Blood glucose and outcomes in critically ill children in Brazilian Amazon: an observational study

Glicemia e mortalidade na criança gravemente doente na Amazônia brasileira: estudo observacional

Glucosa en sangre y mortalidad en niños críticamente enfermos en la Amazonía brasileña: un estudio observacional

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Abstract
Objectives: To determine blood glucose distribution values; to assess the association of admission serum glucose levels with 28-day mortality to the frequency of invasive mechanical ventilation-free days. Design: Retrospective cohort studySetting: Brazilian Amazon Region. Patients: Population (n = 400) composed of patients admitted to the pediatric intensive care unit, from January 2016 to December 2017. Exclusion criteria were patients with length of stay of <24 hours; diabetes mellitus; suspicion or evidence of inborn errors of metabolism; insulin use; palliative care

and brain death. Main outcome measures: The patients were divided into 4 groups: 1) serum glucose <60mg/dL; 2) control group if serum glucose between 60-126 mg/dL; 3) between 127-150mg/dL; or 4) if > 150mg/dL. Results: Serum glucose levels frequency were: <60: 43 (11%); 60-126: 235 (58.7%); 127-150: 51 (13%) and > 150: 71 (18%). Groups 3 and 4 had the highest frequency of external origin, with respectively 24 (47.1%) and 40 (56.3%); the main diagnosis was infection, with 26 (51%) and 50 (70.4%), respectively. Sepsis occurred in 24 (47.1%) and 47 (66.2%) individuals in the groups 3 and 4, respectively, while septic shock was more frequent in the group 4 (46 [4.8%]). Group 2 had predominance of ventilator-associated pneumonia with 11 (36.7%). The estimate of ventilation-free days in group 4 was 2.84 (SD +/- 0.69; 95% CI: 1.5-4.2). Conclusion: Hyperglycemia group had a lower frequency of ventilation-free days and higher 28-day mortality.
Keywords: Blood glucose; Mortality; Risk factors; Intensive care units, Pediatric; Hypoglycemia; Hyperglycemia.

Resumo
Objetivos: Determinar os valores de distribuição da glicose no sangue; Avaliar a associação dos níveis séricos de glicose na admissão com a mortalidade aos 28 dias e a frequência de dias livres de ventilação mecânica invasiva. Delineamento: Estudo de coorte retrospectivo Local: Amazônia Brasileira. Pacientes: População (n = 400) composta por pacientes internados em unidade de terapia intensiva pediátrica, no período de janeiro de 2016 a dezembro de 2017. Os critérios de exclusão foram pacientes com internação <24 horas; Diabetes mellitus; suspeita ou evidência de erros inatos do metabolismo; uso de insulina; cuidados paliativos e morte encefálica. Principais desfechos: os pacientes foram divididos em 4 grupos: 1) glicose sérica <60 mg / dl; 2) grupo controle se a glicemia sérica estiver entre 60-126 mg / dL; 3) entre 127-150 mg / dL; ou 4) se> 150 mg / dL. Resultados: A frequência dos níveis séricos de glicose foi: <60: 43 (11%); 60-126: 235 (58,7%); 127-150: 51 (13%) e> 150: 71 (18%). Os grupos 3 e 4 apresentaram a maior frequência de origem externa, com 24 (47,1%) e 40 (56,3%) respectivamente; o diagnóstico principal foi infecção, com 26 (51%) e 50 (70,4%), respectivamente. A sepse ocorreu em 24 (47,1%) e 47 (66,2%) indivíduos dos grupos 3 e 4, respectivamente, enquanto o choque séptico foi mais frequente no grupo 4 (46 [4,8%]). O Grupo 2 teve predomínio de pneumonia associada à ventilação mecânica com 11 (36,7%). A estimativa de dias sem ventilação no grupo 4 foi de 2,84 (DP +/- 0,69, IC 95%: 1,5-4,2). Conclusão: o grupo hiperglicêmico apresentou menor frequência de dias sem ventilação e maior mortalidade aos 28 dias.
Palavras-chave: Glicemia; Mortalidade; Fatores de risco; Unidades de terapia intensiva pediátrica; Hipoglicemia; Hiperglicemia.

Resumen
Objetivos: Determinar los valores de distribución de glucosa en sangre; evaluar la asociación de los niveles de glucosa sérica al ingreso con la mortalidad a los 28 días con la frecuencia de días libres de ventilación mecánica invasiva. Diseño: Estudio de cohorte retrospectivo Lugar: Región Amazónica brasileña. Pacientes: Población (n = 400) compuesta por pacientes ingresados en la unidad de cuidados intensivos pediátricos, de enero de 2016 a diciembre de 2017. Los criterios de exclusión fueron pacientes con estadía <24 horas; diabetes mellitus; sospecha o evidencia de errores innatos del metabolismo; uso de insulina; cuidados paliativos y muerte cerebral. Principales medidas de resultado: Los pacientes se dividieron en 4 grupos: 1) glucosa sérica <60 mg / dl; 2) grupo de control si la glucosa en suero está entre 60-126 mg / dL; 3) entre 127-150 mg / dL; o 4) si> 150 mg / dL. Resultados: La frecuencia de los niveles de glucosa en suero fue: <60: 43 (11%); 60-126: 235 (58,7%); 127-150: 51 (13%) y> 150: 71 (18%). Los grupos 3 y 4 tuvieron la mayor frecuencia de origen externo, con 24 (47,1%) y 40 (56,3%) respectivamente; el diagnóstico principal fue infección, con 26 (51%) y 50 (70,4%), respectivamente. La sepsis ocurrió en 24 (47,1%) y 47 (66,2%) individuos en los grupos 3 y 4, respectivamente, mientras que el choque séptico fue más frecuente en el grupo 4 (46 [4,8%]). El grupo 2 tuvo predominio de neumonía asociada a ventilador con 11 (36,7%). La estimación de días sin ventilación en el grupo 4 fue 2,84 (DE +/- 0,69; IC del 95%: 1,5-4,2). Conclusión: el grupo de hiperglucemia tuvo una menor frecuencia de días sin ventilación y una mayor mortalidad a los 28 días.
Palabras clave: Glucosa; Mortalidad; Factores de riesgo; Unidades de cuidados intensivos pediátricos; Hipoglucemia; Hiperglucemia.

1. Introduction

Severe sepsis and septic shock, resulted from infection, are the main causes of mortality and morbidity among children, despite advances in prevention and treatment (Farrell & Nadel, 2016) that resulted in a marked reduction in the mortality of cases - especially in developed countries (Garcia et al., 2020).

Glucose homeostasis is altered among children with septic shock, and the systemic inflammation related to such condition results in wide glycemic variation (Güemes et al., 2016; Hartl & Jauch, 2014; Wanek & Wolf, 2007). Thus, it is expected of these children to have a higher risk of developing hyperglycemia during metabolic stress, which favors an

imbalance between the immune and inflammatory responses, evolving with tissue injury and cell death (Baker et al., 2011; Kyle et al., 2010; Lenzen, 2008).

Therefore, hyperglycemia, glycemic variation, and hypoglycemia are related with worse clinical results in children with septic shock, such as longer hospital length of *stay*, mechanical ventilation duration, and high mortality rates (Bagshaw et al., 2009; Branco et al., 2005; Day et al., 2008; Krinsley et al., 2011; Kyle et al., 2010).

Despite the numerous publications in the literature that evaluate the glycemic level and its association with worse clinical outcomes in pediatric septic shock patients, there are few studies in the theme regarding regions with limited socioeconomic and structural resources (Bagshaw et al., 2009; Krinsley et al., 2011; Kyle et al., 2010), such as the Northern region of Brazil, located in the Brazilian Amazon - that has no studies on this topic so far. Pará state stands out among the Amazon states with such profile; it has 144 municipalities subdivided into microregions and mesoregions, and a vast territorial extension of 1,247,689.76 km², and demographic density of 1,315.26 inhabitants per km². In 2018, it had an estimated population of 8,513,497 inhabitants (IBGE, n.d.; Ministério da Saúde, 2018).

Based on the hypothesis that changes in glucose homeostasis are common in patients with septic shock, the objectives of this study were: (1) to determine the frequency of blood glucose values, concerning to the hyperglycemia and hypoglycemia groups; (2) to evaluate the association of serum glucose admission level, with 28-day mortality as the primary outcome and the frequency of ventilation-free days and disease severity as a secondary outcome in this group.

2. Materials and Methods

Study design

Retrospective cohort observational study (Pereira et al., 2018).

Study population

The population consisted of all pediatric patients with septic shock (Rigby et al., 2013), admitted to the pediatric intensive care unit of the Santa Casa de Misericórdia do Pará Foundation (FSCMPA-PICU), a maternal and child referral hospital in Pará state, in the period from January 2015 to December 2017. The following were excluded: patients hospitalized for less than 24 hours; diagnosed with diabetes *mellitus*; with suspicion or evidence of inborn errors of metabolism; insulin use; those in palliative care, and brain death(Güemes et al., 2016).

The FSCMPA-PICU has ten hospital beds and attends children with clinical and non-traumatological diseases, delivered either from the very hospital or from emergency services of the Unified Health System, in addition to wards and surgical sectors of the hospital itself. As it is a humanized PICU, the child responsible remains throughout the entire hospitalization, full time (Pará, n.d.).

Study Variables

Data were obtained through the unit's data system, for the following variables: name, age, sex, date of admission, date of discharge, hospital record, type of discharge, and diagnosis on admission. After initial screening, a survey and confirmation of the data was obtained by consulting the medical records system used at the FSCMPA-PICU, the Electronic Patient Record (MVPEP®, MV, Recife, Brazil), completed by the multidisciplinary team from the unit for all the admitted patients. After compiling the collected data, it was inserted in a previously formulated research protocol, and the analysis was built on a bank and spreadsheets in the Microsoft Office Excel ® 2016 program (Microsoft, Washington, USA).

Age range cutt-off criteria followed the Brazilian Ministry of Heatlh guide, that divides groups into: infants (0 to 1 year and 11 months of age), preschoolers (2 to 5 years and 11 months of age), school-age children (6 to 10 years of age) and adolescents (up to 19 years of age).

All children included in the study had at least one blood glucose value measured in the first 24 hours after admission. In the case of multiple measurements, the closest to the time of admission worst value was selected. Whole blood glucose concentrations were measured from arterial or venous samples using an automatic biomedical blood gas analyzer. The blood glucose concentration was expressed in milligrams per deciliter (mg / dL).

There are no specific criteria for defining hyperglycemia or hypoglycemia among critically ill children. Hyperglycemia was defined as blood glucose level higher than 150 mg / dL, as hypoglycemia was defined as blood glucose level lower than 60 mg / dL. The choice of cut-off values was based on the definitions used by the unit's physicians in clinical practice.

The variables included for analysis were: age; sex; reason for hospitalization (clinical or surgical); primary dysfunction on admission; the presence of comorbidities; admission blood glucose value; primary outcome (mortality within 28 days); secondary outcome (ventilation-free days); Pediatric Risk of Mortality IV (PRISM IV) (Pollack et al., 2016); the presence of Ventilation-Associated Pneumonia (VAP); hemodynamic support (use of vasoactive drugs, insertion of central venous catheter); the need of ventilatory support on admission; corticosteroid (CS) use; the need of nutritional therapy with Parenteral Nutrition (PN); length of stay in the hospital and time on mechanical ventilation.

Statistical analysis

The numerical data were expressed in absolute values and percentages. After applying the Shapiro-Wilk test, a bivariate analysis between the control group and the other groups was initially carried out to assess the association between the case groups and the clinical and epidemiological variables. After applying the Fisher's Exact test, G-Test and Chi-square, multiple logistic regression analysis was applied due to the groups' low frequency. For the variables selection, variables with p <0.05 in the bivariate analysis were tested in the chosen model. Thus, those considered significant for p <0.05 and with 95% CI, had Odds Ratio (OR) calculation in this model. Statistical analyzes were performed using the Minitab® 14.0 program (Minitab, LLC, Pennsylvania, USA).

After determining the variables independently related to the outcome and with the established predictive model, the association of death and ventilation-free days predicted probabilities was calculated; for this analysis, it was established up to 28 days of hospitalization.

This research was approved by the Research Ethics Committee of the Santa Casa de Misericórdia do Pará Foundation, in conformity to the requirements established in the Nuremberg Code and the Declaration of Helsinki (Gandevia & Tovell, 1964; Mainetti, 1947) and was based on the basic principles of bioethics present in Resolution No. 466 / 12 from the National Health Council of Brazil, which provides for research involving human beings, under the opinion number 3.164.138/2019 and Presentation Certificate for Appreciation number 02152818.5.0000.5171.

3. Results

There were 458 admissions to the FSCMPA-PICU during the study period, from which 400 (87.4%) medical records were included in the study. Figure 1 specifies, in a flow chart, the reasons for including and excluding medical records from the research.

Figure 1 - Flow chart of the criteria for inclusion and exclusion of medical records (n = 400).
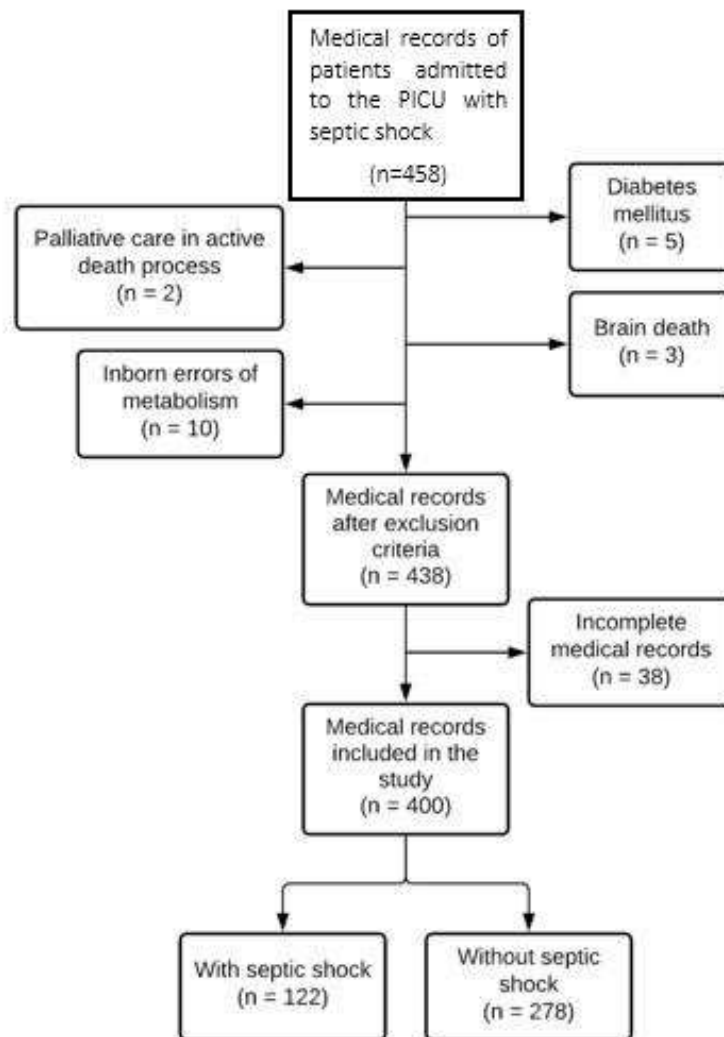
Source: Authors.

Male children (53.8%) had the greatest participation, compared to females (46.2%). Among the patients who developed septic shock, the female population was the majority (54.9%), however, the variable "Gender" did not present a statistical association with the outcome (*p-value* = 0.021) (Table 1).

Infants were most of the population (43.5%), followed by 139 preschoolers (34.8%) and 51 school-age children (12.7%); only 36 (9%) of the admitted patients were part of the adolescent age range. The variable "Age range" was not statistically significant neither between the groups with septic shock or without septic shock (*p-value* = 0.18). (Table 1).

Table 1 – Sociodemographic characterization of the population according to septic shock status, 2015-2017, Belém, Pará state, Brazil. (n=400).

Sociodemographic variables	Septic Shock						
	Without		With		All patitens		
Gender	n	%	N	%	n	%	*p value*
Female	118	42,4	67	54,9	185	46,2	0,021[a]
Male	160	57,6	55	45,1	215	53,8	
	278	100	122	100	400	100	
Age range							
Infants	114	41	60	49,2	174	43,5	0,18[a]
Preschoolers	106	38,1	33	27	139	34,8	
School-age children	33	11,9	18	14,8	51	12,7	
Adolescents	25	9	11	9	36	9	
	278	100	122	100	400	100	
Reason for hospitalization							
Clinical	204	73,4	118	96,7	322	80,5	<0,0001[c]
Surgical	74	26,6	4	3,3	78	19,5	
	278	100	122	100	400	100	
Origin							
Ward	124	44,6	49	40,2	173	43,2	
External	78	28	66	54,1	144	36	<0,0001[c]
Neonatology	56	20,2	3	2,5	59	14,8	
Ambulatory	20	7,2	4	3,2	24	6	
	278	100	122	100	400	100	
Comorbidity							
Present	86	30,9	87	71,3	173	43,3	<0,0001[a]
Absent	192	69,1	35	28,7	227	56,7	
	278	100	122	100	400	100	
Avarage length of stay in days							
Up to 5	97	34,9	33	27	130	32,5	0,08[a]
6 to 10	57	20,5	33	27	90	22,5	
11 to 15	27	9,7	24	19,7	51	12,8	
>15	97	34,9	32	26,3	129	32,2	
	278	100	122	100	400	100	

[a] Pearson chisquare test; [b] G Wilks test; [c] Fisher exact test. Source: The authors.

Regarding the average PICU length of stay, most patients (32.5%) stayed for five days or less. On the other hand, 32.2% of the patients included in the study remained for over 15 days. The average PICU length of stay was not statistically associated with the outcome (*p-value* = 0.08) (Table 1).

Invasive Mechanical Ventilation (IMV) was necessary for most of the sample, accounting for 340 (85%) of the patients, even more important in the group of 177 who evolved with septic shock (95.9%). As for the length of stay, a total of

199 (49.8%) patients stayed at IMV for up to 3 days, of which 55 had septic shock. Both " IMV on admission" and " time on IMV" were statistically associated with the outcome (*p-value* <0.0001) (Table 2).

Table 2 – Clinical characteristics of the population according to the septic shock status**,** 2015-2017, Belém, Pará state, Brazil. (n=400).

Variables	Septic Shock						
IMV on admission	**Absent**		**Present**		**Sample**		
	N	%	n	%	n	%	valor *p*
Yes	223	80,3	117	95,9	340	85	<0,0001[b]
No	55	19,7	5	4,1	60	15	
	278	200	122	200	400	200	
Time on IMV							
Up to 3 days	144	51,8	55	45,1	199	49,8	<0,0001[c]
3 to 7 days	41	14,7	35	28,7	76	19	
8 to 10 days	31	11,1	26	21,3	57	14,2	
11 to 14 days	8	2,9	1	0,8	9	2,3	
>15 days	54	19,5	5	4,1	59	14,7	
	278	100	122	100	400	100	
Vasoactive Support							
Yes	80	28,8	121	99,2	201	50,3	<0,0001[c]
No	198	71,2	1	0,8	199	49,7	
	278	100	122	100	400	100	
CVC use							
Yes	225	80,9	120	98,4	345	86,3	<0,0001[c]
No	53	19,1	2	1,6	55	13,7	
	278	100	122	100	400	100	
Nutritional support therapy with PN							
Yes	19	6,8	19	15,6	38	9,5	0,006[a]
No	259	93,2	103	84,4	362	90,5	
	278	100	122	100	400	100	
CS use							
Yes	114	41	89	72,9	203	50,8	<0,0001[a]
No	164	59	33	27,1	197	49,2	
	278	100	122	100	400	100	
PRISM IV							
Up to 10	133	47,8	14	11,4	147	36,8	
11 to 20	110	39,7	50	41	160	40	<0,0001[a]
21 to 30	16	5,7	29	23,8	45	11,2	
>30	19	6,8	29	23,8	48	12	
	278	100	122	100	400	100	
Admission serum glucose (mg/dL)							

<60	40	14,4	3	2,5	43	10,7	
60-126	183	65,8	52	42,6	235	58,8	
127-150	30	10,8	21	17,2	51	12,7	
>150	25	9	46	37,7	71	17,8	<0,0001[c]
	278	100	122	100	400	100	
VAP							
Yes	46	16,5	13	10,7	59	14,7	0,13[a]
No	232	83,5	109	89,3	341	85,3	
	278	100	122	100	400	100	
IMV-free days							
Over 3	183	82,1	95	81,2	278	81,8	0,01[a]
Under 3	40	17,9	22	18,8	62	18,2	
	223	100	117	100	340	100	
28-day mortality							
Yes	23	8,3	50	41	73	18,2	<0,0001[a]
No	255	91,7	72	59	327	81,8	
	278	100	122	100	400	100	

a) IMV: Invasive Mechanical Ventilation; b) CVC: Central Venous Catheter; c) Parenteral Nutrition; d) CS: Corticosteroid; e) PRISM IV: Pediatric Risk of Mortality; f) VAP: Ventilation Associated Pneumonia.
[a] Pearson chisquare test; [b] G Wilks test; [c] Fisher exact test.
Source: Authors.

Over half of all patients (201 - 50.3%), received vasoactive support, and in the group with present septic shock, vasoactive support accounted for 99.2% of the patients. The CVC was used in most of the sample, accounting for 345 (86.3%) patients. Both variables were statistically associated with the outcome (*p-value* <0.0001) (Table 2).

The PRISM IV index had most frequent score range from 0 to 10, accounting for 147 (36.8%) individuals. In the group of patients who had septic shock, the most frequent score was 11 to 20, which added up to 50 (41%) patients. It was statistically associated with the outcome (P-value <0.0001) (Table 2).

The blood glucose on admission had 117mg / dL avarage, with a 108 median, SD +/- 49.8, IIQ: 93-137, ranging from 20 to 490 mg/dL. In the septic shock group, it had higher average, with 139mg / dL, SD + / -48.3, median 132.5, IIQ: 103-168 with a range from 43 to 482, compared to the group without septic shock with a mean of 106.7mg / dL, median of 102, IIQ: 90-117 and variation from 20 to 490., DP+/-49,8, IIQ: 93-137.

The frequency of serum glucose levels were: 40 cases (14.4%) with blood glucose <60 mg / dL, and 25 cases (9%) above 150 mg / dL, in patients without septic shock. The group with septic shock had frequency of hypoglycemia and hyperglycemia of 3 (2.5%) and 46 (37.7%) cases, respectively. Blood glucose at admission was associated with the outcome (P-value <0.0001) (Table 2).

As for the 28-day mortality, it was present in 73 (18.2%) of the patients, and in the group who had septic shock, it was present in 50 (41%) of the patients. 28-day mortality was associated with progression to septic shock (P-value <0.0001) (Table 2).

Table 3 shows that the chance of the disease to present severity is 5.1% in relation to " Hyperglycemia and septic shock" . While " Hypoglycemia and septic shock" presented zero chance in view of the disease severity.

Table 3 - Effects of hyperglycemia and hypoglycemia on morbidity and mortality according to the state of septic shock.

Serum glucose on admission	Disease severity	IMV-free days	28-day mortality
	OR(CI95%)	*OR*(CI95%)	*OR*(CI95%)
Hyperglycemia and septic shock	5,1(2,8-10,9) [a]	1,8(1-3,2) [a] 0,8(0,5-12) [c]	0,2(0,1-0,4) [a] 1,3(0,1-16,7) [b]
Hypoglycemia and septic shock	-----	0,7(0,06-92) [c]	1,6(0,5-51) [b]

a) IMV: Invasive Mechanical Ventilation.
PRISMIV, Risk Pediatric of Mortality ≥ third quartile; Prolonged ventilation: ventilator-free days <3 days (third quartile); *OR: Odds Ratio;* CI: confidence interval
[a]Cochran-Mantel-Haenszel analysis: there was significant association between the 2 variables of interest when controlled for septic shock, only for hyperglicemia, with respective *p* values: <0,0001;0,037 and <0,0001.
[b]Multiple logistic regression analysis adjusted by control group; there was significant association for Mortality with hyperglicemia and hipoglicemia, with respective *p* values: 0,039 and 0,05
[c]Multiple logistic regression analysis adjusted by control group; there was significant association for ventilator free days with hyperglicemia and hipoglicemia, with respective *p* values: 0,019 and 0,016
Source: Authors.

Regarding the item " IMV-free days" , the Cochran-Mantel-Haenszel analysis associated 2 variables of interest, which when controlled for septic shock, only for hyperglycemia, obtained 1.8% chances of patients with " Hyperglycemia and Septic Shock" to need mechanical ventilation. As for the multiple logistic regression analysis adjusted by the control group, there was a significant association of ventilation-free days with hyperglycemia and hypoglycemia. When compared, the "hyperglycemia and septic shock" group had a 0.8% chance of remaining free of ventilation, while patients in the "hypoglycemia and septic shock" group had a 0.7% chance (Table 3).

Regarding the variable " 28-day mortality" , in relation to the " Hyperglycemia and septic shock" group, also analyzed from the Cochran-Mantel-Haenszel perspective, 0.2% of these patients died within 28 days. The multiple logistic regression analysis adjusted by the control group, presented for the association of Mortality with hyperglycemia and hypoglycemia, showed that patients with hyperglycemia had a 1.3% chance of progressing to death in this period. On the other hand, the chance of a patient with hypoglycemia is 1.6%. There were more deaths in this condition than in relation to hyperglycemia (Table 3).

Figure 2 - Association of blood gluose leves with ventilator free days and mortality.
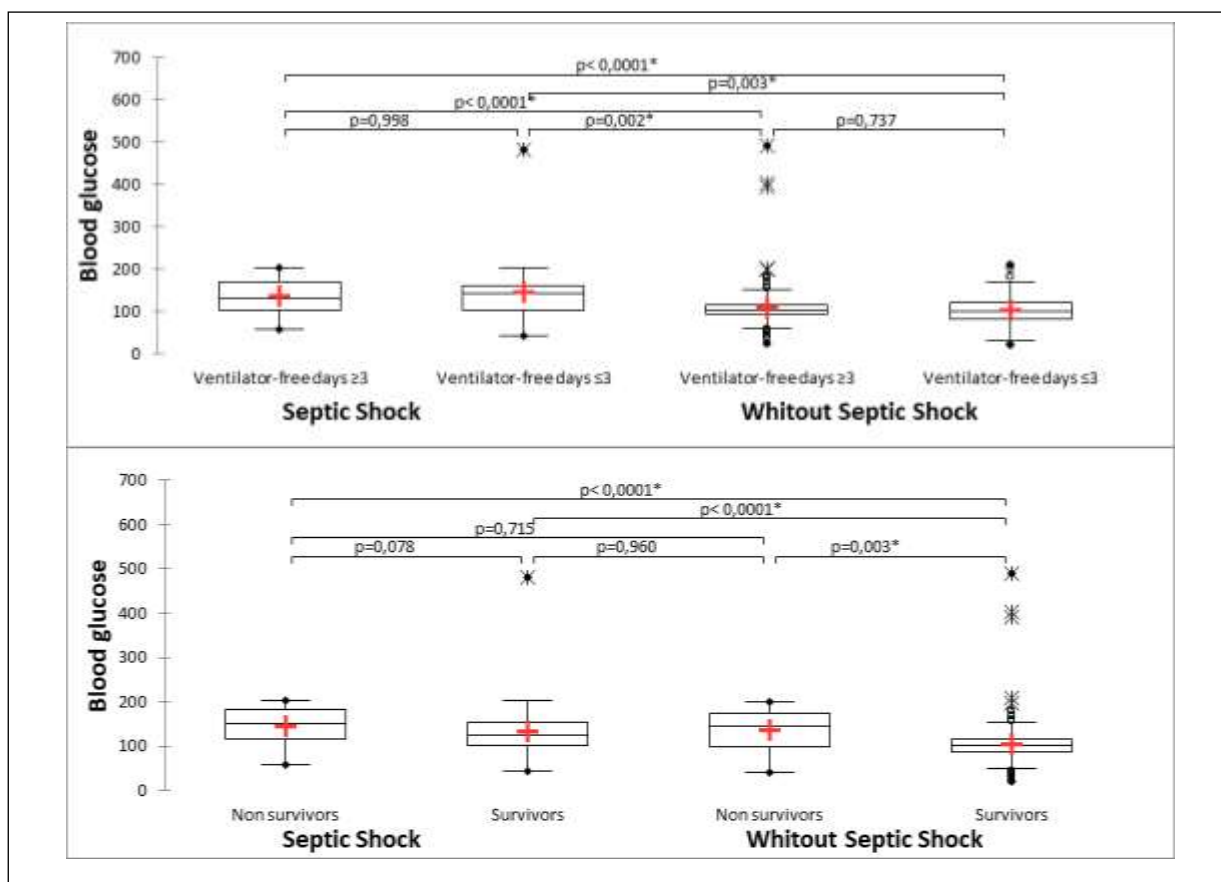
*Comparison of blood glucose levels on mg/dL (Kruskal-Wallis test and Multiple pairwise comparisons using the Steel-Dwass-Critchlow-Fligner procedure/Two-tailed tests) acording to Septic Shock Status effect on Mortality and ventilator free days. Source: Authors.

Among the patients with septic shock, the higher the glucose levels, higher the mortality. The patients who did not have septic shock and evolved with death had, for the most part, higher glucose levels, while survivors in the same condition had a lower glucose rate (Figure 2).

4. Discussion

The pathophysiology of septic shock involves circulatory, cellular, and metabolic responses (Rhodes et al., 2017). Metabolic stress incurs in an increase in proinflammatory cytokines and hyperglycemic hormones (such as growth hormone), and a reduction in the insulin-like growth factor, which leads to an increase in the inflammatory response in the tissues and an imbalance of the immune response (Aleman & Guerrero, 2018; Singer et al., 2016).

Therefore, the glycemic level in critically ill patients with sepsis and septic shock is correlated with worse outcomes, such as multiple organ dysfunction, longer ventilation time, and death; Van Vught et al (2016), Chan et al (2016), and Wang et al (2019) found an association between high blood glucose levels, worse clinical response and increased risk of mortality (Singer et al., 2016; Van Vught et al., 2016; Wang et al., 2019), which corroborates the findings of the present study.

Glycemic variation is a severity marker in critically ill patients, as observed in this study and alluded to by Toro-Polo et al (2018), Okazaki et al (2018), and Kim et al (2019) (Kim et al., 2019; Okazaki et al., 2018; Toro-Polo et al., 2018). For this reason and since it is a low-cost method, several measurements are required during hospitalization, facilitating the continuous assessment of patients in intensive care units (Kim et al., 2019; Okazaki et al., 2018; Toro-Polo et al., 2018).

In this context, El-Sherbini, Marzouk, El-Sayed, and Hosam-ElDin (2018) (El-Sherbini et al., 2018; E. Faustino et al., 2019) related glycemic values equal to or greater than 180mg / dL to worse clinical outcomes; Faustino & Apkon (2005) (E. V. Faustino & Apkon, 2005) found an increased risk of mortality and a longer stay in intensive care when glucose levels exceeded 150mg / dL. These findings are similar to the present study, in which hyperglycemia and septic shock were statistically associated with the severity of the disease, with 28-day mortality, and with IMV-free days.

On the other hand, Faustino et al (2019) (El-Sherbini et al., 2018; E. Faustino et al., 2019) associated blood glucose levels below 40mg / dL with worse short-term results, as well as Toro-Polo et al (Kim et al., 2019; Okazaki et al., 2018; Toro-Polo et al., 2018), who registered a higher risk of death on discharge from PICU patients in Peru (N = 522). In the study carried out at FSCMPA, hypoglycemia was also associated with 28-day mortality, as well as with IMV-free days, but it was more common in patients without shock septic.

Among the key factors that can influence the prognosis of patients with septic shock are the nature of the infection, the presence of underlying diseases, and immunosuppression (Rhodes et al., 2017). However, in regard to the pediatric population hospitalized in the intensive care unit, there are few studies available demonstrating the association between glycemic values and prognosis, even in countries with high socioeconomic and intellectual levels.

This study demonstrated that patients in the hyperglycemic group had a higher incidence of nosocomial infections, mechanical ventilation duration, and death rate. Pulmonary disease in patients with sepsis emphasizes the need for ventilatory support that minimizes lung damage, that is usually elevated the longer the need for mechanical ventilation (Nieman et al., 2017; Zampieri & Mazza, 2017). As for mortality due to septic shock, it can result from late diagnosis and late treatment - scenario in which developing countries lead, given the scarcity of resources (de Souza & Machado, 2019).

The need for CVC can be a gateway for opportunistic pathogens such as *Candida*, especially in cases of longer length of stay (Rhodes et al., 2017). Furthermore, corticosteroids prescription for the management of sepsis and septic shock is controversial; despite being widely used as an adjuvant to reduce state duration, mortality, as well as to prevent its transition to multiple organ dysfunction (Annane et al., 2018; Darmaros et al., 2016), its benefits may depend on variables such as initial risk mortality or may be absent, as demonstrated by Atkinson et al (2014) (Atkinson et al., 2014).

The relevance of this study is in highlighting the data from FSCMPA-PICU and use the glycemic level as a marker of severity, predictor of prognosis, and mortality in patients with sepsis / septic shock. The use of insulin is indicated in order to prioritize the adequate control of serum glucose, however, studies have demonstrated an increased risk of hypoglycemia, and should be used with discretion (Agus et al., 2017; E. Faustino et al., 2019). The study's limitations are related to the retrospective design and its realization in a single-center, with a limited number of patients.

5. Conclusion

The frequency of hypoglycemia was higher in patients without septic shock, while hyperglycemia was higher in those who progressed to such condition. The association between high serum glucose level and septic shock denoted a worse overall outcome for the group, to 28-day mortality – that was higher in this group - and the time free from invasive mechanical ventilation - which was lower – both.

Taking into account the lack of resources present in most of the Brazilian Amazon region and the socioeconomic and cultural disparities of the population, it is extremely important to use low-cost and easily accessible methods to identify patients at greatest risks. It must take in consideration the unfavorable clinical conditions for which patients are admitted to the PICU, so it can be used to obtain better results in scores of severity, mortality rate, survival / quality of life and show the minimum of sequelae - mainly neurological - as possible. For future research, it is suggested that the investigation of factors

that may predispose children from the Brazilian Amazon to unfavorable outcomes, raised by this article, in addition to the analysis of which pathogens are more related to sepsis in this population.

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