Prevalence and Course of Stress Hyperglycemia in Critically Ill Children Admitted to Pediatric Intensive Care Unit of Assiut University Children's Hospital

Amal Abdelsalam Soliman, Safaa Hamed Hussien Abdelaal*, Ismail Lotfy Mohamad
Pediatric Department, Faculty of Medicine, Assiut University, Assiut, Egypt.
***Corresponding Author:** Safaa Hamed Hussien Abdelaal*
***E-mail:** Safaa.20124126@med.aun.edu.eg*

Abstract:

Background*:* Hyperglycemia is a stress reaction in critically ill patients. A great number of studies found a strong relationship between hyperglycemia and poor outcomes in critically ill adults; little is known regarding the occurrence of hyperglycemia and its impact in the pediatric intensive care unit (PICU).

Objectives*:* To detect the prevalence of stress hyperglycemia (SH) in patients admitted to the PICU of Assiut University Children Hospital (AUCH), assess its pattern, course, risk factors, and its relation to the outcome.

Methods*:* The present study was a prospective cohort study, including all children and adolescents admitted to PICU, AUCH, from April 2021 to September 2021. According to the blood glucose (BG) level, the studied participants were divided into two groups [Group I: Patients with SH (BG ≥ 200 mg/dl), and Group II: Patients with normoglycemia (BG < 200 mg/dl)].

Results*:* The study included 268 participants; Group I: n=73 (27.2%), with a mean age of 1.90±2.51 years, which was significantly lower than the mean age of the normoglycemic group ((3.64±4.29 years) (P < 0.001)). Positive family history of diabetes mellitus (DM) was significantly higher in Group I (P < 0.001). Gastrointestinal disorders were the most common causes for PICU admission in the SH group. The mortality for the SH group was significantly higher than that of the normoglycemic group, with a rate of 50.7% versus 34.4% (P = 0.015).

Conclusion*:* Hyperglycemia was a common finding among critically ill children in our study.

Keywords*:* Critically ill children, pediatric intensive care unit, hyperglycemia.

Introduction:

Stress hyperglycemia is a prevalent condition in children with critical illnesses (1), mostly because of increased gluconeogenesis in relation to glucose clearance and the development of insulin resistance, which affects glucose uptake. Increased synthesis of counteracting hormones, such as glucagon, growth hormone, cortisol, norepinephrine, and adrenaline, mediates these pathways (2). Moreover, pro-inflammatory cytokines, oxidative stress, and therapeutic intervention are all associated with stress hyperglycemia. By stimulating α-adrenergic receptors, those factors hinder insulin release from pancreatic β cells, disrupt insulin receptor signaling and/or insulin-regulated glucose channels, and block the appropriate transport and use of glucose in peripheral cells (3).

Numerous research investigations have indicated a correlation between stress-induced hyperglycemia and death in critically ill children. More specifically, it

seems that mortality is correlated with the peak and duration of stress hyperglycemia. Peak blood glucose levels in non-survivors are often significantly greater than in survivors (2, 4).

Similarly, non-survivors are more likely than survivors to have experienced stress hyperglycemia for a longer time (5, 6). Stress hyperglycemia and mortality are associated with a variety of pediatric illness conditions, such as burns, septic shock, traumatic brain injury, post-cardiac surgery, and trauma. Stress hyperglycemia is also linked to longer hospitalizations, as well as an increased risk of nosocomial infections, which include surgical site infections in children who are critically ill (2, 4, 6-9). These studies show that stress hyperglycemia and poor clinical outcomes are strongly correlated, but they do not always show a cause-and-effect relationship (1).

Thus, the main objective of the current study is to detect the prevalence of SH, pattern, course, risk factors, and their relation to the outcome in patients admitted to the PICU of AUCH.

Patients and Methods:

This study was an observational hospital-based prospective cohort study. The study was approved by the regional ethics committee at Assiut University (IRB No 17101438). Informed written consent was obtained from all participants' parents before they were enrolled in the current study.

(A) Patients:

All children aged 1–18 years admitted to PICU at AUCH from the first of April 2021 until the end of September 2021 were enrolled in the current study. Infants (aged less than one year), children with documented diagnosis of DM, and those who refused to participate in the current study were also excluded.

According to the blood glucose level, the studied participants were divided into two groups:

- **Group I (stress hyperglycemia):** BG level ≥ 200 mg\dl).
- **Group II (normoglycemia):** BG < 200 mg\dl).

(B) Data Collection:

All eligible participants were subjected to full history taking including name, age, sex, in addition to risk factors of developing stress hyperglycemia as positive family history of DM, and cause of admission to PICU, vital signs, systematic physical examination, and routine investigations included complete blood picture (CBC), liver function test (LFT), kidney function test (KFT), acute phase reactants: C-reactive protein (CRP), blood glucose level were measured at patients admission and then every six hours, HBA1c, serum electrolytes (Sodium and Potassium), and arterial blood gases (Ph, co2, hco3) were also done. All laboratory data were performed in the hospital's main clinical laboratory.

(C) Statistical Analysis:

Version 22 of SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) was used for all statistical computations. The statistical description of the data was expressed as mean + standard deviation (±SD) or median (range) and compared by Student's t-test or Kruskal-Wallis test, or presented as number (percentages) and compared by Chi-square ($\chi 2$) or Fisher Exact test. P-value set at 0.05.

Results

Demographic Data of the Studied Patients

From the first of January 2021 up to the end of June 2021, a total of 268 patients were admitted to the PICU of AUCH; 73 patients (27.2%) suffered from stress hyperglycemia (SH) group, with a mean age of 1.90±2.51 years, which was significantly lower than the mean age of 3.64±4.29 years in the normoglycemic group (P < 0.001). The gender distribution was comparable between both studied groups with no significant difference (P = 0.331). Positive family history of DM was significantly higher in patients with SH compared to the normoglycemic group (P < 0.001). Among patients with SH, the median

duration of SH was four hours (range: 2 hours to five days), **Table 1**.

Table 1: Characteristics of patients admitted to PICU

Demographic data	Normoglycemia, N=195		Stress Hyperglycemia, n=73		P value
Age (years)					0.001
- Mean ± SD	3.64±4.29		1.90±2.51		
- Range	1 month–16 years		2 months–14 years		
Sex					0.331
- Male	78	(40.0%)	34	(46.6%)	
- Female	117	(60.0%)	39	(53.4%)	
Family history of DM					< 0.001
- Negative	194	(99.5%)	59	(80.8%)	
- Positive	1	(0.5%)	14	(19.2%)	

DM: diabetes mellitus; SH: stress hyperglycemia.

The diagnoses that were most common in the SH group, starting with the highest, were, in order, gastrointestinal, respiratory, postoperative, and CNS diseases. Meanwhile, for the normoglycemic group, the most common diagnoses, from highest to lowest, were respiratory, postoperative, gastrointestinal, and CNS diseases (**Figure 1**.

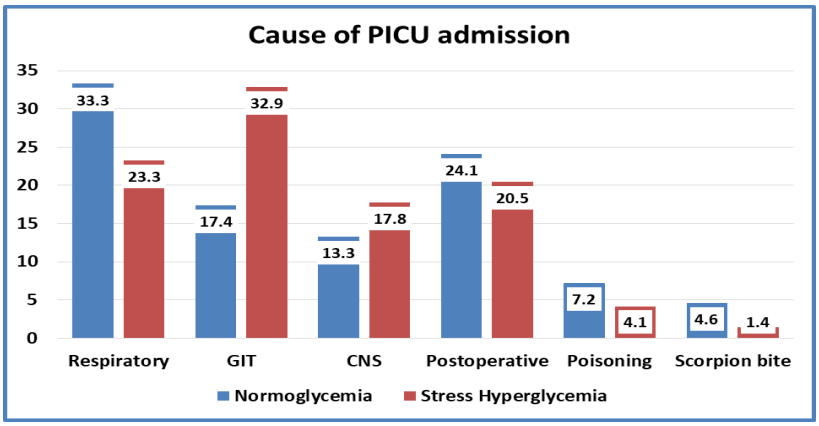

Figure 1: Causes of admission to PICU among the studied patients

Vital Signs among the Studied Patients

Table 2 shows that all studied vital signs (heart rate, respiratory rate, blood pressure, and consciousness level) were comparable between the groups with no significant difference (P = 0.206, 0.172, 0.151, and 1), respectively. Meanwhile, patients with SH were more likely to be feverish than patients with normoglycemia (65.1% vs. 82.2%, P=0.007) in both groups.

Regarding the laboratory data, CBC parameters, liver enzymes, and inflammatory markers (CRP) show no significant difference between the studied groups (P > 0.05, for all), except that serum urea and creatinine were significantly higher in SH patients compared to patients with normoglycemia (P = 0.002).

Table 2: Vital signs and laboratory data of patients admitted to PICU

	Normoglycemia, N=195		Stress hyperglycemia, n=73		P value
Temperature					**0.007**
- Exothermic	68	(34.9%)	13	(17.8%)	
- Feverish	127	(65.1%)	60	(82.2%)	
Heart rate					0.206
- Normal	37	(19.0%)	19	(26.0%)	
- Tachycardia	158	(81.0%)	54	(74.0%)	

	Normoglycemia, N=195		Stress hyperglycemia, n=73		P value
Respiratory rate					0.172
- Normal	36	(18.5%)	19	(26.0%)	
- Tachypnea	159	(81.5%)	54	(74.0%)	
Blood pressure					0.151
- Normal	139	(71.3%)	49	(67.1%)	
- Hypertensive	4	(2.1%)	5	(6.8%)	
- Hypotensive	52	(26.7%)	19	(26.0%)	
Conscious level					1
- Conscious	7	(3.6%)	2	(2.7%)	
- Decreased conscious level	188	(96.4%)	71	(97.3%)	
TLC					0.452
- Normal	82	(42.1%)	27	(37.0%)	
- Raised	113	(57.9%)	46	(63.0%)	
Hemoglobin					0.090
- Normal	42	(21.5%)	23	(31.5%)	
- Low	153	(78.5%)	50	(68.5%)	
Platelets					0.956
- Normal	157	(80.5%)	58	(79.5%)	
- Raised	29	(14.9%)	11	(15.1%)	
- Low	9	(4.6%)	4	(5.5%)	
HBA1c (n=67)					----
- Normal			67	(100.0%)	
- Abnormal			0	(0.0%)	
Liver enzymes					0.111
- Normal	135	(69.2%)	43	(58.9%)	
- Raised	60	(30.8%)	30	(41.1%)	
Urea					**0.002**
- Normal	174	(89.2%)	54	(74.0%)	
- Raised	21	(10.8%)	19	(26.0%)	
Creatinine					**0.002**
- Normal	174	(89.2%)	54	(74.0%)	
- Raised	21	(10.8%)	19	(26.0%)	
CRP					0.739
- Normal	52	(26.7%)	18	(24.7%)	
- Raised	143	(73.3%)	55	(75.3%)	

CRP: C-reactive protein.

Outcome of the Studied Patients with SH According to the Blood Glucose Level

To study the clinical outcomes according to blood glucose (BG) levels, the patients were divided into four BG groups: normoglycemic group, 45≤BG<150mg/dL (195 patients); 200 ≤ BG<250mg/dL (31 patients); 250≤BG<300 mg/dL (14 patients); and ≥300 mg/dL (28 patients). The insulin administration rate of the SH group according to the BG level was 3.2%, 21.4%, and 53.6%, which was significantly higher in patients with higher BG (≥300 mg/dL) compared to other groups (P < 0.001).

The need for mechanical ventilation, the length of hospital stay, and the survival rate show no significant difference between the three studied groups (P=0.250, 0.456, and 0.157), respectively, as shown in **Table 3**.

Table 3: Comparison of outcomes for patients with SH according to the severity of hyperglycemia (n=268)

Treatment	Stress hyperglycemia, n=73						P value
	200 - < 250, n=31		250 - < 300, n=14		> 300, n=28		
Insulin therapy							**<0.001**
- No	30	(96.8%)	11	(78.6%)	13	(46.4%)	
- Yes	1	(3.2%)	3	(21.4%)	15	(53.6%)	
Mechanical ventilation							0.250
- No	12	(38.7%)	7	(50.0%)	7	(25.0%)	
- Yes	19	(61.3%)	7	(50.0%)	21	(75.0%)	
Hospitalization (days)	5 (1–15)		6 (1–27)		7 (1–55)		0.456
Mortality							0.157
- Non-survived	14	(45.2%)	5	(35.7%)	18	(64.3%)	
- Survived	17	(54.8%)	9	(64.3%)	10	(35.7%)	

Outcome of the Studied Patients

The mortality for the SH group was significantly higher than that of the normoglycemic group, with a rate of 50.7% (37/73) compared to 34.4% (67/196) (P=0.015). While the need for mechanical ventilation and the length of hospital stay show no significant difference between the studied groups (P=0.463, 0.210, and 0.505), respectively, **Table 4**.

Table 4: Comparison of outcomes for patients with stress hyperglycemia and normoglycemia

Treatment	Normoglycemia, N=195		Stress hyperglycemia, n=73		P value
Mechanical ventilation					0.210
- No	86	(44.1%)	26	(35.6%)	
- Yes	109	(55.9%)	47	(64.4%)	
Length of hospital stay(days)	4 (1–60)		5 (1–55)		0.505
Mortality					**0.015**
- Dead	67	(34.4%)	37	(50.7%)	
- Survived	128	(65.6%)	36	(49.3%)	

Discussion

Stress hyperglycemia is the name given to a brief rise in plasma glucose levels (often greater than 150 mg/dl) that occurs after an acute sickness or during periods of physical or mental stress and then decreases as the stressful condition passes. While roughly 20–35% of severely ill children in the ICU exceed the cut-off point of 200 mg/dl, 3.8–5% of non-diabetic children presenting to the ED have BG above 150 mg/dl (10). It's a typical physiological reaction to acute stress (11). The present study aimed to detect the prevalence of SH and assess its pattern, course, risk factors, and relation to the outcome in children.

During the six-month interval (from the first of April 2021 to the end of September 2021), 268 patients were admitted to the PICU of AUCH. We defined hyperglycemia as a BG level >200 mg/dl; based on this cut-off value, we observed that the number of patients who suffered SH was 73 cases with a total prevalence of 27.2%. Our findings emphasize comparable SH incidence in critically ill children (12-14).

The prevalence of hyperglycemia was found by Faustino et al. to vary between 16.7% and 75% based on three distinct cut-off values: >120 mg/dl, >150 mg/dl, and >200 mg/dl (7). Hirschberg et al. observed hypoglycemia in 9.7% of patients and hyperglycemia in 56.1% of patients when the cut-off value was >150 mg/dl (4). The prospective cross-sectional analysis of Patki and Chougule reported that 69.3%of

children had SH, using the cut-off BG level >126 mg/dl (>7 mmol/dl) (15). In the study by El-Sherbini et al., hyperglycemia was found in 70% of children receiving care in the PICU (13). In 166 children hospitalized with acute asthma, Mobaireek et al. found that 38.6% of these children had hyperglycemia (14). Recently, the prospective cross-sectional study of Dar et al. observed that 63.0% of children admitted to PICU suffered from SH (12).

In contrast, a lower rate of SH was reported in the recent study of Korakas et al., who reported that 3.9% of hospitalized children and 7.2% of admitted children had SH (16).

A possible reason for the difference between studies could be the difference in the random BG level cut-off value over which the author diagnosed children to have SH, the underlying cause for SH, the baseline data of the studied participants, and the study duration.

Additionally, we observed that the mean age of patients with SH was lower than that of patients with normoglycemia. A similar age range was reported by El-Sherbini et al. (13).

Also, in the current study, we found a significantly higher positive family history of DM among SH patients. Similarly, only one study has identified a connection between SH and DM in the family history (17). Also, a positive family history of DM is the most firmly established risk factor for the development of SH and type 1 DM in critically ill children (18, 19), with a recent study by Awadalla et al. showing that children whose fathers have type 1 diabetes have an odds ratio (OR) of 9.03 (20).

In the current study, we found that the commonest cause for PICU admission in the SH group was gastrointestinal and respiratory disorders in the normoglycemic group. Consistent results were reported in prior studies (16, 21).

Our sample showed that many children with SH were likelier to suffer from higher body temperature than patients with normoglycemia (65.1% vs. 82.2%, P=0.007). In the study by Korakas et al., 60.0% of the studied SH children suffered from fever, with no association observed between body temperature and SH development. Similarly, factors linked to fever did not affect the incidence of SH in the Lee et al. investigation (22).

Stressful situations cause higher levels of pro-inflammatory cytokines and counter-regulatory hormones, which cause fast gluconeogenesis and glycogenolysis and higher blood levels of BG. Glucagon levels rise due to the spike in catecholamines during critical illness, maintaining gluconeogenesis even in the context of raised insulin levels. In critical diseases, the kidney plays a significant role in gluconeogenesis, contributing as much as 40% of the glucose produced in response to catecholamines (1). This mechanism could explain the current finding that the kidney function tests (blood urea and creatinine) were significantly higher in patients with SH. Furthermore, SH causes glucose toxicity in critical illness, which predisposes individuals to acute renal injury and causes endothelial dysfunction, mitochondrial dysfunction, inflammation, apoptosis, and abnormal lipid levels (23). This finding highlights the need for continuous careful monitoring of kidney function among children with SH to avoid the development of acute kidney injury among those patients.

Additionally, we observed longer hospital stays among patients with SH but did not reach a statistically significant difference; this may be due to the small sample size in the current study. Numerous studies examining the detrimental effects of SH in critically ill children have demonstrated that it is linked to longer periods of ICU and hospital stay (4, 6). In the current study, we reported that the total

mortality rate among patients with SH was significantly higher than that of children with normoglycemia, with a rate of 50.7% compared to 34.4% (P=0.015). A similar finding was reported in previous series (13, 15, 24, 25).

According to our data, the percentage of patients who needed to receive insulin therapy was higher among patients with higher BG level (> 300 mg/dl), trying to normalize the blood glucose level to avoid poor outcomes among those patients. Additionally, in line with multiple other studies, we found that hyperglycemia (BG>200 mg/dL) was significantly linked to increased mortality (2, 4, 26). More specifically, it seems that mortality is correlated with the peak and duration of SH. Peak blood glucose concentrations in non-survivors are often significantly greater than in survivors (2, 4). The relationship between SH and mortality is seen in a variety of pediatric illness conditions, including burns, traumatic brain damage, post-cardiac surgery, septic shock, and trauma (3, 27). Thus, stress hyperglycemia in critically ill children is a profound problem that needs more attention in trying to prevent or reduce the underlying causes and needs earlier detection to achieve better outcomes.

Conclusion

Hyperglycemia was common among critically ill children in our study. The requirement for ventilation, length of PICU stay, and mortality rate were higher in SH children. More extensive research in various healthcare settings is needed to elucidate potential risk factors for SH in the pediatric population, both at the individual and parental levels. In all cases, awareness should be increased to ensure early detection, according to our findings, particularly in the case of children who arrive with gastrointestinal diseases or respiratory illnesses.

References:

1. Srinivasan V. Stress hyperglycemia in pediatric critical illness: the intensive care unit adds to the stress! *J Diabetes Sci Technol*. 2012;6(1):37-47. doi:10.1177/ 193229681200600106.
2. Yung M, Wilkins B, Norton L, Slater A. Glucose control, organ failure, and mortality in pediatric intensive care. *Pediatr Crit Care Med*. 2008;9(2):147-152. doi:10.1097/PCC.0b013e3181668c22.
3. Day KM, Haub N, Betts H, Inwald DP. Hyperglycemia is associated with morbidity in critically ill children with meningococcal sepsis. *Pediatr Crit Care Med*. 2008;9(6):636-640. doi:10.1097/PCC.0b013e31818d320b.
4. Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: hyperglycemia and glucose variability are associated with increased mortality and *morbidity. Pediatr Crit Care Med.* 2008;9(4):361-366. doi:10.1097/PCC.0b013e318172d48a.
5. Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V. Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. *Pediatr Crit Care Med*. 2004;5(4):329-336. doi:10.1097/01.PCC.0000123553.22475.E3.
6. Ulate KP, Lima Falcao GC, Bielefeld MR, Morales JM, Rotta AT. Strict glycemic targets need not be so strict: a more permissive glycemic range for critically ill children. *Pediatrics*. 2008;122(4):e898-e904 . doi:10.1542/peds.2008-0669.
7. Faustino EV, Apkon M. Persistent hyperglycemia in critically ill children. *J Pediatr*. 2005;146(1):30-34. doi:10.1016/ j.jpeds.2004.08.076.
8. O'Brien Jr JE, Marshall JA, Tarrants ML, Stroup RE, Lofland GK. Intraoperative hyperglycemia and postoperative bacteremia in the pediatric cardiac surgery patient. *Ann Thorac Surg*. 2010;89(2):578-584. doi: 10. 1016/j. athoracsur. 2009. 10. 042.
9. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. *Pediatrics*. 2006;118(1):173-179. doi:10.1542/peds. 2005-1819.
10. Argyropoulos T, Korakas E, Gikas A, Kountouri A, Kostaridou-Nikolopoulou S, Raptis A, et al. Stress hyperglycemia in children and adolescents as a prognostic indicator for the development of type 1

diabetes mellitus. *Front Pediatr*. 2021;9:670976.doi:10.3389/fped.2021.670976 .

11. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care*. 2013;17(2):305. doi:10.1186/cc12514.
12. Dar MI, Saini G, Parihar RK. Incidence and association of stress hyperglycemia with outcome of critically ill children admitted in pediatric intensive care unit of a tertiary care hospital. *Pediatr Crit Care Med*. 2022;23(11):e543-e550 . doi:10.1097/PCC.0000000000003045.
13. El-Sherbini SA, Marzouk H, El-Sayed R, Hosam-ElDin S. Etiology of hyperglycemia in critically ill children and the impact of organ dysfunction. *Rev Bras Ter Intensiva*. 2018;30(3):286-293. doi:10.5935/0103-507X.20180046.
14. Mobaireek KF, Alshehri A, Alsadoun A, Alasmari A, Alashhab A, Alrumaih M, et al. Hyperglycemia in children hospitalized with acute asthma. *Prog Med Res*. 2018;1:19-25.
15. Patki VK, Chougule SB. Hyperglycemia in critically ill children. *Indian J Crit Care Med*. 2014;18(1):8-13. doi:10.4103/0972-5229.125428.
16. Korakas E, Argyropoulos T, Koliou G-A, Gikas A, Kountouri A, Nikolopoulou SK, et al. Prevalence and prognostic factors of stress hyperglycemia in a pediatric population with acute illness in Greece—a prospective observational study. *J Clin Med*. 2022;11(5):1301. doi:10.3390/jcm 11051301.
17. Bordbar MR, Taj-Aldini R, Karamizadeh Z, Haghpanah S, Karimi M, Omrani GH. Thyroid function and stress hormones in children with stress hyperglycemia. *Endocrine*. 2012;42(3): 653-657.doi:10.1007/s12020-012-9701-4.
18. Marshall A, Chetwynd A, Morris J, Placzek M, Smith C, Olabi A, et al. Type 1 diabetes mellitus in childhood: a matched case control study in Lancashire and Cumbria, UK. *Diabet Med*. 2004;21(9):1035-1040. doi:10.1111/j.1464-5491.2004.01294.x.
19. Vlajinac H, Kocev N, Marinkovi J, Radmanovi S, Deni L. Family history and risk of type 1 diabetes mellitus. *Acta Diabetol*. 2002;39(3):111-114. doi:10.1007/s005920200030.
20. Awadalla NJ, Hegazy AA, Abd El-Salam M, Elhady M. Environmental factors associated with type 1 diabetes development: a case control study in Egypt. *Int J Environ Res Public Health*. 2017;14(6):615. doi:10.3390/ijerph14060615.
21. Levmore-Tamir M, Weiser G, Berliner E, Erlichman M, Levy-Khademi F. Stress hyperglycemia in a pediatric emergency department setting and its relationship to the underlying disease and outcome. *Isr Med Assoc J*. 2020;22(7):431-434.
22. Lee J-Y, Kim J-H, Cho H-R, Lee J-S, Ryu J-M, Yum M-S, et al. Children experiencing first-time or prolonged febrile seizure are prone to stress hyperglycemia. *J Child Neurol*. 2016;31(4):439-443. doi:10.1177/0883073815597757.
23. Gunst J, Schetz M. Clinical benefits of tight glycaemic control: effect on the kidney. *Best Pract Res Clin Anaesthesiol*. 2009;23(4):431-439. doi:10.1016/j.bpa.2009.08.006.
24. Diana Grace R. Clinical profile and outcome of stress hyperglycemia in critically ill children. Madras Medical College, Chennai; 2015.
25. Bae W, Ahn MB. Association between stress hyperglycemia and adverse outcomes in children visiting the pediatric emergency department. *Children (Basel)*. 2022;9(4):505. doi:10.3390/children 9040505.
26. Bhutia TD, Lodha R, Kabra SK. Abnormalities in glucose homeostasis in critically ill children. *Pediatr Crit Care Med*. 2013;14(1):e16-e25 . doi:10.1097/PCC.0b013e3182601177.
27. Tuggle DW, Kuhn MA, Jones SK, Garza JJ, Skinner S. Hyperglycemia and infections in pediatric trauma patients. *Am Surg*. 2008;74(3):195-198. doi:10.1177/ 000313480807400301.