RELATIONSHIP BETWEEN PERFUSION INDEX AND SNAPPE-II SCORES IN NEONATES ADMITTED TO KENYATTA NATIONAL HOSPITAL NEWBORN UNIT

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DECLARATION

I certify that this dissertation is my original work and has not been presented for examination or the award of a degree in any other university.

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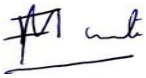
SUPERVISORS APPROVAL

This dissertation has been submitted with our approval as supervisors.

. **Signature:**  **Date:** 21st Jan 2022

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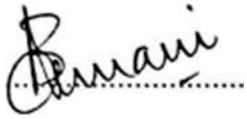
Signature:  **Date:** 21st Jan 2022

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DEDICATION

To my beautiful daughter Grace and loving husband Dr. Musa Misiani. You have been my pillars through it all, you encouraged me to pursue this dream and lovingly held my hand. I am truly thankful for having you in my life.

With gratitude to my father Prof. Elias K. Maranga, in loving memory of my mother Grace Maranga, my three dear sisters-Janet, Nancy and Naomi, you've taught me and given me unconditional support. Thank you for cheering me on in this journey.

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2. Kenyatta National Hospital

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LIST OF ABBREVIATIONS

SNAP	Score for neonatal acute physiology
SNAP II	Score for neonatal acute physiology II
SNAPPE-II	Score for neonatal acute physiology-Perinatal extension II
CRIB	Clinical Risk Index for Babies
CRIB II	Clinical Risk Index for Babies II
PI	Perfusion Index
SET	Signal Extraction Technology
KNH	Kenyatta National Hospital
KNH-UoN ERC	Kenyatta National Hospital-University of Nairobi ethics review committee
NBU	Newborn unit
NICU	Neonatal Intensive Care Unit
KDHS	Kenya Demographic and Health Survey
WHO	World Health Organization
MDG	Millenium Development Goals
PO_2	Arterial partial pressure of oxygen
FiO_2	Fraction of inspired oxygen
PVR	Pulmonary Vascular Resistance
COVID-19	Coronavirus disease 2019

OPERATIONAL DEFINITIONS

Neonate- Infant from 0-28days of life

PI-Perfusion index- A plethysmographic index derived from a pulse oximeter, measured non-invasively, calculated as: AC/DC *100 (ratio of the pulsatile blood flow to the non-pulsatile blood in peripheral tissue). It ranges from 0.03% (vasoconstriction) to 20%(vasodilation).

SNAPPE II score-(Score for Neonatal Acute Physiology-Perinatal Extension II) is a physiologically based score that is derived from 9 variables that are assigned points based on values obtained and a score calculated. The scores obtained categorize disease severity as:

- Mild (0-20),
- Moderate (20-40),
- Severe (>40)

TABLE OF CONTENTS

DECLARATION ..... **i**
ACKNOWLEDGEMENT ..... **iii**
COLLABORATING INSTITUTION(S) ..... **iv**
FUNDING ..... **iv**
LIST OF ABBREVIATIONS ..... **v**
OPERATIONAL DEFINITIONS ..... **vi**
LIST OF FIGURES ..... **x**
LIST OF TABLES ..... **xi**
ABSTRACT xii
1.0 CHAPTER ONE: INTRODUCTION 1
2.0 CHAPTER TWO: LITERATURE REVIEW 3
2.1 Neonatal Morbidity and Mortality 3
2.2 Scores Used in the Assessment of Severity of Neonatal Illness 3
2.2.1 SNAPPE II score 4
2.2 Perfusion Index 5
2.3 Physiology of Transitional Circulation in Newborns 7
2.4 Physiology of Microcirculation in Sick Neonates 8
2.5 Theoretical and Conceptual Framework 9
2.6 Problem Statement 10
2.7 Justification and Significance 10
2.8 Research Question 11
2.8.1 Research question: 11
2.9 Objectives 11
2.9.1 Broad Objective 11
2.9.2 Specific Objectives 11
2.9.3 Secondary Objective 11
3.0 CHAPTER THREE: METHODOLOGY 12
3.1 Study Design 12
3.2 Study Setting 12
3.4 Study Population 12

3.4.1 Inclusion Criteria 12
3.4.2 Exclusion Criteria 12
3.5 Sampling and Sample Size Determination 13
3.5.1 Sampling Technique 13
3.5.2 Sample Size Determination 13
3.6 Study Procedure and Data Collection 13
3.6.1 Participant recruitment and consenting procedure 13
3.7 Data Collection 15
3.7.1 Determination of SNAPPE-II Scores 15
3.7.2 Measurement of Perfusion Index 15
3.8 Quality Assurance Procedures 16
3.9 Ethical Considerations 16
3.10 Data Management and Statistical Analysis 17
3.11 Study Results Dissemination Plan 17
4.0 CHAPTER FOUR: RESULTS 18
4.1 Study Participation 18
4.2 Clinical Characteristics of Neonates Recruited Into the Study 19
4.3 SNAPPE II Score 21
4.4 Perfusion Index 23
4.5 Relationship between Perfusion Index and SNAPPE II Scores 24
4.6 Proposed Cut off Values for Pi 27
4.6.1 Decision Tree 28
5.0 CHAPTER FIVE: DISCUSSION 30
5.1 Perfusion Index in Neonates Admitted in KNH NBU 30
5.2 SNAPPE II Scores of Neonates Admitted in KNH NBU 32
5.3 Relationship between SNAPPE II Score and PI 33
5.4 Proposed Cut off Values for PI 34
5.5 Strengths of the Study 35
5.6 Limitations of the Study 35
5.7 Conclusion 36
5.8 Recommendation 36

REFERENCES 37
APPENDICES 41
APPENDIX I: DATA COLLECTION SHEETS 41
APPENDIX II: ETHICAL APPROVAL LETTER 42
APPENDIX III: CONSENT FORMS 44
APPENDIX IV: SNAPPE II CALCULATOR 50
APPENDIX V: MODIFIED BALLARD SCORE 51
APPENDIX VI: INTERNATIONAL STANDARDS FOR SIZE AT BIRTH (BOYS) 24 – 33 WEEKS 52
APPENDIX VII: INTERNATIONAL STANDARDS FOR SIZE AT BIRTH (BOYS) 33 – 43 WEEKS 53
APPENDIX VIII: INTERNATIONAL STANDARDS FOR SIZE AT BIRTH (GIRLS) 24 – 33 WEEKS. 54
APPENDIX IX: INTERNATIONAL STANDARDS FOR SIZE AT BIRTH (BOYS) 33 – 43 WEEKS 55
PLAGIARISM REPORT 56

LIST OF FIGURES

Figure 1: Conceptual framework of the relationship between perfusion index and SNAPPE II ... 9
Figure 2: Patient flow and recruitment in the study ... 14
Figure 3: Flow of Study Participants in the Study ... 18
Figure 4: Distribution of diagnoses of neonates recruited into the study ... 20
Figure 5: Relationship between SNAPPE II and perfusion index ... 25
... 26
Figure 6: Distribution of mean perfusion indices compared to disease severity classified by SNAPPE II scores ... 26
Figure 7: Receiver operating curve showing the predictive value of PI in disease severity ... 27
Figure 8: Decision Tree Using Mean P1 Classify Disease Severity ... 29

LIST OF TABLES

Table 1: Gestational age, weight, and age at enrollment of neonates in the study 19
Table 2: SNAPPE II Parameters recorded in the study 22
Table 3: Perfusion index in different cohorts of neonates as classified by SNAPPE II parameters 23

ABSTRACT

Background: Neonatal morbidity and mortality remain of worldwide concern, especially in low- and middle-income countries. Early recognition of severe neonatal illness guides the intensity of therapy. This currently employs several validated scoring systems amongst which the SNAPPE-II score has found the most utility. There is however, a continued need for quick and efficient methods in assessing disease severity amongst neonates. Pulse oximetry offers promise in this regard using the perfusion index as a marker of tissue perfusion. Perfusion index is the ratio of pulsatile blood flow to non-pulsatile blood flow in peripheral tissue and is expressed as a percentage. Establishing clarity in the relationship between PI and SNAPPE II could provide a guide to the potential expanded utilization of perfusion index in the assessment of neonatal disease severity.

Study question: What is the relationship between the perfusion index and SNAPPE-II score in neonates admitted to Kenyatta National Hospital NBU?

Broad objective: To investigate the relationship between the perfusion index and SNAPPE-II score in neonates admitted to Kenyatta National Hospital NBU.

Methodology: The study was a descriptive cross-sectional study at Kenyatta National Hospital, Newborn Unit. The study population involved neonates admitted to KNH NBU. The study duration was 6 months and consecutive sampling was used to enroll neonates into the study. A total of 139 neonates completed the study. The SNAPPE-II scores of eligible neonates were recorded within 24 hours of admission. The perfusion index was recorded within 24 h of admission using a Masimo SET Radical-7 pulse oximeter.

Data handling and analysis: Data were cleaned, coded, and entered into R studio and Microsoft excel. Relevant descriptive statistics were used to summarize the data. Correlation between PI and SNAPPE-II score was assessed using Pearson's correlation. A p-value <0.05 was considered statistically significant. Linear regression of the relationship between PI and SNAPPE II scores was done to derive an equation describing the relationship. Receiver operating curves were plotted and the area under the curve was calculated to determine the predictive value of the PI on disease severity. Results are presented using frequency tables and graphs.

Ethics and related procedures: Ethical approval was obtained from the KNH-UON ethics and review committee (KNH-UoN ERC). Permission was also obtained from the KNH administration before the commencement of the study.

Results: A total of 139 neonates completed the study. Out of these, 79 were term infants(57%) and 60 were preterm infants(43%), with female infants accounting for 51.8% and male infants 48.2%. The mean gestational age was 35.9±4.0 weeks with a mean birth weight of 2434.3±865.8 grams. The median SNAPPE II score was 32 with an interquartile range of 16-56. The mean perfusion index was 0.90±0.14 SD. Pearson's correlation coefficient, R, between mean PI and SNAPPE II scores was -0.56 ($p<0.0001$). The PI cut-off values generated were ≥0.88 for mild disease (AUC=0.91) and PI<0.83 for severe disease (AUC=0.74).

Conclusion: Perfusion index has a moderate and statistically significant negative correlation with SNAPPE II scores of neonates. It can therefore be used, in tandem with other assessment tools, to predict the severity of illness in neonates.

1.0 CHAPTER ONE: INTRODUCTION

Neonatal morbidity and mortality present a major public health challenge worldwide (1). Sub-Saharan Africa accounts for the majority of neonatal deaths. Kenya has a neonatal mortality rate of 22 per 1000 live births (2). Timely diagnosis and initiation of treatment is crucial in saving lives. In this regard, the identification of severely ill neonates is important (3). The assessment of the severity of neonatal illness using scoring systems is useful in quantifying initial risk to guide the optimization of care.

Timely diagnosis & assessment of the severity of neonatal illness is crucial in initiating appropriate treatment. Several scores have been used in assessing the severity of illness in neonates. The scoring systems have been used for prognostication of morbidity and mortality and to guide clinicians in quantifying initial risk, optimizing care, and counseling parents on the severity of illness and possible treatment cost. Some of these scoring systems include the Clinical Risk Index of Babies (CRIB) (4,5), Clinical Risk Index of Babies II (CRIB II) (6), Score for Neonatal Acute Physiology (SNAP) (7), Score for Neonatal Acute Physiology-II (SNAP II), Score for Neonatal Acute Physiology-Perinatal Extension (SNAPPE) and the updated Score for Neonatal Acute Physiology-Perinatal Extension (SNAPPE II) (8,9).

The SNAP score, developed by Richardson et al (10) and refined further into the SNAPPE II score, has been validated and found to have good specificity and sensitivity in predicting neonatal outcomes (11). The SNAPPE II score considers nine parameters namely mean blood pressure, PO2/FiO2, lowest temperature, serum pH, multiple seizures, urine output, birth weight, Apgar score and small for gestational age (3). It can be used in the early detection of severely ill infants leading to the early institution of appropriate therapy.

Parameters such as heart rate, blood pressure, acid-base status and urine output are however, not optimal indicators of blood flow changes that attend severe illness in neonates. Plethysmographic indices of blood flow have been shown to be useful in characterizing these fluxes. Perfusion index (PI) is a plethysmographic index and is a surrogate of loco-regional blood flow (12).

The pulsatile (arterial) component is expressed as a percentage of the non-pulsatile (venous and tissue) blood component. It ranges from 0.03% (being vasoconstriction) to 20% (vasodilatation). Thus, changes in blood vessel caliber can therefore be monitored using the PI (12). Various studies have shown that PI provides information about illness severity, early neonatal respiratory outcome, low superior vena cava flow, and hemodynamically significant patent ductus arteriosus (5). Subtle changes in perfusion which are often missed by static haemodynamic parameters can therefore be evaluated using PI.

The relationship between PI and disease severity in neonates continues to be studied (5,13). In these instances, investigators have studied the relationship between PI and SNAP as well as with CRIB II scores. The PI has been found to be an accurate predictor of disease severity. Its use in term neonates and preterm neonates as evaluated by the SNAPPE-II score is yet to be studied. This study therefore seeks to investigate the relationship between PI and SNAPPE-II scores of neonates admitted to Kenyatta National Hospital NBU.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Neonatal Morbidity and Mortality

The neonatal period is a crucial time when children face a high risk of dying from various causes. Globally, the average neonatal mortality rate is 18/1000 live births (1), in Africa 45/1000 live births (1) and in Kenya 22/1000 live births (2). Sub-Saharan Africa had the highest neonatal mortality rate in 2018 at 28 deaths per 1,000 live births. A child born in sub-Saharan Africa is 10 times more likely to die in the first month than a child born in a high-income country (1).

Neonatal mortality in developing countries contributes to a high percentage of infant mortality, thus MDG 4 and 5 were developed to focus on reducing this by targeting improved maternal health and improved care of the neonate. Data from Kenyatta National Hospital and Moi Teaching and Referral Hospital showed the major causes of neonatal morbidity and mortality to be immaturity, respiratory distress, infections and perinatal asphyxia (14,15).

Severe neonatal illness is a major cause of death in the first 28 days of life with the main occurrence in the first week of life. The majority of all neonatal deaths (75%) occur in the first week of life, and about 1 million newborns die within the first 24 hours (1). The three major causes worldwide are: Infection (36%), Prematurity and low birth weight (28%) and perinatal asphyxia (23%) with variations in occurrence across different countries. The majority of severe neonatal morbidity and mortality occurs in low- and middle-income countries thus a window of opportunity exists in providing essential newborn care and early identification and management of high-risk newborns (1).

2.2 Scores Used in the Assessment of Severity of Neonatal Illness

Timely recognition and assessment of severe neonatal illness helps to categorize high-risk neonates for early intervention to prevent further morbidity and mortality (4). Over time, scoring systems have been developed and modified to predict the severity of illness, mortality, and outcomes in the long term (3,8). Scoring systems use appropriately weighted parameters with demographic, physiologic, and clinical data collected on an infant to calculate a score that quantifies its morbidity.

Scoring systems used in neonates include CRIB (clinical risk index for babies) (3) and modified CRIB II, SNAP (score for neonatal acute physiology) modified to SNAPPE and SNAPPE II (score for neonatal acute physiology with perinatal extension). Other neonatal scoring systems that have been studied include Neurobiological Risk Score (NBRS), Neonatal Mortality Prognosis Index (NMPI), and Neonatal Therapeutic Intervention Scoring System (NTISS) (16).

2.2.1 SNAPPE II score

Amongst the neonatal illness scoring systems, SNAPPE II is applicable to both term and preterm neonates. It involves the assessment of physiological variables which affect mortality in the initial hours following the admission of severely ill neonates (17). The variables are assigned points based on values obtained and a score calculated. The higher the score, the worse the outcome (3).
Initially developed and validated in the 1990s as the SNAP score with 34 parameters, it was refined to SNAP II to make the score easier with 6 parameters and to this 3 perinatal variables namely birthweight, APGAR score and gestational age were added to widen its scope thus renamed SNAPPE II (10). The resultant SNAPPE II score has 9 parameters: Mean B.P, lowest temperature, PO2/FiO2 ratio, serum pH, multiple seizures, urine output, birth weight, APGAR score, and small for gestational age (8).

This scoring system has been validated as a useful tool in assessing the severity of illness and prognosis with good specificity and sensitivity irrespective of gestational ages and birth weights (8,9). It assists the clinician in identifying very sick neonates and prioritizing treatment for these neonates. It is a useful tool to predict neonatal mortality in NICU and also finds use in counseling the parents regarding the severity of illness and the probable treatment cost involved (11,18).

SNAPPE II score is easier to compute using 9 physiological variables compared to the original SNAP score which had 34 parameters to measure. The variables represent each of the major organ systems thus the total score gives an overall indication of the physiologic state of the newborn. SNAP-II and SNAPPE-II are empirically validated illness severity and mortality risk scores for newborn intensive care. They are simple, accurate, and robust across populations. In all birth weights, SNAPPE-II had excellent discrimination and goodness of fit. Area under the receiver operator characteristic curve was.91 ± 0.01. Goodness of fit (Hosmer-Lemeshow) was 0.90 (8).

Across Europe and America, the latest validated scoring systems for neonatal illness that have been widely used in NICU are SNAPPE II and CRIB II. Both scoring systems have been shown to have good discrimination for predicting mortality, the main difference being SNAPPE II takes into account neonates of all birthweights and gestational ages while CRIB II takes into account low birth weight neonates with a gestational age <32weeks (19).

A revalidation study was done across 58 Vermont Oxford centers which concluded that current score performance was similar to that observed previously, which suggests that the revised Score for Neonatal Acute Physiology and revised Score for Neonatal Acute Physiology Perinatal Extension have not decalibrated over the years since the first cohort was assembled, despite advances in neonatal care during that period (20).

2.2 Perfusion Index

Plethysmographic indices derived from pulse oximetry provide a simple, quick, accurate, and non-invasive method of monitoring patients. The use of pulse oximetry is relatively widespread in practice including low resource settings (21). Perfusion index is the ratio of pulsatile blood flow (AC) to non-pulsatile (DC) or static blood in peripheral tissue (12).

$$P.I = \frac{AC}{DC} * 100\%$$

It's a non-invasive measure of peripheral perfusion that can be continuously measured by oximetry (22,23). The numerical value obtained is a measure of the strength of different components of the infrared signal returning from the monitoring site reflecting real-time changes in peripheral blood flow. It ranges from 0.03% (being vasoconstriction) to 20% (vasodilatation) (18).

Perfusion index takes into account the pulsatile (arterial) component, which increases in vasodilation and decreases in vasoconstriction, to reflect the peripheral vasomotor tone and changes in blood vessel caliber which can therefore be monitored using the Perfusion Index. PI reflects the circulatory changes that occur in hypovolemia and in low cardiac output states such as shock. In these states, redistributed blood flow shunts blood to critical organs, reducing perfusion to peripheral organs like the skin (5).

A newborn's skin perfusion is high compared to oxygen demand when they are not undergoing any stressful events. In severely ill neonates, the peripheral perfusion is related to the redistribution of cardiac output and oxygen supply to major organs, thus peripheral perfusion is affected (12). Perfusion Index is measured using signal extraction technology (SET) pulse oximetry. This is able to pick the pulse oximeter waveform through low perfusion states and movement artifact (shiver) as long as the signal quality index (SQI) is met.

In addition, peripheral vasoconstriction results in a reduced proportion of pulsatile flow peripherally. This is then evident clinically in signs of cold, pale, and clammy skin and prolonged capillary refill time. The PI is therefore an objective marker of the adequacy of peripheral perfusion as it reflects both global changes in blood flow shunting and local vasoconstriction (24).

Perfusion index has been suggested as a predictor of high illness severity in neonates and is useful in monitoring changes in the peripheral circulation. It uses infrared absorbance as a surrogate of peripheral blood flow(5,18,25). Subtle changes in perfusion which are often missed by static hemodynamic parameters can be evaluated using PI. A PI value < 1.24 is an accurate predictor for high illness severity and is independent of subjective means of interpreting neonatal health status (13).

The PI is obtained non-invasively by placing a sensor probe on the monitoring site and the strength of the infrared signal returning from the monitoring site is measured and reflected on the oximeter as a numerical value which can be documented at a specific point in time or monitored as a trend (13). Recently it has also been incorporated in some of the monitors such as Philips Intellivue and Mindray used in NICUs worldwide. PI is increasingly being recognized as an effective parameter to increase the sensitivity for the detection of important neonatal complications (12).

Pulse oximetry and plethysmographic indices have been monitored from various sites in neonates to obtain preductal or postductal values. When pre-ductal and post-ductal sites are monitored for perfusion, a difference could give insights into hemodynamic significance of patent ductus arteriosus. In a study by Balla et al in 2016 , the PI in the lower limb was found to be lower than pre-ductal PI (26). This fact is probably due to the transitioning circulation in preterm neonates in whom patent ductus arteriosus is not uncommon. Also, the choice of probe site may be difficult in

sick preterm infants. These infants have intravenous lines for fluid infusion or heparin locks for medication infusions on the dorsum of the hands and the feet. Following various studies on probe placement for oximetry in neonates, one needs to pay attention to the limb of measurement when interpreting PI values (27).

2.3 Physiology of Transitional Circulation in Newborns

The transition to life after birth is characterized by major physiological changes in respiratory and hemodynamic function, which are predominantly initiated by breathing at birth and clamping of the umbilical cord (28). This is characterized by changes in circulatory pathways, initiation of ventilation and oxygenation via the lungs instead of the placenta and many changes in metabolism. Some of these changes include:

- Increased systemic vascular resistance with separation from the low-resistance placental vasculature
- Closure of right-to-left shunts
    - Foramen ovale (closes when left atrial pressure greater than right atrial pressure)
    - Ductus arteriosus (left-to-right flow within minutes of ventilation, then closure over days)
- Rapid lowering of pulmonary vascular resistance with onset of ventilation
- Clearance of fluid from airways via active sodium absorption and changes in airway pressure due to ventilation
- Increased metabolic rate leading to higher glucose needs
- Increased catecholamine levels to support blood pressure

The production and release of catecholamines, renin-angiotensin and vasopressin during the birth process is important for the increase in cardiac output that occurs postnatally. Preterm neonates have a slower rise in catecholamine levels but plateau at serum concentrations higher than those found in term infants. Interestingly, compared to the fetus, term neonates have lower thresholds of catecholamine concentrations necessary to produce changes in blood pressure, serum glucose, and free fatty acids, which are necessary for the transition to the extra-uterine environment (28).

Our understanding of the nuanced cardiovascular changes that occur at birth has been advanced by new, non-invasive methods for assessing local perfusion and oxygenation. These include the

perfusion index as a marker of peripheral perfusion and near infrared spectroscopy as a marker of cerebral perfusion. At birth, a consistent PI was observed in healthy term infants and values were higher when compared to infants with sepsis (PI at 1 min 4.50 ± 0.83 vs. 1.74 ± 0.32 and at 5 min 4.42 ± 2.10 vs. 2.18 ± 1.02) (De Felice et al., 2002).

2.4 Physiology of Microcirculation in Sick Neonates

Changes in microcirculation have been recognized as central to many disease processes. Disturbances of the microcirculation play a key role in many disease states.

The microcirculation of the skin in neonates differs in several aspects from that of an adult. The regular architecture has been found to be poorly developed in the newborn (29). At birth, the skin shows a disorderly capillary network and no papillary loops in almost all areas, except the palms, soles and nail folds. The skin is richly supplied by a dense subepidermal plexus demonstrating relatively little regional variation (30). A study by Kroth et al in 2008 compared very preterm infants (gestational age <26 weeks) with preterm neonates (gestational age >28 weeks) (31). They did not find any differences between the two groups in the first month of life with regard to diameter, red blood cell velocity and vessel density. The conclusion was that during the first month of life, gestational or postnatal age do not influence microcirculatory parameters of the skin in preterm infants (31).

It is increasingly being noted that a key component of the peripheral vasculature, the microvasculature, has a significant influence on the overall function of the peripheral vasculature. The microvasculature, as opposed to the macrovasculature, is very important in the delivery of oxygen and nutrients to the tissues of the entire body. Additionally, the flow within the microvasculature reflects the combined action of the central, macro hemodynamic components of the circulation and thus the end point of total cardiovascular efficiency.

The skin has some very specialized microvascular functions and is the most easily accessible site in neonates with regard to monitoring peripheral perfusion. Despite skin blood flow demonstrating a variety of adaptive responses such as thermoregulation, it is part of the wider microcirculation. Evidence has been drawn from animal literature and observational data in human neonates, although the relationship between peripheral microvascular blood flow and measures of neonatal physiologic and cardiovascular stability in the immediate postnatal period had not been

characterized until recently (31). There is emerging evidence that the changes in early microvascular flow are of clinical significance. Laser doppler flowmetry measurements of peripheral microvascular blood flow have been shown to exhibit significant relationships with both clinical illness severity using neonatal scoring systems together with measures of cardiovascular function in particular blood pressure in preterm infants during the first days of postnatal life.

2.5 Theoretical and Conceptual Framework

Disease severity amongst term and preterm neonates can be assessed using the SNAPPE-II score. The perfusion index has been found to correlate to disease severity scores amongst preterm neonates using CRIB II scores. The use of PI in assessing disease severity amongst both term and preterm neonates as well its relationship with the SNAPPE-II score is yet to be described.

SNAPPE II score and Perfusion index are independent variables which are used to characterize neonatal disease severity (Figure 1).

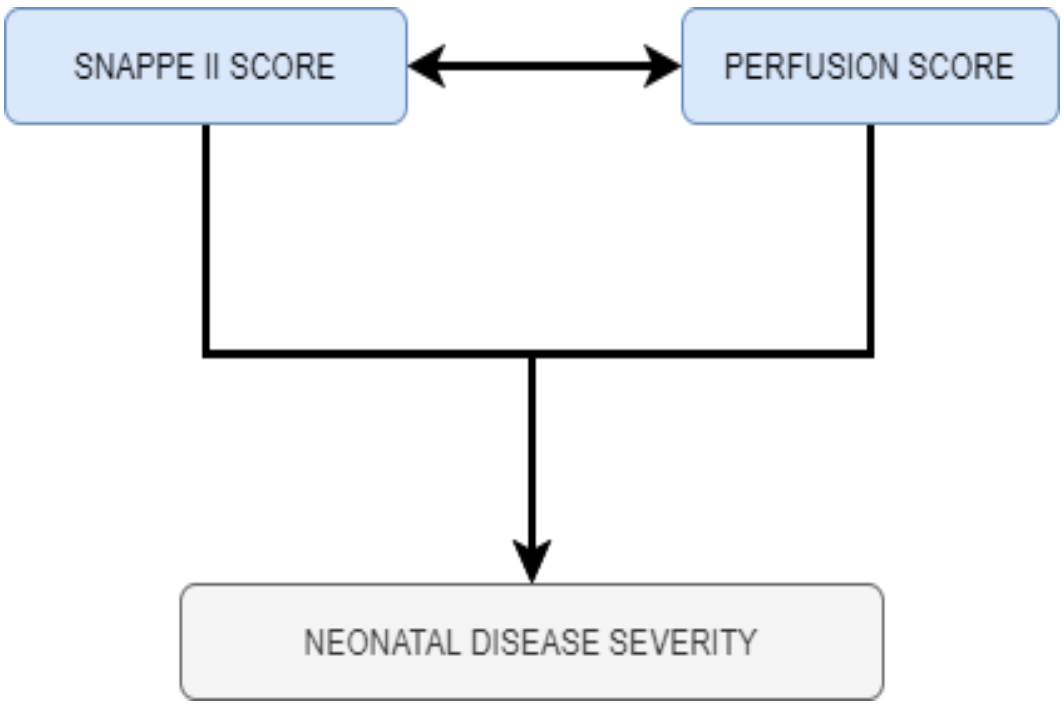

Figure 1: Conceptual framework of the relationship between perfusion index and SNAPPE II

2.6 Problem Statement

Neonatal morbidity and mortality are a devastating burden to healthcare systems and families of hospitalized neonates. Severity scoring of neonatal illness is useful in prompting quick therapy. While severity scoring systems exist for neonatal illness, their utility in practice is limited by their complexity. The need for simple, quick and objective measures of disease severity cannot be overstated. While the use of pulse oximetry is widespread in clinical practice, the use of its derivatives such as the PI to characterize disease severity is limited. This is partly due to the paucity of information regarding its relationship with neonatal disease severity. This study therefore aims to investigate the relationship between the PI and a validated score for neonatal illness severity, the SNAPPE-II score.

2.7 Justification and Significance

Early recognition of severe illness and a high index of suspicion for the same is needed for timely intervention. Prompt initiation of treatment prevents further morbidity and mortality. Delayed recognition of high-risk neonates and lapses in monitoring of clinical status has a profound effect on prolonged morbidity, hospital stay, and worsened outcomes. A simple, quick, objective and reproducible way of assessing the severity of illness and risk of mortality in newborn units will help in:

- Prioritizing specialized care as needed and identifying high-risk neonates
- Reduction of time between recognition of illness and intervention

Despite the widespread use of pulse oximetry in in-hospital settings, its use in evaluating disease severity remains limited. The PI, obtained from pulse oximetry, is a quick objective and easily reproducible measure. Further, in comparison to neonatal severity scores, these qualities of the PI make it a potential rapid measure of assessment of the severity of neonatal disease. Establishing further clarity in the relationship between PI and disease severity in neonates could provide a guide to the potential expanded utilization of plethysmographic indices in neonatal triage. Further, the objectivity, simplicity, and reproducibility of the PI would find ease in adoption in a low resource setting.

2.8 Research Question

2.8.1 Research question:

What is the relationship between the perfusion index and SNAPPE-II score in neonates admitted to Kenyatta National Hospital NBU?

2.9 Objectives

2.9.1 Broad Objective

To investigate the relationship between the perfusion index and SNAPPE-II score in neonates admitted to Kenyatta National Hospital NBU.

2.9.2 Specific Objectives

1. To determine the perfusion index of neonates admitted to KNH NBU.
2. To determine the SNAPPE-II score of neonates admitted to KNH NBU.
3. To determine the relationship between the perfusion index and SNAPPE-II score in neonates admitted to KNH NBU.

2.9.3 Secondary Objective

To propose cut-off values for Perfusion Index in different subgroups of neonates.

3.0 CHAPTER THREE: METHODOLOGY

3.1 Study Design

This was a descriptive cross-sectional study. The study site was the Kenyatta National Hospital, Newborn Unit.

3.2 Study Setting

KNH is the largest national referral facility in Kenya and is affiliated to the University of Nairobi College of Health Sciences as a teaching hospital. The newborn unit of the hospital receives babies born within the hospital and those referred from other hospitals in Nairobi and other parts of Kenya that require specialized care. On average, there are about 300 admissions to the unit every month. This unit comprises an admission area, a six-bed neonatal intensive care unit, high dependency unit, rooms with incubators and cots for the care of the preterm babies stratified by birth weight, an isolation room, and a room for stable babies awaiting discharge.

3.3 Study period: The duration of the study was 6 months, from April to October 2021.

3.4 Study Population

The study population included term and preterm neonates admitted in the newborn unit at KNH.

3.4.1 Inclusion Criteria:

1. Newborns admitted to the newborn unit. This study derived its sample from newborns admitted in the newborn unit of the Kenyatta National Hospital.
2. Newborns whose parents had given consent to participate in the study. Since participation is voluntary, only those whose parents consented were included in the study.

3.4.2 Exclusion Criteria

1. Neonates undergoing therapeutic hypothermia. Hypothermia affects the amplitude of the PI wave and therefore would produce artifacts and affect the validity of the measurements taken.
2. Neonates in whom it was not possible to determine SNAPPE II score due to incomplete records such as missing birth weight and APGAR scores.

3. Neonates with multiple congenital anomalies. Neonates especially with cardiopulmonary malformations may have altered hemodynamics that would have affected the PI.

3.5 Sampling and Sample Size Determination

3.5.1 Sampling Technique

Consecutive sampling of neonates whose parents gave consent to the study was used.

3.5.2 Sample Size Determination

The sample size was calculated using Cochran's formula (32);

$$n = \frac{Z^2 x\ (1 - P)}{d^2}$$

Where,

n = Desired sample size and Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected proportion of neonates with severe neonatal illness- at KNH NBU. A study conducted by Marete. et al (2011) established an 11% proportion of severely ill neonates assessed using CRIB II score.

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.11(1 - 0.11)}{0.05^2} = 150$$

3.6 Study Procedure and Data Collection

3.6.1 Participant recruitment and consenting procedure

The investigator visited the KNH NBU every day between 12 pm and 6 pm for the duration of the study. The registrars rotating in NBU were informed of the study and the investigator took details of newborns from the admission register. Whenever a newborn was admitted, the admitting resident on the floor informed the investigator who then approached the mother to obtain informed consent. The mother was reassured of her and her baby's privacy and confidentiality being maintained and that there were no untoward risks to her baby participating in the study. She was also told that participation was entirely voluntary and that if she declined, her child would still

receive treatment as planned. For the mothers who declined to participate in the study, no consent was signed and she was thanked and her child excluded from the study. The mother who agreed to her child's participation in the study was thanked and the consent form was explained to her. She was then asked to read and sign the consent form. If unable to read, the investigator explained the contents of the consent form in entirety prior to her thumbprint appended to the form. (Appendix 3).

Patient Flow Chart

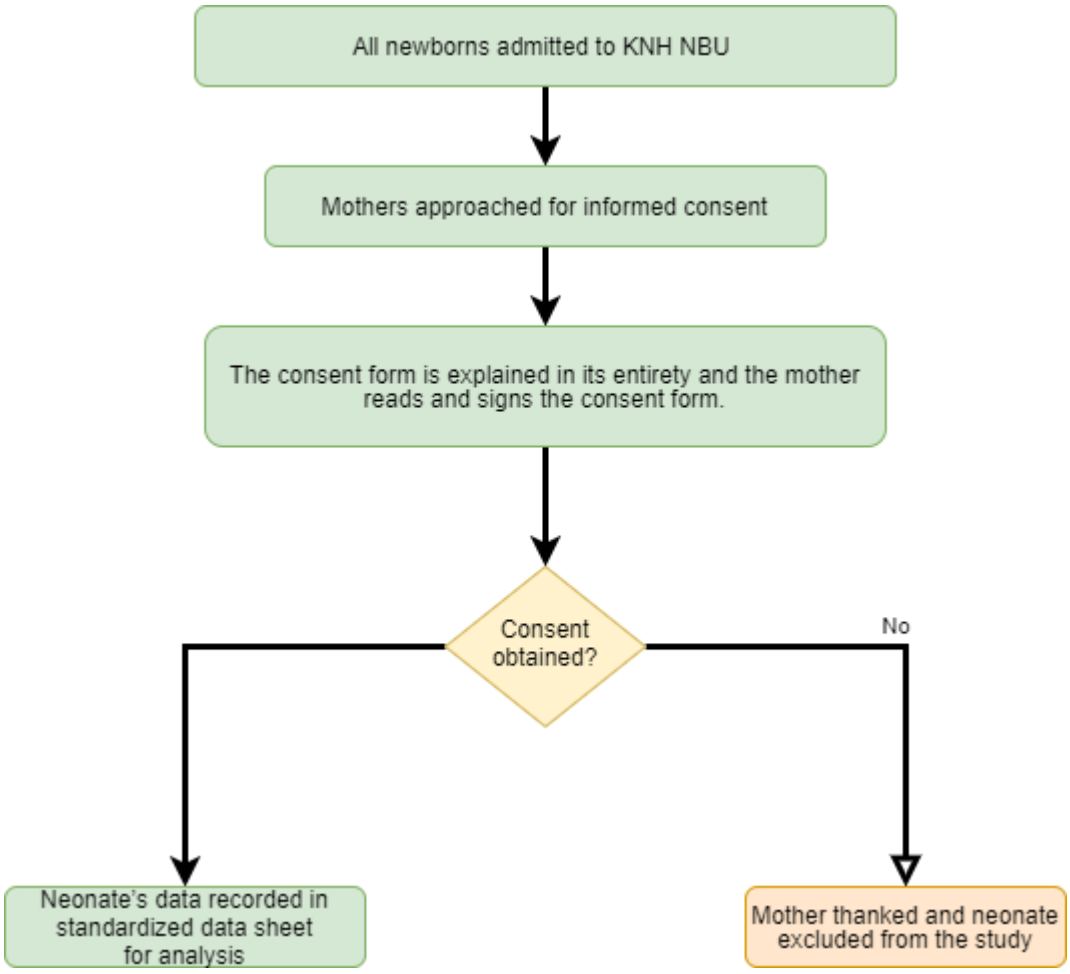

Figure *2*: Patient flow and recruitment in the study

3.7 Data Collection

A standardized structured data sheet (Appendix I) was used in the collection of quantitative data. This included anthropometric, laboratory, and physiological parameters recorded within 24 hours of admission.

3.7.1 Determination of SNAPPE-II Scores

The SNAPPE-II score parameters of eligible neonates were recorded by a trained research assistant within 24hours of admission in tandem with PI measurement done by the investigator who was unaware of the SNAPPE II score. Noninvasive mean blood pressure in (mmHg) was measured with the use of appropriate neonatal cuff size in the left or right arm using a portable Contec™ monitor. An average of three blood pressure readings was recorded. The temperature was measured using a digital thermometer by keeping it for 3 minutes in the axilla. Serum pH and PaO2/FiO2 were calculated from arterial blood gas analysis (ABG) readings obtained from an ABG and electrolytes analyzer ABL 800 FLEX Radiometer™ available in the critical care unit of the hospital. All types of neonatal seizures were included in the calculation of the SNAPPE-II score. Birth-weight of neonates born at KNH was measured by an electronic weighing machine (±5 g error) without clothing. Birth-weight of outborn neonates was recorded from the details indicated on the referral notes. The documented APGAR score record from the delivery unit was used. Urine output (ml/kg/hr) was obtained from catheterization and/or diaper weighing as applicable. Modified Ballard score was used to assess the gestational age. International intrauterine growth chart was used for classification as small for gestational age as birth weight < 10th percentile for gestational age. Treatment of the neonates was continued as per the hospital protocols.

3.7.2 Measurement of Perfusion Index

Perfusion index was recorded within 24 hours of admission using a Masimo SET Radical-7 pulse oximeter, with the probe connected to the right upper limb (preductal) attached to the index and middle finger of the right hand. PI values were taken by the investigator who was unaware of the illness severity scores. The PI was obtained after the pulse wave was verified to be artifact-free, 20 s every minute for 10 minutes. An average of the readings was done. The application of the probe did not affect the baby's environment or other therapeutic interventions. The neonates

remained in a thermoregulated environment in the newborn unit during the PI measurement. The body temperature at the time of PI measurement was also recorded.

3.8 Quality Assurance Procedures

The research proposal was developed with input from supervisors who are well equipped in neonatology. It was reviewed by the Department of Pediatrics and Child Health and final approval to conduct the study was given by the KNH-UoN ERC.

Perfusion Index was measured using signal extraction technology (SET) pulse oximeter. This is able to pick the pulse oximeter waveform through low perfusion states and movement artifact (shiver) as long as the signal quality index (SQI) is met.

The investigator examined the recruited neonates and recorded relevant data herself with assistance from one research assistant. The investigator was working under close supervision from supervisors.

3.9 Ethical Considerations

Ethical approval was sought and given by the Kenyatta National Hospital/University of Nairobi Ethics Review Committee (KNH-UoN ERC). Permission was also sought from KNH administration prior to commencement of study. Participation in the study was on a voluntary basis and consent for recruited neonates was sought through a signed informed consent form. The child's name or parent's details did not appear in the data sheets to protect the child's identity and privacy. The data sheets were stored in a locked drawer and then subsequently keyed in. Data were stored in a password-protected computer with access limited to the investigator. The statistician only accessed coded data for analysis. The consent form was translated to Kiswahili for parents who do not understand English. For those parents who could not read, the consent form was read to them in entirety by the investigator to ensure understanding prior to obtaining their thumbprint sign. Measures to prevent COVID-19 transmission were put in place as the study was conducted. This was done in coordination with the infection prevention control team at KNH. The measures included standard, airborne, droplet, and contact precautions.

3.10 Data Management and Statistical Analysis

Data were cleaned, coded, entered into R Studio and Microsoft Excel. Descriptive statistics using mean and SD for the normally distributed continuous variables, median with interquartile ranges for nonparametric data, and percentages for the categorical variables were used. Correlation between PI and SNAPPE-II score was assessed using Pearson's correlation. A p-value <0.05 was considered statistically significant. Linear regression of the relationship between PI and SNAPPE II scores was done to derive an equation describing the relationship. Receiver operating curves were plotted and the area under the curve was calculated to determine the predictive value of the PI on disease severity. Results are presented using frequency tables and graphs.

3.11 Study Results Dissemination Plan

The investigator ensured proper documentation of SNAPPE-II disease severity scores and the perfusion indices of neonates in KNH NBU. The individual data obtained was stored carefully and feedback was given to the respective parent in collaboration with the attending clinical team to help with decision-making in patient management. The results compiled thereof were submitted to the Department of Paediatrics and Child Health of the University of Nairobi. These shall be presented as a poster to the faculty at the conclusion of the study. Copies of the dissertation shall also be sent to the University of Nairobi library repository for cataloging and storage. The investigator shall also seek channels to share the results with the Department of Paediatrics at KNH as well as the Division of Child Health. The investigator shall also seek to publish the findings of this study in peer-reviewed journals.

4.0 CHAPTER FOUR: RESULTS

4.1 Study Participation

One hundred and sixty-eight neonates were screened for the study. Of these, twenty-nine were excluded; fourteen due to incomplete records, eleven due to multiple congenital defects and four due to declined consent. The targeted sample size of one hundred and fifty neonates was not reached due to low admission numbers in the newborn unit during the study period as an effect of the COVID 19 pandemic. Therefore, a total of one hundred and thirty-nine neonates were considered eligible for the study and their data analyzed (Figure 3).

Study flowchart

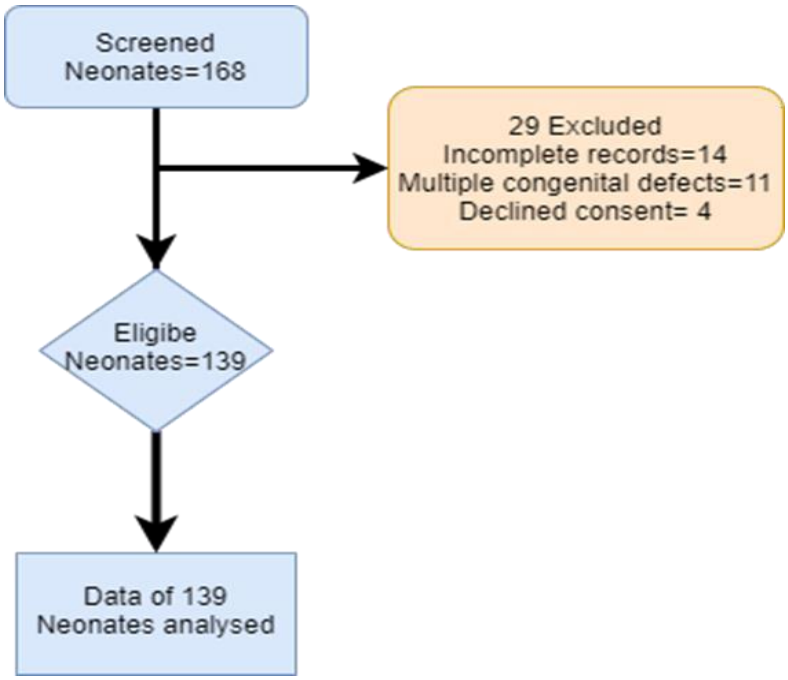

Figure 3: Flow of Study Participants in the Study

4.2 Clinical Characteristics of Neonates Recruited into the Study

There was an almost equal distribution across gender with 51.2% of the neonates being female and 48.2% being male neonates. Moreover, 53.2% of eligible participants were delivered by spontaneous vertex delivery (SVD) while 48.2% were delivered by Caesarean section (C/S). Preterm neonates accounted for 43.1% while term neonates accounted for 56.8%.

The birth weight of the neonates was from 800grams to 4000grams with a mean of 2434.31±865.86. Neonates across all birthweights were included. The gestational age was from 26 to 41 weeks with a mean of 35.91±4.08 weeks. The median and interquartile range for post-natal age at enrollment was 1 day (1-4) while the mean postnatal age at enrollment was 4.11±2.06 days. Table 1 shows the mean birth weight, gestational age, and enrollment ages of participants in the study.

Table 1: Gestational age, weight, and age at enrollment of neonates in the study

Characteristic	**Mean**	**SD**	**Median**	**IQR**
Birthweight	2434.31	865.86	2600	1520-3100
Gestational age (weeks)	35.91	4.08	38	32-39
Age at enrollment (days)	4.11	2.06	1	1-4

The commonest diagnosis amongst the recruited neonates was neonatal sepsis (42.4%) followed by respiratory distress syndrome (38.8%). A further 8.6%, 6.5%, and 2.2% had perinatal asphyxia, prematurity, and neonatal jaundice respectively. Other diagnoses such as neonatal meningitis and meconium aspiration contributed to 1.4%. (Figure 4)

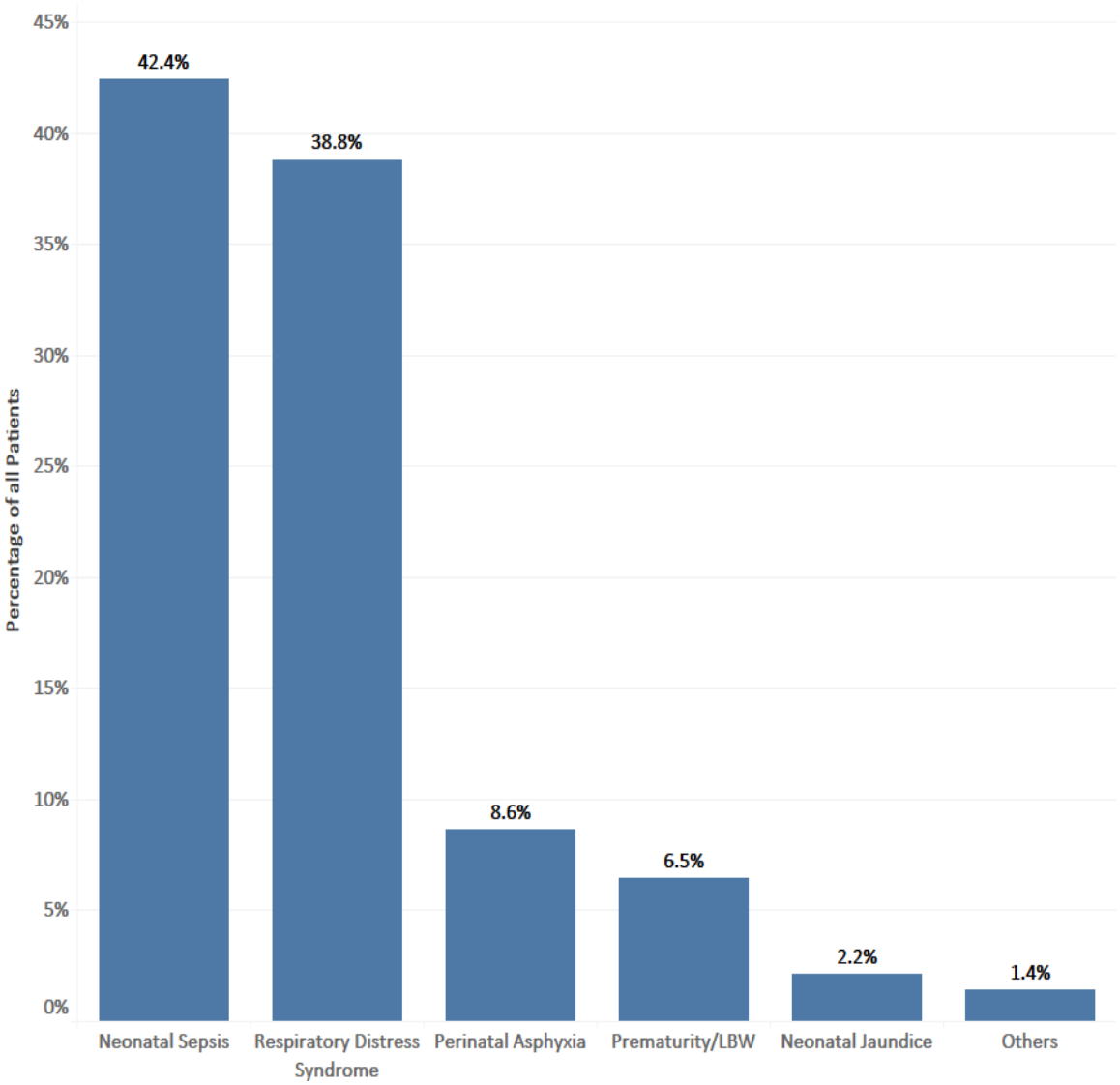

Figure 4: Distribution of diagnoses of neonates recruited into the study

4.3 SNAPPE II Score

The median SNAPPE II score obtained was 32, with an interquartile range of 16 to 56 (range 0-117). The SNAPPE II score was further analyzed to show classes of severity: There were 45(32%) neonates with mild (0-20) scores, 39(28%) with moderate (20-40) scores, and 55(40%) with severe (>40) scores.

Mean arterial pressure ranged from 24 mmHg to 42mmHg with a mean 39.28±8.64mmHg. Lowest body temperature in 24hrs ranged from 35.1℃ to 38.6℃ with a mean 36.8±1.04℃. The mean PO2/FiO2 ratio was 1.47±0.90, while mean serum pH was 7.29±2.4. The various parameters included in the SNAPPE II score are summarized in table 2 below.

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Table 2: SNAPPE II Parameters recorded in the study

VARIABLE	SNAPPE II CLASSIFICATION	FREQUENCY (n=139)
Mean Blood Pressure	>29mmHg (0 points)	101
	20-29mmHg (9 points)	34
	<20mmHg (19 points)	4
Lowest corporal temperature in 24 hours	>36.5℃ (0 points)	124
	35-36.5℃ (8 points)	12
	<35℃ (15 points)	3
Birth weight	>999grams (0 points)	135
	750-999grams (10 points)	4
	<750g (17 points)	0
Small for gestational age (<3rd percentile)	No (0 points)	129
	Yes (12 points)	10
PO2/FiO2 ratio	>2.49 (0 points)	22
	1-2.49 (5 points)	48
	0.3-0.99 (16 points)	62
	<0.3 (28 points)	7
Lowest serum pH	>7.19 (0 points)	97
	7.10-7.19 (7 points)	30
	<7.10 (16 points)	12
Urine output	>0.9ml/kg/hour (0 points)	74
	0.1-0.9ml/kg/hour (5 points)	43
	<0.1ml/kg/hour (18 points)	23
Multiple seizures	No (0 points)	98
	Yes (19 points)	41
Apgar score at 5 minutes	>7 (0 points)	95
	<7 (18 points)	44

4.4 Perfusion Index

The mean perfusion index measured in the study was 0.90±0.14. The perfusion index ranged from 0.57 to 1.43. The median perfusion index value was 0.84 with an interquartile range of 0.81 to 0.95. The mean perfusion index for neonates whose birthweight was more than 1000 grams was 0.95±0.22 while the mean perfusion index for those whose birth weight was less than 1000 grams was 0.89±0.14. The range of measured body temperature during the recording of the PI was 35.0-38.5, with only 3 neonates with hypothermia due to illness. A multivariate analysis showing mean perfusion indices in the different subsets of neonates stratified per the SNAPPE II score are summarized in table 3 below.

Table 3: Perfusion index in different cohorts of neonates as classified by SNAPPE II parameters

VARIABLE	SNAPPE II CLASSIFICATION	MEAN PI±SD
Mean Blood Pressure	>29mmHg (0 points)	0.93±0.16
	20-29mmHg (9 points)	0.85±0.06
	<20mmHg (19 points)	0.69±0.11
Lowest corporal temperature in 24 hours	>35.6℃ (0 points)	0.92±0.16
	35-35.6℃ (8 points)	0.85±0.11
	<35℃ (15 points)	0.85±0.10
Birth weight	>999grams (0 points)	0.95±0.22
	750-999grams (10 points)	0.89±0.14`
	<750g (17 points)	-
Small for gestational age (<3rd percentile)	No (0 points)	0.90±0.15
	Yes (12 points)	0.83±0.08

PO2/FiO2 ratio	>2.49 (0 points)	0.97±0.15
	1-2.49 (5 points)	0.96±0.18
	0.3-0.99 (16 points)	0.87±0.11
	<0.3 (28 points)	0.86±0.04
Lowest serum pH	>7.19 (0 points)	0.93±0.16
	7.10-7.19 (7 points)	0.85±0.08
	<7.10 (16 points)	0.78±0.09
Urine output	>0.9ml/kg/hour (0 points)	0.91±0.12
	0.1-0.9ml/kg/hour (5 points)	0.93±0.19
	<0.1ml/kg/hour (18 points)	0.81±0.09
Multiple seizures	No (0 points)	0.93±0.15
	Yes (19 points)	0.82±0.09
Apgar score at 5 minutes	>7 (0 points)	0.94±0.15
	<7 (18 points)	0.81±0.09

4.5 Relationship between Perfusion Index and SNAPPE II Scores

A moderate, statistically significant ($p<0.0001$) negative correlation was observed between PI and SNAPPE II scores (Figure 5). The figure below shows a linear regression plot that was done and a line of best fit determined. The direction of the slope was top left to bottom right indicating an inverse relationship between PI and SNAPPE II scores. Pearson correlation was done and a coefficient of -0.56 was determined which showed a moderate association. Linear regression between SNAPPE II scores and mean perfusion indexes was done to derive the following equation:

$$SNAPPE\ II\ SCORE = 130.3 - 103.3 \times MEAN\ PI$$

Using this equation, it is possible to quickly predict the SNAPPE II score when a measured PI value is available and substituted in the formula.

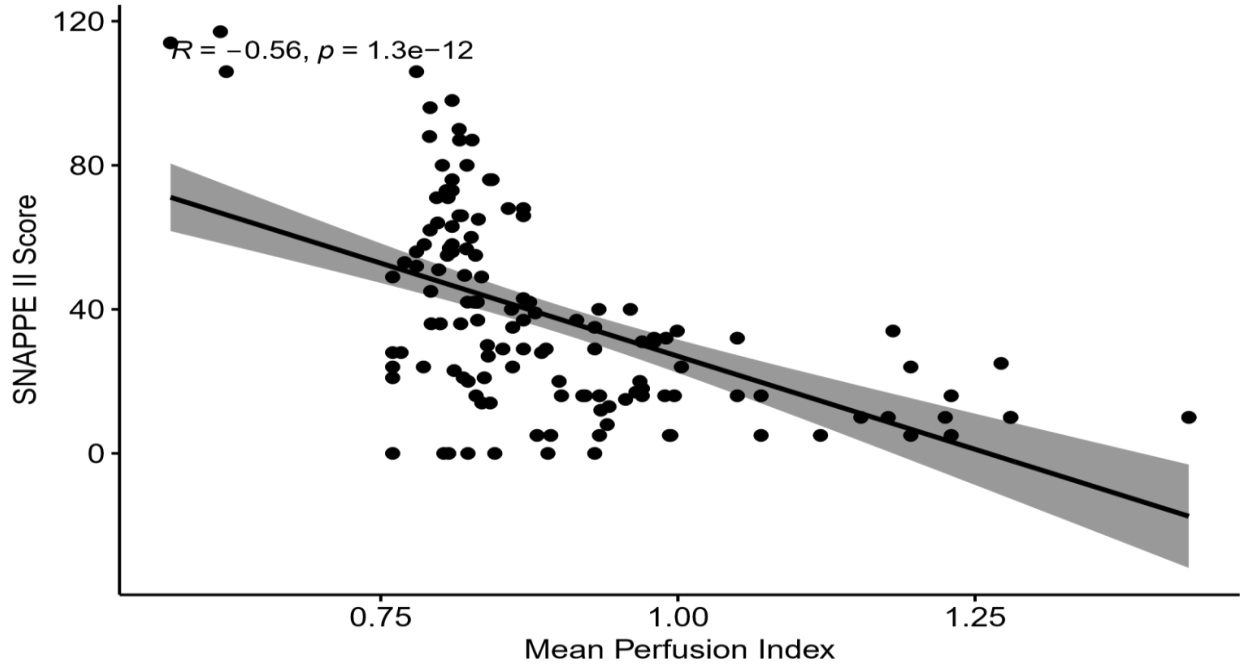

Figure 5: Relationship between SNAPPE II and perfusion index

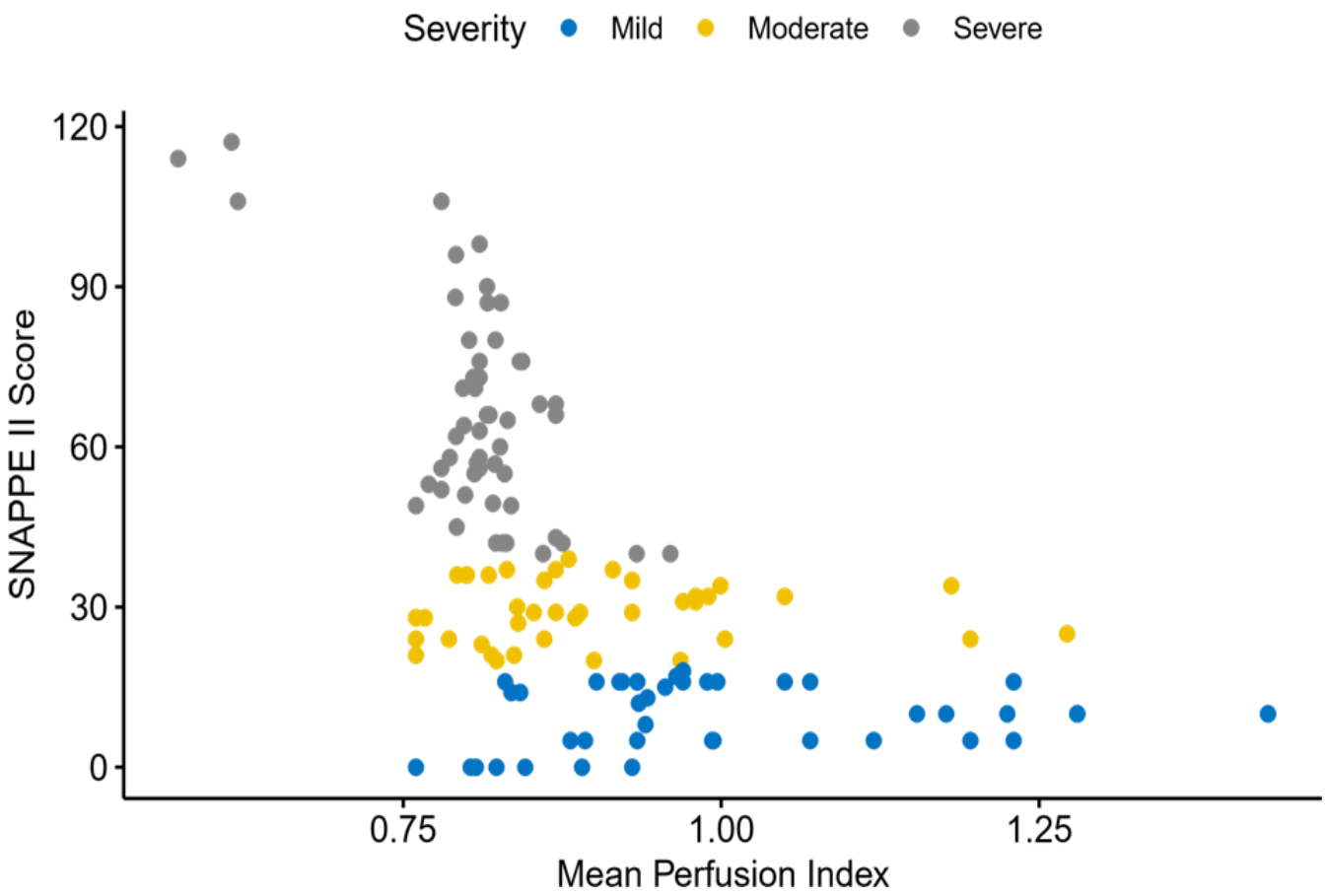

Figure 6: Distribution of mean perfusion indices compared to disease severity classified by SNAPPE II scores

The blue cluster of dots represents the SNAPPE II scores between 0-20 indicating mild illness, the yellow cluster represents SNAPPE II scores of 20-40 indicating moderate illness and the grey cluster represents SNAPPE II scores of >40 indicating severe illness (Figure 6). The high illness severity group shows clustering around lower mean perfusion indices while mild illness severity group shows clustering towards higher mean perfusion indices. This visualizes the different classes of severity of illness as per SNAPPE II score and their inverse relationship with mean PI.

4.6 Proposed Cut off Values for Pi

Receiver operating curves to assess the predictive utility of PI for disease severity showed acceptable sensitivity and specificity in predicting mild and severe disease. However, PI had low sensitivity in predicting moderate disease (Figure 7).

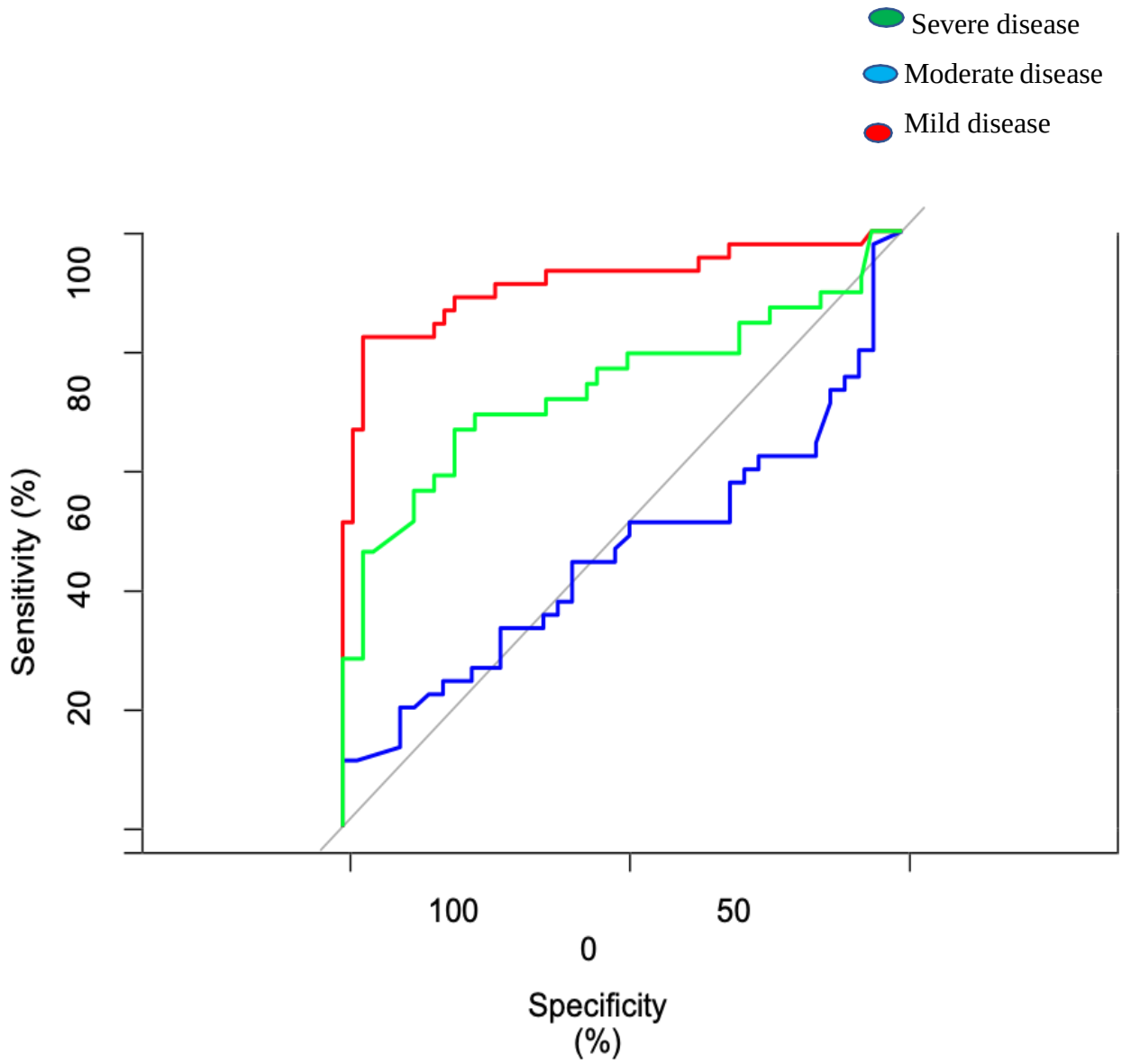

Figure *7*: Receiver operating curve showing the predictive value of PI in disease severity

In figure 7, the red curve represents mild disease with proposed cut off for P.I >= 0.88 with AUC = 0.915, (Sensitivity = 68.9% and Specificity = 84.0%). This showed good discrimination for mild disease with high specificity and good sensitivity. The blue curve represents moderate disease with proposed cut off for P.I >= 0.83-0.875 (AUC = 0.458, Sensitivity = 17.9% and Specificity = 89.0%). There was low sensitivity and discrimination was not good for moderate disease but the negative predictive value was high. The green curve represents severe disease with proposed cut off for P.I < 0.83 (AUC = 0.738, Sensitivity = 87.3% and Specificity = 67.9%). There was good discrimination for severe disease with high sensitivity and good specificity. The positive predictive value for mild disease was 67% with a negative predictive value of 85%. In moderate disease, the negative predictive value was 74% with a positive predictive value of 39%. Severe disease had a positive predictive value of 64% with a negative predictive value of 90%. Across all the classes of illness severity, the perfusion index had a good negative predictive value.

4.6.1 Decision Tree

A decision tree with proposed cut-off values was derived. A mean PI less than 0.88 suggested moderate or severe disease while a mean PI of more than 0.88 indicated mild disease. A mean PI less than 0.83 had good discrimination for severe disease. Because of the low sensitivity of the PI in predicting moderate disease, there wasn't good discrimination and moderate disease corresponded to a mean PI between 0.83-0.86.

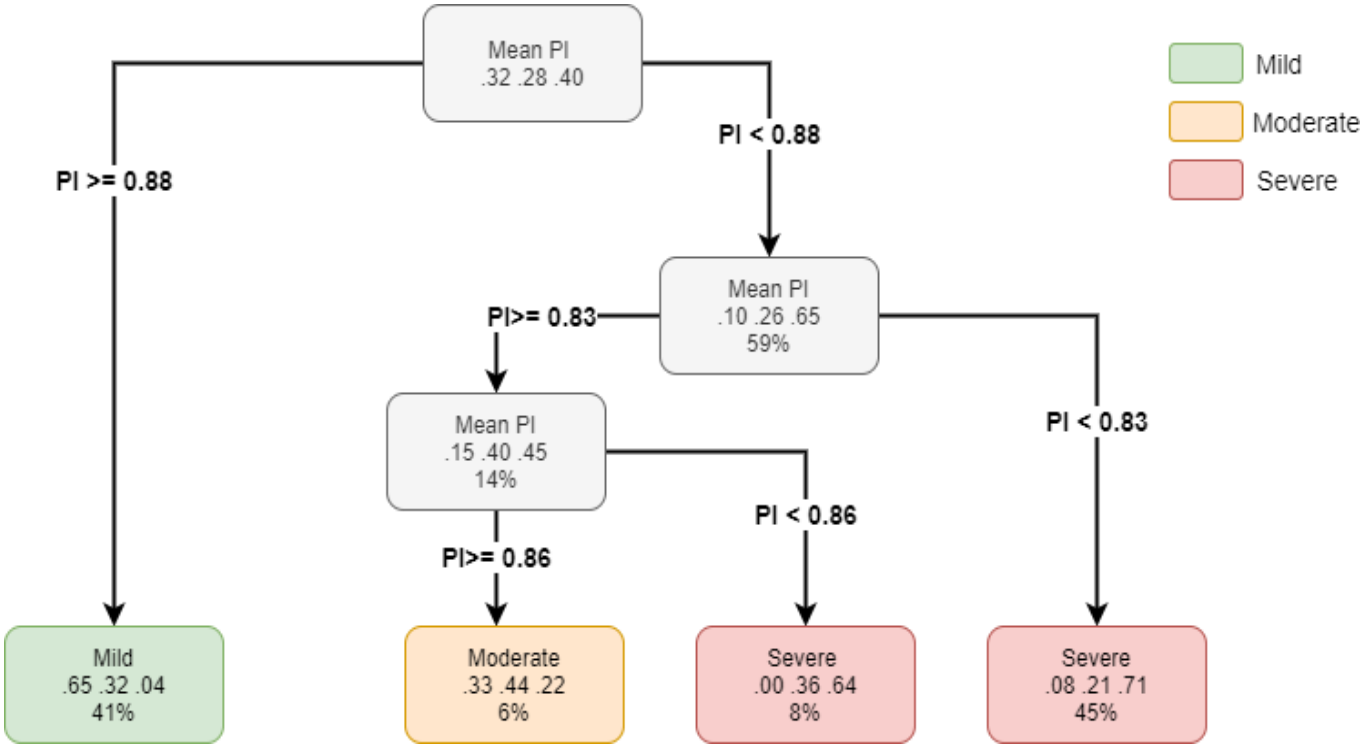

Figure 8: Decision tree using mean PI to classify disease severity

5.0 CHAPTER FIVE: DISCUSSION

This study sought to determine the SNAPPE II scores and perfusion indices of neonates admitted to the KNH NBU and determine the relationship between these two variables. The secondary aim of the study was to propose cut off values for different subgroups of neonates. The relationship thereby would establish possible utility of the PI in assessing for neonatal disease severity. The salient observations in this study include; a moderate negative correlation between PI and SNAPPE II, lower PI in sicker neonates and acceptable sensitivity and specificity of the PI in predicting mild and severe illness.

5.1 Perfusion Index in Neonates Admitted in KNH NBU

The PI of neonates admitted in the KNH NBU ranged from 0.57 to 1.43±0.14 SD. This was lower than predicted physiological PI ranges. Normal PI has been reported to range from 1.99 to 2.38 in healthy neonates born at 35 weeks onwards (33). The mean PI recorded in the present study was also lower than the mean PI recorded by Hakan et al., (2014).

The difference in the recorded PI could be due to the inclusion in the current study of neonates with lower gestational ages as well as the fact that neonates in the current study had varied illnesses. The range of gestational ages in this study was 26 to 44 weeks. Hakan et al., (2014) studied the PI of healthy neonates with gestational ages more than 32 weeks (34).

The PI ranges for preterm neonates in this study were lower compared to term neonates and this concurs with other studies that have shown lower PI values recorded in preterm infants compared to term infants (25,35).

The lower PI ranges recorded also reflected the severity of illness of the neonates who were recruited into this study. The majority of the neonates in this study had a primary diagnosis of neonatal sepsis and needed specialized care in the high dependency unit and NICU. These neonates were classified as severely ill and had lower recorded perfusion indices. A decreased PI is a feature of severe illness in neonates (5,12,13). When assessed in tandem with other parameters such as pulse rate, oxygen saturation and urine output, the PI can provide a measure of worsening perfusion and hence, disease progression (13). This has been demonstrated in neonates born to mothers with subclinical chorioamnionitis (36).

PI reflects the circulatory changes that occur in hypovolemia and in low cardiac output states such as shock. In these states, redistributed blood flow shunts blood to critical organs, reducing perfusion to peripheral organs like the skin (5). A newborn's skin perfusion is high compared to oxygen demand when they are not undergoing any stressful events. In severely ill neonates, the peripheral perfusion is related to the redistribution of cardiac output and oxygen supply to major organs, consequently affecting peripheral perfusion as seen in this current study where lower PI's were seen in the sicker neonates (12).

Peripheral vasoconstriction results in a reduced proportion of pulsatile flow peripherally. This is then evident clinically in signs of cold, pale, and clammy skin, prolonged capillary refill time, and, as observed in the current study, reduced PI (24). The PI can therefore plausibly be a useful marker of the adequacy of peripheral perfusion as it reflects both global changes in blood flow shunting and local vasoconstriction. This current study attempted to propose cut off values especially for mild and severe disease.

In this current study, the preductal site was chosen as the monitoring site and results obtained indicated that lower PI values were consistent with neonates, both term and preterm, who had severe illness. The perfusion index can be monitored from various sites, the right upper limb gives preductal values while values obtained from the feet are postductal values. Balla et al in 2016 studied the difference in preductal and postductal perfusion index values in preterm neonates as a surrogate marker for diagnosing hemodynamically significant patent ductus arteriosus(26). These workers postulated that if ductus arteriosus were to steal a large volume of left ventricular output, it would be at the cost of systemic distal perfusion and thereby reflected in PI. When pre-ductal and post-ductal sites are monitored for perfusion, a difference could give an indication of hemodynamic significance. In that study, the PI in the lower limb was found to be lower than pre-ductal PI. This fact is probably due to the transitioning circulation in preterm neonates in whom patent ductus arteriosus is not uncommon (26).

Piasek et al in 2014 suggested that monitoring perfusion index as a trend is more useful in critical care settings to reflect the changing hemodynamic status of the sick neonates(12). In this current study, the lower PI values that correlate with higher illness severity when monitored as a trend would add value to the clinician's view of the neonate's state. Subtle changes in perfusion are often

missed by static displays, but monitoring PI provides the ability to trend and so capture these changes as they take place.

5.2 SNAPPE II Scores of Neonates Admitted in KNH NBU

SNAPPE II Scores ranged from 0 to 117 with a median score of 32 and an interquartile range of 16-56. There were 45(32%) neonates with mild (0-20) scores, 39(28%) with moderate (20-40) scores, and 55(40%) with severe (>40) scores.

The range of SNAPPE II scores reflected the severity of illness of the neonates admitted in the KNH NBU from analysis of data from 139 neonates in this current study. This was similar to results from a study done by Muktan et al in Nepal, where the best cut off score for predicting mortality was 38, with high sensitivity and specificity (11).SNAPPE-II score was significantly higher among neonates who died compared to those who survived [median (IQR) 57 (42–64) vs. *22* (14–32), $P < 0.001$. In the same study, neonates with a SNAPPE II score of 40 to 60 had a mortality rate of 36.7%, a score of ≥40 had mortality rate of 55.1% and a score of ≥60 had 100% mortality thus showing that the higher the SNAPPE II score, the sicker the neonate and the worse the outcome.

The results from the current study differed from a study done in a tertiary NICU (9) where SNAPPE II score was used to classify illness severity. They found that, out of 116 babies, 56 (48%) had mild SNAPPE-II score, 44 (38%) had moderate score and 16 (14%) had severe score. This difference could be attributed to their recruitment of newborns within 48hrs of birth and also the smaller sample size used in that study.

This current study employed the SNAPPE II scoring system in grading neonates according to illness severity. The original SNAP score which had 34 physiological variables was revised over the years to a simpler SNAPPE II score which has been validated and used worldwide in NICU's to classify illness severity. SNAPPE-II had excellent discrimination and goodness of fit. Area under the receiver operator characteristic curve was.91 ± 0.01. Goodness of fit (Hosmer-Lemeshow) was 0.90 (8). The SNAPPE II score has also been revalidated and has shown consistency even with advances in neonatal care since its initial validation (20).

Results from this current study were different from data on illness severity by Marete et. al (2011). Stratifying neonates into severity levels using CRIB II, these workers found 61% as Level I, 28% as level II, and 11% as level III with the higher levels indicating more severe disease and poorer outcomes (6). The difference in the disease severity prevalence could be due to the different scoring system used in the present study. Although both CRIB II and SNAPPE II are the latest validated neonatal disease severity scoring systems worldwide, SNAPPE II was the preferred scoring system for use in the current study so as to include neonates of all birthweights. Al-Akhd and colleagues have compared CRIB II and SNAPPE II scores and found that the sensitivity and accuracy in predicting neonatal mortality was good for both scoring systems but slightly higher in SNAPPE II score (19).

Higher SNAPPE II scorers correlate with a higher mortality rate (17,37). A SNAPPE II score of ≥38 has an 84.4% sensitivity and 91% specificity at predicting mortality (positive predictive value of 66.7% and negative predictive value of 96.5%) (11). The SNAPPE II score is useful in determination of disease severity and associated mortality and may help in prioritizing treatments and intervention for sick neonates even in resource-poor settings.

5.3 Relationship between SNAPPE II Score and PI

There was a moderate negative correlation between PI and SNAPPE II (Pearson correlation coefficient, R = -0.56) hence a higher SNAPPE II score which is a marker of greater disease severity was associated with a lower PI. Lower mean PI in more severe disease states has been reported in studies reporting the relationship of the PI with SNAP (13)and CRIB (5). Both PI and SNAPPE II have been used separately as measures of disease severity (8,12). In these studies, a higher SNAPPE II score showed worse disease and hence mortality. Similarly, lower PI values are demonstrable in severe illness. There was no effect of analyzing data from one hundred and thirty-nine neonates out of the targeted one hundred and fifty neonates. The inverse relationship between SNAPPE II and PI thus inferred has been demonstrated in the current study.

De Felice and colleagues in 2002 compared the PI with the Score for Neonatal Acute Physiology (SNAP) score. They found that the neonates in the high severity group had a mean PI of 0.87, with 95.5% sensitivity and 93.7% specificity at predicting severer illness. These workers also showed PI <1.24 predicted high illness severity with accuracy. This is similar to the results obtained in the

current study where the mean PI for those with severe illness was 0.83 showing good discrimination with AUC of 0.74, sensitivity of 87.3% and specificity of 67.9%.

Matthew and others in 2019, compared the PI with CRIB scores and reported a mean PI of 0.86 in neonates with high illness severity while those with low severity had an average PI of 1.94 (5). These observations are similar to the observations in the current study where the mean PI for those with severe illness was 0.83 and 0.88 for those neonates with mild disease.

The PI, as observed in the current study, appears to have agreement with different severity classification scores for both term and preterm neonates. As such, it is conceivable to propose the PI as an adjunct tool in the assessment of disease severity in neonates. This has previously been proposed and used in assessment of shock (5), congenital heart defects (18) and in septic shock (24).

5.4 Proposed Cut off Values for PI

In the present study, cut-off value of 0.83 for severe illness was suggested with AUC of 0.91, sensitivity 68%, specificity 84%.

Comparable cut-off values were obtained by de Felice et al. 2002 (0.87) (13) and Mathews et al., (0.86) (5). However, PI cut-off values of 2.03±0.70 and 1.95±1.36 for mild disease were reported by de Felice et al., (2002) and Mathews et al. (2019) respectively. These are higher compared to the cut-off recorded in the current study of 0.88. This could be attributed to the relatively higher proportion of neonates with severe illness recruited into the current study.

The difference in cut-off values could be explained by different patient populations and scoring systems used in classifying disease severity. This difference calls for caution in their interpretation of the PI as an independent assessment tool for assessment of disease severity. The importance of the findings in this study is that, PI, which is easily measured on a pulse oximeter and incorporated in various patient monitors used in intensive care units, can be a good noninvasive objective tool to assess illness severity in neonates. Further validation of the PI as an assessment tool is required prior to the recommendation of the PI for use in routine neonatal clinical assessment. Its use could be as an adjunctive tool to already validated measures of clinical assessment.

5.5 Strengths of the Study

Neonates across all birthweights and gestational ages were included in the study.

The PI was measured using signal extraction technology where the pulse oximetry waveform can be picked and remains stable through low perfusion states and movement artifact (shiver).

Establishing the PI's relationship with disease severity in both term and preterm neonates will form the basis for further study for its use in prognostication.

5.6 Limitations of the Study

The PI readings for the enrolled neonates were not taken at the exact same time after birth for all neonates. The physiological changes in the PI after birth could have contributed to the variability of the recorded PI values. The contribution of local temperature of the site of PI recording was controlled by not altering the neonate's environment during measurement of PI and all readings done in similar ambient temperature in the newborn unit.

The use of recorded APGAR scores and 24hour urine measurement from the neonate's clinical records as part of the SNAPPE II score may have had variability in accuracy since it was dependent on the attending clinician.

Since this was a cross-sectional study, follow-up of neonates throughout their admission was not done thus data may not be used for prognostication nor in outcome prediction.

Selection bias: Neonates recruited in this study were from a specialized unit, the KNH NBU, and included those admitted to the NICU who were severely ill. This may have contributed to a selection bias of very sick neonates and subsequent inclusion in the study. This was minimized by having the person recording the PI blinded to the SNAPPE II score of the neonates.

Confounding factor: A very small proportion of the neonates <0.5% involved in the study had hypothermia as a complication of illness during the measurement of the PI. This was addressed by multivariate analysis and regression models.

5.7 Conclusion

There is a moderate, statistically significant, negative correlation between the mean PI and SNAPPE II scores in neonates admitted to the KNH NBU and the higher the SNAPPE II score, the lower the PI and the severer the illness.

The proposed cut-off values for the PI have good sensitivity and specificity in predicting mild and severe disease.

5.8 Recommendation

Early assessment of sick neonates using SNAPPE II score on admission to the newborn unit would help the clinician stratify the neonates according to severity of illness to guide prompt evaluation and management of the neonates.

The PI is a useful adjunctive tool in monitoring severely ill neonates and can be therefore used, albeit cautiously, to predict severe illness in neonates.

Further research and subsequent follow-up is needed to determine the utility of the PI in predicting clinical outcomes in neonates.

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APPENDICES

APPENDIX I: DATA COLLECTION SHEETS

Serial number_____

Sex _____

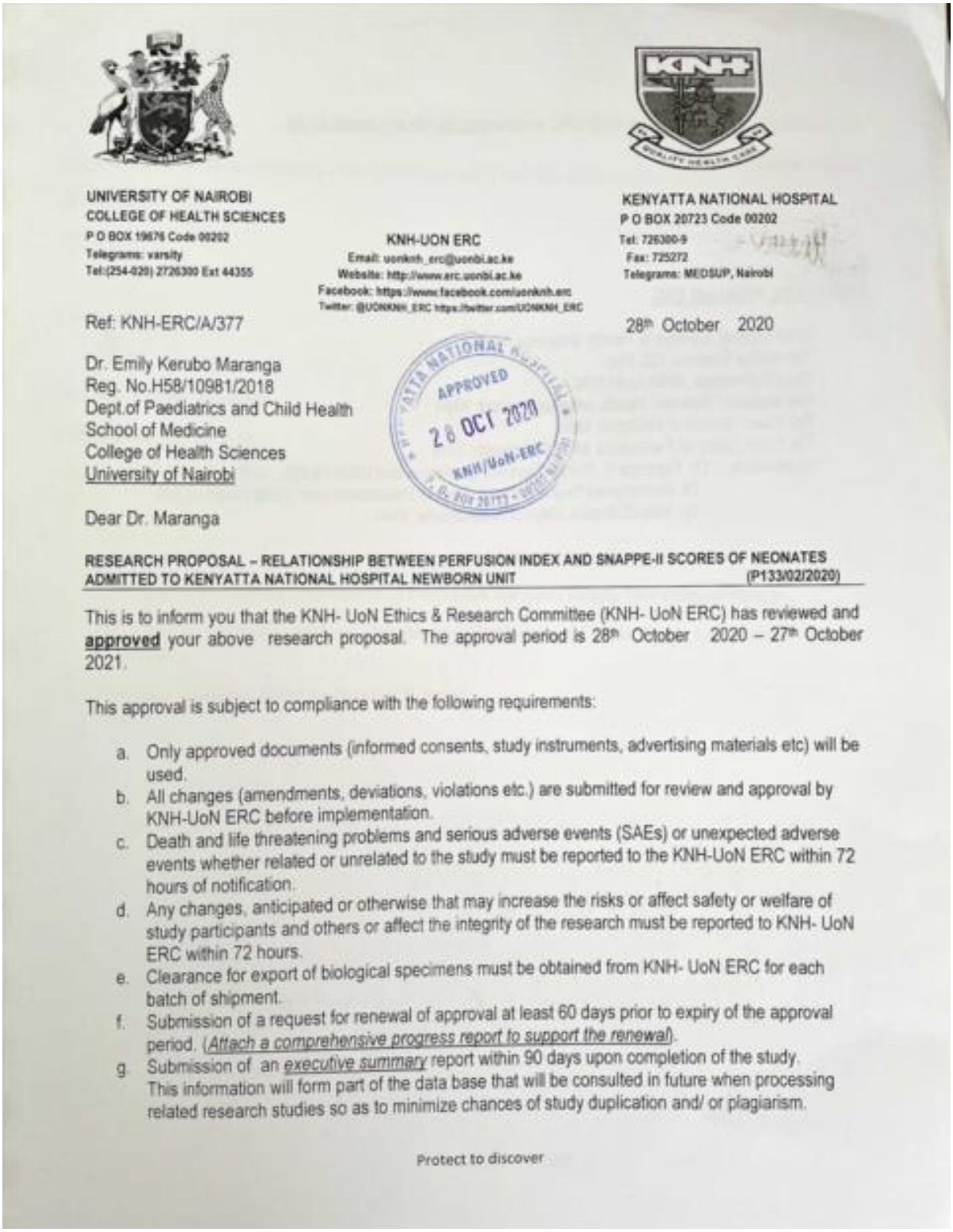
Mode of delivery_____

Anthropometric assessment		**SNAPPE-II parameter**	**Score**
Birthweight (g)		Lowest temperature in 24h	
Gestational age (weeks)		Mean Blood Pressure	
Age at measurement (days)		Serum PH	
Length (cm)		PO_2/FiO_2 ratio	
Head circumference (cm)		APGAR score <7 at 5 min	
Abdominal circumference (cm)		Urine output	
		Multiple seizures	
		Small for gestational age Birth Weight ≤749g	
		TOTAL	

PERFUSION INDEX

Time (Minutes)	1	2	3	4	5	6	7	8	9	10
Perfusion index (20 seconds intervals)										
Average perfusion index										

APPENDIX II: ETHICAL APPROVAL LETTER



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Ref: KNH-ERC/A/377

28th October 2020

Dr. Emily Kerubo Maranga
Reg. No.H58/10981/2018
Dept.of Paediatrics and Child Health
School of Medicine
College of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 28 OCT 2020 KNH/UoN-ERC

Dear Dr. Maranga

RESEARCH PROPOSAL – RELATIONSHIP BETWEEN PERFUSION INDEX AND SNAPPE-II SCORES OF NEONATES ADMITTED TO KENYATTA NATIONAL HOSPITAL NEWBORN UNIT (P133/02/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 28th October 2020 – 27th October 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Paediatrics and Child Health, UoN
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Dr. Mohammed Bashir Admani, Dept.of Paediatrics and Child Health, UoN
Dr. Idris Chikophe, Dept.of Anaesthesia, KNH

APPENDIX III: CONSENT FORMS

Title of Study: RELATIONSHIP BETWEEN PERFUSION INDEX AND SNAPPE-II SCORES OF NEONATES ADMITTED TO KENYATTA NATIONAL HOSPITAL NEW BORN UNIT

Principal Investigator\and institutional affiliation: Dr. Emily Maranga

I am a postgraduate student at the **University of Nairobi** pursuing a **Master of Medicine degree in Pediatrics and Child Health**.

I would like to tell you about a study I am conducting. The purpose of this consent form is to give you the information you will need to help you decide whether or not to allow your child to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if your child participates in the study, the possible risks and benefits and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide your child to be in the study or not. This process is called 'informed consent'. Once you understand and agree to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in a medical research:

i) Your decision to allow your child to participate is entirely voluntary

ii) You may withdraw your child from the study at any time without necessarily giving a reason for your withdrawal

iii) Refusal for your child to participate in the research will not affect the services your child entitled to in this health facility or other facilities.

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee.

WHAT IS THIS STUDY ABOUT?

The purpose of the study is to find out the relationship between perfusion index and neonatal illness severity. Participants in this research study will have the choice to undergo measurements such as pulse oximetry to determine perfusion index. There will be approximately 382 participants in this study. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in this study, the following things will happen:

I will examine the child and record the perfusion index at time of study. To protect your child's privacy, I shall not include his/her names.

Your participation in this study will help me determine the relationship of perfusion index and neonatal illness in our region. The results of this study will help us to monitor and improve early interventions for ill neonates and contribute to research in newborn health.

I will also ask questions on where you live, your age and that of the father and your occupation. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview.

We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be absolutely secure, so it is still possible that someone could find out you were in this study and could find out information about you. Furthermore, all study staff and interviewers are professionals with special training in these examinations.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

You may benefit by receiving counselling, health information on your child's illness. The information you provide will help us better understand the relationship between perfusion index

and neonatal illness. This information is a contribution to science and may help in implementing strategies to improve monitoring of neonates in future.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

There will be no cost transferred to you by participating in this study

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page.

For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.

The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to have your child participate in this research is voluntary. You are free to decline or withdraw participation of your child in the study at any time without injustice or loss of benefits. Just inform the study staff and the participation of your child in the study will be stopped. You do not have to give reasons for withdrawing your child if you do not wish to do so. Withdrawal of your child from the study will not affect the services your child is otherwise entitled to in this health facility or other health facilities.

CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my personal identity confidential. By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study: Yes No

I agree to provide contact information for follow-up: Yes No

Participant printed name: _____

Participant signature / Thumb stamp_____ Date_____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name:_____ Date: _____

Signature_____

Role in the study:_____[i.e. study staff who explained informed consent form.]

For more information contact Dr Emily Maranga at Department of Paediartrics and Child Health on phone number **0726990021**.

Witness Printed Name (If witness is necessary, A witness is a person mutually acceptable to both the researcher and participant)

Name_____ Contact information _____

Signature /Thumb stamp:_____ Date;_____

KNH-UON ERC Secretary: **Prof. M.L. CHINDIA** Telephone: **(254-020) 2726300-9 Ext 44355**

E-mail: **uonknh_erc@uonbi.ac.ke** Website: **www.erc.uonbi.ac.ke**

IDHINI YA KUSHIRIKISHWA KATIKA UTAFITI WA KUANGALIA UHUSIANO WA KIPIMO CHA MSUKUMO WA DAMU NA MAGONJWA KATIKA WATOTO WA UMRI CHINI YA MWEZI MMOJA WALIOLAZWA KWENYE VYUMBA VYA WATOTO KWENYE HOSPITALI KUU YA KENYATTA

JINA LA MTAFITI: Dr. Emily Maranga

Mimi ni mwanafunzi wa Uzamili katika Chuo Kikuu cha Nairobi ninayesomea shahada ya afya na magonjwa ya watoto. Ili kuhitimu shahada hii,ninafanya utafiti juu ya uhusiano wa kipimo cha msukumo wa damu na magonjwa katika Watoto wachanga wenye umri wa chini ya mwezi mmoja. Ushiriki wako katika utafiti huu utanisaidia kuamua idadi ya watoto walio wagonjwa sana na uhusiano na kipimo cha msukumo wa damu inayopimwa. Kusudi kuu ya kukupa habari hizi ni kukuwezesha kuamua iwapo utamruhusu mtoto wako kushirikishwa kwenye utafiti huu.

Iwapo utakubali kuhusishwa kwenye utafiti huu, nitamwangalia mtoto wako na kunukuu vipimo vinavyohitajika kwa utafiti kutoka kwa faili. Pia, taaluma zote za utafiti wa tatizo lake zitanukuliwa kwenye karatasi za utafiti.

Tafadhali elewa yafuatayo: -

i. Ushiriki ni kwa hiari.

ii.Nitaitunza siri yako. Habari za mtoto wako zitahifadhiwa kwenye kompyuta iliyo na neno siri na kufungiwa kwa kabati iliyo na kufuli

iii. Kukataa kushiriki katika utafiti hautavutia adhabu yoyote. Mtoto wako ataendelea kupokea chanjo na ushauri juu ya kukua kwake.

iv. Hakuna hatari inayotarajiwa kwa kushiriki katika utafiti huu. Mtoto ataendelea kutibiwa kulingana na sheria za hospitali. Hakuna fidia ya fedha kwa ajili ya kushiriki katika utafiti huu. Mtoto ataendelea kupokea huduma za afya kwenye hospitali na kliniki ya watoto wachanga

Uko na uhuru wa kukataa kuhusishwa katika utafiti huu wakati wowote. Utakapobadilisha nia ya uhusisho unaweza andika barua pepe au kupiga simu kwa kamati ya maadili ya hospitali kuu ya Kenyatta kwa nambari 2726300 Ext. 44102 or email: uonknh_erc@uonbi.ac.ke. Nimeisoma fomu hii ya idhini na kuelewa inavyoagiza. Nimejadiliana na mshauri wa utafiti barabara na maswali yangu yamejibiwa kwa lugha ninayoielewa. Nimeelezwa hatari na faida za ushirikisho kwa utafiti huu. Ninaelewa kuwa nitapewa nakalaya idhini hii nitakapoisahihisha.

Ninaelewa kuwa siri za mtoto wangu zitatunzwa vyema. Ninaelewa kuwa ushirika wa mtoto wangu katika utafiti huu ni kwa hiari na ninaweza kukataa kuhusishwa kwa utafiti wakati wowote. Katika kusahihisha idhini hii sijasalimisha haki za sheria za mtoto wangu.

Nimekubali kwa hiari kushirikisha mtoto wangu kwa utafiti huu: ndio/la
Nimekubali habari kwa faili ya mtoto wangu kukaguliwa: ndio/la

Jina la mzazi _____

Sahihi ya mzazi_____ Tarehe _____

Kauli ya mtafiti
Mimi niliyesahihisha idhini hii nimeeleza mzazi barabara maelezo muhimu kuhusu utafiti huu na ninaamini kuwa ameelewa na kukubali kushirikishwa katika utafiti huu.

Jina la mtafiti_____ Tarehe _____

Sahihi _____

Jina la shahidi_____ Tarehe _____

Sahihi ya shahidi _____

APPENDIX IV: SNAPPE II CALCULATOR

Variable	Measure	Score
Lowest MAP	> 29 mmHg	0
	20-29 mmHg	9
	< 20 mmHg	19
Lowest temperature	> 35.60 C	0
	35-35.60 C	8
	< 350 C	15
PO2/FiO2 ratio	> 2.49	0
	1.0-2.49	5
	0.3-0.99	16
	< 0.3	28
Lowest pH	> 7.19	0
	7.10-7.19	7
	< 7.10	16
Seizure	none	0
	yes	5
Urine output	> 0.9 ml/kg/hr	0
	0.1-0.9 ml/kg/hr	5
	< 0.1 ml/kg/hr	18
Birth weight	> 999 g	0
	750-999 g	10
	<750 g	17
Small for gestational age	> 3rd percentile	0
	< 3rd percentile	12
APGAR score at 5 minute	> 7	0
	< 7	18

Source: Richardson *et al.*[10]

APPENDIX V: MODIFIED BALLARD SCORE

(a)

Skin	Sticky friable transparent	Gelatinous red, translucent	Smooth pink, visible veins	Superficial peeling &/or rash, few veins	Cracking pale areas, rare veins	Parching deep cracking no vessels	Leathery cracked
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel–toe 40–50mm:–1 <40mm: –2	>50mm no crease	Faint red marks	Anterior transverse crease only	Creases ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola no bud	Stippled areola 1–2 mm bud	Raised areola 3–4 mm bud	Full areola 5–10 mm bud	
Eye/ear	Lids fused loosely: –1 tightly:–2	Lids open pinna flat stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna; soft but ready recoil	Formed & firm instant recoil	Thick cartilage ear stiff	
Genitals male	Scrotum flat, smooth	Scrotum empty Faint rugae	Testes in upper canal Rare rugae	Testes descending Few rugae	Testes down Good rugae	Testes pendulous Deep rugae	
Genitals female	Clitoris prominent Labia flat	Prominent clitoris Small labia minora	Prominent clitoris Enlarging minora	Majora & minora equally prominent	Majora large Minora small	Majora cover clitoris & minora	

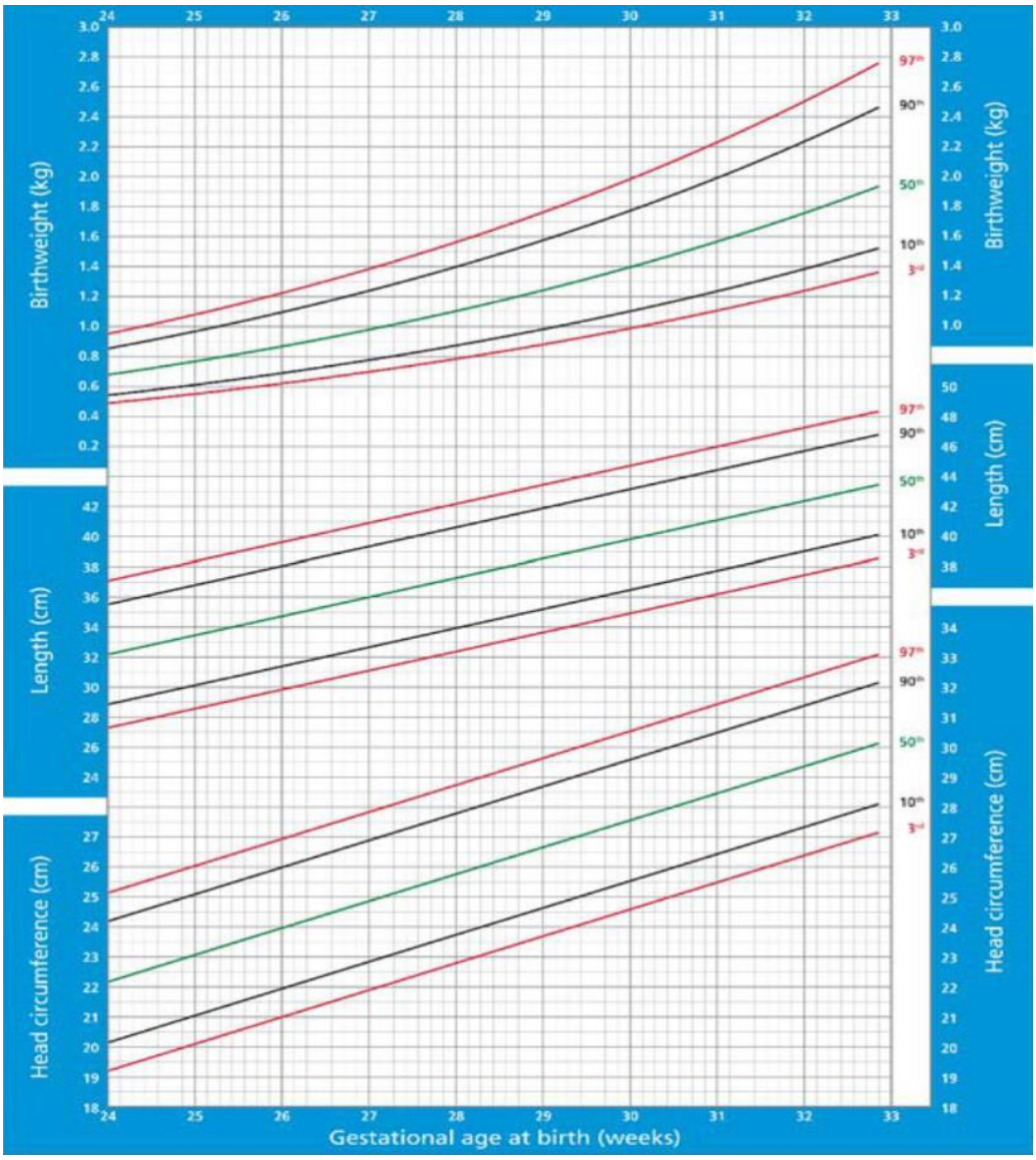
Maturity rating	
Score	Weeks
–10	20
–5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

(b)

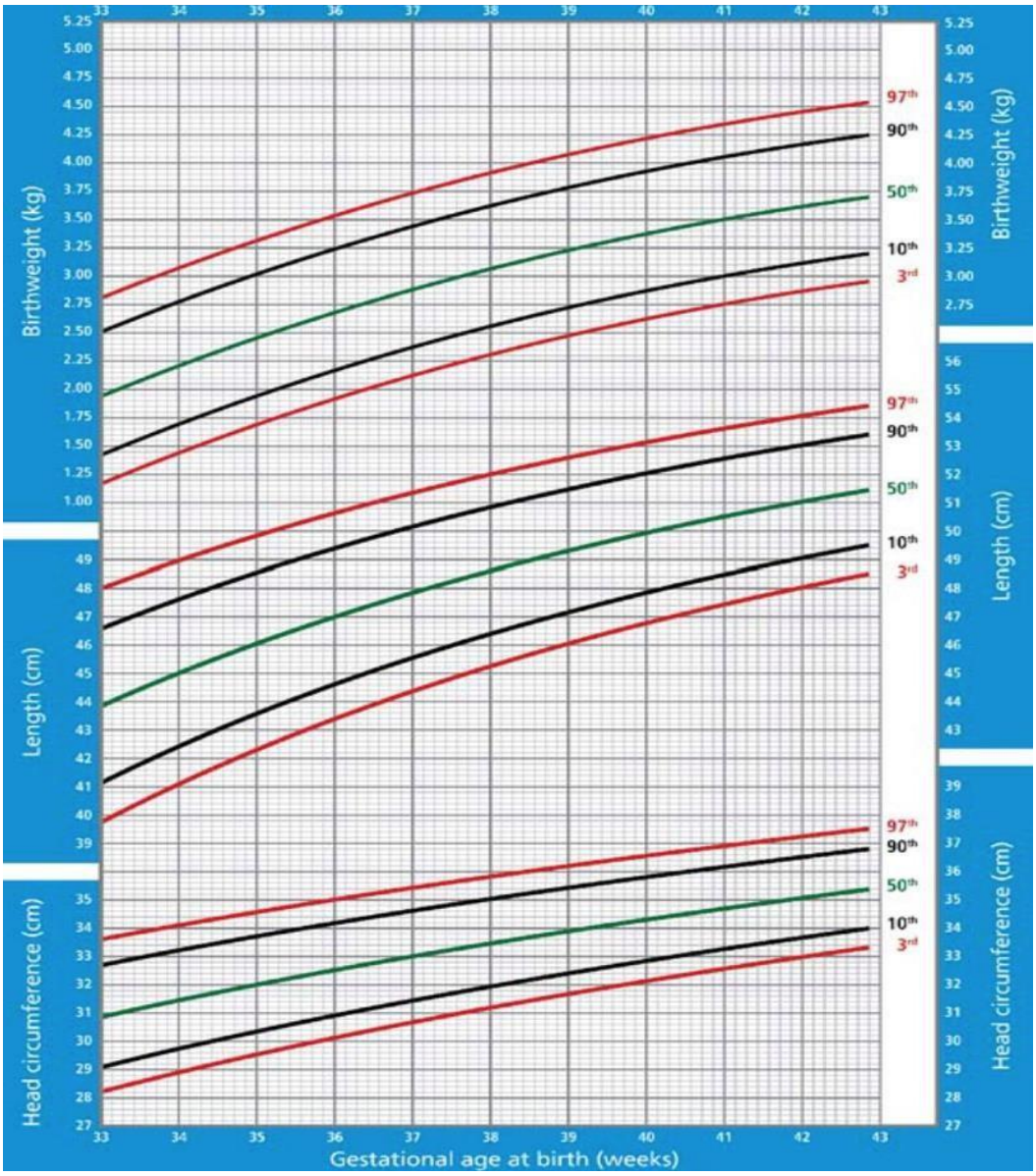
	–1	0	1	2	3	4	5
Posture							
Square window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm recoil		180°	140°–180°	110°–140°	90°–110°	<90°	
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scarf sign							
Heel to ear							

Maturity rating	
Score	Weeks
–10	20
–5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

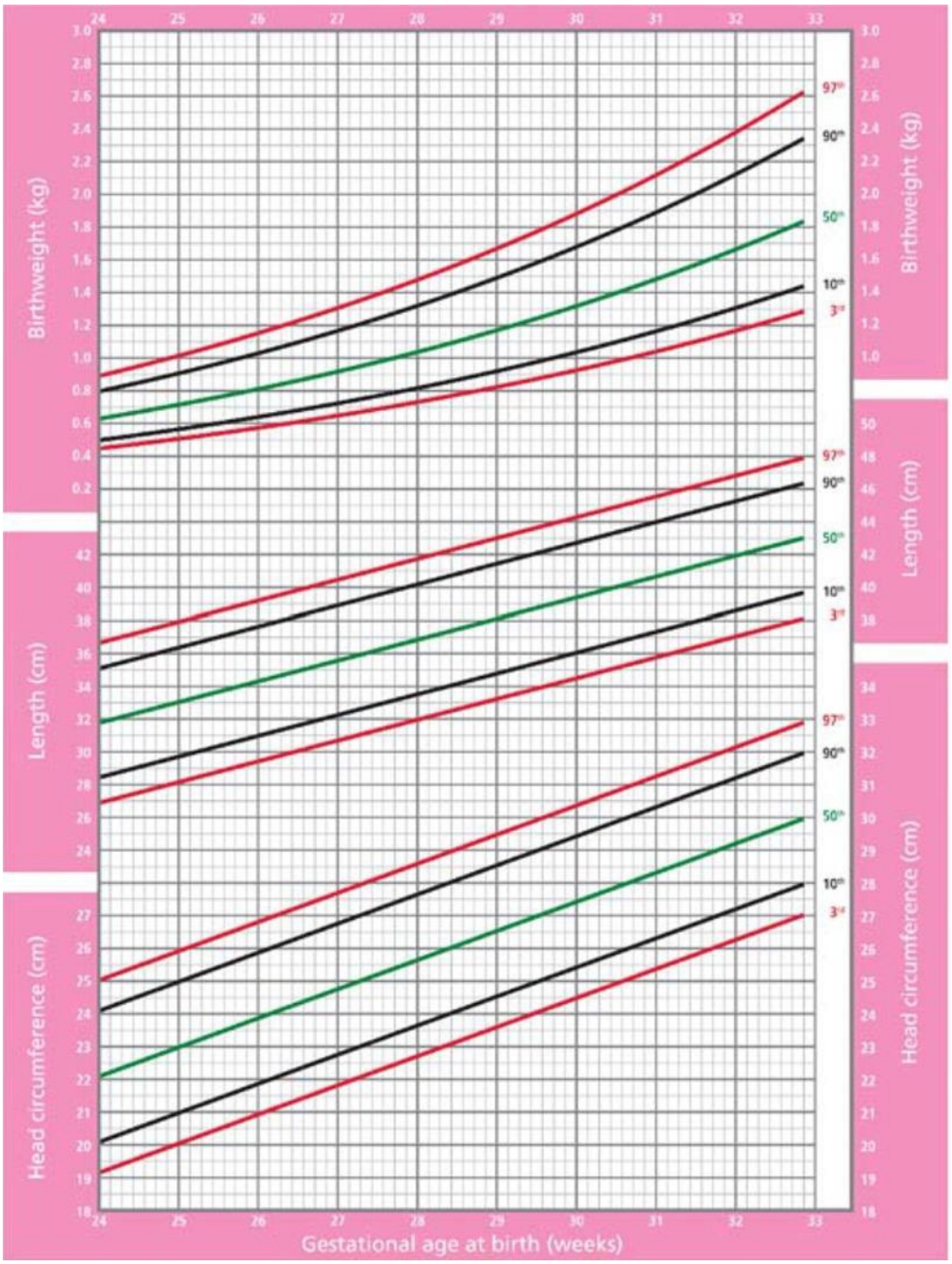
APPENDIX VI: INTERNATIONAL STANDARDS FOR SIZE AT BIRTH (BOYS) 24 – 33 WEEKS



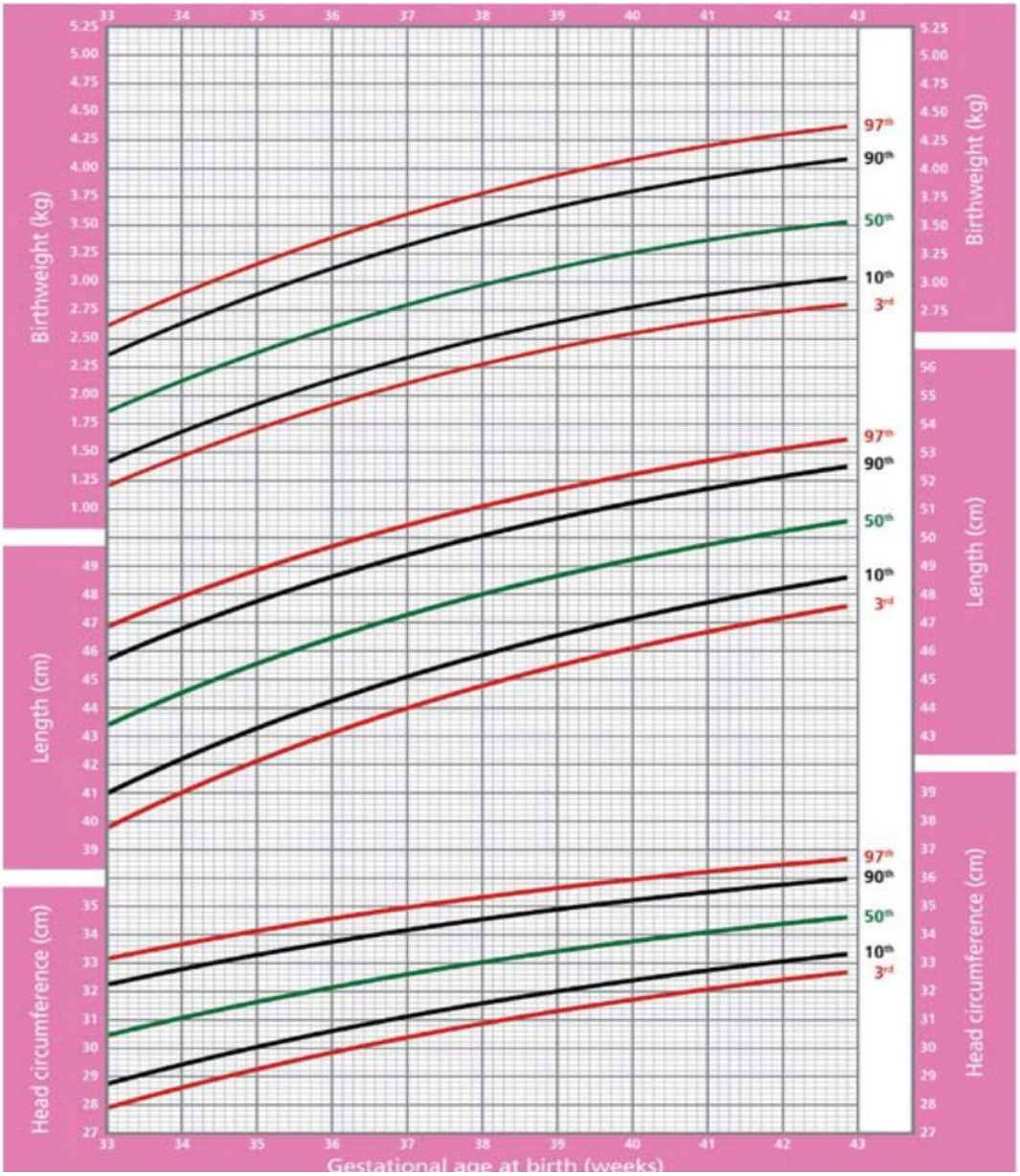
APPENDIX VII: INTERNATIONAL STANDARDS FOR SIZE AT BIRTH (BOYS) 33 – 43 WEEKS



APPENDIX VIII: INTERNATIONAL STANDARDS FOR SIZE AT BIRTH (GIRLS) 24 – 33 WEEKS.



APPENDIX IX: INTERNATIONAL STANDARDS FOR SIZE AT BIRTH (BOYS) 33 – 43 WEEKS



RELATIONSHIP BETWEEN PERFUSION INDEX AND SNAPPE II SCORE IN NEONATES ADIMITTED TO KENYATTA NATIONAL HOSPITAL

by Dr. Emily Kerubo Maranga (Peadiatrics Child Health) Medicine

From Thesis (Medical Records 4**)**

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