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Review Article

Evaluation of main risk factors for high glycemic variability in an Intensive Care Unit

Avaliação dos principais fatores de risco para alta variabilidade glicêmica em uma Unidade de Terapia Intensiva

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ABSTRACT: Glycemic variability (GV) is an important evaluation parameter for cardiovascular complications. We aimed to identify factors associated with the risk of high glycemic variability in an Intensive Care Unit. In this prospective cohort with 168 adult patients, we first described the variables by absolute and relative frequency and then identified the risk factors for high GV by logistic regression within a 95% confidence interval. Of the 168 patients, 22.6% had high GV, 62.5% were male, 51.2% were under 40 years old, 52.4% had a clinical diagnosis, 73.8% were using mechanical ventilation, 12.3% had > 30% mortality risk (Apache II), 17.9% had sepsis, 47.6% were hypertensive, and 28.0% of the patients died. In the final analysis, patients with sepsis (OR: 2.40; 95%CI: 1.10 – 5.94), over 40 years old (OR: 3.23; 95%CI 1.34-7.81) and who evolved to death (OR: 3.15; 95%CI 1.40-7.08) were those who had a greater chance of high GV. Patients with sepsis and those over 40 years old need greater surveillance of glycemic control to reduce mortality in the ICU.

KEY WORDS: Glycemic variability; Blood glucose; Intensive Care Unit; Mortality.

RESUMO: A variabilidade glicêmica (VG) é um importante parâmetro de avaliação para complicações cardiovasculares. Nosso objetivo foi identificar fatores associados ao risco de alta VG em uma Unidade de Terapia Intensiva. Nesta coorte prospectiva com 168 pacientes adultos, primeiro descrevemos as variáveis por frequência absoluta e relativa e, em seguida, identificamos os fatores de risco para alta VG por regressão logística em um intervalo de confiança de 95%. Dos 168 pacientes, 22,6% tinham alta VG, sendo 62,5% do sexo masculino, 51,2% tinham menos de 40 anos, 52,4% tinham diagnóstico clínico, 73,8% usavam ventilação mecânica, 12,3% tinham risco de mortalidade > 30% (Apache II), 17,9% tiveram sepse, 47,6% eram hipertensos e 28,0% dos pacientes foram a óbito. Na análise final, os pacientes com sepse (OR: 2,40; IC 95%: 1,10 – 5,94), com mais de 40 anos (OR: 3,23; IC 95% 1,34-7,81) e que evoluíram para óbito (OR: 3,15; 95% IC 1,40-7,08) foram os que tiveram maior chance de alta VG. Pacientes com sepse e aqueles com mais de 40 anos precisam de maior vigilância do controle glicêmico para reduzir a mortalidade na UTI.

PALAVRAS-CHAVE: Variabilidade glicêmica; Glicose sanguínea; Unidade de Terapia Intensiva; Mortalidade.

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INTRODUCTION

Glycemic control is essential for maintaining health in critical patients in Intensive Care Units (ICU)[1]. Hyperglycemia can be attributed to endocrine-metabolic stress related to acute disease and is associated with increased morbidity and mortality in critically ill patients[2]. However, insulin therapy with strict glycemic control protocols can also harm the critical patient, resulting in hypoglycemia[3,4] and elevation in the glycemic variability (GV), with substantial impact to the ICU patients' prognosis[1,2]. High GV, with glucose fluctuations above 50 mg/dL, is a critical risk factor for short-term mortality. It contributes to increased oxidative stress, endothelial dysfunction, and cardiovascular complications[5-7]. Avoiding high glycemic fluctuations seems to be a safer and more effective strategy to improve the survival in those patients. In this sense, the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) guide the initiation of insulin therapy in critically ill patients when blood glucose is higher than 180 mg/dL, aiming to maintain glycemic control between 140-180 mg/dL, with hypoglycemia correction as blood glucose is lower than 70 mg/dL[8,9].

Critically ill patients are at risk of glycemic fluctuations due to various factors such as glucocorticoids, vasopressor substances, dialysis solutions that use 5% glucose, and interruption of enteral and parenteral diets due to medical procedures[10]. It is essential to monitor these factors to prevent glycemic fluctuations in critically ill patients[2].

Studies have shown that maintaining a lower blood glucose range is favorable for critically ill ICU patients, although there is still no consensus on the safe blood glucose range and the gold standard for determining GV[11,12]. However, the results of the studies with high GV are often not applicable to all ICUs, which use different protocols for glycemic control and meet other patient profiles (clinical and surgical). Therefore, further studies are required to analyze the incidence and factors associated with high VG in critically ill patients, thus contributing to greater surveillance and prevention of the control of blood glucose variation in these patients[13]. This study aimed to identify the incidence of factors associated with high GV in a Brazilian Amazon ICU.

MATERIAL AND METHODS

A prospective cohort study, according to Strobe guidelines, with adult and elderly patients hospitalized in an ICU in Rio Branco, Acre, Brazil. The cohort consisted of 168 patients over 18 years-old admitted to the ICU from August 2017 to March 2018 (Figure 1). Time zero (t_0) of the cohort was the admission of the patient to the ICU and the follow-up time (Δt) was seven days after. Exclusion criteria consisted of people under 18 years-old and open Brain Death (BD) protocol.

We used the Nursing Care Systematization (NCS) protocol and medical record to collect clinical data on admission as well as daily evolution of medical prescription and nutritional protocol. Capillary blood glucose values were daily obtained by electronic glucometers of the same brand/model and specifications, in arm fingers, at 6 AM, 12 PM, 6 PM, and 12AM for seven days, totaling 28 measurements per patient. Elevated GV, assumed by blood GV above 50 mg/dL[6], was the dependent variable.

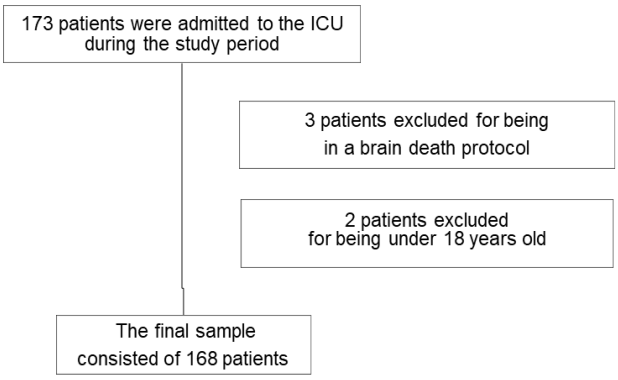

Figure 1 - Population analyzed in the study

The independent variables analyzed were: age (< or ≥ 40 years), sex (male or female), medical diagnosis (clinical or surgical), comorbidities (hypertension, diabetes, or hypertension plus diabetes), mechanical ventilation, adrenergic drugs (noradrenaline or dobutamine), patient severity score assessed by Acute Physiology and Chronic Health Evaluation II (APACHE II) (< or ≥ 30 points), diet suspension, nutritional support (oral, enteral or parenteral nutrition), sepsis, hemodialysis, use of hyperglycemic medications (hydrocortisone or dexamethasone), hypoglycemia (blood glucose below 70 mg/dL), hyperglycemia (blood glucose above 180 mg/dL), length of stay in the ICU (< or ≥ seven days), and clinical outcome (discharge or death). The APACHE II index was taken for the first 24 hours of admission to the ICU with scores between 0 and 8 points obtained for 12 clinical criteria, in addition to age and comorbidities, as described elsewhere[14,15]. Patients received classification in less or greater than 30% mortality risk based on the obtained score in this cohort.

In the studied ICU, the correction of glycemic changes was performed with regular insulin or 50% glucose solution, according to the unit's protocol, as follows: blood glucose between 70 and 180 mg/dL, without the use of insulin; blood glucose below 70 mg/dL, intravenous bolus (30 mL) of hypertonic glucose (50%); blood glucose above 180 mg/dL, use of regular insulin, subcutaneously, following the current recommendation of AACE and ADA[8].

Statistical analysis

We described the independent variables using absolute (n) and relative (%) frequency and verified the association between two categorical variables using the Chi-square test ($\chi 2$) or the Fisher's exact test (FET) for small samples. Differences in distribution, when present, were corrected using standardized adjusted residuals[16]. Factors associated with high GV were analyzed by binary logistic regression, with the measure of

association Odds Ratio (OR) crude and adjusted, considering a confidence interval (CI) of 95%. The Hosmer and Lemeshow tests were used to analyze the adequacy of the final predictive model with adjustment for diabetes. All statistical tests used 5% as the significance level. Data were analyzed by Microsoft Excel and SPSS.

Ethical considerations

This study was approved by The Research Ethics Committee of the Hospital Foundation of Acre State, Brazil, under registry number 3.294.722. Patients, or their guardians, signed the consent or assent term and received a copy of the signed document.

RESULTS

A preliminary comparison between capillary blood glicemic values obtained daily at 6 AM and serum glucose at the same time point showed no significant difference (Table 1), demonstrating the accuracy of the GV values obtained from the capillary blood glucose measurements.

Table 1 - Serum and capillary blood glucose values at 6 AM of patients in an Intensive Care Unit in Rio Branco, Acre, Brazil

	Fasting Blood Glucose		Capillary Blood Glucose		p-Value*
	Average	SD	Average	SD	
Blood Glucose (mg/dL)	167.92	55.11	160.42	42.51	0.478

*p<0.05 means significant difference (Student t-test)

The study evaluated 168 patients and found that 38 (22.6%) had high glycemic variability. In addition, 51.2% were younger than 40 years; 62.5% were male; 52.4% had a clinical diagnosis; 73.8% were on mechanical ventilation; 63.1% used adrenergic drugs; 12.3% had > 30% mortality risk (Apache II); 58.6% had their diet suspended for some period of the seven days of hospitalization; 17.9% had sepsis; 22.6% underwent hemodialysis; 60.7% received hyperglycemic medication; 44.0% had hypoglycemia; 64.3% had hyperglycemia; 75.6% were hospitalized for more than seven days; 47.6% were hypertensive; and 28.0% died (Table 2).

Table 2 - Characterization of patients in an Intensive Care Unit in Rio Branco, Acre, Brazil

Variable	**Total**	**High Glycemic Variability**		
	n (%)	**No**	**Yes**	***p*-Value***
Total	168 (100%)	130 (77.4%)	38 (22.6%)	
Age (years)† > 40 anos	82 (48.8)	53 (40.8)	29 (76.3)	<0.001
Sex† Male	105 (62.5)	87 (66.9)	18 (47.4)	0.030
Diagnosis† Clínical	88 (52.4)	65 (50.0)	23 (60.5)	0.270
Hypertension	39 (23.2)	24 (18.5)	15 (39.5)	0.007
Diabetes	25 (14.9)	11 (8.5)	14 (36.8)	<0.001
Hypertension plus diabetes	19 (11.3)	9 (6.9)	10 (26.3)	0,001
Mechanical ventilation†	125 (73.8)	93 (70.8)	32 (84.2)	0.098
Adrenergic drugs†	106 (63.1)	78 (59.2)	29 (76.3)	0.056
APACHE II* Classification‡				
> 30% mortality risk	19 (12.3)	16 (13.6)	3 (8.1)	0.379
Type of diet† Oral/enteral	69 (41.1)	52 (40.0)	17 (44.7)	0.600
Sepsis†	30 (17.9)	18 (13.8)	12 (31.6)	0.012
Hemodialysis‡	38 (22.6)	35 (22.3)	3 (27.3)	0.704
Hyperglycemic medications†	102 (60.7)	74 (56.9)	28 (73.7)	0.064
Hypoglycemia†	74 (44.0)	63 (48.5)	11 (28.9)	0.034
Hyperglicemia‡	108 (64.3)	70 (53.8)	38 (100.0)	<0.001‡
Length of stay† > 7 days	127 (75.6)	98 (75.4)	29 (76.3)	0.900
Clinical evolution† Discharge	121 (72.0)	101 (77.7)	20 (52.6)	0.002

**p*-Value < 0.05 means significant difference using Pearson's Chi-Square Test† or Fisher's Exact Test‡.

High glycemic variability was associated with: age > 40 years (p<0.001), sex (p=0.030), comorbidity (p=0.02), hypertension (p=0.007), diabetes (p<0.001), sepsis (p=0.012), hypoglycemia (p=0.034), hyperglycemia (p<0.001) and death (p=0.002) (Table 2).

In the final model, septic patients (OR: 2.40; 95%CI:

1.10 – 5.94), aged over 40 years (OR: 3.23; 95%CI 1.34-7.81) and who evolved to death (OR: 3.15; 95%CI 1.40-7.08) were more likely to have high GV. However, patients with lower blood glucose levels were less likely to have high GV (OR: 0.35; 95%CI 0.15 – 0.84) (Table 3).

Table 3 - Factors associated with high glycemic variability in an intensive care unit. Rio Branco, Acre, Brazil

Factor	Gross Odds Ratio (OR) 95% CI	Adjusted Odds Ratio (OR)* 95% CI	P-value
Age > 40 years	4.68 (2.05 – 10.68)	3.23 (1.34 – 7.81)	<0.001
Sex - Female	2.24 (1.07 – 4.68)	1.88 (0.86 – 4.09)	0.029
Hypertension	2.88 (1.31 – 6.32)	1.31 (0.48 – 3.56)	0.007
Diabetes mellitus	6.31 (2.55 – 15.57)	-	<0.001
Sepsis	2.87 (1.23 – 6.69)	2.40 (1.10 – 5.94)	0.012
Hypoglycemia	0.43 (0.19 – 0.94)	0.35 (0.15 – 0.84)	0.033
Evolution to death	3.13 (1.46 – 6.69)	3.15 (1.40 – 7.08)	<0.001

*Adjusted by Diabetes mellitus variable; - Missing

DISCUSSION

Elevated GV in critically ill patients can occur due to the interaction of multiple factors whose knowledge and control can promote a better prognosis and survival[10]. In the present study, septic patients were more likely to have high GV.

Sepsis, a potentially fatal condition resulting from an unregulated host response to infection, is a significant cause of mortality in critically ill patients and is associated with an increase in GV[17]. In this study, septic patients were more likely to exhibit high GV, a finding that aligns with previous research. This heightened GV in sepsis appears to be a neuroendocrine stress response, associated with the secretion of glucagon, cortisol, and adrenaline, which in turn increases glycogenolysis and gluconeogenesis in the liver. This process ensures the supply of energy to vital organs but also leads to increased inflammatory cytokines, decreased insulin secretion, and increased peripheral insulin resistance[18].

Indeed, in a study carried out at the Hospital of the Faculty of Medicine of Siriraj, patients with sepsis had higher GV values associated with sepsis severity[19]. In addition, a retrospective cohort study carried out in an ICU in Taiwan, which evaluated septic patients between 2014 and 2015, found a mean amplitude of 65 mg/dL in GV and identified that 40% of septic patients had high GV on admission, which was associated with an increase in 30-day mortality[20]. Our findings corroborate the results of those studies and demonstrate the need for better glycemic control in critically ill patients who progress to sepsis, especially to control the glycemic amplitude and reduce mortality in the ICUs. In the present study, patients with lower blood glucose levels were less likely to have high GV (OR: 0.35; 95%CI 0.15 – 0.84). This finding may reflect the effectiveness of glycemic control strategies via a reduction in blood glucose fluctuation and values, aiming to reduce mortality in the ICU[21,22]. However, hypoglycemia is one of the adverse effects on glycemic control of critically ill patients and therefore has deleterious implications for their health[23]. Therefore, this finding needs better investigation since the concern of ICU care is to improve the health prognosis of the patient.

Although in our study the presence of hemodialysis and the use of mechanical ventilation were not associated with high VG, a survey conducted in the ICU of the Porto Alegre Hospital of Clinics with 542 critically ill patients, with a mean age of 59 years, 52.5% male, 84.3% with clinical diagnosis and 54.0% hypertensive, a GV above 40 mg/dL was associated with a greater need for renal replacement therapy and mechanical ventilation, in addition to a higher incidence of septic shock - as in our study - but not of increased risk of mortality[23].

Differently, in the present study, patients with high GV had 3.15 times more chance of dying (OR: 3.15; 95%CI 1.40-7.08). However, other studies support these results. In a prospective observational study of 123 patients with a mean age of 65 years admitted to a medical and surgical ICU of a tertiary Indian armed forces hospital, elevated GV was associated with increased mortality[24]. At least to date, the most extensive prospective multicenter study on the subject, the NICE-SUGAR, also reported an increase in 90-day mortality in patients with high GV[25]. In another study, which evaluated a total of 528 patients in an ICU at Songklanagarind Hospital, GV and blood glucose coefficient of variation were the two parameters that most strongly predicted ICU mortality, regardless of pre-existing diabetes mellitus[26].

A history of good glycemic regulation seems to influence this predictive character of GV. In a prospective observational study that included critically ill adult patients (≥ 18 years of age) admitted to the ICU of the San Ángel Hospital, in Mexico, the

mean glucose levels over the previous 90 days, estimated from the glycated hemoglobin (HbA1c) values, were used to calculate the relative glycemic variability, using the GV values obtained during the first seven days of admission. Thus, the study concluded that the previous history of good glycemic regulation attenuated the influence of high GV on mortality[27].

Even if a previous history of good glycemic regulation is a mitigating condition on the effects of high GV, knowledge of the risk factors for increased GV is still essential and may allow the adoption of approaches to provide a better prognosis for the patient in critical condition.

This cohort studied a significant number of critically ill patients, one of its strengths, and sought to fulfill this role, identifying the incidence and factors associated with high GV. The study showed that patients with high glycemic variability are at greater risk of sepsis and death and should be monitored more rigorously in intensive care units.

CONCLUSION

High GV was associated with age greater than 40 years, female gender, hyperglycemia, sepsis, and clinical evolution to death in this cohort. After adjusting for the influence of diabetes, critically ill patients over 40 years of age, females, and those with sepsis were 3.23 (1.34 – 7.81), 1.88 (0.86 – 4.09), and 2.40 (1.10 – 5.94) more likely to have high GV than those aged ≤ 40 years, male and without sepsis, respectively. Patients with high GV were 3.15 (1.40 – 7.08) greater risk of death.

The definition of metabolic control protocols, especially for the risk conditions elucidated here, may reduce mortality in the ICU. In any case, it is clear that, in critically ill patients, high GV during the ICU stay is an indicator of worse clinical outcomes.

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REFERENCES

1. Perez-Calatayud AA, Guillen-Vidana A, Fraire-Felix IS, Anica-Malagon ED, Briones Garduno JC, Carrillo-Esper R. [Metabolic control in the critically ill patient an update: hyperglycemia, glucose variability hypoglycemia and relative hypoglycemia]. Cir Cir. 2017;85(1):93-100, Doi:https://doi.org/10.1016/j.circir.2016.10.026.
2. Balloni A, Lari F, Giostra F. Evaluation and treatment of hyperglycemia in critically ill patients. Acta Biomed. 2016;87(3):329-33.
3. Kushimoto S, Abe T, Ogura H, Shiraishi A, Saitoh D, Fujishima S, et al. Impact of blood glucose abnormalities on outcomes and disease severity in patients with severe sepsis: An analysis from a multicenter, prospective survey of severe sepsis. PloS One. 2020;15(3):e0229919, Doi:https://doi.org/10.1371/journal.pone.0229919.
4. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. Int Care Med. 2017;43(1):1-15, Doi:https://doi.org/10.1007/s00134-016-4523-0.
5. Kovatchev B. Glycemic Variability: Risk Factors, Assessment, and Control. J Diabetes Sci Technol. 2019;13(4):627-35, Doi:https://doi.org/10.1177/1932296819826111.
6. Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. Crit Care Med. 2010;38(4):1021-9, Doi:https://doi.org/10.1097/CCM.0b013e3181cf710e.
7. Sun B, Luo Z, Zhou J. Comprehensive elaboration of glycemic variability in diabetic macrovascular and microvascular complications. Cardiovasc Diabetol. 2021;20(1):9, Doi:https://doi.org/10.1186/s12933-020-01200-7.
8. American Diabetes A. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2019. Diabetes care. 2019;42(Suppl 1):S173-S81, Doi:https://doi.org/10.2337/dc19-S015.
9. Rodriguez-Calero MA, Barcelo Llodra E, Cruces Cuberos M, Blanco-Mavillard I, Perez Axartell MA. Effectiveness of an evidence-based protocol for the control of stress-induced hyperglycaemia in critical care. Enferm Intensiva 2019;30(1):4-12, Doi:https://doi.org/10.1016/j.enfi.2018.01.004.
10. Lanspa MJ, Dickerson J, Morris AH, Orme JF, Holmen J, Hirshberg EL. Coefficient of glucose variation is independently associated with mortality in critically ill patients receiving intravenous insulin. Crit Care. 2014;18(2):R86, Doi:https://doi.org/10.1186/cc13851.
11. Akirov A, Diker-Cohen T, Masri-Iraqi H, Shimon I. High Glucose Variability Increases Mortality Risk in Hospitalized Patients. J Clin Endocrinol Metab. 2017;102(7):2230-41, Doi:https://doi.org/10.1210/jc.2017-00450.
12. Umpierrez GE, B PK. Glycemic Variability: How to Measure and Its Clinical Implication for Type 2 Diabetes. Am J Med Sci. 2018;356(6):518-27, Doi:https://doi.org/10.1016/j.amjms.2018.09.010.
13. Kulkarni H, Bihari S, Prakash S, Huckson S, Chavan S, Mamtani M, et al. Independent Association of Glucose Variability With Hospital Mortality in Adult Intensive Care Patients: Results From the Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Binational Registry. Crit Care Explor. 2019;1(8):e0025, Doi:https://doi.org/10.1097/CCE.0000000000000025.

14. Cheng X, Zhang S, Wen Y, Shi Z. Clinical significance of sirtuin 1 level in sepsis: correlation with disease risk, severity, and mortality risk. Braz J Med Biol Res. 2020;54(2):e10271, Doi:https://doi.org/10.1590/1414-431X202010271.

15. Huang J, Xuan D, Li X, Ma L, Zhou Y, Zou H. The value of APACHE II in predicting mortality after paraquat poisoning in Chinese and Korean population: A systematic review and meta-analysis. Medicine. 2017;96(30):e6838, Doi:https://doi.org/10.1097/MD.0000000000006838.

16. Medronho RA, Block KV, Luiz RR, Werneck GL. Epidemiologia. São Paulo: Editora Atheneu; 2009.

17. Evans L, Rhodes A, Alhazzani W, Antonelli M., Coopersmith C, Craig M, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Med. 2021;49(11):e1063-e1143, Doi: 10.1097/CCM.0000000000005337

18. Garcia de Lorenzo YMA. Seventh Jesus Culebras Lecture. Systemic inflammatory response and multi organic dysfunction/failure following aggression: metabolic implications. Nutr Hosp. 2017;34(1):244-50, Doi:https://doi.org/10.20960/nh.1001.

19. Preechasuk L, Suwansaksri N, Ipichart N, Vannasaeng S, Permpikul C, Sriwijitkamol A. Hyperglycemia and glycemic variability are associated with the severity of sepsis in nondiabetic subjects. J Critical Care. 2017;38:319-23, Doi:https://doi.org/10.1016/j.jcrc.2016.12.005.

20. Chao WC, Tseng CH, Wu CL, Shih SJ, Yi CY, Chan MC. Higher glycemic variability within the first day of ICU admission is associated with increased 30-day mortality in ICU patients with sepsis. Ann Intensive Care. 2020;10(1):17, Doi:https://doi.org/10.1186/s13613-020-0635-3.

21. Nusca A, Tuccinardi D, Albano M, Cavallaro C, Ricottini E, Manfrini S, et al. Glycemic variability in the development of cardiovascular complications in diabetes. Diabetes Metab Res Rev. 2018;34(8):e3047, Doi:https://doi.org/10.1002/dmrr.3047.

22. Saliba L, Cook CH, Dungan KM, Porter K, Murphy CV. Medication-induced and spontaneous hypoglycemia carry the same risk for hospital mortality in critically ill patients. J Critical Care. 2016;36:13-7, Doi:https://doi.org/10.1016/j.jcrc.2016.06.010.

23. Bellaver P, Schaeffer AF, Dullius DP, Viana MV, Leitao CB, Rech TH. Association of multiple glycemic parameters at intensive care unit admission with mortality and clinical outcomes in critically ill patients. Sci Rep. 2019;9(1):18498, Doi:https://doi.org/10.1038/s41598-019-55080-3.

24. Singh M, Upreti V, Singh Y, Kannapur AS, Nakra M, Kotwal N. Effect of Glycemic Variability on Mortality in ICU Settings: A Prospective Observational Study. Indian J Endocrinol Metab. 2018;22(5):632-5, Doi:https://doi.org/10.4103/ijem.IJEM_11_18.

25. Investigators N-SS, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-97, Doi:https://doi.org/10.1056/NEJMoa0810625.

26. Issarawattana T, Bhurayanontachai R. Maximal Glycemic Difference, the Possible Strongest Glycemic Variability Parameter to Predict Mortality in ICU Patients. Crit Care Res Pract. 2020:5071509, Doi: https://doi.org/10.1155/2020/5071509.

27. Cruz Gomes LM, Rodríguez Guillén JH, Monarez Zepeda E, Galindo Martín CA, Pérez Galavis BS, Aportela Vasquéz VA. La variabilidad de la glucemia en pacientes críticamente enfermos: el manejo deberá ser personalizado. Med Crit. 2017;31(2):78-83.

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