Unit at Shri Maharaja Gulab Singh Hospital, Jammu, the findings may not be generalizable to other settings with different patient populations, practices, or resources. The relatively small sample size of 204 children may limit the ability to detect smaller effects or interactions. Although multivariate analysis was performed, unmeasured confounding factors such as underlying comorbidities, variations in clinical management, and nutritional support may have influenced the results. Additionally, the study did not assess the impact of specific glycemic control interventions over time, limiting insights into how management strategies might affect outcomes.

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Conclusion

SH is a strong indicator of illness severity of in critically ill children, especially those with CNS and respiratory conditions. Thus, the relationship between hyperglycemia and increased mortality should prompt more careful monitoring and appropriate control of blood glucose levels. However, the findings also suggest that not only the presence of hyperglycemia, but also its progression and interaction with other clinical factors, influence outcomes. Prospective, large-scale multicenter clinical trials are necessary to improve our understanding of SH and to develop evidence-based guidelines that optimize care for this vulnerable population.

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Ethical Considerations

Study commenced only after due approval from departmental meeting followed by approval from institute ethics committee vide no: IEC/GMC/2020/211 Dated: 28-10-2020.

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Conflict of interest

The authors declare no conflicts of interest.

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