College of Medicine

THE ASSOCIATION BETWEEN SEVERELY DERANGED VITAL SIGNS AND DYSGLYCAEMIA IN SEVERELY ILL CHILDREN ADMITTED TO QUEEN ELIZABETH CENTRAL HOSPITAL (QECH), BLANTYRE MALAWI

BY

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DECLARATION

I, Ednas Billiat Mayani, hereby declare that this dissertation is my original work and has not been presented for any other awards at the University of Malawi or any other university.

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ABSTRACT

Abnormal blood glucose level commonly occurs in children presenting to the hospitals in low income settings. The presence of low blood glucose levels could be a marker of disease severity. Vital signs are routinely checked in sick children and most settings use a combination of deranged vital signs to determine disease severity. Blood glucose is a quick, bed side test and could serve as a complementary indicator of disease severity in low resource settings. The study aims to determine the association between the presence of severely deranged vital signs and dysglycaemia in severely ill children admitted to a tertiary hospital in Malawi. This was a cross-sectional study which used secondary data from Paediatric department collected from December 2016 to January 2019. Multinomial logistic regression was used to determine the association between severely deranged vital signs and dysglycaemia. A total of 5247 children, aged 0 to 18years were recruited into the study. 353(6.7%) had lowglycaemia,105(2.0%) had hypoglycaemia and 771(14.7%) had hyperglycaemia. The presence of any severely deranged vital sign, specifically, hypoxia (oxygen saturation <90%) and coma score of<2 were associated with both hypoglycaemia and hyperglycaemia. The Adjusted Odds Ratio (AOR) for the association of any severely deranged vital sign with hypoglycaemia was 1.76(95% CI 1.2–2.6) and 1.5(95% CI 1.3–1.8) with hyperglycaemia. Hypoxia had odds ratio of 2.0(95% CI 1.2–3.4) for hypoglycaemia and 1.5 (95% CI 1.2–1.9) for hyperglycaemia whilst for reduced coma score the odds was 6.5(95% CI 4.2–10.2) and 2.3(95% CI 1.8–2.9) respectively.

The results have shown that the presence of any severely deranged vital sign is associated with dysglycaemia especially hypoglycaemia and hyperglycaemia. As such dysglycaemia might be used as a complementary marker of disease severity in low resource settings.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

˚c	Degree Celsius
AOR	Adjusted Odds Ratio
ARI	Acute Respiratory Tract Infections
Bpm	Beats per minute
COM	College of Medicine
COMREC	College of Medicine Research and Ethics Committee
ED	Emergency Department
ETAT	Emergency Triage Assessment and Treatment
ICU	Intensive Care Unit
IDDM	Insulin-Dependent Diabetes Mellitus
MDHS	Malawi Demographic and Health Survey
pCO_2	Partial Pressure for Carbon dioxide
PICU	Paediatric Intensive Care Unit
pO_2	Oxygen Saturation
PR	Pulse Rate
QECH	Queen Elizabeth Central Hospital
RR	Respiratory Rate

SBP	Systolic Blood Pressure
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization

CHAPTER 1: INTRODUCTION AND OBJECTIVES OF THE STUDY

1.1 Introduction

In the year 2018, a global estimate of 6.2 million children under the age of 15 died and most deaths occurred from preventable causes [1].The 2015-2016 Malawi Demographic and Health Survey (MDHS) reported that the overall under- five mortality rate was 63 deaths per 1,000 live births [2]. In sub-Saharan Africa, many of these deaths are due to malnutrition, malaria, lower respiratory tract infections and diarrheal diseases [3]. Access to health care services is also associated with child mortality [4,5] in sub-Saharan Africa. Distance to health care service, cost of healthcare service and time available to access health service are some of the factors that determine access to health care service [4,5].These factors contribute to a greater number of children reporting to hospitals whilst severely ill on arrival requiring emergency treatment [3]. For those that report to the hospital, a number of them die within the first 24 hours [6,7]. Early identification and stabilization of severe illness is essential to reduce mortality in children [3]. The World Health Organization (WHO) introduced Emergency triage and treatment (ETAT) guidelines in 2005 to ensure that severely ill children are rapidly identified for early treatment and stabilization [8]. This intervention has been reported to have brought a positive impact towards management of severely ill children. It is reported that inpatient mortality reduced from 10-18% to 6-8 % after implementing ETAT [9].

Blood glucose is the primary source of energy in the body. A strong association is reported between abnormal blood glucose levels and mortality [10]. Critically ill children often develop endocrine and metabolic changes, particularly disruptions of glucose homeostasis that result in dysglycaemia [11]. Dysglycaemia is defined as an abnormal blood glucose levels which can

either be too low or too high compared to the normal range. It is reported that dysglycaemia is common in severely ill children with a prevalence ranging from 11% to 34% [12,13]and up to 25% rate of early death compared to those with normal glycaemia [6]. A previous study reported that critically ill children with dysglycaemia were 3 times more likely to die and 4.8 times more likely to develop complications compared to those with normal glycaemia [14]. Mostly, hypoglycaemia as well as hyperglycaemia and increased glucose variability have been reported to be associated with increased morbidity and mortality in acutely ill children in different settings [6,13] but low glycaemia is also reported to be associated with a high risk of mortality compared to children with normoglycaemia [7,15]. In critically ill children in tropics, the prevalence of hypoglycemia has been assessed using different thresholds because there is no universal applicable definition [13,16].

The presence of severely deranged vital signs is known to be associated with a high mortality rate [17]and so is dysglycaemia [14]. Dysglycaemia may be a marker of disease severity and poor outcomes and can also be used to triage in severely illness.

1.1.1 Hypoglycaemia

WHO defines hypoglycaemia as plasma glucose level below 2.5mmol/L in well-nourished children [18]. The prevalence of hypoglycaemia in severely ill children in low income settings ranges from 4.2 to 8.2% [6,10]. This has been assessed using different thresholds in the children (refer to Table 1).

Disease- specific data shows high prevalence of hypoglycaemia (6.6% to 30%) in children with severe malaria, anaemia, Respiratory Tract Infections, diarrhoea and malnutrition [10,16].
The possible long-term effects of severe, prolonged hypoglycemia in children are neurologic damage which may lead to mental retardation, transient cognitive impairment, neurological deficit and recurrent seizure activity [19]. Hypoglycemia is associated with poorer prognosis in sick children with infections, malnutrition, diarrhea and dehydration [15]. Mortality is high (20% to 24.6%) in children admitted with hypoglycaemia in low income setting [6,7,20,21].

1.1.2 Low glycaemia

Studies have also shown a high risk of mortality in children with low glycaemia that is blood glucose of 2.5 – 5.0mmol/L [7,15] questioning the current cutoff used for defining hypoglycaemia. The cutoff for hypoglycaemia is based on experts' opinion and not evidence based. The reported prevalence of low glycaemia in children admitted to hospitals in resource-limited settings ranges from 20.0% to 28.2% [6,13,15]. The risk of early death in low glycaemia is reported to be four-fold higher compared to children with normal blood glucose levels [6].The presence of hypoglycaemia and low glycaemia could be a marker of disease severity or low glycaemia could represent a transient state which progresses to hypoglycemia and associated increased mortality risk as the disease progresses [6].

1.1.3 Hyperglycaemia

Hyperglycaemia is defined as a blood glucose concentration above the normal physiological upper limit for non-diabetic children. It is considered as an adaptive mechanism to improve the chances of survival in early phases of acute illness but it has shown to be associated with multi-

organ dysfunction as well as increased risk of mortality which led to the introduction of tight glycaemic control in patients admitted in Intensive Care Units [13,22,23]. Several studies define hyperglycaemia as any blood glucose >10.0mmol/L [7,10,23]. Previous studies reported the prevalence of hyperglycaemia between 10.9% and 16.6% [13,23,24] using different thresholds (refer to Table 1).

Table 1: Cut-off values recommended or used for hypoglycaemia, low glycemia and hyperglycaemia in children

Hypoglycaemia Threshold* mmol/l	**Low glycaemia Threshold* mmol/l**	**Hyperglycaemia Threshold* mmol/l**	**Context**	**Reference**
< 2.2	2.2 – 4.4	≥ 8.3	Non Malaria	Sambany et al 2013 [13]
< 2.2	2.2 – 4.4	≥ 8.3	Non Malaria	Bareness et al 2016 [6]
< 2.5	2.5 – 5.0	-	Febrile Illness	Nadjm et al 2013 [15]**
< 2.2	-	> 10.0	On admission	Osier et al 2003 [10]
< 2.5	-	-	Well nourished	WHO 2005 [18]
< 3.0	-	-	Severe malnutrition	WHO 2005 [18]
< 2.2	-	-	Sick children	Achoki et al 2010 [20]
	< 5.0	>10.0	Severely ill children	Ngwalangwa et al 2019 [7]**
<2.2	-	> 6.6	HIV infected children	Anigilaje et al 2017 [12]
< 2.5	-	-	On admission	Elusiyan et al 2005 [16]**
-	-	> 8.3	Severe malnutrition	Tumwebaze et al 2018 [24]
<2.5	-	> 8.3	Acute illness	Ameyaw et al 2014 [14]

*To convert to mg/dl: multiply the result in mmol/L by 18

** Same threshold were used in the current study at QECH, Blantyre, Malawi.

1.1.4 Severely deranged vital signs

Vital signs play a very crucial role to indicate the patient's condition but also help in predicting trends and disease progress [25]. In an Emergency Department (ED), vital signs are used for triage of patients, aid diagnostics and identify deterioration in patients including the potential need for Intensive Care Unit (ICU) transfers [17].In triage, that is sorting of sick children, vital signs are used to identify those in need of immediate treatment, children are prioritized according to their medical need to ensure that the sickest children at the greatest risk of deterioration are rapidly identified [8,26,27].

The vital signs that are commonly assessed are: Oxygen Saturation (pO2), Respiratory Rate (RR), Pulse Rate (PR), Systolic Blood Pressure(SBP) and temperature. Children have specific cut offs used to define severely deranged vital signs [28].

The prevalence of severely deranged vital signs in an intensive care unit in low- resource settings range from 16-18% [29,30]. Severely deranged vital signs are reported to be associated with increased one-day mortality, 30-day mortality and ICU admission [17].The more the vital signs deviate from the normal range, the larger the odds of mortality or ICU admission [29]. Studies have shown that the presence of any one severely deranged vital signs is associated with the risk of mortality and the risk increases with increase in number of deranged vital signs [31].

1.2 Literature review

It is reported that compared to children with blood glucose concentrations within the normal range, children with dysglycaemia have a higher risk of death[13,23]. Dysglycaemia reflects

increased severity of an acute medical condition in children and in particular children with hyperglycaemia, hypoglycaemia and glucose variability are reported to have a significantly longer Paediatric Intensive Care Unit (PICU) length of stay [23].

Another study also observed an association between both hypoglycaemia and hyperglycaemia with increased risk of death but this association was not observed in children with low glycaemia [13]. A study done in Kenya, reported a 34.2% mortality rate in dys-glycaemic children as compared to a 7.6% rate in children with normal glycaemia [10]. It is written that compared to normoglycaemic children, the odds ratio for death was 3.3 for low glycaemia (2.5- <5.0 mmol/L) and 9.8 for hypoglycaemia (<2.5mmol/L) [15].The presence of hypoglycaemia and low glycaemia and hyperglycaemia on admission is known to be significantly associated with dying within 24 hours of admission [7,16].

Studies have shown that severely deranged vital signs are associated with ICU admission [17,29,30], longer length of ICU stay [32] cardiac arrests and mortality [30] with up to 35% rate of experiencing the mentioned critical events in patients with abnormal vital signs as compared to 2.5% in patients with normal vital signs [30]. It is also reported that the vital signs which predict in-hospital mortality are saturation of peripheral Oxygen (S_PO_2), Respiratory rate and Systolic Blood Pressure [33].

Hypoglycaemia is associated with an increase in heart rate and cardiac contractility which leads to increase in cardiac output and a transient decrease in plasma volume [34]. However, this study was done on normal adult men as such it is hard to apply this evidence in children. In a separate

study, cardiac arrest was more frequently observed in hypoglycaemic adult trauma patients [35]. In addition, hypoglycemia has shown to be associated with hypoxemia (SaO2) [6].

Hyperglycaemia has been associated with a number of conditions such as hyperthermia (>39℃), septic shock and hypothermia [13].

While both severely deranged vital signs and dysglycaemia have been shown to be associated with an increased poor outcomes including mortality, it has not been clarified whether dysglycaemia is completely an independent risk factor for mortality or has a clear association with derangement of vital signs [7].

1.3 Rationale

Many studies have reported that the presence of dysglycaemia in children admitted to hospital in low- resource settings is associated with poor outcome and hence, increased mortality. As such the association between dysglycaemia and mortality is well established. Similarly, the relationship between severely deranged vital signs and mortality is also known [33].The presence of dysglycaemia in severely ill children could thus be an added marker of disease severity. Vital signs are routinely checked in sick children and most settings using a combination of deranged vital signs to determine the severity of diseases [32]. In many hospital setting in low income countries, the availability of equipment to measure and record vital signs is a challenge [36]. Blood glucose however is a bed side test that requires one measurement which takes less than 3 minutes to have the results and could be added as a complementary indicator of disease severity in low resource settings. Understanding the association between severely deranged vital signs

and dysglycaemia could assist in identifying severely ill children in need of emergency treatment and increased monitoring. Incorporating the assessments of blood glucose concentration in triaging of children could potentially assist health care workers to immediately identify more children at great risk of poor outcomes. The findings of this study provides information for health policy makers in Malawi and other countries in sub-Saharan Africa to understand the likely impact of assessing, monitoring and using blood glucose concentrations for better outcomes in severely ill children.

1.4 Research question

Is there an association between the presence of severely deranged vital signs and dysglycaemia in severely ill children aged between 0–18 years admitted to a tertiary hospital in Malawi?

1.5 Research objectives

1.5.1 Broad objective

To determine the association between the presence of severely deranged vital signs and dysglycaemia in severely ill children admitted to Queen Elizabeth Central Hospital (QECH) in Malawi.

1.5.2 Specific objectives

1. To determine the association between any severely deranged vital signs and dysglycaemia in severely ill children at QECH.

2. To determine the association between each severely deranged vital sign (heart rate, respiratory rate, oxygen saturation and temperature, coma score) and dysglycaemia in severely ill children at QECH.

CHAPTER 2: METHODOLOGY

2.1 Type of study

This study is a cross-sectional study which used secondary data that were extracted from the paediatric database at a tertiary referral hospital in Malawi.

2.2 Study place

The study was conducted at Queen Elizabeth Central Hospital(QECH), a tertiary referral hospital in Blantyre, the southern part of Malawi and it has a total of 1100 beds. The QECH paediatric emergency department introduced the Emergency Triage, Assessment and Treatment (ETAT) protocol in 2001 to identify severely ill children requiring immediate treatment. Triage is a process of rapidly screening sick children soon after arrival in hospital in order to identify those with an **emergency sign** for immediate emergency treatment. ETAT uses WHO emergency signs to identify severely ill children requiring emergency treatment such that anyone presenting with any of the WHO emergency sign is considered severely ill. The WHO emergency signs are 1) Obstructed/absent breathing, 2) Central cyanosis ,3) Severe respiratory distress, 4) Coma, 5) Convulsion, 6) Severe dehydration and 7) Shock [8].

2.3 Study population

All children aged 0 to 18 years who were admitted through the QECH pediatric resuscitation room between December 2016 and January 2019 were included in the study. Children with missing blood glucose values were excluded from the study.

2.4 Study period

This study used data from December 2016 to January 2019. The project was conducted in a period from January 2020 to April 2021.

2.5 Sample size and power

The study used an already existing data set. We therefore, had to find out if the data set had enough power to demonstrate the differences in primary variable of interest. This was calculated using the website: https://www.openepi.com/Power/PowerCohort.htm

Table 2 : Power calculation

	Any severely deranged vital sign present	Without any severely deranged vital sign
Dysglycaemia	692	537
No Dysyglycaemia	1935	2083
Total	2627	2620

Confidence interval was set at 95%

Risk of dysglycaemia in those with any severely deranged vital sign (%) =692/2627=26.3%

Risk of dysglycaemia in those without any severely deranged vital sign (%) =537/2620 = 20.5%

This gave a power of 99.9% to demonstrate the above difference at 95%confidence interval.

2.6 Data collection

Standard procedure at QECH is that nurses in the resuscitation room records information for all children admitted through the resuscitation room at QECH by filling in a form covering information on demographic data, vital signs, blood glucose level and nutritional status, the admission danger sign(s) and hours of fasting on admission (appendix1, data collection form) and this data was anonymised for analysis.

The blood glucose tests were conducted routinely using capillary blood drawn from a finger prick. Hemocue Glucose 201RT point of care analyser was used to determine the glucose levels and it provides glucose level recordings within a minute. The analyser is manufactured by HemoCue AB, Sweden. Quality control checks of the glucometers were performed weekly using GlucoTrol-NG control fluids.

2.7 Data management and data analysis

2.7.1 Data management

The data were transferred from the paediatric database to excel sheet for cleaning, duplicates were removed. Data were cross-checked for a few selected records to verify accuracy and no gaps were identified. The clean data were imported into Stata Version 14.0 for analysis.
The exposure variable for this study is presence of any severely deranged vital sign defined as presence of any one of these; severely deranged oxygen saturation (%), severely deranged respiratory rate/min, severely deranged pulse rate (bpm), severely deranged temperature (˚c) and severely deranged Blantyre Coma Score. The outcome variable is blood sugar concentrations. Other covariates include malnutrition, fasting hours, age and gender.

Table 3: Classification of severely deranged vital signs by age[1]

Vital Sign	Age	Severely Deranged
Respiratory rate (breaths/ minute)	<1 month	<20 or >80/min
	1month-<1year	<15 or >60/min
	1 year-<5 years	<10 or >50/min
	5years-12 years	<8 or >40/min
	>12 years	<8 or >30/min
Saturation (%)	All	<90%
Pulse rate (beats/minute)	<1 month	<80 or >200bpm
	1 month -<1 year	<80 or >180bpm
	1 year-<5 years	<70 or >170bpm
	5 years-12years	<60 or >150bpm
	>12years	<40 or >130bpm
Blantyre Coma Score	All	≤ 2/5
Axillary temperature (degrees Celsius)	<1 month	<35.5 or >38.5
	≥ 1 month	<34 or >40

[1] *Specific cut-offs to determine severely deranged vital signs derived from a previous study based on local and international guidelines* [7]

2.7.2 Data analysis

Statistical analysis was performed using Stata version 14.0. Descriptive analysis was conducted to describe the baseline characteristics of the study participants and were presented as means, medians and proportions as appropriate.

The outcomes of interest were analyzed as categorical that is (a) normoglycaemia (≥5.0 - ≤10.0mmol/L) (b) hypoglycaemia (<2.5mmol/l) (c) low glycaemia (≥2.5 - <5.0mmol/l) and (d) hyperglycaemia (>10.0mmol/L). Multinomial logistic regression was used to analyse the association between severely deranged vital signs and dysglycaemia. Multivariable multinomial logistic regression analysis was used to control for confounding effect of each predictor variable. Age specific cutoffs were used to determine the presence of severely deranged vital signs as explained in a previous study [7]. See Table 2 for the cutoffs of severely deranged vital signs.

The presence of any severely deranged vital sign and also each of the severely deranged vital sign was analyzed. Odds ratio and its corresponding 95% confidence interval was presented and a significant level set at 5%. Apart from the severely deranged vital signs, other variables included in the regression analysis were gender, age, severe acute malnutrition as diagnosed by the admitting clinician and fasting hours. Clinicians classified severe acute malnutrition as: the presence of visible severe wasting, bilateral pitting oedema and/or mid upper arm circumference (MUAC) <11.5 cm or <70% of weight for height for an average child of the same age as per WHO guidelines [37]. A reported fasting time of more than eight hours was considered as prolonged fasting. All missing values were imputed with normal values. Sensitivity analysis was conducted by imputing them as abnormal values and there was no difference in the results.

CHAPTER 3: RESULTS

3.1 Baseline characteristics

The total number of children who were assessed and treated in the resuscitation room at QECH between December 2016 and January 2019 was 5273. Blood glucose concentrations were not recorded for 26 (0.5%) patients. These were excluded from the study, as such data for 5247 patients were included in the analysis. The mean age of the children was 3.5years with a standard deviation of 3.9 (range 1 day to 18 years). A total of 3078 (58.7%) were males. Half the study population (50.1%) had any severely deranged vital sign. The majority of patients (n=4018, 76.2%) were normoglycaemic, thus a blood glucose concentration between 5.0mmol/L and 10.0mmol/L. Low-glycaemia was recorded in 353 (6.7%) patients while 105 (2.0%) had hypoglycaemia and 771 (14.7%) had hyperglycaemia. The presence of any severely deranged vital sign was most common in children with hypoglycaemia (62.9%) (Table 3). A quarter of the patients (n=1314, 25.0%) had been fasting for over eight hours prior to assessment in the resuscitation room. Severe acute malnutrition was present in 340 (6.5%) patients.

Table 4:Baseline characteristics of 5247 children admitted at the Accident and Emergency Room, Queen Elizabeth Central Hospital

Variable	All	Normoglycaemia (≥5- ≤10mmol/l)	Lowglycaemia (2.5 -<5mmol/l)	Hypoglycaemia (<2.5mmol/l)	Hyperglycaemia (>10mmol/L)
	N=5247	N= 4018	N= 353	N=105	N=771
	N (%)	N (%)	N (%)	N (%)	N(%)
Age					
<1 year	1874 (35.7)	1490 (37.1)	91 (25.8)	25 (23.8)	268 (34.8)
≥ 1yr- <5yrs	1973 (37.6)	1476 (36.7)	178 (50.4)	52 (49.5)	267 (34.6)
≥5yrs	1400 (26.7)	1052 (26.2)	84 (23.8)	28 (26.7)	236 (30.6)
Fasting hours					
< 8 hours	3933 (75.0)	3110 (77.4)	185 (52.4)	46 (43.8)	592 (76.8)
≥ 8 hours	1314 (25.0)	908 (22.6)	168 (47.6)	59 (56.2)	179 (23.2)
Sex					
Male	3078 (58.7)	2346 (58.4)	212 (60.1)	57 (54.3)	463 (60.0)
Female	2169 (41.3)	1672 (41.6)	141 (39.9)	48 (45.7)	308 (40.0)
Severe malnutrition					
No	4907 (93.5)	3781 (94.1)	301 (85.2)	88 (83.8)	737 (95.6)
Yes	340 (6.5)	237 (5.9)	52 (14.8)	17 (16.2)	34 (4.4)
Any severely deranged vital sign					
Absent	2620 (50.0)	2083 (51.8)	175 (49.4)	39 (37.1)	323 (41.9)
Present	2627 (50.0)	1935 (48.2)	178 (50.6)	66 (62.9)	448 (58.1)
Severely deranged Respiratory rate					
Absent	3861 (73.6)	2954 (73.5)	267 (75.6)	86 (81.9)	554 (71.9)
Present	1386 (26.4)	1064 (26.5)	86 (24.4)	19 (18.1)	217 (28.1)
Severely deranged Pulse rate					
Absent	4373 (83.3)	3372 (83.9)	301 (85.3)	89 (84.8)	611 (79.3)

Present	874 (16.7)	646 (16.1)	52 (14.7)	16 (15.2)	160 (20.7)
Severely deranged Temperature					
Absent	5053 (96.3)	3888 (96.8)	332 (94.0)	102 (97.1)	731 (94.8)
Present	194 (3.7)	130 (3.2)	21 (6.0)	3 (2.9)	40 (5.2)
Severely deranged O_2 Saturation					
Absent	4556 (86.8)	3530 (87.9)	305 (86.4)	84 (80.0)	637 (82.6)
Present	691 (13.2)	488 (12.1)	48 (13.6)	21 (20.0)	134 (17.4)
Severely deranged Comascore					
Absent	4776 (91.0)	3754 (93.4)	297 (84.1)	65 (61.9)	660 (85.6)
Present	471 (9.0)	264 (6.6)	56 (15.9)	40 (38.1)	111 (14.4)

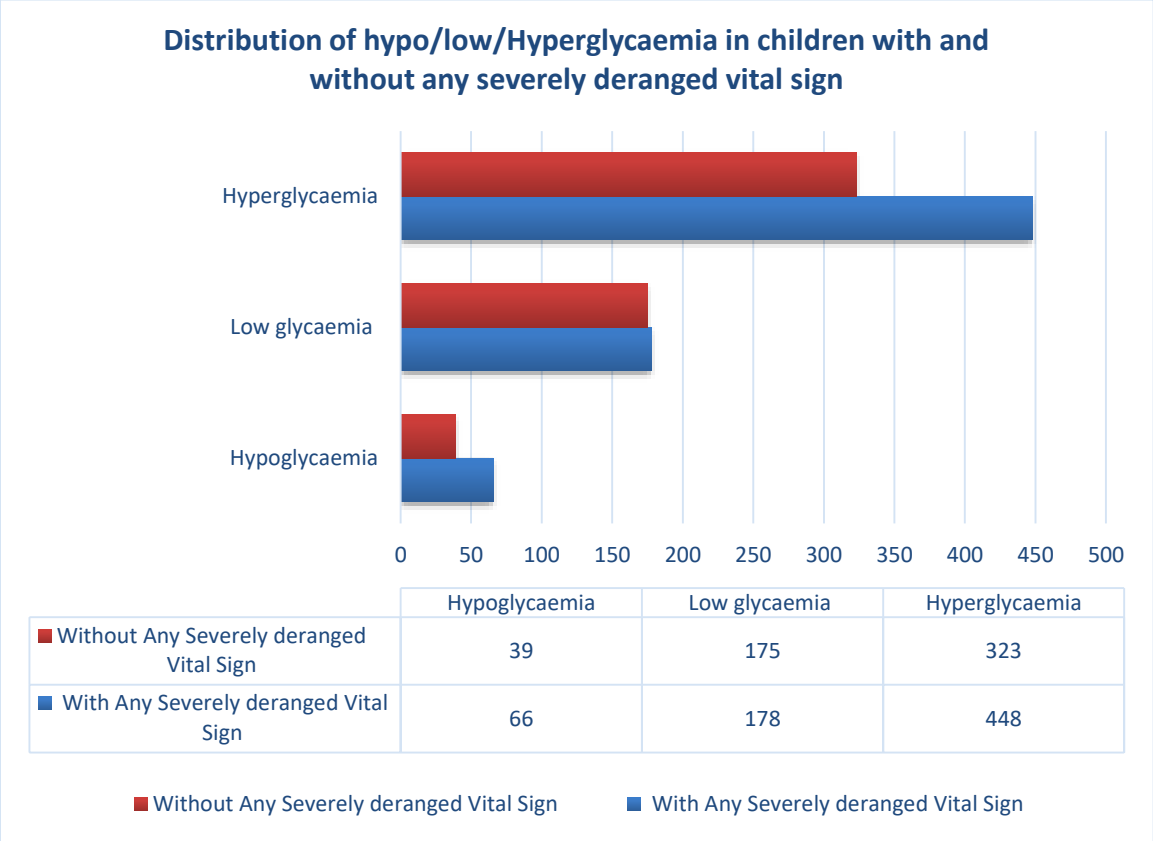

Figure 1: A graphical presentation of abnormal blood glucose and the presence of any severely deranged vital signs

3.2 Association of any severely deranged vital sign with dysglycaemia

26.3% of children with any severely deranged vital sign had dysglycaemia whilst 20.5% of children without any severely deranged vital sign had dysglycaemia. The presence of severely deranged vital sign was associated with an increased prevalence of hypoglycaemia, with adjusted odds ratio (AOR) of 1.76 (95% CI 1.2–2.6). Specific vital signs associated with hypoglycaemia were severely deranged oxygen saturation and severely deranged coma score with an AOR of 2.0 (95% CI 1.2 - 3.4) and 6.5 (95% CI 4.2 – 10.2), respectively (Table 4).

Low glycaemia was not associated with overall severely deranged vital sign but the presence of severely deranged temperature and coma score with AOR of 1.9 (95% CI 1.1–3.1) and AOR 2.0, (95% CI 1.4–2.8) respectively (Table 5).

The presence of any severely deranged vital sign was associated with hyperglycaemia and the AOR was 1.5 (95% CI 1.3–1.8). Hyperglycaemia was associated with all the severely deranged vital signs except severely deranged respiratory rate. The AOR for the severely deranged temperature was 1.5 (95% CI 1.1–2.2), for the severely deranged oxygen saturation was 1.5 (95% CI 1.2–1.9), for the severely deranged pulse rate was 1.3 (95% CI 1.1–1.6) and for the severely deranged coma score was 2.3 (95% CI 1.8–2.9) (Table 6).

Table 5: The association between the presence of severely deranged vital sign and hypoglycaemia (Blood glucose <2.5 vs >5.0 – 10mmol/L)

Hypoglycaemia	UOR	P Value	95%CI	AOR	P value	95%CI
Any severely deranged vital*	1.82	0.003	1.22 2.72	1.76	0.006	1.17 2.64
Severely deranged RR**	0.61	0.056	0.37 1.01	0.71	0.201	0.42 1.20
Severely deranged saturation**	1.81	0.017	1.11 2.94	2.01	0.009	1.19 3.41
Severely deranged PR**	0.94	0.817	0.55 1.61	0.80	0.460	0.45 1.43
Severly deranged temperature	0.88	0.817	0.28 0.28	0.59	0.412	0.17 2.09
Severely deranged comascore**	8.75	<0.001	5.79 13.23	6.54	0.000	4.19 10.2

UOR Unadjusted Odds Ratio, AOR Adjusted Odds Ratio, CI Confidence Interval

*Adjusted for Age, sex, severe acute malnutrition and prolonged fasting, ** Adjusted for Age, sex, severe acute malnutrition and prolonged fasting and each of the vital sign

Table 6 : The association between the presence of severely deranged vital sign and low glycaemia (Blood glucose ≥2.5- <5 vs ≥5.0 – 10mmol/L)

Lowglycaemia	UOR	P Value	95%CI	AOR	P value	95%CI
Any severely deranged vital*	1.09	0.414	0.88 1.36	1.05	0.650	0.84 1.32
Severely deranged RR**	0.89	0.386	0.69 1.15	0.96	0.744	0.73 1.25
Severely deranged saturation**	1.14	0.425	0.83 1.57	1.14	0.475	0.82 1.59
Severely deranged PR**	0.90	0.508	0.66 1.22	0.80	0.174	0.58 1.10
Severely deranged temperature	1.89	0.008	1.17 3.03	1.86	0.017	1.12 3.09
Severely deranged comascore**	2.68	<0.001	1.96 3.66	2.00	0.000	1.44 2.79

UOR Unadjusted Odds Ratio, AOR Adjusted Odds Ratio, CI Confidence Interval

*Adjusted for Age, sex, severe acute malnutrition and prolonged fasting** Adjusted for all Age, sex, severe acute malnutrition and prolonged fasting and each of the vital sign

Table 7: The association between the presence of severely deranged vital sign and hyperglycaemia (Blood glucose >10 vs ≥5.0 – 10mmol/L)

Hyperglycaemia	UOR	P Value	95%CI	AOR	P value	95%CI
Any severely deranged vital*	1.49	<0.001	1.25 1.71	1.52	0.000	1.31 1.79
Severely deranged RR**	1.09	0.339	0.92 1.29	1.08	0.416	0.90 1.28
Severely deranged saturation**	1.52	<0.001	1.23 1.87	1.50	0.000	1.21 1.87
Severely deranged PR**	1.37	0.002	1.13 1.66	1.30	0.010	1.06 1.58
Severely deranged PR**	1.64	0.008	1.14 2.35	1.51	0.032	1.04 2.19
Severely deranged comascore**	2.39	<0.001	1.89 3.03	2.28	0.000	1.79 2.91

UOR Unadjusted Odds Ratio, AOR Adjusted Odds Ratio, CI Confidence Interval

*Adjusted for Age, sex, severe acute malnutrition and prolonged fasting, ** Adjusted for Age, sex, severe acute malnutrition and prolonged fasting and each of the vital sign

CHAPTER 4: DISCUSSION

We found that the presence of any severely deranged vital sign was associated with dysglycaemia especially hypoglycemia and hyperglycemia in severely ill children admitted to QECH. In addition, hyperglycemia was associated with all the severely deranged vital signs except respiratory rate whilst hypoglycaemia was associated with severely deranged oxygen saturation and coma score only. Low glycaemia was associated with severely deranged temperature and severely deranged coma score. Despite these findings, a lot of children with normal vital signs had dysglycaemia. Thus, assessing the blood glucose might add value in identification of children at risk of poor outcomes since dysglycaemia is reported to be an independent risk for death [7].

The findings that hypoglycaemia is associated with severely deranged vital signs may not be surprising as both hypoglycaemia and severe deranged vital signs have been associated with increased risk of mortality and the presence of hypoglycaemia may be a marker of disease severity in the same way severely deranged vital signs are. The presence of any severely deranged vital sign and in particular, severely deranged oxygen saturation, severely deranged coma score was associated with an increased risk of hypoglycaemia. The findings of an association between deranged oxygen saturation and hypoglycemia has also been shown in a previous study which reported a strong association between hypoglycaemia and deep breathing and hypoxemia reflecting unfavorable prognosis [6]. Hypoglycaemia could be a causal pathway to hypoxia and poor outcomes as a study has shown that hypoglycemia modulates the hypoxic ventilatory response in humans [38]. Since severely deranged oxygen saturation is considered as a marker of disease severity [17,31], and associated with high mortality [6] hypoglycaemia could

also mean the presence of severe illness and a marker of poor prognosis. The association between the presence of severely deranged coma score and hypoglycaemia is not surprising as hypoglycaemia is a known causative factor for coma through deprivation of brain energy [16,39]. In addition, poor feeding is known to commonly occur in patients with coma [40] and poor feeding has shown to be associated with hypoglycemia [40]. This might indicate that some sick children may not necessarily require intensive treatment but rather a glucose infusion .Though a case report showed an association between severely deranged body temperature and hypoglycaemia [41]. Our study did not observe the association probably because this was observed in an adult male which is different from our study population.

Hyperglycaemia is associated with severely deranged vital signs. Presence of hyperglycemia has been found in severely ill children in intensive care units and was initially thought to be a normal physiological response to decreasing blood glucose [13,23]. However, it has shown to be associated with mortality as well. Both hyperglycaemia and severe deranged vital signs have been associated with increased risk of mortality. Specifically, children with severely deranged pulse rate, severely deranged oxygen saturation, severely deranged body temperature and severely deranged coma score had a high risk for hyperglycaemia.

The findings that hyperglycaemia is associated with deranged pulse rate may be due to the fact that hyperglycaemia is known to cause heart rate variability, as shown in patients with diabetes and impaired fasting glucose [42]. In a separate study, the risk of mortality related to hyperglycaemia was common in people with cardiac conditions [43]. Abnormal heart rate is a known predictor of mortality and therefore a marker of disease severity [44].

The findings that hyperglycaemia is associated with severely deranged body temperature concur with the findings of another study in Madagascar which reported an association between hyperglycaemia and elevated body temperature [13]. A study conducted in adult diabetic patient has shown that people with diabetes have a harder time keeping their temperatures in control [45] and even in healthy people with glucose infusion or excessive carbohydrate consumption tend to have a spike in body temperatures [46]. A laboratory based study found that injection of insulin modulates hypothalamic neurons that regulates body temperature [47]. In addition, most diseases that cause severe illness in low income countries present with abnormal body temperature [48] and hyperglycaemia is common in these severe illness. Presence of hyperglycaemia could be a marker of disease severity or causative factor for abnormal body temperatures increasing risk of mortality. These findings might suggest that the use of insulin in sick children with hyperglycaemia should be explored as this may probably be the most needed intervention to avoid poor outcomes.

Contrary findings of a study done in Canada reported that pulse rate of >110bpm was a protective factor independently associated with not having a recurrent hyperglycaemia episode [49]. This differs from our study findings, which showed that the presence of severely deranged pulse rate is associated with an increased risk of hyperglycaemia, possibly because the other study was done in a high income country and in adults with diabetes mellitus.

The findings that hyperglycaemia did not show association with respiratory rate may not be surprising as it was previously reported that patients with hyperglycaemia had reduced inflammatory response which might help reducing the rate of respiratory distress [50]. Another

study in Uganda, reported that respiratory distress was associated with hyperglycaemia [51]. This differs from our findings probably because our study enrolled children with different underlying illnesses and a wide range of age group. Hyperglycaemia has been associated with increased risk of mortality in children [13,23,24] as such it could be considered as a marker of severe illness. The findings that low glycaemia did not show association with the presence of any deranged vital signs may indicate that low glycaemia is a transient state which progresses to hypoglycaemia as disease severity progresses. However, the association of low glycaemia with severely deranged temperature and severely deranged coma score may mean that children presenting with low glycaemia should still be handled with extra attention as it is also reported to be associated with the risk of mortality [6].

CHAPTER 5: STUDY LIMITATIONS AND STRENGTHS

The study had some limitations. It was an observational study which can only suggest an association between severely deranged vital signs and dysglycaemia but cannot establish causality. It used a single recording of blood glucose which may not give an accurate picture of the disease process. There are different cut offs for hypoglycaemia, low glycaemia and hyperglycaemia as such this limited the application of other studies. The strength is that this study used a large sample which yields more reliable results and the sick children had a variety of underlying conditions and in all paediatric age groups making the study population more representable.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusions

In conclusion, the findings emphasize that severely deranged vital signs is associated with dysglycaemia especially hypoglycaemia and hyperglycaemia. Blood glucose alterations could be a causal pathway to severe illness leading to severely deranged vital signs and high risk for mortality. Dysglycaemia is therefore a marker of disease severity and can be used as an additional triage sign to determine severely ill children presenting to the hospitals in low resource settings.

6.2 Recommendations

We recommend that determination of blood glucose concentration should be added to assessment of vitals in severely ill children to help identify children at a higher risk of deterioration. Severely ill children found with dysglycaemia should be given immediate attention.

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APPENDICES

Appendix 1: Data collection tool

1: Code for severity: 1= Immediately life-threatening; 2= very sick but not life-threatening; 3= sick but stable

2: Code for Emergency Signs: 1 = Obstructed or absent breathing; 2 =Central cyanosis; 3= Severe respiratory distress; 4= Shock; 5 = Coma; 6= Convulsions; 7 = Severe dehydration; 8= Clincal concern

3: Fasted: Number of hours since last intake of energy (e.g: food, milk, sugary drink)

4: Referred: Was the child referred to QECH from a health centre or other health facility?

Name	Age	Sex	Blood Glucose mmol/l	Time of test	Vital Signs. Note: If Blood Glucose <5 CALL RESEARCH TEAM URGENTLY!								Notes/ comments
					Temp °C	O2 sats %	Pulse rate /min	BCS / 5	Emerg signs[2] (note all)	Malnutrition Y N	Fasted[5] hrs	Admission number |___|___|___|___|___|	
		M F			Resp Rate /min	Receiving O2 Y N	SBP mmHg	Referred[6] Y N	Severity[1] 1 2 3	MUAC (cm)	Nurse initial		
					Temp °C	O2 sats %	Pulse rate /min	BCS / 5	Emerg signs[2] (note all)	Malnutrition Y N	Fasted[5] hrs	Admission number |___|___|___|___|___|	
		M F			Resp Rate /min	Receiving O2 Y N	SBP mmHg	Referred[6] Y N	Severity[1] 1 2 3	MUAC (cm)	Nurse initial		
					Temp °C	O2 sats %	Pulse rate /min	BCS / 5	Emerg signs[2] (note all)	Malnutrition Y N	Fasted[5] hrs	Admission number |___|___|___|___|___|	
		M F			Resp Rate /min	Receiving O2 Y N	SBP mmHg	Referred[6] Y N	Severity[1] 1 2 3	MUAC (cm)	Nurse initial		
					Temp °C	O2 sats %	Pulse rate /min	BCS / 5	Emerg signs[2] (note all)	Malnutrition Y N	Fasted[5] hrs	Admission number |___|___|___|___|___|	
		M F			Resp Rate /min	Receiving O2 Y N	SBP mmHg	Referred[6] Y N	Severity[1] 1 2 3	MUAC (cm)	Nurse initial		
					Temp °C	O2 sats %	Pulse rate /min	BCS / 5	Emerg signs[2] (note all)	Malnutrition Y N	Fasted[5] hrs	Admission number |___|___|___|___|___|	
		M F			Resp Rate /min	Receiving O2 Y N	SBP mmHg	Referred[6] Y N	Severity[1] 1 2 3	MUAC (cm)	Nurse initial		

Date …../…../20…. QECH Paediatric Rescusitation admission room form

Appendix 2: Certificate of Ethics Approval

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.06/20/3079 - The association between the presence of severely deranged vital signs and low blood sugar in severely ill children admitted to Queen Elizabeth Central Hospital. by Ednas Biliati Mayani

On 31-Mar-21

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC some of which are indicated on the next page for your study

31-Mar-21

Prof. E. Umar -Chairperson (COMREC) — Date

Approved by College of Medicine
31-Mar-2021
(COMREC) Research and Ethics Committee