Title:

Acute Kidney Replacement Therapy in Children with Acute Kidney Injury at Nelson Mandela Children Hospital: a single-centre experience.

By:

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Thesis Approval Statement:

As the candidate's supervisor, I have/have not approved this thesis for submission.

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Declaration

I Gabriel Lindokuhle Mahlase declare that

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Dedication

This work is dedicated to my family, whose unwavering love and support have been my greatest source of strength and inspiration throughout this journey. I am profoundly grateful for your endless patience, understanding, and prayers.

I also acknowledge my Lord and Savior, Jesus Christ, for His guidance and grace throughout this project. I am reminded of His promise in Philippians 1:6, "Being confident of this very thing, that he which hath begun a good work in you will perform it until the day of Jesus Christ." His faithfulness has been my foundation, and I trust in His perfect plan for my life.

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Overview of the thesis

Title

Acute Kidney Replacement Therapy in Children with Acute Kidney Injury at Nelson Mandela Children's Hospital: A Single Centre Experience

Background

Acute kidney injury (AKI) requiring kidney replacement therapy (KRT) is a critical condition in paediatric patients, necessitating specialised care. We present a retrospective study conducted at Nelson Mandela Children's Hospital, analysing the outcomes of children undergoing acute KRT for AKI.

Methods

Retrospective data from January 2018 to January 2023 were collected from medical records via RedCap® and analysed. Demographic, clinical, and laboratory data were reviewed, focusing on AKI severity (KDIGO classification), dialysis modalities used, and patient outcomes. Ethical approval was obtained (BREC/0005680/2023).

Results

Seventy-two paediatric patients received acute KRT, with 52 meeting the inclusion criteria. The cohort predominantly consisted of males (62%) with a mean age of 29 months. AKI severity was predominantly severe (KDIGO stage 3, 67%). Common indications for KRT included post-operative cardiac surgery (37%) and acute respiratory distress syndrome (15%). Significant associations with mortality included weight < 10 kg ($p=0.026$), concurrent use of inotropes ($p=0.005$), and metabolic acidosis ($p=0.010$).

Conclusion

This single-centre experience at Nelson Mandela Children's Hospital reveals significant insights into the utilisation and outcomes of CKRT in paediatric patients with AKI. Our

findings underscore the critical impact of early recognition and appropriate management strategies in improving outcomes for these young, critically ill patients. The study highlights that paediatric AKI requiring KRT predominantly affects younger patients, often with severe illness. Notably, the high mortality observed in patients weighing less than 10 kg emphasises the urgent need for pediatric-specific CKRT machinery to better cater to this vulnerable subset of critically ill children. This study advocates for continued research and quality improvement initiatives to advance pediatric AKI care, aiming to mitigate the substantial morbidity and mortality associated with this condition.

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Abbreviations

AKI	Acute Kidney Injury
APIGN	Acute Post-Infectious Glomerulonephritis
ATN	Acute Tubular Necrosis
BREC	Biomedical Research Ethics Committee
CKD	Chronic Kidney Disease
CKRT	Continuous Kidney Replacement Therapy
CV	Conventional Ventilation
CVVH	Continuous Veno-Venous Hemofiltration
CVVHD	Continuous Veno-Venous Hemodialysis
CVVHDF	Continuous Veno-Venous Hemodiafiltration
ECMO	Extracorporeal Membrane Oxygenation
ESKD	End-Stage Kidney Disease
GFR	Glomerular Filtration Rate
HFOV	High-Frequency Oscillatory Ventilation
HICs	High-Income Countries
HIV	Human Immunodeficiency Virus
HSP	Henoch-Schönlein Purpura
HUS	Haemolytic Uremic Syndrome

KDIGO	Kidney Disease Improving Global Outcomes
KRT	Kidney Replacement Therapy
MIS-C	Multisystem Inflammatory Syndrome in Children
N-GAL	Neutrophil Gelatinase-Associated Lipocalin
NICU	Neonatal Intensive Care Unit
NSAIDs	Non-steroidal Anti-Inflammatory Drugs
NS	Nephrotic Syndrome
PD	Peritoneal Dialysis
PICU	Paediatric Intensive Care Unit
RAAS	Renin-Angiotensin-Aldosterone System
SCr	Serum Creatinine
SLE	Systemic Lupus Erythematosus
TB	Tuberculosis
TLS	Tumour Lysis Syndrome
UO	Urine Output

1. Background, Introduction and Literature Review

Nelson Mandela Children's Hospital (NMCH) was established in 2016, with most departments commencing full operations in 2018. The hospital represents a cornerstone of paediatric healthcare innovation in the region, and the facility is dedicated to providing comprehensive medical care to children across various specialities. As it is still in its developmental phase, some services, most notably oncology, nuclear medicine, and orthopaedics, are not yet offered at the facility.

The Intensive Care Unit (ICU) complex at NMCH comprises both a Paediatric Intensive Care Unit (PICU) and a Neonatal Intensive Care Unit (NICU), making it a comprehensive treatment centre for critically ill infants and children. This complex is outfitted with the latest technology in critical care, allowing for advanced treatments such as Continuous Kidney Replacement Therapy (CKRT), Extracorporeal Membrane Oxygenation (ECMO), and advanced ventilatory support. The ICU's multidisciplinary approach ensures that all aspects of a child's condition are addressed, ranging from acute medical management to long-term rehabilitation needs.

The importance of this study stems from the increasing incidence of acute kidney injury (AKI) in children, particularly those undergoing major surgeries like cardiac procedures. NMCH, with its robust ICU infrastructure and a high volume of paediatric cardiac surgeries, provides an ideal setting for conducting this research. This study aims to analyse the outcomes and efficacy of various modalities of kidney replacement therapy in the context of NMCH's ICU complex, with the aim of shedding new light on optimal practices and potential areas for improvement in the management of paediatric AKI.

1.1 Introduction

Acute kidney injury (AKI) is defined as a sudden deterioration in kidney function, characterised by an increase in serum creatinine (SCr) and, or a decrease in urine output (UO), resulting in a reduction in the glomerular filtration rate (GFR). (1, 2) This syndrome leads to compromised fluid, acid-base, and electrolyte equilibrium regulation. (3) Severe forms of AKI are associated with prolonged hospitalisation, increased morbidity and mortality, and the need for kidney replacement therapy (KRT) in both children and adults. (2, 4)

AKI can affect individuals of all ages, but children, particularly infants, exhibit heightened vulnerability to this condition. (1, 5) Children have a unique physiology predisposing them to

AKI. Their immature kidneys possess a limited capacity for filtration and reabsorption, making them more susceptible to insults that disrupt normal kidney function, including altered blood flow and inflammation. (1, 6) Furthermore, children are often exposed to specific risk factors that increase their susceptibility to AKI. (7) Conditions like gastroenteritis, haemolytic uremic syndrome (HUS) and sepsis are frequently encountered in paediatrics. (8) If these are not attended to timeously or managed correctly, they can further progress and result in acute tubular necrosis (ATN), systemic inflammation and AKI. (6, 9) In addition, certain medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics such as aminoglycosides, and contrast agents used in diagnostic procedures, can profoundly impact the developing kidneys. (10-13)

1.2 The definition of AKI

There has been considerable diversity in the definitions of AKI, leading to challenges in comparing findings across different studies. (14) This variation has impeded the validation of novel concepts, such as biomarkers, and has hindered the overall advancement in understanding the AKI syndrome. (15)

RIFLE, which stands for Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (ESKD), was the first consensus definition developed by the Acute Quality Dialysis Initiative. (16) Subsequently, RIFLE was modified to pediatric RIFLE (pRIFLE), which helped take into account paediatric patients and looked more at changes in the GFR than just serum creatinine (SCr) alone. (4, 17, 18)

In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) expanded this definition to accommodate children without previous blood test results by using specific upper-limit reference ranges. (19) Table 1 shows the different stages of AKI according to the KDIGO classification. (19)

Despite these efforts, the definition of AKI in children is still limited. (20) This is primarily because of the reliance on serum creatinine and urine output as biomarkers for AKI. (21) Serum creatinine is not a perfect biomarker, as it may be influenced by various factors, such as sex, muscle mass, age, and nutritional status. (21, 22) Additionally, a significant rise in serum creatinine is typically observed only when approximately 25-50 % of kidney function has already been compromised. (4, 23, 24)

These limitations have led to the development of biomarkers such as Neutrophil Gelatinase-Associated Lipocalin (N-GAL) to detect early subclinical AKI that may occur before serum creatinine rises. (25) However, these biomarkers remain primarily a research tool and are yet to be widely integrated into clinical practice. (23)

Our study used the KDIGO definition in accordance with the universal standardise recommendation to maintain consistency and uniformity in the definition of AKI. (Table 1)(19)

Table 1 AKI stages according to KDIGO definitions (19, 26)

Stage	Serum creatinine criteria	Urine output criteria
1	1.5 to 1.9 times baseline 1.5-1.9 OR ≥26 μmol/L (≥ 0.3 mg/dL) increase	< 0.5 mL/kg/h for 6-12 hrs
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for > 12 hours
3	Serum creatinine increase 3.0 times baseline OR Increase in serum creatinine ≥ 354 mmol/L (≥ 4 mg/dL) OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m^2	< 0.3 ml/kg/h for > 24 hours OR Anuria for > 12 hours

1.3 The incidence of AKI in children

The exact incidence of paediatric AKI is unknown partly because of a lack of consensus over the definition as to what constitutes AKI. (1, 14, 20) However, there is growing evidence that the incidence and prevalence of paediatric AKI are steadily increasing. (27) This rise may be attributed to both harmonising the definition as well as advancements made in the care of critically ill children. (17-19)

The incidence of AKI varies according to the level of hospital care. (28) It has been noted that the number of patients who are treated in general hospital settings ranges from one to five percent in general hospital settings to 30 – 50 % in tertiary institutions that care for more severely ill patients. (11, 29, 30)

The "Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in Critically Ill Children" (AWARE) study used the KDIGO classification to analyse a cohort of 5200 children from 10 countries. (4) The results showed an overall AKI incidence of 27 % in the critically ill children. In addition, 12 % of patients were classified as having KDIGO Stage 2 or 3 (4). This study remains the benchmark for the incidence of AKI in paediatrics based on its size and comprehensive scope. (4)

1.3.1 The incidence of AKI in Sub-saharan Africa

Data on the incidence of AKI in sub-Saharan Africa are almost nonexistent, and there is a high likelihood that the few available studies underestimate the true incidence of AKI in these countries. (31, 32) This is because there is generally a centralisation of advanced medical care and paediatric nephrology subspecialists in tertiary centres in these countries. (31, 33) The reporting of tertiary-based care generally omits the epidemiology of AKI in rural areas, where the vast majority of community-acquired AKI cases are likely to occur. (31-33) Even though the study by Olowu *et al*. does not address the incidence per se, it does provide insight into the differences between high-income countries (HICs) and low-income countries (LICs), most importantly, the late presentation of patients and the lack of access to dialysis in the LICs.(31)

1.4 The causes of AKI in children

The traditional classification of AKI is based on anatomical aetiology, namely, pre-renal, renal, and post-renal AKI. (34) However, other classifications exist, such as hospital versus community-acquired AKI and oliguric versus non-oliguric AKI. (14) In addition, the discovery of new biomarkers has also shifted the classification to include "functional". (25) In these cases, there is neither structural damage nor a rise in SCr, and AKI is suspected only due to the presence of a positive biomarker. (22, 25, 35, 36) However, the traditional classification remains convenient for understanding mechanisms of diagnosis and management approaches and will be primarily employed in this chapter.

1.4.1 Pre-renal AKI

In the physiological state, 25 % of the cardiac output is directed to the kidneys, making them susceptible to significant changes related to the effective blood volume. (37) Pre-renal AKI in children is usually caused by community-acquired conditions that lead to dehydration, often due to inadequate fluid intake or excessive fluid loss. (38) These conditions include diarrhoea, vomiting, and excessive sweating. (6) However, some overhydration states with poor effective volume, such as poor cardiac output, liver disease, and nephrotic syndrome, can also cause pre-renal AKI. (36, 39, 40)

Reduced renal blood flow activates the renin-angiotensin-aldosterone system (RAAS), which is pivotal in regulating blood pressure and fluid balance. (41) The activation of the RAAS leads to vasoconstriction of the renal blood vessels, further reducing renal blood flow as the body tries to increase blood pressure and increase the volume of effective circulation. (42) Angiotensin II also results in sodium and water retention, resulting in diminished urine output and a decreased fraction excretion of sodium, the hallmarks of pre-renal AKI. (43)

Ultimately, if pre-renal AKI persists, the prolonged reduction in kidney perfusion may lead to tubular injury and dysfunction. (37, 38) When this happens, the kidney tubules, responsible for reabsorbing essential substances and excreting waste products, become compromised, resulting in impaired kidney function. (38) Timely recognition and intervention to address the underlying cause is crucial to prevent the progression of pre-renal AKI to the more severe forms of kidney injury in children. (44)

1.4.2 Renal AKI

Intrinsic paediatric AKI can stem from various elements within the kidney, including glomerular, tubulointerstitial, and vascular components. (37) However, for renal AKI, the primary factor contributing to AKI is ATN due to ischemia. (45)

Glomerular causes of renal AKI

Common causes include conditions that cause inflammation and/or loss of integrity of the glomerulus, namely nephrotic syndrome (NS), acute post-infectious glomerulonephritis (APIGN), and systemic lupus erythematosus (SLE). (45, 46)

Tubulointerstitial causes of renal AKI

This form of AKI is related to injury and/or death of the tubular cells due to direct insult from agents that are deemed to be nephrotoxic, such as non-steroidal anti-inflammatory drugs (NSAIDs), antimicrobial agents such as aminoglycosides, and iodine-based contrast medium, which are used in radiological imaging studies such as CT scanning. (10-13)

Vascular causes of renal AKI

Vascular causes of AKI in children are conditions related to compromised perfusion of the kidney due to vascular injury from multifactoral aetiologies. (6) These conditions are commonly associated with systemic autoimmune diseases, such as SLE, Henoch Schönlein Purpura (HSP), and ANCA-associated vasculitis. (47) However, some conditions, such as haemolytic uremic syndrome (HUS), may be localised to the kidney microvasculature, resulting in AKI in addition to haematological manifestations. (48)

1.4.3 Post-renal causes of AKI

Post-renal AKI is usually caused by partial or complete obstruction of one or both kidneys. (14) The obstruction may be related to congenital abnormalities of the kidney and urinary tract, such as posterior urethral valves, or it may be related to acquired causes, such as nephrolithiasis, clots, or neoplastic disease. (49, 50) In most instances, if the underlying cause of the obstruction is timeously relieved, the kidney function will usually recover completely. (51)

It is important to note the differences in the aetiology of paediatric AKI between high-income countries (HICs) and those in Sub-Saharan Africa. For example, a meta-analysis by Olowa *et al.* examining the outcomes in children and adults with AKI in Sub-Saharan Africa found that most of the causes of AKI were secondary to infections. (31) This is unlike what is seen in HICs, where hospital-acquired sepsis is now one of the leading causes of AKI. (38) Infections in sub-Saharan Africa that might cause AKI include community-acquired diseases such as malaria, human immunodeficiency virus (HIV), tuberculosis (TB), and infectious gastroenteritis complicated by severe dehydration. (31, 33, 52)

1.5 The significance of AKI in children

Several studies have demonstrated that AKI is associated with higher morbidity, longer length of hospital stay, prolonged ventilation duration, and higher mortality rates. (53, 54) Sutherland *et al*. looked at over 3000 children receiving critical care and found that AKI was independently associated with longer ventilation time and that patients who developed AKI while on ventilatory support needed at least two to four days longer on respiratory support than those who did not have AKI. (53, 55)

In non-critically ill children, Zappitelli *et al*. studied five hundred and fifty-seven children who developed AKI after aminoglycoside exposure and found that AKI was associated with increased length of stay and cost regardless of the definition employed to define AKI. (11)

1.6 Acute Kidney Replacement Therapy

Although AKI is often considered the main indication for acute KRT, there are other indications for KRT. (56) In addition, it should be noted that although this section focuses on KRT in the intensive care unit setting, in many low- and middle-income countries, delivery of KRT, especially acute PD, may well be undertaken in a ward or emergency room setting because of a lack of ICU beds. (57-59)

The indications for acute KRT are often summarised using the mnemonic "AEIOU" as follows: hyperammonaemia and/or intractable acidosis, electrolyte abnormalities (e.g.hyperkalaemia), intoxications, fluid overload, and uraemia or hyperuricaemia such as is seen in tumour lysis syndrome (TLS). (60, 61)

In the acute setting, different modes of acute KRT can be chosen, namely peritoneal dialysis (PD), continuous kidney replacement therapy (CKRT), and acute intermittent haemodialysis (IHD). (62) The choice depends on the availability of the modes, local expertise, and/or the presence of contraindications to using a single mode. (58, 62)

1.6.1 Peritoneal dialysis

The PD method requires the insertion of a PD catheter into the peritoneal cavity, followed by the infusion of a highly osmolar fluid (the dialysate) into the peritoneal cavity. (63) A functional peritoneal membrane must be present to facilitate both the diffusion of solutes and the ultrafiltration of water from the intravascular compartment through the interstitial tissue and

into the peritoneal cavity, from where it will be drained and then replaced in a continuous cyclical fashion. (63)

Georgie *et al*. found that PD is underutilised for AKI in the ICU setting, especially in high-income countries. (64) In contrast, the rate of use of PD for AKI is approximately 46 % in developing countries. (64) With its aim being to facilitate the establishment of acute PD facilities in low-resource areas that do not have access to HD, the Saving Young Lives (SYL) initiative has contributed significantly to increasing the use of peritoneal dialysis in children with AKI in low-income countries. (58, 59, 65)

PD is the preferred method used in small neonates and haemodynamically unstable patients who might pose a vascular access challenge (Figure 1). (59, 66, 67) PD leads to better preservation of local kidney haemodynamics and is more physiological, less inflammatory, and cheaper than HD. (59, 68, 69) In many centres, it is the preferred mode to use in post-cardiac surgery patients, especially in those patients at risk for developing AKI, such as those who undergo prolonged bypass time. (59, 70) In these cases, the surgeon will often insert the PD catheter at the time of the cardiac surgery in anticipation of the need for post-op KRT. (59, 71) In addition, several studies have reported reasonable survival rates in patients treated with peritoneal dialysis, particularly in resource-limited countries. (72, 73)

The disadvantages of acute PD include the risks of leakage, peritonitis, catheter migration, and/or blockage. (59, 74) Also, ultrafiltration is not as easily controlled as it is with the various haemodialysis modes. (59)

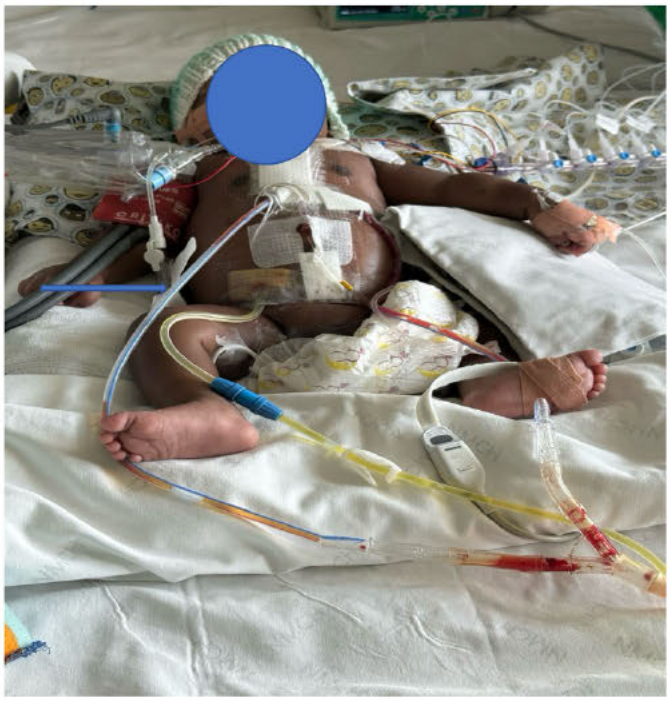

Figure 1: Post-cardiac surgery infant undergoing peritoneal dialysis, blue arrow shows peritoneal dialysis catheter. (picture taken with consent from the parent- attached under appendices)

1.6.2 Continuous Kidney Replacement Therapy

CKRT is an important intervention used in the management of AKI, particularly in the critical care setting. (75) It requires vascular access, dialysis and/or replacement fluids, an appropriately sized filter, and a CKRT machine (Figure 2). (76, 77) The aim of CKRT is to simulate the physiological process during AKI. (76, 78) CKRT entails using the principles of both diffusion of solutes (HD) and/or convection through haemofiltration (HF) in a continuous fashion to achieve the clearance and ultrafiltration goals needed for the patient. (78) Convection, central to HF, occurs when fluid is pushed across the membrane, carrying with it dissolved solutes in a process known as solute drag. (76) The above modalities can be used in combination (CVVHDF) or in isolation (CVVH/CVVHD) depending on the indication for CKRT. (79)

The advantages of CKRT include gradual fluid removal and solute clearance, which is better tolerated in haemodynamically unstable patients. (78) Additionally, CKRT allows for precise control of balance, which is crucial in the paediatric population, where minor haemodynamic changes can have significant consequences. (78) CKRT has also been proposed to mitigate the inflammatory response in patients undergoing ECMO, and it can also be used for non-renal indications like liver diseases and inborn errors of metabolism. (80-82)

It is important to note that CKRT presents challenges in the paediatric population, especially relating to issues such as difficult vascular access, the maintenance of circuit durability, and determining the optimal timing for its initiation to improve outcomes. (83) Additionally, the lack of paediatric-specific machines, such as the Cardio-Renal Paediatric Dialysis Emergency Machine (CARPEDIEM™), for CKRT in most centres results in the off-label use of adult CKRT machines, which are not designed to handle the delicate haemodynamics of small children and often require blood priming for use. (83, 84)

Nelson Mandela Children's Hospital (NMCH) in Johannesburg is able to offer PD, CKRT, IHD, and ECMO services to children treated in the ICU complex but, up until now, an audit of KRT modes used for AKI at NMCH has not yet been carried out.

In this study, we aimed to describe the demographic characteristics and outcomes of a cohort of patients treated for AKI at NMCH between January 2018 and January 2023.

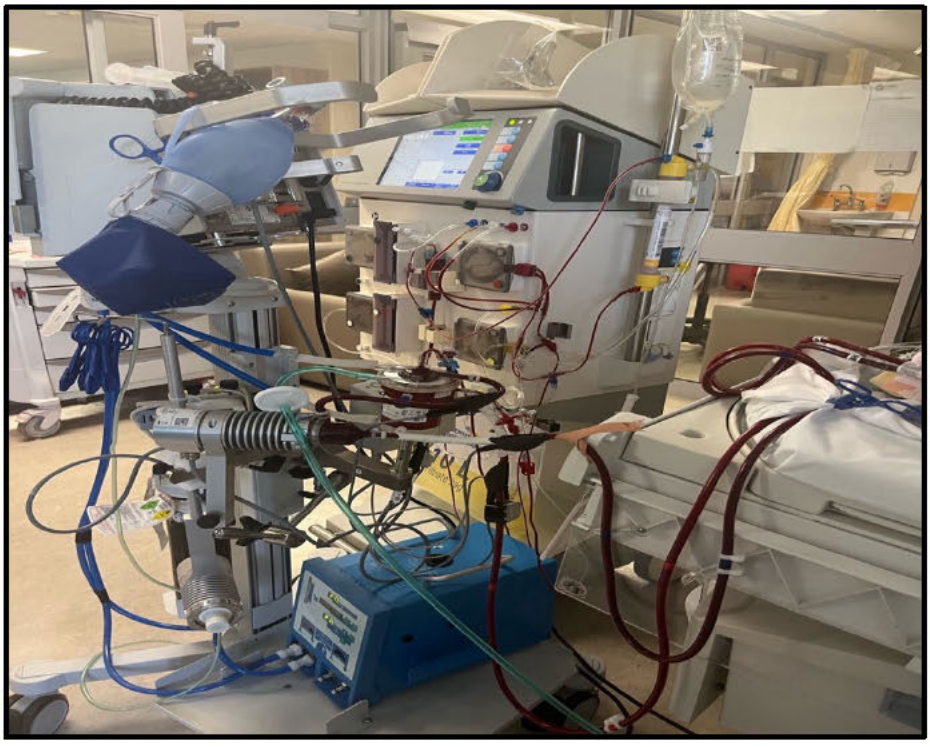

Figure 2: Neonate on ECMO and CKRT connected via the ECMO circuit.

2 Methods

2.1 Data Collection

Ethical approval was obtained from the University of Kwa-Zulu Natal Biomedical Research Ethics Committee (BREC/0005680/2023).

Data for this retrospective chart review was collected from the medical records of paediatric patients treated for AKI, using the KDIGO definition, at Nelson Mandela Children's Hospital (NMCH) between January 2018 and January 2023. The decision as to whether a child would need CKRT was taken after a joint discussion between the intensivist and the nephrologist on call. The mode selection and device settings were determined by the nephrologist on call, while the fluid loss rate was adjusted by the intensivist on call based on the immediate fluid balance requirement of the individual patient. The study included patients who received kidney replacement therapy (KRT) during their stay in the pediatric intensive care unit (PICU) or neonatal intensive care unit (NICU). Detailed patient information such as demographic data, medical history, underlying conditions, type of KRT received, and outcomes were extracted using a standardised data collection form. The data was entered into an Excel spreadsheet for further analysis (Appendix 3)

2.2 Kidney Replacement Therapies

2.2.1 Continuous Kidney Replacement Therapy

For CKRT, NMCH utilises the Fresenius MultiFiltrate® machine equipped with pediatric-specific circuits. These circuits include the Fresenius Midi® with a priming volume of 135 ml and the smaller Fresenius paediatric circuits with a priming volume of 74 ml. The commonly used filters were the AVPaed® (Filter Surface Area 0.2 m^2) and the AV 400S® (Filter Surface Area 0.7 m^2). The blood pump speeds used ranged between 6 – 8 ml/kg/minute, and the total dialysis/exchange dose used was, on average, 35 ml/kg/hour. The filters, line sets, and machine settings were selected by the nephrologist on call to match the specific weight and body surface area of the patient being treated. Blood prime was used whenever the extracorporeal circuit's volume exceeded 10 % of the patient's total blood volume.

2.2.2 Peritoneal Dialysis

Peritoneal dialysis at NMCH is performed through the insertion of Tenckhoff style catheters, which are typically placed bedside or in the operating theatre by the paediatric surgical team or in theatre by the cardiothoracic surgeons where there is prolonged cardiopulmonary bypass time or anticipated post-operative AKI. In two neonates, paediatric nephrologists performed bedside insertion of Cook® catheters under ultrasound guidance.

2.3 Statistical Analysis

The statistical analysis was performed using statistical tools and resources provided by the website Social Science Statistics (https://www.socscistatistics.com).

Categorical variables were described using frequencies and percentages and were compared using *Chi-squared* testing for variables containing more than five groups and *Fisher's exact* testing for variables containing five or less groups.

Continuous variables were described using means, standard deviation (SD), standard error (SE), and confidence intervals (CI), as appropriate. The continuous variables were then tested for skewness. Normally distributed data was compared using the *two-sample t-test*, and skewed data was compared using the *Mann-Whitney U* test.

The significance level for all statistical tests was set at $p < .05$.

2.4 Inclusion criteria

All patients admitted to the NMCH PICU and NICU, diagnosed with AKI using the KDIQO definition, and who received KRT between January 2018 and January 2023.

2.5 Exclusion criteria

1. Patients who were assessed to have established chronic kidney disease (CKD) at their initial acute presentation
2. Patients with AKI who did not receive KRT

3 Results

Seventy-two patients received acute KRT in our PICU/NICU complex between January 2018 and January 2023. Of these, 20 were in kidney failure due to CKD and were excluded from the data analysis. A complete set of data was available for the remaining 52 patients in the original cohort, which was used for the data analysis.

Most patients came from Gauteng province, with 31 (60 %) referred to our PICU/NICU complex from a community or district hospital and 21 (40 %) from an academic or tertiary institution. The majority of patients were treated in the PICU. (Table 1)

Table 1. Place of origin, referral centre, and ICU

n = 52	#	%
Gauteng	42	81
Mpumalanga	5	10
North West Province	3	6
Kwa-Zulu Natal	2	4
Referred from a community hospital	31	60
Referred from an academic hospital	21	40
PICU	48	92
NICU	4	8

The primary reasons for ICU admission are depicted in Table 2, with post-operative cardiac surgery and acute respiratory distress syndrome comprising the majority of the cases. The primary kidney-related causes of AKI in the cohort were made up of four cases of SLE nephritis and three cases of HUS (Table 2).

Table 2. Primary diagnosis

n = 52	#	%
Post-op cardiac surgery	19	37
Acute Respiratory Distress Syndrome	8	15
Acute gastroenteritis	4	8
Systemic Lupus Erythematosus	4	8
Haemolytic Uraemic Syndrome	3	6
Septic Shock	3	6
MIS-C	2	4
Acute Fulminant Liver Failure	2	4
Aminoglycoside toxicity	1	2
Constrictive pericarditis	1	2
Dilated Cardiomyopathy	1	2
Meconium Aspiration Syndrome	1	2
Metabolic disorder	1	2
Non-accidental injury with rhabdomyolysis	1	2
Tumour Lysis Syndrome	1	2
Tracheo-oesophageal repair	1	2

There were 32 males (62 %) and 20 females (38 %). Two (4 %) patients were HIV-positive. The mean age of the final cohort was 29 months (*SD*, 39 months), with 24 (46 %) patients younger than 12 months and 28 (54 %) at 12 months and older. Of the 24 children younger

than 12 months of age, 19 were under the age of 6 months, and five were aged from 6 months to 12 months. (Table 3)

The mean weight of the final cohort was 12 kg (*SD*, 10 kg), with 26 (50 %) weighing less than 10 kg and 26 (50 %) weighing 10 kg or more. Of the 26 children weighing less than 10 kg, 15 weighed less than 5 kg, and 11 weighed between 5 kg and 10 kg. (Table 3)

At the time of connection to KRT, the mode of ventilation was conventional intermittent positive pressure ventilation (CV) in 45 (87 %) patients and high-frequency oscillatory ventilation (HFOV) in 7 (13 %) of patients. Extracorporeal membrane oxygenation (ECMO) was used along with one of the ventilation modes in 16 patients (31 %). Inotropic cardiac support was used in 44 (85 %) patients. (Table 3)

Fluid overload (the presence of oedema and a positive fluid balance of more than 10 % of the dry body weight) was present in 49 (94 %) patients, and diuretics were used in 47 (90 %) patients. Hyponatremia was present in 29 (56 %) patients, hyperkalaemia in 34 (65 %), and metabolic acidosis in 42 (81 %). Seventeen (33 %) were classified as KDIGO 2 and 35 (67 %) as KDIGO 3. (Table 3)

Peritoneal dialysis was the first mode of dialysis in 17 patients (33 %). Of these patients, 13/17 (76 %) were able to remain on PD, while four (24 %) had to be switched to CKRT due to failed PD or a blocked or migrated PD catheter. (Table 3)

CKRT was used in 39 (75 %) patients, including four patients who had to be switched from PD to CKRT. (Table 3)

None of the patients were treated with intermittent haemodialysis (IHD).

Twenty-eight patients (54 %) survived until ICU discharge. Of these, 26 (93 %) had complete recovery of kidney function, while two (7 %) had to go to our chronic KRT program. (Table 3)

Table 3. Demographic characteristics at the time of connection to CKRT

n = 52	#	%
Male	32	62
Female	20	38
HIV Positive	2	4
Age < 6 months	19	37
Age 6m – 12 months	5	9
Age >= 12 months	28	54
Weight < 5kg	15	29
Weight 5 - 10kg	11	21
Weight > =10kg	26	50
CV	45	87
HFOV	7	13
ECMO	16	31
Inotropes	44	85
Fluid Overload	49	94
Diuretics	47	90
Hyponatraemia	29	56
Hyperkalaemia	34	65
Metabolic acidosis	42	81
KDIGO 2	17	33
KDIGO 3	35	67
PD	17	33
PD alone	13	25
PD to CKRT (out of 17 who started on PD)	4	24
CKRT (including the 4 who switched from PD)	39	75
AKI Recovery (out of 28 survivors)	26	93
Died while on KRT	24	46

When comparing the group of survivors to the group of non-survivors, the variables that were statistically significantly associated with death while on KRT were a weight less than 10 kg (*p* 0.026), the concomitant use of inotropes (p 0.005), and the presence of metabolic acidosis (*p* 0.0.1). (Table 4)

Apart from the statistically significantly fewer males than females in the group of children who weighed less than 5 kg compared to those who weighed from 5 kg to 10 kg (*p* 0.05), there were no other differences between these two groups. (Table 5).

When comparing the group weighing less than 10 kg to the group weighing 10 kg or more, patients weighing < 10 kg were significantly more likely to have had cardiac surgery (*p* 0.03) and to have been on ECMO (*p* 0.03) than those weighing > 10 kg. They were also more likely to have been treated with PD alone rather than CKRT (*p* .087). (Table 6).

When examining the effect of cardiac surgery on mortality, there was no difference in mortality between all the post-operative cardiac surgery cases and all the non-cardiac surgery patients (Table 4), and no difference in the mortality of the post-operative cardiac patients who weighed less than 10 kg and those who weighed 10 kg or more (Table 7).

When examining the effect of the use of ECMO on mortality, there was no difference in mortality between all the children who received ECMO and those who did not, and also no difference in the mortality of the children who weighed less than 10 kg and who received ECMO, and those who weighed 10 kg or more, and who did not. (Table 8)

When examining the effect of the use of PD on mortality, there was no difference in mortality between the children who received PD alone and those who did not, and also no difference in the mortality of the children who weighed less than 10kg and who were treated with PD alone, and those who weighed 10 kg or more, and who were treated with PD alone. (Table 8)

However, although there was no difference noted in the risk of mortality while on CKRT for the whole cohort (Table 4), there was a statistically significant increased risk of mortality while on CKRT for the cohort of children who weighed less than 10kg, where 10/15 (67 %) died while on CKRT, as compared to those who weighed 10kg and above, where 7/24 (29 %) died while on CKRT (*p* .05) (Table 8)

Table 4. Comparison of survivors and non-survivors

	Survivors (n = 28)		Deaths (n = 24)		
n = 52	#	%	#	%	*p*
Male	17	64	15	58	NS
Female	11	36	9	42	
Weight < 10kg	***10***	***36***	***16***	***67***	**0.026**
Weight > =10kg	***18***	***64***	***8***	***33***	
Gauteng	23	82	19	79	NS
Other	5	18	5	21	
Referred from an academic hospital	10	36	11	46	NS
Referred from a community hospital	18	64	13	54	
PICU	26	93	22	92	NS
NICU	2	7	2	8	
HIV Positive	0	0	2	8	NS
CARDIAC	9	32	10	42	NS
Other	19	68	14	58	NS
CV	24	86	21	88	NS
HFOV	4	14	3	13	NS
ECMO	6	21	10	42	NS
Inotropes	***20***	***71***	***24***	***100***	***0.005***
Fluid Overload	26	93	23	96	NS
Diuretics	24	86	23	96	NS
KDIGO 2	9	32	8	33	NS
KDIGO 3	19	68	16	67	
Hyponatraemia	13	46	14	58	NS
Hyperkalaemia	17	61	17	71	NS
Metabolic acidosis	***19***	***68***	***23***	***96***	***0.010***
Hyperammonaemia	1	4	1	4	NS
PD alone	6	21	7	29	NS
CKRT (including those who switched)	22	79	17	71	NS
PD to CKRT	2	25	2	22	NS

Table 5. Comparison of the under 5 kg and the 5 – 10 kg groups

	<5 kg (n = 15)		>5 kg-10 kg (n = 11)		
n = 26	#	%	#	%	*p*
Male	***6***	***40***	***9***	***82***	***0.05***
Female	***9***	***60***	***2***	***18***	
Gauteng	12	80	11	100	NS
Other	3	20	0	0	
Referred from an academic hospital	5	33	8	73	NS
Referred from a community hospital	10	67	3	27	
PICU	12	80	11	100	NS
NICU	3	20	0	0	
HIV Positive	1	7	0	0	
CARDIAC	9	60	6	55	NS
Other	6	40	5	45	
CV	13	87	10	91	NS
HFOV	2	13	1	9	
ECMO	7	47	5	45	NS
Inotropes	14	93	10	91	NS
Fluid Overload	15	100	10	91	NS
Diuretics	15	100	10	91	NS
KDIGO 2	4	27	7	64	NS
KDIGO 3	11	73	4	36	
Hyponatraemia	11	73	5	45	NS
Hyperkalaemia	10	67	8	73	NS
Metacidosis	11	73	10	91	NS
Hyperammonaemia	1	7	0	0	NS
PD alone	7	47	4	36	NS
CKRT	8	53	7	64	
PD to CKRT (out of 10 starting PD)	3	30	1	20	NS
AKI Recovery	6/6	100	4/4	100	NS
Died while on KRT	9	60	7	64	NS

Table 6. Comparison of the under 10 kg vs >= 10 kg groups

	<10 kg (n = 26)		>=10 kg (n = 26)		
n = 52	#	%	#	%	*p*
Male	15	58	17	65	NS
Female	11	42	9	35	
Gauteng	23	88	19	73	NS
Other	3	12	7	27	
Referred from an academic hospital	13	50	8	31	NS
Referred from a community hospital	13	50	18	69	
PICU	22	85	26	100	NS
NICU	4	15	0	0	
HIV Positive	1	4	1	4	NS
CARDIAC	***15***	***58***	***4***	***15***	***0.003***
Other	11	8	22	85	
CV	23	88	22	85	NS
HFOV	3	12	4	15	
ECMO	***12***	***46***	***4***	***15***	***0.03***
Inotropes	24	92	20	77	NS
Fluid Overload	25	96	24	92	NS
Diuretics	25	96	22	85	NS
KDIGO 2	11	42	6	23	NS
KDIGO 3	15	58	20	77	
Hyponatraemia	16	62	13	50	NS
Hyperkalaemia	18	69	16	62	NS
Metabolic acidosis	21	81	21	81	NS
Hyperammonaemia	1	4	1	4	NS
PD alone	***11***	***42***	***2***	***8***	***0.087***
CKRT	***15***	***58***	***24***	***92***	
PD to CKRT	4	27	0	0	NS
AKI Recovery Y	10/10	100	16/18	89	NS
Died while on KRT	***16***	***62***	***8***	***31***	***0.026***

Table 7. Comparison of the post-op cardiac survivors and non-survivors

	Survivors (n = 9)		Deaths (n = 10)		
n = 19	#	%	#	%	*p*
Male	6	67	2	20	NS
Female	3	33	8	80	
Weight < 10 kg	7	78	8	80	NS
Weight > =10 kg	2	22	2	20	
Gauteng	9	100	8	80	NS
Other	0	0	2	20	
Referred from an academic hospital	8	89	5	50	NS
Referred from a community hospital	1	11	5	50	
PICU	9	100	10	100	NS
NICU	0	0	0	0	
HIV Positive	0	0	0	0	NS
Cardiac bypass Y	*7*	*78*	*9*	*90*	NS
CV	8	89	9	90	NS
HFOV	1	11	1	10	NS
ECMO	3	33	4	40	NS
Inotropes	8	89	10	100	NS
Fluid Overload	9	100	10	100	NS
Diuretics	9	100	10	100	NS
KDIGO 2	6	67	4	40	NS
KDIGO 3	3	33	6	60	NS
Hyponatraemia	5	56	7	70	NS
Hyperkalaemia	6	67	7	70	NS
Metacidosis	6	67	10	100	NS
Hyperammonaemia	0	0	0	0	NS
PD alone	5	56	4	40	NS
CKRT	6	67	7	70	NS
PD to CKRT	1	20	1	25	NS

Table 8. Effect of the different modes of therapy on mortality

	Survivors (n = 28)		Deaths (n = 24)			
n = 52	#	%	#	%	Total	*p*
CV	24	53	21	47	45	NS
HFOV	4	57	3	43	7	
Post op cardiac	9	47	10	53	19	NS
Other	14	42	19	58	33	
PD alone	6	46	7	54	13	NS
CKRT	22	56	17	44	39	
PD alone < 10 kg	4	50	4	50	8	NS
PD alone > 10 kg	2	40	3	60	5	
CKRT < 10 kg	***5***	***33***	***10***	***67***	***15***	***0.05***
CKRT > 10 kg	***17***	***71***	***7***	***29***	***24***	
PD alone < 10 kg	4	50	4	50	8	NS
CKRT < 10 kg	5	33	10	67	15	
PD alone > 10 kg	2	40	3	60	5	NS
CKRT > 10 kg	17	71	7	29	24	
ECMO	6	38	10	63	16	NS
Group excluding ECMO	22	61	14	39	36	
ECMO < 10 kg	4	33	8	67	12	NS
ECMO > 10 kg	2	50	2	50	4	
ECMO < 10 kg	4	33	8	67	12	NS
Group < 10 kg no ECMO	6	43	8	57	14	
ECMO > 10 kg	2	50	2	50	4	NS
Group > 10 kg no ECMO	16	73	6	27	22	

4 Discussion

Nelson Mandela Children's Hospital in Johannesburg is a tertiary care hospital in sub-Saharan Africa which opened in December 2016. Although there is growing evidence that the incidence and prevalence of paediatric AKI are steadily increasing (27), only a few centres are able to provide acute KRT in Gauteng. In this study, we aimed to describe the demographic characteristics and outcomes of a cohort of patients treated for AKI at NMCH between January 2018 and January 2023.

The size of the cohort was much smaller than that of two similar larger studies, reported from centres with similar resources to ours, in the region. McCulloch *et al.* reviewed the data of 593 children with AKI requiring KRT at the Red Cross War Memorial Hospital in Cape Town over a 20-year period (85), and a similar study conducted in South Sudan over a 7-year period included 455 children with AKI who required KRT. (73) In explaining our much lower annual CKRT numbers compared to these two studies, it is important to note that while the two large studies referred to above were carried out in well-established paediatric hospitals offering a full range of sub-speciality services, NMCH does not yet have a paediatric oncology unit, burns unit, or orthopaedic service, and also does not have an emergency department, all of which would have contributed to the large numbers of patients reported in the two studies above. (73, 85)

While the vast majority of the patients in this AKI cohort were from the Gauteng Province, reflecting the referral base of our ICUs, it is worth noting that the majority of the 20 patients diagnosed with CKD at the time of KRT (and therefore excluded from the study) came from the Limpopo province.

Most of the patients were referred to our PICU/NICU complex from a community or a district hospital rather than an academic or tertiary institution. We speculate that this might have been because the other tertiary institutions in our area also have paediatric and neonatal ICUs that are able to provide an acute KRT service, and so they would not refer a patient to NMCH unless they either did not have a bed for the child, or the child needed urgent ECMO or cardiothoracic surgery. In the public health sector in Johannesburg, these services are only offered at NMCH.

The majority of the cohort were treated in the PICU rather than the NICU. One reason for this is that, at NMCH, post-cardiac surgery neonates who require ECMO are transferred to the PICU, where nursing and medical staff are experienced in caring for patients receiving ECMO and CKRT. A second reason for this is that NMCH does not have dedicated neonatal KRT machines, such as the CARPEDIEM™ and, as a result, in cases where PD is unable to be performed, such as cases of perforated necrotising enterocolitis (NEC) or recent abdominal surgery, these neonates do not survive if they do not respond to the conservative management of AKI.

The most common primary diagnosis was post-operative cardiac surgery. While this is in keeping with studies on the causes of AKI from both Cape Town and other high-income countries (85) (86), it is not the same as the more common causes of severe AKI reported from low-income countries, such as gastroenteritis and infection-related causes like sepsis and malaria. (73, 86, 87) In high-income countries, the literature indicates that post-cardiac surgery is a significant cause of severe AKI. (86) Yuan *et al.* highlight that AKI complicates the post-operative course in a substantial proportion of paediatric cardiac surgery patients, with a marked increase in morbidity and mortality. (86) This finding has been demonstrated in other studies as well, where there is a suggestion that post-cardiac surgery is indeed a major factor leading to severe AKI and the potential need for KRT in children. (88)

Only four percent of the patients were HIV-positive. The HIV-infected children did not have a higher mortality rate than the HIV-negative patients which may have been due to the small numbers of the cohort. This finding is consistent with the findings of Keeling *et al.,* who found no difference in mortality between HIV-infected and HIV-negative children in the ICU setting at an academic hospital in Soweto. (89) While we did not assess the overall HIV infection rate in the NICU and PICU at NMCH, there has been a well-documented decline in the rate of HIV infections and AIDS mortality of children in South Africa since the introduction of effective anti-retroviral therapy. (89, 90)

The mean age of the cohort was 29 months, and almost half of the cohort was younger than a year of age, with more than half of the children younger than 12 months being under the age of six months. This is comparable to the two studies from the sub-Saharan region referred to above. (73, 85) In the Sudanese study, the majority of the patients were neonates, while the

cohort from Cape Town had a median age of 8 months, and just over half of the study population was less than one year of age. (73, 85) Also, in keeping with our findings, Alobaidi *et al.* found that the incidence of severe AKI was greater in children younger than one year of age, suggesting that a significant portion of severe AKI occurs in this age group (91)

The mean weight of the cohort was 12 kg, with 50 % of the cohort weighing less than 10 kg and 29 % of the cohort weighing less than five kilograms. In the Cape Town cohort, the median weight was seven kilograms, with around 62 % weighing less than 10 kg and 38 % weighing less than five kilograms, while the paper from Sudan only reported on age and not on weight. (73, 85)

At the time of connection to CKRT, CV was the mode of ventilation used in the majority of patients and ECMO was used in 31% of the cohort. CKRT, used alongside ECMO, is increasingly being used to manage AKI and the fluid overload that occurs in these critically ill patients (27). The high rate of ECMO use in our cohort highlights the level of illness in the ICUs. Neither the paper from Cape Town nor Sudan reported their mode of ventilation at the time of commencement of KRT. (73, 85)

The majority of the cohort had signs of fluid overload despite the use of diuretic therapy. This finding is consistent with other studies that have shown that severe AKI will often present with substantial fluid overload. (78, 92) In these cases, CKRT is the preferred mode of therapy, resulting in better fluid removal control in patients with haemodynamic instability. (78)

PD was used as the first mode of dialysis in 33 % of the cohort, and of these patients, 24 % had to be switched to CKRT due to failed PD or a blocked or migrated PD catheter. In the study by McCulloch *et al.*, 78.1 % received PD first, but while their overall PD complication rate was similar to ours at 22.7 %, they had to switch to another mode of dialysis in only around three percent of their PD cases. (85) In the cohort from Sudan, conservative therapy was used in around 28 %, PD in 52 %, IHD in 14 %, and a combination of PD and HD in three percent. (73) In their cohort, only five percent of the patients who originally started on PD had to switch to IHD. (73)

In our cohort, CKRT was used in 75 % of the cohort, and none of the patients were treated with intermittent haemodialysis (IHD). All children under 10kg who were not on ECMO were

treated with PD first, while all those under 10kg who were on ECMO were treated with CKRT first as the venous access was easy off the ECMO circuit.

In the Cape Town study, data on the mode used was available for 115 of the 130 children who received extracorporeal dialysis. (85) Of these 115 patients, CKRT was used in around 36 %, CARPEDIEM™ CKRT was used in 7 %, CKRT and HD was used in around 24 %, and HD alone was used in 22 %. (85)

While CKRT may be preferred for patients with haemodynamic instability, the literature does not unequivocally support the support superiority of one modality or the other regarding mortality or kidney recovery outcomes in the paediatric population. (93) In some instances, like TLS and hyperkalemia, IHD is preferred due to efficiency in the clearance in such cases or instances. (61, 94) Only one patient had TLS in our cohort, and the patient died before they could be transferred to an oncology centre.

The overall mortality rate of our cohort was 46 %. This high value was most likely due to the critically ill and complex nature of our cohort. Children who weighed less than 10 kg made up 50 % of the cohort, but the deaths from this weight category made up 67 % of the total number of deaths. The mortality rate for children weighing less than 10 kg was significantly greater (62%) than the mortality rate of those who weighed more than 10 kg (31%), but there was no difference in mortality between those who weighed less than five kilograms and those who weighed between five and 10 kg. The study from Cape Town also noted higher mortality in neonates and infants under 1 year of age compared to older children and also in children weighing less than 10 kg. (85) Although the study from Sudan did not comment on the weights of their patients, almost 63 % of the deaths were in children under a year of age. (73) In a first-world setting, Askenazi *et al.* evaluated 84 children under 10 kg with AKI requiring KRT and compared them to their counterparts who weighed > 10kg. (83) The mortality rate in the under 10 kg group was significantly higher (57%) than that of the group who weighed 10 kg or more (36%). (83)

There was no difference in mortality between children who received PD alone and those who did not. In addition, in our cohort of children who weighed less than 10 kg, there was also no statistical difference in mortality between those treated with PD versus those treated with CKRT (*p* .44). We are not aware of any study that has randomised paediatric patients with

severe AKI to mode of dialysis and then analysed their outcomes. Most studies have identified the need for KRT in general as an independent risk factor for mortality in critically ill children. (95)

There was also no difference in mortality between the post-operative cardiac surgery cases and the non-cardiac surgery patients. Although patients on ECMO made up 21 % of the survivors and 42 % of the patients who died, this difference was not statistically significant (p .11). Despite this, it is important to note that ECMO is a risk factor for developing severe AKI associated with a high mortality rate. (96)

ECMO provides temporary cardiorespiratory support when conventional treatment fails, while CKRT addresses acute kidney injury and fluid overload (FO) in the haemodynamically unstable patient. (97) In our institution, ECMO is associated with a high rate of AKI and fluid overload, but not all patients on ECMO required CKRT. Our study did not assess the different ECMO modalities, namely venovenous ECMO vs. veno-arterial ECMO, or the outcome of AKI in the various ECMO modes. However, studies have demonstrated more unfavourable outcomes with veno-arterial ECMO than venovenous ECMO. (98) This is more likely related to the underlying primary disease, as veno-arterial ECMO is more commonly used in cardiac conditions than venovenous ECMO, which is more widely used in primary lung pathology and has fewer kidney perfusion-related issues. (99)

Although there was no difference noted in the risk of mortality while on CKRT for the whole cohort, there was a statistically significant increased risk of mortality while on CKRT for the cohort of children who weighed less than 10 kg compared to those who weighed 10 kg and above. This was consistent with the findings from the Prospective Paediatric Renal Replacement Therapy (ppCRRT) registry, which has noted that their subset with a weight of less than 10 kg had a lower survival rate (43%) when compared to children who weighed more than > 10 kg (64%). (100) Additionally, the registry highlighted that CKRT circuit characteristics differ for patients who weigh less than five kilograms compared to those who weigh between five and 10 kg, with the former group more commonly needing blood priming and higher blood flow rates relative to body weight than the children weighing between five and 10 kg. (100)

Because NMCH did not have a paediatric-specific CKRT machine, we used adult machines with paediatric-adapted circuits. These machines are not specifically designed for the unique physiology and size of neonates and small infants. Studies comparing adult-adapted platforms with paediatric-specific machines such as the CARPEDIEM™ suggest that they may offer improved survival rates and less use of blood products for priming the circuits. (101)

In our cohort, the association of a weight of less than 10 kg and mortality highlights the challenges of providing CKRT to small children using adapted conventional machines and emphasises the need for dedicated infant machines like the CARPEDIEM™ for those patients whom PD fails or is contraindicated.

Fifty-four percent of the cohort survived to discharge from the ICU. Of these, 93 % had complete recovery of kidney function, while two (7 %) had to go to our chronic KRT program. McCulloch *et al.* reported that just under one percent of their cohort went on to develop chronic kidney disease, and the study from Sudan reported that just under six percent of their cohort developed CKD. (73, 85) It is interesting to note that the two patients who progressed to our chronic kidney disease program had kidney-related primary diagnoses *viz* HUS and Lupus nephritis. However, even though it appears the recovery of paediatric AKI appears to be good, long-term follow-up of these patients is recommended as it is known that survivors of paediatric AKI are prone to "second hits" and progression to CKD.(102)

4.1 Summary

Nelson Mandela Children's Hospital (NMCH) in Johannesburg is a tertiary care hospital in sub-Saharan Africa which opened in December 2016 and is one of only a few centres capable of providing an acute paediatric KRT service in Gauteng. In this study, we aimed to describe the demographic characteristics and outcomes of a cohort of patients treated for AKI at NMCH between January 2018 and January 2023.

The most common primary diagnosis was post-operative cardiac surgery, and almost half of the cohort were less than a year of age and weighed less than 10kg. Almost a third of the cohort were also on ECMO, and most of the cohort had features of fluid overload despite the use of diuretic therapy prior to starting CKRT,

Of importance, there was a significantly increased risk of mortality while on CKRT for the cohort of children who weighed less than 10 kg compared to those who weighed 10 kg and above. We speculate that this may have been because, at NMCH, non-paediatric CKRT machines are used rather than paediatric-specific platforms such as the CARPEDIEM®.

Of the survivors, the vast majority had a complete recovery of their kidney function, with only seven percent needing to go onto our chronic KRT program.

4.2 The strengths and limitations of the study

4.2.1 Strengths

Significant Regional Contribution: Despite its relatively small size, to the best of our knowledge, this study represents the third largest review of paediatric acute kidney injury (AKI) requiring kidney replacement therapy (KRT) on the African continent. This positions the study as a significant contribution, providing crucial insights into the management of the paediatric AKI landscape within this regional context.

Diverse Pathology: The study encompasses a wide diversity of pathologies that span conditions commonly found in both high-income and low-income countries. This breadth of data ensures that the findings are representative and applicable across different healthcare settings, thereby enhancing the study's relevance and utility in global paediatric AKI discussions.

Focus on Cardiothoracic Cases: With a high representation of cardiothoracic cases, the study offers detailed and specific insights into the outcomes of post-cardiac surgery patients at NMCH. This focus is particularly valuable as it provides a deep dive into the complexities and challenges of managing AKI in this vulnerable group, offering a clear picture of the procedural impacts and recovery trajectories specific to this demographic.

Insight into CKRT in a State-Funded Setting: As one of the few centres in South Africa providing CKRT in a state-funded setting, the study sheds light on the capabilities and high level of care possible in a resource-limited country. This aspect of the study highlights the skills and dedication of the medical team and provides valuable benchmarks and insights for other

state hospitals aiming to implement or improve their AKI management protocols in their paediatric patients.

4.2.2 Limitations

The study has several limitations that should be noted and considered when interpreting the results. While the accuracy of the data collected by the primary investigator was repeatedly checked and verified, because of the retrospective nature of the data, it is possible that errors in the capture of the original data set may have crept in. In addition, the short study period did not allow for a full analysis of the long-term kidney outcome of the cohort, and the relatively small size of the cohort may have a negative impact on the generalizability of our findings to similar cohorts. Also, the fact that NMCH is a tertiary-quaternary referral centre with a large cardiac surgery service implies that the spectrum of disease seen at NMCH is unlikely to be reflective of the range of pathology, or even the disease severity, that might more typically be seen at other state-funded centres across the country.

5 Conclusions and recommendations

We feel that this study provides novel insight into our local data and underscores the critical role of acute KRT in the management of paediatric patients with severe AKI in the ICU setting in the state-funded service in South Africa. The high prevalence of severe AKI at the initiation of CKRT and the need for intensive supportive measures like ECMO reflect the complexity of the nature of patients looked after at NMCH and also reflects the systemic impact of AKI in this population.

CKRT emerged as the predominant mode modality in our population, while PD, though initially used in a third of the cases, presented challenges in our subset. This may reflect the need for further training of our staff using programs like Saving Young Lives, where critical care staff and nephrology staff are trained to insert, commence, and troubleshoot PD in the context of AKI.

As much as it was a small study, the overall recovery rate of AKI is encouraging. However, it should be remembered that AKI survivors are still at risk of a "second hit" and progression to CKD, and so ongoing close follow-up is required for these patients.

Our mortality rate is in keeping with other centres, but the under 10 kg mortality rate is concerning and unacceptably high. This fact, combined with other significant factors like the need for inotropic support and metabolic acidosis, could be used to guide clinicians in risk stratification and in devising guidelines on early consultation and intervention for "at-risk" patients.

Our high mortality, particularly in the under 10 kg group, highlights the need for dedicated paediatric machines like CARPEDIEM™ for this subset of patients or the need for better PD care for the non-ECMO patients that are small, especially < 10kg.

We hope that our data will provide a baseline for future studies in the field of critical care nephrology, especially in the resource-limited setting. Future research should focus on including all patients with AKI, and not only the subset that require KRT, to enhance the generalisability of the results and widen the number of participants for proper assessment of practice and outcomes.

Based on the above data, we hope to investigate and create standardised protocols for AKI and KRT initiation and modality of choice, particularly to improve our PD care and practice. Additionally, long-term follow-up studies are needed to understand the trajectory of the AKI survivors and the impact of early interventions on CKD development in paediatric AKI survivors.

Finally, exploring new therapies and the acquisition of a dedicated paediatric machine could potentially improve our management of severe AKI in critically ill children.

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7. Appendices

Appendix 1: The final study protocol

Research Protocol

Acute Kidney Replacement Therapy in children with Acute Kidney Injury at Nelson Mandela Children Hospital: a single centre experience.

Master of Medicine (MMed) Research Proposal

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Table of Contents

Abbreviations

AKI	Acute kidney injury
APD	Automated peritoneal dialysis
CKD	Chronic kidney disease
CKRT	Continuous kidney replacement therapy
CPD	Continuous manual peritoneal dialysis
CVVH	Continuous veno-venous haemofiltration
CVVHD	Continuous veno-venous haemodialysis
CVVHDF	Continuous veno-venous haemodiafiltration
ECMO	Extracorporeal membrane oxygenation
ESKD	End-stage Kidney failure
GFR	Glomerular filtration rate
HD	Haemodialysis
ICU	Intensive Care unit
IHD	Intermittent haemodialysis
NICU	Neonatal intensive care unit
PD	Peritoneal dialysis
PICU	Paediatric intensive care unit

Introduction

Nelson Mandela Children's Hospital (NMCH) is a paediatric tertiary centre that cares for critically ill children at high risk for acute kidney injury (AKI). The critical care units at NMCH offer different modes of acute kidney replacement therapy (KRT), ranging from intermittent haemodialysis (HD) and peritoneal dialysis (PD) to continuous kidney replacement therapy (CKRT). However, since the hospital's inception in 2018, no study has examined the incidence, epidemiology, and outcome of patients with severe AKI who have required acute KRT. Having this data available would enable us to evaluate our practice, develop quality improvement projects, and initiate protocol-based therapy, to improve our outcomes going forward.

Background

Acute kidney injury (AKI) is defined as a sudden deterioration of renal function. It is recognised when there is a reduction in urine output and an increase in serum creatinine as a result of a reduced glomerular filtrate rate (GFR). (1-3) AKI is a common yet under-recognised syndrome. (1) According to adult North American data, it affects up to 1.2 million in-patients per year.

Historically, there has been a wide variation of what constitutes AKI in children. (1,2) This has made it difficult to compare results across studies and validate new concepts such as biomarkers. It has also hampered progress in the understanding of the syndrome of AKI. (1) Therefore, it is essential to have a universally accepted definition of what constitutes AKI and to recognise AKI in a consistent and familiar manner. (4-6)

There have been various attempts to do this over the years, and the formulation of the RIFLE criteria (Risk, Injury, Failure, Loss, and End-stage Kidney), as developed by the Acute Quality Dialysis Initiative, was the first consensus definition to be proposed. RIFLE was subsequently modified to the paediatric RIFLE for use in children, and this focused on changes in the GFR rather than just serum creatine alone. (7, 8) The Kidney Disease Improving Global Outcomes (KDIGO) took this forward, amending the definition by focussing on both changes in serum creatinine and urine output, and by allocating specific upper limit reference ranges to those children for whom prior blood results were not available. (2, 7, 8) The different stages are listed in table 1 below.

Table 1: Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline OR >26.5 umol/L increase	<0.5 ml/kg/hr for > 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/hr for> 12 hours
3	3.0 times baseline OR Increase in serum creatinine to >353 umol/L OR Initiation of kidney replacement therapy OR In patients < 18 years, decrease of eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/hr for >24hours OR Anuric for> 12hrs

Ongoing challenges with the diagnosis of AKI in children relate to the use of creatinine as a biomarker. (9) Serum creatinine is an old marker that is affected by gender, age, muscle mass, and metabolic processes. (2,9) In addition, creatinine levels only increase once 25-50% of renal function has already been affected, thus decreasing its usefulness as a biomarker in AKI. (2, 9-11)

In paediatrics, there is limited data on the incidence of AKI across the world, but one of the few benchmark studies that have been carried out, the AWARE study (Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology), found that the incidence of AKI in critically ill children was as high as 27%.

A recent local study focusing on neonatal AKI found that the mortality rate was as high as 29% in a cohort of critically ill neonates. (21) To the best of our knowledge there is no other local data on the outcome of AKI in critically ill patients in the PICU.

In terms of the causes of AKI in children, there is wide variation depending on the geographic and socio-economic setting. (6,12) However, the most common causes include septic shock, cardiovascular disease, respiratory disease, malaria, and surgical and trauma-related injuries. (6) Recently, AKI has also been documented in viral infections such as the coronavirus disease 2019 (COVID-19). (3, 13, 14)

Kidney Replacement Therapy is indicated in the severe forms of AKI in an attempt to restore homeostasis through the removal of fluid and toxins, to restore acid-base

balance, and/or to correct electrolyte abnormalities.(15, 16) However, performing KRT can be a challenge in resource-limited countries like South Africa, where there is a shortage of paediatric nephrologists and where very few centres will have the trained personnel and technology to offer KRT. (16, 17)

Children admitted to the ICU setting who develop AKI have been shown to have poorer outcomes than those who do not. (18) Of those who develop AKI, those who go on to have KRT will have even poorer outcomes. (17, 18) The mode of dialysis selected for these children seems to be resource-dependent, with the more resource-rich areas being able to offer CKRT to even neonates, while most centres in developing countries will only able to provide PD, if anything, at all, for KRT in AKI. (19) The "0 by 25" AKI initiative aims to prevent all avoidable deaths from AKI worldwide by 2025.The prevention of fluid overload is associated with improved outcomes, and this suggests that early institution of dialysis can save lives. (17-19)

Purpose of the study

Problem statement

Data on paediatric AKI is lacking, and although NMCH can provide KRT for the treatment of AKI, the epidemiology and outcomes of severe AKI requiring kidney replacement has not been established in our institution.

Aims

To describe the epidemiology of children with severe AKI at NMCH, and to describe their management in terms of the KRT mode used and their outcomes.

To use this information to make suggestions for future management of these patients going forward.

Objectives

1. To describe the demographic data of all patients who developed AKI and received KRT at NMCH in the study period
2. To describe the primary diagnosis of this cohort
3. To describe the mode of KRT used
4. To describe the rate of mode switch while on KRT
5. To describe the outcome of these patients in terms of their mortality, recovery, and progression to chronic kidney disease or to end-stage kidney disease

Definitions:

1. AKI - AKI as defined using the KDIGO guidelines
2. KRT – Kidney replacement therapy using either Automated Peritoneal Dialysis (APD), Continuous Manual Peritoneal Dialysis (CPD), Continuous Veno-Venous Haemodialysis (CVVHD), Continuous Veno-Venous Haemofiltration (CVVH), or Continuous Veno-Venous Haemodiafiltration (CVVHDF).
3. Mode switch – needing to switch from one mode to another due to mode failure
4. eGFR – Estimated Glomerular Filtration Rate using the Modified Schwartz Formula (2009) = 36.5 X Ht (cm) / Serum Creatinine (umol/L). (20)

Methodology

Study design

This will be a retrospective descriptive review of the records of the patients who underwent acute kidney replacement therapy at Nelson Mandela Children's Hospital.

Site of study

Nelson Mandela Children's Hospital Neonatal and Paediatric Intensive Care Units (NICU and PICU, respectively)

Population

Inclusion criteria

All patients admitted to NMCH PICU and NICU who were diagnosed with AKI and who received KRT between January 2018 and January 2023.

Exclusion criteria

1. Patients who were assessed to have established chronic kidney disease (CKD) at their initial acute presentation
2. Patients with AKI who did not receive KRT

Data Collection

Data will be manually collected from the files and the unit's computerised databases of children who received kidney replacement therapy. These files are kept in the Nephrology Unit of NMCH, and the data will be entered directly into a password-protected REDCap® database. (Appendix A).

Data Management and Statistics Analysis

Data will be stored in a password-protected REDCap® database. For statistical analysis, STATA® will be used, and a statistician will be consulted for advice on the statistical testing.

A value of $p < 0.05$ will be considered significant. Categorical data will be described using percentages, graphs, and tables. Continuous data will be tested for skewness and then described using means and standard deviations for normally distributed data, and medians and interquartile ranges for skewed data.

Ethical clearance

The study will be conducted in full conformance with the principles of the Declaration of Helsinki, Good Clinical Practice and within the laws and regulations of South Africa. The interests of the patients will be safeguarded, and their anonymity guaranteed. Data will be collected from the patient files and entered into a password protected REDCap® database. Patient confidentiality will be maintained throughout; no identifying details will be included in the database.

Permission for the study will be obtained from the Chief Executive Officer of NMCH, the heads of the PICU, NICU, and Renal Unit, and the Research and Ethics Committee of NMCH.

Ethical approval for this study will also be obtained from the Human Research Ethics Committee (Medical) and the Postgraduate Committee of the University of KwaZulu-Natal before the commencement of the study.

Funding

The study will be self-funded. The only expected cost will be that of printing and binding for submission.

Strengths and limitations

The strength of the study is that it will establish a data baseline that will be useful when conducting further studies and which will allow for reference and comparison with similar units nationwide and internationally.

The study's main limitation is the relatively short study period (NMCH has only been operating since 2018), which will limit the size of the population studied, reducing the number of groups on which we will be able to perform statistical analysis.

Another potential form of bias is that the NMCH PICU is a tertiary-quaternary care referral center and mainly provides care to critically ill children requiring cardiac surgery or ECMO. For this reason, the spectrum of disease seen at NMCH is unlikely to reflect the range of pathology, or even the disease severity, that might more typically be seen at the other academic tertiary centers across the country.

In addition, as this is a retrospective study, we will rely on clinical notes and data filed in the databases of the various units, some of which may not be completely or correctly recorded.

Time plan and study logistics

Year	2022		2023									
Month	Nov	Dec	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct
Literature review												
Preparing protocol												
Ethics application												
Protocol assessment												
Collecting data												
Data analysis												
Writing and submission												

References

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Appendix 2 Ethics approval letter

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

11 July 2023

Dr Gabriel Lindokuhle Mahlase (211560694)
School of Clinical Medicine
Medical School

Dear Dr Mahlase,

Protocol reference number: BREC/00005680/2023
Project title: Acute Kidney Replacement Therapy in children with Acute Kidney Injury at Nelson Mandela Children Hospital: a single centre experience
Degree: MMed

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 11 July 2023. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 11 July 2023. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on RIG on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 08 August 2023.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

INSPIRING GREATNESS

Appendix 3 Data Collection Tool

Demographic information

Patient number	_____
Basic demographics	
Date of birth	_____
Age at the time of consult	_____
Gender	◯ Male ◯ Female ◯ Unidentified
Province of residence	◯ Eastern Cape ◯ Free State ◯ Gauteng ◯ KwaZulu-Natal ◯ Limpopo ◯ Mpumalanga ◯ Northern Cape ◯ North West
Referring hospital	_____
Referral unit at NMCH	◯ PICU ◯ NICU
Clinic data	
Weight in kg	_____
Height in cm	_____
Primary diagnosis	_____
Secondary diagnosis	_____
HIV status	◯ Negative ◯ Positive ◯ Unknown
Inotropes at the time of consult	◯ Yes ◯ No
Oliguria at the time of consult	◯ Yes ◯ No

Diuretics at the time of consult	◯ Yes ◯ No
Clinical Fluid Overload at the time of consult	◯ Yes ◯ No
Ventilation mode	◯ CV ◯ HFOV
ECMO	◯ Yes ◯ No
Hyperkalaemia at the time of consult (K> 5.1 mmol/L)	◯ Yes ◯ No
Hyponatraemia at the time of consult (Na< 135 mmol/L)	◯ Yes ◯ No
Metabolic acidosis at the time of consult (Bicarbonate < 23 mmol/L)	◯ Yes ◯ No
Hyperammonaemia at the time of consult (above the upper limit for age)	◯ Yes ◯ No
Serum creatinine at the time of consult(umol/L)	_____
eGFR at the time of consult (ml/min/1.73m2)	_____
AKI KDIGO Classification at the time of consult	◯ 1 ◯ 2 ◯ 3
Mode of dialysis	☐ APD ☐ CPD ☐ CKRT
PD switch to CKRT	◯ Yes ◯ No

Outcomes

Death	◯ Yes ◯ No
AKI recovery	◯ Yes ◯ No
CKD program (as defined by the failure of kidney function recovery and/or need for chronic kidney replacement therapy beyond 3 months from the time of initial consult)	◯ Yes ◯ No

Appendix 4 Consent to use Figure 1

Nelson Mandela Children's Hospital
A family dedicated to care

CARE:2036140 PMI:1031931Dr. Matbivha, Khathu (0814358) [illegible]
Nelson Mandela Children's Hospital
Mst. PRINCE NDLOVU
D:27.12.2023 GENDER:M AGE:014(Y)
NHC

MEDICAL AID:	NATIONAL HEALTH INSURANCE PH1	TEL (W):
MEDICAL AID #:	041026	TEL (H): 0742509994 – 8
MAIN MEMBER:	Miss CATHRINE NDLOVU	[illegible]
MEMBER ID#:	28.10.2004	ROODEPOORT
DEPENDANT:	01	ROODEPOORT
AUTHORISATION #:	2936140	1725

0747446945 (JULIET - GRAN)

SECTION B - PHYSICIAN, SURGEON AND HEALTH CARE PRACTITIONER'S STATEMENT

I certify that I have explained the nature of this treatment, its associated risks, benefits and the possible alternatives, including the likely consequences of not having the treatment, to the patient's guardian, or both.

Name of Physician, Surgeon or Health Care Provider (HCP)	DR. K. NAIDOO	Date	22/01/24
Signature of Physician, Surgeon or HCP	[redacted]	Time	13 h 20

Summary of complications discussed:
* RE-OPERATION
* BLEEDING
* INFECTION
* DEATH
* OPEN CHEST
* EXTRA-CORPOREAL LIFE SUPPORT

If consent is obtained via interpreter, please complete this section

Name of Interpreter		Signed	
Language (s) used to obtain consent			

SECTION C - TELEPHONIC CONSENT

I have discussed the treatment (s) and associated benefits and risks on the telephone with the (tick one) ________ the patient / ________ **patient guardian** who has given verbal authorisation for the treatment.

Name of Physician/ Surgeon/ HCP		Date	
Signature		Time	h
Witnessed by		Date	
Signature		Time	h

SECTION D - ANAESTHESIOLOGIST

I confirm that I understand that I / my child will receive sedation / general / regional anaesthesia for this procedure.
I have received the information sheet about anaesthesia and have had any questions answered to my satisfaction.

Where applicable: I understand the methods to be used for pain relief / the need for special monitoring / the need for ICU after the procedure (for example, cardiac or major surgery).

Name	Signature	Date	

Statement by the Anaesthetist: I confirm that I have explained the type of anaesthetic, if any, required for this procedure. In addition, I have discussed the following:

Name of Anaesthesiologist		Date	
Signature		Time	h

SECTION E - BLOOD TRANSFUSION / MANUFACTURED BLOOD PRODUCTS

I have discussed the possible need for transfusion of blood products with the (tick) ________ the patient / ✓ ________ patient guardian and the expected benefits, risks, side effects, alternative(s) and the likely consequences of not having a transfusion if it becomes necessary during treatment. Please tick one

☑ **Agreement to transfusion has been given** ☐ **Agreement to transfusion has NOT been given**

Name of the Physician/ Surgeon/ HCP	DR. K. NAIDOO [redacted]	Date	22/01/24
Signature	[redacted]	Time	13 h 20

Nelson Mandela **Children's** Hospital
A family dedicated to care

CASE:2936140 PMI:10315310r. Methivha, Khaibu	(3914350) 30.01.2024 14:22
IDA:	
Mst. PRINCE NDLOVU	Nelson Mandela Children's Hospital PR:0703087/02070 Tel: +27 10 101 0005 Fax
ID:27.12.2023 GENDER:M AGE:014(D)	MHC
MEDICAL AID: NATIONAL HEALTH INSURANCE PH1	TEL (M):
MEDICAL AID #: 041026	TEL (H): 0742009004 – B
MAIN MEMBER: Miss CATHRINE NDLOVU	720 DURBAN DEEP
MEMBER ID#: 26.10.2004	ROODEPOORT
DEPENDANT: 01	ROODEPOORT
AUTHORISATION #: 2936140	1709

Patients and their families
If you want help reading this form, or have questions, please ask your docotor or nurse. When we use the word treatmen on this form, we mean treatment, test or operation.
Please complete all appropriate sections on page.

CONSENT TO TREATMENT DOCUMENT

SECTION A - PATIENT or GUARDIAN CONSENT

Name of the patient

I agree to the treatment (s) ARTERIAL SWITCH OPERATION & ABDOMINAL
(Treatment - please print)
TENCKHOFF CATHETER INSERTION
(Treatment - please print)

I confirm that DRS. K. NAIDOO / S. BHIKA [redacted]
(Name of doctor or health care practitioner (HCP))
Dr Mahlake (Request to take the picture of the patient)
Has explained why this treatment is necessary and what will happen during the treatment. He / she has explained the chances of the treatment not working and the possible complications that might happen with the treatment.

I also agree to other treatments that may be needed while the doctor is doing this treatment. I understand that my doctor may ask other doctors and fellows to do all or part of this treatment. I understand the information on this form and have had the opportunity to ask the doctor questions about the treatment.

Signature of Patient (If the child ~~is 12 years or older and if competent to~~ sign a consent)		Date	22/1/24
Name of Parent / ~~Guardian~~	> Cathrine Ndlovu	Time	h
Signature of Parent / ~~Guardian~~	> C Ndlovu		
Witnessed by	Name [redacted]		
	Sign [redacted]		

If a child is between six and twelve years old, and is deemed competent to give assent for his / her procedure, he / she should indicate that here:

NMCH-CONSENT TO TREATMENT (V)

FORMAX 011 700 0000