TITLE PAGE

TITLE: Hypoglycemia and risk factors for death in 13 years of pediatric admissions in Mozambique

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ABSTRACT

Hypoglycemia is a life-threatening complication of several diseases in childhood. We describe the prevalence and incidence of hypoglycemia among admitted Mozambican children, establishing its associated risk factors. We retrospectively reviewed 13 years of clinical data collected through a morbidity surveillance system ongoing in Manhiça District Hospital, in rural Mozambique. Logistic regression was used to identify risk factors for hypoglycemia and death. Minimum community-based incidence rates for hypoglycemia were calculated using data from the Demographic Surveillance System.

Of the 49,089 children <15 years hospitalized in Manhiça District Hospital, 45,573 (92.8%) had a glycemia assessment on admission. 1478 children (3.2%) presented hypoglycemia (<3mmol/L), of which about 2/3 (972) with levels <2.5mmol/L. Independent risk factors for hypoglycemia on admission and death among hypoglycemic children included prostration, unconsciousness, edema, malnutrition, bacteremia. Hypoglycemic children were significantly more likely to die (OR 7.11; p<0.001), with an associated CFR of 19.3% (245/1267). Overall Minimum community-based incidence rate of hypoglycemia was 1.57 episodes/1000 CYAR, significantly decreasing throughout the study period. Newborns showed the highest incidences (9.47 episodes/1000 CYAR, p<0.001). Hypoglycemia remains a hazardous condition for African children. Symptoms and signs associated to hypoglycemia should trigger the verification of glycemia and the implementation of life-saving corrective measures.

INTRODUCTION

Critical illness seriously deranges metabolism in children and adults[1, 2, 3]. Alterations in blood glucose homeostasis are the most common metabolic abnormalities found in critically ill children[4] and both, hyper- and hypoglycemia are associated with poor outcomes[1, 3, 4]. Hyperglycemia in critically ill patients is an adaptive response to stress related to hypovolemia, surgery, sepsis or trauma[5, 6]. The prevalence in tropical settings has been estimated between 2.9% and 10.9%[7, 8] and its presence on admission associated with mortality [1, 9, 10]. Insulin therapy is the treatment of choice, but is often unavailable in resource-constrained settings and can also cause iatrogenic hypoglycemia, potentially more harmful than sustained hyperglycemia.

On the other side of the spectrum, hypoglycemia is also a common and life-threatening complication of several diseases such as severe malaria, bacterial sepsis, severe malnutrition and neonatal illness, among others[11, 12, 13, 14, 15]. Hypoglycemia has been extensively reported to have important influence on the outcome of very ill patients, both in children and adults[1, 16, 17]. In Africa, its prevalence among pediatric admissions has been estimated to range between 1.8% and 7.3% [7, 18]. Use of toxic herbal preparations and delays in seeking medical assistance may all cause or further aggravate hypoglycemia in these settings. Severe and prolonged hypoglycemia can result in mental retardation, neurological deficits and recurrent seizures[19, 20]. Management of hypoglycemia according to WHO guidelines[11] includes the rapid administration of exogenous glucose, preferably through an intravenous access. In the developing world, hypoglycemia remains an insufficiently recognized killer of children, as it is seldom diagnosed and whenever detected, often poorly managed, mainly in relation to the lack of simple equipment or trained staff.

We analyzed data collected throughout 13 consecutive years of systematic morbidity surveillance among children admitted to a rural Mozambican hospital to determine prevalence, incidence and risk factors associated with hypoglycemia on admission and mortality in those children.

MATERIAL AND METHODS

Study site and population

The study was conducted in Manhiça, in Southern Mozambique. The Manhiça Health Research Center (CISM) runs a Demographic Surveillance System (DSS) in the area and a morbidity surveillance system (MSS) at Manhiça District Hospital (MDH), which admits around 3000 children annually. Malaria, pneumonia, diarrhea, malnutrition and neonatal pathologies are among the main causes of admission and under-five mortality in Manhiça[21], where HIV prevalence is among the highest in the world[22]. A detailed description of MDH, CISM and the study area can be found elsewhere[23]. CISM provides personnel as well as valuable resources and laboratory diagnosis to MDH.

Study design

We present a retrospective analysis of data collected through the Manhiça MSS from children younger than 15 years who were admitted to MDH during a 13-year long period (2001-2013).

Hospital surveillance system

A standardized admission questionnaire, which includes demographic, clinical, laboratory and outcome data, was filled-in for all hospitalized children < 15 years of age by a clinician. Upon arrival a finger prick blood sample was collected to measure packed cell volume (PCV) and blood glucose concentration, and thick and thin blood films prepared to quantify *Plasmodium falciparum* parasitemia. Blood cultures were

systematically collected to all children under the age of 2 years, or in older children with clinical severity, as part of the routine microbiological surveillance ongoing in MDH. HIV status information was not routinely collected. Upon discharge or death, up to four final diagnoses -based on the ICD-10 classification of diseases- were recorded on the questionnaire after review of all available results.

Laboratory methods

Glycemia was determined using Accu-Chek® (Roche Inc., Manheim, Germany) at the bedside, with blood being usually collected by fingerprick. Glycemia results were provided either in mmol/L or mg/dL units. To simplify the analysis, all mg/dL values were converted into mmol/L by multiplying them by 0.0555. PCV was measured using a microcentrifuge and a Hawksley hematocrit reader card (Hawksley & Sons Ltd, Lancing, UK). Thick and thin blood films for malaria diagnosis and blood cultures were processed as previously described[24, 25].

Clinical definitions

All case definitions were based on admission data from the standardized questionnaires. Children were categorized into three groups according to blood glucose levels: 1) Hypoglycemia: blood glucose levels <3.0 mmol/L (categorized as severe if <2.5mmol/L), 2) Hyperglycemia: glycemia >11mmol/L, and 3) Normoglycemia: values between 3 and 11mmol/L.

A malaria case was defined as a child admitted with a clinical diagnosis of malaria with a *P. falciparum* asexual parasitemia > 0 parasites/μL. Prostration was defined as the inability to sit unsupported or breast/feed in children not yet capable of sitting. Impaired consciousness was defined as a child having a Blantyre coma score less than 5. Severe anemia was defined as a PCV < 15% on admission. Hypothermia was defined as

axillary temperature <35ºC. Increased respiratory rate followed age-specific WHO definitions[11]. Respiratory distress included the presence of deep breathing or indrawing. Nutritional status was based on weight-for-age Z scores (WAZ), calculated using the least mean square method and the WHO and CDC Growth Charts[26]. Malnutrition was defined if WAZ-score was <-1 and severe malnutrition as WAZ of <-3.

Case management

Children with hypoglycemia were managed according to Mozambican national guidelines, based on the WHO guidelines[11], which recommend a rapid intravenous correction with 5 ml/kg of 10% glucose or dextrose solution, repeated if necessary. 10% dextrose in normal saline or Ringer´s lactate for maintenance infusion was used to prevent further episodes, and feeding encouraged as soon as possible. Facilities for intensive care are not available at MDH. All clinical assistance and treatment of admitted children is free of charge. Children requiring specialized care were transferred to Maputo Central Hospital.

Data management and statistical methods

All admission questionnaires were double entered using a program written in FoxPro version 5.0 (Microsoft Corp., Seattle, WA, USA). Statistical analyses were done with Stata 13.1 (Stata Corp., College Station, TX, USA).

Minimum community-based incidence rates (MCBIRs) for hypoglycemia were calculated referring cases to population denominators establishing time at risk (child years at risk (CYAR)) inferred from the DSS. Children did not contribute to the numerator or denominator for a period of 28 days after each episode of hypoglycemia or when they were outside the study area. The analysis of MCBIRs only takes into account children with a permanent identification number issued by the demography department

allowing the linkage of their demographic data with the morbidity surveillance. Children not living within the study area were excluded for incidence calculations. Negative binomial regression models with random effects using Likelihood Ratio Test were used to assess differences in incidence rates between calendar years or age groups.

Case fatality rates (CFRs) were calculated for different glycemia levels as the number of patients who died with a specific glycemia level divided by the total number of patients with known outcome admitted in the study period. These CFRs represent in-hospital mortality and do not include patients absconding or being transferred.

Qualitative variables were compared using a χ^2 test or Fisher´s exact test. Means of normally distributed variables were compared using the Student´s test or ANOVA.

Multivariate logistic regression was used to investigate 1) Adjusted associations for potential risk factors for hypoglycemia on admission; 2) Adjusted associations for potential risk factors for hypoglycemia-related deaths. In the second analysis, given that the dependent variable was the final outcome (dead/alive), only children with a known outcome were included in the analysis (those absconding or being transferred were excluded). P-values from analyses performed in large samples may be confounded because of their dependence on sample size and may reach the significance level even when the association is negligible. Thus, significant associations will be interpreted in accordance with the effect size (OR) and classified as small (< 2), medium (2-3) or large (> 3)[27].

Ethics

This study retrospectively assessed data collected in the context of routine clinical practice. The morbidity surveillance in place at MDH has been approved by the

Mozambican Ethics Committee. The analytical plan of this specific analysis was assessed and approved by Manhiça's Internal Scientific committee.

RESULTS

During 13-year study period (1st January 2001-31st December 2013), 49,089 children <15 years of age were admitted to MDH, including 17,115 infants and 2774 newborns. Median age on admission was 18 months (interquartile range (IQR) 8-35). Glycemia results were available for 45,573 (92.8%) children (Figure 1) and in-hospital outcome information was missing in 4013 (8.2%) cases. Children without glycemia data were excluded from the analysis.

Prevalence of dysglycemia

On admission 1478/45,573 (3.2%) children had hypoglycemia, 2/3 of these episodes (972; 2.1%) being severe. Hyperglycemia was detected in 770/45,573 (1.7%) patients. By age group, hypoglycemia prevalence was the highest among newborns (8.8%), but present in all ages. Hyperglycemia was low and present in all age groups (Figure 2).

Clinical presentation and case fatality rate of children with hypoglycemia admitted to the hospital

Table 1 compares some key characteristics in children with hypoglycemia and normoglycemia. A significantly higher proportion of the patients with hypoglycemia were newborns, but median age was not significantly different between the two glycemia groups. Children with hypoglycemia were significantly more prone to refer feeding difficulties, have hypothermia or neurological impairment than their normoglycemic peers. They were also significantly more malnourished, with lower mean weight and WAZ scores, more frequently severely anemic or bacteremic.

Vomiting and diarrhea were not associated with having more hypoglycemia on admission. The odds of dying in the hospital was higher among hypoglycemic children (OR 7.11, 95%CI 6.11-8.27; associated CFR 19.3% vs. 3.3%, p<0.001). Figure 3 summarizes CFRs by categorized glycemia. CFRs increased with decreasing glycemia, peaking at 33.3% in patients with values <1mmol/L. Importantly, CFRs also rose significantly for patients with hyperglycemia (associated CFR of 12.1%, p<0.001 when compared to CFR of normoglycemia).

The multivariate analysis showed nine risk factors independently associated with the presence of hypoglycemia on admission (Table 2). History of seizures, unconsciousness, refusing to feed, malnutrition, edema, jaundice, prostration, *P. falciparum* infection and having a positive blood culture were all associated with hypoglycemia, while a history of cough was protective against it. All identified factors showed small effect size (OR <2 for all risk factors and OR > 0.5 for history of cough), except unconsciousness, whose effect size was medium: OR = 2.13, 95% CI (1.66, 2.72).

Risk factors for death in children admitted with hypoglycemia

Two hundred and forty-five children died out of the 1267 children with hypoglycemia on admission and outcome results, yielding an overall CFR of 19.3%. Independent risk factors for death in children admitted with hypoglycemia included anorexia and malnutrition with a small effect size (OR < 2), prostration and edema with medium effect size (OR 2-3), and unconsciousness, oral candidiasis positive blood culture and respiratory distress with large effect size (OR > 3) (Table 3).

Minimum community-based incidence rates

Overall MCBIR throughout the study period was 1.57 episodes/1000 CYAR. MCBIR trends for hypoglycemia in all pediatric age groups during the thirteen-year long study period are shown in figure 4. MCBIR peaked at 3.73/1000 CYAR in 2001 (first year of the study) and significantly decreased subsequently, reaching the nadir in 2013 (0.50/1000 CYAR; $p<0.001$). MCBIR were significantly higher for newborns (9.47 episodes/1000 CYAR), than for any other age group (table 4, $p<0.001$).

DISCUSSION

The morbidity surveillance system ongoing at MDH, in rural Mozambique, has allowed us to retrospectively review the prevalence of hypoglycemia in nearly 50,000 pediatric admissions, spanning across a 13-year long period. This is perhaps the largest series examined in the developing world for the occurrence of this common (3.2% of children in this series) albeit insufficiently highlighted life-threatening complication. A study performed in an urban referral center in Mozambique two decades ago[28] showed a higher prevalence (7.1%), similarly to studies conducted in a rural Kenyan hospital[7] and in a Nigerian pediatric Emergency ward[29]. Other more recent studies in a high malaria-endemic area in Mali[30], or among febrile children in Tanzania[12] have shown hypoglycemia prevalence similar to ours. More important than its frequency, its associated mortality risk needs to be overemphasized. Indeed, in this series, a fifth of all hypoglycemia cases on admission ended up dying. While it remains to be seen how much did hypoglycemia contribute to each individual outcome, it is clear, and has robustly been shown, that hypoglycemia carries an excessive and unacceptable risk of death[7, 12, 24, 28, 29] even if only detected as a single episode[31, 32]. The CFR associated with hypoglycemia was lower in this cohort (19.3%) than in other studies[12, 29]. This possibly reflects variations in case-management and access to healthcare, but also relates to the

fact that no clear consensus has yet been reached regarding the glycemia cut-off level at which to define hypoglycemia. Indeed, different authors have proposed different hypoglycemia thresholds, particularly in the presence or not of malaria in the area[7, 8, 12, 29]. To allow comparisons, simplify guidelines and homogenize management, the scientific community should align in defining a unique value. Irrespective of the threshold used, mortality dramatically increases with glycemia lower than 3mmol/L, with a linear and steep inverse relationship between mortality and glycemia levels below this value. In our series, however, borderline values still carried a worse prognosis, with risk of death doubling in children with admission glycemia between 3-4 mmol/L when compared to those with higher levels.

15.9% of all hypoglycemia episodes affected newborns, and 8.8% of all admitted newborns had hypoglycemia, highlighting the importance of hypoglycemia in this age group. However, hypoglycemia also commonly affected –and killed- children of all ages, which justifies universal screening for hypoglycemia among all admitted children in the developing world.

Most studies describing the incidence of hypoglycemia and associated outcomes are based on the determination of glycemia at a fixed point, usually admission. Our results are also limited by this lack of follow-up. We probably missed children who were normoglycemic on admission, but developed hypoglycemia subsequently. So we may be underestimating the incidence of hypoglycemia and the OR of death associated with hypoglycemia occurring during hospitalization. Similarly, we were unable to determine how many recurrent hypoglycemia episodes occurred in our series. Few studies in developing countries have monitored glycemia throughout the whole hospitalization. This is now possible through the innovative use of continuous glucose monitoring

(CGM). CGM can be performed through a subcutaneous sensor that measures the interstitial glucose level -closely related to the blood glucose level- every 5 minutes, uninterruptedly 24 hours a day, and for as long as a week. CGM is slowly being introduced in pediatric intensive care units from developed countries[33, 34], but has not reached yet the developing world, possibly due to its high cost.

Our large sample size gave us sufficient power to assess the association of different clinical and laboratorial characteristics with the presence of hypoglycemia on admission or with hypoglycemia-related mortality. Although many of such factors have been previously described in the literature, three major groups of factors stand out as significantly associated in our series with the risk of having hypoglycemia: 1) Not being able to feed[35] (as directly reported by the mother, or as a consequence of an altered clinical condition decreasing the capacity to feed (altered consciousness or coma[25, 40-42], prostration, a history of seizures)); 2) Malnutrition (including edema as a common sign typically associated with this condition); and 3) Concomitant infections such as invasive bacterial disease or *P. falciparum* malaria. Additionally, jaundice was also identified as an important risk factor for hypoglycemia, a finding also previously reported in Tanzania[12].

Fasting is a recognized risk factor causing hypoglycemia in children[35]. During fasting, plasma glucose levels are maintained within narrow limits by a delicate balance between endogenous glucose production deriving from glycogenolysis and gluconeogenesis[36]. Studies performed in children with malaria have demonstrated a relationship between fasting, hypoglycemia, severity of disease and mortality[7, 37]. Conditions that decrease consciousness may also result in a prolonged fasting state, explaining the strong association found between consciousness level and the risk of

hypoglycemia. However, as hypoglycemia *per se* is a cause of decreased consciousness, interpreting the direction of the association is not straightforward. Hypoglycemia should, however, always be investigated in the presence of a child unable to feed or unconscious.

The association between malnutrition and hypoglycemia has also been firmly established in the past[11, 13, 38]. In malnourished patients glucose homeostasis[38] can be compromised in several ways, including a lack of exogenous nutritional intake, decreased absorption of disaccharides because of intestinal villous atrophy, increased oxidative stress, or glucose uptake compromised by intestinal bacteria. In our series, 62% of all hypoglycemic children showed were malnourished, with 19.4% being severely malnourished. Kenyan[7] and Tanzanian[12] studies had already shown a strong association between severe malnutrition (WAZ <-3) and hypoglycemia, but not with WAZ <-1.

The association of hypoglycemia with bacterial sepsis[14, 18,25, 26, 42] or malaria[7, 14, 26] is also well documented. Our series also support these associations, as risk of hypoglycemia was increased by 68% among bacteremic patients, and by 30% in malaria-infected patients. In bacterial disease, hypoglycemia has been attributed to a series of factors, including high circulating levels of cytokines such as tumor necrosis factor and interleukin-6, both powerful stimulators of insulin secretion, which can then cause among other things inhibition of the gluconeogenic pathways[39, 40]. Decreased levels of glycemia secondary to the consumption of glucose by the *Plasmodium* parasite, hyperinsulinism caused by quinine, impaired gluconeogenesis and lack of adequate supplementation/oral intake are possible explanations in malaria[37, 41, 42, 43].

Independent risk factors associated with hypoglycemia mortality are similar to those found associated with the risk of hypoglycemia. Again, factors related to feeding difficulties, or the presence of a clinical condition hindering feeding (unconsciousness, prostration, respiratory distress), malnutrition and concomitant severe infections (in this case only bacteremia) were all significantly and independently associated with a higher odds of dying among patients with hypoglycemia. In these patients, the multivariate analysis also identified edema and oral candidiasis as important prognostic factors. The association between mortality and these factors has not been properly described in the literature, but it is likely that edema is associated with kwashiorkor (protein deficient malnutrition) and oral candidiasis is a proxy of HIV co-infection, highly endemic in the Manhiça area[22] and highly prevalent among malnourished patients[13].

Regarding hyperglycemia, we found a prevalence of 1.7%, and a significantly higher associated CFR (12.1%, $p<0.001$) when compared to normoglycemia. Other studies in similar settings have shown similar[7] or higher[8, 44] prevalence rates. Hyperglycemia is an insufficiently well-known risk factor for death[10] in the developing world, and efforts for its early detection and correction should parallel those devoted to hypoglycemia. Glucose variability (GV) has recently emerged as a new concept and is considered to have important influence on the outcome of critically ill patients[45, 46] and possibly cause more harm than sustained hyperglycemia. More studies are required, possibly using CGM, to specifically address this issue.

We report for the first time minimum-community based incidence rates for hypoglycemia in Sub-Saharan Africa. Overall MCBIR throughout the study period were

1.57 episodes/1000 CYAR, peaking at 3.73 episodes/1000 CYAR in 2001, underscoring the high burden of this particularly dangerous complication. Reasons for the decreasing trends observed throughout the study period still need to be clarified, although we could hypothesize a better and earlier access to medical care or lower incidence of malaria and/or malnutrition in the last years in the study area. Newborns showed the highest incidence rates of hypoglycemia, underscoring the need to carefully follow this complication in this particularly vulnerable age group.

Hypoglycemia is a silent and under-recognized killer of African children, and needs to be properly exposed, because the correction of hypoglycemia is simple and has rapid effects on the health of the child. However, in resource-constrained settings where dextrose infusion is not readily available or is operationally challenging, other alternatives to intravenous administration should be investigated and promoted in order to correct hypoglycemia in children unable to feed. In this respect, sublingual sugar or pre-prepared dextrose gel appear as promising treatments for the prevention and correction of hypoglycemia in children with hypoglycaemia[30].

Our study had several limitations. There are concerns with the accuracy of commercial finger-prick blood glucose assays. Advances in glucose meter technology have resulted in significant improvement of accuracy and precision of meters. However, those meters are not available in developing countries due to the higher cost. Other limitation is the use of the glucose meters instead of a formal laboratory serum or plasma glucose concentration to measure glycemia, since there are physical differences between the glucose concentration in compared to capillary blood, but this technology was not available to verify the diagnosis of hypoglycemia in our setting. Unfortunately, study subject only had one determination of glycemia measured on admission, and we were

unable to know if any recurrent hypoglycemia episodes occurred in our study. Due to there is no universally applicable definition of hypoglycaemia, we used the threshold established by national guidelines. Different glycemia cut-off levels could modify the results.

CONCLUSION

Hypoglycemia is a common complication of many conditions causing hospitalization in Mozambican children, and is associated with unacceptable adverse outcomes. In settings similar to Manhiça, all admitted children should be screened for hypoglycemia, and aggressively managed when found to be hypoglycemic. A single determination on admission is not enough, and glycemia should be recurrently screened during hospitalization. Better, cheaper and more innovative diagnostic and therapeutic alternatives need to be urgently investigated to better address the consequences of hypoglycemia in developing countries.

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FIGURE LEGENDS

Figure 1: Study profile

Figure 2: Distribution of normo, hypo and hyperglycemia according to age group

Figure 3: Case fatality rates according to glycemia level

Figure 4: Minimum community-based incidence rates of hypoglycemia according to year (vertical bars indicate 95% confidence intervals)

TABLE LEGENDS

Table 1: Univariate analysis of clinical variables and diagnosis according to glycemia group

Table 2: Multivariate analysis of independent risk factors associated to hypoglycemia on admission

Table 3: Multivariate analysis of independent risk factors associated to mortality in children with hypoglycemia upon admission

Table 4: Minimum community based incidence rates (MCBIR) of hypoglycemia among children admitted to Manhiça district Hospital, according to age group

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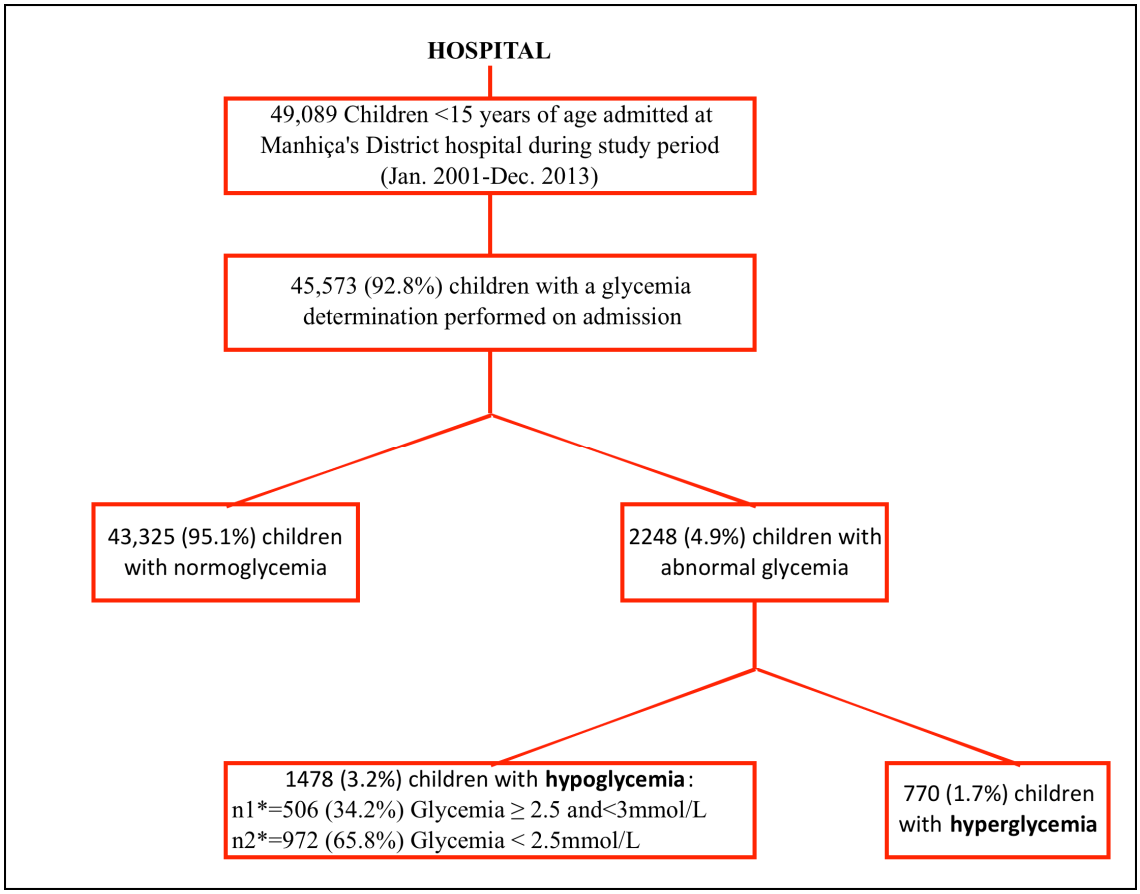

Figure 1: Study profile

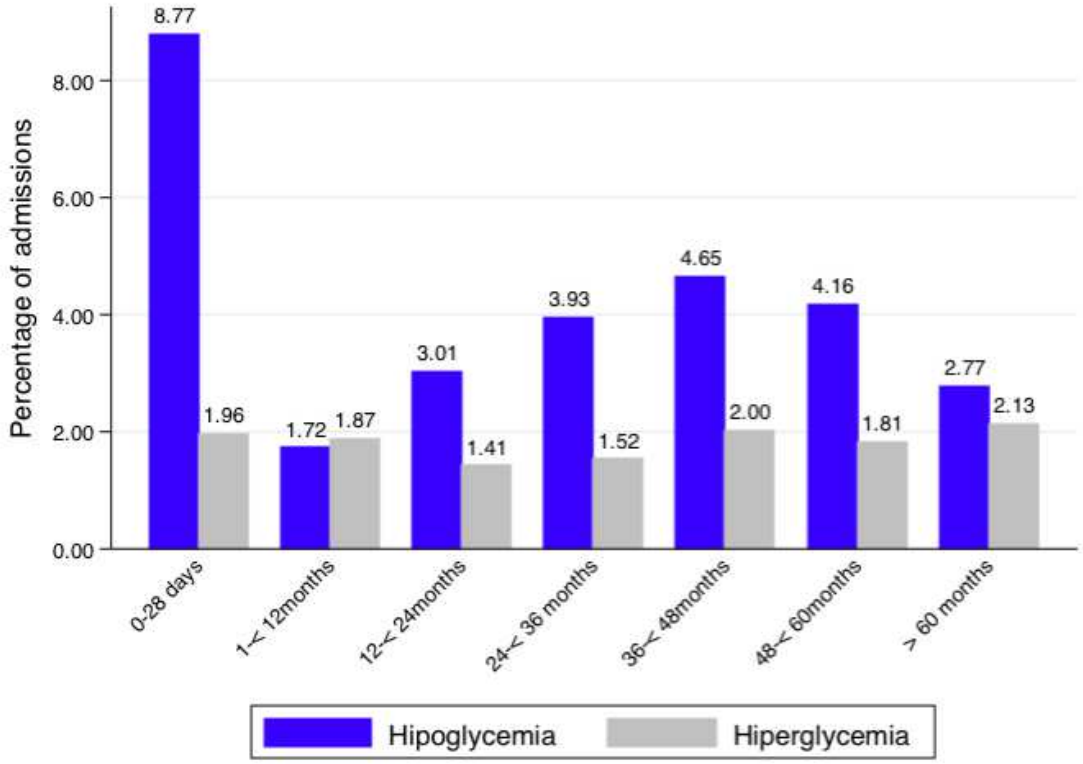

Figure 2: Distribution of glycemic status, by age group

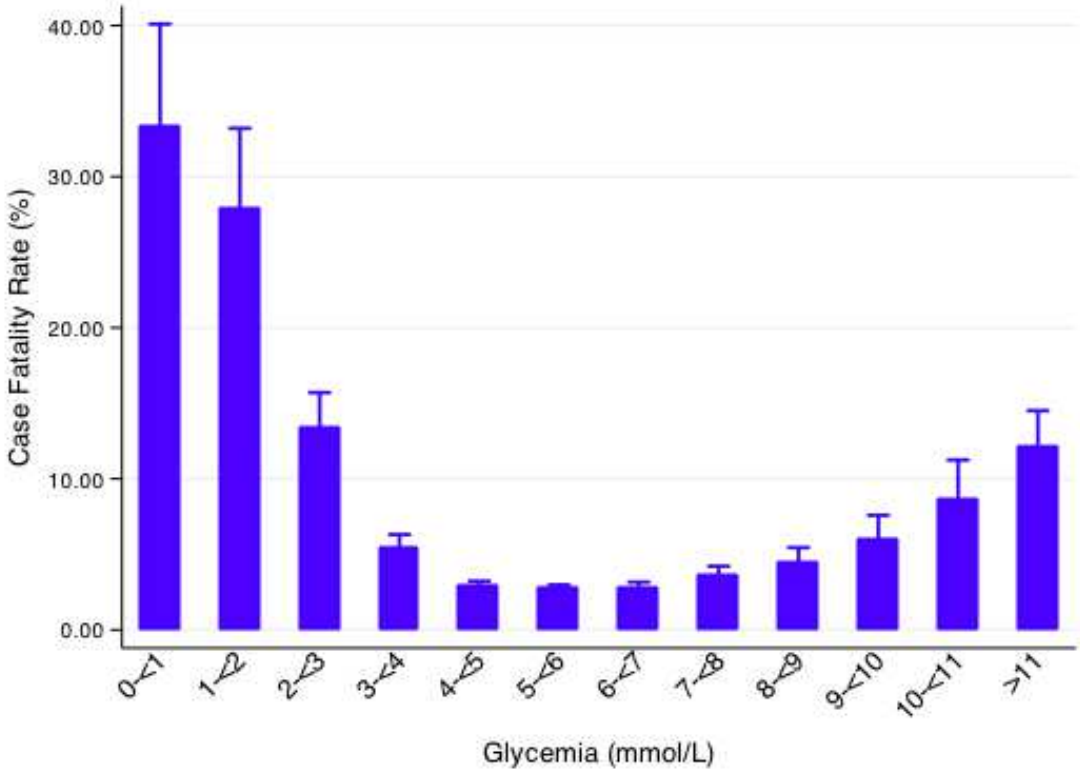

Figure 3: Case fatality rates according to glycemia level

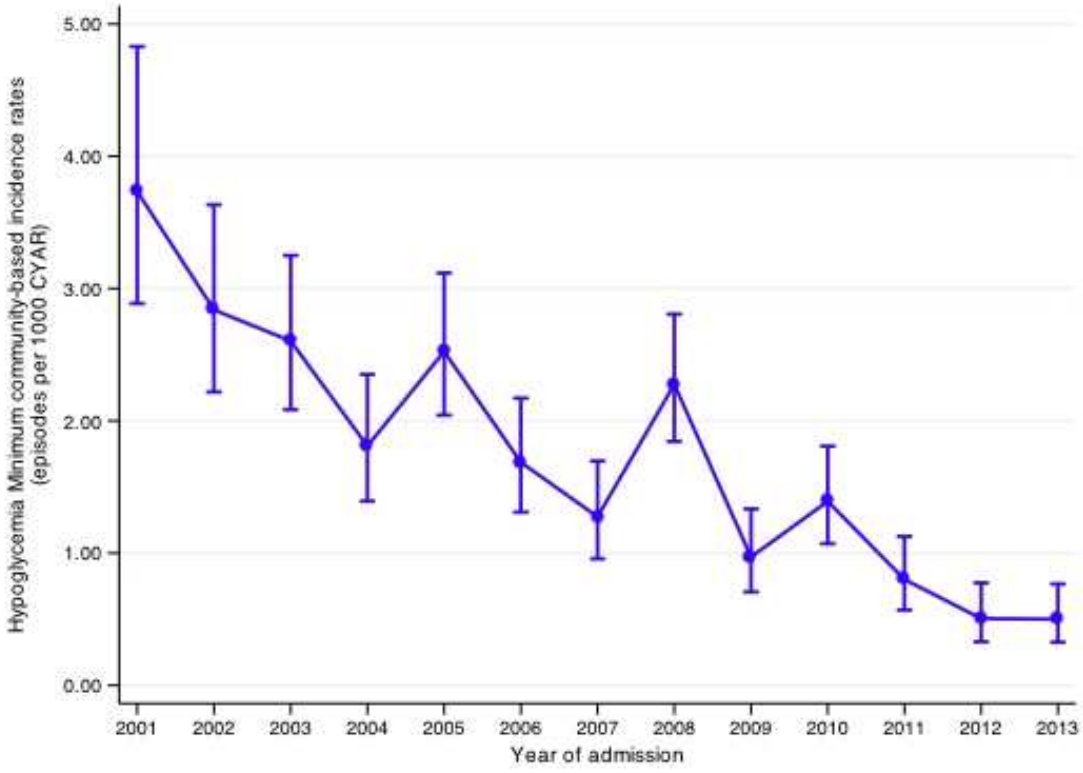

Figure 4: Minimum community-based incidence rates of hypoglycemia according to year (vertical bars indicate 95% confidence intervals)

Table 1: Univariate analysis of clinical variables and diagnosis according to glycemia group

Variables	Normoglycaemia n=43,325	Hypoglycaemia n=1478	OR and 95%CI	p value
Socio-demographic characteristics				
Age in months (Median, IQR)	17 (8-34)	21 (8-37)	1.00	0.068*
Newborn n(%)	2,304 (5.3)	226 (15.3)	3.21 (2.77-3.73)	**<0.001**
Male Gender n(%)	23,249 (53.7)	841 (57.0)	1.14 (1.03-1.27)	**0.013**
Symptoms before admission				
Fever n(%)	39,655 (91.5)	1,207 (81.7)	0.41 (0.36-0.47)	**<0.001**
Cough n(%)	28,429 (65.6)	825 (55.8)	0.66 (0.60-0.73)	**<0.001**
Vomiting n(%)	10,134 (23.4)	362 (24.5)	1.06 (0.94-1.20)	0.32
Diarrhea n(%)	9,326 (21.5)	308 (20.8)	0.96 (0.84-1.09)	0.52
Difficulties to breastfeed/anorexia n(%)	5,291 (13.5)	406 (30.1)	2.76 (2.45-3.12)	**<0.001**
Seizures n(%)	3,486 (8.1)	211 (14.3)	1.90 (1.64-2.21)	**<0.001**
Anthropometrics				
Weight in Kg (mean±SD)	10.3 (5.9)	9.6 (5.9)	0.98 (0.97-0.99)	**<0.001**
Malnutrition (WAZ <-1DS) n(%)	24,111 (55.7)	908 (61.4)	1.27 (1.14-1.41)	**<0.001**
Severe malnutrition(WAZ<-3DS) n(%)	5,884 (14.6)	252 (19.4)	1.41 (1.22-1.62)	**<0.001**
WAZ score (mean±SD)	-1.41 (1.5)	-1.76 (1.4)	1.17 (1.13-1.22)	**<0.001**
Symptoms and signs on admission				
Axillary temp. (ºC) (mean±SD)	37.9 (1.3)	37.6 (1.5)	0.86 (0.83-0.89)	**<0.001**
Hypothermia (ax. temp. <35ºC) n(%)	99 (0.2)	26 (1.8)	7.82 (5.06-12.09)	**<0.001**
Respiratory rate (mean±SD)	45.5 (15.2)	47.0 (18.5)	1.01 (1.00-1.01)	**<0.001**
Increased respiratory rate n(%)	24,211 (55.9)	834 (56.5)	1.02 (0.92-1.14)	0.67
Respiratory distress n(%)	9,373 (21.7)	427 (29.0)	1.47 (1.31-1.65)	**<0.001**
Dehydration n(%)	6,935 (16.0)	292 (19.8)	1.29 (1.14-1.47)	**<0.001**

Pallor n(%)	7,789 (18.0)	316 (21.4)	1.24 (1.09-1.41)	**<0.001**
Jaundice n(%)	613 (1.4)	55 (3.7)	2.69 (2.03-3.57)	**<0.001**
Edema n(%)	2,678 (6.2)	134 (9.1)	1.51 (1.26-1.81)	**<0.001**
Stiff neck n(%)	399 (0.9)	20 (1.4)	1.48 (0.94-2.33)	0.09
Prostration n(%)	6,613 (15.3)	489 (33.1)	2.75 (2.45-3.07)	**<0.001**
BCS on admission (mean ±SD)	4.9 (0.5)	4.5 (1.2)	4.10 (3.72-4.52)	**<0.001**
Unconsciousness (BCS <5) n(%)	2,270 (5.3)	289 (19.7)	4.42 (3.85-5.06)	**<0.001**
Deep coma (BCS ≤2) n(%)	693 (1.6)	146 (9.9)	6.77 (5.61-8.17)	**<0.001**
Investigation				
P. falciparum Malaria n(%)	22,186 (54.4)	716 (56.2)	1.07 (0.96-1.20)	0.21
HIV n(%)	341 (22.1)	12 (27.9)	0.73 (0.37-1.45)	0.37
Severe anemia n(%)	1,653 (4.2)	77 (6.5)	1.59 (1.26-2.02)	**<0.001**
Positive blood culture n(%)	2,803 (7.9)	177 (14.8)	2.02 (1.72-2.38)	**<0.001**
Clinical severe pneumonia (WHO criteria) n(%)	9,934 (23.0)	370 (25.1)	1.12 (1.00-1.27)	0.053
Outcome				
Length of admission (mean ±SD)	4.8 (5.8)	5.0 (6.1)	1.00 (0.99-1.01)	0.21
Died n(%)	1,307/ 40,063(3.3)	245/1267 (19.3)	7.11 (6.11-8.27)	**<0.001**

*Mann-whitney test for the difference of two medians. WAZ: Weight-for-Age Z score;BCS: Blantyre Coma Score;

Table 2: Multivariate analysis of independent risk factors associated to hypoglycemia on admission

Risk factors	Hypoglycaemia n=1478	Adjusted OR	95% CI		p-value
			Lower	Upper	
Newborn n(%)	226 (15.3)	1.05	0.56	1.95	0.879
Male sex n(%)	841 (57.0)	1.12	0.96	1.30	0.143
Malnutrition (per unit WAZ decrease) n(%)	908 (61.4)	1.12	1.07	1.18	**<0.001**
History of fever n(%)	1,207 (81.7)	0.72	0.50	1.02	0.062
History of cough n(%)	825 (55.8)	0.82	0.69	0.97	**0.020**
Hypothermia on admission n(%)	26 (1.8)	3.21	0.79	12.94	0.101
History of seizures n(%)	211 (14.3)	1.47	1.18	1.84	**0.001**
Anorexia/refusing to feed n(%)	406 (30.1)	1.67	1.38	2.02	**<0.001**
Unconsciousness (BCS <5) n(%)	289 (19.7)	2.13	1.66	2.72	**<0.001**
Edema n(%)	134 (9.1)	1.56	1.17	2.08	**0.002**
Oral candidiasis n(%)	66 (4.5)	1.14	0.74	1.74	0.550
Jaundice n(%)	55 (3.7)	1.95	1.25	3.03	**0.003**
Respiratory distress n(%)	427 (29.0)	1.22	0.97	1.54	0.092
Pallor n(%)	316 (21.4)	1.20	0.99	1.45	0.066
Dehydration n(%)	292 (19.8)	0.94	0.76	1.15	0.536
Neck stiffness n(%)	20 (1.4)	1.00	0.57	1.77	0.994
Positive blood culture n(%)	177 (14.8)	1.66	1.32	2.09	**<0.001**
P. falciparum malaria n(%)	716 (56.2)	1.29	1.09	1.52	**0.003**
Prostration n(%)	489 (33.1)	1.64	1.36	1.98	**<0.001**

*Number and proportion of children with hypoglycemia who had severe malnutrition (i.e WAZ<-3)

Table 3: Multivariate analysis of independent risk factors associated to mortality in children with hypoglycemia upon admission

Risk factors for adverse outcome	Hypoglycemia deaths n/N(%) N=245	Adjusted OR	95% CI		p-value
			Lower	Upper	
Newborn	46/245 (18.8)	0.99	0.39	2.49	0.977
History of fever	182/245 (74.3)	0.52	0.23	1.15	0.106
History of seizures	53/245 (21.6)	1.08	0.59	1.98	0.798
Anorexia/refusing to feed	117/224 (52.2)	1.74	1.02	2.97	**0.042**
Hypothermia on admission	11/245 (4.5)	0.58	0.04	9.03	0.695
Unconsciousness (BCS <5)	106/245 (43.3)	3.10	1.75	5.49	**<0.001**
Prostration	160/245 (65.3)	2.34	1.30	4.23	**0.005**
Oral candidiasis	31/244 (12.7)	4.80	1.80	12.8	**0.001**
Edema	45/245 (18.4)	2.67	1.25	5.71	**0.011**
Pallor	72/245 (29.4)	1.40	0.81	2.42	0.225
Dehydration	67/245 (27.4)	1.06	0.59	1.89	0.846
Jaundice	17/245 (6.9)	2.43	0.84	7.06	0.102
Positive blood culture	75/211 (35.6)	3.24	1.85	5.66	**<0.001**
P. falciparum malaria	77/206 837.4)	0.62	0.37	1.04	0.069
Malnutrition (per unit WAZ decrease)	143/245 (58.4)*	1.21	1.03	1.42	**0.019**
Respiratory distress	139/245 (56.7)	2.03	1.25	3.30	**0.004**

*Number and proportion of children who died with hypoglycaemia and severe malnutrition (i.e WAZ<-3)

Table 4: Minimum community based incidence rates (MCBIR) of hypoglycemia among children admitted to Manhiça district Hospital, according to age group

Age groups	Subjects	Episodes	Time At Risk (CYAR)	Rate estimations		Model estimations		
				Incidence Rate (Episodes per 1000 CYAR)	95% Conf. Interval	IRR	95% Conf. Interval	p-value
Newborns	38442	28	2957.53	9.47	(6.54, 13.71)	1	-	< 0.0001
28days-<1year	42682	117	33651.90	3.48	(2.90, 4.17)	0.37	(0.24, 0.55)	
1-<2years	41429	170	34865.01	4.88	(4.20, 5.67)	0.51	(0.34, 0.76)	
2-<3years	39774	139	33825.08	4.11	(3.48, 4.85)	0.43	(0.29, 0.65)	
3-<4years	38418	113	33157.82	3.41	(2.83, 4.10)	0.35	(0.23, 0.53)	
4-<5years	37461	55	32422.22	1.70	(1.30, 2.21)	0.17	(0.11, 0.27)	
5-<15years	63103	82	276806.07	0.30	(0.24, 0.37)	0.03	(0.02, 0.05)	
TOTAL	90472	704	447685.62	1.57	(1.46, 1.69)	-	-	-

p-value from Negative binomial regression model with random effects using Likelihood Ratio Test

CYAR: Children-years at risc
IRR: Incidence Rate Ratio