

ARTIGO ORIGINAL



Prevalence and Risk Factors of Spontaneous Hypoglycemia in Hospitalized Patients: Cross-Sectional Observational Study and Literature Review

Prevalência e Fatores de Risco de Hipoglicemia Espontânea em Pacientes Hospitalizados: Estudo Observacional Transversal e Revisão de Literatura

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Introduction: Spontaneous hypoglycemia is a blood glucose level below 70 mg/dL unrelated to insulin or oral hypoglycemic agents. **Objectives:** To assess the prevalence of spontaneous hypoglycemia (<70 mg/dL) in adult patients admitted to Hospital Santa Izabel in 2023. Additionally, a narrative review was conducted to evaluate the prevalence, risk factors, main contributing factors, and mortality associated with spontaneous hypoglycemia in hospitalized patients. **Methods:** A cross-sectional observational study reviewed an electronic medical record database of adult patients. Capillary blood glucose measurements from patients admitted to general wards, intensive care units (ICUs), and emergency services at Hospital Santa Izabel (HSI) in 2023 were analyzed. A narrative review was also performed through a non-systematic PubMed search using the terms hypoglycemia, mortality, hospital, and individuals without diabetes. The search yielded 61 articles, which, along with reference analysis, brought the total to 81 articles. After excluding duplicates and studies irrelevant to the topic, 10 articles were selected for analysis. **Results:** In 2023, HSI recorded 6,609 episodes of hypoglycemia, accounting for 2.63% of the blood glucose measurements. The prevalence of spontaneous hypoglycemia in the reviewed articles ranged from 0.01% to 0.51%. Spontaneous hypoglycemia occurs more frequently in ICU patients and the elderly. Common risk factors included heart failure, renal failure, malignancy, and pre-existing diabetes. Severe conditions such as cirrhosis, multiple organ failure, polytrauma, and sepsis were also associated with hypoglycemia. Moreover, spontaneous hypoglycemia was linked to higher mortality, with 5 out of 10 studies showing mortality rates 2 to 3 times higher in patients who experienced at least one episode. This association was not commonly observed in insulin-induced hypoglycemia. **Conclusion:** Spontaneous hypoglycemia in hospitalized patients is a rare event, typically associated with severe acute conditions and advanced age. It is more frequently linked to higher mortality compared to medication-induced hypoglycemia, with mortality rates correlating with the severity of the hypoglycemic episodes.

Keywords: Hypoglycemia; Hospital Mortality; Risk Factors; Intensive Care Units; Inpatient.

Introdução: A hipoglicemia espontânea é definida como glicemia inferior a 70mg/dL, não relacionada ao uso de insulina ou medicações hipoglicemiantes orais.

Objetivos: avaliar a prevalência de hipoglicemia (<70mg/dl) em pacientes adultos admitidos no Hospital Santa Izabel no ano de 2023. Adicionalmente, foi conduzida uma revisão narrativa sobre a prevalência, fatores de risco, principais fatores contribuintes e a mortalidade relacionados à hipoglicemia hospitalar espontânea. Métodos: Foi realizado um estudo observacional de corte transversal através da avaliação de banco de dados do prontuário eletrônico de pacientes. Foram avaliadas todas as glicemias capilares realizadas em pacientes adultos internados em unidades abertas, fechadas e pronto-atendimentos no ano de 2023 no Hospital Santa Izabel (HSI). Também foi realizada uma revisão narrativa conduzida por meio de busca não sistemática no PubMed dos termos: hipoglicemia, mortalidade, hospital em indivíduos sem diabetes. A busca resultou em 61 artigos que, complementados pela análise das referências, totalizaram 81 artigos. Após exclusão de dados repetidos e os que não tratavam do assunto em avaliação, restaram 10 artigos para a análise. Resultados: No ano de 2023, no HSI, ocorreram 6609 episódios de hipoglicemias, representando 2,63% das glicemias. Não foi possível diferenciar, pela natureza dos dados coletados, as hipoglicemias espontâneas das induzidas por medicações. A prevalência de hipoglicemia espontânea nos artigos avaliados variou entre 0,01% e 0,51%. Hipoglicemias espontâneas ocorreram mais frequentemente em pacientes internados em unidades fechadas e em idosos. Os fatores de risco mais comuns foram insuficiência cardíaca, renal, malignidade e diabetes prévio. Condições clínicas graves como cirrose, falência múltipla de órgãos, politraumatismo e sepse também estiveram associadas às hipoglicemias. Hipoglicemia espontânea correlacionou-se com maior mortalidade, com 5 de 10 estudos demonstrando taxas de mortalidade de 2 a 3 vezes mais altas em pacientes que apresentaram ao menos um episódio. Essa relação não foi observada na maioria dos casos de hipoglicemia induzida por insulina. Conclusão: Hipoglicemia de qualquer etiologia é evento comum no Hospital Santa Izabel. A hipoglicemia espontânea no hospital é um evento de prevalência incomum a raríssima e geralmente está associada a condições agudas graves e idade avançada. Relaciona-se mais frequentemente a mortes do que a hipoglicemia medicamentosa, e a mortalidade é proporcional à severidade da hipoglicemia.

Palavras-chave: Hipoglicemia; Mortalidade Hospitalar; Fatores de Risco; Diabetes Mellitus; Unidades de Terapia Intensiva; Enfermarias.

Hypoglycemia is defined as a plasma glucose level below 70 mg/dL, per the International Hypoglycaemia Study Group (IHSG) guidelines.¹ Symptoms and signs of hypoglycemia, collectively known as Whipple's triad, typically appear when glucose levels fall below 55 mg/dL. The IHSG, endorsed by international health organizations, classifies hypoglycemia into three severity levels: level 1, where glucose is <70 mg/dL; level 2, with glucose <54 mg/dL; and level 3, which is characterized by an altered mental state or physical incapacity, requiring external assistance for recovery, regardless of glucose value.

In individuals with diabetes, a blood glucose level below 70 mg/dL necessitates prompt attention and treatment, often leading to adjustments in their therapeutic regimen. When glucose levels drop below 55 mg/dL, it is considered a severe and clinically significant condition.¹ Hypoglycemia is most commonly seen in people with diabetes, particularly those on insulin or oral hypoglycemic agents

that stimulate insulin secretion. However, in individuals without diabetes, hypoglycemia is a rare event. When it does occur, it is typically due to drug effects, alcohol consumption, critical illness, hormonal deficiencies, or, in rare cases, insulin-secreting tumors.²

Hypoglycemia is a common occurrence in hospitalized patients, with its incidence and prevalence varying based on the definition used (e.g., glucose levels below 60 or 70 mg/dL), the patient's underlying health conditions (such as the presence or absence of diabetes), and the clinical setting (critical care vs. non-critical care units). A North American study across 126 hospitals reported a prevalence of hypoglycemia <70 mg/dL at 10.1% and severe hypoglycemia (<40 mg/dL) at 1.9%.³ Similarly, data from the National Audit of Inpatients with Diabetes in the United Kingdom in 2012 showed a 22%⁴ prevalence of hypoglycemia in hospitalized patients. Studies in critically ill patients receiving insulin therapy for strict glycemic control have reported hypoglycemia

prevalence as high as 45%.⁵ A more recent study by Gallo and colleagues noted a prevalence of 7.4% among patients with diabetes.⁶

Most hospital-based studies focus on hypoglycemia in individuals with diabetes or those receiving insulin therapy. In contrast, spontaneous hypoglycemia—occurring without the use of insulin or other hypoglycemic medications—has been less frequently studied and is considered a rare event in hospitalized patients.

Both medication-induced and spontaneous hypoglycemia have been linked to severe adverse events, including acute coronary syndrome,⁷ falls, prolonged hospital stays,⁸ higher hospitalization costs, and increased mortality both during hospitalization and after discharge.⁸⁻¹⁰ However, the role of hypoglycemia as an independent risk factor for mortality remains controversial.^{11,12} Some studies suggest that spontaneous hypoglycemia may serve as a biomarker of underlying disease severity rather than being a direct cause of death.¹³⁻¹⁵

The objective of this observational cross-sectional study, supplemented by a narrative review, is to evaluate the prevalence of hypoglycemia of any etiology at Hospital Santa Izabel in 2023. Additionally, the narrative review will explore the prevalence, risk factors, and mortality associated with spontaneous hypoglycemia in hospitalized patients. We hypothesize that hypoglycemia is a frequent occurrence at HSI.

Materials and Methods

A search was conducted using the electronic medical record database. The eligibility criteria included all patients hospitalized during the study period with available blood glucose records in their electronic medical records. Adult patients admitted to Hospital Santa Izabel under both the SUS (Unified Health System) and private health insurance plans were included, spanning various care

units: clinical and surgical wards, intensive care units (ICUs), semi-intensive care units, the hemodynamics unit, the surgical center, general and specialized emergency rooms, gastric inpatient units, and the day hospital. The data collection period covered admissions from January 1, 2023, to December 31, 2023. The search included all relevant units at Hospital Santa Izabel based on the following search argument:

1st Intern Unit Conde Pereira; 2nd Intern Unit Conde Pereira; 3rd Intern Unit Conde Pereira; 4th Intern Unit Conde Pereira; 5th Intern Unit Conde Pereira; 6th Intern Unit Conde Pereira; Surgical Center I; Surgical Center III; Hemodynamics; Health Insurance Hospitalization; SUS Hospitalization; Joaquim Neto 1st Floor - Wing A; Joaquim Neto 1st Floor - Wing B; Joaquim Neto 2nd Floor; Joaquim Neto 2nd Floor - Level 2; Joaquim Neto 3rd Floor - Wing A; Joaquim Neto 3rd Floor - Wing B; Otorhinolaryngology - Observation; Adult Dentistry - Annex; Adult Dentistry - Observation; Adult Dentistry - Virtual; Orthopedic Dentistry; ENT PA / Orthopedic PA; Pediatric PA - Observation; Adult Semi-Intensive Care; UCO - Hemodialysis; Ophthalmology ASL Unit; Gastroenterology Inpatient Unit; Pre-Procedure Unit; Cardiology ICU; Surgical ICU 2; Adult Surgical ICU; Adult Clinical ICU; Adult Clinical ICU 2; Adult Clinical ICU 3; Adult Clinical ICU 4; Neuroclinical ICU 2; UTP - Patient Transition Unit.

Note: Unit names and patient profiles may have varied over the evaluation period.

Information on Blood Glucose Levels in Hospital Santa Izabel – 2023 (Closed Units)

The electronic medical record database was searched to identify adult patients from both the SUS and private health insurance plans who were admitted to Hospital Santa Izabel between January 1, 2023, and December 31, 2023. The analysis focused on patients admitted to the following closed units: semi-intensive care, cardiology ICU, surgical ICU 2, adult surgical ICU, adult clinical ICU, adult clinical ICU 2, adult clinical ICU 3, adult clinical ICU 4, and neuroclinical ICU 2. Note: Unit names and patient profiles may have changed during the evaluation.

Glycemic Control Committee and Blood Glucose Assessment at Hospital Santa Izabel

Since 2018, Hospital Santa Izabel has employed glucose meters for capillary blood glucose measurement using remote laboratory testing guidelines and ANVISA regulation, RDC 302. These glucose meters ensure the traceability of the entire capillary blood glucose measurement process, including calibrations. They simultaneously transmit results to the patient's electronic medical record via Wi-Fi, minimizing manual input errors and streamlining the overall process.

The hospital's Glycemic Control Committee (CCGH) utilizes the UniPOC® Data Management System to manage and analyze real-time blood glucose data. Authorized users with access permissions can view all patient blood glucose readings in a structured, accessible format, detailing the time of measurement, glucose levels, patient ID, unit, and the individual who performed the test. The system also supports creating reports and graphs to track glucose trends.

Blood glucose measurements are conducted using Freestyle Precision Pro® devices, which integrate seamlessly with the hospital's Business Intelligence system. This integration allows for real-time capture of glucose data, enabling analysis to improve hospital performance indicators and glycemic control management.

Literature Review

Selection of Article

We conducted a non-systematic search using the PubMed database for this narrative review. The following search terms were applied: "hypoglycemia," "mortality," and "hospital." The search was restricted to studies involving adults admitted to open clinical, surgical, and intensive care units while excluding individuals with diabetes, pregnant women, children, and emergency admissions.

A Medical Subject Headings (MeSH) strategy was employed, using the following terms: (((("Hypoglycemia"[Mesh]) AND "Hospital Mortality"[Mesh]) AND "Adult"[Mesh]) NOT "Diabetes Mellitus"[Mesh]).

The initial search yielded 61 articles. A manual review of references and citations brought the total to 81 thoroughly analyzed articles. Ultimately, 10 studies were selected and summarized in Table 1.

Results

Blood Glucose Levels Performed at Hospital Santa Izabel (HSI) in 2023

In 2023, 241,177 blood glucose measurements were recorded for adult patients admitted to Hospital Santa Izabel. Of these, 91.69% of the patients had their first blood glucose measurement (to monitor for hospital hyperglycemia) performed within the first 24 hours of admission (Table 2). In closed units (including intensive care and specialized units), 88,755 blood glucose tests were conducted, with 92.06% of patients receiving their first test within 24 hours of admission (Table 3).

Prevalence of Hypoglycemia

Among the recorded measurements, the prevalence of hypoglycemia (blood glucose <70 mg/dL) was 2.63% across non-intensive care units, intensive care units, and emergency rooms. Within intensive care units (ICUs), the prevalence was slightly higher at 3.18%. Blood glucose levels ≤ 40 mg/dL were observed in 0.35% of total cases, and in closed units, this figure rose to 0.59%.

Prevalence of Hyperglycemia

Blood glucose levels ≥ 180 mg/dL were noted in 20.99% of the cases overall, with an increased prevalence of 23.17% in closed units (Tables 2 and 3).

Table 1. Description of the selected studies.

Author	Year	N	Design	Unit	Prevalence	Dx/RF Associated with Hypoglycemia	Mortality
Switzer ¹⁶	2021	2,133	Retrospective	Surgical ICU	21/2133 (0.01%)	Cirrhosis, multiple trauma, organ failure, infections, fasting	Not reported
Akirov ⁹	2017	28,948	Prospective cohort	Non-insulin treated	1594 (5.5%) <70 mg/dL 141 (0.5%) <40 mg/dL	Diabetes, malignancy, HF, CKD	Moderate: 50.7% vs 28% Severe: 70.9% vs 28%
Saliba ¹⁷	2016	642	Retrospective	Medical or surgical ICU	Not reported	Not reported	26.7% (spontaneous vs medication-induced OR: 1.22 [0.77-1.93])
Boucai ¹³	2011	31,970	Retrospective cohort	Wards	1714/31970 (0.05%)	Renal failure, HF, diabetes, COPD	1 episode HR 1.73 2 episodes HR 3.78 3 episodes HR 4.86
Kosiborod ²⁰	2009	7,820	Retrospective cohort	Patients with AMI	136/4775 (0.02% - spontaneous hypoglycemia)	-	18.4% vs. 9.2% (OR 2.32 [1.31-4.12])
Krinsley ¹⁸	2007	5,365	Retrospective	ICU	28% non reported spontaneous hypoglycemia	Septic shock, mechanical ventilation	Not reported in non-insulin patients
Mannucci ¹⁹	2006	678	Retrospective cohort	Geriatric units	55/678 (0.08%)	Respiratory failure, dementia, CKD, HF, infections, malignancy, malnutrition	2.17 [1.25-3.85]
Kagansky ²¹	2003	5,404	Case-control	Geriatric and nursing	211/5404 (0.039%)	Sepsis, hypoalbuminemia, neoplasms, elevated alkaline phosphatase, elevated creatinine	72 patients (26%) in the hypoglycemia group (with and without use of insulin and secretagogues) and 38 (14%) in the group without hypoglycemia died (P.001).
Shilo ¹²	1998	143	Case-control	General and geriatric	60 vs 83 (0.51%)	Renal failure, liver disease, malignancy, advanced age, fasting, malnutrition	48% vs 18% (OR 3.67 [1.15-11.21])
Fischer ²²	1986	7,736	Retrospective cohort	Not specified	94/7736 (0.01%)	Older age, neoplasia, HF, renal failure, liver disease, burn, infection, shock	Not reported

Dx: diagnosis; RF: risk factors; Tx: treatment; ICU: Intensive Care Unit; CKD: chronic kidney disease; HF: Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; OR: Odds Ratio; HR: Hazard Ratio; AMI: Acute Myocardial Infarction; UTI: Urinary Tract Infection.

Table 2. Total number of blood glucose levels performed and tracking in the first 24 hours and classification of blood glucose ranges reported in 2023 in all units with hospitalized adult patients according to the indicators of the Brazilian Diabetes Society (classification not yet published).

Data	Quantity
Total number of blood glucose tests (2023)	241,177
Number of hospitalized patients tested	15,755
First blood glucose test within 24 hours	14,445 (91.69%)
Blood Glucose Categories	Total of Patients
70-180 mg/dL	183,976 (76.3%)
100-180 mg/dL	133,641 (55.4%)
<70 or >250 mg/dL	23,071 (9.5%)
<54 or >250 mg/dL	18,680 (7.74%)
<70 mg/dL	6,609 (2.63%)
≤40 mg/dL	844 (0.35%)
≥180 mg/dL	50,623 (20.99%)

Figure 1. Distribution of blood glucose levels according to glycemic ranges in all adult patients admitted in 2023.

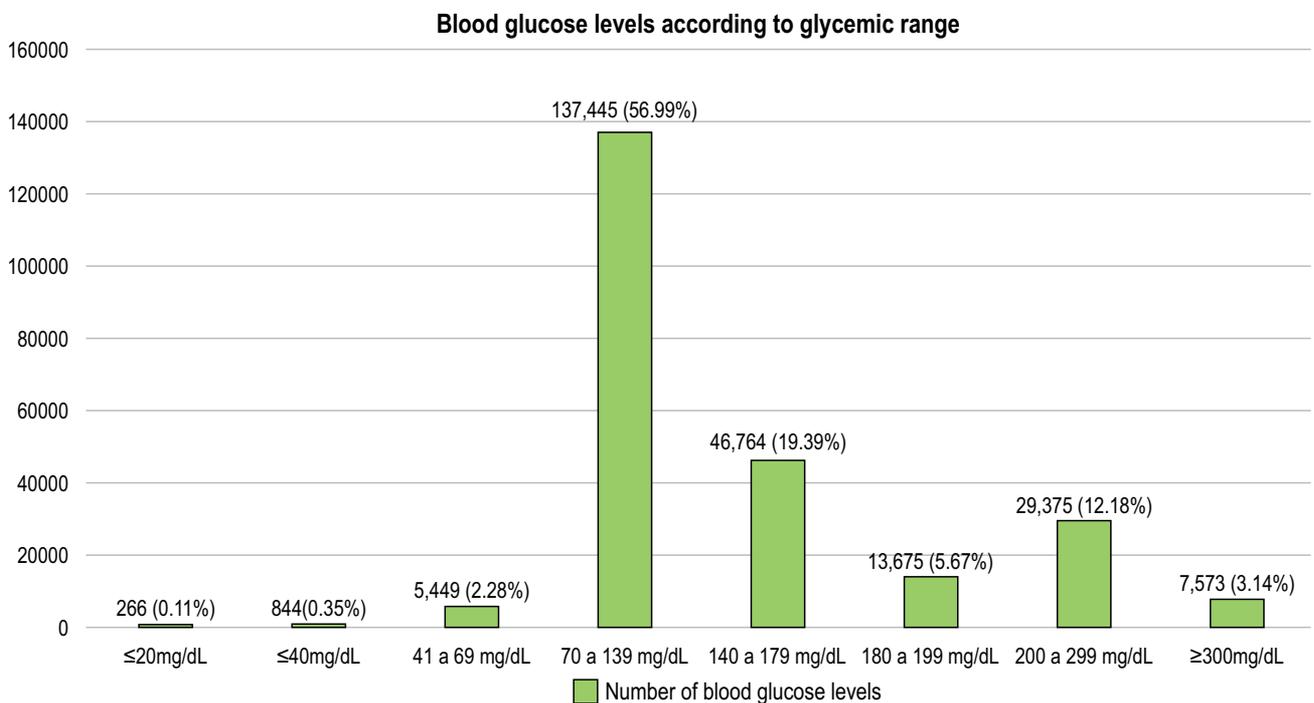
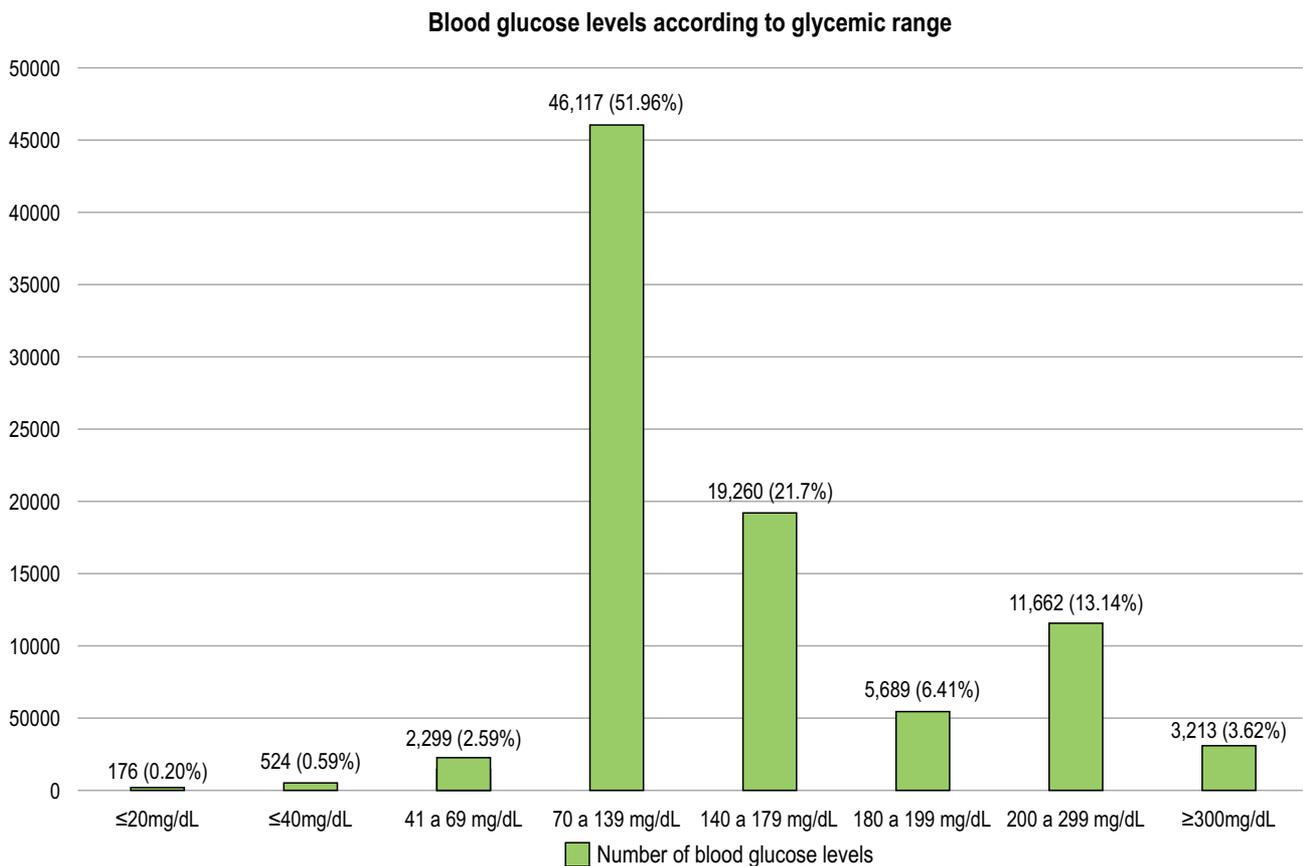


Table 3. Total number of blood glucose tests performed, first 24-Hour testing, and classification of blood glucose ranges in 2023 in closed units with hospitalized adult patients.

Data	Quantity
The number of blood glucose tests performed	88,755
The number of patients who tested blood glucose and were hospitalized	4,585
First blood glucose test within 24 hours	4,221 (92.06%)
Blood Glucose Categories	Total of Patients
70-180 mg/dL	65,320 (73.6%)
100-180 mg/dL	50,333 (56.7%)
<70 or >250 mg/dL	9,564 (10.8%)
<54 or >250 mg/dL	7,788 (8.8%)
<70 mg/dL	2,999 (3.18%)
≤40 mg/dL	524 (0.59%)
≥180 mg/dL	20,564 (23.17%)

Figure 2. Distribution of blood glucose levels according to glycemic ranges in adult patients admitted to closed units in 2023, based on indicators from the Brazilian Diabetes Society (pending publication).



Tables 2 and 3 provide detailed breakdowns of the prevalence of blood glucose ranges, further stratifying cases by unit type and glycemic categories based on indicators from the Brazilian Diabetes Society.

Prevalence

In the selected studies, the prevalence of spontaneous hypoglycemia ranged from 0.01% to 0.51%, demonstrating considerable variability. Switzer and colleagues¹⁶ found the lowest prevalence, with 0.01% in patients admitted to a surgical ICU, with 34.3% of episodes being spontaneous. Shilo and colleagues¹² reported the highest prevalence (0.51%) in non-diabetic geriatric patients, indicating that older age may contribute to increased prevalence.

Risk Factors

Most cases of spontaneous hypoglycemia were observed in patients admitted to closed units, where heart failure, renal failure, and malignancy were consistently identified as predominant risk factors across five of the nine studies analyzed. In a study by Bourcai, Southern, and Zonstein,¹³ they found that patients with renal failure (24.1% vs. 7.0%), heart failure (28.2% vs. 14%), and diabetes (51.3% vs. 31.9%) were more likely to experience hospital-acquired hypoglycemia compared with those who did not. Similarly, Switzer and colleagues¹⁶ highlighted four patient groups with greater susceptibility to hypoglycemia in surgical ICUs: patients with cirrhosis, multiple organ failure, polytrauma, and soft tissue infections, emphasizing the link between severe clinical conditions and the risk of hypoglycemia.

Other factors associated with the occurrence of spontaneous hypoglycemia include fasting, malnutrition, shock, sepsis, mechanical ventilation, the use of antibiotics, advanced age, hypoalbuminemia, low weight, and burns. For elderly individuals, the risk factors mirrored those

in other studies, with sepsis, hypoalbuminemia, and neoplasia being the most strongly associated with spontaneous hypoglycemia.¹¹

Mortality

The correlation between increased mortality and spontaneous hypoglycemia is extensively documented in the literature, with seven of the analyzed studies examining this association. Akirov and colleagues⁹ reported an overall mortality rate of 6.3%, noting significantly higher rates in groups experiencing moderate (13.9% vs. 12.9%) and severe (41.8% vs. 24.9%) spontaneous hypoglycemia compared to those treated with insulin.

In a retrospective observational study by Saliba and colleagues,¹⁷ the mortality rate was found to be higher in the spontaneous hypoglycemia group (26.7%) compared to those with medication-induced hypoglycemia; however, this association did not reach statistical significance (OR 1.22 [0.77-1.93]).

Boucai, Southern, and Zonszein¹³ observed an increased relative risk for mortality associated with a higher number of episodes of spontaneous hypoglycemia: the hazard ratio (HR) for one episode was 1.73 [1.17-2.57], for two episodes, it was 3.78 [2.32-6.15], and for three episodes it reached 4.86 [3.11-7.60]. However, when adjusted for comorbidities, this association diminished (HR 1.11 [0.76-1.64]), suggesting that these episodes might be a marker for severe disease rather than a direct cause of death. Furthermore, Kosiborod and colleagues¹⁸ found a notable association between spontaneous hypoglycemia and mortality (18.4% vs. 9.2%, OR 2.32 [1.31-4.12]) when comparing a retrospective cohort of 7,820 patients with insulin-using controls.

In elderly patients, mortality was nearly twice as high during hospitalization (26% vs. 14%, $p < .001$) and continued to be elevated up to three months post-discharge.

Discussion

Physiologically, the body possesses defense mechanisms against decreased blood glucose levels, including decreased insulin secretion, increased glucagon secretion, and increased epinephrine secretion in the absence of these responses. The loss of the ability to express these counterregulatory mechanisms is termed hypoglycemia-associated autonomic failure (HAAF). This condition can be found in patients with diabetes mellitus, severe comorbidities, advanced age, and a history of recurrent hypoglycemia. Additionally, carbohydrate intake is crucial as a behavioral defense triggered by the perception of symptoms mediated by sympathetic activity.² Failures in any of these mechanisms predispose individuals to episodes of symptomatic hypoglycemia.

In this cross-sectional study combined with a narrative review, we investigated the prevalence of hypoglycemia and the distribution of blood glucose levels measured at Hospital Santa Izabel (HSI) in 2023. Our narrative review evaluated the prevalence, risk factors, and mortality associated with hypoglycemia episodes not caused by insulin use in the selected articles. In 2023, among adult patients admitted to HSI, the prevalence of hypoglycemia (defined as blood glucose levels <70 mg/dL) was found to be 2.63% in non-intensive, intensive, and emergency units, while the prevalence was slightly higher at 3.18% for patients admitted to intensive care units. This frequency of hypoglycemia is standard and significantly higher than the spontaneous hypoglycemia evaluated in the narrative review. The review highlighted that the included studies portrayed hypoglycemia induced by insulin or other medications, making it difficult to distinguish between the types of hypoglycemia during data collection.

In comparison, an extensive North American study conducted across 126 hospitals³ reported a prevalence of hypoglycemia (<70 mg/dL) of any etiology that was also common. However, it

exceeded the prevalence reported at HSI. In non-intensive care units, the prevalence was 3.5%, while in intensive care units, it was significantly higher at 10.1%. However, the indicator used at Santa Izabel had the denominator as "patient-sample," while the North American study used "patient-day," which could account for the discrepancies in the findings. The narrative review revealed significant variability in the prevalence of spontaneous hypoglycemia across the ten publications evaluated, ranging from 0.01% to 0.51%. This variability characterizes spontaneous hypoglycemia as an event that can be classified as very rare to uncommon. The differences observed between the HSI data and those from the reviewed literature emphasize the importance of understanding the context in which hypoglycemia occurs and the various factors influencing its prevalence and impact on patient outcomes.

The study of spontaneous hypoglycemia reveals that the associated risk factors generally correspond to severe conditions, often linked with high mortality rates. As a result, spontaneous hypoglycemia is more frequently observed in critically ill patients with advanced diseases, frequently in the final stages of life. While there is evidence indicating an association between spontaneous hypoglycemia and an increased risk of death—particularly in patients not treated with insulin—this relationship has not been consistently reported across all studies. The higher prevalence of spontaneous hypoglycemia in geriatric and intensive care units underscores the frequent presence of risk factors such as advanced age and severe clinical comorbidities, which impair counter-regulatory mechanisms. The specific characteristics of intensive care units further elevate the risk of hypoglycemia due to factors like limited food availability, prolonged fasting periods between meals, and unforeseen deviations in hospital care protocols.⁸ For instance, Switzer and colleagues¹⁶ noted a lower prevalence

of spontaneous hypoglycemia in surgical units despite potentially long fasting periods. Their study reported only 32 episodes of hypoglycemia among 2,133 patients (0.01%), with 34% classified as spontaneous. This low prevalence could be attributed to more favorable clinical characteristics of the patients in surgical units, who are typically electively operated on. A significant limitation in the reviewed studies is the lack of a clear distinction between medication-induced hypoglycemia and spontaneous hypoglycemia. This ambiguity can hinder the interpretation of findings and may obscure the true prevalence and implications of spontaneous hypoglycemia in different patient populations. Thus, future studies should strive for clarity in categorizing hypoglycemia to better understand its risk factors, prevalence, and impact on patient outcomes.

Most of the risk factors for spontaneous hypoglycemia identified in the studies we reviewed align closely with those previously documented in the literature. A systematic review of hypoglycemia in hospitalized patients highlighted associations between patient age, severe comorbidities (such as sepsis, renal dysfunction, malignancy, hypoalbuminemia, anemia, liver failure, and heart failure), endocrine disorders (including adrenal insufficiency, growth hormone deficiency, hyperthyroidism, or hypothyroidism), and low body weight with episodes of hypoglycemia in general. Episodes of hypoglycemia are particularly prevalent among patients with kidney disease, as evidenced by 6 of the 10 studies included in our review. This increased prevalence is attributed to several mechanisms, including a decrease in gluconeogenesis (mainly in the kidneys), reduced insulin degradation in peripheral tissues, decreased insulin clearance by the kidneys, anorexia, and autonomic neuropathy. Collectively, these factors elevate the risk of both iatrogenic and spontaneous hypoglycemia.²⁰ For instance, Boucai, Southern, and Zonstein¹³ reported a higher incidence of renal failure (24.1%

vs. 7.0%) among individuals who experienced spontaneous hypoglycemia episodes.²⁰ Similarly, liver disease predisposes patients—both diabetic and non-diabetic—to hypoglycemia due to its essential roles in carbohydrate metabolism, gluconeogenesis, and glycogenolysis. Liver dysfunction has been linked to an increased risk of hypoglycemia, particularly in septic patients and those with low albumin concentrations.²⁰

Seven of the 10 studies in our review investigated the relationship between mortality and hospital-acquired hypoglycemia, distinguishing between patients who developed hypoglycemia spontaneously and those whose hypoglycemia resulted from hypoglycemic therapies. The occurrence of spontaneous hypoglycemia has been associated with a higher mortality rate compared to hypoglycemia induced by therapies like insulin.^{9,17,18} This discrepancy can, in part, be explained by the notion that spontaneous hypoglycemia often reflects a severe underlying disease process. In contrast, drug-induced hypoglycemia is an anticipated clinical outcome resulting from stricter glycemic control measures¹⁰ and insulin use. For instance, Kosiborod and colleagues¹⁸ found a significantly higher mortality rate in patients with acute myocardial infarction who experienced spontaneous hypoglycemia (18.4% vs. 9.2%, $p < 0.001$). No such difference was observed in those treated with insulin (10.4% vs. 10.2%, $p = 0.92$). Severe hypoglycemia episodes can lead to serious cardiac complications, such as QT interval prolongation and reentrant arrhythmias, potentially resulting in sudden cardiac death. Additionally, increased sympathetic activity during these episodes may destabilize atherosclerotic plaques, heightening the risk of cardiovascular events.²¹ The emergence of recurrent spontaneous hypoglycemia episodes in critically ill patients, mainly those refractory to clinical interventions, may serve as a marker of imminent death, indicating multiple organ failure and dysfunction of endogenous mechanisms vital for maintaining homeostasis.

Conclusion

The prevalence of hypoglycemia of any etiology at Hospital Santa Isabel is significant and aligns closely with findings from an extensive North American study on hospital-acquired hypoglycemia. In contrast, spontaneous hypoglycemia is categorized as an very rare to sporadic occurrence within hospital settings, predominantly affecting critically ill and elderly patients, and is associated with increased mortality rates. The identification of key risk factors—such as advanced age, malignancy, sepsis, and liver and kidney diseases—underscores the necessity for vigilant monitoring of these vulnerable populations. These findings highlight the importance of implementing targeted preventive strategies to reduce the risk of hypoglycemia among at-risk groups and enhance the understanding of its implications in diverse clinical scenarios.

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