PREDICTING MORTALITY IN A RESOURCE LIMITED NEONATAL UNIT:

University Teaching Hospital of Kigali (CHUK) experience

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DECLARATION

I Dr NYALIHAMA Alain, declare that this Dissertation contains my own work except where specifically acknowledged.

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Registration number: 213003799

Date: April 21th 2016

DEDICATION

To The Almighty God for His love.

To my wife Esperance for her encouragement and patience.

To our children Gania and Gavin.

To my parents for your education.

To my sister and brothers.

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ABSTRACT

INTRODUCTION

Disease severity risk evaluation is an important concept in neonatal practice. For a long time, birth weight and Apgar score were used to assess that risk. Later on, a new way of evaluation through the use of another score was developed. Our study aimed at evaluating the mortality risk of newborns in CHUK neonatal unit using this more modern and complex scoring system.

METHODS

From September 21st 2015 to February 12th 2016 we conducted a longitudinal prospective study in the CHUK neonatal unit. Our objectives were to assess the performance of a simplified SNAPPE II score and additional different risk factors in predicting neonatal mortality in this particular setting.

RESULTS

The overall mortality rate was 10.4%. The mortality rate in neonates who had hyperglycemia was 100%. A simplified SNAPPE II score of 30 was found to be the best cut off in mortality prediction.

A univariable analysis of the simplified SNAPPE II score, birth weight and gestational age significantly predict mortality. By multivariable analysis and adjusting for confounders, the predictive performance was insignificant.

KEYWORDS

- ✓ **SNAPPE II:** Score for Neonatal Acute Physiology Perinatal Extension II was developed in 2001.it was reported in various studies to be an excellent predictor of neonatal mortality.
- ✓ **Neonatal mortality:** refers to the death in neonatal period from birth to 28 days of life.
- ✓ **Neonatal unit:** A hospital area where sick neonates are admitted.

LIST OF SYMBOLS AND ACRONYMS

- ✓ CHUK: Centre Hospitalier Universitaire de Kigali or University Teaching Hospital of Kigali.
- ✓ CMJAH: Charlotte Maxeke Johannesbourg Academic Hospital.
- ✓ KCMC: Kilimanjaro Christian Medical Center.
- ✓ CMHS: College of Medicine and Health Sciences.
- ✓ IRB: Institutional review board.
- ✓ SNAP: Score for Neonatal Acute Physiology.
- ✓ SNAP II: Score for Neonatal Acute Physiology II.
- ✓ SNAPPE II: Score for Neonatal Acute Physiology Perinatal Extension II.
- ✓ WHO: World Health Organization.
- ✓ MBP: Mean blood pressure.
- ✓ SGA: Small for gestational age.
- ✓ GA: Gestational age.
- ✓ BW: Birth weight.
- ✓ NCPAP: Nasal continuous positive airways pressure.
- ✓ CPAP: Continuous positive airways pressure
- ✓ MOH: Ministry of Health.
- ✓ ROC: Receiver operating characteristic.
- ✓ AUC: Area under the curve.
- ✓ PI: Principal investigator.
- ✓ SD: Standard deviation.
- ✓ NICU: Neonatal intensive care unit.
- ✓ RR: Respiratory rate.
- ✓ UN: United Nations.
- ✓ BVM: Bag valve mask

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1. INTRODUCTION

1.1. BACKGROUND

As Pollack MM. et al reported, rapid assessment of disease severity was since long time importantly considered in neonatal practice. Birth weight and Apgar scores were used in neonatal intensive care units (NICUs) as morbidity and mortality risk evaluation materials[1].However, with the tremendous advancement in neonatal critical care with a new era of mechanical ventilation and surfactant therapy, it was shown that these variables do not consistently correlate with mortality[1].

Since then, a new way of predicting morbidity and mortality was implemented by using different scores.

Vasudevan A. et al, in their study, found that these scores can help predict morbidity and mortality, therefore they can serve to enhance utilization of the limited resources available in developing countries[2].

As J.S. Dorling et al reported in their studies, these scores can also help to compare study groups for similarity of risk, audit the severity of illness in different units, compare the performance of different units, determine trends in outcomes overtime, review whether infants are treated appropriately for risk, compare rates of preventable and non-preventable complications, give prognostic information, stratify infants in trials

(To ensure similarity currently needed in trials), and determine individual treatment.[3]

According to J.S. Dorling's et al view, a score is clinically important when:

- ✓ It has a good calibration. This refers to the ability to closely match the predicted and observed outcomes. A well calibrated score will produce no statistical significant differences between predicted and observed outcomes variables. Calibration will be assessed by goodness of fit test, the commonly used method is Hosmer Lemeshow test .[3]

- ✓ It has a good discrimination. This refers to ability to differentiate participant with different outcomes. This assessment is made by a Receiver Operating Characteristic (ROC) curve constructed by plotting true positive against false positive rate. The Area under the Curve (AUC) measurement is a good indicator for score discriminating ability. [3]

  An ideal AUC of 1 means that the score is 100% truly predictive of outcome and there is no false positive events .Many attempts have been made to perfect these scores.[3]However, a balance must be made between a complex score that is difficult to calculate because of too many variables, and a simple one, which would be easier to fill but not as accurate. [3]

1 .2. AIM AND OBJECTIVES

1.2.1. Aim

Our aim is to test the practicality and accuracy of a standardized tool to assess the mortality risk in neonates admitted in CHUK neonatal unit.

1.2.2. Objectives

- ✓ Evaluate the mortality rate of neonates admitted in CHUK neonatal unit.
- ✓ Assess the simplified, based on physical findings, SNAPPE II score performance in predicting mortality in CHUK neonatal unit.
- ✓ Evaluate additional other risks factors predicting mortality in CHUK neonatal unit.

1.2.3. Research questions

- ✓ Can a simplified, SNAPPE II score based on physical findings predict mortality in neonates admitted in the CHUK neonatal unit? .
- ✓ What clinical, social, demographic factors, independently from simplified SNAPPE II, predict mortality in the CHUK neonatal unit? .

1.3. RATIONALE FOR THE STUDY

As reported by the UN, the 4thMillennium Development Goal was to reduce child mortality[4]. Although much progress has been made in decreasing under-five mortality, much less progress has been made in the field of neonatal mortality[4]. Because of this, neonatal mortality now accounts for 43% of under-five deaths as of 2011. Sub-Saharan Africa has the highest neonatal mortality rate (34 deaths per 1000 live births). [4] According to the WHO report, Rwanda's neonatal mortality rate is estimated to be 21 per 1000 live births as of 2012 [5]. Given our high rate of neonatal mortality, illness severity assessment scores will help to predict mortality, thus allowing us to identify high-risk neonates in order to optimize their management with our available resources.

2. LITTERATURE REVIEW

In 1993, Richardson et al developed the complex Score for Neonatal Acute Physiology (SNAP). It consists of 26 physiological parameters measured within 24 hours after admission.[6]

Shortly after, Richardson et al added birth weight, a 5 minute Apgar score, and whether the infant was small for gestational age to produce the more complex Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE).[7]

In 2001, Richardson et al published a simplified and updated version of SNAP and SNAPPE entitled, respectively, SNAP II and SNAPPE II.[8] He sampled a large cohort of neonates from New England, California and Canada born between 1996 and 1997 to determine which of the original SNAP variables most closely correlated with mortality risk.[8] SNAP II was reduced to 6 parameters while SNAPPE II became 9 by adding birth weight, Apgar score at 5th minute, and whether the infant was small for gestational age.[8] Data collection was made within 12 hours of admission from birth. Both SNAP II and SNAPPE II were associated with high predictive power for neonatal mortality.[8]

In that study Richardson et al found that SNAPPE II was associated with excellent discrimination. The SNAPPE II ROC AUC for all BW was 0.91±0.001. When considering BW<1500gr and BW≥1500gr, AUC was respectively 0. 85±0.01 and 0.87±0.03. The SNAPPE II showed an excellent goodness of fit, Hosmer Lemeshow value for all BW was 0.91, whereas it became respectively 0.86 and 0.63 for BW<1500gr BW≥1500gr.[8]

SNAPPE II predictive performance was compared to other neonatal mortality scores performance.

Zardo et al in Brazil, compared SNAP, SNAPPE, SNAP II, SNAPPE II, CRIB and birth weight, their results were as follow.[9]:

- ✓ ROC analysis showed that SNAP, SNAPPE, SNAPII, SNAPPE II and BW AUC was respectively 0.85; 0.90; 0.88; 0.91 and 0.81. SNAPPE II producing the best AUC. [9]
- ✓ Considering neonates with BW≤1500gr, the ROC AUC was respectively 0.93; 0.94; 0.91; 0.82 for SNAPPE, SNAPPEII, CRIB and BW. SNAPPE II continued to exhibit the best AUC. [9]

SNAPPE II predictive performance was evaluated in developing world:

Mia Ra et al , in their study performed in Indonesia found SNAPPE II in non-survival was significantly higher than in survival (P=0.0001). SNAPPE II had a good discrimination with AUC of 0.863. The cut off predictive score was 30 with a sensitivity, specificity, positive and negative predictive value of 78.6%; 76.9%; 64.7%; 87% as well .[10]

James Timothy et al in Indonesia, found a significant correlation between SNAPPE II and mortality prediction (P=0.0007). The cut - off point to predict mortality was 51.The SNAPPE II had an excellent discrimination and calibration computed respectively as 0.933 and 1.69 (P=0.97). .[11]

Shivanna Sree et al, in India had the following results: [12] There was a statistical significant difference between mean SNAPPE II in deceased versus survived neonates (P<0.001). [12]The cut off score to predict mortality was 37 with respectively a positive predictive value, sensitivity and specificity of 95.3%; 76.9%; 87.1%[12]. The SNAPPE II AUC was 0.849 (95%CI: 0.79-0.87). [12]

Malileh Kadivar et al in Iran, found that gestational age (P=0.003), birth weight (P=0.02), Apgar score at 5th minute (P=0.001) and SNAPPE II (P=0.04) were significantly related to neonatal death. Using logistic regression, they found SNAPPE II and Apgar at the 5th minute significantly predicting mortality.[13]

These results are confirming that SNAPPE II is an excellent, reliable and efficient score that can be used to predict neonatal mortality in developed and developping world as well. This emphasize our need to evaluate it in our resource limited developping setting.

Other independent risks factors predicting neonatal mortality were evaluated in further studies.

Narang et al, in their study at a referral center in New Delhi, found that transportation time>1 hour was a significant predictor of neonatal mortality (OR: 5.58 95% CI: 1.41-22 P=0.01) .[14]

Berry et al found that a transfer from another NICU and presence of congenital anomalies were independent predictors of neonatal mortality with OR: 1.92 (P= 0.04) and OR: 7.28 (P <0.01) respectively[15].

Sehgal et al found that metabolic derangements such as hypothermia, hypoglycemia and prolonged capillary refill time (a marker for peripheral perfusion) were significant neonatal mortality predictors[16].

In their study done in Shaanxi Province in China, Li et al found that the odds of neonatal mortality were higher in multiparous women (OR3.34,95% CI 1.84-6.40) and those who did not attend antenatal care services in first trimester (OR2.49,95% CI 1.41-4.40). [17] Li et al therefore discovered that attending a junior high school or higher is protective of neonatal death (OR:0.15 95% CI:0.04-0.57). [17]

Daynia E. Ballot et al ,in their retrospective study performed in CMJAH neonatal unit, in Johannesburg, reported that birth weight <1001gr (OR:10.41 95% CI:6.62-16.6) and GA <28 weeks (OR:11.97 95% CI:7.1-20.1) were significant predictors of neonatal mortality. [18]

Margret Van der Lugh et al, in their retrospective study discovered that neonates with hyperglycemia (they defined as blood glucose>10mmol on two separate measurements within a 12 hours period), by multivariate analysis, had a significant increase in mortality (P=0.001). [19]

They found a significant association with mortality in extremely preterm (BW≤1000gr) with P=0.005 and gestational age: 24-28 weeks with P= 0.009 as well. [19]

Georgios Alexandrou et al, at Karolinska university hospital, between January 2004 and December 2006, prospectively studied association of hyperglycemia in first week of life, mortality and cerebral injury in the extremely preterm. They found that hyperglycemia (with cut off value>8.3mmol) during the first 24 hours is significantly associated with mortality (OR: 3.7; 95%CI: 1.3-10.6) (P=0.01). [20]

Mohamed Kazem Sabzehei et al, in Iran, found that neonatal hyperglycemia (they defined blood glucose>150mg/dl) was significantly associated with mortality

(OR: 4.42, 95%CI: 1.28-6.49) (P=0.01). [21] From these findings we learn that in spite of SNAPPE II performance in predicting mortality, additional risks factors associated with neonatal mortality exist and need to be considered.

We conclude that mortality prediction is a broad concept. Through use of an adapted, reliable score and by measuring additional socio demographic, physiological, metabolic risks factors we shall predict neonatal mortality in our setting.

3. MATERIALS AND METHODS

3.1. STUDY DESCRIPTION

It is a longitudinal prospective study.

3.2. STUDY POPULATION

The study population was (preterm or term babies) born during our study period and meeting the inclusion criteria.

3.3. SAMPLE SIZE

All neonates who met the inclusion criteria admitted in CHUK neonatal unit during our study period were eligible.

Based on an approximated monthly admissions over 5 months (30 neonates per month), we estimated our sample size to be 150 neonates.

3.4. INCLUSION AND EXCLUSION CRITERIA

3.4.1. Inclusion criteria

All newborn (inborn and out born) referred to neonatal unit during our study period.

3.4.2. Exclusion criteria

We excluded all newborns with the following criteria:

- ✓ Antenatal or prenatally diagnosed lethal, incompatible with life, anomalies.
- ✓ Died within 12 hours of admission, as we would not be able to score some of the simplified SNAPPE-II criteria.
- ✓ Admitted in neonatal unit at >48 hours of age.
- ✓ Whose parents or caregivers do not consent to the study.
- ✓ Who were transferred to other hospitals.
- ✓ Who were transferred to CHUK pediatric intensive care unit (PICU).

3.5. VARIABLES

3.5.1. Outcome variable

Outcome (or dependent) variable was:

- ✓ In hospital neonatal mortality.

3.5.2. Explanatory Variables

Based on study specific objectives and taking into consideration the literature review the following explanatory (independent) variables were selected to be included in the questionnaire:

- Maternal variables:
  - ✓ Mother's age, parity, mode of delivery, birth order, educational level, presence or absence of antenatal care during first trimester.
  - ✓ Newborn presentation.
- Neonatal variables:
  - ✓ Simplified SNAPPE II score.
  - ✓ Gender, place of birth, gestational age, birth weight, maternal steroid treatment in case of prematurity, APGAR at 5th minute, presence or absence of SGA status, use of CPAP required at admission, respiratory rate during the 12 hours from admission, resuscitation at birth and capillary refill time at admission.
  - ✓ Presence or absence of hypothermia, hypoglycemia and hyperglycemia.

3.6. STUDY SITE

The study site was CHUK neonatal unit. CHUK is the main university teaching and referral center of Rwanda .Its neonatal unit comprises 28 beds (including incubators and cribs) and 4 radiant warmers. Respiratory support is achieved by non-invasive means through NCPAP machines. More invasive support with intubation and ventilation is not available and no blood gases are being sampled.

3.7. DATA COLLECTION PROCEDURES

We enrolled neonates (inborn and out born) meeting the inclusion criteria during our study period. Data regarding the neonate's birth and maternal prenatal status were gathered.

At admission, mothers were asked the following questions:

- ✓ Education level.
- ✓ Neonate place of birth in case of out born.

Through maternal medical records (inborn) and transfer notes (out born), the following information was gathered:

- ✓ Maternal parity, birth order, age, antenatal care consultation, mode of delivery and presentation at birth.
- ✓ 5^{th} minute post-delivery Apgar score.

Through a complete physical exam at admission the following variables were assessed:

- ✓ Plotted birth weight (SGA was defined as BW<10^{th} centiles per WHO).
- ✓ Gestational age, calculated according to last menstrual period for term and Ballard score for preterm neonates.

During the 12 hours from admission, the following variables were evaluated:

- ✓ Temperature every 6 hours.
- ✓ Respiratory rate was assessed every 6 hours and the highest was recorded. If apnea or pause occurred they were recorded as well.
- ✓ MBP but inconsistently taken due to absence appropriate cuffs and equipment failure.
- ✓ Urine output by every 6 hours diaper weight measurement; an empty diaper was measured before putting it to the neonate then we measured again after 6hours. The difference in grams was converted in milliliter and then calculated in terms of ml/kg/hour.
- ✓ The presence or absence of seizures; when a seizure occurred, the neonate was treated with anticonvulsants available and underlying cause investigated.
- ✓ Capillary blood glucose was sampled randomly once using glucometer and strips (gluococard® and codefree®), in case of hypoglycemia
  (We defined as RBG<45mg/dl) or hyperglycemia
  (We defined as RBG>180mg/dl), it was corrected accordingly and one or more RBGs were taken until a normal glucose level was achieved.
- ✓ Simplified SNAPPE II score was calculated as the sum of scores recorded during a period of 12 hours for the following:

- Lowest temperature.
- Multiple versus single or absence of seizures.
- Urine output (ml/kg/hour).
- Birth weight.
- 5th minute Apgar score.
- Small for gestational age (BW<10th centiles).

3.8. DATA ANALYSIS

3.8.1. Simple descriptive statistics

Was used to measure baseline mothers and neonates variables as follow:

- ✓ Mean and standard deviation was used for continuous, normally distributed variables.
- ✓ Frequency (by proportions) was used for categorical variables.[22]

3.8.2. Logistic regression analysis

- **Logistic function model**

This was used to find simplified SNAPPE II best cut off score to predict neonatal mortality.

- **Univariable analysis**

Variables reported in the literature which significantly predict neonatal mortality were entered in the model. P values were used to measure whether or not there was significant association with neonatal mortality and Odds ratios used to measure the strength of association[23].

- **Multivariable analysis**

Variables found to be significantly predictive of mortality in univariable analysis as well as potential confounders, were entered in multivariable model to generate adjusted odds ratios.[23]

The level of significance was <0.05 for P value.

Odds ratios were interpreted as follow:

- ✓ OR>1: explanatory variable was predictive of neonatal mortality.
- ✓ OR=1: no association was noted.
- ✓ OR<1: explanatory variable was protecting from neonatal mortality.

The following software were used:

- ✓ Epidata for data entry.
- ✓ STATA 13 for simple descriptive statistics and logistic function model.
- ✓ SAS for univariable and multivariable logistic analysis.

3.9. ETHICAL CONSIDERATIONS

3.9.1. Informed consent

A description of the study written in Kinyarwanda was given to neonate's parent (father or mother). Details regarding the aim of the study, the benefit of the study to the community, the inclusion and exclusion criteria and how data will be collected was explained to parent. Participation was voluntary and those who agreed signed a consent form and received a copy.

3.9.2. Confidentiality

It was maintained and only the principal investigator (PI) had a key of which study number correlates with patient and answered questionnaires were kept in a protected file.

3.9.3. Ethical approval

Our research proposal was submitted and approved by the University of Rwanda institutional review board (IRB) and University teaching hospital of Kigali (CHUK) ethical and research committee as well.

4. RESULTS

4.1. General considerations

From September 21st 2015 to February 12th 2016, 237 inborn and out born neonates were admitted to CHUK neonatal unit. Of the 237, 36 neonates were excluded:

- ✓ 17 neonates were admitted after more than 48 hours from birth.
- ✓ 7 neonates died before completion of 12 hours from admission.
- ✓ 5 neonates were transferred to other health facilities (1 to King faisal hospital Rwanda, 1 to Rwanda military hospital and 3 to CHUK pediatric intensive care unit).
- ✓ 3 left the unit without being discharged and against medical doctor advice thus we missed collecting some essential information.
- ✓ 3 out born neonates had incomplete information on the transfer note.
- ✓ 1 refused to consent.

Thus 201 neonates fulfilled the inclusion criteria then were followed from admission day until the final outcome. Of them 21 died, the overall mortality was 21/201 (10.4%). Table 1 illustrate the leading causes of deaths

CAUSES OF DEATHS	FREQUENCY
Complications of prematurity	
-Respiratory distress syndrome	17/21 (80.9%)
-Necrotizing enterocolitis	2/21 (9.5%)
Neonatal sepsis	4/21 (19%)
-Escherichia coli	1
-Klebsiella species	1
-Acinetobacter species	1
-Coagulase negative staphylococcus	1
Birth asphyxia	5/21(23.8%)
Haemorrhagic shock	1/21 (4.8%)

Table 1: Neonatal mortality leading causes

4.2. MATERNAL BASELINE CHARACTERISTICS

Baseline maternal characteristics are summarized in table 2

The overall mean maternal age was 29.5 (5.8).Among 201 mothers, 9 were grand multiparous and within this group there was one neonatal mortality (11.1%).

Of 201 mothers, 42 were educated up to the university level and none within this group had a neonate die. 42 mothers had no education and among this group there were seven neonatal deaths (16.7%).

VARIABLE		MORTALITY		TOTAL
		YES	NO	
Mother parity	Grand multi para	1(11.1%)	8(88.9%)	9 (100%)
	Multi para	3 (8.6%)	32(93.4%)	35 (100%)
	Pauci para	9 (10.7%)	75 (89.3%)	84 (100%)
	Primipare	8 (11%)	65 (89%)	73 (100%)
Mother birth order	Triplet	0 (0%)	3 (100%)	3 (100%)
	Twin	3 (15%)	17 (85%)	20 (100%)
	Single	18 (10.1%)	160 (89.9%)	178 (100%)
Mother age (Mean, SD)		27.3 ±7.0	29.7±5.6	29.5 ±5.8
Mother mode of delivery	Emergent caesarean section	8 (9.6%)	75 (90.4%)	84 (100%)
	Elective caesarean section	1 (3.2%)	30 (96.8%)	31 (100%)
	spontaneous delivery	12 (13.8%)	75 (86.2%)	87 (100%)
Presentation at birth				
	Transverse	2 (50%)	2 (50%)	4 (100%)
	Breech	4 (25%)	12 (75%)	16 (100%)
	Cephalic	15 (8.3%)	166 (91.7%)	181 (100%)
Mother level of Education	None	7 (16.7%)	35 (83.3%)	42 (100%)
	Primary	7 (10.4%)	60 (89.6%)	67 (100%)
	Vocational	0 (0%)	7 (100%)	7 (100%)
	Secondary	7 (16.3%)	36 (83.7%)	43 (100%)
	University	0 (0%)	42 (100%)	42 (100%)
Antenatal care consultation in first trimester	No	0 (0%)	2 (100%)	2 (100%)
	Yes	21 (10.6%)	178 (90.4%)	199 (100%)

Table 2: Maternal baseline variables

4.3. BASELINE CHARACTERISTICS OF ENROLLED NEONATES

Baseline neonatal characteristics are summarized in table 3.

Male and female were respectively 103 and 98 with an overall mortality of 9 (8.7%) and 12 (12.2%). Of 201 enrolled neonates:

- ✓ 189 were born in CHUK maternity.
- ✓ 12 had hypoglycaemia, 3 among them died (25%).
- ✓ 5 neonates had hyperglycaemia and all of them died (100%).
- ✓ 1 of 3 neonates with BW <1500gr (34.8%) died.

Mortality increased as the GA and BW was decreasing.

50% of neonates who were resuscitated with bag valve mask ventilation associated with chest compression died.

VARIABLES		MORTALITY		TOTAL
		YES	NO	
.Gender	Male	9 (8.7%)	94 (91.3%)	103 (100%)
	Female	12 (12.2%)	86 (87.8%)	98 (100%)
.Place of birth	CHUK	18 (9.5%)	171 (90.5%)	189 (100%)
	Private clinic	1 (100%)	0 (0%)	1 (100%)
	District hospital	1 (12.5%)	7 (87.5%)	8 (100%)
	Health centre	1 (50%)	1 (50%)	2 (100%)
Hypothermia	Yes	6 (17.1%)	29 (82.9%)	35 (100%)
	No	15 (9%)	151 (91%)	166 (100%)
Hypoglycaemia	Yes	3 (25%)	9 (75%)	12 (100%)
	No	18 (9.5%)	171 (90.5%)	189 (100%)
Hyperglycaemia	Yes	5 (100%)	0 (0%)	5 (100%)
	No	16 (8.2%)	180 (91.8%)	196 (100%)
GA	<28weeks	4 (57.1%)	3 (42.9%)	7 (100%)
	28-<34weeks	13 (25%)	39 (75%)	52 (100%)
	34-<37weeks	2 (4.3%)	44 (95.7%)	46 (100%)
	>37weeks	2 (2.1%)	94 (97.9%)	96 (100%)
GA (Mean, SD)		30.4±3.6	36.5 ±3.6	35.9±4.1
preterm≤	None	7 (36.8%)	12 (63.2%)	19 (100%)
34weeks	1 dose	4 (57.1%)	3 (42.9%)	7 (100%)
Antenatal steroids	2 doses	1 (8.3%)	11 (91.7%)	12 (100%)
use	3 doses	2 (18.2%)	9 (81.8%)	11 (100%)
	>3doses	4 (16%)	21 (84%)	25 (100%)
Birth weight (Mean, SD)		1298.8±547.4	2553.6±915.5	2421.8±963.6
Birth Weight	<1500gr	16 (34.8%)	30 (65.2%)	46 (100%)
	≥1500gr	5 (3.2%)	149 (96.8%)	154 (100%)
APGAR score	<4	0 (0%)	1 (100%)	1 (100%)
5th minute	4-6	13 (44.8%)	16 (55.2%)	29 (100%)
	7-10	8 (4.7%)	163 (95.3%)	171 (100%)
Capillary refill time	>3seconds	0 (0%)	1 (100%)	1 (100%)
	2-3seconds	1 (25%)	3 (75%)	4 (100%)
	<2seconds	20 (10.2%)	176 (89.8%)	196 (100%)

VARIABLES		YES	NO	TOTAL
SGA	Yes	7 (17.1%)	34 (82.9%)	41 (100%)
	No	14 (8.8%)	146 (91.2%)	160 (100%)
Use of CPAP at admission	Yes	21 (26.6%)	58 (73.4%)	79 (100%)
	No	0 (0%)	122 (100%)	122 (100%)
Resuscitation At delivery	No information	1 (50%)	1 (50%)	2 (100%)
	BVM and chest compressions	2 (50%)	2 (50%)	4 (100%)
	BVM ventilation	8 (38.1%)	13 (61.9%)	21 (100%)
	5Rescue breaths	4 (13.8%)	25 (86.2%)	29 (100%)
	Drying and stimulating	6 (4.1%)	139 (95.9%)	145 (100%)
RR during 12 hours from admission	Apnoea	1 (100%)	0 (0%)	1 (100%)
	<30 cycles	1 (100%)	0 (0%)	1 (0%)
	>60 cycles	13 (18.3%)	58 (81.7%)	71 (100%)
	30-60 cycles	6 (4.7%)	122 (95.3%)	128 (100%)

Table 3: Neonatal baseline variables

4.4. LOGISTIC FUNCTION ANALYSIS

We assessed for simplified SNAPPE II distribution and found that it was not following the normal Gaussian distribution (figure 1). Thus mean score was not used.

Using logistic function model, by plotting simplified SNAPPE II score against probability of dying [Which graded between 0 (survival) and 1 (mortality)] we constructed an S shaped curve. We plotted a probability of 0.5 against a simplified SNAPPE II cut off score of 30 (figure 2).

Assuming that a probability of 0.5 or higher predicts that the risk of death is elevated. We concluded that neonates with a simplified SNAPPE II score more or equal than 30 will be more likely to die compared to those with a score less than 30.

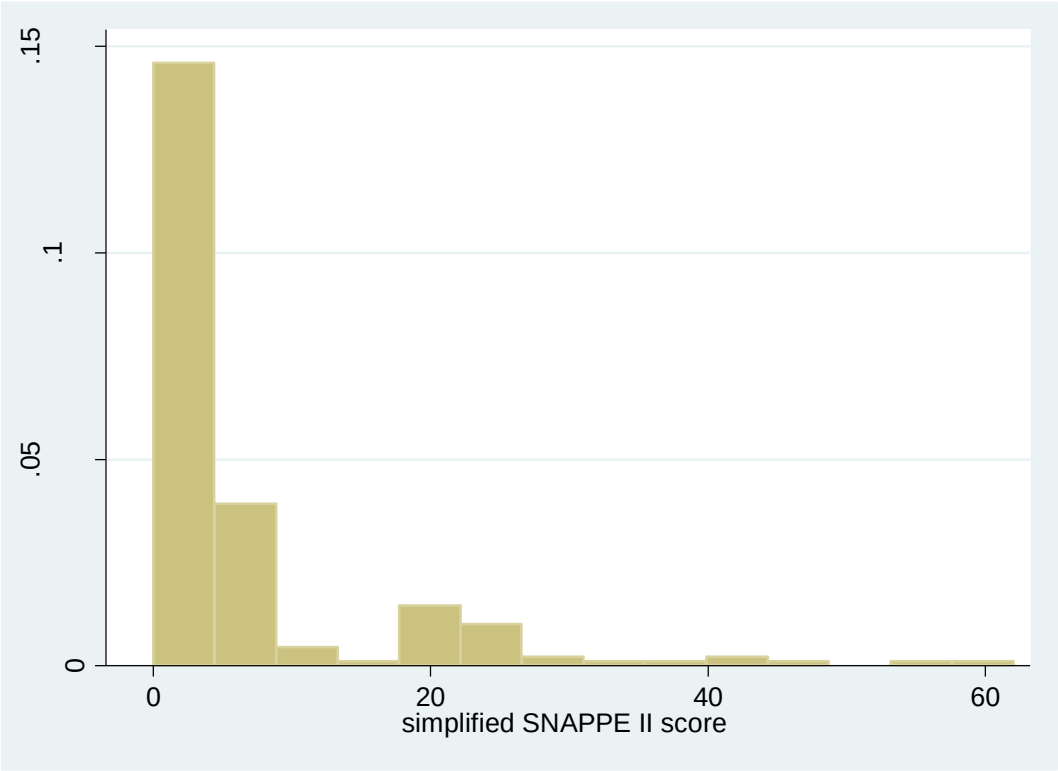

Figure 1: Simplified SNAPPE II score distribution

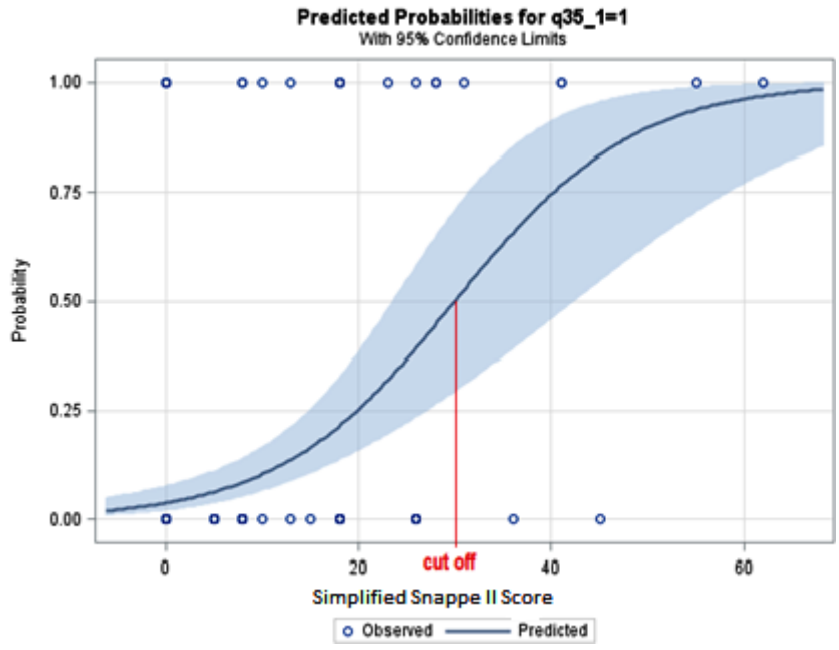

Figure 2: Simplified SNAPPE II correlation with mortality predicted probability

4.5. UNIVARIABLE ANALYSIS

Univariable analysis findings are summarized in table 4.

We assessed the association and strength between explanatory variables (simplified SNAPPE II ,hypothermia, hypoglycaemia , hyperglycaemia, gestational age, birth weight, APGAR score on 5th minute, SGA, use of CPAP at admission, resuscitation manoeuvers at delivery, and respiratory rate at 12 hours from admission) and the outcome variable (mortality). We found the following results:

- ✓ The Odds of dying are significantly 27.78 times higher in neonates with simplified SNAPPE II score more than or equal to 30 compared to those with a score less than 30 (OR=27.78 95% CI:4.99-154.86 P =0.0001).
- ✓ The odds of dying are significantly 20.8 times higher in neonates whose gestational age is below 33 weeks compared to those with more than or equal to 33 weeks gestational age (OR=20.8 95% CI=6.98-62.91 P<0.0001).
- ✓ The odds of dying are significantly 15.49 times higher in neonates with birth weight less 1500gr compared to those with birth weight more than or equal to 1500gr (OR=15.49 95% CI: 5.41-46.71 P<0.001).

It must be noted that CPAP and hyperglycaemia were not analysed through univariable and multivariable models to generate strength of association and adjust for confounders. This is due to presence of 0 on our 2x2 table which makes it impossible to compute with our software (Sas).

VARIABLES		MORTALITY		P VALUE	ODD RATIO	95% CI
		YES	NO			
Simplified SNAPPE II	≥30 <30	71.4% 8.2%	28.6% 91.8%	0.0001	27.78	4.99-154.86
Hypothermia	Yes No	17.1% 9%	82.9% 91%	0.16	2.08	0.74-5.81
Hypoglycaemia	Yes No	25% 9.5%	75% 90.5%	0.10	3.17	0.79-12.70
Hyperglycaemia	Yes No	100% 8.2%	0% 91.8%	<0.0001		
GA	<33 ≥33	43.2% 2.9%	56.7% 97.1%	<0.0001	20.8	6.98-62.01
BW	<1500gr ≥1500gr	34.8% 3.2%	65.2% 96.8%	<0.001	15.89	5.41-46.71
Apgar 5th minute	<4 4-6 7-10	0% 44.8% 4.7%	100% 55.2% 95.3%	0.96	16.55	5.97-45.88
SGA	Yes No	17.1% 8.8%	82.9% 91.2%	0.13	2.14	0.80-5.73
Use of CPAP at admission	Yes No	26.6% 0%	73.4% 100%	<0.001		
Resuscitation at delivery	BVM and chest compression BVM ventilation 5 Rescue breaths	50% 38.1% 13.8%	50% 61.9% 86.2%	0.21 0.24 0.19	23.17 14.26 3.71	2.77-193.68 4.29-47.40 0.97-14.08
RR at admission	>60 cycles 30-60cycles	18.3% 4.7%	81.7% 95.3%	0.99	4.56	1.65-12.60

Table 4: Neonatal mortality predictors univariable analysis

4.6. MULTIVARIABLE ANALYSIS

Multivariable analysis findings are summarized in table 5.

Simplified SNAPPE II score and birth weight were analysed in multivariable model. We adjusted for confounding variables by adding gender to the model.

We did not include gestational age in the model. The rationale is that this later was found to be positively correlating with birth weight (correlation coefficient=0.87).

No variable was found to be significantly associated with neonatal mortality.

- ✓ Simplified SNAPPE II score, birth weight and male gender were respectively found to predict mortality (OR=13.4 95% CI=0.36-498.72); (OR=3.14 95%CI=0.14-66.88); (OR=2.61 95%=0.55-12.44).

However those associations were respectively found by 16%, 47% and 23% due to chance (P=0.16) ;(P=0.47) ;(P=0.23).

VARIABLES		MORTALITY		P VALUE	Adjusted Odd ratio	95% CI
		YES	NO			
Gender	Male	8.7%	91.3%	0.23	2.61	0.55-12.44
Simplified SNAPPE II	>30	71.4%	28.6%	0.16	13.40	0.36-498.72
Birth weight	<1500gr	34.8%	65.2%	0.47	3.14	0.14-66.88

Table 5: Neonatal mortality predictors multivariable analysis

5. DISCUSSION

5.1. NEONATAL UNIT MORTALITY

Our mortality rate is 10.4%, which is comparable to Kadivar et al who found 12.6% in a study done in Teheran (Iran) university of medical sciences affiliated children medical centre NICU to assess neonatal mortality risk.

Similar results were found by Blandina Mmbaga et al, in their retrospective cohort study performed at KCMC in Tanzania. Their mortality rate was 10.7%[24].

5.2. SIMPLIFIED SNAPPE II SCORE PREDICTIVE PERFORMANCE ASSESSMENT

In our study we found that a simplified SNAPPE II score ≥ 30 was highly predictive of dying when compared to neonates with <30 score thus a score of 30 as a cut off. This is a unique finding and in our literature review we did not find any study in which a particular simplified SNAPPE II score was evaluated to predict neonatal mortality.

When comparing our cut off with those found in different studies evaluating *standard* SNAPPE II score in predicting neonatal mortality, the following results were found:

- ✓ Mia RA et al, in their study performed at Soetomo Hospital in Indonesia found a score 30 as the best cut off in predicting neonatal mortality, which is quite similar to our findings.
- ✓ Shivanna et al, in their study performed at Indira Gandhi institute for child heath in India, found a cut off 37 as the best predictor of neonatal mortality.
- ✓ Timothy J et al, at Hasan Sadikin general hospital in Indonesia calculated a cut off of 51.
- ✓ Dammann O. et al in their inter institutional analysis of SNAPPE II prediction of mortality in less than 28 weeks gestational age, determined a score of 45 as the best cut off as well[25].

Those two higher cut off (respectively 51 and 45) can be explained by a high survival rate in those institution compared to ours where there are limited resources without ventilator and surfactant available.

Using univariable analysis, a simplified SNAPPE II score was found to significantly predict neonatal mortality (OR=27.78 95% CI: 4.99-154.86 P =0.0001).This association at the significance level was observed by Shelley Reid et al in their study,

(OR=1.075 95% CI: 1.064-1.085). [26]

From these findings we can objectively observe a large difference in odds ratios and confidence intervals with the most likely reason being the difference in sample size with 201 in our study and 1,777 in the Shelley Reid study.

Using multivariable analysis we found that our simplified SNAPPE II score was insignificantly predicting neonatal mortality ((OR=13.4 95% CI=0.36-498.72).These findings could be explained by the small sample size as well.

Based on our findings and our review of the literature we think that a simplified SNAPPE II could be a good predictor of mortality in a resource limited facility. Further studies with larger sample size are needed to re-evaluate and confirm the predictive performance of the cut-off score we propose.

5.3. BIRTH WEIGHT AND GESTATIONAL AGE PREDICTIVE PERFORMANCE ASSESSMENT

The overall mean birth weight was 2421.8 (963.6) gr .The mean birth weight for deceased and survived neonates was respectively 1298.8 (547.4) gr and 2553.6 (915.5.) gr.

This is comparable with results found in Kadivar et al study performed in Iran where the overall mean birth weight was 2479.8 (29.4)gr.

Our findings are not consistent with Mia et al results in Indonesia where they found 2173 (869) grams as mean birth weight for deceased neonates whereas we calculated the mean birth weight of 1298.8 (547.4) for deceased neonates. This emphasizes the important role of prematurity with very low birth weight in our unit neonatal deaths.

The overall, deceased and survived neonates mean GA was respectively 35.9 (4.1); 30.4 (3.6) and 36.5 (3.6) weeks. This is comparable with Kadivar et al who found an overall mean GA of 35.8 (0.2) weeks and Mia et al whose mean GA for deceased and surviving neonates was respectively 34.96 (4.38) and 36.42 (3.01) weeks.

Using univariable analysis, a significant association of birth weight ≤1500gr and neonatal mortality was found (OR=15.49 95% CI: 5.41-46.71 P<0.001).

Douglas K. Richardson et al had results that were similar with respectively odds ratios of 19.22 (95%CI: 8.27-44.65); 6.93 (95% CI: 3.19-15.04); 1.92(95%CI: 0.87-4.22) for neonates with birth weight ≤749gr; 750-999gr; 1000-1499gr.

Daynia E. Ballot et al, in South Africa demonstrated a significant association between birth weight and gestational age with neonatal mortality as well. OR were respectively 10.41 (95%CI: 6.62-16.6) and 11.97 (95% CI: 7.1-20.1) in <1001 grams and <28weeks neonates.

We found through univariable analysis that gestational age <33weeks was significantly associated with mortality (OR=20.8 95% CI=6.98-62.91 P<0.0001). This significant association was also found by N. Y.Boo in Malaysia (P <0.01). [27]

A positive correlation between birth weight and gestational age was found in our study

(Correlation coefficient=0.87).This is similar to Daynia E. Ballot et al, findings in South Africa where their correlation coefficient was 0.717.

A GA <33 weeks and BW <1500 gr can still be seen as a strong predictor of neonatal mortality in our facility. However, further study with larger sample size is advised in order to perform multivariable analysis and re-adjust for confounders.

We predict that mortality can be decreased and survival can be increased by the availability of mechanical ventilation and surfactant in our unit.

5.4 .HYPERGLYCEMIA PREDICTIVE PERFORMANCE ASSESSMENT

Mortality in hyperglycaemic neonates was 100% (P=<0.0001). All were preterm with BW <1500gr and GA<33weeks.

Hyperglycaemia was found in different studies to be significantly associated with neonatal mortality.

Margret Van Der Lught et al found a mortality rate of 41% in hyperglycaemic versus 8% in non-hyperglycaemic neonates (P<0.001).

LS. Kao et al, in their multivariate analysis found that severe hyperglycaemia

(Defined as blood glucose≥180mg/dl) in the first three postnatal days was significantly associated with mortality (OR=15.7 95%CI: 3.74-65.9 P<0.001). [28]

Even though we were not able to compute hyperglycaemia using logistic regression analysis we think that hyperglycaemia can be considered as highly predicting mortality in our facility.

5.5. CPAP PREDICTIVE PERFORMANCE ASSESSMENT.

All neonates who died had been placed on CPAP at admission thus significant association with mortality (P<0.001).Of 21 deceased neonates, 16 (76.5%) were preterm with BW<1500gr and GA <33weeks.2 (9.5%) were preterm with LBW and respectively GA =33 and 34 weeks. At admission they were diagnosed with respiratory distress syndrome and were managed with CPAP as the only non-invasive respiratory support that is used in CHUK neonatal unit. No major complications associated with its uses were significantly reported in the literature (Adam G. Buckmaster et al) [29]. This scenario can be explained as follow:

- ✓ BW<1500 (OR=15.49 95% CI: 5.41-46.71 P<0.001) and GA<33weeks (OR=20.8 95% CI=6.98-62.91 P<0.0001) respectively were predictors of neonatal mortality on univariable analysis. As noted above this population was the most user of CPAP at 76.5%.This findings demonstrate that CPAP was

mostly used on higher mortality risk neonates. By that we can understand the high mortality rate observed with CPAP use.

- ✓ Since CPAP is the only non-invasive respiratory support that is used in our unit, we think that the high mortality rate observed with CPAP use can be most likely due to CPAP failure and not complications.
- ✓ Some neonatal devices were reported to be colonized by nosocomial bacteria during infection control procedures. We think that hospital acquired sepsis, probably by contaminated circuits or other used devices had played a role in higher mortality rate observed with CPAP use.

Studies done previously highlight early and late onset neonatal infections as significant cause of mortality in NICU.

- As reported by Joy Ewan et al, in their study, severe Infections (26%), preterm birth (28%) and complications of asphyxia (23%) were globally the most common causes of neonatal mortality[30].
- Kailash Aggarwal et al, during their descriptive hospital record based study, performed in a tertiary care unit located in New Delhi, India found that early and late onset sepsis was the most common cause of neonatal mortality respectively accounting 20% and 70% of deceased neonates[31].
- Ekwochi et al, in their longitudinal study, performed at Enugu State University teaching hospital in Nigeria concludes that sepsis accounted 27% all deaths classifying as the second leading cause of neonatal mortality[32].
- Blandina Mmbaga et al, in retrospective cohort study performed at KCMC in Tanzania, found that infections (8.6%) was among the leading causes of neonatal mortality[24].
- Of 21 deceased neonates, in our study, 4 were diagnosed with neonatal sepsis. This diagnosis is confirmed by a positive blood culture. Gram negative bacteria (Escherichia coli, Acinetobacter and Klebsiella) were the most commonly isolated bacteria (table 1).

The similar findings were reported by Neema Kayange et al, in their cross sectional study performed at Bugando medical centre neonatal unit in Tanzania. Gram negative bacteria covered 61.1% of all positive blood cultures[33].

Our conclusion is that neonatal infections acquired vertically or horizontally is an important risk factor for neonatal mortality. Infection control measures in NICUs will reduce considerably its incidence.

6. STUDY LIMITATIONS

Our study had some limitations

- ✓ We evaluated the predictive performance of a simplified SNAPPE II score, it is different from standard SNAPPE II score because it doesn't include the following variables: the lowest Pa O_2/FiO_2 ratio, the lowest serum PH and lowest MBP.
- ✓ PO_2/FiO_2 ratio and serum PH were not included because our facility didn't perform blood gases measurement.
- ✓ Mean blood pressure was included at the beginning of the study, but unfortunately was inconsistently measured and later on was removed from our variables because of two reasons:

Inappropriate blood pressure cuffs considering different GA/BW which lead to false results and consistent blood pressure monitor failure.

- ✓ Urine output was obtained through diaper measurement every 6 hours. The current literature report urine output measured through diaper change every 3 hours (Candice Torres de Melo Bezerra et al study) [34] or Collection bags (B.D. Gupta et al study) [35].
- ✓ Finally the sample size was small comparing to other studies that evaluated SNAPPE II score efficacy in predicting mortality. This resulted in some statistically insignificant results and less precisions (wide confidence intervals).
- ✓ Standard and simplified SNAPPE II scores are admission scores, they don't predict events occurring during neonate hospital stay
  (Example: hospital acquired infections) that can and be highly associated with mortality.

7. CONCLUSION AND RECOMMENDATIONS

7.1. CONCLUSION

In our study, we found a neonatal mortality rate of 10.4%. The mortality was 100% for neonates with hyperglycaemia.

Mortality increase as gestational age and birth weight decrease with VLBW, ELBW and less than 33 weeks neonates affected considerably.

All neonates who died (100%) required CPAP at admission.

Simplified SNAPPE II score of 30 was found to be the best cut off to predict neonatal mortality.

On univariable analysis, simplified SNAPPE II score, birth weight and gestational age were found to be significantly predicting neonatal mortality.

7.2. RECOMMENDATIONS

- **To University Teaching Hospital of Kigali (CHUK)**
  - ✓ Avail blood pressure machines and their respective appropriate for gestational age/weight cuffs.
  - ✓ Advocate for the availability of advanced mechanical ventilation in neonatal unit for neonates who fail CPAP. Eventually make surfactant available.
  - ✓ Advocate for availability of accurate permanent blood gases measurement.
  - ✓ Work together with different stakeholders to implement a neonatal intensive care unit with trained staff where critically ill neonates can be managed properly.
  - ✓ Increase awareness among health practitioners about neonatal hyperglycaemia.
  - ✓ Improve glucose management to avoid both hyper and hypo-glycaemia.

- **To Ministry of Health**
  - ✓ Work together with different stakeholders to improve the neonatal intensive care unit in public university teaching hospitals, optimize training of staff and use of equipment.
  - ✓ Provide support to researchers in order to conduct a large cohort study to assess the efficacy of a simplified SNAPPE II score in predicting neonatal mortality in resources limited settings for further validation.
- **To Researchers**

✓ Conduct a large cohort study to evaluate the efficacy of a simplified SNAPPE II score in predicting neonatal mortality in resources limited settings for further validation.

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9. APPENDIX

9.1 STANDARD SNAPPE II SCORE

Variables	Measurement	Score
Mean blood pressure(mmHg)	>30	0
	20-29	9
	<20	19
Lowest temperature (Celsius)	≥35.6	0
	35-35.5	8
	<35	15
PO_2/FiO_2 ratio	>2.5	0
	1-2.49	5
	0.3-0.99	16
	<0.3	28
Lowest serum PH	>7.2	0
	7.1-7.19	7
	<7.1	16
Seizures	None/single	0
	Multiple	19
Urine output(ml/kg/hr)	≥0.91	0
	0.1-0.9	5
	<0.1	18
Birth weight (gr)	≥1000gr	0
	750-999gr	10
	<750gr	17
SGA	No	0
	Yes	8
APGAR at 5th minute	7-10	0
	<7	18
Final score		

9.2. QUESTIONAIRE

Identification number: **Outcome Variable: Died: No: 0 Yes: 1**

9.2.1. Simplified, based on physical findings, SNAPPE II score

Variables	Measurement	Score
Lowest temperature (Celsius)	≥35.6	0
	35-35.5	8
	<35	15
Seizures	None/single	0
	Multiple	19
Urine output(ml/kg/hour)	≥0.91	0
	0.1-0.9	5
	<0.1	18
Birth weight (gr)	≥1000gr	0
	750-999gr	10
	<750gr	17
SGA	No	0
	Yes	8
APGAR at 5th minute	7-10	0
	<7	18
Final score		

9.2.2. Maternal variables

Variables	Measurement	Observations/response
Mother parity (including current delivery)	Primipare (delivered once)=0 Paucipare (delivered 2 or 3 times)=1 Multipara (delivered 4 or 5 times)=2 Grand multipara (delivered more than 5 times)=3	
Mother birth order	Singleton=0 Twin=1 Triple=2	
Mother age (years)		
Antenatal care during first trimester	Yes=0 No=1	
Mother mode of delivery	Spontaneous vaginal=0 Elective caesarian section=1 Emergent caesarian section=2	
Presentation at birth	Cephalic=0 Breech=1 Transverse=2 front=3 face=4	
Mother level of education (traduction in kinyarwanda: Mwize amashuri angahe?)	Achieved university=0 Achieved secondary school=1 Achieved vocational school=2 Achieved primary school=3 None=4	

9.2.3 Neonatal variables

Variables	Measurement	Observation/response
Gender	Female=0 Male=1	
Place of birth	CHUK maternity=0 Private clinic=1 District hospital=2 Health center=3 Home=4 During the way to health facility=5	
Hypothermia (temperature<36.5)	No=0 Yes=1	
Hypoglycemia (defined as a random blood glucose <45mg/dl or 2.5mmol/l)	No=0 Yes=1	
Hyperglycemia (defined as a random blood glucose 200mg/dl or 11.1mmol/l)	No=0 Yes=1	
Gestational age	Total WGA	
Birth weight	Total in grams	
If preterm <34 WGA, Maternal treatment with antenatal steroids	>3 doses=0 3 doses=1 2 doses=2 1 doses=3 None=4	
APGAR at 5th minute after birth	7-10=0 4-6=1 < 4=2	
Small for gestational age (<3rd centiles)	No=0 Yes=1	
Use of CPAP required at admission	Yes=0 No=1	
Resuscitation after delivery	None=0 Rescue breaths=1 BVM ventilation=2 BVM ventilation and chest compression=3 No information=4	
Capillary refill time at admission	<2 seconds=0 2-3seconds=1 >3 seconds=2	
Respiratory rate during 12 hours after birth	30-60cycles=0 >60cycles=1 <30cycles=2 respiratory pauses (1 or more)=3 Apnea (1 or more)=4	

9.3. ETHICAL CLEARANCE

UNIVERSITY OF RWANDA — COLLEGE OF MEDICINE AND HEALTH SCIENCES

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 16/10/2015
Ref: CMHS/IRB/316/2015

Dr NYALIHAMA Alain
School Medicine and Pharmacy, CMHs, UR

Dear Dr NYALIHAMA Alain

RE: ETHICAL CLEARANCE

Reference is made to your application for ethical clearance for the study entitled **"Predicting Mortality in a Resource limited Neonatal Unit: Kigali University Teaching Hospital (CHUK) experience".**

Having reviewed your application and been satisfied with your revised version incorporating the comments from the IRB, your study is hereby granted ethical clearance. The ethical clearance is valid for one year starting from the date it is issued and shall be renewed on request. You will be required to submit the progress report and any major changes made in the proposal during the implementation stage. In addition, at the end, the IRB shall need to be given the final report of your study.

We wish you success in this important study.

Professor Kato J. NJUNWA
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:
- Principal College of Medicine and Health Sciences, UR
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