# EVALUATING EPIDEMIOLOGICAL RISK FACTORS FOR PEDIATRIC ACUTE KIDNEY INJURY GLOBALLY: FROM THE UNITED STATES AND A LOW-RESOURCED SETTING IN MALAWI

Erica C. Bjornstad

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2019

Approved by:

Emily W. Gower

Steve W. Marshall

Yvonne M. Golightly

Amy K. Mottl

Keisha Gibson

## ABSTRACT

Erica C. Bjornstad: EVALUATING EPIDEMIOLOGICAL RISK FACTORS FOR PEDIATRIC ACUTE KIDNEY INJURY GLOBALLY: FROM THE UNITED STATES AND A LOW-RESOURCED SETTING IN MALAWI
(Under the direction of Emily Gower)

Background: Acute kidney injury (AKI) can be fatal if unrecognized. This work aimed to evaluate pediatric AKI epidemiology in two distinct hospital settings—a United States database and a prospective cohort of Malawian trauma patients. Many African hospitals are hampered by limited AKI diagnostics. So, we validated a novel AKI dipstick (NGALds®) that relies on minimal resources.

Methods: The U.S. evaluation of hospitalized children used the Kids' Inpatient Database (nationally-representative sample of pediatric discharges). Linear regression models looked at sociodemographic risk factors associated with AKI. In Malawi, we prospectively evaluated AKI amongst trauma patients. We evaluated several AKI definitions to optimize baseline creatinine estimation, which is not standardized. We calculated univariate relative risks (RR) for hypothesis-generation of potential risk factors associated with AKI in trauma patients. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) evaluated the validity of the NGALds® to diagnose AKI.

Results: In the U.S., AKI occurred in approximately 12.3/1000 pediatric hospitalizations, which translates to almost 30,000 children nationally. Uninsured children were more likely to suffer

AKI compared to children with Medicaid (adjusted risk difference 14/1000 hospitalizations, 95% confidence interval (CI) 12-16). In Malawi, depending on baseline creatinine definition, AKI incidence ranged from 4-10%. Almost one in ten children died, but those with AKI were at significantly higher risk of death compared to those without AKI (RR 6.5, 95% CI 2.2-19.1). The NGALds® had sensitivity 44.4%, specificity 73.5%, PPV 19.5%, and NPV 90.2% for predicting AKI. AKI was associated with an increased risk of mortality (RR 3.9, 95% CI 1.9-8.2), but it was greatly increased amongst children who first had a positive (≥150ng/mL) NGALds® (RR 12.0, 95% CI 1.8-78.4).

Conclusion: In the US, we identified that lack of insurance was a key risk factor for AKI. In the first analysis of AKI in African pediatric trauma patients, we showed that AKI significantly increases mortality risk. More promising is the validation we conducted of a novel dipstick for point-of-care identification and risk stratification of AKI amongst trauma patients. This dipstick may drastically improve our AKI epidemiological studies and clinical care algorithms, saving lives throughout Africa.

## ACKNOWLEDGEMENTS

First and foremost, I wish to thank the support and patience that my family, especially my husband and son, gave me as I completed this work. Without them this work would not have been possible. In addition, I am incredibly thankful for the support and mentorship from all of my mentorship team, particularly my primary advisor Emily Gower who really helped me navigate the intricacies of global health research. I also want to acknowledge the support of all of my collaborators in Malawi, Kamuzu Central Hospital (particularly the surgery department and dialysis unit), UNC Project Malawi, and Malawi Surgical Initiative. I also want to acknowledge the participation of all of our research participants without which this work would not have been possible. My time spent in Malawi would also not have been possible without the support and teamwork of my colleagues at the UNC Kidney Center who helped care for my clinical patients while I was traveling.

TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AKI | Acute Kidney Injury |
| APOL1 | apolipoprotein L1 |
| CKD | Chronic Kidney Disease |
| eGFR | estimated Glomerular Filtration Rate |
| HCUP | Hospital Care and Utilization Program |
| IMCI | Integrated Management of Childhood Illnesses |
| KCH | Kamuzu Central Hospital |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| KID | Kids' Inpatient Database |
| NGAL | Neutrophil Gelatinase-Associated Lipocalin |
| NPV | negative predictive value |
| PPV | positive predictive value |
| SES | socioeconomic status |
| UNC | University of North Carolina at Chapel Hill |
| U.S. | United States |
| WHO | World Health Organization |

# CHAPTER 1: INTRODUCTION

Acute kidney injury (AKI), previously known as "Acute Renal Failure", can be fatal if untreated. Unlike chronic kidney disease (CKD), an AKI episode is usually reversible, assuming timely and accurate diagnosis and treatment. AKI is defined as the sudden decrease in kidney function, over a period of hours or days but less than 3 months (which would classify the dysfunction as CKD). In efforts to standardize the definition, several classifications have been proposed over the past two decades. Previously, clinicians and researchers used their own definitions, and a systematic review in 1994 found that of 28 articles on AKI, 28 different definitions were used.[1] Most commonly used definitions rely on serum creatinine and urine output changes for AKI diagnosis. Currently, the Kidney Disease: Improving Global Outcomes (KDIGO) definition is the most well-known and universal, as it can be applied to both adults and children.[2] However, it has only been around since 2012. KDIGO states that AKI occurs if serum creatinine rises by absolute ≥0.3mg/dL or relative ≥50% increase from a baseline creatinine in 48 hours or if urine output drops below 0.5ml/kg/hour for six hours or more (Table 1.1).

**Table 1.1. Kidney Disease Improving Global Outcomes (KDIGO)-definition of AKI**

| AKI STAGE | eGFR/Creatinine Changes | Urine Output Changes |
|---|---|---|
| **Stage 1** | Increase in creatinine ≥0.3mg/dL<br>Or increase in creatinine 1.5-1.9 x baseline<br>Within 48 hours | <0.5 ml/kg/hour for 6-11 hours |
| **Stage 2** | Increase in creatinine 2-2.9 x baseline | <0.5 ml/kg/hour for ≥12 hours |
| **Stage 3** | Increase in creatinine ≥3 x baseline<br>Or absolute creatinine ≥4 mg/dL<br>Or requirement for dialysis<br>Or eGFR <35 ml/min/1.73m$^2$ (if <18 years) | <0.3 ml/kg/hour for ≥24 hours<br>Or anuric for ≥12 hours |

AKI increases both morbidity and mortality for children.[3–6] AKI results in escalating levels of urea and waste products in the bloodstream, leading to dangerous imbalances in serum electrolytes, and an inability to remove excess fluid, which can lead to fatal pulmonary edema and cardiac stress. Long-term complications have been shown to occur with any severity of AKI, though they are more pronounced with more severe disease. Complications include persistent kidney dysfunction, such as chronic hypertension or proteinuria, and some patients ultimately never fully recover and remain with CKD and progress to Chronic Kidney Failure.[7–9]

With the standardization of AKI's definition, epidemiological studies have been able to more fully depict the global burden of AKI. Global estimates are limited but suggest AKI may occur annually in 13.3 million people, which is seven times greater than the annual incidence of human immunodeficiency virus.[10,11] However, our current epidemiological studies are limited to higher income countries and more critically ill patients, where it is easier and more reliable to obtain the daily laboratory tests and urine output measurements essential to our current definitions. The first large prospective cohort studies for pediatric AKI recently began in 2014[4,6]. The AWARE and the AWAKEN trials are large multi-national studies to evaluate the incidence, epidemiology and outcomes of pediatric AKI in middle- and high-income countries for critically ill children and neonates, respectively.[4,6] There remain gaps in our understanding of pediatric AKI risk factors in high-income settings.

However, larger gaps in AKI knowledge exist in low-resourced areas. Even though trauma is the leading cause of mortality for children and young adults worldwide, no studies have evaluated the epidemiology of AKI in pediatric trauma patients in Africa.[12] Trauma is a known risk factor for AKI.[13] Only a handful of studies have looked at the epidemiology of AKI

in adult trauma patients in Africa. A large hindrance for evaluating the epidemiology of AKI in Africa is the limited laboratory infrastructure, necessary for AKI diagnosis.

Serum creatinine is the current gold standard for AKI diagnosis, yet it is known to be flawed, particularly in children. Creatinine levels can fluctuate with hydration and muscle mass, not truly reflecting a child's kidney function. In addition, changes with creatinine can take several days to appear even after a severe kidney injury. Urine NGAL (neutrophil gelatinase-associated lipocalin), a novel biomarker consistently shown to predict subsequent AKI diagnosis, in high-resourced settings may be able to aid in earlier AKI detection.[14–20] Urine NGAL rises within minutes to hours of a kidney injury and does not rely on muscle mass. However, the urine NGAL biomarker still relies on robust laboratory infrastructure. Yet, a novel dipstick for urine NGAL (NGALds® dipstick) was developed for use in low-resourced settings. If it proves equally efficacious as the laboratory urine NGAL, it could be quite promising for improving AKI diagnostics in low-resourced areas because it requires no laboratory infrastructure and minimal electricity requirements (currently temperature-resistant for one month).

# CHAPTER 2: SPECIFIC AIMS

Acute kidney injury (AKI), previously known as "Acute Renal Failure", can be fatal if untreated. Unlike chronic kidney disease, an AKI episode is usually reversible, assuming timely and accurate diagnosis and treatment. Currently, the most well-known and universal AKI definition, as it can be applied to both adults and children, is the Kidney Disease: Improving Global Outcomes (KDIGO) definition.[2] With the standardized definition, more global attention has been brought to the impact AKI has on both mortality and long-term morbidity in children.[3–6]

Global estimates are limited but suggest AKI may occur annually in 13.3 million people, which is 7 times greater than the annual incidence of human immunodeficiency virus infection.[10,11] However, our current epidemiological studies are limited to higher income countries and more critically ill patients, where it is easier and more reliable to obtain the daily laboratory tests essential to our current definitions that rely on laboratory-based creatinine measurements. Even epidemiological studies in the U.S. are limited and have not explored in depth the sociodemographic risk factors that may be associated with pediatric AKI.

Worldwide, trauma is a leading cause of mortality for children and young adults (5-29 years of age).[12] Organ failure, including AKI, is the third leading cause of mortality in trauma patients, after bleeding and brain injuries.[13] Yet, the majority of studies worldwide have only looked at *critically ill* adult trauma patients and suggests AKI rates are 18-25% (but range 1-50%).[21–26] However, AKI rates for trauma patients in Africa are almost unknown, particularly amongst children.

Severe under-reporting and lack of epidemiological studies on AKI in low-resourced areas can be partly attributed to the difficulties of laboratory confirmation of AKI in these settings. The only standardly accepted diagnostic test for AKI (serum creatinine) continues to rely on laboratory infrastructure, which is limited or non-existent in most low-resourced settings. Urine NGAL (neutrophil gelatinase-associated lipocalin) has been shown to consistently predict subsequent AKI diagnosis in both adults and children.[14–17] It also rises within hours of a renal insult, while serum creatinine can take 24-72 hours to indicate renal injury. However, the urine NGAL biomarker still relies on robust laboratory infrastructure and consistent power supplies.

Recently, a novel dipstick for urine NGAL (NGALds® dipstick) was developed for use in low-resourced settings. If equally as efficacious as the laboratory urine NGAL, it could be quite promising for improving AKI diagnostics in low-resourced areas, because it requires no laboratory infrastructure and is temperature-resistant for at least one month.

We propose to evaluate the incidence and epidemiological associations of pediatric AKI in two disparate settings. We also propose to evaluate a novel diagnostic test for AKI (NGALds® dipstick) for use in low-resourced settings. If the novel diagnostic test is successful, it could drastically enhance our epidemiological studies of AKI and the clinical diagnosis and management of patients at risk for AKI in these settings. Specifically, our aims are:

1) **To determine if there are disparities in the incidence of AKI according to sociodemographic factors amongst a national pediatric cohort within the U.S.'s Hospital Care and Utilization Program (HCUP) Kids' Inpatient Database (KID);**[27]
2) **To evaluate the incidence and epidemiology of AKI amongst a prospective cohort of pediatric trauma patients in sub-Saharan Africa in collaboration with a well-established hospital-based trauma surveillance registry in Malawi; and**

3) **To validate the urine NGAL biomarker and new NGALds® dipstick for the diagnosis of AKI amongst adult and pediatric trauma patients in a low-resourced environment.**

# CHAPTER 3: RACIAL AND HEALTH INSURANCE DISPARITIES IN PEDIATRIC ACUTE KIDNEY INJURY IN THE UNITED STATES

## 3.1 Background

Acute kidney injury (AKI) can be fatal if untreated, but, unlike chronic kidney disease (CKD), an AKI episode is usually reversible, assuming timely and accurate diagnosis and treatment. AKI, which historically was termed "acute renal failure," is defined as a sudden decrease in kidney function, over a period of 48 hours or more but less than 3 months. Clinical factors associated with the development of AKI amongst hospitalized children include systemic illnesses, exposure to nephrotoxic medications, invasive procedures, and iodinated contrast.[28]

Pediatric AKI is estimated to occur in approximately 5% of all hospitalized children, and up to 25% of all critically-ill children.[4,29] AKI results in high rates of short-term morbidity and mortality as well as increased hospital costs and length of stay.[3,30] Moreover, up to 50-60% of patients may have long-term sequelae such as CKD or hypertension.[7] Knowing which subsets of patients or parameters indicate the greatest risk for AKI is paramount to instituting healthcare guidelines and policies aimed at decreasing these high rates.

Few studies have evaluated sociodemographic risk factors for AKI in pediatric populations. Those that have done so tend to focus on subsets of the pediatric population. One retrospective study in post-operative congenital cardiac surgery patients found that age less than 12 months was a risk factor for AKI.[31] Another study found that nephrotic children who were non-Caucasian were at higher risk of AKI than Caucasian children.[32] None have looked at race

or other broad sociodemographic risk factors for AKI in a large, diverse pediatric population, yet we know from adult studies that those of minority populations or lower socioeconomic status have worse kidney outcomes.[33–35]

We sought to determine if there are disparities in the incidence of AKI according to sociodemographic factors amongst a national pediatric cohort within the Hospital Care and Utilization Program (HCUP) Kids' Inpatient Database (KID).[27] HCUP KID provides detailed information on a nationally-representative sample of pediatric inpatients. In high-income countries, over 99% of pediatric AKI is diagnosed in the inpatient setting.[36]

## 3.2 Methods

*Design:* This study is a secondary analysis of the most recent release (2012) of KID data to assess for sociodemographic differences in the diagnosis of pediatric AKI (age 1-20 years). We used weighted sampling methods to obtain national estimates.

*Data Source:* The KID, developed by the Agency for Healthcare Research and Quality's HCUP, is the largest nationally representative sample of pediatric discharges from >4100 community hospitals throughout the United States. The database includes discharge summary-level data only. Each unit of observation is a hospitalization, so it is possible for individuals to be included twice if they had two separate hospitalizations in 2012. However, AKI is also recurrent, and an individual is at risk for AKI with each hospitalization. For 2012, 44 states were included; not included were Alabama, Delaware, Idaho, Maine, Mississippi, and New Hampshire.

*Inclusion/Exclusion Criteria:* All admitted children in the KID aged 1-20 years on admission were included. Children <1 year of age were not included due to their drastically different etiologies of AKI and higher likelihood of AKI coding errors due to the difficulty with

AKI recognition. The kidneys in infants <1 year are also still maturing and reaching their maximal functional potential. Patients were excluded if they had ICD-9 codes for renal transplants (v42.0), end stage renal disease/chronic dialysis (585.6, 585.5, 792.5, v45.1, v45.11, v45.12, v56.0-v56.2, v56.31, v56.32, v56.8), or if they were missing data on primary diagnosis.

*Outcome:* AKI was a binary outcome and could occur at any point during the hospitalization. AKI was defined by ICD-9 codes (584.5-584.9, acute renal failure; 586, renal failure unspecified; 580.0, 580.4, 580.8, 580.9, acute glomerulonephritis; 593.9, acute renal disease; 866, injury to kidney with unspecified injury; 958.5, renal failure following crushing; 997.5, renal failure due to a medical procedure).

*Exposures:* Race/ethnicity was self-reported and categorized as Caucasian, African American, Hispanic, Asian or Pacific Islander, Native American, and Other. Health insurance status was categorized as Private, Medicaid, Other, or No insurance. Household urbanization was defined in six categories ("central" metropolitan counties with ≥1 million population, "fringe" metropolitan counties with ≥1 million population, metropolitan counties with 250,000-999,999 population, metropolitan counties with 50,000-249,999 population, micropolitan counties, or not metropolitan or micropolitan counties). Gender was dichotomous as either male or female. Age was continuous in years.

*Covariates:* In addition to the above sociodemographic factors, we felt that a child's comorbidities may be a strong confounder in assessing some of the relationships. Comorbidities were defined by HCUP through the chronic condition indicator tool.[37] The tool was developed to facilitate health services research and readily determine if a patient has a chronic condition according to administrative data. The tool uses an advanced algorithm, originally reported by Hwang et al,[38] to classify all ICD-9 codes into chronic or not chronic conditions. Examples of

included chronic conditions that may influence AKI are cancer, congenital heart disease, chronic kidney disease, cystic fibrosis, diabetes mellitus, diabetes insipidus, and inflammatory bowel disease.

*Analysis:* Descriptive statistics were calculated for patient demographics, hospital characteristics, and hospital region stratified by racial/ethnic differences as our primary exposure of interest. HCUP provides weights to allow for national estimates based on post-stratification of hospital ownership, bed size, teaching status, urbanization of hospital location, region, and status as a freestanding children's hospital. Further information about the KID sampling design and procedures can be found at: http://www.hcup-us.ahrq.gov/kidoverview.org.[27]

Given the large sample size and method of data collection, we were able to accurately determine the risk of AKI in this population. Hence, to give a broader understanding of the public health impact of our results, we present risk differences (RD) as our contrast estimate of choice, rather than relative risks or odds ratios that can be inflated depending on the true proportion affected. Therefore, linear risk regression models with binomial distributions were used to assess the relationship between our primary sociodemographic exposures and the diagnosis of AKI.

A useful tool to evaluate important confounders in a potential exposure-outcome relationship is a causal diagram, or a *Directed Acyclic Graph (DAG).* It allows visualization of your primary exposure (e.g., race) and outcome (e.g., AKI) in relationship to all other potential variables. It helps ensure there are not mediators or colliders included in adjustment analyses which could introduce bias. We provide simplified descriptions of key variables as *DAGs* can get quite complicated; for example, confounders can be hidden on indirect pathways. More in-depth descriptions and explanations of causal diagrams can be found in this overview in *CJASN*[39] or in

the epidemiological literature.[40,41] A confounder by definition is a variable that potentially impacts the primary exposure and the outcome, and visually is displayed on a *DAG* as a variable with an arrow pointing towards both the exposure and the outcome. A mediator on the other hand has an arrow coming from exposure (into mediator) and then pointing towards the outcome. Modifiers cannot be directly visualized on DAGs. A DAG was drawn for our exposures and outcome (Figure 3.1). Depending on the relationship assessed, we evaluated potential

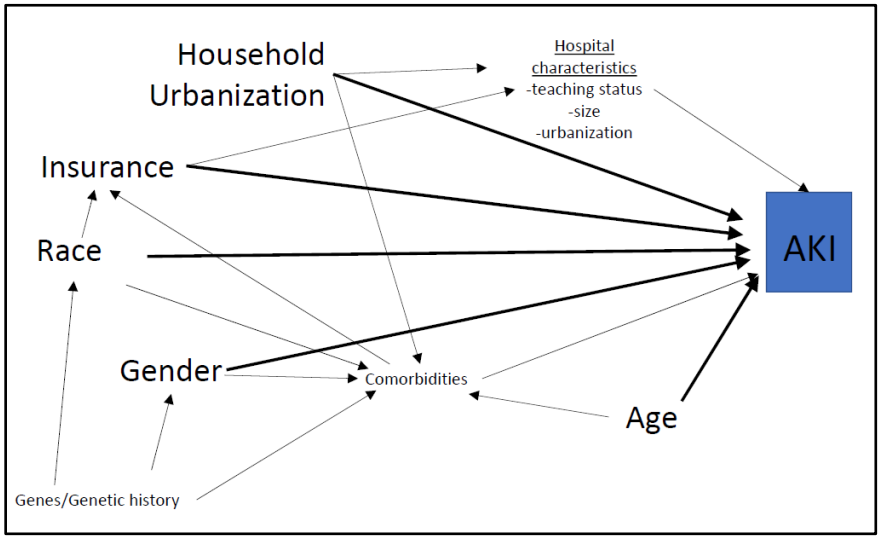



**Figure 3.1. A Simplified Directed Acyclic Graph of the Potential Relationships between Sociodemographic Factors and Acute Kidney Injury.**
Primary Exposures: Race, Health insurance status (Insurance), Household urbanization, Gender, Age
Primary Outcome: Acute Kidney Injury (AKI)
Confounders are variables that have an arrow going towards exposure and towards outcome (directly or indirectly). Examples would be genetic history between Race and AKI (indirectly via comorbidities).
Mediators are variables along the causal pathway (arrow coming from exposure and then arrow going towards outcome). Example would be Hospital characteristics as a mediator between Insurance and AKI. Mediators are variables not typically controlled for in multivariate modelling as they can then introduce bias.

Confounders of comorbidities and the other exposures based on the DAG and substantive knowledge from the literature to more explicitly evaluate each individual exposure-outcome relationship. Both traditional methods of model adjustment and stratification were used to control for potential confounders in our analyses.

All statistical analyses were conducted in SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). The institutional review board at the University of North Carolina at Chapel Hill reviewed this secondary data analysis of de-identified data.

*Sensitivity Analysis:* Roughly 8% of patients in the KID were missing data on race/ethnicity. We conducted a sensitivity analysis using multiple imputation to correct for missing race/ethnicity. The imputation model included all covariates listed in the Covariates section.

## 3.3 Results

*Patient Characteristics:* The KID contained 3,195,782 hospitalizations in 2012, and 1,699,841 of these met our study cohort criteria. The majority excluded were due to age <1 year. Applying the HCUP weights to this subset translates to about 2.4 million hospitalizations for 2012 across the United States. The majority of patients were Caucasian (46.3%), followed by African Americans and Hispanics (Table 3.1). Most children were female across race/ethnicities. The majority of hospitalizations occurred in large, urban teaching hospitals. While only a minority of children hospitalized did not have health insurance (4.3%), this extrapolates to over 100,000 children nationally. Lack of insurance differed by race/ethnicity, ranging from 3.7-5.5% (Table 3.1). Also, more Caucasian and Asian/Pacific Islander children had private insurance, while Medicaid was carried by more African American, Hispanic, and Native American children (Table 3.1).

Approximately 30,000 children aged 1-20 years were diagnosed with AKI while hospitalized (Table 3.2). The crude risk of an AKI episode for a pediatric hospitalization in 2012 was 1.2%, or 12.3 cases per 1000 pediatric hospitalizations.

**Table 3.1.** Demographics of Hospitalized Pediatric Patients by Race and Ethnicity Weighted for National Estimates

| | Total[a] | Caucasian | African American | Hispanic | Asian/ Pacific Islander | Native American | Other |
|---|---|---|---|---|---|---|---|
| | n=2,392,031 | n=1,107,114 | n=431,738 | n=488,040 | n=50,553 | n=22,232 | n=112,779 |
| **Gender (female)[b], col %** | 59.1 | 58.0 | 60.9 | 61.8 | 53.9 | 62.5 | 57.3 |
| **Age[c], median (IQR)** | 14 (6, 18) | 15 (6, 18) | 15 (6, 18) | 14 (5, 18) | 11 (3, 17) | 15 (5, 18) | 13 (4, 18) |
| **Prevalence of CKD, col %** | 0.3 | 0.3 | 0.4 | 0.3 | 0.4 | 0.2 | 0.3 |
| **Number of chronic illnesses[d], median (IQR)** | 0.5 (0, 1.8) | 0.6 (0, 1.9) | 0.6 (0, 1.7) | 0.1 (0, 1.3) | 0.5 (0, 1.7) | 0.3 (0, 1.5) | 0.4 (0, 1.7) |
| **Type/location of hospital, col %** | | | | | | | |
| **Rural** | 9.3 | 12.7 | 5.7 | 4.1 | 5.1 | 23.6 | 4.8 |
| **Urban, non-Teaching** | 24.6 | 25.6 | 21.2 | 30.6 | 20.0 | 22.0 | 22.9 |
| **Urban, teaching** | 66.1 | 61.7 | 73.1 | 65.4 | 74.9 | 54.4 | 72.3 |
| **Size of hospital[e], col %** | | | | | | | |
| **Small** | 10.6 | 10.7 | 9.2 | 9.5 | 7.7 | 15.4 | 11.4 |
| **Medium** | 23.5 | 24.2 | 23.9 | 24.1 | 29.0 | 18.1 | 20.6 |
| **Large** | 65.9 | 65.1 | 66.9 | 66.3 | 63.4 | 66.5 | 68.0 |
| **Location in the United States, col %** | | | | | | | |
| **New England** | 3.5 | 4.4 | 2.4 | 3.5 | 4.2 | 0.4 | 4.0 |
| **Middle Atlantic** | 14.1 | 13.9 | 17.2 | 12.4 | 16.5 | 4.0 | 29.4 |
| **East North Central** | 14.8 | 18.2 | 18.9 | 5.5 | 9.0 | 6.0 | 12.7 |
| **West North Central** | 7.4 | 7.0 | 4.1 | 1.1 | 2.2 | 10.5 | 3.2 |
| **South Atlantic** | 20.2 | 19.3 | 32.7 | 12.5 | 8.9 | 9.0 | 14.1 |
| **East South Central** | 3.8 | 6.3 | 3.4 | 0.7 | 1.4 | 0.7 | 1.0 |
| **West South Central** | 15.0 | 13.2 | 13.2 | 23.9 | 7.8 | 22.2 | 17.7 |
| **Mountain** | 6.7 | 7.1 | 2.0 | 9.4 | 6.3 | 29.5 | 5.7 |
| **Pacific** | 1.3 | 10.7 | 6.1 | 31.0 | 43.7 | 17.7 | 12.2 |
| **Insurance Status[f], col %** | | | | | | | |
| **No insurance** | 4.3 | 3.9 | 4.4 | 5.5 | 3.7 | 4.9 | 5.1 |
| **Private insurance** | 39.3 | 51.1 | 23.3 | 23.1 | 50.2 | 21.8 | 36.1 |
| **Medicaid** | 51.3 | 39.5 | 67.6 | 66.6 | 40.9 | 63.7 | 52.6 |
| **Other** | 5.1 | 5.3 | 4.4 | 4.7 | 4.9 | 8.7 | 5.8 |

| | Total[a] | Caucasian | African American | Hispanic | Asian/ Pacific Islander | Native American | Other |
|---|---|---|---|---|---|---|---|
| **Urbanization[g], col %** | | | | | | | |
| **Central metropolitan counties with ≥1 million Population** | 31.1 | 18.3 | 45.1 | 49.0 | 46.1 | 12.0 | 43.9 |
| **Fringe metropolitan counties with ≥1 million Population** | 22.1 | 25.4 | 20.4 | 15.5 | 22.3 | 9.4 | 23.4 |
| **Metropolitan counties with 250,000-999,999 Population** | 20.4 | 21.7 | 17.7 | 21.4 | 19.5 | 19.0 | 15.4 |
| **Metropolitan counties with 50,000-249,999 Population** | 9.4 | 11.5 | 7.5 | 6.6 | 4.0 | 14.3 | 7.0 |
| **Micropolitan Counties** | 10.3 | 13.9 | 6.1 | 5.0 | 6.5 | 20.2 | 6.1 |
| **Rural counties** | 6.4 | 9.0 | 3.0 | 2.0 | 1.0 | 25.0 | 3.2 |

[a]128,742 patients missing data on race/ethnicity (unweighted)
[b]138 patients missing data on gender (unweighted)
[c]6,304 patients missing data on age (unweighted)
[d]Chronic conditions defined by the chronic condition indicator of HCUP (Hospital Care and Utilization Program). Examples of included chronic conditions that may influence AKI include chronic kidney disease, diabetes mellitus, diabetes insipidus, developmental delays, inflammatory bowel disease, cystic fibrosis, congenital heart disease, and cancer.
[e]Hospital size category is determined based on a combination of location, teaching status, and region.
[f]4,274 patients missing data on health insurance status (unweighted)
[g]6,561 patients missing data on household urbanization (unweighted)

*Race/Ethnicity Differences:* Crude risk of AKI was highest amongst Asian/Pacific Islander children (14.9 cases/1000 pediatric hospitalizations) and lowest amongst Hispanic children (10.0 cases/1000 hospitalizations) (Table 3.2). When adjusted for comorbidities, insurance status, gender, age, and household urbanization, disparities by

| Table 3.2. Univariate Risk Estimates for Sociodemographic Differences in Pediatric AKI Episodes | | | | | | |
|---|---|---|---|---|---|---|
| | % of all hospitalizations n=2,392,031 | % of all AKI episodes n=29,391 | Risks | Risk Differences | 95% CI | P-value |
| **Race/Ethnicity**[a] | | | | | | |
| Caucasian | 46.3 | 47.6 | 12.6 | Reference | | |
| African American | 18.0 | 19.6 | 13.4 | 0.7 | -0.1, 1.5 | |
| Hispanic | 20.4 | 16.6 | 10.0 | -2.7 | -3.6, -1.7 | <0.0001 |
| Asian/Pacific Islander | 2.1 | 2.6 | 14.9 | 2.2 | 0.4, 4.1 | <0.01 |
| Native American | 0.9 | 0.8 | 10.9 | -1.8 | -4.6, 1.1 | |
| Other | 4.7 | 4.5 | 11.6 | -1.0 | -2.4, 0.3 | |
| **Insurance Status**[b] | | | | | | |
| Medicaid | 51.2 | 40.4 | 9.7 | Reference | | |
| No insurance | 4.3 | 8.1 | 23.1 | 13.4 | 11.7, 15.1 | <0.0001 |
| Private insurance | 39.2 | 43.6 | 13.7 | 4.0 | 3.4, 4.6 | <0.0001 |
| Other | 5.1 | 7.8 | 18.6 | 8.9 | 6.9, 11.0 | <0.0001 |
| **Gender**[c] | | | | | | |
| Female | 59.1 | 43 | 8.9 | Reference | | |
| Male | 40.9 | 57 | 17.1 | 8.2 | 7.6, 8.8 | <0.0001 |
| **Age**[d] | | | | | | |
| 1-5 years | 22.9 | 12.3 | 6.6 | Reference | | |
| 6-10 years | 12.7 | 10.7 | 10.3 | 3.7 | 3.1, 4.4 | <0.0001 |
| 11-15 years | 17.0 | 16 | 11.6 | 5.0 | 4.2, 5.8 | <0.0001 |
| 16-20 years | 47.0 | 59.9 | 15.6 | 9.0 | 8.4, 9.7 | <0.0001 |
| **Household Urbanization**[e] | | | | | | |
| Central metropolitan counties with ≥1 million population | 31.2 | 30.2 | 11.9 | Reference | | |
| Fringe metropolitan counties with ≥1 million population | 22.2 | 23.1 | 12.9 | 0.9 | 0, 1.9 | 0.05 |
| Metropolitan counties with 250,000-999,999 population | 20.5 | 21.3 | 12.8 | 0.9 | -0.3, 2.0 | |
| Metropolitan counties with 50,000-249,999 population | 9.5 | 9.4 | 12.3 | 0.4 | -0.9, 1.6 | |
| Micropolitan counties | 10.3 | 9.7 | 11.6 | -0.3 | -1.4, 0.7 | |
| Rural (neither metro- or micropolitan) counties | 6.4 | 5.7 | 10.9 | -1.0 | -2.2, 0.1 | |

All risks and risk differences are per 1000 hospitalizations.
AKI=Acute kidney injury; RD=risk difference; CI=confidence interval.
[a]128,742 patients missing data on race/ethnicity (unweighted)

[b]4,274 patients missing data on health insurance status (unweighted)
[c]138 patients missing data on gender (unweighted)
[d]6,304 patients missing data on age (unweighted)
[e]6,561 patients missing data on household urbanization (unweighted)

race/ethnicity were attenuated (Table 3.3). However, AKI risks among African American (RD 2.5 cases/1000 hospitalizations, 95% confidence interval (CI) 1.7-3.3), Hispanic (RD 1.7 cases/1000 hospitalizations, 95% CI 0.9-2.5), and Asian/Pacific Islander children (RD 4.5 cases/1000 hospitalizations, 95% CI 2.9-6.0) remained elevated compared to Caucasian children.

**Table 3.3. Multivariate Modelling by Sequential Addition of Potential Confounders**

| Potential Confounders: | race+chronic | race+chronic+ age+urban | race+chronic+age+urban+ insurance+gender |
|---|---|---|---|
| **HEALTH INSURANCE** | | | |
| Medicaid | **Reference** | Reference | Reference |
| No insurance | **14.4 (12.7, 16.2)****** | 12.9 (11.3, 14.6)**** | 11.8 (10.2, 13.4)**** |
| Private insurance | **3.4 (2.8, 4.0)****** | 3.4 (2.9, 4.0)**** | 2.8 (2.3, 3.4)**** |
| Other | **6.7 (4.8, 8.5)****** | 6.4 (4.5, 8.3)**** | 5.7 (3.8, 7.6)**** |
| **GENDER** | | | |
| Female | - | **Reference** | Reference |
| Male | - | **7.3 (6.7, 7.9)****** | 6.8 (6.2, 7.4)**** |
| **RACE/ETHNICITY** | | | |
| Caucasian | - | - | **Reference** |
| African American | - | - | **2.5 (1.7, 3.3)****** |
| Hispanic | - | - | **1.7 (0.9, 2.5)****** |
| Asian/Pacific Islander | - | - | **4.5 (2.9, 6.0)****** |
| Native American | - | - | **0.7 (-2.1, 3.5)** |
| Other | - | - | **1.4 (0.3, 2.5)*** |

Race=race/ethnicity; Chronic=chronic illnesses; Age=age in years; Urban=household urbanization.
Bold indicates ideal set of confounders to evaluate according to DAG depicted in Figure 3.1. Additional confounders shown for comparison but may potentially introduce additional bias.
* <0.05
** <0.01
*** <0.001
**** <0.0001

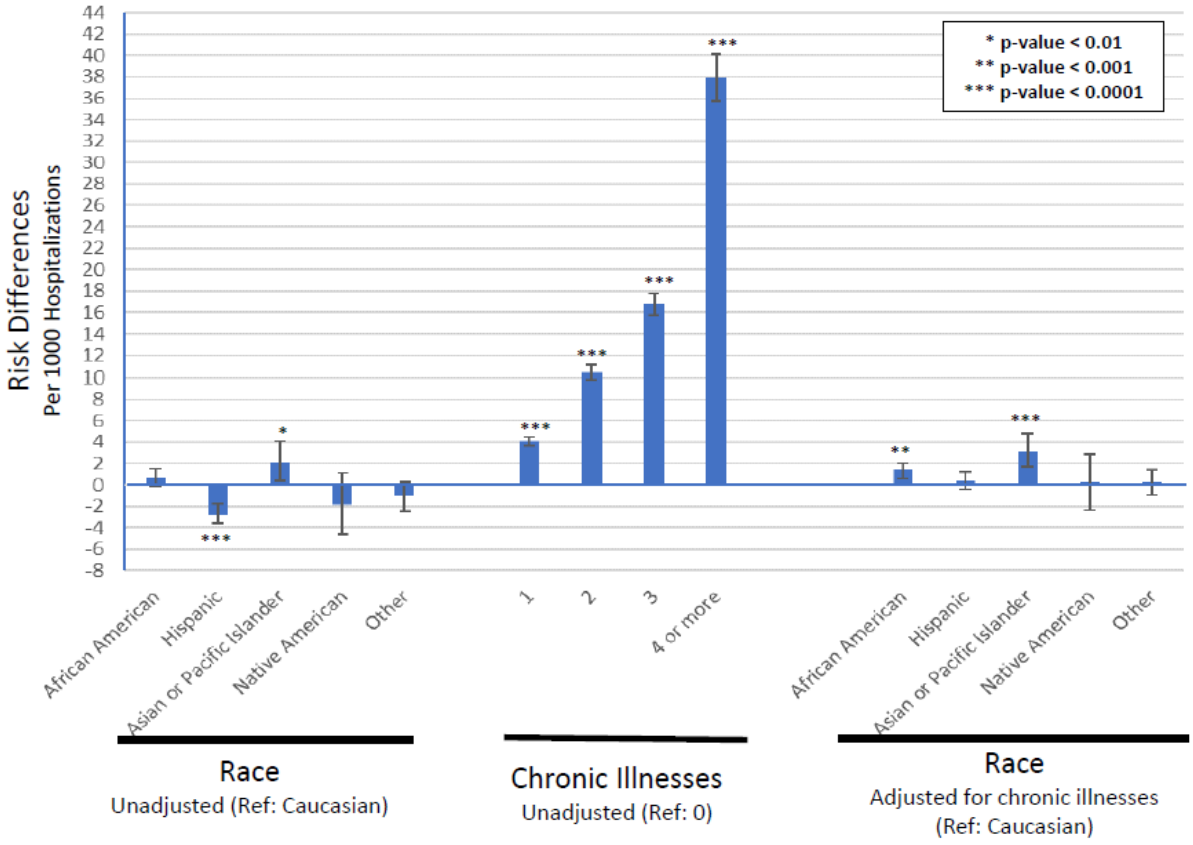



**Figure 3.2. Risk of Acute Kidney Injury by race/ethnicity and chronic illnesses.** Error bars represent 95% confidence intervals.

Crude analyses indicated that having chronic comorbidities were a significant risk factor for AKI, and the risk increased with increasing number of chronic illnesses (Figure 3.2). Adjusting for comorbidities alone greatly attenuated the racial disparities seen with AKI risks (Figure 3.2). We conducted a sensitivity analysis using multiple imputation to correct for the 8% missing race/ethnicity and found no meaningful differences in our results.

*Health Insurance Status:* Lack of health insurance was the sociodemographic risk factor most strongly associated with AKI in hospitalized children (Table 3.2). The uninsured population had double the crude risk of AKI compared to all pediatric inpatients (23.1 cases/1000 hospitalizations amongst the uninsured versus 12.3 cases/1000 hospitalizations overall). The

absolute risk difference for those without insurance versus Medicaid was 14.4/1000 hospitalizations, which suggests that if 70 hospitalized children currently without insurance were able to receive Medicaid, one AKI episode might be prevented (number needed to treat is 70, 95% CI 62-79).

After adjusting for chronic illnesses, Medicaid remained a protective factor against AKI even when stratified further by race and gender (Figure 3.3). Model including chronic illnesses

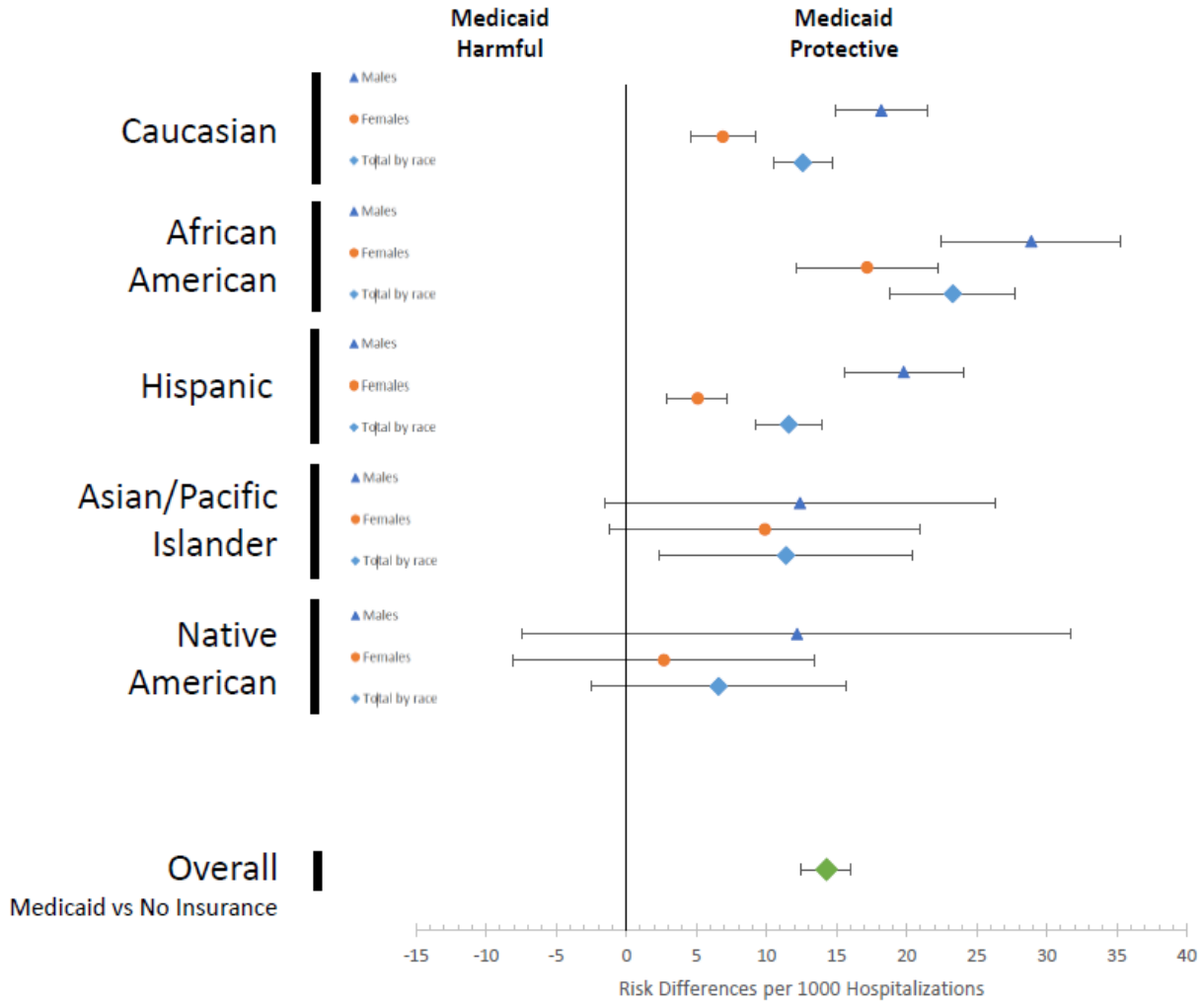



**Figure 3.3. Risk Differences of AKI for those with No Health Insurance versus those with Medicaid, adjusted for chronic illnesses and stratified by race/ethnicity and gender.** Error bars represent 95% confidence intervals.

And race yielded similar results (Table 3.3). We conducted a sensitivity analysis excluding 19- and 20-year-old patients as these patients may have different access to health insurance (i.e., typically not able to access Medicaid as easily as those ≤18 years old) and in our population almost half of those without insurance were 19-20 years of age (47.1%) (Table 3.4). Interestingly, the risk of AKI remained higher for those without insurance versus Medicaid but it was greatly attenuated (RD 4.4, 95% CI 2.8-5.9) in this sensitivity analysis, controlling for race/ethnicity and comorbidities.

**Table 3.4. Multivariate Modelling by Sequential Addition of Potential Confounders, excluding 19- and 20-year-olds**

| Potential Confounders: | race+chronic | race+chronic+ age+urban | race+chronic+age+urban+ insurance+gender |
|---|---|---|---|
| **HEALTH INSURANCE** | | | |
| Medicaid | **Reference** | Reference | Reference |
| No insurance | **4.4 (2.8, 5.9)****** | 4.0 (2.6, 5.5)**** | 3.8 (2.4, 5.3)**** |
| Private insurance | **2.2 (1.6, 2.8)****** | 2.1 (1.5, 2.7)**** | 2.0 (1.4, 2.6)**** |
| Other | **5.4 (3.1, 7.6)****** | 5.2 (2.9, 7.5)**** | 5.1 (2.8, 7.4)**** |
| **GENDER** | | | |
| Female | - | **Reference** | Reference |
| Male | - | **3.1 (2.6, 3.6)****** | 2.9 (2.5, 3.4)**** |
| **RACE/ETHNICITY** | | | |
| Caucasian | - | - | **Reference** |
| African American | - | - | **1.2 (0.4, 2.0)**** |
| Hispanic | - | - | **1.7 (0.8, 2.7)***** |
| Asian/Pacific Islander | - | - | **4.1 (2.3, 5.9)****** |
| Native American | - | - | **0.2 (-3.1, 3.5)** |
| Other | - | - | **1.0 (-0.2, 2.3)** |

Race=race/ethnicity; Chronic=chronic illnesses; Age=age in years; Urban=household urbanization.
Bold indicates ideal set of confounders to evaluate according to DAG depicted in Figure 3.1.
Additional confounders shown for comparison but may potentially introduce additional bias.
* <0.05
** <0.01
*** <0.001
**** <0.0001

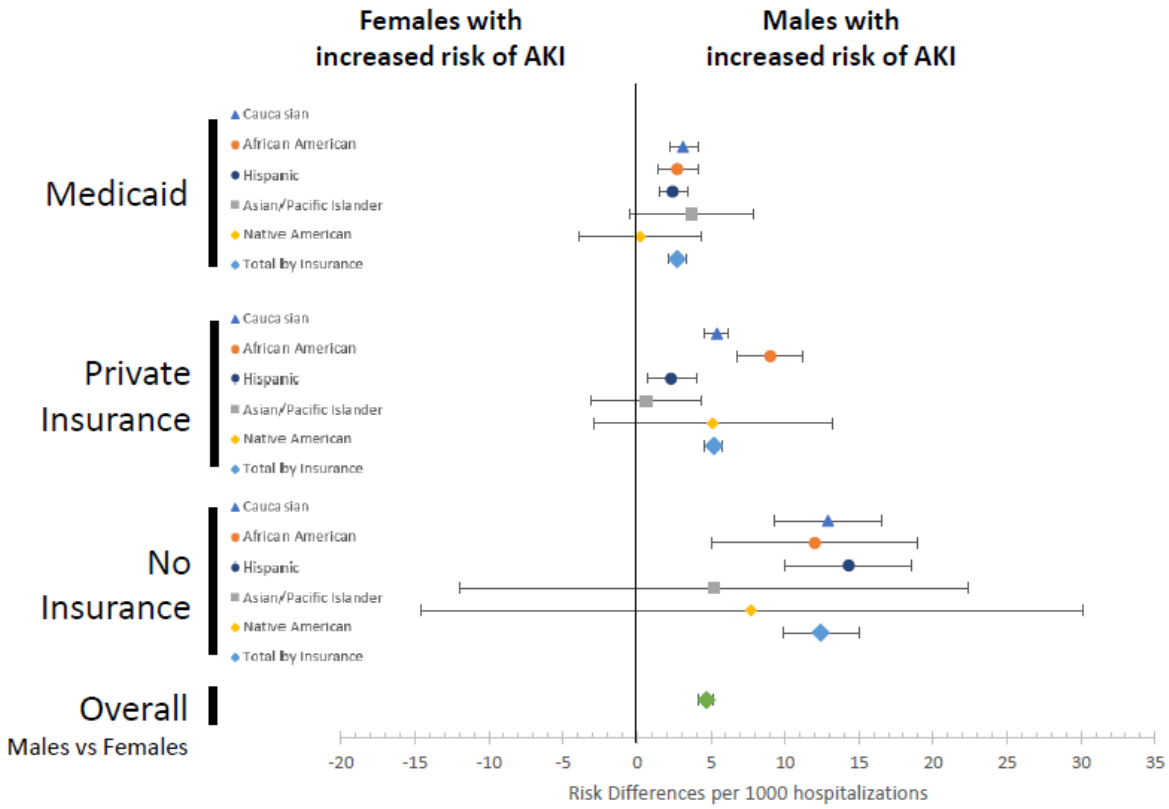



**Figure 3.4. Risk Differences of AKI for Males versus Females, adjusted for chronic illnesses and stratified by health insurance status and race/ethnicity.** Error bars represent 95% confidence intervals.

*Household Urbanization:* Our one neighborhood-level factor (household urbanization) was not a significant risk factor for AKI. Only fringe vs central metropolitan counties with ≥1 million population had a risk difference of 0.9 per 1000 hospitalizations (95% CI 0-1.9) with p-value 0.05 (Table 3.2).

*Gender Differences:* Compared to female patients, males were associated with a higher risk of AKI (RD 8.2/1000 hospitalizations, 95% CI 7.6-8.8) (Table 3.2), and this difference persisted after adjustment for chronic conditions (Figure 3.4). This increased risk was present for all Caucasian, African American, and Hispanic boys, regardless of insurance strata (Figure 3.4). The risk remained after modelling controlled for comorbidities, race/ethnicity, age, and

household urbanization (RD 7.3, 95% CI 6.7-7.9), but was again attenuated with sensitivity analysis removing 19- and 20-year-olds (RD 3.1, 95% CI 2.6-3.6, Table 3.4).

*Age Differences:* Older age was associated with a higher risk of AKI diagnosis (Table 3.2).

## 3.4 Discussion

This is the first large, nationally representative pediatric kidney study to show that lack of health insurance is a risk factor for poor kidney outcomes. Only slight racial differences existed for AKI. Chronic illnesses also were associated with pediatric AKI, and they attenuated the racial disparities. Male gender was a risk factor for increased risk of pediatric AKI, and the increased risk in males was highest amongst racial minorities and uninsured children.

*Health Insurance Status:* Medicaid was the most protective sociodemographic factor against AKI. Compared to uninsured children, if a hospitalized child had Medicaid, his/her absolute risk of being diagnosed with AKI decreased by 14 per 1000 hospitalizations, controlling for comorbidities and race. These results should be interpreted with caution since our study is limited to administrative data. We cannot account for all unmeasured confounding in this observational study. However, our results are consistent with a large national study that found lack of insurance in pediatric patients was independently associated with increased all-cause inpatient mortality.[42]

Prior research evaluating insurance disparities has grouped Medicaid and no insurance into one "low-income" category.[43] Our research indicates these populations should be evaluated separately. Insurance in children holds a different connotation than in adults. In all states, many children who are not eligible for private insurance are eligible for some form of government-assisted insurance, such as Medicaid.[44–46] Pediatric patients who have no insurance are a unique

group of patients, typically due to eligibility issues such as citizenship status (rarely financial), family decisions to decline coverage, or healthcare illiteracy and misunderstandings about eligibility for children who would otherwise be eligible. However, since 2016, California, Illinois, Massachusetts, New York, Oregon, Washington, and Washington D.C. have decreased barriers to insuring children and providing state health insurance regardless of citizenship status.[47] Though we argue that health insurance status is unique in the pediatric population, it is still considered a social determinant of health by the Healthy People 2020 initiative.[48] We still contend that health insurance status is a marker of one's ability to access the healthcare system and preventative services.

A unique feature of AKI risk amongst patients uninsured in this population is that it seems to be worst amongst the 19- and 20-year-olds. This may be a true risk or a glimpse at the under-diagnosis of AKI in younger children. Nineteen- and twenty-year-old patients may be a high-risk population that are no longer eligible for most state Medicaid programs (47% of uninsured patients are 19-20 years of age). However, older pediatric patients have greater muscle mass and hence higher baseline creatinine levels making them more akin to adult levels, which may allow easier recognition and subsequently improved coding of AKI amongst older children. This was also seen as gender AKI risks were attenuated when we removed 19- and 20-year-olds from the analysis.

The only other pediatric kidney study to look at social determinants of health focused on parental, self-reported income level in children with chronic kidney disease, and they found no difference in the rate of kidney disease decline based on income.[49] However, that study was limited by its smaller size (n=572) and inclusion only of children actively involved in medical care, creating a selection bias against those with poor access to care and without insurance. We

found that the individual-level determinant of health, health insurance, was associated with increased AKI risk. However, we found no increased AKI risk with the neighborhood-level determinant of health, household urbanization.

Potentially, our data reflect our medical system's ability to reach even the poorest or most remote neighborhoods. Perhaps, the more important sociodemographic factor to prevent AKI is one's individual ability to gain access to our medical system, both preventative and emergency services, without worry of cost. This seems congruent with our findings that those with private insurance had slightly higher risk of AKI than Medicaid. Patients with private insurance often have higher co-pays, different levels of coverage depending on their insurer, and may fluctuate in and out of insurance depending on parental job stability. The experience for those with Medicaid differs in that they have minimal to no co-pays and the same standard coverage across a state regardless of parental employment status. We were limited in our ability to assess additional indicators for social determinants of health at the individual level (e.g., income, parents' level of education) or neighborhood level (e.g., percent in poverty, employment rates, percent with high school diploma).

*Race/Ethnicity:* Disparities among populations with lower socioeconomic status (SES) and racial minorities often are intertwined due to their co-existence. Just as lower SES groups are more likely to experience poorer health outcomes, minority groups have been more likely to report poorer health status compared to Caucasians.[33,34,50] As an example, a recent study on appendiceal ruptures saw improvements in all racial groups after insurance coverage increased, but more pronounced improvements amongst minorities.[51]

Though the differences are small, our finding of increased AKI risk in minority groups is of significance given the large number of hospitalized pediatric patients at risk of AKI annually

in the United States. This analysis of a large, nationally-representative cohort allowed us to see these small differences that may be missed in smaller studies. These risks are not completely attenuated after stratifying by insurance status and controlling for comorbidities. Asian/Pacific Islander, African American, and Hispanic children have a slightly higher risk of AKI compared to Caucasian children. The pediatric nephrology literature suggests similar disparities for racial minorities in accessing pediatric renal transplants.[52,53]

Part of the racial differences seen in this study may be due to differing levels of medical care in hospitals predominantly caring for minority groups or other SES factors we were unable to capture in this analysis. Chronic conditions alone are also a major risk factor for AKI, and they attenuated much of the racial disparities seen in this study, suggesting the possibility of a genetic component or other uncaptured confounder of the association between race and AKI. Risk variants of the apoliprotein L1 (APOL1) gene have been consistently cited to explain much of the racial burden of chronic kidney disease as APOL1 is more prevalent in African Americans, but this has not been consistently shown in AKI literature.[54–58] A large adult cohort study did not find evidence that APOL1 risk variants had a higher risk of AKI compared to those without these variants; though this evaluation assessed APOL1 risk variants found in chronic renal conditions.[59] A large genome-wide association study in AKI found two risk alleles in APOL1 distinct from APOL1 risk alleles in chronic kidney disease.[60]

Further research is needed to evaluate the higher AKI incidence in Asian/Pacific Islander children as this has not been seen in other studies. However, other studies often focus only on Caucasian, African American, and/or Hispanic sub-groups, excluding Asian and Pacific Islander children due to sample size issues. It is known in adults that people from the Pacific Islands have higher rates of chronic renal failure than any other racial or ethnic group.[61]

*Gender:* Our study also found a higher AKI risk amongst male patients when compared with females, after controlling for comorbidities, race/ethnicity, age, and household urbanization. While adult AKI studies also show males to be at increased risk, this is often explained by the gender differences in undiagnosed comorbid conditions (e.g., hypertension, hyperglycemia), which are less common in the pediatric population. The gender differences in pediatric AKI risk may be related to underlying disease rate differences in congenital conditions, such as congenital anomalies of the kidney and urinary tract, which are more common in boys. There also may be a differential bias in detection of AKI, perhaps due to differing muscle mass in the adolescent population.

*Age:* The AKI risk found in older children in this study should be viewed with caution as the outcomes of AKI are from administrative data only. There may be a true increasing risk of AKI with increasing age, but our study may also be highlighting the lack of recognition of AKI in younger children and not a true increased risk. Younger children with low baseline creatinine levels (e.g., 0.2-0.4mg/dL) may have a significant AKI with doubling of their creatinine and still remain with creatinine levels ≤1mg/dL (normal for an adult), an easy miss for providers less familiar with pediatric variations in creatinine levels.

*Limitations:* This study is a secondary analysis of voluntary, administrative data submitted by hospitals to a national database. Hospitals can choose whether to participate, which may potentially introduce bias to the available data. The unit of measurement is a hospitalization, so recurrent AKI episodes in one individual in separate hospitalizations is possible. We are unable to link individuals and consequently cannot account for potential repeat outcomes. Our primary outcome relies solely on appropriate recognition and ICD coding, which has been shown

to be flawed with significant underreporting, in particular for AKI.[62–65] Hence, it is likely that our estimates under-report the true incidence of disease and perhaps the disparities that exist.

We attempted to evaluate both an individual social determinant of health and a neighborhood-level factor. In assessing these variables, we consider both the individual's access to medical care as well as geographic barriers to care. This analysis was limited by the available indicators for social determinants of health. Evaluating other factors, such as citizenship status, census tract income level, parental education level, may provide a clearer understanding of the higher risk of AKI amongst lower-resourced or lower SES populations as seen in this study.

However, this study also has important strengths. By analyzing such a large national database with a diverse patient population that represents almost every state in the country, we can provide an overview of the AKI burden and associated disparities at a national level that would not otherwise be apparent. Specifically, we are able to include a large proportion of minorities who are often not represented in kidney research (Hispanics, Asian/Pacific Islanders, and uninsured populations). Unlike other research on insurance disparities, we are able to distinguish Medicaid from no insurance, highlighting a distinct risk difference associated with AKI risk in these two different populations.

## 3.5 Conclusions

Pediatric AKI occurs in 12 of every 1000 pediatric hospitalizations. In the largest, nationally-representative cohort, the biggest protective factor against developing AKI is a child having health insurance. Our research should be confirmed with data sources other than administrative data, such as prospective cohorts and collaborations amongst hospitals that provide laboratory data to more accurately capture all AKI episodes. However, our data suggest

that we could potentially prevent 1 episode of AKI for every 73 uninsured hospitalized children provided with Medicaid. Our study showed that racial disparities exist amongst those with pediatric AKI. Though these risks are greatly attenuated by chronic conditions, racial minorities had higher risks compared to Caucasians. Also hospitalized boys were at an increased risk of AKI compared to girls, controlling for comorbidities, race, age, and household urbanization. More granular data is needed to explore the sociodemographic disparities seen in this large cohort. We need to evaluate if these disparities persist when we can evaluate all episodes of AKI and not just those recognized and subsequently coded by clinicians as these are just the tip of the iceberg. Expanding health insurance coverage to children currently uninsured should be explored further as a potential preventative approach for pediatric AKI, particularly amongst a potentially high-risk population 19- and 20-year-olds.

# CHAPTER 4: INCIDENCE AND EPIDEMIOLOGY OF ACUTE KIDNEY INJURY IN A PEDIATRIC MALAWIAN TRAUMA COHORT

## 4.1 Background

Estimates suggest that 13.3 million people worldwide are affected by AKI annually, 85% of whom live in developing countries.[10,66] Further it is estimated that up to 1.7 million deaths occur each year from AKI.[10,66] A large meta-analysis analyzing AKI incidence globally suggests that 1 in 3 hospitalized children experience AKI.[67] Yet, no high-quality studies could be found in Africa to be included.[67]

Previous studies of AKI in Africa have focused on infection-related AKI (e.g., AKI in those with malaria) or non-surgical-related AKI,[68–70] but trauma is also a likely culprit. There has been a paucity of investigation into AKI associated with trauma in Africa, despite the high burden of trauma in children.

Trauma is a leading cause of morbidity and mortality throughout Africa and the leading cause of mortality worldwide for children and young adults (5-29 years of age).[12] Organ failure, including AKI, is the third leading cause of mortality in trauma patients, after bleeding and brain injuries.[13] Traumas typical in low-resourced settings – road traffic injuries, burns, crushing in earthquakes or structural collapses – can result in AKI secondary to fluid loss, hemorrhage, and rhabdomyolysis from crush injuries. The majority of studies worldwide have looked at *critically ill* adult trauma patients and AKI rates are highly variable, ranging 1-50%.[21–26] Though pediatric trauma studies on AKI are scarce, a California study suggests 13% of pediatric post-traumatic

rhabdomyolysis patients experience AKI.[71] No studies have evaluated AKI rates amongst pediatric trauma patients in Africa.

We conducted the first prospective cohort study of pediatric trauma patients in sub-Saharan Africa to investigate AKI amongst a well-established hospital-based trauma surveillance registry in Malawi. We sought to determine the incidence of AKI amongst admitted pediatric trauma patients at this single center and determine if there were any sociodemographic, injury-related, and/or clinical risk factors for those who develop AKI.

## 4.2 Methods

*Design:* This is a single center, prospective observational cohort study evaluating the epidemiology of AKI in admitted adult and pediatric trauma patients in Lilongwe, Malawi.

*Study Population:* Kamuzu Central Hospital (KCH) and the Malawi Surgical Initiative have had a trauma registry in place for the past decade to characterize the burden of trauma in the Central Region of Malawi. KCH is the tertiary-level referral center for the Central Region of Malawi and is located in the capital city of Lilongwe. It has a catchment area of about 5 million people. It is the largest trauma center in the country, with 8 permanent surgical consultants. The larger study included both adults and children. This analysis included only the pediatric patients (≤18 years). Patients presenting to KCH for acute trauma between June and October 2019 were eligible for enrollment in our study. Additional inclusion criteria included age between 6 months and 18 years of age, weight >3kg, and expected admission >24 hours. A parent or a caregiver had to be present and provide written informed consent. Exclusion criteria included those with trauma that occurred >5 days prior to hospital arrival and those whose primary language was not English or Chichewa (the Malawian official and national languages, respectively). All admission

laboratory diagnostics had to occur within 18 hours of hospital arrival. All patients were prospectively followed throughout their hospitalization.

*Outcome:* The primary outcome of interest was AKI as defined by creatinine-only Kidney Disease Improving Global Outcomes (KDIGO) criteria (Table 1.1).[2] Serum creatinine was obtained on admission and again 48-72 hours later. In Malawi, it is not routine for kidney function tests or electrolytes to be collected on trauma patients, due to resource limitations. It is also not routine for urine volumes to be captured. To maximize our accuracy for diagnosing AKI, we chose to obtain two values 48 hours apart to assess a change in creatinine and better apply the KDIGO AKI criteria.[2] Medical teams could obtain more laboratory tests when they deemed them medically necessary.

Knowing a child's healthy baseline creatinine prior to injury or illness is an important component to the KDIGO criteria. This is rarely known in Malawi and many other sub-Saharan African countries. No studies have evaluated the optimal method for estimating a baseline creatinine (or by extrapolation, estimated glomerular filtration rate (eGFR)) in an African pediatric population. *A priori*, we defined a normal baseline eGFR as 120ml/min/1.73m$^2$.[72] We identified at least 4 potential definitions to estimate a child's baseline creatinine: (1) *lowest creatinine* during admission (if 2 or more values obtained); using patient's height and eGFR of 120ml/min/1.73m$^2$ calculated with (2) *old Schwartz equation* (eGFR=k*height/serum creatinine, where k=0.55 for children >1 year of age and k=0.45 if ≤1 year of age)[73], (3) *new (bedside) Schwartz equation* (eGFR=*k**height/serum creatinine, where k=0.413, height is in centimeters, and creatinine in mg/dL)[74], and (4) *new Schwartz equation modified for use in low-resourced settings (India equation)* that use Jaffe methods, where k=0.42 instead.[75] This latter equation was derived in a pediatric population in India, where *k*=0.42 was determined to be most predictive of

actual glomerular filtration rate when only height/weight are measured and Jaffe methods are used, as may be encountered in low-resourced settings.[75] Briefly, both Jaffe and enzymatic methods are lab-based methods to determine serum creatinine. Jaffe methods are more prone to interfering substances yet are drastically cheaper than the newer enzymatic methods. The *old Schwartz equation* was based on Jaffe methods, while the *new (bedside) Schwartz equation* was based on enzymatic methods.

The University of North Carolina Project Malawi Laboratory, a state-of-the-art laboratory on-site at KCH, performed all laboratory testing to ensure reliable and consistent laboratory results. Creatinine and potassium values were obtained on fresh serum and evaluated on Roche Cobas C311 analyzers. Creatinine was determined using Jaffe analytic methods. Hemoglobin values were obtained by trained study nurses with a point-of-care HemoCue Hb 201+ analyzer.

*Covariates:* As this was an exploratory analysis for hypothesis generation of potential sociodemographic and clinical risk factors associated with AKI amongst pediatric trauma patients in sub-Saharan Africa, we assessed for multiple potential exposures.

(1) Demographic variables included age in years, sex (binary), tribal association (collapsed to be binary of Chewa versus Other due to small numbers), and home district (collapsed to be binary of Lilongwe versus Other due to small numbers).

(2) Comorbidities were determined by patient/care-giver self-report with the exception of a few specific diseases in which we confirmed with laboratory testing due to their potential impact on kidney function. These diseases included: anemia (defined as hemoglobin<11g/dL by World Health Organization classification,[76]) by point-of-care hemoglobin, sickle cell disease by hemoglobin electrophoresis, and malaria by blood smears. Human immunodeficiency virus serostatus was determined by self-report of

infection or hospital-based testing and documentation as per Malawian national guidelines. Hospital disposition was defined as discharged alive, left against medical advice, or death.

(3) Environmental exposures are known to be nephrotoxic. Potential exposures we obtained from patient/caregiver report included: primary drinking water source (categorical: river or lake, community pipe, individual potable water outside the home, potable water inside the home), previous herbal remedies obtained in past 7 days (yes/no), and previous over-the-counter medications obtained in past 7 days (yes/no).

(4) Several socioeconomic status variables were evaluated as no single variable has been shown to best capture an individual's socioeconomic status in African studies.[77,78] We obtained common variables for socioeconomic status used in other African studies: parental and child's level of education (continuous integer), mother and father vital status (alive/dead), crowding (number of people living in the home divided by the number of rooms in the home), type of roofing (categorical: thatch, tile, tin/iron), type of flooring (categorical: dirt, cement, tile), and possession of common items (refrigerator, television, cell phone, working vehicle, chicken(s), cow(s)).

(5) Trauma-related factors included type of trauma (categorical: burn, fall, road traffic injury, other), body location of trauma (categorical: head/neck, trunk, extremity, face), and multiple injuries (yes/no). We attempted to obtain Kampala Trauma Score (a validated score for injury severity in low-resourced settings)[79] on patients, but insufficient patients had all variables documented in their hospital records to calculate it (n=2).

*Sample Size:* To estimate AKI incidence in children (≤18 years of age), we aimed to enroll 240 pediatric trauma patients admitted to KCH. This target sample size would allow us to detect a 17% incidence with precision of +/- 5% and allow for a 10% loss-to-follow-up rate for patients leaving against medical advice prior to the second creatinine value. We estimate an incidence of 17% based on a study in Blantyre, Malawi that found AKI in 17% of adults admitted to general medical wards.[80] There were no published estimates of pediatric AKI in Malawi at the time of study planning.

*Analysis:* The primary outcome of interest was the incidence of AKI, defined by creatinine-only KDIGO criteria.[2] Descriptive analyses were used to assess the four different methods for estimating a child's baseline creatinine to determine the optimal method for this patient population. As there is no gold standard for estimating a baseline creatinine in pediatrics, we determined that the lowest creatinine method would provide the least biased estimate as no assumptions are made *a priori.* Descriptive statistics evaluated epidemiological factors and mortality associated with those who developed AKI versus those who did not. Comparisons of sociodemographic factors, exposure history and clinical characteristics between those who did and did not develop AKI were evaluated with ANOVA and chi-square tests for categorical and continuous variables, respectively. For variables with p-values <0.1, we further evaluated measures of association for AKI with univariate linear and log-linear regression models to assess potential univariate risk factors. Sample size/outcome were too small for multivariate modelling of risk factors.

Data were double-entered into REDCap electronic data capture tools hosted at the University of North Carolina at Chapel Hill (UNC) to ensure accuracy of translating paper forms to an electronic database.[81] All statistical analyses were conducted in SAS, version 9.4 (SAS

Institute, Inc., Cary, North Carolina). The institutional review board at UNC and Malawi's National Health Science Research Committee approved this study.

## 4.3 Results

A total of 4547 adult and pediatric trauma patients presenting to KCH were screened, and 674 (14.8%) were eligible for enrollment (Figure 4.1). However, only 343 (50.9%) of the eligible participants were enrolled in the overall study, primarily due to arrival times (i.e., evenings and

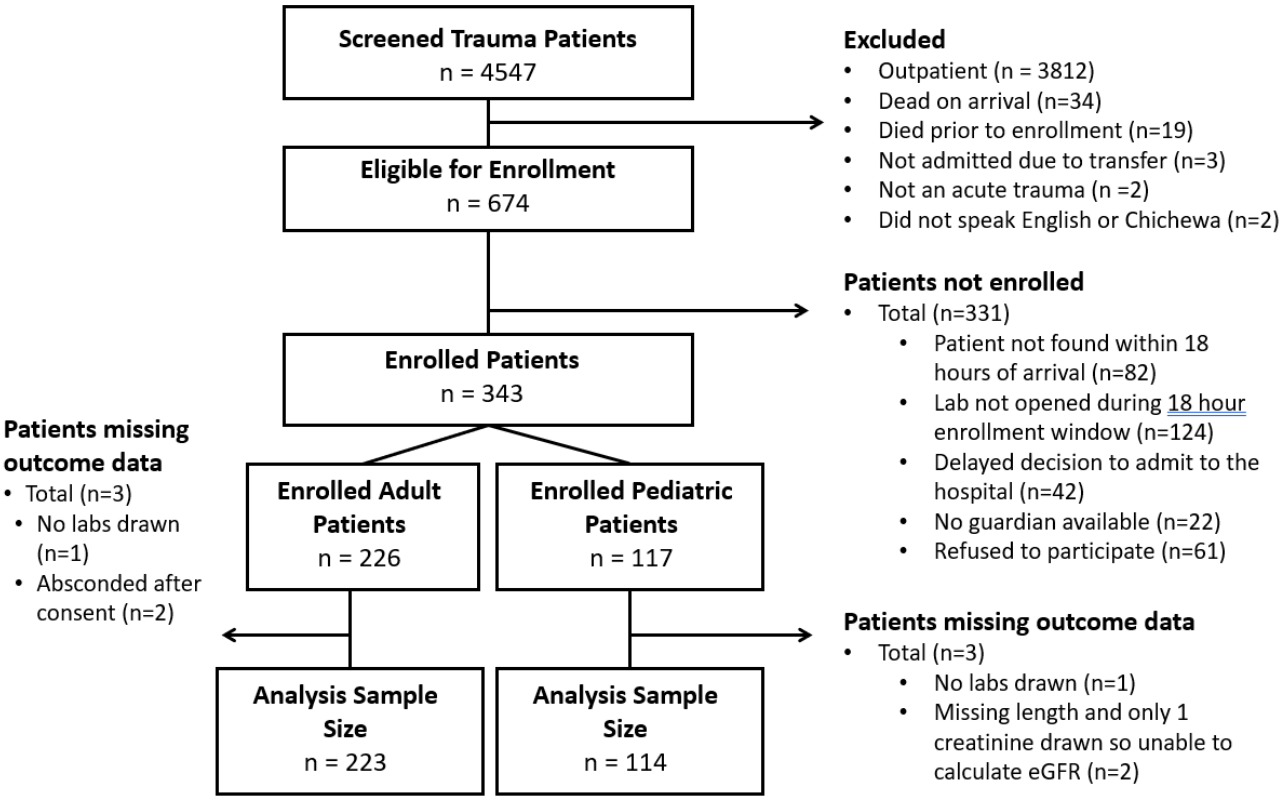



**Figure 4.1. Patient Enrollment Flow Chart.** Patient enrollment flow chart for the larger study. For this analysis only the pediatric patients are analyzed.

Sundays when the laboratory was not open) and inability to find participants within the allotted enrollment time period. A total of 114 pediatric participants were enrolled and available for analysis.

**Table 4.1. Demographics of Pediatric Trauma Patients Admitted to Malawian Hospital by Development of AKI**

| | Total<br>N=114 | AKI<br>11 (9.7) | No AKI<br>103 (90.4) | Missing |
|---|---|---|---|---|
| **Age (years) (mean, STD)** | 8.1 (5.1) | 7.0 (6.0) | 8.2 (5.0) | 0 |
| **Gender (female)** | 42 (37.2) | 4 (36.4) | 38 (37.3) | 1 |
| **Tribe** | | | | 2 |
| **Chewa** | 74 (66.1) | 8 (72.7) | 66 (65.4) | |
| **Other** | 38 (33.9) | 3 (27.3) | 35 (34.7) | |
| **District of Injury Location** | | | | 1 |
| **Lilongwe** | 75 (66.4) | 8 (72.7) | 67 (65.7) | |
| **Other District** | 38 (33.6) | 3 (27.3) | 35 (34.7) | |
| **Mortality** | 10 (9.0) | 4 (36.4) | 6 (6.0) | 7[a] |
| **Length of Stay[b] (days) (median, IQR)** | 12 (7, 26) | 19.5 (9, 35) | 12 (7, 25) | 7[a] |
| **Time of Presentation to Hospital** | | | | |
| **Day of the week (weekend, Saturday-Sunday)** | 12 (10.5) | 2 (18.2) | 10 (9.7) | 0 |
| **Time of Day (daytime, 08:00-16:00)** | 42 (37.5) | 6 (54.6) | 36 (35.6) | 2 |
| **Comorbidities** | | | | |
| **Anemia** | 72 (63.2) | 7 (63.6) | 65 (63.1) | 0 |
| **Malaria** | 18 (16.2) | 1 (9.1) | 17 (17.0) | 3 |
| **Sickle Cell Disease[c]** | | | | 4 |
| **Sickle Cell Disease** | 0 (0) | 0 (0) | 0 (0) | |
| **Sickle Cell Trait** | 5 (4.6) | 0 (0) | 5 (5.1) | |
| **Normal Hemoglobin** | 105 (95.5) | 11 (100) | 94 (95.0) | |
| **Malnutrition[d] (median, IQR)** | | | | |
| **Weight-for-age Z-score[e]** | -0.3 (-1.4, 0.3) | -1.7 (-1.7, -1.7) | -0.2 (-1.3, 0.5) | 85 |
| **Height-for-age Z-score** | -0.9 (-1.9, 0.3) | -0.8 (-2.2, 0.2) | -0.9 (-1.9, 0.3) | 7 |
| **Weight-for-length Z-score** | -0.3 (-1.2, 0.4) | -0.6 (-2.1 ,1.0) | -0.3 (-1.2, 0.4) | 69 |
| **Past Medical History (self-report)** | | | | 0 |
| **Prematurity** | 2 (1.9) | 0 (0) | 2 (2.1) | 7 |
| **Seizures** | 5 (4.4) | 1 (9.1) | 4 (3.9) | 0 |
| **Asthma** | 1 (0.9) | 0 (0) | 1 (1.0) | 0 |
| **None** | 108 (94.7) | 10 (90.9) | 98 (95.1) | 0 |

All expressed as N and column percent except where specified.
AKI=Acute kidney injury; IQR=interquartile range; STD=standard deviation.
[a]4 patients absconded, 3 patients missing files
[b]Length of stay is determined only for patinets discharged alive.
[c]Sickle cell disease status was determined by hemoglobin electrophereisis.
[d]Malnutrition z-scores obtained using WHO AnthroPlus software, 2007 WHO reference data.

[e]Weight-for-age Z scores are only provided for children up to age 10 years, WHO does not provide referent values after 10 years of age.
KDIGO criteria used to define AKI and new Schwartz equation estimated baseline creatinine.

*Demographics:* The majority of participants were male (62.8%) and average age was 8.1±5.1 years (Table 4.1). Participants were primarily local, coming from within the Lilongwe district (66.4%). Nine percent of participants died (10 of 114). Overall, the participants were malnourished, a large majority had anemia (63.2%), and 16.2% had malaria. HIV status was missing for 73.7% of patients.

*Outcome:* The incidence of AKI varied depending on the method utilized to estimate a child's 'baseline creatinine.' The *new (bedside) Schwartz* equation seemed to perform best in this patient population, giving an AKI incidence of 9.7%. The old Schwartz equation estimated the lowest incidence (5.3%). The average incidence using all 4 approaches was 8.4%. The lowest creatinine method made the least assumptions but required that two creatinine values were obtained from a patient, so it is the least versatile for a low-resourced setting.

To determine the equation method that estimated baseline creatinine closest to the lowest creatinine method, we limited the analyses to those who had two creatinine values. The estimated incidences were the same for all methods (8.8%) except the old Schwartz equation (4.4%) (Table

**Table 4.2. Incidence of AKI by Estimated Baseline Creatinine Method[a]**

| AKI Definition | AKI # | AKI % | AKI Stage 2 or 3 % |
|---|---|---|---|
| Absolute 0.3 change or one of | -- | -- | -- |
| ≥1.5 rise of lowest creatinine | 8 of 91 | 8.8% | 2.2% (n=2) |
| ≥1.5 rise of baseline creatinine (estimated by Old Schwartz)[18] | 4 of 91 | 4.4% | 1.1% (n=1) |
| ≥1.5 rise of baseline creatinine (estimated by New Schwartz)[19] | 8 of 91 | 8.8% | 1.1% (n=1) |
| ≥1.5 rise of baseline creatinine (estimated by modified New Schwartz, for low-resourced settings)[20] | 8 of 91 | 8.8% | 1.1% (n=1) |

[a]Restricted to only those with 2 creatinine values

4.2). Figure 4.2 provides a visualization for the estimated baseline creatinine using the four different methods. Since the lowest creatinine method makes no assumptions about a baseline eGFR or equation, we used this as the 'gold standard' comparator. The best approximator to the lowest creatinine value appears to be the new Schwartz equation using the original kappa (0.413) or the kappa (0.42) (India equation). For ease of use and consistency with other literature, we used the new Schwartz equation for further analyses. We conducted a sensitivity analysis with kappa=0.42 and found no differences in our results.

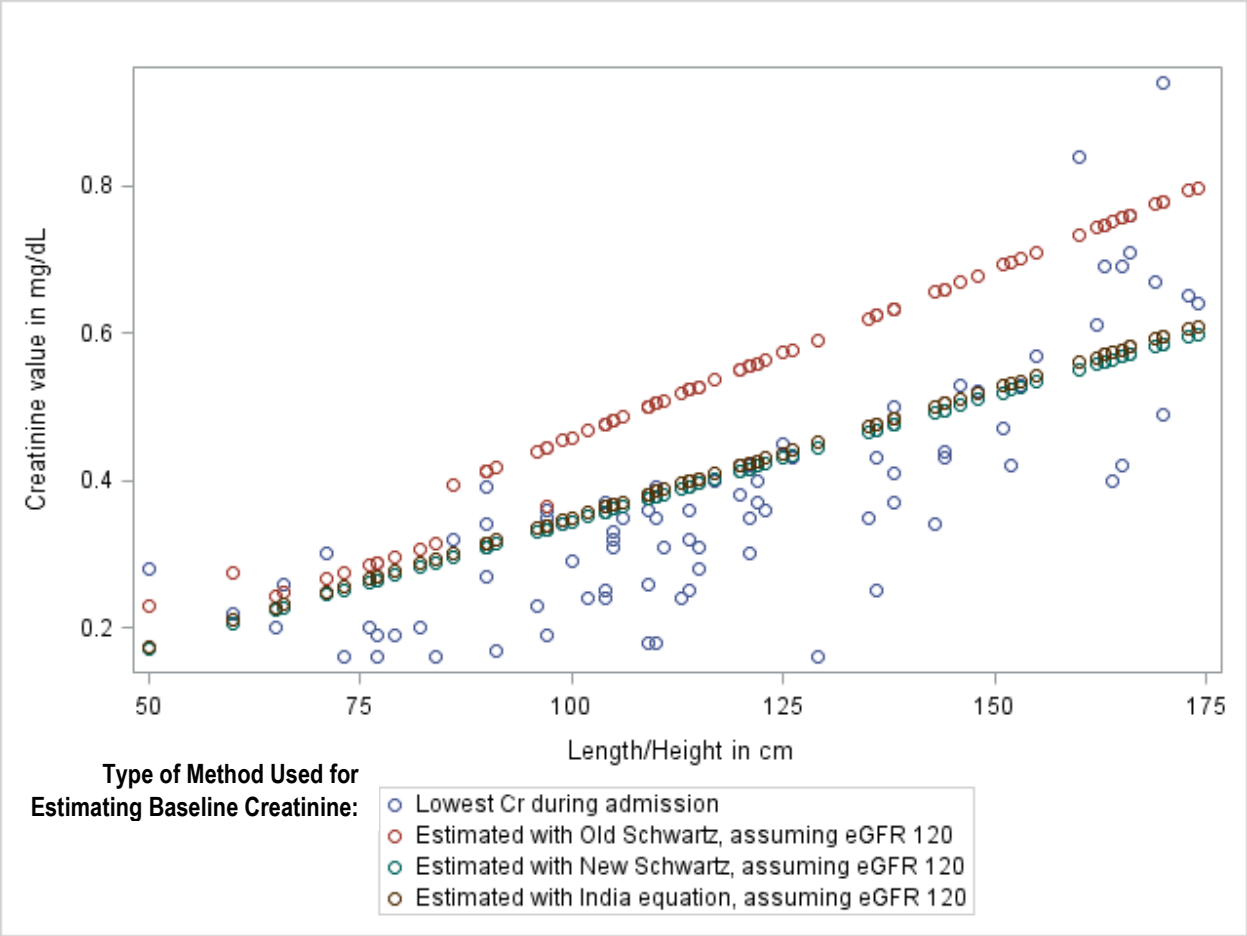



**Figure 4.2. Scatterplot of Baseline Creatinine Estimation by Child's Length/Height Using 4 Different Methods.** Only patients who had 2 creatinine values were used for this analysis, since the method using the lowest creatinine during admission requires a minimum of two values.

*Mortality:* A total of 10 children died prior to hospital discharge. The risk of death was much higher (RR 6.5, 95% confidence interval (CI) 2.2-19.1) for those who developed AKI (4/10, 40.0%) than those who did not develop AKI (6/97, 6.2%).

*Length of Stay:* Participants who survived to discharge were hospitalized a median of 12 days (interquartile range (IQR) 7-26) (Table 4.1). Participants with AKI tended to have a longer length of stay (19.5 days, IQR 9-35) compared to those without AKI (12 days, IQR 7-25).

*Potential risk factors:* A third of participants had burns (33.3%) and falls (30.6%), yet two-thirds of participants who developed AKI had burn injuries (63.6%) (Table 4.3). Trauma-related factors that were associated with AKI included burn injuries, multiple injuries (versus a single injury), trunk and facial injuries (Table 4.4).

We evaluated the potential for concurrent exposures to increase one's risk of developing AKI, including drinking water source, medications and herbal remedies prior to arrival, and iodinated contrast (Table 4.3). Only two children had computed tomography exams (neither with iodinated contrast). Amongst concurrent potentially nephrotoxic exposures, only herbal remedies taken within the preceding seven days was identified as a potential risk factor (RR 6.1, 95% CI 1.9-19.6) (Table 4.4), but this result should be viewed with caution as only four patients received herbal remedies prior to arrival.

We found no trends for a variety of socioeconomic status indicators impacting AKI risk (Table 4.5).

**Table 4.3. Trauma-related and Nephrotoxic Exposure-related Factors Amongst Admitted Pediatric Trauma Patients in Malawi by Development of AKI**

| | Total | AKI | No AKI | Missing |
|---|---|---|---|---|
| | N=114 | 11 (9.7) | 103 (90.4) | |
| **Type of Trauma** | | | | 6 |
| **Burn** | 36 (33.3) | 7 (63.6) | 29 (29.9) | |
| **Fall** | 33 (30.6) | 2 (18.2) | 31 (32.0) | |
| **Road Traffic Injury** | 24 (22.2) | 2 (18.2) | 22 (22.7) | |
| **Other** | 15 (13.9) | 0 (0) | 15 (15.5) | |
| **Primary Location of Trauma** | | | | 1 |
| **Head/Neck** | 21 (18.6) | 1 (9.1) | 20 (19.6) | |
| **Trunk** | 23 (20.4) | 4 (36.4) | 19 (18.6) | |
| **Extremity** | 56 (49.6) | 3 (27.3) | 53 (52.0) | |
| **Face** | 13 (11.5) | 3 (27.3) | 10 (9.8) | |
| **Multiple Injuries** | 56 (49.1) | 8 (72.7) | 48 (46.6) | 0 |
| **All Trauma Locations**[a] | | | | 1 |
| **Head/Neck** | 31 (27.4) | 3 (27.3) | 28 (27.5) | |
| **Trunk** | 38 (33.6) | 6 (54.6) | 32 (31.4) | |
| **Extremity** | 81 (71.7) | 8 (72.7) | 73 (71.6) | |
| **Face** | 23 (20.4) | 4 (36.4) | 19 (18.6) | |
| **Drinking Water Source** | | | | 3 |
| **River/Lake** | 6 (5.4) | 0 (0) | 6 (6.0) | |
| **Community Pipe/Bore hole** | 79 (69.3) | 7 (63.6) | 72 (69.9) | |
| **Piped (Exterior)** | 17 (15.3) | 3 (27.3) | 14 (14.0) | |
| **Piped (Interior)** | 9 (8.1) | 1 (9.1) | 8 (8.0) | |
| **Medications taken in previous 7 days** | 34 (29.8) | 3 (27.3) | 31 (30.1) | 0 |
| **Herbal remedies taken in previous 7 days** | 4 (3.5) | 2 (18.2) | 2 (1.9) | 0 |

All expressed as N and column percent except where specified.
Categories are mutually exclusive except where specified.
AKI=Acute kidney injury.
[a]Multiple categories allowed.
KDIGO criteria used to define AKI and new Schwartz equation estimated baseline creatinine.

**Table 4.4. Potential AKI Risk Factors in Admitted Pediatric Trauma Patients in Malawi**

| Exposure | Total | AKI Episodes | Crude Risks | Risk Differences | 95% CI | Relative Risks | 95% CI |
|---|---|---|---|---|---|---|---|
| **Burn Injury** | 36 | 7 | 19.4% (8.2-36.0%) | 13.9% | -0.1 to 27.9 | 3.5 | 1.1 to 11.2 |
| **Non-burn Injury** | 72 | 4 | 5.6% (1.5-13.6%) | Reference | | Reference | |
| **Multiple Injuries** | 56 | 8 | 14.3% (6.4-26.2%) | 9.1% | -1.7 to 19.9 | 2.8 | 0.8 to 9.9 |
| **Single Injury** | 58 | 3 | 5.2% (1.1-14.4%) | Reference | | Reference | |
| **Primary Location of Trauma[a]** | | | | | | | |
| **Head/Neck** | 21 | 1 | 4.8% (0.1-23.8%) | -0.6% | -11.5 to 10.3 | 0.9 | 0.1 to 8.1 |
| **Trunk** | 23 | 4 | 17.4% (5.0-38.8%) | 12.0% | -4.5 to 28.6 | 3.2 | 0.8 to 13.4 |
| **Face** | 13 | 3 | 23.1% (5.0-53.8%) | 17.7% | -5.9 to 41.4 | 4.3 | 1.0 to 19.0 |
| **Extremity** | 56 | 3 | 5.4% (1.1-14.9%) | Reference | | Reference | |
| **Any Trunk Injury** | 38 | 6 | 15.8% (4.2-27.4%) | 9.1% | -3.8 to 22.0 | 2.4 | 0.8 to 7.3 |
| **Non-trunk Injuries** | 75 | 5 | 6.7% (1.0-12.3%) | Reference | | Reference | |
| **Herbal remedies taken in previous 7 days** | 4 | 2 | 50.0% (6.8-93.2%) | 41.8% | -7.5 to 91.1 | 6.1 | 1.9 to 19.6 |
| **None** | 110 | 9 | 8.2% (4.9-16.6%) | Reference | | Reference | |

AKI=Acute kidney injury; CI=confidence interval.
KDIGO criteria used to define AKI and new Schwartz equation estimated baseline creatinine.
[a]Category is mutually exclusive

**Table 4.5. Socioeconomic Status Factors Amongst Admitted Pediatric Trauma Patients in Malawi by Presence of AKI.**

| | Total<br>N=114 | AKI<br>11 (9.7) | No AKI<br>103 (90.4) | Missing |
|---|---|---|---|---|
| **Education level completed in years (median, IQR)** | | | | |
| **Patient** | 2 (0, 4) | 1 (0, 5) | 2 (0, 4) | 10 |
| **Mother** | 6 (4, 10) | 5 (2, 10) | 6 (4, 10) | 13 |
| **Father** | 8 (4, 10) | 6.5 (0, 10) | 8 (4, 10) | 21 |
| **Crowding factor[a] (median, IQR)** | 1.5 (1.2, 2.0) | 1.5 (1.2, 2.0) | 1.5 (1.2, 2.0) | 2 |
| **Type of Roof** | | | | 0 |
| **Thatch** | 45 (39.5) | 5 (45.5) | 40 (38.8) | |
| **Tin/Iron** | 69 (60.5) | 6 (54.6) | 63 (61.2) | |
| **Type of Floor** | | | | 1 |
| **Dirt** | 60 (53.1) | 6 (54.6) | 54 (52.9) | |
| **Cement** | 53 (46.9) | 5 (45.5) | 48 (47.1) | |
| **Parent's deceased[b]** | | | | |
| **Mother** | 4 (3.6) | 0 (0) | 4 (4.0) | |
| **Father** | 10 (9.1) | 0 (0) | 10 (10.1) | |
| **Both** | 4 (3.6) | 0 (0) | 4 (4.0) | |
| **Possessions[b]** | | | | |
| **Refrigerator** | 13 (11.5) | 2 (18.2) | 11 (10.8) | 1 |
| **Television** | 26 (23.2) | 3 (27.3) | 23 (22.8) | 2 |
| **Cell Phone** | 88 (78.6) | 8 (72.7) | 80 (79.2) | 2 |
| **Agricultural Land** | 58 (52.3) | 5 (50.0) | 53 (52.5) | 3 |
| **Working vehicle** | 6 (5.4) | 0 (0) | 6 (6.0) | 3 |
| **Cow(s)** | 5 (4.5) | 0 (0) | 5 (5.0) | 2 |
| **Chicken(s)** | 46 (41.1) | 2 (18.2) | 44 (43.6) | 2 |
| **Goat(s)** | 21 (18.8) | 2 (18.2) | 19 (18.8) | 2 |
| **Bicycle** | 40 (36.0) | 3 (27.3) | 37 (37.0) | 3 |
| **Ox Cart** | 4 (3.6) | 0 (0) | 4 (4.0) | 2 |

All expressed as N and column percent except where specified.
Categories are mutually exclusive except where specified.
AKI=Acute kidney injury; IQR=interquartile range.
[a]Crowding factor is number of people living in a home divided by number of rooms in the home
[b]Categories are not mutually exclusive
KDIGO criteria used to define AKI and new Schwartz equation estimated baseline creatinine.

## 4.4 Discussion

To our knowledge, this is the first African AKI study in pediatric trauma patients. The incidence of AKI was 9.7% amongst admitted pediatric trauma patients at this single center in Malawi. Only a few AKI studies in trauma patients have occurred in Africa, but all are in adult patients and were performed at one center in South Africa.[82–85] Our estimate that 10% of pediatric trauma patients have AKI is less than the incidence found in one of the adult South African studies of critically-ill patients (15%)[83], but it is higher than what was found for AKI on presentation in a similar setting of adult trauma patients (5.6%).[84] Therefore, our incidence is likely an accurate assessment of AKI in pediatric trauma patients in Africa, yet further studies should be conducted in other regions to assess if incidences are similar.

Our study is unique as it is the first in pediatric trauma in Africa, a high-risk group of patients. The previous meta-analysis on pediatric AKI incidence worldwide found a much higher incidence (33%) than our study.[67] However, these children were from high income settings and likely of higher acuity. Only two studies occurred in low- or low-middle income countries and zero studies occurred in Africa. Higher income settings can screen for AKI daily, which is not a reality throughout Malawi or many other sub-Saharan African countries. Rarely are two screening creatinine values obtained on a patient outside of the research setting in sub-Saharan Africa and many other low-resourced areas. Patients may have repeat creatinine values if they are known to already have kidney failure, but routine screening to monitor for impending kidney failure remains uncommon. It is also possible that children in higher income settings are exposed to additional nephrotoxins once hospitalized that are not available in Malawi (i.e., iodinated contrast, certain nephrotoxic antimicrobials). The AKI incidence in our cohort mirrors that of a recently published cohort of hospitalized children in Blantyre, Malawi (11%).[86] These

discrepancies of AKI incidence highlight the need for additional robust epidemiological studies of AKI in Malawi and other sub-Saharan African countries as well as the inclusion of such sites in future efforts to understand and improve management of pediatric AKI worldwide.

AKI is a well-known risk factor for mortality in children with sepsis, malaria, and critical illness.[3,4,6,68–70] AKI in adult trauma patients is also known to increase the risk of death,[87–91] but little is known about AKI in pediatric trauma patients. To our knowledge, this is only the third (and the first in Africa) study to show that AKI in children with trauma significantly increased the risk of death compared to those without AKI (40% vs 6.5%, RR 6.5 with 95% CI 2.2-19.1). A previous retrospective study in 88 pediatric general trauma patients in the United States who were critically ill and intubated also saw an increase in mortality with AKI (23% mortality in those with AKI versus 5.5% mortality in those without AKI).[92] Another retrospective study in children with burns only (n=119) saw higher mortality in those with AKI than those without AKI (8.9% vs 1.5%).[93]

Given the limited knowledge about the AKI risk in pediatric trauma patients, little is also known about potential risk factors. What is known about AKI risk factors in trauma is drawn from the adult literature. The potential risk factors we identified in our study (multiple injuries and burns) have also been shown in adult patients. Several studies have identified high rates of AKI in adult burn patients.[87–89,94,95] The retrospective study on pediatric burn patients also found a high incidence of AKI and that development of sepsis was an independent risk factor for AKI.[93] We did not evaluate for sepsis in our study due to the additional associated costs.

In addition, we found that trunk and facial injuries as well as consumption of herbal remedies were potential risk factors for AKI in trauma patients. These have not been seen in other studies of trauma patients, but it is also possible these were not evaluated in prior studies.

A large multicenter study in France found that hemorrhagic shock and associated hypoperfusion laboratory values were associated with a higher risk of AKI,[13] yet these are not evaluations readily available in Malawi, and similarly other low-resourced areas. Trunk injuries seem like a reasonable risk factor given the anatomical location of the kidneys in the trunk. Similarly herbal remedies are known nephrotoxins so it also is plausible for this to be a risk factor. However, all of these potential risk factors (and potentially others we did not explore such as sepsis) deserve further investigations with larger sample sizes as the study was powered for determining the incidence of AKI.

When we evaluated only patients surviving to discharge, we found a trend towards a longer length of stay in patients with AKI versus those without (19.5 days vs 12 days). While this trend lacked statistical significance, the large difference in our small patient population suggests that further investigation in a larger study powered to detect these differences is warranted. Longer hospitalizations are seen in adult AKI trauma studies.[21,96] If this trend is also reflected in pediatric trauma patients, this is potentially an outcome measure that needs continued study as this impacts not only the patients' health, but also the financial impact on healthcare systems and families.

*AKI Definitions:* An essential component to AKI assessment according to KDIGO criteria is knowing a child's healthy baseline creatinine value. No pediatric study in Africa has evaluated the optimal method for estimating a child's baseline creatinine when it is not known. Zappitelli et al, performed a retrospective analysis in the U.S. and compared baseline creatinine estimations with true known values to assess which method performed best.[72] They did not compare different equations for back-calculating a creatinine value, but instead compared the estimated baseline creatinine back-calculated from the old Schwartz method with normative

values and admission creatinine values. They found that using an eGFR of 120ml/min/1.73m$^2$ for baseline outperformed an eGFR of 100ml/min/1.73m2, normative values and admission creatinine values. Ideally, we would have been able to do something similar, but no patients in our study had a known baseline creatinine value, which is common in Malawi and other low-resourced areas. Zappitelli et al, and others have shown that depending on how one defines AKI, the incidences will vary.[5,72]

Building upon previous work, we assumed a baseline eGFR of 120ml/min/1.73m$^2$ and evaluated several different equations to subsequently back-calculate a baseline creatinine. We compared them to our *a priori* defined gold standard of 'lowest creatinine' during hospitalization. We assumed the lowest creatinine during admission to be the most accurate assessment of a baseline creatinine as the only significant factor that should falsely lower it would be fluid overload (almost no patients receive fluid resuscitation prior to hospital arrival).

Using the new (bedside) Schwartz equation seemed the best estimation of a patient's baseline creatinine in this population with no known baseline values for several reasons. First, the new Schwartz equation allowed us to include all patients, even if only one creatinine value was obtained. We also felt that this would be more realistic for other low-resourced settings that also are rarely able to obtain multiple creatinine values. Second, visual inspection of all estimated creatinine values based on height (Figure 4.2) demonstrated that new Schwartz outperformed old Schwartz, particularly after one year of age when the constant changes in old Schwartz equation. Our creatinine values were obtained with Jaffe methods, so we expected the old Schwartz equation (based on Jaffe methods) to outperform the new Schwartz equation (based on enzymatic methods), but this did not seem to be the case and likely relates to the fact that the old Schwartz equation overestimates eGFR in children.[74] Third, though the new Schwartz

equation and the India equation appear similar, the new Schwartz equation is more commonly used and would allow for greater comparisons worldwide.

*Limitations:* We powered our study to evaluate the incidence of AKI in this pediatric trauma population, and evaluation of risk factors was a secondary aim. Thus, risk factors that were significant certainly deserve further exploration, but those that were not significant should not be excluded from future studies or clinical consideration as we had insufficient sample size to achieve adequate power.

This was the first pediatric AKI study in African trauma patients, yet due to resource limitations we were only able to obtain at most two creatinine values on a patient and no urine output, which may have led to some missed cases of AKI. There is not a consensus on estimating a baseline creatinine when one is not known for this population, but we used several methods to investigate a potential optimal method for this setting. This is an area that deserves further research to also help align research and diagnostic management plans accordingly.

We did not reach our goal enrollment due to logistical and financial constraints, but we still enrolled >100 patients. Given the lack of electronic medical records and paucity of data in paper records, we collected all data prospectively to maximize accurate data collection. A large number of eligible patients were missed due to logistical reasons (n=270). We compared those patients missed with those enrolled and found no significant differences in gender, age, or mechanism of trauma. Based on our enrollment criteria, we did miss enrolling more patients who presented on weekends.

## 4.5 Conclusion

AKI occurs in about 10% of admitted pediatric trauma patients in Malawi, though the incidence varies depending on how one estimates a baseline creatinine. In this patient population, the new (bedside) Schwartz equation appeared to perform best. A high index of suspicion for AKI should be considered for pediatric trauma patients, as early management may improve outcomes. Strikingly, those with AKI were 7 times as likely to die as compared to those without AKI. Further research should confirm these findings and explore if early identification of AKI in pediatric trauma patients can be combined with management strategies to decrease mortality in this high-risk population.

# CHAPTER 5: VALIDITY OF URINE NGALds® DIPSTICK FOR ACUTE KIDNEY INJURY IN A MALAWIAN TRAUMA COHORT

## 5.1 Background

Sub-Saharan African countries routinely are not included in large surveillances and analyses of acute kidney injury (AKI).[4,11] Difficulties with laboratory confirmation of AKI likely contributes to the severe under-reporting and paucity of epidemiological studies on AKI in low-resourced areas. The only diagnostic test for AKI (serum creatinine) continues to rely on laboratory infrastructure, which unfortunately remains limited or non-existent in low-resourced settings. Currently, the only alternative, low-cost method for 'diagnosing' AKI in some low-resourced settings is assessing a patient's urine output but this requires intensive nursing care and can be flawed even in the highest resourced settings.

The Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines suggest a substantial portion of management relies on preventing further nephrotoxic exposure, diligent fluid management, and blood pressure control before the need for dialysis (limited or non-existent in low-resourced settings).[2] All of these management tasks (excluding dialysis) could easily be adapted for low-resourced settings.

Serum creatinine has been used as the practical gold standard for AKI diagnosis for decades. Yet serum creatinine is known to be limited, particularly in children, due to hydration fluctuations and muscle mass differences. For example, young children have lower levels of creatinine than adults, and malnourished patients (children or adults) will have lower creatinine

levels than well-nourished age- and gender-matched patients. In addition, serum creatinine can take 24-72 hours to rise after a significant injury. So, there has been much interest throughout high-income countries to find novel biomarker(s) that might diagnose AKI prior to the rise in serum creatinine to help with preventing AKI sequelae and improving its management.

Urine NGAL (neutrophil gelatinase-associated lipocalin) is one such biomarker that has been shown in both adults and children to consistently predict subsequent AKI diagnosis in high-resourced settings.[14–20] It rises within a few hours of a renal injury. Clinical researchers are starting to show the clinical utility of real-time trending of urine NGAL to predict and manage AKI, thereby improving patient care.[14] However, the current urine NGAL biomarker relies on robust laboratory infrastructure and consistent power supplies. Recently, a novel dipstick for urine NGAL (NGALds® dipstick) was developed for use in low-resourced settings. If it proves equally efficacious as the laboratory urine NGAL, it could be quite promising for improving AKI diagnostics in low-resourced areas as it requires no laboratory infrastructure and minimal electricity requirements (currently temperature-resistant for one month).

Malawi, a landlocked country in southeastern Africa, is regularly classified as one of the five poorest countries in the world (based on gross domestic product per capita).[97] There are two large, central teaching hospitals in the country that provide the only nephrology care for a population of 18.6 million.[98] Their laboratory services frequently experience shortages of reagents and power outages, limiting services at times quite severely. A novel diagnostic test for AKI that does not rely on reagents, electricity, or experienced laboratory technicians could be invaluable in this setting.

Nested within a larger prospective cohort study of trauma patients in Malawi, we aimed to validate the urine NGAL biomarker and new NGALds® dipstick in a low-resourced

environment. We also assessed both the lab-based NGAL (NGAL Test™) and the NGALds® dipstick test characteristics for diagnosing AKI, defined by creatinine-only KDIGO criteria.[2]

## 5.2 Methods

*Design:* This validation study was nested within a prospective cohort study to evaluate the incidence of AKI amongst admitted trauma patients (Chapter 4). The study was conducted at Kamuzu Central Hospital (KCH) in Lilongwe, Malawi.

*Study Population:* The larger prospective cohort study included all admitted acute trauma patients at KCH. The parent study inclusion criteria were age ≥6 months, weight >3kg and an expected admission >24 hours. Patient (if ≥7 years) and caregiver had to provide written informed consent/assent. Participants were excluded if trauma occurred >5 days prior to hospital arrival and if primary language was not English or Chichewa (the Malawian official and national languages, respectively). Enrollment (consent and laboratory diagnostics) had to occur within 18 hours of hospital arrival. The parent study screened 4547 patients and enrolled 337 participants. This included 21 participants from a pilot study. For this nested validation study, an additional requirement for inclusion was the ability to provide a fresh urine sample on either admission or follow-up at 48-72 hours.

*Outcome:* The primary outcome of interest was the validity of the urine NGALds® dipstick as compared to the (1) urine NGAL laboratory test (The NGAL Test™) and (2) gold-standard AKI diagnosis as defined by creatinine-only KDIGO criteria.[2] Serum creatinine, urine lab-based NGAL, and urine NGALds® dipstick results were obtained within 18 hours of arrival and again 48-72 hours later. In Malawi, it is not routine for renal function tests or electrolytes to be obtained on any trauma patients. To maximize our accuracy for AKI by KDIGO, we chose to

obtain two values 48 hours or more apart. Medical teams could obtain more laboratory tests as they deemed medically necessary. No participants had a baseline creatinine value prior to admission. For adult participants, we assumed *a priori* a baseline eGFR of 75ml/min/1.73m$^2$ and back-calculated a baseline creatinine using the Modification of Diet in Renal Disease (MDRD) Study equation, per KDIGO guidelines[2], and excluding the race variable as is preferred in African populations.[99–102] For pediatric participants, we assumed *a priori* a baseline eGFR of 120ml/min/1.73m$^2$ based on previous literature.[72] We subsequently back-calculated a baseline creatinine using the new (bedside) Schwartz equation based on our previous work in Malawian children (Chapter 4).[74]

As mentioned above, routine laboratory testing is quite unreliable at KCH's main public laboratory. To ensure reliable and consistent laboratory results, all laboratory testing was conducted at the University of North Carolina (UNC) Project Malawi Laboratory, which is a state-of-the-art research laboratory on-site at KCH. This laboratory maintains a constant supply of reagents, quality control and assurance measurements, and back-up generators to ensure high-quality laboratory performance for several research projects. Creatinine values were obtained on fresh serum using the Jaffe method on Roche analyzer Cobas C311. Urine lab-based NGAL tests were obtained on fresh urine samples using the same analyzer with daily control standards checked. The urine lab-based NGAL (NGAL Test$^{TM}$) was reported as a continuous value in ng/mL. The novel urine NGALds® dipstick was conducted at the bedside by trained study nurses. On a fresh urine sample, 0.1mL of urine was pipetted into a pre-prepared freeze-dried reagent test tube. Buffer was

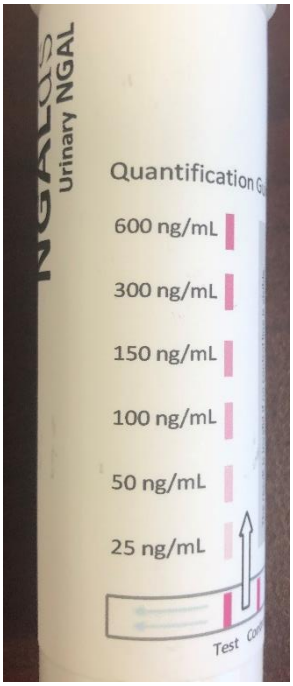



**Figure 5.1.** NGALds® Dipstick Color Category Reference

added for 5 minutes. Dipstick inserted and after 10 minutes, if control line was positive, then the NGALds® dipstick was compared to color categorized NGAL values (0 if no color appeared, 25, 50, 100, 150, 300, and 600 ng/mL) for the closest comparison (Figure 5.1).

*Covariates:* To determine if the novel dipstick performed differently than other potential variables that may be more readily available in resource limited settings, we compared two other variable "tests" to the gold-standard AKI diagnosis. The participant or caregiver's self-report of urine output was assessed on arrival and 48-72 hours later; variable was categorized as decreased or absent versus no change. In addition, a standard urine dipstick for assessing proteinuria was assessed on arrival. Proteinuria was classified categorically as negative/trace, 1+ (0.3gm/L), 2+ (1.0gm/L), 3+ (3.0gm/L), or 4+ (≥20gm/L).

Additional covariates obtained included gender (binary), age (in years), mechanism of trauma (categorical), body location of injury (categorical), and laboratory-confirmed comorbidities (anemia, sickle cell disease, malaria).[79] In addition, we assessed each participant's final hospital outcome (discharged home, transferred, died, or left against medical advice) and length of hospitalization.

*Sample Size:* The parent study aimed to enroll a total of 480 trauma patients (50% children ≤18 years of age) who were admitted to KCH (Chapter 4). This study used all available trauma participants in the parent study who met inclusion/exclusion criteria.

*Analysis:* We assessed demographic and injury-related characteristics with descriptive statistics. Spearman rank correlation coefficients (R) assessed categorical groups of NGAL values for the urine NGALds® dipstick and lab-based NGAL test. Categories included negative (≤50ng/mL), low risk (51-149ng/mL), medium risk (150-299ng/mL), and high risk (≥300ng/mL). We used sensitivity, specificity, positive predictive value (PPV), and negative

predictive value (NPV) to evaluate the validity of the urine NGAL Test™ (quantitative lab-based values) and urine NGALds® dipstick (categorical values) to diagnose AKI. Sub-analyses were conducted to assess if the dipstick performed differently by age or gender. Additionally, self-report of urine output and proteinuria by urine dipstick were individually compared to the gold-standard AKI by creatinine-only KDIGO criteria for sensitivity, specificity, NPV, and PPV.

Data were double-entered into REDCap electronic data capture tools hosted at UNC to ensure accuracy of translating paper forms to the electronic database.[81] All statistical analyses were conducted in SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). The institutional review board at UNC and Malawi's National Health Science Research Committee approved this study.

## 5.3 Results

Of the 337 participants enrolled in the parent study, 307 (91.1%) had urinary data available for analysis. Twenty-one participants were in the pilot study and urine samples were frozen prior to NGAL testing. We were unable to obtain urine specimens on nine participants.

*Demographics:* Participants were young (median age 25 years, interquartile range (IQR) 13-38 years) (Table 5.1), a third were children (32.6%), and the majority were male (78.8%). Trauma-related AKI was significantly associated with a higher risk of death compared to those who did not develop AKI (24.3% versus 6.2%), p-value <0.001. There was a high prevalence of anemia in this population (48.5%).

*Dipstick vs Lab-based NGAL:* NGALds® dipstick categories correlated relatively well with the lab-based NGAL test results (R=0.74) on admission (Table 5.2) and on hospital day 3 (R=0.71). Twenty-two of 26 (84.6%) participants with high-risk NGAL values on laboratory

**Table 5.1. Demographics of Trauma Patients Admitted to Malawian Hospital by Development of Acute Kidney Injury**

| | Total N=307 | AKI 39 (12.7) | No AKI 268 (87.3) | Missing |
|---|---|---|---|---|
| **Age (years) (median, IQR)** | 25 (13, 38) | 30 (18,40) | 25 (12,38) | 2 |
| **Children ≤18 years** | 100 (32.6) | 10 (25.6) | 90 (33.6) | 2 |
| **Gender (male)** | 241 (78.8) | 32 (82.1) | 209 (78.3) | 1 |
| **Type/Location of Trauma** | | | | |
| **Burns** | 36 (12.0) | 9 (23.1) | 27 (10.3) | 6 |
| **Motor Vehicle-related** | 130 (43.2) | 17 (43.6) | 113 (43.1) | 6 |
| **Assaults** | 59 (19.6) | 7 (18.0) | 52 (19.9) | 6 |
| **Truncal Injury** | 85 (27.9) | 16 (42.1) | 69 (25.8) | 2 |
| **Multiple Injuries** | 160 (52.5) | 27 (71.1) | 133 (49.8) | 2 |
| **Comorbidities** | | | | |
| **Anemia** | 149 (48.5) | 26 (66.7) | 123 (45.9) | 0 |
| **Malaria** | 25 (8.3) | 1 (2.6) | 24 (9.1) | 4 |
| **Sickle Cell Trait[a]** | 22 (7.5) | 3 (8.1) | 19 (7.5) | 15 |
| **Length of Stay[b] (days) (median, IQR)** | 11 (6, 28) | 13 (8, 49) | 11 (6, 26) | 15[c] |
| **Mortality** | 25 (8.5) | 9 (24.3) | 16 (6.2) | 12[d] |

All data presented as n(percent) unless otherwise specified.
[a]No patients had sickle cell disease (HgSS), so only sickle cell trait (HgAS) is presented.
[b]Length of stay is for those discharged alive (n=267).
[c]6 absconded, 6 had lost files, 3 discharge dates could not be confirmed.
[d]6 absconded, 6 had lost files.

**Table 5.2. Categorical Comparisons of Urine Neutrophil Gelatinase-Associated Lipocalin (NGAL) Values on Admission in Malawian Trauma Patients**

| | | Lab-based NGAL | | | | Spearman Rank Correlation |
|---|---|---|---|---|---|---|
| | | Negative (≤50) | Low Risk (51-149) | Moderate Risk (150-299) | High Risk (≥300) | |
| NGALds® Dipstick | Negative (≤50) | 128 | 26 | 2 | 0 | 0.74 |
| | Low Risk (51-149) | 13 | 17 | 2 | 3 | |
| | Moderate Risk (150-299) | 4 | 15 | 4 | 1 | |
| | High Risk (≥300) | 2 | 8 | 18 | 22 | |

Test characteristics conducted on admission urine samples only (n=265).
NGAL=neutrophil gelatinase-associated lipocalin; KDIGO=Kidney Disease Improving Global Outcomes; AKI=Acute Kidney Injury; PPV=positive predictive value; NPV=negative predictive value

testing also had high-risk NGAL values on the dipstick. Similarly, the dipstick captured 45 of 52 participants (86.5%) with moderate- or high-risk NGAL values on lab-based testing. Sub-group analyses revealed that results were similar for adult and pediatric participants.

*NGAL's Ability to Diagnose AKI:* A total of 273 participants had urine samples for dipstick testing and hospital outcome data (mortality) available. 12.5% of these participants developed AKI. Figure 5.2 demonstrates that if we screened all trauma participants with dipsticks, subsequently tested creatinine for AKI confirmation amongst only those with positive dipsticks (≥150ng/mL), then we would have captured 44% of AKI episodes (15 of 34) with the dipstick.

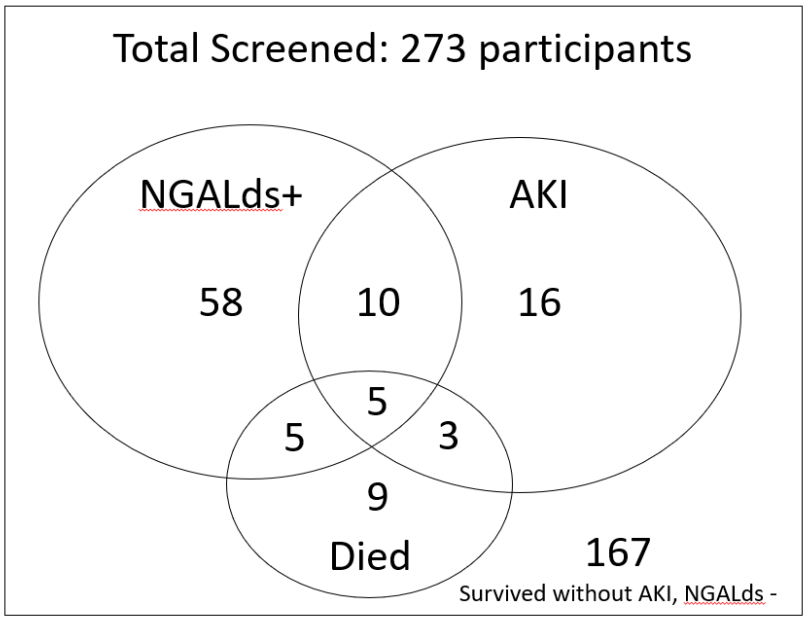



**Figure 5.2. Admitted Malawian Trauma Patients Screened with NGALds® Dipstick and Interplay of Positive Dipstick, AKI, and Mortality.** Total screened participants, n=273. Participants with NGALds+, n=78. Participants with AKI, n=34. Participants that died, n=22. Participants that survived without AKI and had NGALds-, n=167. Abbreviations: AKI=acute kidney injury. NGALds+ refers to NGALds® dipstick results ≥150ng/mL. NGALds- refers to NGALds® dipstick results <150ng/mL.

However, we would have also drastically reduced the number of participants we screened with creatinine tests from 273 down to 78, an almost 75% reduction in testing. In addition, the NGALds® dipstick was elevated (≥150ng/mL) in 10 of 22 patients that died (45%). Proteinuria ≥0.3gm/L as an indicator of AKI performed similarly to the NGALds® dipstick for capturing AKI, but it did worse for capturing participants who died (only capturing 30%).

Table 5.3 provides the test characteristics of NGALds® dipstick on admission urine samples compared to creatinine-only KDIGO defined AKI diagnosis based on all possible thresholds. Globally, a consensus has not yet been reached for the ideal threshold of NGAL as a marker of AKI. A threshold of 150ng/mL has been used commonly, and based on this threshold, the dipstick had moderate sensitivity (44.4%), but reasonable specificity (73.5%). As expected, specificity improved, but sensitivity worsened if the threshold was raised to 300ng/mL. Sub-group analyses revealed consistent results in adults and children. However, amongst children, the threshold of 150ng/mL provided a higher specificity (84.2%) with sensitivity of 22.2% for detecting AKI.

**Table 5.3. Urine NGALds® Dipstick Test Predictive Characteristics Using KDIGO-defined AKI (Creatinine-only*) in Malawian Trauma Patients**

| Urine NGALds® Dipstick Category | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| **25** | 97.2 | 3.6 | 12.7 | 90.0 |
| **50** | 61.1 | 47.0 | 14.3 | 89.3 |
| **100** | 58.3 | 61.0 | 17.8 | 91.0 |
| **150** | 44.4 | 73.5 | 19.5 | 90.2 |
| **300** | 36.1 | 82.7 | 23.2 | 90.0 |
| **600** | 22.2 | 90.0 | 24.2 | 88.9 |

*Using admission urine samples only (n=285).
NGAL=neutrophil gelatinase-associated lipocalin; KDIGO=Kidney Disease Improving Global Outcomes; AKI=Acute Kidney Injury; PPV=positive predictive value; NPV=negative predictive value

The lab-based NGAL test performed similarly to the dipstick test for characterizing AKI (Table 5.4). Specifically, if we evaluate the lab-based NGAL test at a common threshold for NGAL that is also available on the dipstick, a threshold of 150ng/mL on the lab-based NGAL test gives sensitivity 38.9%, specificity 82.8%, PPV 25.5%, and NPV 90.0%.

**Table 5.4. Urine Lab-based NGAL Test Predictive Characteristics Using KDIGO-defined AKI (Creatinine-only) in Malawian Trauma Patients**

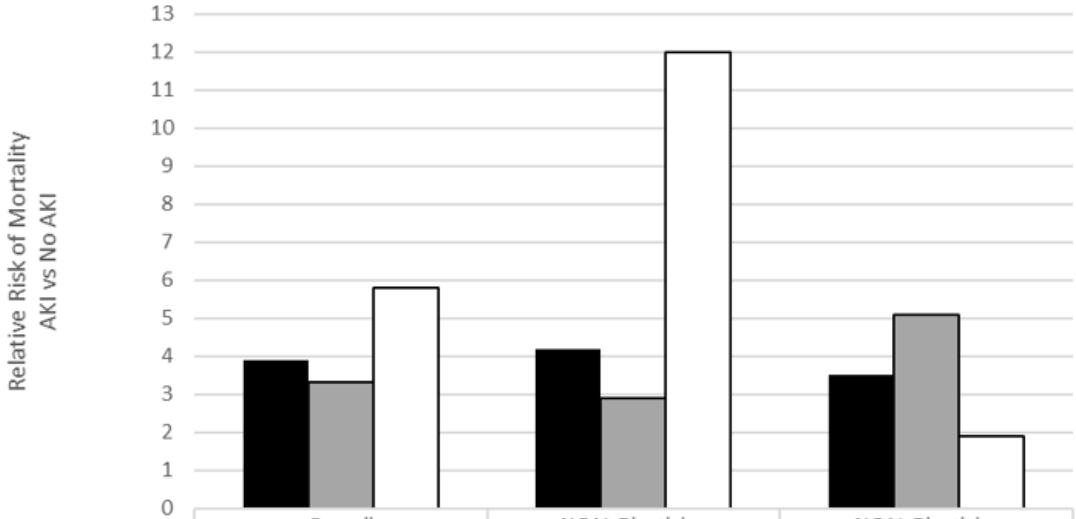
| Urine Lab-based NGAL | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| 20 | 83.3 | 32.8 | 15.8 | 92.9 |
| **25** | **83.3** | **36.1** | **16.5** | **93.5** |
| **50** | **61.1** | **56.3** | **17.5** | **90.5** |
| **100** | **38.9** | **74.4** | **18.7** | **88.9** |
| **150** | **38.9** | **82.8** | **25.5** | **90.0** |
| 200 | 33.3 | 88.2 | 30.0 | 89.7 |
| 250 | 30.6 | 91.2 | 34.4 | 89.7 |
| **300** | **30.6** | **92.9** | **39.3** | **98.8** |
| 350 | 27.8 | 94.1 | 41.7 | 89.6 |
| 400 | 27.8 | 95.4 | 47.6 | 89.7 |
| 450 | 27.8 | 96.2 | 52.6 | 89.8 |
| 500 | 27.8 | 97.5 | 62.5 | 89.9 |
| 550 | 25.0 | 97.9 | 64.3 | 89.6 |
| **600** | **25.0** | **98.3** | **69.2** | **89.7** |
| 650 | 25.0 | 98.7 | 75.0 | 89.7 |
| 700 | 22.2 | 98.7 | 72.7 | 89.4 |

Test characteristics conducted on admission urine samples only (n=274).
NGAL=neutrophil gelatinase-associated lipocalin; KDIGO=Kidney Disease Improving Global Outcomes; AKI=Acute Kidney Injury; PPV=positive predictive value; NPV=negative predictive value

Interestingly, low-grade proteinuria or higher (≥0.3gm/L) revealed similar test characteristics for diagnosing AKI (sensitivity 46.0%, specificity 79.6%, PPV 24.6%, NPV 91.0%). As expected, the higher the proteinuria the higher the specificity, but the sensitivity dropped off precipitously to <3% at 3.0gm/L and higher. We also evaluated if a participant or caregiver's report of decreased or absent urine output could perform similarly but it was a very

poor indicator for AKI (sensitivity 16.1%, specificity 86.4%). In addition, it was not information available at admission for 20.5% of participants (n=63).

*Mortality:* In our population, participants who developed AKI had 3.9 times higher risk of death compared to those who did not develop AKI (RR 3.9, 95% CI 1.9-8.2) (Figure 5.3). When stratified by age, children had slightly higher risk (RR 5.8, 95% CI 1.7-20.4). However, children who first had a positive NGAL dipstick (≥150ng/mL) and developed AKI had the highest risk of mortality (RR 12.0, 95% CI 1.8-78.4). Sub-group analyses by gender found no differences, though our sample size of female participants was small (n=66).




| | Overall | NGAL Dipstick + | NGAL Dipstick - |
|---|---|---|---|
| ALL participants | 3.9 (1.9-8.2) | 4.2 (1.4-12.7) | 3.5 (0.8-15.7) |
| Adults | 3.3 (1.3-8.2) | 2.9 (0.7-11.6) | 5.1 (1.1-23.8) |
| Children | 5.8 (1.7-20.4) | 12.0 (1.8-78.4) | 1.9 (0.1-35.5) |

**Figure 5.3. Relative Risk of Mortality for Malawian Trauma Patients with Acute Kidney Injury stratified by Age and NGALds® Dipstick Results.** The figure presents the relative risk (RR) of mortality for those with and without AKI. The left section presents RR of mortality amongst everybody (further stratified by age). The middle section presents the RR of mortality amongst only those with first a positive NGAL dipstick on admission (further stratified by age). The right section presents the RR of mortality amongst only those with first a negative NGAL dipstick on admission (further stratified by age). Actual RR presented at the bottom with 95% confidence intervals presented in parentheses. AKI=Acute kidney injury; NGAL=neutrophil gelatinase-associated lipocalin; Dipstick +=positive NGALds® dipstick (≥150ng/mL); Dipstick -=negative NGALds® dipstick (<150ng/mL)

## 5.4 Discussion

In the world's first validation study of the novel NGALds® dipstick for the diagnosis of AKI, there is promising evidence that the dipstick can rule out AKI in trauma patients. It may potentially be more useful in identifying high-risk pediatric trauma patients because those children with an elevated dipstick level and AKI had a much higher risk of mortality than those who had neither. The dipstick correlated well with the lab-based NGAL results. The dipstick was used by study nurses at the bedside, and participants/caregivers were easily recruited into the study, indicating its ease of use in this low-resourced area.

*NGALds® Dipstick to Rule Out AKI:* The dipstick proved to be a useful tool to rule out AKI (specificity 73.5%, NPV 90.2%). One wants to prioritize a high specificity for a diagnostic test to rule out disease, rather than sensitivity which helps to rule in disease. In a country that currently uses subjective clinical signs on a routine basis for AKI diagnosis, ruling out which patients need closer monitoring is imperative and, at this stage, one could argue more important than AKI confirmation. We do not believe that the NGALds® dipstick will replace a serum creatinine test, but in an impoverished area, the dipstick might be useful to triage which one of twenty trauma patients gets to take the last seat in a transport vehicle for a 6+ hours trip to the tertiary level hospital.

*NGALds® Dipstick and Mortality:* The dipstick seems to be even more promising for predicting mortality (after subsequent AKI diagnosis) in children (RR 12.0, 95% CI 1.8-78.4) compared to adults (RR 2.9, 95% CI 0.7-11.6). This makes sense because the current diagnosis of AKI worldwide relies on a change in serum creatinine. As a lab test that relies on muscle mass, creatinine is flawed as an assessment of kidney function, but it is even worse in children. So, if NGAL is a better indicator of kidney tubule injury, it makes sense that it would be more

highly associated with mortality amongst children than adults. NGAL has also been shown to be a better predictor of AKI in pediatrics compared to adults.[105] NGALds® dipstick for triage and indicator of higher mortality risk amongst subsequent AKI patients could be a valuable tool for trauma triage in the field and incorporated into clinical algorithms or care bundles for AKI recognition and management.

*NGALds® Dipstick Ease of Use and Cost-Savings:* This was the first large field test for the NGALds® dipstick and it correlated well with the lab-based NGAL Test™ (R=0.74). It was not perfect, but we learned some invaluable lessons in the field that should be incorporated into future designs. For example, given the unpredictability of electricity, the lighting in the environment for the dipstick was not consistent and certainly might have impacted our results. Yet, the test was non-invasive, and urine could be obtained on >97% of participants. Given the promising results for the dipstick to rule out AKI and its association with mortality, if the technical components are overcome and it is improved upon, the earlier detection of AKI could save many lives in areas that lack access to routine laboratory testing.

The dipstick could also be a more cost-effective screening tool than serum creatinine. If a robust, point-of-care test is kept at < $3 USD per test, it could annually save healthcare systems in sub-Saharan Africa thousands of dollars. In approximately four months for our study recruitment period, 674 patients were eligible, which extrapolates to 2022 admitted trauma patients at KCH annually. Currently at KCH, a serum creatinine costs 5000MWK ($6.80 USD, exchange rate 1USD=735 MWK). A potential AKI protocol would be to screen all admitted trauma patients for AKI given its high association with mortality, but that would cost the hospital more than $13,750USD annually (not including the cost of syringe and test tube needed per patient). However, if all patients were first screened with an NGALds® dipstick at most $3USD

per test, then the screening cost drops more than half to $6066USD. Assume 25% of those screened would be positive, so creatinine would be tested on only 506 patients, an additional $3437USD. In total, NGAL dipstick screening could be done at half the cost, and laboratory support would only focus on the high-risk patients, offloading low-yield testing from an already overburdened system.

*Potential Expansion of AKI Screening with a Point-of-Care Test:* Currently the only point-of-care diagnostic tests routinely available and clinically in use for AKI are expensive and require temperature-controlled units.[107,108] Given the limited laboratory infrastructure and unreliability of testing, clinicians in Malawi and many other low-resourced areas often wait until a patient is anuric for 24+ hours before diagnosing AKI. This is often too late for preventative and management strategies to effectively change the AKI course and prevent the need for dialysis, which is often a death sentence in these areas that have little or no access to acute dialysis care. We demonstrated in this study that a novel point-of-care dipstick can be used and readily acceptable by participants and clinical staff. The NGALds® dipstick is promising as it capitalizes on using a kidney injury biomarker to predict AKI and can be used in austere environments. AKI screening could expand to more remote areas at district hospitals and health centers that frequently do not have the ability to get creatinine values, expediting transfer of the most at-risk trauma patients for AKI prior to the onset of kidney failure when it is often too late to intervene.

Other point-of-care tests continue to be explored and should be studied as it is not clear which point-of-care test will ultimately prove most reliable, predictable, robust, and cost-effective. We do know that the current point-of-care tests that rely on temperature-controlled conditions are not practical. Perhaps, the urine protein dipstick may prove useful, but the

NGALds® dipstick was a better predictor of mortality than proteinuria alone. Others have evaluated saliva urea nitrogen (SUN) dipstick as a point-of-care test for bedside kidney function assessment.[109,110] A few studies on SUN have shown promising results as well in AKI, but they have not evaluated it in a trauma population that cannot always produce saliva.[111–113] Future analyses on SUN from our larger trauma cohort study will be forthcoming.

*Lab-based NGAL as Marker of AKI in Trauma:* A number of pediatric and adult studies have shown that urine lab-based NGAL is a good diagnostic marker for AKI.[14–17] Similarly, it has been shown to predict AKI and to be independently associated with mortality in trauma patients.[103,104] Depending on the cut-off level chosen (typically 50-200ng/mL), urine lab-based NGAL has proven to have sensitivity of 60-100% and specificity 50-100%.[15,105,106] With cut-off values closer to 100-200ng/mL, the sensitivities and specificities approach 80-90%.[105,106] Our study is one of the first for lab-based NGAL prediction of AKI in Africa, and we found similar specificities (74-93% depending on the cut-off). Our sensitivity results were not as good as previous lab-based NGAL studies, but we were limited in our diagnosis of AKI to only 2 creatinine values at least 48 hours apart so we may also have missed some AKI diagnoses.

*Limitations:* This was the first validation study of this novel NGALds® dipstick. Given resource limitations and costs, we were only able to obtain at most two creatinine values on participants. As other AKI studies tend to obtain 4-7 daily creatinine values, it is possible that we under-diagnosed AKI events. In addition, there is no standard consensus for defining the baseline creatinine amongst children, and we previously showed that in children, the definition of baseline creatinine estimation has a strong impact on the incidence of AKI (Chapter 4). We based our estimation of baseline creatinine on our previous work in the same Malawian

population (Chapter 4). KDIGO does state a consensus for estimating a baseline creatinine amongst adult patients, which is what we used for this analysis.[2]

This study was a secondary aim of a larger study and so it is possible with more participants we could refine the test characteristics of the dipstick. Even though we enrolled >300 participants, only 39 participants developed AKI. Future studies may benefit from larger numbers so that more participants are captured with AKI. Unfortunately, retrospective or case-control studies are difficult in low-resourced areas that are not routinely obtaining creatinine values, hence why our study was prospective to ensure we had creatinine values on everyone involved.

## 5.5 Conclusions

AKI can be silent, asymptomatic, until it is quite severe or fatal. In areas where diagnostic tests are limited, a point-of-care test to diagnose and prevent the severe sequelae of AKI that does not rely on electricity, temperature control, or expert technicians could be life saving for many. This is the first validation study of the novel NGALds® dipstick that holds such promise. We showed that in a trauma population in Malawi, the dipstick was good at ruling out AKI, and it may have even more promise in the pediatric population for predicting who is most at risk of death following trauma. The dipstick has potentially far-reaching possibilities beyond trauma in Malawi: other parts of Africa, disaster settings, conflict zones, rural areas in high income countries, and even as a diagnostic tool in other disease-related AKI episodes that deserve further investigations.

# CHAPTER 6: CONCLUSION

AKI is a growing concern worldwide due to its increased recognition and impact on morbidity and mortality. With the recent unification of a global consensus on the definition (KDIGO 2012), epidemiological evaluations of AKI have started advancing rapidly. However, there remain gaps in our knowledge, particularly regarding children and low-resourced areas, such as Africa. This work aimed to evaluate the epidemiology of pediatric AKI in both the United States and Malawi, Africa, as well as to validate a novel AKI diagnostic tool, the urine NGALds® dipstick. Limited diagnostic testing is a key reason for gaps in understanding AKI epidemiology in low-resourced areas. We hoped with the validation of a novel point-of-care diagnostic tool for AKI to reduce the diagnostic testing barrier, thus laying the groundwork to advance the field of AKI.

*Pediatric AKI Epidemiology in the United States:* Compared to low-income countries, epidemiological studies can be more in-depth and thorough in high-income countries, like the U.S. These settings have routine laboratory screening and follow-up for AKI amongst a large portion of hospitalized children. In addition, high-income countries more routinely have electronic medical records and large surveillance databases which can facilitate retrospective and secondary data analyses. These rich data allow for investigations into more nuanced risk factors for AKI development. Despite that, only a handful of studies have previously evaluated the sociodemographic risk factors of AKI in children, and none had done so from a national perspective.

We found that AKI occurs in at least 12 of every 1000 pediatric hospitalizations in the U.S. Using a large, nationally representative database, we identified that lack of insurance was a key risk factor for AKI. In addition, racial minority groups and male sex were associated with higher risk of AKI. This is one of the first nationally representative, large analyses in the U.S. to show this in children, though adult literature has consistently shown that males and racial minorities are at higher risk of AKI.

Though we were limited to administrative data, our nationally representative cohort gives us a broad picture of the problem and risk factors. Further, research should confirm these findings in settings not limited by administrative data only, such as linked electronic medical records or large cohorts across multiple states that can use full laboratory data for AKI confirmation. Other investigations have suggested AKI incidence to be as much as five times higher than our incidence, suggesting that administrative data is just the tip of the iceberg. AKI episodes captured with administrative data are likely correct, but this data likely misses a large portion of unrecognized, or undocumented, AKI episodes. Further research must explore if there are also sociodemographic biases in hospitals more or less likely to recognize and/or document AKI episodes, which may explain some of our findings. It is likely that the best way to approach this will be with a large prospective cohort. AKI can be silent and only detected with appropriate laboratory testing, so screening and testing for AKI may differ by hospital characteristics. Therefore, retrospective analyses relying on laboratory data (though better than administrative data) may also not give an unbiased view of the epidemiology of pediatric AKI in the U.S.

*Pediatric AKI Epidemiology in Malawi:* Despite the high burden of pediatric trauma in Africa, this was the first analysis of AKI in pediatric trauma patients in Africa. We found that approximately 10% of all admitted pediatric trauma patients developed AKI.

We found that AKI significantly increases the risk of mortality in pediatric trauma patients in Africa. Globally, there has been a growing interest to better understand AKI. In both children and adults, multiple studies have shown that AKI increases the risk of mortality as well as long-term morbidity complications in a multitude of conditions. Several studies have also seen this in Africa. Yet, despite the high burden of trauma worldwide, and in Africa in particular, very few studies have evaluated AKI's association with trauma-related mortality. We showed that if children with trauma developed AKI, they were seven times more likely to die than children who did not develop AKI.

As the first study on pediatric AKI in trauma patients in Africa, we evaluated a multitude of potential risk factors in this patient population. These risk factors and others deserve further attention as this was meant as a hypothesis-driving analysis. However, we did find that children who presented with burns, multiple injuries, or had recent intake of herbal remedies tended to have a higher risk of AKI.

Another interesting dilemma in understanding pediatric AKI, particularly in Africa, is that there is not a worldwide consensus on defining a child's healthy baseline creatinine, a key component to the KDIGO definition of AKI. In particular, there are no equations validated in an African population. In our evaluation, we found that the new (bedside) Schwartz equation performed best at estimating a child's baseline creatinine, though depending on the equation used for estimating the baseline creatinine, the incidence of AKI changed (4-10%). Based on the new (bedside) Schwartz equation, we estimated that approximately 10% of all admitted pediatric trauma patients in Malawi developed AKI.

Our epidemiological findings should all be confirmed in other Malawian regions and sub-Saharan African countries. Trauma is the leading cause of mortality for children and young

adults worldwide. If it is true that at least 10% develop AKI, then that is a large unrecognized burden that requires further research and resources to develop evidenced-based triage, recognition, and management approaches to prevent the associated sequelae and potential mortality.

We found intuitive risk factors (burns and multiple injuries) but also that herbal remedies may be associated with higher risk of AKI in admitted pediatric trauma patients. If common risk factors can be identified worldwide, then there is the potential for clinical care algorithms to use these risk factors for stratification and prioritization for further testing and monitoring, and perhaps incorporation into commonly used guidelines, such as the World Health Organization's (WHO's) Integrated Management of Childhood Illnesses (IMCI) for hospitalized children or WHO's Trauma Care Checklist for acute trauma care.

*Novel Dipstick for AKI Diagnosis (NGALds®):* Limited diagnostics throughout sub-Saharan Africa hamper our ability for more in-depth epidemiological studies on AKI. A point-of-care test to diagnose and prevent the severe sequelae of AKI that does not rely on electricity, temperature control, or expert technicians could be life saving for many in low-resourced areas. This is the first study to validate the novel dipstick (NGALds®) as just such a tool. We found that it was accurate for AKI diagnosis and perhaps risk stratification for those at higher risk of mortality after AKI development. This could aid not only in epidemiological studies, but also clinical care algorithms that could save lives in many low-resourced areas.

This was the first field validation study of the point-of-care NGALds® dipstick. It is promising as a tool for triage and risk stratification in a busy, low-resourced setting. Modifications are needed to improve its accuracy. However, it was quite robust and readily acceptable by clinical staff and participants/caregivers. If these technical challenges can be

overcome, the dipstick has potentially far-reaching possibilities beyond trauma in Malawi: other parts of Africa, disaster settings, conflict zones, rural areas in high income countries, and even as a diagnostic tool in other disease-related AKI episodes. Validation will be needed in these additional settings. Ultimately, the dipstick will need interventional trials to see if it can be a tool that truly changes outcomes, rather than simply diagnosing AKI. Then, it may prove to be a vital, life-saving tool in remote areas worldwide that currently suffer in silence due to lack of diagnostics.

# REFERENCES


1. Novis BK, Roizen MF, Aronson S, Thisted RA. Association of Preoperative Risk Factors with Postoperative Acute Renal Failure. *Anesth Analg*. 1994;78(1):143-149. doi:10.1213/00000539-199401000-00023

2. Kellum AJ. OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int*. 2012. doi:10.1159/000339789

3. Alkandari O, Eddington KA, Hyder A, et al. Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: A two-center retrospective cohort study. *Crit Care*. 2011. doi:10.1186/cc10269

4. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. *N Engl J Med*. 2017. doi:10.1056/NEJMoa1611391

5. Sutherland SM, Byrnes JJ, Kothari M, et al. AKI in hospitalized children: Comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol*. 2015. doi:10.2215/CJN.01900214

6. Jetton JG, Boohaker LJ, Sethi SK, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. *Lancet Child Adolesc Heal*. 2017;1(3):184-194. doi:10.1016/S2352-4642(17)30069-X

7. Greenberg JH, Coca S, Parikh CR. Long-term risk of chronic kidney disease and mortality in children after acute kidney injury: a systematic review. *BMC Nephrol*. 2014. doi:10.1186/1471-2369-15-184

8. Ball EF, Kara T. Epidemiology and outcome of acute kidney injury in New Zealand children. *J Paediatr Child Health*. 2008. doi:10.1111/j.1440-1754.2008.01373.x

9. Mammen C, Al Abbas A, Skippen P, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: A prospective cohort study. *Am J Kidney Dis*. 2012. doi:10.1053/j.ajkd.2011.10.048

10. Mehta RL, Cerdá J, Burdmann EA, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): A human rights case for nephrology. *Lancet*. 2015. doi:10.1016/S0140-6736(15)60126-X

11. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: A meta-analysis. *Clin J Am Soc Nephrol*. 2013. doi:10.2215/CJN.00710113

12. World Health Organization. *Injuries and Violence:The Facts 2014*.; 2014. doi:ISBN 978 92 4 150801 8

13. Harrois A, Soyer B, Gauss T, Hamada S, Raux M, Duranteau J. Prevalence and risk factors for acute kidney injury among trauma patients: a multicenter cohort study. *Crit Care*. 2018;22(1):344. doi:10.1186/s13054-018-2265-9

14. Varnell CD, Goldstein SL, Devarajan P, Basu RK. Impact of Near Real-Time Urine Neutrophil Gelatinase–Associated Lipocalin Assessment on Clinical Practice. *Kidney Int Reports*. 2017. doi:10.1016/j.ekir.2017.05.012

15. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet*. 2005. doi:10.1016/S0140-6736(05)74811-X

16. Parikh CR, Coca SG, Thiessen-Philbrook H, et al. Postoperative Biomarkers Predict Acute Kidney Injury and Poor Outcomes after Adult Cardiac Surgery. *J Am Soc Nephrol*. 2011. doi:10.1681/ASN.2010121302

17. Bennett M, Dent CL, Ma Q, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: A prospective study. *Clin J Am Soc Nephrol*. 2008. doi:10.2215/CJN.04010907

18. Zappitelli M, Washburn KK, Arikan AA, et al. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: A prospective cohort study. *Crit Care*. 2007. doi:10.1186/cc6089

19. Nickolas TL, O'Rourke MJ, Yang J, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med*. 2008. doi:10.7326/0003-4819-148-11-200806030-00003

20. Makris K, Markou N, Evodia E, et al. Urinary neutrophil gelatinase-associated lipocalin (NGAL) as an early marker of acute kidney injury in critically ill multiple trauma patients. *Clin Chem Lab Med*. 2009. doi:10.1515/CCLM.2009.004

21. Harrois A, Libert N, Duranteau J. Acute kidney injury in trauma patients. *Curr Opin Crit Care*. 2017. doi:10.1097/MCC.0000000000000463

22. Reilly JP, Anderson BJ, Mangalmurti NS, et al. The ABO histo-blood group and AKI in critically ill patients with trauma or sepsis. *Clin J Am Soc Nephrol*. 2015. doi:10.2215/CJN.12201214

23. Bagshaw SM, George C, Gibney RTN, Bellomo R. A multi-center evaluation of early acute kidney injury in critically ill trauma patients. *Ren Fail*. 2008. doi:10.1080/08860220802134649

24. Eriksson M, Brattström O, Mårtensson J, Larsson E, Oldner A. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015. doi:10.1097/TA.0000000000000727

25. Fujinaga J, Kuriyama A, Shimada N. Incidence and risk factors of acute kidney injury in the Japanese trauma population: A prospective cohort study. *Injury*. 2017. doi:10.1016/j.injury.2017.08.022

26. Santos PR, Monteiro DLS. Acute kidney injury in an intensive care unit of a general hospital with emergency room specializing in trauma: An observational prospective study. *BMC Nephrol*. 2015. doi:10.1186/s12882-015-0026-4

27. HCUP Kids' Inpatient Database (KID). Healthcare Cost and Utilization Project (HCUP). 2012. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/kidoverview.org. Published 2012. Accessed August 1, 2018.

28. Sutherland SM, Ji J, Sheikhi FH, et al. AKI in hospitalized children: Epidemiology and clinical associations in a national cohort. *Clin J Am Soc Nephrol*. 2013. doi:10.2215/CJN.00270113

29. McGregor TL, Jones DP, Wang L, et al. Acute kidney injury incidence in noncritically ill hospitalized children, adolescents, and young adults: A retrospective observational study. *Am J Kidney Dis*. 2016. doi:10.1053/j.ajkd.2015.07.019

30. Hessey E, Morissette G, Lacroix J, et al. Healthcare utilization after acute kidney injury in the pediatric intensive care unit. *Clin J Am Soc Nephrol*. 2018;13(5):685-692.

31. Park S-K, Hur M, Kim E, et al. Risk Factors for Acute Kidney Injury after Congenital Cardiac Surgery in Infants and Children: A Retrospective Observational Study. *PLoS One*. 2016. doi:10.1371/journal.pone.0166328

32. Rheault MN, Zhang L, Selewski DT, et al. AKI in children hospitalized with nephrotic syndrome. *Clin J Am Soc Nephrol*. 2015. doi:10.2215/CJN.06620615

33. Nicholas SB, Kalantar-Zadeh K, Norris KC. Socioeconomic disparities in chronic kidney disease. *Adv Chronic Kidney Dis*. 2015. doi:10.1053/j.ackd.2014.07.002

34. Shoham D a, Vupputuri S, Kaufman JS, et al. Kidney disease and the cumulative burden of life course socioeconomic conditions: the Atherosclerosis Risk in Communities (ARIC) study. *Soc Sci Med*. 2008. doi:10.1016/j.socscimed.2008.06.007

35. Vart P, Gansevoort RT, Joosten MM, Bültmann U, Reijneveld SA. Socioeconomic disparities in chronic kidney disease: A systematic review and meta-analysis. *Am J Prev Med*. 2015. doi:10.1016/j.amepre.2014.11.004

36. Mehta RL, Burdmann EA, Cerdá J, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: A multinational cross-sectional study. *Lancet*. 2016. doi:10.1016/S0140-6736(16)30240-9

37. HCUP Chronic Condition Indicator (CCI). Healthcare Cost and Utilization Project (HCUP). 2012. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp. Published 2012. Accessed May 1, 2018.

38. Hwang W, Weller W, Ireys H, Anderson G. Out-of-pocket medical spending for care of chronic conditions. *Health Aff*. 2001. doi:10.1377/hlthaff.20.6.267

39. Staplin N, Herrington WG, Judge PK, et al. Use of causal diagrams to inform the design and interpretation of observational studies: An example from the study of heart and renal protection (SHARP). *Clin J Am Soc Nephrol*. 2017. doi:10.2215/CJN.02430316

40. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999. doi:10.1097/00001648-199901000-00008

41. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004. doi:10.1097/01.ede.0000135174.63482.43

42. Abdullah F, Zhang Y, Lardaro T, et al. Analysis of 23 million US hospitalizations: uninsured children have higher all-cause in-hospital mortality. *J Public Health (Bangkok)*. 2010;32(2):236-244. doi:10.1093/pubmed/fdp099

43. Shen JJ, Cochran CR, Mazurenko O, et al. Racial and insurance status disparities in patient safety indicators among hospitalized patients. *Ethn Dis*. 2016. doi:10.18865/ed.26.3.443

44. Centers for Medicare & Medicaid Services. Medicaid.gov. https://www.medicaid.gov. Published 2018. Accessed August 7, 2018.

45. Centers for Medicare & Medicaid Services. Healthcare.gov. https://www.healthcare.gov/medicaid-chip/. Published 2018. Accessed August 7, 2018.

46. Benefits.gov. State Children's Health Insurance Program. https://benefits.gov/benefits/benefit-details/607. Published 2018. Accessed August 8, 2018.

47. Ollove M. More immigrant children in U.S. illegally to receive health care. The Pew Charitable Trusts. https://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2017/08/08/more-immigrant-children-in-us-illegally-to-receive-health-care. Published 2017. Accessed December 3, 2019.

48. Office of Disease Prevention and Health Promotion. Social Determinants of Health | Healthy People 2020. Healthy People 2020 Topics and Objectives. https://www.healthypeople.gov. Published 2015.

49. Hidalgo G, Ng DK, Moxey-Mims M, et al. Association of income level with kidney disease severity and progression among children and adolescents with CKD: A report from the chronic kidney disease in children (CKiD) study. *Am J Kidney Dis*. 2013. doi:10.1053/j.ajkd.2013.06.013

50. Shone LP, Dick AW, Brach C, et al. The role of race and ethnicity in the State Children's Health Insurance Program (SCHIP) in four states: are there baseline disparities, and what do they mean for SCHIP? *Pediatrics*. 2003. doi:10.1542/peds.112.6.SE1.521

51. Scott JW, Rose JA, Tsai TC, et al. Impact of ACA Insurance Coverage Expansion on Perforated Appendix Rates Among Young Adults. *Med Care*. 2016. doi:10.1097/MLR.0000000000000586

52. Patzer RE, Amaral S, Klein M, et al. Racial disparities in pediatric access to kidney transplantation: Does socioeconomic status play a role? *Am J Transplant*. 2012. doi:10.1111/j.1600-6143.2011.03888.x

53. Furth SL, Garg PP, Neu AM, Hwang W, Fivush BA, Powe NR. Racial differences in access to the kidney transplant waiting list for children and adolescents with end-stage renal disease. *Pediatrics*. 2000. doi:10.1542/peds.106.4.756

54. Olabisi OA, Heneghan JF. APOL1 Nephrotoxicity: What Does Ion Transport Have to Do

With It? *Semin Nephrol*. 2017. doi:10.1016/j.semnephrol.2017.07.008

55. Ng DK, Robertson CC, Woroniecki RP, et al. APOL1-Associated glomerular disease among African-American children: A collaboration of the chronic kidney disease in children (CKiD) and nephrotic syndrome study network (NEPTUNE) cohorts. *Nephrol Dial Transplant*. 2017. doi:10.1093/ndt/gfw061

56. Woroniecki RP, Ng DK, Limou S, et al. Renal and Cardiovascular Morbidities Associated with APOL1 Status among African-American and Non-African-American Children with Focal Segmental Glomerulosclerosis. *Front Pediatr*. 2016. doi:10.3389/fped.2016.00122

57. Parsa A, Kao WHL, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med*. 2013. doi:10.1056/NEJMoa1310345

58. Friedman DJ. A Brief History of APOL1: A Gene Evolving. *Semin Nephrol*. 2017. doi:10.1016/j.semnephrol.2017.07.003

59. Grams ME, Matsushita K, Sang Y, et al. Explaining the Racial Difference in AKI Incidence. *J Am Soc Nephrol*. 2014. doi:10.1681/ASN.2013080867

60. Zhao B, Lu Q, Cheng Y, et al. A Genome-wide association study to identify single-nucleotide polymorphisms for acute kidney injury. *Am J Respir Crit Care Med*. 2017. doi:10.1164/rccm.201603-0518OC

61. United States Renal Data System. 2017 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda,. doi:10.1053/j.ajkd.2017.01.020

62. Grams ME, Waikar SS, MacMahon B, Whelton S, Ballew SH, Coresh J. Performance and limitations of administrative data in the identification of AKI. *Clin J Am Soc Nephrol*. 2014. doi:10.2215/CJN.07650713

63. Ko S, Venkatesan S, Nand K, Levidiotis V, Nelson C, Janus E. International statistical classification of diseases and related health problems coding underestimates the incidence and prevalence of acute kidney injury and chronic kidney disease in general medical patients. *Intern Med J*. 2018. doi:10.1111/imj.13729

64. Borzecki AM, Cevasco M, Chen Q, Shin M, Itani KMF, Rosen AK. How valid is the AHRQ Patient Safety Indicator "postoperative physiologic and metabolic derangement"? *J Am Coll Surg*. 2011. doi:10.1016/j.jamcollsurg.2011.01.001

65. Waikar SS, Wald R, Chertow GM, et al. Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. *J Am Soc Nephrol*. 2006;17(6):1688-1694. doi:10.1681/ASN.2006010073

66. Lewington AJP, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: A global perspective of a silent killer. *Kidney Int*. 2013. doi:10.1038/ki.2013.153

67. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: A meta-analysis. *Clin J Am Soc Nephrol*. 2013. doi:10.2215/CJN.00710113

68. Imani PD, Odiit A, Hingorani SR, Weiss NS, Eddy AA. Acute kidney injury and its

association with in-hospital mortality among children with acute infections. *Pediatr Nephrol*. 2013. doi:10.1007/s00467-013-2544-2

69. Conroy AL, Hawkes M, Elphinstone RE, et al. Acute kidney injury is common in pediatric severe malaria and is associated with increased mortality. *Open Forum Infect Dis*. 2016. doi:10.1093/ofid/ofw046

70. Chami N, Kabyemera R, Masoza T, et al. Prevalence and factors associated with renal dysfunction in children admitted to two hospitals in northwestern Tanzania. *BMC Nephrol*. 2019;20(1):79.

71. Talving P, Karamanos E, Skiada D, et al. Relationship of creatine kinase elevation and acute kidney injury in pediatric trauma patients. *J Trauma Acute Care Surg*. 2013. doi:10.1097/TA.0b013e318278954e

72. Zappitelli M, Parikh CR, Akcan-Arikan A, Washburn KK, Moffett BS, Goldstein SL. Ascertainment and epidemiology of acute kidney injury varies with definition interpretation. *Clin J Am Soc Nephrol*. 2008. doi:10.2215/CJN.05431207

73. Schwartz G, Haycock G, Edelmann CJ, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics*. 1976;58(2).

74. Schwartz GJ, Munoz A, Schneider MF, et al. New Equations to Estimate GFR in Children with CKD. *J Am Soc Nephrol*. 2009. doi:10.1681/asn.2008030287

75. Hari P, Biswas B, Pandey R, Kalaivani M, Kumar R, Bagga A. Updated height-and creatinine-based equation and its validation for estimation of glomerular filtration rate in children from developing countries. *Clin Exp Nephrol*. 2012. doi:10.1007/s10157-012-0618-2

76. World Health Organization. *Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity: Vitamin and Mineral Nutrition Information System*.; 2011. doi:2011

77. Howe LD, Galobardes B, Matijasevich A, et al. Measuring socio-economic position for epidemiological studies in low-and middle-income countries: A methods of measurement in epidemiology paper. *Int J Epidemiol*. 2012. doi:10.1093/ije/dys037

78. Psaki SR, Seidman JC, Miller M, et al. Measuring socioeconomic status in multicountry studies: Results from the eight-country MAL-ED study. *Popul Health Metr*. 2014. doi:10.1186/1478-7954-12-8

79. Kobusingye OC, Lett RR. Hospital-based trauma registries in Uganda. *J Trauma - Inj Infect Crit Care*. 2000. doi:10.1097/00005373-200003000-00022

80. Evans RDR, Hemmilä U, Craik A, et al. Incidence, aetiology and outcome of community-acquired acute kidney injury in medical admissions in Malawi. *BMC Nephrol*. 2017. doi:10.1186/s12882-017-0446-4

81. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing

translational research informatics support. *J Biomed Inform*. 2009. doi:10.1016/j.jbi.2008.08.010

82. Skinner DL, Laing GL, Bruce J, Biccard B, Muckart DJJ. Validating the utilisation of venous bicarbonate as a predictor of acute kidney injury in crush syndrome from sjambok injuries. *South African Med J*. 2017. doi:10.7196/SAMJ.2017.v107i5.12213

83. Skinner DL, Hardcastle TC, Rodseth RN, Muckart DJJ. The incidence and outcomes of acute kidney injury amongst patients admitted to a level i trauma unit. *Injury*. 2014. doi:10.1016/j.injury.2013.07.013

84. Skinner DL, Kong VY, de Vasconcellos K, et al. Acute kidney injury on presentation to a major trauma service is associated with poor outcomes. *J Surg Res*. 2018. doi:10.1016/j.jss.2018.06.069

85. Bashir AA, Kong V, Skinner D, et al. Contrast-induced nephropathy following CT scan for trauma is not rare and is associated with increased mortality in South African trauma patients. *European Journal of Trauma and Emergency Surgery*. 2018.

86. Evans RDR, Docherty M, Seeley A, et al. Incidence, etiology, and outcomes of community-acquired acute kidney injury in pediatric admissions in Malawi. *Perit Dial Int*. 2018. doi:10.3747/pdi.2017.00253

87. Rakkolainen I, Lindbohm J V., Vuola J. Factors associated with acute kidney injury in the Helsinki Burn Centre in 2006-2015. *Scand J Trauma Resusc Emerg Med*. 2018. doi:10.1186/s13049-018-0573-3

88. Clark AT, Li X, Kulangara R, et al. Acute kidney injury after burn: A cohort study from the parkland burn intensive care unit. *J Burn Care Res*. 2019. doi:10.1093/jbcr/iry046

89. Demsey D, Mordhorst A, Griesdale DEG, Papp A. Improved outcomes of renal injury following burn trauma. *Burns*. 2019. doi:10.1016/j.burns.2019.04.001

90. Perkins ZB, Captur G, Bird R, Gleeson L, Singer B, O'Brien B. Trauma induced acute kidney injury. *PLoS One*. 2019. doi:10.1371/journal.pone.0211001

91. Søvik S, Isachsen MS, Nordhuus KM, et al. Acute kidney injury in trauma patients admitted to the ICU: a systematic review and meta-analysis. *Intensive Care Med*. 2019. doi:10.1007/s00134-019-05535-y

92. Prodhan P, McCage LS, Stroud MH, et al. Acute kidney injury is associated with increased in-hospital mortality in mechanically ventilated children with trauma. *J Trauma Acute Care Surg*. 2012. doi:10.1097/TA.0b013e31825ab14f

93. Palmieri T, Lavrentieva A, Greenhalgh D. An assessment of acute kidney injury with modified RIFLE criteria in pediatric patients with severe burns. *Intensive Care Med*. 2009. doi:10.1007/s00134-009-1638-6

94. Stewart IJ, Tilley MA, Cotant CL, et al. Association of AKI with adverse outcomes in burned military casualties. *Clin J Am Soc Nephrol*. 2012. doi:10.2215/CJN.04420511

95. Wu G, Xiao Y, Wang C, et al. Risk Factors for Acute Kidney Injury in Patients with Burn

Injury: A Meta-Analysis and Systematic Review. *J Burn Care Res*. 2017. doi:10.1097/BCR.0000000000000438

96. Lai WH, Rau CS, Wu SC, et al. Post-traumatic acute kidney injury: A cross-sectional study of trauma patients. *Scand J Trauma Resusc Emerg Med*. 2016. doi:10.1186/s13049-016-0330-4

97. The World Bank. GDP per capita (current US$). https://data.worldbank.org/indicator/ny.gdp.pcap.cd?year_high_desc=false. Accessed April 4, 2019.

98. The World Bank. Population, Total. https://data.worldbank.org/indicator/sp.pop.totl. Accessed April 4, 2019.

99. Moodley N, Hariparshad S, Peer F, Gounden V. Evaluation of the CKD-EPI creatinine based glomerular filtration rate estimating equation in Black African and Indian adults in KwaZulu-Natal, South Africa. *Clin Biochem*. 2018. doi:10.1016/j.clinbiochem.2018.06.014

100. Bukabau JB, Sumaili EK, Cavalier E, et al. Performance of glomerular filtration rate estimation equations in Congolese healthy adults: The inopportunity of the ethnic correction. *PLoS One*. 2018. doi:10.1371/journal.pone.0193384

101. Madala ND, Nkwanyana N, Dubula T, Naiker IP. Predictive performance of eGFR equations in South Africans of African and Indian ancestry compared with 99mTc-DTPA imaging. *Int Urol Nephrol*. 2012. doi:10.1007/s11255-011-9928-7

102. Van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ. Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft-Gault equations. *Clin Chem*. 2008. doi:10.1373/clinchem.2007.099085

103. Yang HT, Yim H, Cho YS, et al. Assessment of biochemical markers in the early post-burn period for predicting acute kidney injury and mortality in patients with major burn injury: Comparison of serum creatinine, serum cystatin-C, plasma and urine neutrophil gelatinase-associated lipocalin. *Crit Care*. 2014. doi:10.1186/cc13989

104. Stewart IJ, Glass KR, Howard JT, et al. The potential utility of urinary biomarkers for risk prediction in combat casualties: A prospective observational cohort study. *Crit Care*. 2015. doi:10.1186/s13054-015-0965-y

105. Haase M, Bellomo R, Devarajan P, et al. Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney Injury: A Systematic Review and Meta-analysis. *Am J Kidney Dis*. 2009. doi:10.1053/j.ajkd.2009.07.020

106. Zhang A, Cai Y, Wang PF, et al. Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: A systematic review and meta-analysis. *Crit Care*. 2016. doi:10.1186/s13054-016-1212-x

107. Gibney RTN, Sever MS, Vanholder RC. Disaster nephrology: Crush injury and beyond. *Kidney Int*. 2014. doi:10.1038/ki.2013.392

108. Tran NK, Godwin Z, Bockhold J, Kost GJ. Point-of-care testing at the disaster-

emergency-critical care interface. *Point Care*. 2012. doi:10.1097/POC.0b013e318265f7d9

109. Raimann JG, Kirisits W, Gebetsroither E, et al. Saliva urea dipstick test: Application in chronic kidney disease. *Clin Nephrol*. 2011. doi:10.5414/CN106826

110. Evans R, Calice-Silva V, Raimann JG, et al. Diagnostic Performance of a Saliva Urea Nitrogen Dipstick to Detect Kidney Disease in Malawi. *Kidney Int Reports*. 2017. doi:10.1016/j.ekir.2016.12.006

111. Calice-Silva V, Vieira MA, Raimann JG, et al. Saliva urea nitrogen dipstick - a novel bedside diagnostic tool for acute kidney injury. *Clin Nephrol*. 2014. doi:10.5414/CN108370

112. Calice-Silva V, Sacomboio E, Raimann JG, et al. Diagnostic performance of salivary urea nitrogen dipstick to detect and monitor acute kidney disease in patients with malaria. *Malar J*. 2018. doi:10.1186/s12936-018-2627-4

113. Evans RDR, Cooke W, Hemmila U, et al. A Salivary Urea Nitrogen Dipstick to Detect Obstetric-Related Acute Kidney Disease in Malawi. *Kidney Int Reports*. 2018. doi:10.1016/j.ekir.2017.10.002