BURDEN OF ACUTE KIDNEY INJURY AND ASSOCIATED FACTORS AMONG NEONATES ADMITTED TO THE NEWBORN UNIT, MOI TEACHING AND REFERRAL HOSPITAL – ELDORET KENYA.

ALICE NDUTA GICHEMI

A RESEARCH THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN CHILD HEALTH AND PAEDIATRICS

MOI UNIVERSITY

DECLARATION

I declare that this is my original work and it has not been presented in any other university or institution for an award of a degree or any academic credit. No part of this work may be reproduced or transmitted in any form without prior permission from the author and Moi University.

ALICE NDUTA GICHEMI

SM/PGCHP/06/15

Department of Child Health and PaediatricsSchool of medicine

Signature…… Date ……

Supervisor's Declaration

Prof. Ganda Bonface. O. K

Department of Child Health and Paediatrics

Moi University, School of Medicine

Signature…… Date ……

Dr Nabakwe Esther

Senior lecturer Department of Child Health and Paediatrics

Moi University, School of Medicine

Signature…… Date ……

Dr Cheptinga Philip. K

Directorate of Paediatrics,

Moi Teaching And Referral Hospital, Eldoret.

Signature…… Date ……

DEDICATION

I dedicate this work to my daughter, my greatest motivator, and to my father James Gichemi for the support throughout the years.

ACKNOWLEDGEMENT

I acknowledge my supervisors, Prof. Ganda, Dr Cheptinga, and Dr Nabakwe, my biostatistician Prof. Mwangi, the department of child health and paediatrics ,friends and colleagues for their input in the development of this work.

ACRONYMS AND ABBREVIATIONS

AKI	Acute Kidney Injury
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
CRRT	Continuous Renal Replacement Therapy
eCCL	estimated Creatinine Clearance
GFR	Glomerular Filtration Rate
HIE	Hypoxic Ischaemic Injury
IRRT	Intermittent Renal Replacement Therapy
KDIGO	Kidney disease: Improving Global Outcomes
MTRH	Moi Teaching and Referral Hospital
NBU	New born Unit
NICU	Neonatal Intensive Care Unit
NIH	National Institute of Health
RBF	Renal Blood Flow
RRT	Renal replacement therapy
SCr	Serum Creatinine

DEFINITION OF TERMS

ACUTE KIDNEY INJURY abrupt (within 48 hours) absolute increase in serum creatinine of ≥ 0.3 mg/dL (≥ 26.5 μmol/L), or a percentage increase in serum creatinine of ≥ 50% (1.5-fold from baseline) according to the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup AKI definition (J. G. Jetton et al., 2016)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Acute Kidney Injury (AKI) is the sudden deterioration in kidney function leading to inability to maintain fluid and electrolyte balance. The immature neonatal kidney is vulnerable to insult due to its reduced renal blood flow, high renal vascular resistance, and poor auto-regulation capacity thus compromising its efficiency. The incidence of AKI in neonatal intensive care units is estimated at 8% to 24% with a mortality rate of between (10-61%). Studying the burden of AKI and factors associated with it, will aid in formulation of standards of care and thereby reduce mortality and morbidity.

Objectives: To determine prevalence, describe associated factors and outcomes of acute kidney injury among neonates in the newborn unit at Moi Teaching and Referral Hospital (MTRH).

Methods: A prospective descriptive study was carried out at the new born unit of MTRH from October 2017 to March 2018. Systematic sampling technique was used. Data on the socio-demographic and clinical characteristics of 280 neonates surviving 48 hours of life was collected. Associated factors studied included gender, sepsis, 5 minute APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score, prematurity, birth weight, gestational age, respiratory distress, and exposure to nephrotoxic drugs. Blood samples were obtained on the day of recruitment and subsequent samples were taken after 7 days or earlier if there were clinical indications. Analysis of serum creatinine was done using the Jaffe method. Cases of AKI identified were classified using the neonatal Kidney Disease: Improving Global Outcomes (KDIGO) classification based on serum creatinine. Follow up was done until death, discharge or 28 days of life whichever came earlier. Chi-square and Fisher's exact test were used to test association of categorical variables while Wilcoxon Rank Sum test was used to compare initial serum creatinine between the two groups; all analysis was at 95% CI.

Results: A total of 280 neonates were recruited with a male to female ratio of 1:1.1. The prevalence of AKI was 55(19.8%). The majority were in stage 3 at 38(69.1%) while stage 1 and 2 had 13(23.6%) and 4(7.3%) respectively. Clinical and socio-demographic factors had no statistically significant associations with AKI. Amongst those discharged before 28 days, there was no statistically significant difference in the length of stay between those with and those without AKI. Among those with AKI 19(34.6%) died; AKI was associated with a fourfold increased mortality ((OR 3.999; 95% CI 2.006, 7.973; p=0.000)). None of the neonates with AKI underwent renal replacement therapy.

Conclusion: One in five neonates had Acute kidney injury. Having Acute kidney injury was associated with a four fold increased odds of mortality. There were no statistically significant associations with socio-demographic and clinical factors.

Recommendations: Higher index of suspicion for AKI in neonates and initiation of appropriate management to reduce mortality.

CHAPTER ONE: INTRODUCTION

1. 1 Background

Acute kidney injury (AKI) refers to abrupt decline in kidney function, required for, removal of waste products and maintenance of fluid and electrolyte homeostasis. Acute kidney injury has been estimated to occur in upto 8% -24 % of admissions in neonatal intensive care units (Andreoli, 2002). The modified KDIGO criteria defines acute kidney injury as an abrupt (within 48 hours) absolute increase in serum creatinine of ≥ 0.3 mg/dL (≥ 26.4 μmol/L), or a percentage increase in serum creatinine of ≥ 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour > 6 hours).

Due to the "immature kidney" in this age bracket, most of the cases are usually not detected and documented since non oliguric AKI forms the bulk of neonatal AKI. However not enough studies have been done on the same, largely owing to lack of consistent definitions of neonatal AKI (D. J. Askenazi et al., 2009a). The factors associated with neonatal AKI can be both neonatal and maternal, they include maternal exposure to non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors; neonatal factors include sepsis, hypoxia, hypotension, prematurity, low APGAR scores, and nephrotoxic medication.

1.2 Problem Statement

WHO sustainable development goal 3: 2015- 2030 is geared at ending preventable deaths of newborns, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births**.** According to the Kenya demographic health survey 2014, neonatal mortality rate stands at 22 per 1000 live births. The prevalence of neonatal AKI has been found to be high and its contribution to mortality significant. Andreoli S.P reported the incidence of neonatal acute kidney to be between 8% and 24 %. Mortality rates were also high at 10% to 61 % (Andreoli, 2009b). According to a

meta-analysis by Ricci et al, done on studies that had RIFLE classification of AKI from 2004 -2007, comparison between those with and without AKI having adjusted for severity of illness and comorbidities, showed significant increase in mortality with deterioration in kidney function. The relative risk of mortality among patients classified as Risk, Injury and Failure was (RR) 2.4, 4.15, and 6.37 respectively($P < 0.0001$ for all) (Ricci et al., 2008) . It is important to note that acute kidney injury has consistently been found to be an independent risk factor for mortality after adjusting for comorbidities and severity of other illnesses. (D. J. Askenazi et al., 2009b; Koralkar, Ambalavanan, Levitan, Goldstein, et al., 2011; Li et al., 2013). Moreover, while it was thought that neonates recovered well from AKI, recent studies from animals, critically ill children, and adults have shown an increased risk of chronic kidney disease that might manifest months or even years later (Andreoli, 2009a; Greenberg et al., 2014; Mammen et al., 2012). In a Canadian Study, Mammen et al reported that 10% of children who developed AKI in the paediatric intensive care unit (PICU) had GFR <60 mL/min/1.73 m^2, 1 to 3 years later. Perhaps even more alarming was the finding that nearly 50% of this cohort was found to be "at risk" for CKD (Mammen et al., 2012).

Anecdotal information from mortality and morbidity audits in the newborn Unit of Moi Teaching and Referral Hospital shows that elevated serum creatinine will not necessarily lead to inclusion of AKI in the diagnosis other than in very sick neonates. This leads to a gross underestimation of the morbidity of AKI in our set-up. Such underestimations lead to down playing of the contribution of AKI to morbidity and mortality rates and a general lack of proper vigilance on the condition.

Paediatric nephrologists in resource poor settings are few and therefore there is a growing need to develop protocols for care of paediatric patients and more so neonates with acute kidney injury. There are currently no protocols for neonatal AKI in Kenya,

and no baseline survey to base them on. The scarcity or absence of data makes it difficult to address the problem that is neonatal acute kidney injury in a strong, consistent manner.

1.3 Study Justification

This study is in line with the global kidney research agenda on neonatal AKI; to map out the epidemiology of neonatal AKI using a standardized neonatal AKI definition that is in line with paediatric and adult definitions. This was obtained through a multicenter multidisciplinary international committee that looked into defining a research agenda on acute kidney injury epidemiology using a modified three-step Delphi process (Cerdá, Lameire, et al., 2008). They found that knowledge of incidence and risk factors of AKI is crucial in guiding the efforts on diagnosis and management of this condition. There was a glaring difference in incidence rates between developed and developing nations. The developing nations seemed to report lower incidences, which could be attributable to underreporting rather than a true picture of the current situation (Cerdá, Lameire, et al., 2008). This is compounded by lack of reliable databases for use in epidemiological assessment. In order to improve mortality and morbidity from Acute kidney injury, especially in developing countries, they concluded that it is essential to carry out epidemiological studies using the standardized definitions of AKI to achieve early detection intervention and improved patient outcomes.

There are currently very few studies done on the prevalence of AKI on all neonates with different risk factors. This will be the first such study conducted in our country.

Our study aims at establishing the true incidence of AKI in the New Born Unit (NBU) of Moi Teaching And Referral Hospital (MTRH). It is the second largest referral hospital in Kenya (one of the two level 6 hospitals in the country) and a leading renal research centre. It is also a training centre for clinical staff for lower level hospitals and

a major contributor to clinical guidelines used in Kenya. Baseline epidemiological data will help in informing development of standards of care/protocols. Since our populations are similar to the populations in different NBUs' in Kenya our findings can inform the prevention measures and management of neonatal AKI in other NBU centers in Kenya. Prevention is key in avoiding the heavy burden of mortality and morbidity associated with AKI. This will only come about through increasing awareness of the true incidence and clinical impact of AKI. This study is essential in acquiring information that will aid in reducing morbidity and mortality from AKI and ultimately putting us on the path to achieving the sustainable development goal 3:2, (reducing neonatal mortality). Ours being a resource poor setting, this data will help us make targeted adjustments in terms of health care resources both financial and in terms of human resources and policy making to deal with neonatal AKI.

1.4 Research Questions

What is the prevalence and associated factors of acute kidney injury among neonates in the New Born Unit of Moi Teaching and Referral Hospital?

1.5 Study Objectives

1.5.1 Broad Objective

To determine the burden of acute kidney injury and the associated factors among neonates in the newborn unit of MTRH

1.5.2 Specific Objectives

1. To determine the prevalence of acute kidney injury among neonates in the NBU of MTRH.
2. To describe the factors associated with acute kidney injury in the NBU of MTRH.
3. To describe the outcomes of neonates with acute kidney injury.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Acute Kidney Injury (AKI) is a clinical syndrome in which an abrupt, within 48 hrs decline in kidney function leads to derangements including the kidney's ability to clear nitrogenous waste products , maintain water and electrolyte balance and acid-base balance. AKI is an important factor in morbidity and mortality in critically ill neonates. It has been shown to be an independent mortality factor after adjusting for other co-morbid states and severity of illness (D. J. Askenazi et al., 2009b).

Until 2008, different studies had used arbitrary cut offs to define neonatal AKI. This was due to lack of acceptable definitions of neonatal AKI that could be used and that were comparable to paediatric and adult definitions. In addition many studies have focused on sub-groups of neonates such as those with Hypoxic ischaemic encephalopathy, low birth weight, those undergoing cardiac surgery with very few looking into the prevalence and associated factors of the wider population of sick neonates.

Attempts have been made to get an acceptable definition of neonatal AKI. What has been generally acceptable is the use of percentage rises of serum creatinine to determine AKI and urine output measurements. However it is noted that the majority of neonatal AKI cases are non-oliguric (J. G. Jetton & Askenazi, 2012).

In 2007 Arikan et al proposed a modified (paediatric Risk, Injury Failure, Loss, End stage renal disease) pRIFLE criteria to characterize AKI in the paediatric population (Table 1) (Akcan-Arikan et al., 2007).

Table 1: Modified (Paediatric Risk, Injury Failure, Loss, End Stage Renal Disease) pRIFLE

CRITERIA	ESTIMATED Creatinine Clearance (eCCL)	URINE OUTPUT
Risk	eCCl decrease by 25%	0.5 mL/kg/hr for 8 hr
Injury	eCCl decrease by 50%	0.5 mL/kg/hr for 16 hr
Failure	eCCl decrease by 75% or eCCl 35ml/min/1.73 m2	0.3 mL/kg/hr for 24 hr or anuric for 12 hr
Loss	Persistent failure 4 wk	
End-stage	End-stage renal disease (persistent failure 3 mo)	

This definition was not suitable for neonatal population due to the changing and unique physiology of the neonatal kidney as well as the gestation age related variability of GFR and maternal creatinine interference.

Subsequent studies mathematically demonstrated that it was possible to use SCr increments only, without necessarily calculating GFR to diagnose AKI. (Özçakar et al., 2009) . Later the Acute Kidney Injury Network (AKIN) group revised the AKI classification and adopted the percentage SCr increment to diagnose AKI, recognizing that eGFR was not necessary.

In March 2007 the Acute Kidney Injury Network (AKIN), a collaborative group made up of researchers from major critical care and nephrology societies came up with the 3 stages of acute kidney injury. It adopted the percentage SCr increment to diagnose AKI, recognizing that eGFR was not necessary. This classification had mild AKI (stage 1), moderate AKI (stage 2) severe AKI (stage 3). The major changes from RIFLE include decreasing the change in serum creatinine (SCr) threshold (0.3 mg/dl) to be classified as mild AKI, and classifying anyone on dialysis as having class 3 AKI. In addition, the AKIN criteria included a time requirement to denote the acute changes in kidney function, where changes need to be abrupt: within 48 h .stage 1 -150%,

Stage II - 200%, stage III -300%. In 2012 through the NIDDK (The National Institute of Diabetes and Digestive and Kidney Diseases) a Kidney Disease: improving global outcomes (KDIGO) work group was formed to define a research agenda for kidney disease. It came up with the current KDIGO classification of AKI and clinical management guidelines (JA Kellum, 2013). In 2013 the neonatal KDIGO AKI workshop comprising of an international group of neonatologists, paediatric nephrologists intensivists and National Institute of Health (NIH) representatives came up with the neonatal AKI definition. Several challenges in defining neonatal AKI were identified including; 1) At birth the SCr concentration reflect maternal levels, 2) The SCr after birth decreases abruptly over days then slowly over weeks and months and gets to adult levels at between 1-2 years of age, 3) The rate of SCr drop varies widely depending on gestational age, birth weight, rate of weight loss and fluid balance 4) There are no established normal creatinine values in this age group or even 'normal' rates of SCr reduction thus this measurements are unique to each individual neonate, 5) Tubular function matures even more slowly than glomerular function and the kidney concentrating ability in neonates is poor thus urine output will not necessary match AKI status (D. Askenazi et al., 2019; J. G. Jetton et al., 2016; Zappitelli et al., 2017). In the Neonatal KDIGO definition therefore each serum creatinine is compared to the previous lowest SCr measurement (considered baseline) taken, to determine both an absolute rise as well as percentage increase in SCr level. The consensus is that the current definition is the most suitable for this age group but is likely to change further as epidemiological data improves. The definition has been revised severally as shown in Table 2 below.

Table 2: Proposed neonatal AKI definition modifications from KDIGO pediatric AKI definition, using SCr and urine output criteria

	Serum creatinine criteria (in mg/dl)			Urine output criteria (in ml/kg/h)[a]		
Stage	**Pediatric definition**	**Neonatal modification: 2012**	**Neonatal modification: 2015–2016**	**Pediatric definition**	**Neonatal modification: 2013**	**Neonatal modification: 2016**
1	≥0.3 Rise within 48 h or ≥1.5–1.9 × rise from baseline within 7 days	≥0.3 rise or ≥1.5–1.9 × rise from baseline (defined as previous lowest/trough value)	≥0.3 rise within 48 h or ≥1.5–1.9 × rise from baseline (previous lowest value) within 7 days	<0.5 for 8 hours	<1.5 for 24 h	≤1 for 24 h
2	≥2–2.9 × rise from baseline	Unchanged	Unchanged	<0.5 for ≥16 h	<1 for 24 h	≤0.5 for 24 h
3	≥3 × rise from baseline or ≥4.0 or eGFR<35 ml/min per 1.73 m^2 or RRT initiation	≥3 × rise from baseline or ≥2.5 or RRT initiation	≥3 × rise from baseline or ≥2.5 or RRT initiation	<0.3 for ≥24 h or anuria for ≥12 h	<0.7 for 24 h or anuria for 12 h	≤0.3 for 24 h

From: **Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop** (Zappitelli et al., 2017)

AKI, acute kidney injury; eGFR, enhanced glomerular filtration rate; RRT, replacement therapy; SCr, serum creatinine concentration.

[a]The published KDIGO definition proposes timing cutoffs for low urine output to be >6 h for stage 1 (instead of >8 h) and >12 h for stage 2 (instead of >16 h). The pediatric literature to date has consistently utilized urine output decrease timing cutoffs as displayed in the table.

[b]Baseline SCr: no clear guideline on how to define pediatric baseline SCr. In the literature, baseline SCr has most commonly been defined as the lowest SCr measured in the previous 3 months.

2.2 Prevalence of acute kidney injury in newborn

Published studies estimate that the prevalence of AKI in critically ill neonates is between 8% and 24% and that mortality rates are between 10% and 61% (Andreoli, 2002). Several studies have been conducted using the neonatal KDIGO classification. The AWAKEN study (Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates) the largest multinational multicenter study on neonatal AKI to date, found a prevalence of 30% when using both serum creatinine and urine output criteria and a prevalence of 18% when serum creatinine alone was used (J. G. Jetton et al., 2017). A study done on neonatal AKI in a level II and III NICU in Saudi Arabia reported a prevalence 56% (Shalaby, Sawan, Nawawi, Alsaedi, Al-Wassia, et al., 2018).

Looking at studies conducted on different sub-sets of neonates using the neonatal KDIGO classification; A study done in the United States of America by Rhone et al on nephrotoxic medication exposure among very low birth weight neonates found a prevalence of 26.2% (Rhone et al., 2014) while Carmody et al found a prevalence of 39.8% among very low birth weight neonates (Carmody et al., 2014b). Both studies were conducted at the University of West Virginia level IV NICU. Lee et al in a level III and IV NICU in Taiwan found a prevalence of 56% among very low birth weight neonates (C. Lee, 2017).

Most of these studies found that the majority of neonates were in Stage 1 AKI as compared to stages 2 and 3 AKI as shown in Table 3 below.

Table 3: Acute kidney injury by stage in various studies using the neonatal KDIGO classification.

Title/	Author	Stage 1	Stage 2	Stage 3
Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. (USA, Canada, Australia, India)	(J. G. Jetton et al., 2017)	14%	7%	9%
Incidence, risk factors, and outcome of neonatal acute kidney injury: a prospective cohort study (Saudi Arabia)	(Shalaby, Sawan, Nawawi, Alsaedi, Al-Wassia, et al., 2018)	55%	28.3%	16.7%
Nephrotoxic medication exposure in very low birth weight infants (USA)	(Rhone et al., 2014)	75%, ,	21.4%,	3.6%
Recognition and reporting of AKI in very low birth weight infants (USA)	(Carmody et al., 2014b)	25.7%	11.2%	2.9%
Incidence and outcomes of acute kidney injury in extremely-low-birth-weight infants (Taiwan)	(C. C. Lee et al., 2017)	30%	17%	9%

When looking at studies done in NICUs that used a serum creatinine cut-off of ≥ 1.5mg/dl , Youssef et al in Egypt found a prevalence of 10.8% (Youssef, Abd-Elrahman, et al., 2015), Zulic et al in Bosnia found a prevalence of 6.84% (Zulic & Hadzic, 2015),

Pradhan et al in India found a prevalence of 7.4% (Pradhan et al., 2018), while Momtaz et al in India found a prevalence of 1.54% (Sabzehei et al., 2014).

In Kenya studies done on neonatal AKI have been on a subset of the hospital neonatal population in Kenyatta National Hospital, the largest Teaching and Referral Hospital in the country. Alaro et al conducted a study in term neonates with perinatal asphyxia and found a prevalence of 11.7% (D Alaro, 2014) while Munyendo et al studied AKI in neonates with sepsis and found a prevalence of 36.1% (Munyendo, 2016).

Of note is reviews done on AKI comparing prevalence in developing countries versus developed countries have raised concern on underreporting of AKI in developing countries and lack of databases on the same therefore reducing the awareness on the seriousness of AKI and lack of proper resource allocation on the same (Bouchard & Mehta, 2016; Cerdá, Bagga, et al., 2008; Ponce & Balbi, 2016).

2.3 Factors associated with Acute Kidney Injury

Acute kidney injury in the neonate is often multifactorial resulting from a combination of susceptibility factors and exposures in the pre-natal, intrapartum and post-natal period. Risk factors for development of neonatal acute kidney injury include maternal drug intake such as non-steroidal anti-inflammatory drugs , ACE inhibitors and antibiotics , lower birth weight ,low 5-minute APGAR score, respiratory distress syndrome, intubation at birth (may lead to hypovolemia and hypotension.), birth asphyxia, patent ductus arteriosus, nephrotoxic drug use (non-steroidal anti-inflammatory drugs, antibiotics, diuretics) etc, as shown in Table 4 below). This is also supported by various

reviews on factors associated with neonatal AKI. (Andreoli, 2009a; J. G. Jetton, 2016; Nada et al., 2017; Selewski et al., 2015)

Table 4: Risk factors and etiology

Prerenal Azotemia	Intrinsic Acute Kidney Injury	Obstructive Renal Failure
Loss of effective blood volume Absolute loss -Hemorrhage - Dehydration Relative loss ↑ Capillary leak - Sepsis -NEC -RDS - ECMO - Hypoalbuminemia Renal hypoperfusion Congestive heart failure Pharmacologic agents - Indomethacin -Tolazoline -ACE inhibitors	Acute tubular necrosis - Severe renal ischemia - Nephrotoxins Infections -Congenital infections -Pyelonephritis -Bacterial endocarditis Renal vascular causes -Renal artery thrombosis -Renal vein thrombosis -DIC Nephrotoxins - Aminoglycosides - Indomethacin -Amphotericin B -Radiocontrast dyes - Acyclovir Intrarenal obstruction - Uric acid nephropathy -Myoglobinuria -Hemoglobinuria Congenital malformations -Bilateral renal agenesis - Renal dysplasia - Polycystic kidneys	Congenital malformations -Imperforate prepuce - Urethral stricture - PUV -Urethral diverticulum -Ureterocele - Megaureter -UPJ obstruction Extrinsic compression -Sacrococcygeal teratoma -Hematocolpos Intrinsic obstruction - Renal calculi - Fungus balls Neurogenic bladder

*Textbook of Avery's Disease of the Newborn Ninth Edition, Part XVII, pg 1208

A study done in Egypt showed the predisposing factors for AKI to be sepsis in 63% of the cases, respiratory distress syndrome in 55.6%, mechanical ventilation in 51.9%, peri-

natal asphyxia in 18.5%, dehydration in 14.8%, surgical operation in 11.1%, congenital heart disease in 7.4%, sub-galeal hematoma in 3.7%, polycythemia in 3.7% and intra-ventricular hemorrhage in 3.7% of the cases (Youssef, Abd-Elrahman, et al., 2015). This study however like most studies done on neonates did not look at the statistical significance of this factors.

Conditions that predispose to hypovolemia, hypoxemia, and septicemia overall lead to hypoperfusion and reduction in GFR. This leads to activation of the renin -angiotensin and sympathetic nervous systems causing renal vasoconstriction. The reduction of oxygen delivery to tissue predisposes to acute tubular necrosis.

Sepsis -It has been proposed that AKI in sepsis is not only mediated by hypoperfusion but also by direct injury to the kidneys as evidenced by AKI in sepsis despite good maintenance of systemic blood pressure. Momtaz et al, and Satvik et al found sepsis to be significantly associated with AKI (Bansal et al., 2017; Momtaz et al., 2014).

Prematurity – Lower gestation age neonates are at an increased risk of AKI due to incomplete nephrogenesis and the lower number of nephrons not being able to cope with insult. Several studies that found lower gestation age to be associated with AKI (Carmody et al., 2014b; C. C. Lee et al., 2017; Momtaz et al., 2014; Shalaby, Sawan, Nawawi, Alsaedi, Al-Wassia, et al., 2018).

Interestingly the AWAKEN study found a U- curved distribution of AKI indicating that extremes of age were at increased risk of AKI. However they had an age category that is yet to be reported in other studies of >29 weeks- < 36 weeks (J. G. Jetton et al., 2017).

The higher gestation age risk was postulated to be due to the higher likelihood of older neonates presenting with more severe illness.

Lower birth weight- Several studies have been done on the various birth weight categories and demonstrated an association between AKI and lower birth weight (Bolat et al., 2013; Koralkar, Ambalavanan, Levitan, McGwin, et al., 2011; Mathur et al., 2006; Selewski et al., 2013). The relation can be attributed to lower birth weight neonates having less mature kidneys and less nephron numbers predisposing them to higher risk of damage from insult to the kidney.

Perinatal asphyxia and low apgar score Perinatal asphyxia is the most common cause of neonatal AKI. It causes a predominantly non- oliguric AKI. Following ashyxia there is impaired renal perfusion which leads to a reduction in GFR.

Hypoxic-ischemic encephalopathy accounts for 23% of neonatal deaths globally. In a study by Karlowicz and Adelman they found that Acute renal failure was present in 20 of 33 (61%) of neonates with severe asphyxia scores and 0 of 33 with moderate asphyxia scores ($P<0.0001$). (Karlowicz & Adelman, 1995) . In a case–control analysis that matched for gestational age and birth weight the incidence of AKI in neonates with 5 min Apgar scores ≤ 6 was 56% compared to 4% in controls ($p=0.002$) (Aggarwal et al., 2005). Other studies that have demonstrated an association between lower apgar score and AKI including (Cataldi et al., 2005; Gadepalli et al., 2011; Koralkar, Ambalavanan, Levitan, McGwin, et al., 2011; Selewski et al., 2013)

Studies done in Kenyatta National Hospital on prevalence of AKI in neonates with birth asphyxia showed a 15 fold increase in risk of developing AKI in HIE III versus HIE I, p=0.034. (D Alaro, 2014).

Nephrotoxic drug use- The 'immature' neonatal kidney is especially vulnerable to insult resulting from use of nephrotoxic medication such as aminoglycosides. Studies have been sparse on neonatal AKI due to nephrotoxic drugs compared to paediatric and adult studies. This may be due to the fact that the unique physiology of the neonatal kidney makes it difficult to attribute causality (Rhone et al., 2014). For example it is difficult to apportion a case of AKI to the use of the drug or the pathology (sepsis) that necessitated such drug and the antecedent prematurity and incomplete nephrogenesis that could have predisposed to AKI. Rhone et al conducted a study on nephrotoxic drug use in very low birth weight neonates and found a prevalence of 26.2 %, Infants with AKI received more nephrotoxic medications per day than those who did not (0.24 versus 0.15; p=0.003) and that there was a linear association between total nephrotoxic medication days and peak creatinine (mg/dL) with AKI, this association persisted in multivariable models accounting for birth weight or gestational age. Koralkar et al also found nephrotoxic drug use to be associated with AKI (Koralkar, Ambalavanan, Levitan, McGwin, et al., 2011).Surprisingly it is postulated that the same neonatal renal physiology may be protective of AKI in the neonate: the immature tubular transport function may hinder nephrotoxic drugs from reaching their full toxic potential compared to the same exposure in an older child (Suzuki, 2009).

Persistent **Hypothermia** causing hypoperfusion to the kidney with resultant acute tubular necrosis can be a cause of AKI in neonates. In a study done in Egypt, Ghobrial found that lower temperature of the neonate was significantly associated with AKI (Ghobrial et al., 2018).

Bolat et al in Turkey and Lee et al in Taiwan both found mechanical ventilation to be significantly associated with AKI (Bolat et al., 2013; C. C. Lee et al., 2017). Koralkar et al in the United States and Bolat et al in Turkey both found umbilical vein catheterization to be associated with AKI (Bolat et al., 2013; Koralkar, Ambalavanan, Levitan, McGwin, et al., 2011). Lee et al in Taiwan and Koralkar et al in the United States found high-frequency ventilation support and inotropic agent use to be associated with increased risk of AKI while maternal pre-eclampsia was found to be a protective factor (Koralkar, Ambalavanan, Levitan, McGwin, et al., 2011; C. C. Lee et al., 2017). Other factors that have been found to be significantly associated with AKI include; maternal illness (Ghobrial et al., 2018) Pregnancy-induced hypertension , preterm prolonged rupture of membranes, administration of antenatal corticosteroid, and ibuprofen therapy for patent ductus arteriosus (Bolat et al., 2013); clinical risk index for babies score (Carmody et al., 2014b; Shalaby, Sawan, Nawawi, Alsaedi, Al-wassia, et al., 2018); the presence of patent ductus arteriosus, (C. C. Lee et al., 2017). In this study Maternal pre-eclampsia was found to be a protective factor.

Renal and urinary tract abnormalities in this age group is **c**aused by congenital bilateral obstruction of the urinary tract. Prompt removal of the obstruction usually reverses AKI.

2.4 Short term outcomes of neonates with acute kidney injury.

2.4.1 Mortality

Published studies estimate that mortality rates in critically ill neonates are between 10% and 61% (Andreoli, 2009b). More importantly ,AKI has been found to be an independent risk factor for mortality after adjusting for comorbidities and severity of other illnesses. According to a meta-analysis by Ricci et al, done on studies that had RIFLE classification of AKI from 2004 -2007, comparison between those with and without AKI having adjusted for severity of illness and comorbidities, showed significant increase in mortality with deterioration in kidney function. The relative risk of mortality among patients classified as Risk, Injury and Failure was (RR) 2.4, 4.15, and 6.37 respectively($P < 0.0001$ for all) (Ricci et al., 2008) , showing an increased mortality with increasing severity of AKI. This findings were consistent with studies done by Gadepelli et al and zweirs et al, who also demonstrated increased mortality risk with increasing severity of AKI (Gadepalli et al., 2011; Zwiers et al., 2013). In a study done in Kenyatta National Hospital on neonates with perinatal asphyxia, a 24 fold increased risk of death in neonates with AKI was reported., $p=0.001$ (D Alaro, 2014). A number of other studies have found significantly higher mortality in neonates with AKI (Agras et al., 2004; Carmody et al., 2014a; DJ Askenazi, 2009; Koralkar, Ambalavanan, Levitan, McGwin, et al., 2011; Mathur et al., 2006; Shalaby, Sawan, Nawawi, Alsaedi, Al-wassia, et al., 2018; Viswanathan et al., 2012) .

2.4.2 Length of Hospital Stay

Neonates with AKI have been reported to have a prolonged length of hospitalization compared to those without. In a study by Alabbas et al on cardiac surgery associated AKI in neonates , while AKI was not independently associated with an increased length of PICU and overall hospital stay they found that only higher AKI stage (Stage 3 AKIN) was associated with increased length of hospital stay (Alabbas et al., 2013). AKI predicting length of stay has been demonstrated in many other studies (J. G. Jetton et al., 2017).

Some studies however have not found AKI to be associated with increased length of hospital stay. In a study done in Cairo, Egypt, there was no statistically difference in the mean hospital stay among neonates with AKI 24.6 ± 13.3 days compared to those without 25 ± 17.4 days (p-value = 0.84) (Ghobrial et al., 2018). In a study by Shalaby et al, the median length of hospitalization was higher for neonates with AKI compared to those without AKI, however when survivors only were assessed, AKI did not predict the length of hospital stay (Shalaby, Sawan, Nawawi, Alsaedi, Al-Wassia, et al., 2018).

CHAPTER THREE: METHODOLOGY

3.1 Research Design

This was a prospective descriptive study design.

3.2 Study Area

The study was conducted at the new born unit, Riley mother and baby hospital part of Moi teaching and referral hospital**.** Moi Teaching and Referral Hospital (MTRH) is located in Eldoret town, Uasin Gishu County, which is 350 Kilometers North West of Nairobi. MTRH is a level 6 health facility serving as a teaching hospital for Moi University, School of Medicine, Nursing, Public Health and Dentistry. Other institutions that also utilize this facility include Kenya Medical Training Center (KMTC), Eldoret and University of Eastern Africa Baraton School of Nursing. MTRH is also a training center for medical, clinical and nursing officer interns. It serves as the main referral hospital for the Western part of Kenya and North Rift and has a catchment population of approximately 13 million people. Riley Mother and Baby Hospital is a unit within MTRH which houses the hospital's maternity unit, obstetric theatre and the new born unit. The newborn unit has a 50 bed capacity and admits neonates with medical and surgical conditions from the hospital as well as referrals-in.

The new born unit admits approximately 200 newborn babies monthly, 60 % of which are born within the maternity unit and 40% being referrals from other facilities.

3.3 Study Population

All neonates admitted to NBU MTRH from September 2017 to March 2018.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

All neonates admitted to Riley Mother and Baby new born unit and surviving at least 48 hrs of life.

3.4.2 Exclusion criteria

1. Neonates brought to the new born unit for observation or accommodation.

2. Neonates surviving 48 hrs of life but were marked for observation and /discharge.

All neonates that meet the inclusion criteria and whose parents consented to inclusion into the study had a serum creatinine test done at recruitment, thereafter they were followed up for development of acute kidney injury. Factors associated with AKI were assessed using a questionnaire.

3.5 Sample size

The sample size was calculated using Fisher's formula where:

$$n = \frac{Z^2 \times p \times q}{d}$$

$$n = \frac{1.96^2 \times 0.24 \times 0.76}{0.05^2}$$

$$n = 280$$

Where;

n = sample size;

Z = the Z core value corresponding to 95% confidence =1.96

q=(1-p)

p = prevalence of AKI among neonates admitted to neonatal care units 24% (Andreoli, 2002).

d = margin of error

3.6 Sampling Procedure

Systematic sampling technique was used. The average number of admissions to the new born unit in a month is approximately 200 neonates. With an intent of data collection minimum period of 5 months k=3. We listed the neonates who fit the inclusion criteria as per their admission date and time and picked every 3rd for inclusion into the study with replacement until the minimal sample size was achieved. The starting point was selected through simple random sampling.

3.7 Data Collection, Tools and Procedures

Informed consent was sought for every 3rd neonate who fitted the inclusion criteria. At recruitment the relevant social demographic and clinical data was collected by the principle investigator/research assistant. The principle investigator or research assistant took a venous blood sample for serum creatinine of the neonate using aseptic technique (Appendix 5). A Cobas C 111 machine using the Jaffee method was used for analyzing the sample.(Appendix 6). Other labs already collected for the participant by the primary doctor or clinician were recorded including urea/electrolyte/creatinine, Blood Gas Analysis, culture results. Clinical notes were also checked to evaluate for risk factors as per Table 4. Renal Congenital anomalies were evaluated only for those who had imaging done. The mothers were interviewed to gauge maternal risk factors and information recorded in the questionnaire. Medical records review were also used to further assess neonatal risk factors. This information was obtained from both the clinical team and from

the records in the files daily and all results recorded daily for the first 7 days of life and thereafter weekly snapshots were recorded. Weekly snapshots included the first, best and worst parameter available for the week. All creatinine levels done and recorded throughout the neonate's stay were used in determination of AKI. If a neonate with risk factors for acute kidney injury had no serum creatinine ordered, then the investigator brought it to the attention of the clinical team and a consensus was reached on suitability to take a sample. For those without a repeat sample for serum creatinine within 7 days, a sample was taken.

Follow up was done daily until death, discharge or 28 days of life, whichever came earlier. During the study period the interpretation of, and response to SCr values was left to the medical team. However, the research team would notify the clinical team of any derangements for their action. There were no specific interventions in terms of medical management that was done by the research team.

Recruitment of the study subjects, filling of the data collection tool and sample taking was done by the principle investigator and two research assistants (clinical officers). They had undergone a one week training on the study including on ethics and informed consent, phlebotomy practices in neonates, study procedure and protocol prior to the beginning of the study .

Quality Assurance

Callibration of the machines used were done in accordance to the Moi Teaching and Referral Hospital standard operating procedure . The MTRH labs are ISO certified laboratories.

3.8 Methods of Data Analysis

Statistical analysis were conducted using STATA version 13 SE. Descriptive data was presented as numbers (percentages) or mean (standard deviation), frequency tables, as appropriate. Test of associations between the neonatal/ maternal factors and the study outcomes were performed using Chi-square test and fisher's exact test for categorical variables and comparisons of means and medians were done using student's T test and Mann Whitney U test respectively. A p-value of less than 0.05 was considered statistically significant.

3.9 Ethical Considerations

Permits: Ethical approval to conduct the study was sought from the Institutional Research Ethics Committee (IREC) at the Moi Teaching and Referral Hospital/ Moi University School of Medicine on behalf of the National Commission of Science, Technology and Innovations (NACOSTI). Approval to conduct the study at MTRH was obtained from The Chief Executive Officer MTRH. The primary doctor was informed of any derangements in serum creatinine for action.

Consent: Voluntary and written informed consent was obtained from the parents. Only those who freely consented were allowed to participate in the study, and no one was coerced to participate. Participants were also informed that they had the right to withdraw at any point of participation in the study.

3.10 Dissemination plan

Upon completion, this work will be disseminated at the departmental level, child health and paediatrics ,school of medicine ,moi university, Moi university library and moi university website library.

Once approved, it will be submitted for publication in a peer review journal.

CHAPTER FOUR: RESULTS

4.1 Population Description

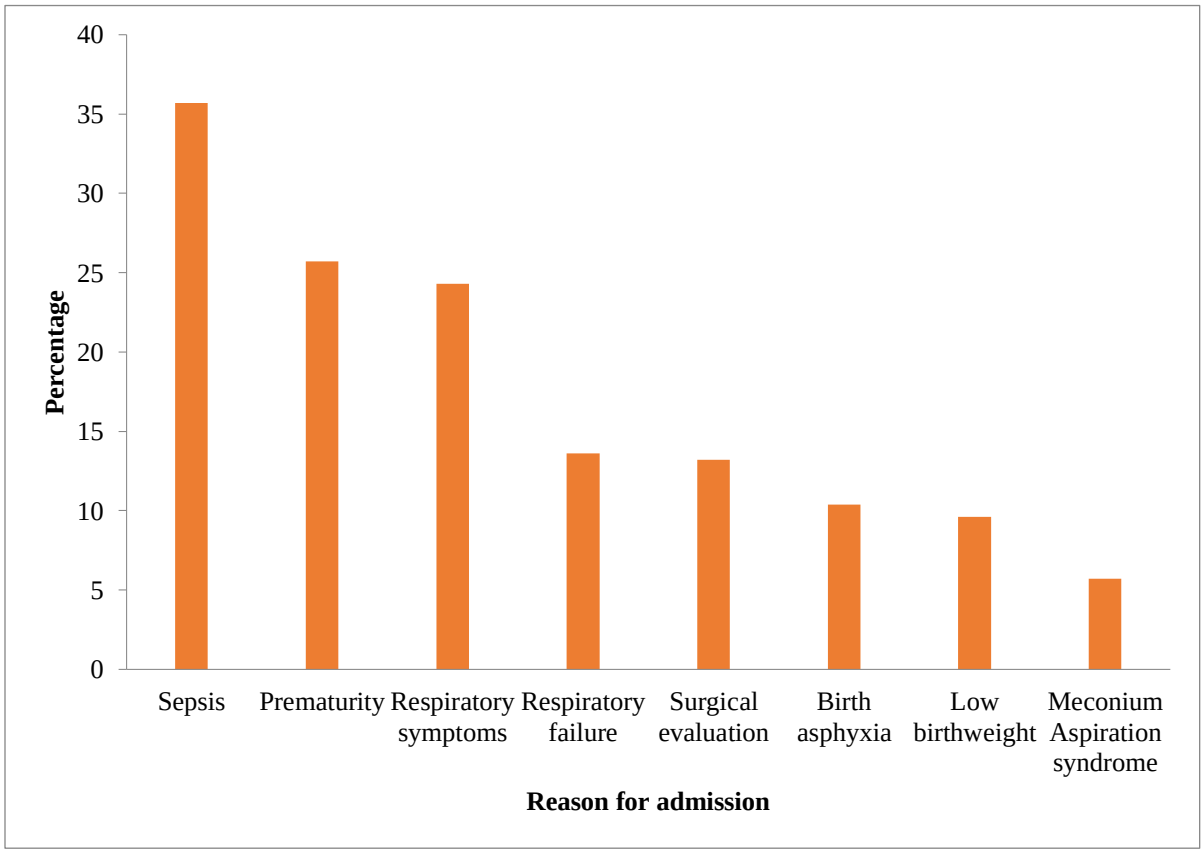
A total of 280 neonates were recruited and studied. The male to female ratio was 1:1.1. Those born and admitted directly from Riley Mother and Baby Hospital (Inborn) were 152 (46.1 %).

4.1.1 Neonatal characteristics

Table 4.1: Neonatal Characteristics

Variable	**Freq (%)**
Gender	
Female	148 (52.9)
Male	132 (47.1
Site of delivery	
Inborn	129 (46.1)
Outborn	151 (53.9)
Mode of delivery	
Scheduled C-section	21 (7.9)
Unscheduled C-section	35 (13.1)
Vaginal breech	7 (2.6)
Vaginal vertex	217 (77.5)
APGAR at 5 minutes	
Missing	31 (11.1)
3 to 5	26 (9.3)
6 to 7	45 (16.1)
8 to 10	178 (63.6)
Birthweight in grams	
<1000	9 (3.2)
1000 to1500	28 (10.0)
>1500-2500	85 (30.4)
>2500	158 (56.4)
Gestation age in Weeks	
Missing	16 (5.7)
<35 weeks	78 (27.9)
>=35 weeks	186 (66.4)
Resuscitation	
Chest compressions	1 (0.4)
None	167 (59.6)
PPV	22 (7.9)
Supplemental oxygen	88 (31.4)
Unknown	2 (0.7)

4.1.2 Reason for admission



The most common reasons for admission was sepsis at 35.7% , prematurity at 25.7% and Respiratory symptoms at 24.3%.

*Respiratory symptoms (all diagnoses)

*Respiratory failure (all diagnoses)

Figure 1: Reason for admission

4.1.3 Maternal characteristics

The median age of the mothers was 25 years (IQR 22, 29). The majority reported no complications during pregnancy

Table 4.2: Characteristics of the Mothers

Variable	Freq (%)
Maternal age in years	
Mean (std)	25.5 (5.6)
Median (IQR)	25 (22,29)
Parity	
Parity 1-2	216 (77.1)
Parity >2	64 (22.9)
Education Level	
Primary	104 (37.1)
Secondary	124 (44.3)
Tertiary	52 (18.6)
Maternal Drugs	
ACE-Inhibitors	7 (2.5)
Beta blockers	10 (3.6)
Warfarin	1 (0.4)
NSAIDs	1 (0.4)
None	259 (92.5)
Unknown	2(0.7)
Intrapartum complication	
Meconium	19 (6.8)
None	243 (86.8)
Nuchal cord	3 (1.1)
Severe maternal vaginal bleeding	1 (0.4)
Unknown	14 (5.0)

4.1.4 Frequency of Maternal Factors

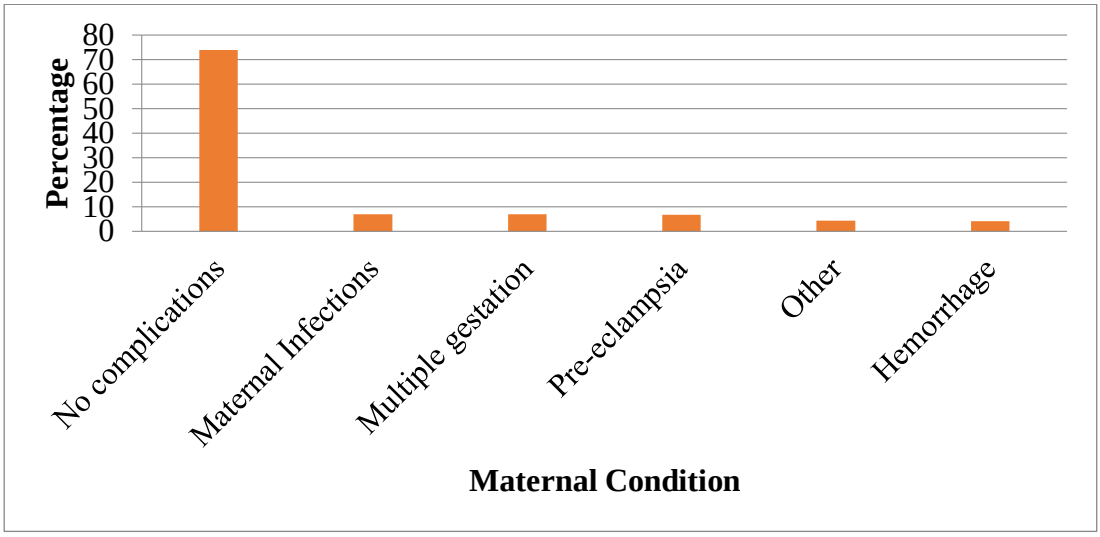


Figure 2: Frequency of Maternal Factors

4.2 Prevalence of acute kidney injury among neonates admitted in NBU of MTRH

Prevalence was 19.78% **(95%CI: 15.27, 24.96).**

Excluding the 2 neonates with missing data. We did a best and worst-case scenario with inclusion of the two and found a prevalence of 19.64% and 20.35% respectively which was within the confidence interval (95% CI: 15.27, 24.96) hence no major impact on the prevalence.

Table 4.3: Prevalence of AKI by Stage.

Majority of the neonates with AKI had stage 3 AKI at 13.67%.

AKI	Freq	Percent
Stage 1	13	4.68
Stage 2	4	1.44
Stage 3	38	13.67
None	223	80.22

Table 4.4: The median time to development of AKI

Time to development of AKI	Median (Days)	IQR
From Birth	**7 days**	**(4, 16)**
From Admission	**5 days**	**(4, 9)**

The median time to development of AKI was 7 days, IQR (4,16), with median time to development of AKI from day of admission being 5 days, IQR (4,9).

4.3 Factors associated with acute kidney injury in the NBU of MTRH.

Among both the neonatal and maternal factors that we looked at, none of them attained statistical significance.

Table 4.5 Factors Associated with AKI

Variable	NO AKI	AKI	p-value
	Freq (%)	Freq (%)	
Maternal age	25 (22,29)	24.5 (21,27)	0.271
Median (IQR)			
Education			
Primary	84 (80.8)	20 (19.2)	0.719
Secondary	101 (81.5)	23 (18.5)	
Tertiary	38 (76)	12 (24)	
Parity			
Nulliparous	11 (73.3)	4 (26.7)	0.515
Para 1-2	153 (78.9)	41 (21.1)	
Para >2	54 (84.4)	10 (15.6)	
Site of delivery			
Inborn	108 (83.7)	21 (16.3)	0.144
Outborn	108 (76.6)	33 (23.4)	
Mode of delivery			
Vaginal	178 (80.2)	44 (19.8)	0.853
C-section	45 (80.4)	11 (19.6)	
Gender			
Female	116 (78.4)	32 (21.6)	0.346
Male	107 (82.3)	23 (17.7)	
APGAR at 5 minutes			
3 to 5	25 (96.2)	1 (3.8)	0.074
6 to 7	34 (75.6)	11 (24.4)	
8 to 10	145 (82.6)	31 (17.4)	
Birth weight in grams			
<1000	5 (55.6)	4 (44.4)	0.192
1000 to1500	23 (82.1)	5 (17.9)	
1500-2500	72 (84.7)	13 (15.3)	
>2500	123 (78.8)	33 (21.2)	
Gestation age in weeks			
<35 weeks	60 (78.9)	16 (21.1)	0.832
>=35 weeks	149 (80.1)	37 (19.9)	
Respiratory symptoms			
No	115 (81)	27 (19)	0.742
Yes	108 (79.4)	28 (20.6)	
Respiratory support			

CPAP	29 (76.3)	9 (23.7)	0.360
Nasal Cannula	85 (77.3)	25 (22.7)	
No support	109 (83.9)	21 (16.1)	
Sepsis			
No	135 (82.3)	29 (17.7)	0.292
Yes	88 (77.2)	26 (22.8)	
Bacteremia			
No	27(81.8)	6 (18.2)	0.527
Yes	23(79.3)	6(20.7)	
Aminoglycoside use			
No	98(80.3)	24(19.7)	0.967
Yes	125(80.1)	31(19.9)	

4.4: Outcome of neonates with acute kidney injury.

4.4.1 Mortality versus AKI

A total of 45 (16%) neonates died with a median time to death from admission of 7 days (IQR: 6,13) mean=9.3 (std=13.49).

Acute Kidney injury was significantly associated with mortality with a 19 (34.6%) mortality rate p<0.001.

Table 4.6: Mortality versus AKI

AKI status	Status at 28 days		p-value (OR, 95% CI)
	Alive	Dead	
No AKI	197 (88.34)	26 (11.66)	<0.001 (3.999; 2.006 - 7.973)
AKI	36 (65.45)	19 (34.55)	

4.4.2 Mortality by stage

Of the neonates with AKI who died 16 (84.2%) had AKI stage 3, 2(10.5%) had stage 2 and only 1(5.1%) in stage 1 AKI.

There was no association between mortality and AKI stage p=0.212.

Table 4.7. Mortality by AKI stage

Variable	Alive	Dead	P-value
Stage 1	11 (84.62)	2 (15.38)	0.212
Stage 2	3 (75.0)	1 (25.0)	
Stage 3	22 (57.9)	16 (42.1)	

4.3.2 Length of stay in hospital among those who were discharged

There was no statistically significant difference in the length of stay in the NBU between those with and those without AKI among those discharged before 28 days of life with the median being 7(6,12) and 7(6,14) days for No AKI and AKI groups respectively with a P value of 0.537.

Table 4.6 Length of Hospital Stay

	No AKI	AKI	
Median length of stay*	N=140 7 (6,12)	N=20 7 (6,14)	0.537

CHAPTER FIVE

5.0 DISCUSSION

5.1 Prevalence of acute kidney injury among neonates admitted in the newborn unit of MTRH

In this study, the prevalence of AKI among neonates was reported as 19.78% (n=55). This is close to the AWAKEN study using the Neonatal KDIGO classification while analyzing AKI by serum creatinine only, which found a prevalence of 18.8% (J. G. Jetton et al., 2017). While the prevalence in our study was lower in comparison, The Awaken study had a more stringent selection criteria (intravenous fluids as the primary source of hydration/nutrition for the first 48hrs of life) to ensure that only those with increased risk of developing AKI were studied. Considering a more critically ill population in the AWAKEN study we would speculate that our prevalence could have been higher if the same inclusion criteria was applied. In comparison, a study done on AKI in neonates in Egypt showed a prevalence of 10.8%. However, AKI in this study was defined by SCr greater than 1.5mg/dl which may lead to an underestimation of the prevalence.

The findings of this study differed with proportions reported in other regions. Higher prevalence of AKI was reported in a Saudi Arabian study at 56% (Shalaby, Sawan, Nawawi, Alsaedi, Al-Wassia, et al., 2018). This Saudi Arabian study targeted neonates in level II and III NICUs with a higher severity of illness as opposed to the current study conducted in a general newborn unit. However, the prevalence of AKI at MTRH was higher than in a study in the United States of America at 12.5% (Viswanathan et al., 2012); Bosnia at 6.84% (Zulic & Hadzic, 2015); India at 7.54% (Pradhan et al., 2018) and Iran at 1.54% (Momtaz et al., 2014). This could be explained by the difference in the definitions of AKI in this studies.

This study further reported that neonates with stage III AKI were the highest, followed by those with stage I and II respectively. These findings contrast those in the AWAKEN study (J. G. Jetton et al., 2017),a study in Saudi Arabia (Shalaby, Sawan, Nawawi, Alsaedi, Al-wassia, et al., 2018) and a Taiwan study (C. C. Lee et al., 2017) who found stage I AKI as the most prevalent. The lower prevalence could be attributed to a lower frequency of sampling done in this study compared to other studies that have had frequent sampling done. An observation from the AWAKEN study was that centers with more frequent sampling of SCr had the highest prevalence of AKI while those with lower sampling reported lower prevalence of AKI. Frequent serum creatinine measures increase the likelihood of early intervention while reducing the risk of disease progression.

5.2 Socio-demographics characteristics

The ratio of males to females' neonates with AKI was 1:1.1. Other studies have found a male predominance which has been attributed to boys having a higher risk of perinatal adverse conditions such as , neonatal sepsis and respiratory distress and lower survival rates. Youssef D et al, Mortazavi et al and Airede et al, all found a male predominance with male to female ratios of 1.3:1 , 2:1, and 3.3:1 respectively (Airede et al., 1997; Mortazavi & Sakha, 2009; Youssef, Abd-elrahman, et al., 2015). Studies that have found a female predominance include Evlijana et al (Evlijana & Devleta, 2015).

The most common reason for admission contributing to AKI was Sepsis evaluation (35%), prematurity (24%) and respiratory symptoms (23%). This are the most common conditions found in the neonatal population and would lead to admission in hospital and correspond to what has been found in other studies. The most common reasons for

admission in the Awaken study was prematurity, respiratory failure and sepsis evaluation accounting for 52.1%, 46.1%, and 50.2% respectively (J. Jetton et al., 2017).

5.3 Factors associated with acute kidney injury in neonates

This study found no association between neonatal and maternal characteristics and the occurrence of acute kidney injury. These findings contrast those conducted in Egypt (Ghobrial et al., 2018), India (Mathur et al., 2006), Saudi Arabia (Shalaby, Sawan, Nawawi, Alsaedi, Al-Wassia, et al., 2018) and Taiwan (C. C. Lee et al., 2017).

In the Egyptian study, maternal illness was significantly associated with neonatal acute kidney injuries (Ghobrial et al., 2018). However, the Egyptian study also found no statistically significant association between neonatal sepsis, prematurity, Respiratory distress syndrome, congenital heart disease, hypoxic ischaemic encephalopathy and the use of aminoglycosides. The difference between the current study findings and Ghobrial's study could be attributed to differences in study designs and target population. The current study adopted a prospective study design among neonates in a general new-born unit while Ghobrial's study was a 1:2 case-control study in a neonatal intensive care unit (NICU) among neonates with and without acute kidney injury (Ghobrial et al., 2018).

In India, it was reported that birth weight (p-value = 0.008), gestational age of less than 35 weeks (p=0.010) and neonatal sepsis (p=0.03) were associated with the occurrence of neonatal sepsis (Mathur et al., 2006). The authors of this Indian study conducted a case-control study among 200 out-born neonates in a NICU. This could explain the reason for the deviance between the current study's findings and those from Indian study (Mathur et

al., 2006). In Saudi Arabia (Shalaby, Sawan, Nawawi, Alsaedi, Al-wassia, et al., 2018), gestational age ($p < 0.001$) and perinatal depression (RR = 10; 95% CI = 2-46) were associated with AKI.

In a study done in Taiwan, Low birth weight was associated with occurrence of acute kidney injury. (C. C. Lee et al., 2017). The Taiwanese study further reported an association of AKI with high frequency of ventilation ($p<0.001$), presence of patent ductus arteriosus ($p<0.001$), lower gestational age and ionotropic agents, while pre-eclampsia was found to be protective against AKI. This study was carried out among extremely low birth weight neonates who due to their incomplete nephrogenesis could be at increased risk of developing AKI, more so than among neonates in a general population of sick neonates like in our study.

5.4 Neonatal outcomes following acute kidney injury

5.4.1 Mortality following acute kidney injury

The study found a strong relationship between mortality and acute kidney injury ($p<0.001$). The current's study findings were comparable to the majority of studies looking at AKI as a predictor of mortality in neonates whereby, AKI has been found to be associated with increased mortality..(Agras et al., 2004; Ghobrial et al., 2018; J. G. Jetton et al., 2017; Koralkar, Ambalavanan, Levitan, McGwin, et al., 2011; C. C. Lee et al., 2017; Viswanathan et al., 2012).

However, in the study by Viswanathan in The United States the mortality percentage for those with AKI 70% was much higher than that in our study (34.6%) or even in any other studies reviewed (Viswanathan et al., 2012) This could be explained by the difference in

study population from ours of a general neonatal population compared with one of extremely low birth weight neonates and a subsequently higher mortality expected in Extremely low birth weight neonates. Both the current study and that of Viswanathan found a statistically significant relationship between acute kidney injury and neonatal mortality.

5.4.2 Length of hospital stay following acute kidney injury

This study found no association between acute kidney injury and the length of stay(LOS) ($p=0.537$). This was similar to the findings of (Ghobrial et al., 2018; Shalaby, Sawan, Nawawi, Alsaedi, Al-wassia, et al., 2018) who did not find any association between acute kidney injury and length of hospital stay. Ghobrial et al found a median duration of LOS of 22.5 days for those with AKI and 22 days for those without AKI $p=0.84$. The crude duration of hospital stay had a mean difference of 14 (95% CI 5.5 -23) days between those with AKI versus those without however, after adjustment for gestational age, AKI was not associated with the length of hospital stay ($p= 0.133$). In a retrospective study conducted in a children's hospital in Vancouver – Canada among neonates following cardiac surgery, neonates with acute kidney injury spent nearly seven (7) more days in the hospital compared to those without. This was a statistically significant ($p<0.05$) relationship (Alabbas et al., 2013). In the AWAKEN study neonates with AKI who survived had a statistically significant longer median hospital stay of 23 (IQR: 11-64) days compared to 19 days (IQR: 9-36) $p<0.0001$ (J. G. Jetton et al., 2017). In Michigan – USA, the mean neonatal ICU stay was 15.4 ± 5.3 days among those with AKI compared to those without 11 ± 5.9 days, with a statistically significant association of p-value = 0.014 (Sewelski *et al*, 2013). Our study compared with all this studies had a lower

median LOS for both those with AKI 7(6-12) and those without AKI 7(6-14) days . This could be attributed to having a more general new-born unit where you have a combination of neonates who do not require intensive care and those who are critically ill with the majority being those that require only a short duration of hospitalization thus making it difficult to make comparisons with duration of stay in centres with higher level NICU set-up.

5.5 Limitations

While this study aims to look at the prevalence and associated factors of AKI, it did not evaluate for congenital anomalies and post renal risk factors requiring imaging in all patients. Only those whose imaging had already been done were evaluated for presence or absence of that risk. We did not have any control on the timing of subsequent creatinine samples for neonates and furthermore our new born unit has no set guidelines on the timings of sample taking for the various categories of neonates. The current international guidelines still call for individualized timing of serum creatinine samples in evaluation of AKI. This could potentially contribute to lack of early detection of cases.

CHAPTER SIX

6.0 CONCLUSIONS, RECOMMENDATIONS

6.1 Conclusions

1. The prevalence of acute kidney injury among neonates seen at the newborn unit of MTRH is high (one in five neonates were found to have AKI), comparable to worldwide statistics, with majority being in more severe stages of AKI.

2. There was no statistically significant association between socio-demographic, clinical factors and acute kidney injury.

3. There was an increased odds of mortality among those with AKI.

6.2 Recommendations

1. There is need for higher index of suspicion for AKI among clinicians with increased screening and surveillance for acute kidney injury.

2. More studies on the associated factors of acute kidney injury should be conducted.

3. Closer monitoring and appropriate management for those with AKI due to the high mortality.

REFERENCES

Aggarwal, A., Kumar, P., Chowdhary, G., Majumdar, S., & Narang, A. (2005). Evaluation of renal functions in asphyxiated newborns. *Journal of Tropical Pediatrics*, *51*(5), 295–299.

Agras, P. I., Tarcan, A., Baskin, E., Cengiz, N., Gürakan, B., & Saatci, U. (2004). Acute renal failure in the neonatal period. *Renal Failure*, *26*(3), 305–309.

Airede, A. I., Bello, M., & Weerasinghe, H. D. (1997). Acute renal failure in the newborn: Incidence and outcome. *Journal of Paediatrics and Child Health*, *33*(3), 246–249.

Akcan-Arikan, A., Zappitelli, M., Loftis, L. L., Washburn, K. K., Jefferson, L. S., & Goldstein, S. L. (2007). Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney International*, *71*(10), 1028–1035.

Alabbas, A., Campbell, A., Skippen, P., Human, D., Matsell, D., & Mammen, C. (2013). Epidemiology of cardiac surgery-associated acute kidney injury in neonates: A retrospective study. *Pediatric Nephrology*, *28*(7), 1127–1134.

Alaro, D., Bashir, A., Musoke, R., & Wanaiana, L. (2014). Prevalence and outcomes of acute kidney injury in term neonates with perinatal asphyxia. *African health sciences*, *14*(3), 682-688.

Andreoli, S. P. (2002). Acute renal failure. In *Current Opinion in Pediatrics 14*(2) 183–188) Curr Opin Pediatr.

Andreoli, S. P. (2009). Acute kidney injury in children. *Pediatric nephrology*, *24*(2), 253.

Andreoli, S. P. (2009b). Acute kidney injury in children. *Pediatric Nephrology*, *24*(2), 253–263.

Askenazi, D. J., Ambalavanan, N., & Goldstein, S. L. (2009a). Acute kidney injury in critically ill newborns: What do we know? What do we need to learn? In *Pediatric Nephrology 24*, (2), 265–274

Askenazi, D. J., Ambalavanan, N., & Goldstein, S. L. (2009b). Acute kidney injury in critically ill newborns: What do we know? What do we need to learn? *Pediatric Nephrology*, *24*(2), 265–274.

Askenazi, D. J., Griffin, R., McGwin, G., Carlo, W., & Ambalavanan, N. (2009). Acute kidney injury is independently associated with mortality in very low birthweight infants: a matched case–control analysis. *Pediatric Nephrology*, *24*(5), 991-997.

Askenazi, D., Abitbol, C., Boohaker, L., Griffin, R., Raina, R., Dower, J., ... & Milner, L. (2019). Optimizing the AKI definition during first postnatal week using Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) cohort. *Pediatric research*, *85*(3), 329-338.

Bansal, S. C., Nimbalkar, A. S., Kungwani, A. R., Patel, D. V., Sethi, A. R., & Nimbalkar, S. M. (2017). Clinical profile and outcome of newborns with acute kidney injury in a level 3 neonatal unit in western India. *Journal of Clinical and Diagnostic Research*, *11*(3), SC01–SC04.

Bolat, F., Comert, S., Bolat, G., Kucuk, O., Can, E., Bulbul, A., Uslu, H. S., & Nuhoglu, A. (2013). Acute kidney injury in a single neonatal intensive care unit in Turkey. *World Journal of Pediatrics*, *9*(4), 323–329.

Bouchard, J., & Mehta, R. L. (2016). Acute Kidney Injury in Western Countries. *Kidney Diseases*, *2*(3), 103–110.

Carmody, J. B., Swanson, J. R., Rhone, E. T., & Charlton, J. R. (2014a). Recognition and reporting of aki in very low birth weight infants. *Clinical Journal of the American Society of Nephrology*, *9*(12), 2036–2043.

Carmody, J. B., Swanson, J. R., Rhone, E. T., & Charlton, J. R. (2014b). Recognition and reporting of AKI in very low birth weight infants. *Clinical Journal of the American Society of Nephrology : CJASN*, *9*(12), 2036–2043.

Cataldi, L., Leone, R., Moretti, U., De Mitri, B., Fanos, V., Ruggeri, L., Sabatino, G., Torcasio, F., Zanardo, V., Attardo, G., Riccobene, F., Martano, C., Benini, D., & Cuzzolin, L. (2005). Potential risk factors for the development of acute renal failure in preterm newborn infants: A case-control study. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, *90*(6), 514–519.

Cerdá, J., Bagga, A., Kher, V., & Chakravarthi, R. M. (2008). The contrasting characteristics of acute kidney injury in developed and developing countries. In *Nature Clinical Practice Nephrology 4*(3), 138–153.

Cerdá, J., Lameire, N., Eggers, P., Pannu, N., Uchino, S., Wang, H., Bagga, A., & Levin, A. (2008). Epidemiology of Acute Kidney Injury. *Clinical Journal of the American Society of Nephrology*, *3*(3), 881–886.

Gadepalli, S. K., Selewski, D. T., Drongowski, R. A., & Mychaliska, G. B. (2011). Acute kidney injury in congenital diaphragmatic hernia requiring extracorporeal life support: an insidious problem. *Journal of pediatric surgery*, *46*(4), 630-635.

Ghobrial, E. E., Elhouchi, S. Z., Eltatawy, S. S., & Beshara, L. O. (2018). Risk factors associated with acute kidney injury in newborns. *Saudi Journal of Kidney Diseases and Transplantation*, *29*(1), 81.

Greenberg, J. H., Coca, S., & Parikh, C. R. (2014). Long-term risk of chronic kidney disease and mortality in children after acute kidney injury: a systematic review. *BMC nephrology*, *15*(1), 184.

Jetton, J. G., & Askenazi, D. J. (2012). Update on acute kidney injury in the neonate. *Current opinion in pediatrics*, *24*(2), 191.

Jetton, J. G., Boohaker, L. J., Sethi, S. K., Wazir, S., Rohatgi, S., Soranno, D. E., ... & Sridhar, S. (2017). Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. *The lancet child & adolescent health*, *1*(3), 184-194.

Jetton, J. G., Guillet, R., Askenazi, D. J., Dill, L., Jacobs, J., Kent, A. L., ... & Ambalavanan, N. (2016). Assessment of worldwide acute kidney injury epidemiology in neonates: design of a retrospective cohort study. *Frontiers in pediatrics*, *4*, 68.

Karlowicz, M. G., & Adelman, R. D. (1995). Nonoliguric and oliguric acute renal failure in asphyxiated term neonates. *Pediatric nephrology*, *9*(6), 718-722.

Kellum, J. A., Lameire, N., & KDIGO AKI Guideline Work Group. (2013). Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Critical care*, *17*(1), 204.

Koralkar, R., Ambalavanan, N., Levitan, E. B., McGwin, G., Goldstein, S., & Askenazi, D. (2011). Acute kidney injury reduces survival in very low birth weight infants. *Pediatric research*, *69*(4), 354-358.

Lee, C. C., Chan, O. W., Lai, M. Y., Hsu, K. H., Wu, T. W., Lim, W. H., ... & Lien, R. (2017). Incidence and outcomes of acute kidney injury in extremely-low-birth-weight infants. *PloS one*, *12*(11), e0187764.

Li, P. K. T., Burdmann, E. A., Mehta, R. L., Riella, M., Feehally, J., Erk, T., Beerkens, P., Garcia-Garcia, G., Couser, W. G., Abraham, G., Shay, P., Segantini, L., & Martin, S. (2013). Acute kidney injury: Global health alert. *Journal of Nephropathology*, *2*(2), 90–97. https://doi.org/10.12860/JNP.2013.15

Mammen, C., Al Abbas, A., Skippen, P., Nadel, H., Levine, D., Collet, J. P., & Matsell, D. G. (2012). Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *American Journal of Kidney Diseases*, *59*(4), 523-530.

Mathur, N. B., Agarwal, H. S., & Maria, A. (2006). Acute renal failure in neonatal sepsis. *Indian Journal of Pediatrics*, *73*(6), 499–502.

Momtaz, H. E., Sabzehei, M. K., Rasuli, B., & Torabian, S. (2014). The main etiologies of acute kidney injury in the newborns hospitalized in the neonatal intensive care unit. *Journal of clinical neonatology*, *3*(2), 99.

Mortazavi, F., & Sakha, S. H. (2009). *Kidney Diseases Acute Kidney Failure in Neonatal Period*. *3*(3), 136–140.

Munyendo, C. (2017). *Prevalence of Acute Kidney Injury and Its Risk Factors for Severity in Neonates With Suspected Sepsis at Kenyatta National Hospital* (Doctoral dissertation, University of Nairobi).

Nada, A., Bonachea, E. M., & Askenazi, D. J. (2017). Acute kidney injury in the fetus and neonate. *Seminars in Fetal and Neonatal Medicine*, *22*(2), 90–97.

Özçakar, Z. B., Yalçinkaya, F., Altas, B., Ergün, H., Kendirli, T., Ateş, C., Elhan, A. H., & Ekim, M. (2009). Application of the new classification criteria of the Acute Kidney Injury Network: A pilot study in a pediatric population. *Pediatric Nephrology*, *24*(7), 1379–1384.

Ponce, D., & Balbi, A. (2016). Acute kidney injury: risk factors and management challenges in developing countries. *International journal of nephrology and renovascular disease*, *9*, 193.

Pradhan, D., Meher, B., Panda, S., & Samal, D. (2018). Prevalence and factors affecting prognosis in neonates with acute kidney injury in a neonatal intensive care unit. *Journal of Clinical Neonatology*, *7*(4), 237.

Rhone, E. T., Carmody, J. B., Swanson, J. R., & Charlton, J. R. (2014). Nephrotoxic medication exposure in very low birth weight infants. *Journal of Maternal-Fetal and Neonatal Medicine*, *27*(14), 1485–1490.

Ricci, Z., Cruz, D., & Ronco, C. (2008). The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney international*, *73*(5), 538-546.

Sabzehei, M., Rasuli, B., Torabian, S., & Momtaz, H. (2014). The main etiologies of acute Kidney injury in the newborns hospitalized in the neonatal intensive care unit. *Journal of Clinical Neonatology*, *3*(2), 99.

Selewski, D. T., Charlton, J. R., Jetton, J. G., Guillet, R., Mhanna, M. J., Askenazi, D. J., & Kent, A. L. (2015). Neonatal acute kidney injury. *Pediatrics*, *136*(2), e463-e473.

Selewski, D. T., Jordan, B. K., Askenazi, D. J., Dechert, R. E., & Sarkar, S. (2013). Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. *Journal of Pediatrics*, *162*(4), 725-729.

Shalaby, M. A., Sawan, Z. A., Nawawi, E., Alsaedi, S., Al-Wassia, H., & Kari, J. A. (2018). Incidence, risk factors, and outcome of neonatal acute kidney injury: a prospective cohort study. *Pediatric Nephrology*, *33*(9), 1617-1624.

Shalaby, M. A., Sawan, Z. A., Nawawi, E., Alsaedi, S., Al-Wassia, H., & Kari, J. A. (2018). Incidence, risk factors, and outcome of neonatal acute kidney injury: a prospective cohort study. *Pediatric Nephrology*, *33*(9), 1617–1624.

Suzuki, M. (2009). Children's toxicology from bench to bed-Drug-induced Renal Injury (4): Effects of nephrotoxic compounds on fetal and developing kidney. *The Journal of Toxicological Sciences*, *34*(Special_), SP267-SP271.

Viswanathan, S., Manyam, B., Azhibekov, T., & Mhanna, M. J. (2012). Risk factors associated with acute kidney injury in extremely low birth weight (ELBW) infants. *Pediatric Nephrology*, *27*(2), 303–311.

Youssef, D., Abd-elrahman, H., Shehab, M. M., & Abd-elrheem, M. (2015). *of Kidney Diseases and Transplantation Original Article Incidence of Acute Kidney Injury in the Neonatal Intensive Care Unit*. *26*(1), 67–72.

Youssef, D., Abd-Elrahman, H., Shehab, M. M., & Abd-Elrheem, M. (2015). Incidence of acute kidney injury in the neonatal intensive care unit. *Saudi journal of kidney diseases and transplantation*, *26*(1), 67.

Zappitelli, M., Ambalavanan, N., Askenazi, D. J., Moxey-Mims, M. M., Kimmel, P. L., Star, R. A., ... & Morgan, C. M. (2017). Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop. *Pediatric Research*, *82*(4), 569-573.

Zulic, E., & Hadzic, D. (2015). Acute renal failure in the newborns hospitalized at the intensive care unit, University Clinical centre Tuzla. *Sanamed*, *10*(1), 47-50.

Zulic, E., & Hadzic, D. (2015). Acute renalfailure in the newborns hospitalized at the Intensive Care Unit, University clinical centre Tuzla. *Sanamed*, *10*(1), 47–50.

Zwiers, A. J. M., de Wildt, S. N., Hop, W. C. J., Dorresteijn, E. M., Gischler, S. J., Tibboel, D., & Cransberg, K. (2013). Acute kidney injury is a frequent complication in critically ill neonates receiving extracorporeal membrane oxygenation: A 14-year cohort study. *Critical Care*, *17*(4)

APPENDICES

APPENDIX I: CONSENT FORM

Investigator: My name is Dr Gichemi Alice. I am a qualified doctor, registered with the Kenya Medical Practitioners and Dentists Board. I am currently pursuing a Masters degree in Child Health and Paediatrics at Moi University.I am conducting a study on Acute kidney injury and its risk factors under the title: **Burden of acute kidney injury and Associated risk factors among neonates at Newborn unit, Moi Teaching Referral Hospital, Kenya.**

You are being asked to take part in a research study. This information is provided to tell you about the study. Please read this form carefully. You will be given a chance to ask questions. If you decide to be in the study, you will be given a copy of this consent form for your records.

Taking part in this research study is voluntary. You may choose not to take part in the study. You will still receive other treatments. Saying no will not affect your rights to health care or services. You are also free to withdraw from this study at any time. If after data collection you choose to quit, you can request that the information provided by you be destroyed under supervision and thus not used in the research study. You will be notified if new information becomes available about the risks or benefits of this research. Then you can decide if you want to stay in the study.

Purpose: This study will seek to determine the burden of acute kidney injury and Associated risk factors among neonates in the newborn unit,MTRH.

Procedure: Your child has been identified for this study because they have risk factors for development of acute kidney injury. We will take a blood sample for baseline serum

creatinine if one is not already available. Thereafter multiple samples may be taken depending on your childs' condition. We will follow up your child to see if other risk factors emerge/ or are persisting. Your primary clinician will be notified on all and any discoveries. There shall be no payment required as all tests done will be free.

Benefits: There will be no direct benefits of participating in this study but the results of the tests will be incorporated into the care of the child.

Risks. Some degree of pain is expected in taking a blood sample. Multiple blood samples can lead to anaemia.

Confidentiality: All information obtained in this study will be treated with utmost confidentiality and shall not be divulged to any unauthorized person

Rights to Refuse: Participation in this study is voluntary, there is freedom to refuse to take part or withdraw at any time. This study has been approved by the Institutional Research and Ethics Committee (IREC) of Moi University/Moi Teaching and Referral Hospital.

Sign or make a mark if you agree to take part in the study

Parent: …… Investigator: …….Date: ……

APPENDIX II: QUESTIONNAIRE

IP number _____
Telephone number_____
Database subject number _____

BASELINE
FORM

Maternal information:

[redacted]

 Maternal age at delivery in years _____
Gravida _____
Parity _____

Level of Education
□ No formal education
□ Primary
□ Secondary
□ Tertiary

Maternal conditions – check all that apply

□ No complications

□ Maternal infections at or near the time of delivery including bacterial and viral infections.

□ Maternal diabetes

□ Maternal hypothyroidism

□ Maternal chronic hypertension

□ Maternal history of kidney disease

□ Maternal pre-eclampsia

□ Maternal eclampsia

□ IUGR

□ Oligohydramnios

□ Polyhydramnios

□ Maternal hemorrhage

□ Multiple gestation,

□ all fetuses survived to birth

□ demise of one or more fetuses

□ no information is available about other fetuses

□ twin-twin transfusion

□ Unknown

□ Drugs documented used during this pregnancy – check all that apply

□ None

□ Maternal steroids for fetal maturation

□ ACE-inhibitors (captopril, enalapril, lisinopril, benazepril, fosinopril, quinapril, enalaprilat),

□ NSAIDs (including aspirin, ibuprofen, paracetamol, other over-the-counter pain relievers),

□ beta blockers (propranolol, atenolol, carvedilol, metoprolol, esmolol, labetalol),

□ calcium channel blockers (amlodipine,nifedipine, felodipine, isradipine, nicardipine),

□ vasodilators (hydralazine, minoxidil, nitroprusside),

□ central alpha-agonists (clonidine),

□ indomethacin (when given intrapartum for tocolysis)

□ illicit drugs (such as cocaine, heroin, THC, and any other street drugs; also include drugs used in drug treatment programs such as methadone, subutex) by history or drug screening,

□ tobacco,

□ alcohol,

□ SSRIs (citalopram/Celexa®, escitalopram/Lexapro®, fluvoxamine/Luvox®, paroxetine/Paxil®, fluoxetine/Prozac, ® sertraline/Zoloft®).

□ Heparin

□ Warfarin

□ unknown

□ Assisted conception

□ Yes

□ No

□ unknown

□ Intrapartum complications – check all that apply

□ none

□ nuchal cord

□ meconium

□ severe maternal vaginal bleeding

□ cord rupture

□ shoulder dystocia

□ unknown

IP number _____
Database subject number _____

Neonatal information

□ Site of delivery

□ Inborn

□ Outborn

Gestational age at birth — Weeks ___ ___

Days ___ ___

Birthweight, grams ___ ___ ___ ___

□ If outborn, admission weight (grams) ___ ___ ___ ___

Length , centimeters ___ ___ ___ ___

□ If outborn, admission length (cms) ___ ___ ___ ___

Head circumference, centimeters ___ ___ ___ ___

□ If outborn, admission head circumference (cms) ___ ___ ___ ___

Admission temperature (°C): ___

□ None available

□ Mode of delivery

□ vaginal, vertex
□ vaginal, breech
□ vaginal, unknown presentation
□ scheduled C-section (no labor)

□ unscheduled C-section
□ C-section, no other details known
□ unknown delivery mode

Resuscitation

 Apgar scores, enter all that are documented

1 minute _____
5 minute _____
10 minute _____

 Cord blood gas results

arterial pH _____
arterial base excess _____
venous pH _____
venous base excess _____
vessel unspecified pH _____
□ vessel unspecified base excess _____

□ none available

 If no cord blood gases are available, enter a blood gas obtained during the first hour, if available.

pH _____
base excess _____
none available _____

IP number _____
Database subject number _____

 Resuscitation provided to the infant in the delivery room , check all that apply

□ none (aside from drying and stimulation)

□ supplemental oxygen

□ PPV (positive pressure -CPAP or Neopuff)

□ intubation

□ chest compressions

□ epinephrine

□ normal saline

□ blood transfusion (whole blood or red blood cells)

□ unknown

 Reason for admission

□ "prematurity" if gestational age at birth is < 35 weeks;

□ Respiratory symptoms (requiring observation and close monitoring and support no greater than supplemental oxygen via low flow nasal cannula, < 2L/min), all diagnoses

□ Respiratory failure (continued need for respiratory support including mechanical ventilation, non-invasive ventilation(mask), CPAP, or High Flow

Nasal Cannula ≥ 2L/min), all diagnoses

□ Sepsis evaluation

□ HIE (Hypoxic ischemic encephalopathy, birth asphyxia; 5-minute Apgar score < 6; initial pH < 7.0)

□ Seizures (can be clinical or electrographic or both)

□ Hypoglycemia (blood glucose < 2.2mmol/l)

□ Hyperbilirubinemia (including need for phototherapy or exchange transfusion)

□ Dehydration
□ Feeding Difficulties

□ Metabolic evaluation (inborn error of metabolism, etc.)

□ Chromosomal anomaly (indicate if trisomy 21 or other chromosomal anomaly, unspecified)

□ Congenital heart disease

□ NEC

□ Omphalocele, Gastroschisis

□ Other surgical evaluation

□ Meningomyelocele

□ Other intracranial abnormalities

□ SGA (< 3%ile)

□ Other /specify_____

IP number _____
Database subject number _____

WEEK ONE DATA

PLEASE NOTE: DAY OF BIRTH = DAY 1

Physiologic parameters: Please enter the highest, lowest and value closest to midnight (first)

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date						
Weight (g)						
Systolic BP						
Highest						
Lowest						
First						
Diastolic BP						
Highest						
Lowest						
First						
Mean Arterial BP						
Highest						
Lowest						
First						

Respiratory parameters:

1 High frequency ventilation
2 Conventional mechanical ventilation
3 Noninvasive ventilation(mask)
4 CPAP
5 Nasal cannula
6 No respiratory support

		Day 2	Day 3	Day 4 Day 6	Day 7	Day 5	
Date							
Mode							
Max FiO2							

Fluid balance:

Fluid IN

Day	Date	Quantifiable IV fluids No=0 Yes=1	If yes, IV fluid volume	Quantifiable enteral fluids No=0 Yes=1	If yes, Enteral fluid Volume
1					
2					
3					
4					
5					
6					
7					

Fluid Out

Day	Date	Was there fluid out in 24 hour period? No = 0 Yes = 1	Quantifiable? No=0 Yes=1	If yes, Total volume
1				
2				
3				
4				
5				
6				
7				

Urine output

Day	Date	Was there urine out in 24 hour period? No = 0 Yes = 1	Quantifiable? No=0 Yes=1	If yes, Total volume
1				
2				
3				
4				
5				
6				
7				

ID number _____
Database subject number _____

Medications: "0" = no; "1" = yes for any part of that day

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
date							
Aminoglycoside							
Vancomycin							
Piperacillin-Tazobactam							
Amphotericin							
Acyclovir							
Indomethacin							
ibuprofen							
hydralazine							

ACE-inhibitors

Dopamine							
Dobutamine							
Milrinone							
Epinephrine							
Norepinephrine							
Furosemide							
Bumetanide Chlorothiazide							
Ethacrynic acid							
Spironolactone							
Theophylline							
Caffeine							

Laboratory values: Include "worst" for day if more than one value obtained (highest creatinine, highest BUN, lowest albumin, lowest hemoglobin or hematocrit, highest and lowest sodium)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							
BUN							
Albumin							
Hemoglobin							
Hematocrit							
Sodium							
Highest							
Lowest							
Blood culture = negative = positive = not done							
CSF culture = negative = positive = not done							
Urine culture = negative = positive = not done							

IP number _____
Database subject number _____

WEEKLY DATA

Physiologic parameters: Please enter the highest, lowest and value closest to midnight for **the day closest to the first day of each week (day 8, 15, 22, etc.)**

	Week 2	Week 3	Week 4	End
Date				
Weight(g)				
SystolicBP				
Highest				
Lowest				
First				
Diastolic				
Highest				
Lowest				
First				
Mean arterial pressure				
Highest				
Lowest				
First				

Respiratory parameters:
1 High frequency ventilation
2 Conventional mechanical ventilation
3 Noninvasive ventilation(mask)
4 CPAP
5 Nasal cannula

6 No respiratory support

IP number

_____

Database subject number

_____

Fluid balance: Enter intake/output **for first day of each week (day 8, 15, 22)**

Intake

Week	Date	Quantifiable IV fluids? No=0 Yes=1	Total IV fluids volume	Quantifiable Enteral fluids? No=0 Yes=1	Total enteral fluid Volume
2					
3					
4					
Exit					

Total fluid output (urine plus other)

Week	Date	Was there fluid output? No = 0 Yes = 1	Quantifiable? No=0 Yes=1	Total volume
2				
3				
4				
Exit				

Medications: "0" = no; "1" = yes **for the first day of each week**

	Week 2	Week 3	Week 4	Exit
Date				
Aminoglycoside				
Vancomycin				
Piperacillin-Tazobactam				
Amphotericin				
Acyclovir				
Indomethacin				
Ibuprofen				
Hydralazine				
ACE-inhibitors				
Dopamine				
Dobutamine				
Milrinone				
Epinephrine				
Norepinephrine				
Furosemide				
Bumetanide				
Chlorothiazide				
Ethacrynic acid				
Spironolactone				
Theophylline				
Caffeine				

Laboratory values: Include "worst" **for first day of each week** if more than one value obtained (highest creatinine, highest BUN, lowest albumin, lowest hemoglobin/hematocrit, highest and lowest sodium)

	Week 2	Week 3	Week 4	Exit
Date				
BUN				
Albumin				
Hemoglobin				
Hematocrit				
Sodium				
Highest				
Lowest				
Blood culture 0 = negative 1 = positive 2 = not done				
CSF culture 0 = negative 1 = positive 2 = not done				
Urine culture 0=Negative 1=Positive 2=Not Done				

IP number _____

Database subject number _____

Creatinine Values

Date	Time (if more than one creatinine level on the same date)	Value

IP number _____

Database subject number _____

DISCHARGE FORM

Disposition/"Status"

□ Discharged home prior to 28 days of age

□ Still in NBU at ≥ 28 days of age

□ Transferred to community hospital, other facility, or other hospital unit for convalescent care prior to 28 days

□ Transferred to another hospital, facility or hospital unit, for escalation of care prior to 28 days

□ Died in hospital at ≤ 28 days

Date of disposition/"status" __/__/____

[redacted]

Measurements at "status"

[redacted]

Weight in grams _____

Length in cms _____

 Head circumference in cms _____

Discharge medications

□ antibiotics for urinary tract infection (UTI) prophylaxis

□ yes

□ no

□ diuretics

□ yes

□ no

□ antihypertensives:

□ yes

□ no

Discharge Diagnoses

□ Cardiac

□ PDA confirmed

□ Anatomic cardiac anomaly

□ Systemic hypertension

□ no medications at discharge

□ medications at discharge

□ Pulmonary

□ BPD

□ requiring continued non-invasive ventilation or CPAP at 36 weeks' CGA

□ requiring supplemental oxygen by nasal cannula or hood at 36 weeks' CGA

□ Persistent pulmonary hypertension confirmed

□ Neurologic

□ HIE (hypoxic ischemic encephalopathy/birth asphyxia)

□ Seizures

□ GI

□ NEC

□ Bell Stage 2 – medically treated

□ Bell Stage 2 – surgically treated

□ Jaundice requiring an exchange transfusion

□ Hematologic

□ DIC (disseminated intravascular coagulation)

□ Infectious Disease

□ Culture negative sepsis (negative culture but treated with antibiotics for ≥ 5d)

□ Bacteremia

□ Meningitis/encephalitis, include both bacterial and viral infections

□ Metabolic abnormalities

□ Endocrine abnormalities

□ Genetic abnormalities

□ Other major diagnoses

□ Specify_____

Renal diagnoses

□ Nephrology consult obtained during this admission.

□ Acute kidney injury or acute renal failure

□ Urinary tract infections. Please include only if there was a positive urine culture

□ Medullary nephrocalcinosis/calcifications/kidney stones. Must be documented on renal ultrasound.

Congenital abnormalities of the kidney. (use most severe on Renal US or Discharge summary) Please circle all that apply from the list provided. See MOP for description

			Right						Left		
Hypoplasia/Dysplasia	Yes			NO				Yes		NO	
Multicystic Dysplastic	Yes			NO				Yes		NO	
Kidney											
Renal agenesis	Yes			NO				Yes		NO	
Polycystic kidney											
Disease											
	Yes, recessive										
	Yes, dominant										
	Unknown										
Horseshoe kidney					YES						
						NO					
Renal Ectopia	Yes			NO				Yes		NO	
Hydronephrosis	Yes			NO				Yes		NO	
	Mild		MOD Severe				Mild		MOD Severe		
UPJ	Yes			NO				Yes		NO	
Hydroureter	Yes			NO				Yes		NO	
Duplicated System	Yes			NO				Yes		NO	
Posterior urethral					YES						
Valves						NO					

Vesicoureteral reflux	Yes			NO			Yes		NO	
	1	2	3	4	5	1	2	3	4	5
				Abnormality Present						
Urethral stricture					YES					
						NO				
Bladder exstrophy					YES					
						NO				
Neurogenic Bladder					YES					
						NO				
Prune Belly Syndrome					YES					
						NO				

Renal replacement therapy:

o yes

o no

 If YES,

How many days did the patient receive any form of renal replacement therapy during the hospitalization? _____

o Modality (please choose all that apply):

□ Peritoneal dialysis

□ intermittent hemodialysis

APPENDIX III: SAMPLE COLLECTION AND ANALYSIS.

The puncture site was cleaned using an alcohol/ spirit swab. A venous blood sample with a minimum of 0.5mls of blood was drawn using broken needle technique and collected in the clot activator tube BD vacutainer. The specimen would then be labelled and transported to the laboratory with an accompanying fully filled laboratory request form. The blood sample was tested in the MTRH laboratory for urea, creatinine and electrolyte levels. Analysis was by an ISO- certified Cobas C 111 machine using the Jaffe method (Appendix 5). In the laboratory, the sample was centrifuged at a speed of 3000 revolutions per minute for 10 minutes to obtain 100µL - 400µL of serum which was then be placed in a sample cup and fed into the Cobas C 111 machine in a designated slot. The name and I.P number and age of the patient was entered into the machine. Analysis would be done and an automated value of urea creatinine and electrolyte given.

APPENDIX IV: STUDY TIMELINE

DATE	DURATION	ACTIVITY
Feb 2016 – March 2016	1 month	Presentation of the concept paper to the department
March 2016 – May 2016	2 months	Proposal writing
May 2016 – September 2016	-	Submission to IREC
Jan 2017 – march 2017	3 months	Data collection
April 2017- August 2017	5 months	Writing thesis
2017	-	Submission of the thesis
2018	1 month	Oral defense

APPENDIX V: BUDGET

ITEM	**Quantity**	**COST**
Reams of printing papers @ 500	10	5000
Pens@ 25, pencils@ 15,rubber@30, Box file@ 100	10,6,2, 6 respectively	1000
Flash disks	2	2000
Research proposal printing@15 per page		2000
IREC fee		2000
Research assistants 8000p.m=3 mo	2	48000
Data analysis		10000
Printing and binding thesis		5000
Airtime		5000
Biostatistician		50,000
Urea electrolytes and Creatinine @1500 per sample	592	888,000
Urine bags@ 70 per bag	4144	290,080
Miscellaneous		10,000
TOTAL		**1,318,080**

We will apply for funding with Nacosti, MTRH and ISN. If not successful the principal investigator will fund.

APPENDIX VI: TEST PRINCIPLE- CREATININE

Buffered kinetic Jaffe reaction without deproteinization . In alkaline solution creatinine reacts with picrate to form a yellow- red adduct.

Creatinine + picric acid $\xrightarrow{\text{Alkaline pH}}$ Yellow-red complex

The rate of dye formation (colour intensity) is directly proportional to the creatinine concentration in the specimen. It is determined by measuring the increase in absorbance at 512nm. Serum and plasma samples contain proteins which react non-specifically in the Jaffe method. For compensation of serum and plasma results, values are automatically corrected by -18 umol/L(0.2 mg/dL).

APPENDIX VII: IREC APPROVAL

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2016/167

27th September, 2017

Approval Number: 0001762

Dr. Alice Nduta Gichemi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
27 SEP 2017
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dear Dr. Gichemi,

RE: CONTINUING APPROVAL

The Institutional Research and Ethics Committee has reviewed your request for continuing approval to your study titled:-

"Burden of Acute Kidney Injury and Associated Risk Factors among Neonates at Newborn Unit, Moi Teaching and Referral Hospital".

Your proposal has been granted a Continuing Approval with effect from 22th September, 2017. You are therefore permitted to continue with your study.

Note that this approval is for 1 year; it will thus expire on 26th September, 2018. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

DR.S NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc:

	CEO	-	MTRH
	Dean	-	SOM
	Dean	-	SPH
	Dean	-	SOD
	Dean	-	SON

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2016/167
Approval Number: 0001762

16th October, 2017

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
16 OCT 2017
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dr.Alice Nduta Gichemi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Gichemi ,

RE: APPROVAL OF AMENDMENT

The Institutional Research and Ethics Committee has reviewed the amendment made to your proposal titled:-

"Burden of Acute Kidney Injury and Associated Risk Factors among Neonates at Newborn Unit, Moi Teaching and Referral Hospital".

We note that you are seeking to make amendments as follows:-

1. To add an objective "To describe outcomes of neonates with acute kidney injury"
2. To change the sampling method from consecutive to systematic sampling method
3. To change sample size calculation p=24%
4. To make changes to the questionnaire format

The amendment has been approved on 16th October, 2017 according to SOP's of IREC. You are therefore permitted to continue with your research.

You are required to submit progress(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change(s) or amendment(s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc: CEO - MTRH Dean - SPH Dean - SOM
Principal - CHS Dean - SOD Dean - SON