THE INDICATIONS FOR AND TIMING OF HAEMODIALYSIS IN CRITICALLY ILL PATIENTS WITH ACUTE KIDNEY INJURY AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

Johannesburg, 2020.

DECLARATION

<u>Student's contribution to article and agreement of co-authors</u>

I, Patricia Mary Brown, student number 0317431P, declare that this dissertation is my own work and that I contributed adequately towards research findings published in the article stated below which are included in my dissertation report.

Signature of Student ……………………………………….**Date**……………………………

Name of Primary Supervisor: Prof Shahed Omar

Signature of Primary Supervisor…………………………**Date** ……………………………

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his/her Thesis/Dissertation/Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 1: Title: The indications for and timing of haemodialysis in critically ill patients with acute kidney injury in Johannesburg

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LETTER OF CONTRIBUTION

To whom it may concern,

The MMed titled 'The indications for and timing of haemodialysis in critically ill patients with acute kidney injury in Johannesburg, in submissible format (for the Journal of Southern African Critical Care) is primarily my work.

I, Dr Patricia Mary Brown, student number 0317431P, wrote the protocol, collected the data personally without any assistance, and conceived the idea for the study and performed the statistics with assistance from my supervisors, and I wrote the final paper.

Prof Omar and Dr Redford assisted in supervisory roles with my work. They received the protocol and manuscripts and provided guidance in fine tuning the work.

Yours sincerely

Patricia Mary Brown

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DEDICATION

To my Mumples for leading me to believe I can do anything.

To my Dad for affording me the opportunity to do anything.

To my Husband Eric, for his unwavering support.

To my son Jett, for making it all worthwhile.

ACKNOWLEDGMENTS

To my research supervisors Prof Shahed Omar and Dr Lindsey Redford, the completion of this project would have never been possible without your patience, mentorship and support. Thank you immensely.

To Prof Mathiva and the administrative staff of the Chris Hani Baragwanath Academic Hospital's ICU for allowing access to their patient records.

To the doctors and nurses working in ICU who charted the invaluable information captured for this study.

This research was presented at the Congress of Critical Care Society of Southern Africa last year as a poster. As such it was included in a publication of the abstracts of the research presented.

Abstracts of scientific presentations at the 2019 National Annual Congress of the Critical Care Society of Southern Africa in Cape Town, South Africa - Brenda Morrow.

ABSTRACT

Background

Acute kidney injury (AKI) is common amongst patients admitted to the intensive care unit (ICU). It is an independent risk factor for morbidity and mortality. The optimal timing of renal replacement therapy (RRT) remains unknown resulting in a wide variation in observed current practices. There is a paucity of data on current practices within South African ICU's.

Objectives

The aim of this study was to describe current practices in the timing of RRT in patients with AKI admitted to the ICU.

Methods

A retrospective, descriptive study in an adult academic ICU in Soweto from 1st January 2013 to 31 December 2014.

Results

There were 2152 ICU admissions over 2 years. Seventy-six (3.5%) patients required RRT. Sepsis was present in 83%. The most common indication for RRT was oliguria/anuria 38 (50%) followed by worsening urea/creatinine 22 (29%), metabolic acidosis 9 (11.8%), refractory hyperkalaemia 4 (5.3%), fluid overload 2 (2.6%) and other 1 (1.3%). Forty two patients (55%) had RRT instituted on admission day (D_0), while 34 (45%) after D_0 (D_{1-21}). Ninety percent (90%) of D_0 RRT and 94% of D_{1-21} RRT group had KDIGO stage 3 AKI. Once a decision to initiate RRT was made, the median time to starting RRT was 4 hours (IQR 4). The composite outcome of death, RRT dependence and diuretic dependence at ICU discharge was 21% with no difference between the two groups (p=0.22). The ICU mortality was 3%.

Conclusion

The sampled population was young, predominantly male and post emergency surgery with a high burden of sepsis and human immunodeficiency virus. The observed current threshold for RRT was late (stage 3 AKI with classical/emergent indications) with outcomes comparable to literature reviewed.

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ABBREVIATIONS

AKI – Acute Kidney Injury

BUN – Blood Urea Nitrogen

ICU – Intensive Care Unit

IHD – Intermittent Haemodialysis

RRT – Renal Replacement Therapy

S_{Cr} – Serum Creatinine

HIV- Human Immunodeficiency Virus

GFR – Glomerular Filtration Rate

STATEMENT

The Research Report consists of a literature review, draft article, study proposal and appendices. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the rest of the Research Report in order to comply with the author guidelines of the Southern African Journal of Critical Care, the journal to which it is intended to be submitted.

SECTION 1: **REVIEW OF THE LITERATURE**

1.1. Background

Acute kidney injury (AKI) represents a broad spectrum of pathological processes ranging from clinically undetectable changes to severe injury which is associated with either reversible or permanent and complete loss of renal function (1,2). AKI is common amongst patients admitted to the Intensive Care Unit (ICU). Historically, the incidence ranges from 1-70% depending on the classification used to diagnose AKI as well as the dominant demographic of patients within the reporting ICU (1–4). There is evidence that even mild reversible AKI confers significant independent risk for morbidity and mortality (5–12), and contributes to increased healthcare costs (13). Mortality rates quoted range from 15-82% (4,5,12). As a result of the significant burden of disease that AKI confers both in the short and long term there is growing concern for it in health care (14). Long term risks associated with AKI include coronary vascular events, cerebrovascular accidents, chronic kidney disease with dialysis dependency and mortality (15). Despite apparent resolution of AKI, there still exists a risk of mortality (6,7). There is a scarcity of data to quantify the incidence of AKI in South African ICU's, however, due to the burden of disease associated with AKI (human immunodeficiency virus (HIV), diarrheal disease, malaria and nephrotoxins), and delayed presentation of patients to healthcare facilities it is likely to be higher than that of the developed countries (8).

1.2. Defining and classifying AKI

Prior to 2004 there was no clear consensus for the definition and classification of AKI. The range of severity and varied aetiologies resulted in as many as 200 definitions for AKI (16). This resulted in significant clinical confusion with respect to the diagnosis and subsequent management of AKI. Furthermore, data comparison between studies were not feasible (16). Progress in clinical research was hampered prompting the development of clearer definitions and classifications for AKI. In 2004, the Acute Dialysis and Quality Initiative group consisting of experts in nephrology and intensive care, developed the Risk, Injury, Failure, Loss and End Stage (RIFLE) classification to standardise the definition and classification of AKI (12,16). The RIFLE classification takes into consideration changes in serum creatinine values or glomerular filtration rate (GFR) from baseline, in addition to urine output to determine the diagnosis and stage of disease. If the criteria are fulfilled the patient is then classified accordingly in terms of severity as either risk, injury, failure, or clinical outcome as either loss or end stage (17). The RIFLE classification was identified as having shortcomings. The major problem identified was that the classification relies on a baseline serum creatinine which is not always available and thus an estimate is used (12). As a result, the scoring system does not always detect the presence of acute renal impairment. The Acute Kidney Injury Network (AKIN) proposed revised guidelines in an attempt to improve the AKI classification and to increase the sensitivity and reliability. Four main adjustments were applied to the RIFLE criteria including (7,12):

- adding an increase in serum creatinine equal to or greater than 0.3mg/dl to define AKI
- applying a time frame of 48 hours instead of from baseline when considering the rise in creatinine
- if RRT was required to immediately classify as stage three
- Risk, Injury, and Failure have been replaced with stage 1, 2, and 3 respectively and the outcome categories Loss and End stage renal disease have been eliminated.

In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) published Clinical Practice Guidelines for AKI in which the important advances in knowledge surrounding AKI were presented as well as the numerous deficits that still require further research and validation (18). AKI is defined as any of the following (7):

- an increase in serum creatinine by ≥0.3mg/dl (≥26.5µmol/l) within 48 hours
- an increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
- urine output volume <0.5ml/kg/hr for 6 hours.

The severity is staged according to the criteria which is similar to that of the AKIN classification. The RIFLE, AKIN and KDIGO classifications are summarised in Table 1.1 (7,19).

Table 1.1: Rifle, AKIN, and KDIGO classification for AKI

	S_{Cr} and GFR Criteria	**Urine Output Criteria**
	RIFLE Category	
Risk	S_{Cr} increase by 1.5 fold or GFR decrease by >25% from baseline	<0.5 ml/kg/h for ≥6 hours
Injury	S_{Cr} increase by 2 fold or GFR decrease by >50% from baseline	<0.5 ml/kg/h for ≥12 hours
Failure	S_{Cr} increase by 3 fold or GFR decrease by >75% from baseline or S_{Cr} ≥354µmol/L with an acute increase of at least 44µmol/L	Anuria for ≥12 hours
Loss	Complete loss of function (RRT for > 4 weeks)	
ESRD	RRT >3 months	
	AKIN Criteria	
Stage 1	S_{Cr} increase ≥27 µmol/L or 1.5-2 fold from baseline	<0.5 ml/kg/h for ≥6 hours
Stage 2	S_{Cr} increase >2-3 fold from baseline	<0.5 ml/kg/h for ≥12 hours
Stage 3	S_{Cr} increase > 3 fold from baseline or S_{Cr} ≥354 µmol/L with an acute increase of least 44 µmol/L or Need for RRT	<0.3 ml/kg/h for ≥24 hours or anuria for ≥12 hours
	KDIGO Criteria	
Stage 1	S_{Cr} increase ≥27 µmol/L or 1.5-1.9 fold from baseline	<0.5 ml/kg/h for 6-12 hours
Stage 2	S_{Cr} increase >2-2.9 fold from baseline	<0.5 ml/kg/h for ≥12 hours
Stage 3	S_{Cr} increase > 3 fold from baseline or S_{Cr} ≥354 µmol/L or need for RRT	Anuria for ≥12 hours

In the study by Joaniddis et al (4) the AKIN classification detected 9% of cases missed by the RIFLE classification, of which 90.7% were AKIN stage 1, whilst the RIFLE classification picked up 26.9% of cases that the AKIN classification missed of which 30% were RIFLE class risk and 41% were RIFLE class failure. The RIFLE classification was shown to better detect AKI within the first 48 hours of ICU admission. This study illustrated that both RIFLE and AKIN classification can be used for the diagnosis and staging of AKI in an attempt to not miss patients with AKI. The guidelines published in 2012 (20), recommend using the KDIGO classification which combines the RIFLE and AKIN classifications and has gained global acceptance.

Despite the improvements made in the classification of AKI, there are still numerous deficits not only in the diagnosis and classification system, but in recommendations for treatment of AKI (20). There is a need for more sensitive modalities to diagnose patients with early AKI. The reason for this is that the kidney is a relatively forgiving organ and thus, tolerates insults without signs of structural or functional changes. Acute small changes signify severe systemic disease which infers a worsened prognosis (4).

1.3. Measurement of renal function

Renal function is assessed using surrogate markers for GFR. Inulin is the gold standard used to measure GFR as it is handled by the kidney in a unique way. It is only filtered by the kidney, while no reabsorption or secretion of inulin occurs. GFR measurement using inulin is, however, impractical as it requires a continuous intravenous infusion and significant laboratory resources to be performed. As a result blood urea nitrogen (BUN) was initially used to calculate GFR and to make the diagnosis of AKI. Subsequently, creatinine was considered a better indicator of GFR and was adopted in its measurement and thus, forms part of the diagnosis of AKI today. Creatinine is non-toxic and has a complex metabolism with multiple factors affecting serum levels independent of the GFR. These factors include volume status, altered production, reduced muscle mass, and drug effects on the tubular excretion of creatinine. Creatinine secretion in the proximal tubule may account for as much as 60% of creatinine elimination in patients with renal disease. The result is that the use of creatinine to calculate GFR in critically ill patients is unreliable as it over estimates GFR (1,4,15).

In an attempt to more accurately diagnose early AKI and prognosticate outcomes, research focused on potential biomarkers is underway. Three groups of biomarkers have been identified. These include (4,21,22):

- Inflammatory biomarkers - neutrophil gelatinase-associated lipocalin, interleukin 16 and interleukin 18
- Cell injury biomarkers - kidney injury molecule 1, liver fatty acid binding protein, sodium/hydrogen exchanger 3 and netrin 1
- Cell cycle markers – urinary tissue inhibitor of metalloproteinase 2, and insulin like growth factor binding protein 7.

With the use of these biomarkers information on the timing of the initial insult to the kidneys, and thus duration of the AKI may be revealed. In addition, it is hoped that differential expression between the biomarkers may be able to distinguish the aetiology (septic versus non-septic) and thus guide management (22).

1.4. Aetiology of AKI

The aetiology of AKI in patients admitted to the ICU is likely multifactorial with multiple risk factors having been identified. These include (1):

- hypotension
- pulmonary disease
- liver failure
- sepsis
- hypovolaemia
- advanced age
- hypertension
- pre-existing renal disease
- heart failure
- intravenous contrast use
- multiple nephrotoxic medications.

Worldwide data suggests that the leading cause of AKI in ICU admitted patients is sepsis related (32-48%) with a mortality rate of 40%, which increases to 60% if RRT is required (1,8,23). Acute tubular necrosis as a result of ischaemic or nephrotoxic injury to the tubules was thought to be the common pathophysiological pathway which results in AKI (24). The kidney is highly vulnerable to injury related to ischaemia in part due to the structural association between the renal tubules and the blood vessels in the medulla (25). Ischaemia compromises vital nephron structures in this area leading to cell injury and eventually cell death via necrosis and apoptosis (25). In addition, the nephron (functional unit of the kidney) functions to filter, concentrate and reabsorb many substances from the tubular lumen. If the concentration of these substances reaches toxic levels this can contribute to injury of the surrounding cells (25). However, more recently it has been suggested that there should be discrimination between AKI secondary to sepsis versus other causes. The reason for this is that septic AKI may be characterised by distinct pathophysiology which may confer distinct differences in clinical outcomes and responses to treatment (23). AKI in the setting of sepsis is unique from other causes in that it occurs at renal blood flows that are altered but not necessarily in the ischaemic range and may in fact be increased (26). As such, AKI in the setting of sepsis cannot be explained on the basis of hypoperfusion and thus other mechanisms have been sought (26). The exact pathophysiology is not yet fully understood and appears quite complex, however, an interplay of inflammation, diffuse microcirculatory flow abnormalities and cell bioenergetics adaptive responses to injury are thought to be central to understanding the process (26,27).

1.5. Management of AKI – RRT

The treatment of AKI focuses on the prevention of worsening the injury, whilst supporting renal function. RRT is a modality of treatment which replaces the normal blood filtering (non-endocrine) function of the kidney. Current prevention strategies are inadequate and treatment options other than RRT are non-existent (28). RRT is either peritoneal or haemo-based. Both allow for water and solutes to pass through a semipermeable membrane and the waste products can be discarded. Solute and water movement occur as a result of two processes, diffusion clearance (dialysis) and convective clearance (ultrafiltration). Diffusive clearance occurs when solutes move via a concentration gradient from a high concentration to a low concentration. This occurs effectively for small solutes and can result in either the addition or removal of a solute from the plasma depending on the relative concentration of the solute on either side of the semipermeable membrane. Water will also move along a gradient, ultimately following the solute. Convective clearance utilises a pressure gradient which forces water through the membrane down a pressure gradient which effectively drags solutes with it (ultrafiltration) (24,29).

Peritoneal dialysis uses the patient's peritoneum to serve as a natural semipermeable membrane for diffusive removal of solutes. In the setting of AKI, peritoneal dialysis is not employed due to logistical as well as practical limitations with the technique. Firstly, a surgical procedure is required to insert a peritoneal dialysis catheter. Secondly, the technique is limited by a low solute clearance rate as well as pulmonary restriction due to expansion of the peritoneal cavity. In addition, it is contra-indicated in patients who are post abdominal surgery or require abdominal drains (10).

Haemo-based RRT can either be intermittent, continuous or a hybrid of the two. The type of clearance employed is also included in the naming of the modality which has led to considerable confusion with an array of nomenclature. Modalities include (29,30):

- Intermittent haemodialysis (IHD)
- Continuous renal replacement therapy (CRRT)
    - Continuous veno-venous haemodialysis (CVVHD)
    - Continuous veno-venous haemofiltration (CVVHF)
    - Continuous veno-venous haemodiafiltration (CVVHDF)
- Hybrid therapies/prolonged intermittent renal replacement therapies
    - Sustained low-efficiency daily dialysis (SLEDD)
    - Extended daily dialysis (EDD)

Acute haemo-based RRT requires a two lumen, large-bore catheter to be sited in a central vein. The KDIGO guidelines recommend the following sites in order of preference for vascular access; right jugular vein, femoral vein, left jugular vein and subclavian vein (31). The blood circuit is connected to both ports of the central venous catheter. Blood is removed from the circulation by one lumen and passes through a peristaltic pump that allows the generation of pressure to drive ultrafiltration across a biosynthetic haemofiltration membrane into the dialysate. Solute can be removed by diffusion and/or convection. The gradient by which diffusion occurs is maintained by counter current - the patient's blood and the dialysate flow in opposite directions. Where solute is removed via convection, large volumes of ultrafiltrate are required and this then necessitates replacement of fluid and electrolytes, either via the dialysis machine or via a peripheral line. Blood is then returned to the circulation via the second lumen of the central venous catheter (24).

Solute clearance in IHD is via diffusion, whilst water removal is via haemofiltration which produces the ultrafiltrate. The advantage of IHD is the rapid removal of solute and volume, however, the disadvantage of this is the potential risk of systemic hypotension which occurs in 20-30% of treatments. Due to this haemodynamic effect, approximately 10% of patients with AKI cannot be treated with IHD. Continuous veno-venous haemodialysis was developed for the treatment of such patients as well as patients in which IHD failed to control metabolic derangements or volume status.

To date there has been no data to support the superiority of either IHD or CRRT with regard to mortality or renal recovery (32–34). However, common sense dictates that there is an advantage of CRRT in the critically ill patient. Possible advantages include less haemodynamic instability with the avoidance of intradialytic hypotension and thus, decreased risk for exacerbating kidney injury further. Furthermore, there are more gentle shifts in electrolytes and fluid, with the added benefit of maintaining fluid balance without compromising the patient's nutritional needs. The disadvantages of continuous haemodialysis are that it tends not to be continuous with down time experienced as a result of the circuit clotting, in addition to requiring more labour intensive nursing (24).

Complications of dialysis relate to the vascular access required and those inherent of the dialysis itself which include (4,35,36):

- intradialytic hypotension
- hypersensitivity to the extracorporeal circuit
- arrhythmias
- fluid and electrolyte imbalances
- nutrient losses
- decreased temperature
- loss of trace elements
- vitamin depletion
- bleeding secondary to anticoagulation and circuits that have clotted
- difficulty in dosing of drugs especially antibiotics
- exposure to relatively high doses of anti-coagulation.

Complications caused by the vascular access include:

- catheter related infections
- catheter induced thrombosis
- arrhythmias
- vascular injury
- pneumothorax
- venous air embolus
- bleeding

1.6. Timing of RRT

There are many studies that have attempted to decipher the conundrum of the optimal timing for treatment to be initiated. Initially RRT was reserved for patients with imminent death following uremic complications (37). Over time this has changed and as a result of the high morbidity and mortality associated with AKI it was postulated that initiating dialysis prior to the classical or absolute indications for RRT might confer better outcomes. The risks associated with RRT need to be balanced against the possible benefits of early RRT, especially considering that some patients with severe AKI may have spontaneous recovery of renal function (35,38). Early initiation of RRT prior to the onset of severe AKI could potentially prevent kidney specific damage and remote organ injury resulting from fluid overload, electrolyte and metabolic imbalance and systemic inflammation, whilst promoting greater kidney recovery (39,40).

1.7. Clinical Research (Pre RIFLE/AKIN classification)

Despite the lack of consensus in the definition of AKI prior to 2004, a number of studies looking at RRT timing were conducted. In 1960, a study was published which introduced the idea of prophylactic haemodialysis (41). This was in an endeavour to prevent uraemia and its associated complications. RRT was initiated at urea levels of ≥57mmol/l. This study with a sample size of 15 prompted further research into the merits of early initiation of RRT in patients with AKI. The earliest was a retrospective study by Parsons et al in 1961 (42). They divided the sample of 33 into either early (BUN of 120-150mg/dl) or late (BUN >200mg/dl) initiation of RRT. Survival for early and late initiation was 75% and 12% respectively. A number of other retrospective studies were done but had differing definitions for early and late initiation of RRT according to BUN levels (See Table 1.2). Despite the different values used to initiate treatment, they all showed greater survival with earlier initiation (43).

Table 1.2: Summary of retrospective studies done prior to 2004 evaluating the timing of initiation of RRT

Study	Year	Mode of RRT	Sample size	Early	Late	Early	Late
				BUN at initiation of RRT (mg/dl)		Survival (%)	
Parsons et al (42)	1961	IHD	38	120-150	>200	75	12
Fischer et al (44)	1966	IHD	162	≤150	>200	43	26
Kleinknecht et al (45)	1972	IHD	500	<93	>163	73	58
Gettings et al (46)	1999	CRRT	100	<60	>60	39	20

Prior to 2004, three randomised control trials (RCT) where conducted comparing late versus early initiation of RRT. The first was in 1975 (47) with a sample size of 18 looking at patients with post traumatic AKI being alternatively assigned to early and late initiation groups. The early intensive treatment group received dialysed to maintain a BUN level of less than 70mg/dl and a creatinine of less than 5mg/dl. In contrast, the late non- intensive group were only dialysed when the BUN level approached 150mg/dl and the intensive group were only dialysed when the BUN level approached 150mg/dl and the creatinine 10mg/dl or when clinical indications for dialysis were present. The early intensive group showed greater survival of 64% compared to 20% in the late, non-intensive group ($p<0.10$). The second RCT was in 1986 (48). This study had a sample size of 34 and aimed to evaluate the efficacy of vigorous dialysis in the management of AKI. Patients were stratified according to the aetiology of AKI and randomised to an intensive or non-intensive group. The intensive group was dialysed to maintain a BUN level of <60mg/dl and approximately 100mg/dl in the non-intensive group. The average time to initiation was 5 ±2 days in the intensive group and 7 ±3 days in the non-intensive group. The mortality was 47.1% in the non-intensive group versus 58.8% in the intensive group, which was reported as not significant by the researchers, although, a p-value was not given. The results for both of these studies were not statistically significant. The third study was a prospective RCT conducted in 2002, the only one conducted until recently. (49). It had a number of differences in comparison to the two previous studies including:

- The use of continuous haemodialysis where the other two used IHD
- It had three arms (early low volume, early high volume, late low volume) as opposed to two.

Thus, in addition to early and late initiation, the dosing of the dialysis was also considered. The sample consisted of 106 critically ill patients with AKI across two centres. They were randomised to either early high volume haemofiltration (n=35), early low volume haemofiltration (n=35) or late low volume haemofiltration (n=36). High volume haemofiltration was defined as 3 litres/hr (median 48ml/kg/hr) compared to low volume haemofiltration defined as 1-1.5litres/hr (median 19ml/kg/hr). RRT was initiated within 12 hours of meeting inclusion criteria (oliguria >6hrs despite haemodynamic optimisation, measured creatinine clearance <20ml/min on a 3 hour timed urine collection) in the early groups. In the late group, RRT was initiated at a BUN of >112mg/dl, a potassium >6.5mEq/l or evidence of pulmonary oedema. No significant differences ($p=0.8$) in the three groups in terms of survival was found. These results should be interpreted with caution as there was a low sample size resulting in low statistical power. In addition, the overall mortality of the 106 participants was only 27% which was much lower than the mortality rates reported by other studies of patients with AKI admitted to ICU. Moreover, six of the 36 patients in the late group never received dialysis as two died prior to meeting the study criteria and the other four recovered renal function without the need for dialysis.

1.8. Clinical research (post RIFLE/AKIN classification)

Post 2004, analysis on the timing of RRT in patients with AKI post cardiac surgery was performed in Turkey (50) and the United Kingdom (51). Both studies were single centre retrospective studies. Demirkiliç et al (50), had a sample size of 61 patients who underwent cardiac surgery between March 1992 and September 2001 who required post-operative CVVHDF. Patients were assigned to one of two groups. In group one (n=27) dialysis was started when serum creatinine >5mg/dl or the potassium was persistently >5.5mmol/l despite medical treatment and independent of urine output. Group two (n=34) were dialysed when urine output was <100ml over 8 hours despite receiving a furosemide challenge. Group one were dialysed on day 2.6 ± 1.7 post surgery compared to 0.9 ± 0.3 days in group two. Early initiation was associated with decreased ICU (17.6% vs 48.1%) and hospital mortality (23.5% vs 55.5%) both of which were statistically significant (p=0.014 and p=0.016 respectively). Early initiation was also associated with decreased length of mechanical ventilation and ICU length of stay.

Elahi et al (51), enrolled 64 patients who received cardiac surgery between January 2002 and January 2003 who required post-operative CVVH. Patients were assigned to either group one or two. Group one (n=28) had dialysis initiated at a BUN >84mg/dl, creatinine >2.8mg/dl or potassium >6mEq/l despite medical treatment and regardless of the urine output. In group two (n=36) dialysis was initiated if urine output was <100mls in 8 hours despite furosemide infusion. The interval between surgery and initiation of RRT was 2.6 ± 2.2 days in group one and 0.8 ± 0.2 days in group two. Hospital mortality was 43% in group one versus 22% in group two (p<0.05). Both studies had similar baseline demographics and clinical characteristics. Similar results were demonstrated in the analysis of 80 oliguric patients with sepsis associated AKI, half of which were treated with early-isovolemic haemofiltration whilst the other half were treated with conventional supportive therapy (52).

Jamale et al (53), conducted a study in western India where they enrolled 208 patients who had developed community acquired AKI. They were randomised to receive early (BUN≥70mg/dl or SCr ≥7mg/dl (618.8mmol/l)) or late (clinical decision by nephrologist) initiation of RRT. The in-hospital mortality was 20.5% and 12.2% for the early and late groups respectively (relative risk, 1.67; 95% CI, 0.88-3.17; p=0.2), which was not statistically significant.

Despite this large body of data, results are not easily comparable due to a wide variety of definitions used both for diagnosis of AKI and for what constitutes early initiation. Poor research methodology, including retrospective design and small sample size further compound the short comings. In addition, studies performed in homogenous patient populations such as post cardiac surgery studies cannot be generalised to other population groups who develop AKI from a variety of aetiologies. (23,35)

1.9. Systematic reviews and meta-analysis

Joannidis et al (17) reviewed a number of prospective randomised trials conducted between 2000 and 2009 with a sample size greater than 150. They observed that RRT is usually initiated at serum creatinine levels of approximately 3.4 – 5.1mg/dl (300-450mmol/l) or a BUN of 50-110mg/dl (17.85 – 39.28mmol/l). These values have been devised by the clinicians making the decisions and thus, reflect current practice albeit without validation.

In 2008, a systematic review and meta-analysis was carried out to determine whether early versus late initiation of RRT in critically ill patients is associated with a survival benefit (54). The study included five RCT, one prospective cohort and 17 retrospective cohorts. Meta-analysis of the RCT studies showed a 36% mortality reduction with early initiation of RRT, however, this was not statistically significant (risk reduction (RR), 0.64; 95% confidence interval (CI), 0.4 to 1.05; p=0.08). In contrast, the meta-analysis of the cohort studies showed a 28% mortality risk reduction with early initiation of RRT which was statistically significant (RR, 0.72; 95%CI, 0.64-0.82; p <0.001). The authors concluded that early RRT may confer improved survival in patients with AKI.

Similarly, in 2011 a systematic review and meta-analysis which included two RCT, four prospective and nine retrospective cohorts was conducted (40). This study showed a 28-day mortality reduction with early RRT which was significant (OR 0.45; 95% CI 0.28-0.72). Like the previous study, the authors concluded that there may be benefit in terms of mortality reduction to early initiation of RRT in critically ill patients. In 2016, a further meta-analysis was performed which included 36 studies (55). This included seven RCT, seven prospective and 19 retrospective studies. Of these studies, only nine (six RCT, one prospective and two retrospective cohorts) were deemed to be of high enough quality to be included for analysis. This study infers that there is no benefit to early initiation of RRT (OR 0.665; 95% CI 0.384-1.1153, p=0.146).

1.10. AKIKI, ELAIN and IDEAL-ICU trial

Subsequently, three large prospective RCT have been conducted. The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial (56), the Effect of Early versus Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill patients With Acute Kidney Injury (ELAIN) trial (57) and the Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial (58).

The AKIKI trial had a sample size of 620 patients and looked at a primary endpoint of 60-day mortality. The study found no significant difference in mortality between the early and delayed initiation of RRT groups (p=0.79). There were also a number of patients in the delayed group that did not receive dialysis and they found that patients in the early group had a higher rate of catheter related bloodstream infections. The ELAIN trial consisted of 231 patients and the primary endpoint was 90-day mortality. The study showed favourable outcomes for the early initiation group with a mortality rate of 39.3% versus 53.7% in the late group (HR, 0.66, 95% CI 0.45-0.97). They found that more patients in the early initiation group recovered renal function by 90 days (OR 0.55, 95% CI .032-0.93). In addition, the early group had decreased hospital stay and duration of RRT. The difference in results between these two studies can in part be attributed to important methodological differences (39). See Tables 1.3 and 1.4.

The AKIKI trial was a multicentre study that screened 5528 patients, eventually enrolling and randomising 11% of them. The ELAIN trial was single centred and screened 604 almost exclusively post-surgical and trauma patients to include 231 (38%) subjects. This suggests potential for selection inclusion and treatment bias. In addition, the ELAIN trial consisted of mostly post cardiac surgery patients, whereas the AKIKI trial was predominantly medical patients where sepsis was present in 80% of them as compared to 32% of the ELAIN trials subjects. The contrast in patient populations between the two trials infer differing aetiologies for AKI with different pathophysiology and prognosis. Patients with pulmonary oedema were excluded from the AKIKI trial but accounted for three quarters of those included in the ELAIN trial.

The ELAIN trial used definitions that lead to very early RRT initiation. It has been noted that the progression from stage 2 to stage 3 AKI will only occur in less than half of patients (38,59), hence a number of patients in the early arm of the ELAIN trial might not have benefited from the RRT. In addition, in clinical practice a very small number of patients with stage 2 AKI and the minority of patients with stage 3 AKI will require RRT (37).

This was evident in the AKIKI trial where only 51% of patients randomised to the delayed group went on to receive dialysis in part due to spontaneous resolution of disease not requiring RRT (56).

Patients included in the ELAIN trial also received delayed RRT earlier than their AKIKI counter parts (25.5 hours versus 57 hours). Of note, in addition to the mortality benefit reported by the ELAIN trial in the early RRT group, they also required a shorter duration of RRT (2 weeks) and had a shorter length of hospital stay (4 weeks) compared to the delayed group. These results are not congruent with a difference in RRT initiation of less than a day (37).

In addition, a meta-analysis which included the AKIKI and ELAIN trial was conducted in 2016 (60). This study only included 9 RCT studies and no cohorts. The primary outcome assessed was mortality. The meta-analysis showed no difference between early and late RRT with a mortality rate of 38% and 41.4% respectively (RR, 0.93; 95% CI, 0.74-1.18). However, further statistical analysis indicated that there was insufficient evidence to draw conclusions.

The ELAIN and AKIKI trial are often compared in the literature, however, there are significant differences between the studies and the ELAIN trial has been found to have a number of faults which place the results of this study into question. It has been suggested that the ELAIN trial is more suited to comparison with the Early High Volume Hemofiltration versus Standard Care for Post-Cardiac Surgery Shock (HEROICS) study (37,61). The HEROICS study (62), enrolled 224 patients with severe shock requiring high dose catecholamines 3-24 hours post cardiac surgery. These patients were randomised into an early group which received high volume haemofiltration (80ml/kg/h) for 48 hours followed by CVVHDF or a conservative group which was initiated on CVVHDF only when clinically indicated. At thirty days the mortality rate in both groups was 36% (Odds ratio, 1.00; 95% CI, 0.64-1.56; p=1.0). In addition only 57% of the control group went on to receive RRT. Thus, this study does not support the results of the ELAIN trial.

Table 1.3: Comparison of the ELAIN, AKIKI and IDEAL-ICU trial

STUDY CHARACTERISTICS	ELAIN, n =231	AKIKI, n = 629	IDEAL-ICU, n=488
Sites	1	31	29
Country undertaken	Germany	France	France
Number of patients screened	604 (231/604=38%)	5528 (629/5528=11%)	3573 (488/3573=14%)
Predominant patient profile	Surgical (93%) of which 46.75% post cardiac surgery	Medical	Septic Shock
Sepsis frequency	32 %	80%	100%
Initial RRT	CVVHDF protocol	Modality and dosing at discretion of site	Intermittent or continuous but according to defined protocol

Most recently the IDEAL-ICU trial was conducted in France (58). See Tables 1.3 and 1.4. This was a multicentre study looking at patients with early septic shock in the failure stage of the RIFLE classification (analogous to KIDGO stage 3). The sample size was 488 with 246 patients assigned to the early group and 242 assigned to the late group. The early group were dialysed within 12 hours of meeting the criteria, whilst the delayed group were delayed until 48 hours if renal function had not recovered. They assessed 90-day mortality between the two groups, which was found not to be significant (p=0.38). Of note, in the delayed group 41 patients required emergency dialysis prior to 48 hours for classical indications for dialysis. Furthermore, 38% of patients in the delayed group weren't dialysed at all and of these patients 75% had spontaneous recovery of renal function. This trial was terminated early after a planned interim analysis by an independent data and safety monitoring board as further enrolment was unlikely to change the results of the trial. This trial is more similar to the AKIKI trial in its design and thus favours comparison.

Table 1.4 Comparison of ELAIN, AKIKI, and IDEAL-ICU early and late groups

ELAIN, n =231		AKIKI, n = 629		IDEAL-ICU, n=488	
Early RRT, n= 112	Delayed RRT, n= 119	Early RRT, n= 311	Delayed RRT, n= 308	Early RRT, n= 246	Delayed RRT, n=242
CRITERIA FOR INITIATION OF RRT					
<8 h of reaching KDIGO stage 2 AKI	<12h of reaching KDIGO stage 3 AKI, BUN>47mg/dl, K^+ >6mmol/L Mg^{2+} >9.7mg/dl, or UO <200ml/12h	<6h after reaching KDIGO stage 3 AKI	Presence of BUN>112mg/dl, K^+>6mmol/L, pH <7.15, Fluid overload with pulmonary oedema anuria>72h	Within 12 hours of reaching failure stage of the RIFLE classification for AKI	48 hours after reaching failure stage of the RIFLE classification for AKI OR K^+ >6.5mmol/L pH <7.15 Fluid overload refractory to diuretics with pulmonary oedema
SOFA SCORE AT RANDOMISATION					
15.6±2.3	16.0±2.3	10.9±3.2	10.8±3.1	12.2±2.9	12.4±2.9
AGE (years)					
65.7±13.5	68.2±12.7	64.8±14.2	67.4±13.4	69.3±11.6	68.7±12.8
RECEIVED RRT					
112 (100%)	108 (91%)	305 (98%)	157 (51%)	239 (97%)	149 (62%)
SERUM CREATININE AT INITIATION OF RRT (mmol/l)					
168.0±53.04	212.2±88.4	291.72±123.76	468.5±203.3	283.8±130.8	300.6±141.44
BUN (mg/dl)					
38±16	48±22	52±24	90±34	59.2±26.9	63.1±30.0
TIME TO RRT ONCE RANDOMISED (IQR) h					
6.0(4.0-7.0)	25.5(18.8-40.3)	4.3(2.7-5.9)	57(28-83)	7.6(4.4-11.5)	51.5(34.6-59.5)
MORTALITY 28/60/90 days %					
30.4/38.4/39.3	40.3/50.4/54.7	41.6/48.5/-	43.5/49.7/-	45/-/58	42/-/54

1.11. Ongoing RCT

In 2015, a pilot RCT was carried out in Toronto with a sample size of 100 (35). They compared early (within 12 hours of meeting criteria) versus late initiation (classical indication for dialysis used). The inclusion criteria for this study were(35):

- presence of severe AKI (defined by the presence of two of the following three criteria: (i) a twofold increase in serum creatinine from baseline, (ii) urine output <6 ml/kg in the preceding 12 h, or (iii) whole-blood NGAL ≥400 ng/ml)
- the absence of urgent indications for RRT initiation (defined as serum potassium ≤5.5 mmol/l and serum bicarbonate ≥15 mmol/l)
- low likelihood of volume-responsive AKI (defined as central venous pressure≥8 mm Hg

Importantly, within the late initiation group a number of patients were never dialysed. No conclusions were drawn from the study as it was a pilot study. This study has been followed up with a large multicentre RCT (STARRT-AKI) which has recently completed recruitment of 3000 patients in 15 countries across 168 centres (63). The results of this study will be comparable with those of the AKIKI and IDEAL-ICU trials.

1.12. Conclusion

Although haemodialysis has been adopted internationally for many years there still remains a wide variation in its application. The timing of initiation, modality, dose and length of treatment remains controversial (4). Current recommendations for initiation of RRT in the setting of AKI are not graded due to a lack of high quality evidence. The recommendations by the KDIGO guidelines are that the broader clinical context should be assessed for conditions which can be modified by RRT, and trends in laboratory data should guide decision making rather than using isolated laboratory thresholds (16). A wide variation in interpretation and implementation of RRT amongst clinicians has resulted.

Although the proposed study will not begin to fully answer these questions, it will provide information on current practices (albeit in one centre) which previously have not been described. In addition, it may guide future practice in resource limited settings.

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SECTION 2: **AUTHOR'S GUIDELINES**

Note: These guidelines have been edited to only include relevant information for the proposed submission

2.1. Author Guidelines

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

2.2. Scope of the Journal

This Journal publishes scientific articles related to multidisciplinary critical and intensive medical care and the emergency care of critically ill humans.

2.3. Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)
If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions. Author contributions should be listed/described in the manuscript.

2.4. Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

2.5. Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript as accompanying documentation. A copy of the ethics approval letter must be uploaded as a supplementary file.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

2.6. Protection of rights to privacy

2.6.1. Research Participants

Information that would enable identification of individual research participants should not be published in written descriptions, photographs, radiographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

2.7. Manuscript preparation

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- Medical drugs should be referred to by their generic name although the trade name may be used in brackets in the text once if unique.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

2.8. Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The title of the manuscript should concisely describe the study but should not include the outcome. The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. At the end of the introduction clearly state the aim or objective of the study. The primary and secondary outcomes should be specified.

In the Methods section describe in sufficient detail so that others would be able to replicate the study should they need to. Sections of the methods that have been described in previous publications need only be referenced. The statistical methods should be described. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered.

Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

The discussion should be confined to an interpretation of your results with respect to your stated aim and if applicable, a comparison to the results of similar studies. The strengths and weaknesses of your study should be discussed.

The conclusion should be confined to an interpretation of the results of the study and a recommendation if applicable.

- May include up to 6 illustrations or tables.
- References should only include the most recent and relevant articles. A maximum of 30 references is advised.

Structured abstract

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    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the research tools/instruments, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
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- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
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SECTION 3: **DRAFT ARTICLE**

The indications for and timing of haemodialysis in critically ill patients with acute kidney injury at Chris Hani Baragwanath Academic Hospital

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3.1. Abstract

Background

Acute kidney injury (AKI) is common amongst patients admitted to the intensive care unit (ICU). It is an independent risk factor for morbidity and mortality. The optimal timing of renal replacement therapy (RRT) remains unknown resulting in a wide variation in observed current practices. There is a paucity of data on current practices within South African ICU's.

Objectives

The aim of this study was to describe current practices in the timing of RRT in patients with AKI admitted to the ICU.

Methods

A retrospective, descriptive study in an adult academic ICU in Soweto from 1st January 2013 to 31 December 2014.

Results

There were 2152 ICU admissions over 2 years. Seventy-six (3.5%) patients required RRT. Sepsis was present in 83%. The most common indication for RRT was oliguria/anuria 38 (50%) followed by worsening urea/creatinine 22 (29%), metabolic acidosis 9 (11.8%), refractory hyperkalaemia 4 (5.3%), fluid overload 2 (2.6%) and other 1 (1.3%). Forty two patients (55%) had RRT instituted on admission day (D_0), while 34 (45%) after D_0 (D_{1-21}). Ninety percent (90%) of D_0 RRT and 94% of D_{1-21} RRT group had KDIGO stage 3 AKI. Once a decision to initiate RRT was made, the median time to starting RRT was 4 hours (IQR 4). The composite outcome of death, RRT dependence and diuretic dependence at ICU discharge was 21% with no difference between the two groups (p=0.22). The ICU mortality was 3%.

Conclusion

The sampled population was young, predominantly male and post emergency surgery with a high burden of sepsis and human immunodeficiency virus. The observed current threshold for RRT was late (stage 3 AKI with classical/emergent indications) with outcomes comparable to literature reviewed.

3.2. Introduction

Acute kidney injury (AKI) represents a broad spectrum of pathological processes ranging from clinically undetectable changes to severe injury which is associated with either reversible or permanent and complete loss of renal function [1]. There is evidence that even mild reversible AKI confers significant independent risk for morbidity and mortality [2–7], and contributes to increased healthcare costs [8]. There is a scarcity of data to quantify the incidence of AKI in South African intensive care units (ICU), however, it is likely to be higher than that of the developed world as a result of the burden of disease associated with AKI in this region [3].

As a result of the high morbidity and mortality associated with AKI it was postulated that initiating dialysis prior to the development of classical indications may be beneficial. The risks associated with renal replacement therapy (RRT) need to be balanced against the possible benefits of early RRT, especially considering that some patients with AKI may have spontaneous recovery of renal function [9]. Early initiation of RRT prior to the onset of severe AKI could potentially prevent kidney specific damage and remote organ injury resulting from fluid overload, systemic inflammation, electrolyte and metabolic imbalance, whilst promoting greater kidney recovery [10,11]. Three large prospective randomised control trials (RCT) have been conducted to assess the value of early RRT. The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial [12], the Effect of Early versus Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill patients With Acute Kidney Injury (ELAIN) trial [13], and the Initiation of Dialysis Early versus Delayed in The Intensive Care Unit (IDEAL-ICU) trial [14]. The results of the AKIKI and IDEAL-ICU found that there is no mortality benefit in early initiation of RRT (p=0.79 and p=0.38 respectively), whereas the ELAIN trial found that there was, with a mortality rate of 39.3% versus 53.7% in the late group (HR, 0.66, 95% CI 0.45-0.97). A recent meta-analysis [15] which included a further 7 RCT concluded no difference in mortality between early and late initiation (p=0.97).

Current recommendations for initiation of RRT in the setting of AKI are not graded due to a lack of high quality evidence [2]. A wide variation in interpretation and implementation of RRT amongst clinicians has resulted [16]. In the literature reviewed a paucity of local data was identified thus we undertook to describe local practices in managing RRT in AKI in a low to middle income country.

3.3. Methods

3.3.1. Design and Setting

A retrospective, chart review was performed at the Chris Hani Baragwanath Academic Hospital Main ICU which is a combined adult and paediatric multidisciplinary ICU. Ethical approval was obtained from the Human Research Ethics Committee at the University of the Witwatersrand (M170684). The study period extended from 1 January 2014 to 31 December 2015.

3.3.1. Patients and data

All adult patients with AKI who underwent RRT were eligible for inclusion, whilst those with known chronic kidney disease, and prior nephrectomy were excluded. Data was collected on the day of admission as well as on the day of RRT if they differed. Data points pertaining to demographics, metabolic, renal, ventilation, oxygenation, haemodynamic, septic and haematological markers as well as patient outcome were entered into a Microsoft Excel® spreadsheet. In addition the simplified acute physiology score (SAPS) II and the sequential organ failure assessment (SOFA) scores were calculated. This was performed by the principal investigator.

3.3.1. Objectives

The primary objective was to describe local practices in managing RRT in AKI in a low to middle income country. The secondary objectives were to describe the patient characteristics, severity of illness scores, staging at initiation of RRT, outcome at ICU discharge and to estimate and describe delays in the initiation of RRT.

3.3.1. Statistical analysis

All data was assessed for normality. All independent medians were compared with the Mann-Whitney U test, while dependent medians were compared with the Wilcoxon matched pairs test. Categorical data was assessed with Chi-squared test. Data analysis was carried out using statistica version 13.3. The 5% significance level was used.

Calculation of sample size was based on an estimated incidence of RRT of 5-10%, 95% confidence and a precision of 5%. The minimum required sample size was 73 patients. We studied a 2 year period from 1 January 2014 until 31 December 2015 to ensure this minimum sample size.

3.4. Results

There were 2171 ICU admissions over the 2 year study period. Of these admissions 1315 did not meet criteria for the diagnosis of AKI (see Figure 1). The overall incidence of AKI was 39.4% (856/2171).”Insert Figure 1 here”

The median age of the sampled population was 35.5 (IQR, 21), with the majority of them being male (59.47%). The median SAPS II score (43) gave a predicted mortality of 30.6%. The indications for RRT are summarised in Table 3.1. “Insert Table 3.1 here”

A total of 42 patients (55%) had RRT instituted on admission day (D_0 RRT), while 34 (45%) were initiated after D_0, between day 1 and 21 (D_{1-21} RRT). Table 3.2 summarises the relative frequencies of the KDIGO stage for AKI between the two groups on admission day and the day of initiation of RRT. “Insert Table 3.2 here”

Patients admitted in KDIGO stage 1 and 2 were significantly less likely to undergo RRT on admission day (OR 0.21, CI 0.06-0.73). Overall, the KDIGO stage increased significantly from D_0 to RRT day for the D_{1-21} RRT group (p=0.0004). Significant differences between the two RRT groups (D_0 RRT vs D_{1-21} RRT) are provided in Table 3.3. “Insert Table 3.3 here”

Medical patients were the largest group requiring RRT (37%), however, the cumulative number of the surgical sub-specialities makes post-surgical patients the largest group (63%). The diagnostic groups and co-morbidities are provided in Table 3.4 and 3.5 respectively. “Insert table 3.4 and 3.5 here”

Thirty five of the 36 patients who underwent surgery prior to ICU admission had emergency surgery. Baseline admission characteristics of patients undergoing RRT are given in Table 3.6. “Insert Table 3.6 here”

There was no difference in median SOFA score (10, IQR 4) on the day of RRT between the two groups, (p=0.67, n=76). However, in the group undergoing RRT after D_0, the SOFA score increased from a median of 7 (IQR 5) on admission to 10 (IQR 4) on the RRT day, (p=0.0004, n=30).

Once a decision to initiate RRT was made, the median time to starting RRT was 4 hours (IQR 4), n=68. There was no significant difference between the D_0 RRT group and the D_{1-21} RRT group, p=0.34.

The composite of death, RRT dependence and diuretic dependence at ICU discharge was 21% (16/76 patients). There was no significant difference in the composite outcome between the two groups, p=0.22. The overall in ICU mortality was 3% (2/76 patients).

3.5. Discussion

The incidence of AKI was 39.4% in our study. Internationally, the incidence of AKI in ICU patients ranges from 20-50% [1]. Our study included admissions to a single unit consisting of both ICU and high dependency beds. The inclusion of the high dependency group with a lower severity of illness may have resulted in a lower than expected AKI incidence. This may be compounded by a higher admission and turnover rate in the high dependency unit compared to the ICU. The same factors may also explain the RRT incidence of 4.5% which appears lower than the incidence of RRT internationally (5-10%) [17].

Our study population is unique when compared to others in the literature. The median age of the study population was 35.5 years. The majority of the patients were surgical (63%) with more than a third of these being trauma patients. Additionally, all but one of the patients who underwent surgery prior to ICU admission were emergency surgical cases. There was a high burden of human immunodeficiency virus (HIV) amongst the population group with a frequency of 13.2%. This is in line with the reported prevalence of HIV in South Africa of 13.5% [18]. There was also a high frequency of sepsis (83%) in the population sampled. This is in contrast to the study populations in the ELAIN, AKIKI and IDEAL-ICU trials where the median age of all groups was more than 60 years, reported emergency surgery incidences were about 12% and HIV was not a significant co-morbidity [12–14].

Overall, 90% or more of our study group underwent RRT after reaching KDIGO stage 3. Although earlier studies, mostly non-randomised, suggested that early initiation of RRT prior to the development of the classical indications for RRT may confer improved outcomes [2,5–7,19–22], the most recent evidence of over 2000 patients from randomised trials show no benefit from this early RRT strategy [15]. A significant proportion of AKI patients in both AKIKI and IDEAL-ICU studies spontaneously recovered when RRT was withheld providing no classical/emergent indications for RRT arose [12,14]. The practice observed in our study was in keeping with these more recent findings with initiation of RRT in stage 3 AKI (late), using predominantly classical/emergent indications.

The observed median level of serum creatinine at which RRT was started was 505µmol/L (IQR 459) in the D_0 RRT group and 331µmol/L (IQR 203) for the D_{1-21} RRT group. The difference may be explained by delayed admission to the ICU. This is not unexpected in a resource limited setting. However, once patients were in ICU, access to RRT was better.

The admission predicted mortality in our study was around 30% (SAPS II score). The median SOFA score for both the D_0 RRT group and the D_{1-21} RRT group was 10 on the day RRT was initiated. Using the AKIKI trial population for comparison, although the severity of illness for our group was lower at admission, the organ dysfunction (SOFA score) at RRT initiation was similar indicating a common threshold to initiate RRT. The discrepancy between severity of illness and organ dysfunction may be explained by the fact that our group had similar organ dysfunction necessitating support but, a greater underlying reversibility when compared to the AKIKI trial.

Despite a composite outcome of death, RRT dependence and diuretic dependence of 21%, the early mortality was only 3% at ICU discharge. Several factors may explain this finding. The first is that in a resource limited setting patients admitted to the ICU are strictly triaged to make sure that resources are distributed equitably. This may result in a selection bias where patients with likely better outcomes being admitted. Secondly, it is likely that a similar selection bias for RRT within the ICU exists for the same resource constraints. Finally, outcomes at ICU discharge are generally lower than at hospital discharge and at 90 days. Unfortunately, we did not look at all the patients with AKI to assess if any patients who required RRT did not receive it. Decisions not to escalate therapy including RRT were also not examined and it is possible that patients with a better prognosis may have been selected.

The most common indication for RRT was oliguria or anuria (50%) followed by worsening renal function as evidenced by increasing urea/creatinine (29%). Classic indications were therefore the predominant trigger for RRT initiation in our study. This is in keeping with the delayed groups of the IDEAL ICU and AKIKI trials [12,14]. Using the IDEAL-ICU study for comparison, the delayed group in that study had RRT initiated for metabolic acidosis (8%), hyperkalaemia (4%), fluid overload (2.6%) and other (2%) prior to the stipulated RRT time. Our RRT indications are comparable; metabolic acidosis (11%), hyperkalaemia (5.3%), fluid overload (2.6%) and other (1.3%).

There were 42 (55%) patients that received RRT on their admission day. Of these patients the majority (90%) were stage 3 AKI according to the KDIGO classification with no patients falling into stage 1 or 2. Of the remaining 34 (45% of total) patients who received dialysis thereafter (D_{1-21}), 47% were classified as either having no AKI (20.6%), stage 1 (14.7%) or stage 2 (11.8%) AKI. By the time that RRT was instituted AKI stage had increased significantly in the D_{1-21} group with the majority (94%) in stage 3 AKI. This latter group is of great interest. The ability to predict deterioration before it happens may provide a therapeutic or preventative window.

3.6. Limitations

Retrospective, small study size, single centre, potential selection bias, and patients with AKI who were not dialysed and were not assessed further.

3.7. Conclusion

The sampled population was young, predominantly male and post emergency surgery with a high burden of sepsis and HIV. The observed current threshold for RRT was late (stage 3 AKI with classical/emergent indications) with outcomes comparable to literature reviewed. Further research in the form of large multicentre trials with follow up to hospital discharge are needed in South Africa as well as Africa.

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Author contributions: Primary author, Dr PM Brown, MMed student, performed all the data collection and write up with supervision from Prof Omar and Dr Redford.
Conflict of interest: None

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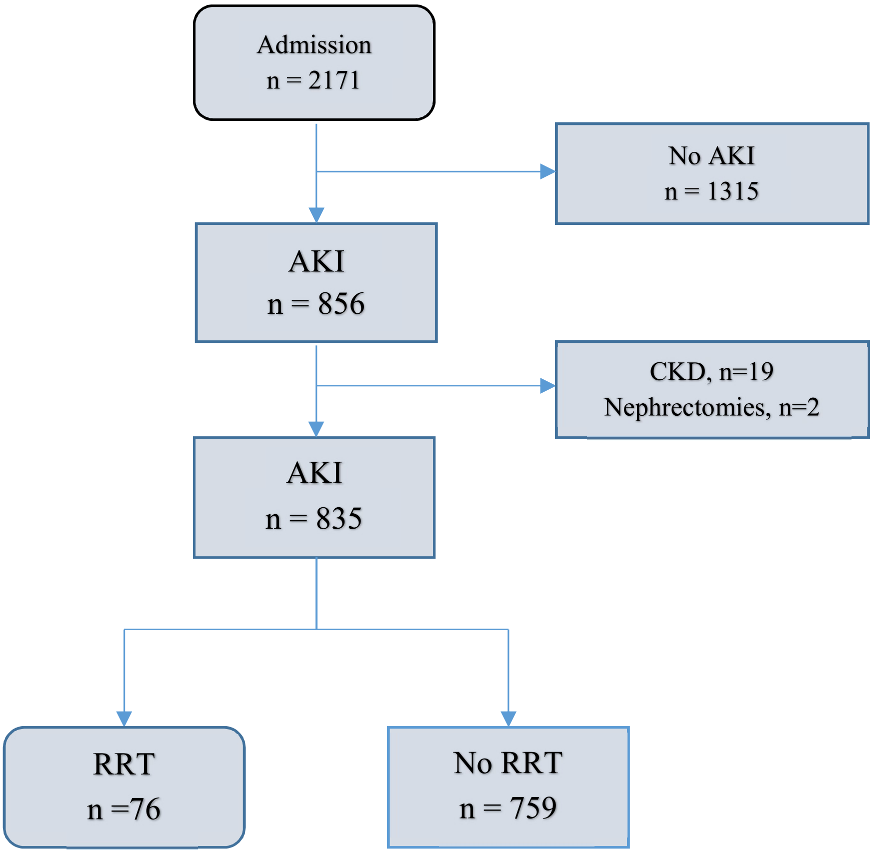

Figure 1: Flow diagram showing patient realisation

Table 3.1: The relative frequencies of the indications for RRT

Indication	N	Percentage (%)
Oliguria/anuria	38	50
Worsening urea/creatinine	22	29
Acidosis	9	11.8
Refractory hyperkalaemia	4	5.3
Fluid overload	2	2.6
No absolute indication	1	1.3

Table 3.2: AKI staging of the two patient groups

KDIGO Stage	Staging on admission		Staging on RRT day	
	D_0 RRT n (%)	D_{1-21} RRT n (%)	D_0 RRT n (%)*	D_{1-21} RRT n (%)
No AKI	0 (0%)	7 (20.6%)	-	0 (0%)
Stage 1	0 (0%)	5 (14.7%)	-	0 (0%)
Stage 2	4 (10%)	4 (11.8%)	-	2 (6%)
Stage 3	38 (90%)	18 (53%)	-	32 (94%)

*Results are the same as those on admission (day of RRT was the same)

Table 3.3: Comparison of the characteristics between RRT at D_0 vs D_{1-21}

Characteristic	D_0 RRT Median (IQR)	N	D_{1-21} RRT Median (IQR)	N	p value
BE meq/l	-12.1 (7.9)	34	-7.2 (7.2)	34	0.001
S_{Cr} µmol/l	505 (459)	42	331 (203)	34	0.03
INR	1.29 (0.37)	32	1.49 (0.6)	10	0.04
Cumulative fluid balance ml	0 (0)	42	2303 (1730)	34	0.001

Table 3.4: Diagnostic categories

Category	N	Percentage (%)
General Surgery	15	20
Internal medicine	28	37
Obstetrics and gynaecology	13	17
Trauma	17	22
Orthopaedics	3	4

Table 3.5: Relative frequencies of co-morbidities

Co – morbidities	N	Percentage (%)
Nil known	47	61.8
HIV	10	13.2
Hypertension	8	10.5
Diabetes	5	6.6
Multiple	6	7.9

Table 3.6: Admission (D_0) characteristics

Metabolic	D_0 (Median IQR)	n
pH	7.25(0.2)	76
BE (mmol/l)	-10.8 (9)	76
Lactate (mmol/l)	3.1 (4.4)	76
K^+ (mmol/l)	4.7 (1.4)	76
S_{Cr} (µmol/l)	349 (438)	76
Ca^{2+} (mmol/l)	2.08 (0.34)	57
Albumin (g/l)	24 (8.5)	72
Phosphate (mmol/l)	1.61 (1.29)	56
Na^+ (mmol/l)	137 (9.5)	76
Bilirubin (mmol/l)	13.5 (20)	70
Respiratory rate (breaths per minute)	26 (13)	76
P_aC02 (mmHg)	32 (5)	76
P/F ratio	264 (183)	76
Peak ventilator pressure (mmHg)	20 (13)	53
MAP (mmHg)	71 (29)	76
Heart rate (min)	123 (34)	76
Vasopressor use (n)	12 (33%)	36
Invasive ventilation (n)	53 (70%)	76
White cell count (g/dl)	12.1 (9.7)	76
C reactive protein (mg/l)	195 (159)	55
Procalcitonin (µg/l)	38 (76)	12
Sepsis present	63 (83%)	76
Hb (g/dl)	9.2 (3.4)	76
Platelet ($x10^9$/l)	168 (185)	76
INR	1.31 (0.34)	62
aPTT (sec)	40 (17.5)	48

SECTION 4: **PROPOSAL**

The indications for and timing of haemodialysis in critically ill patients with acute kidney injury in Johannesburg

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4.1. Introduction and problem statement

Acute kidney injury (AKI) is common amongst patients admitted to the intensive care unit (ICU), with incidences of between 1-70% being reported in developed countries depending on the classification used to diagnose AKI as well as the dominant demographic of the patients within the reporting ICU (1–4). AKI is an important disease entity as there is evidence that even mild reversible AKI confers significant independent risk for morbidity and mortality (5–12), and contributes to increased health care costs (13). Mortality rates quoted range from 15-82% (2,5,12). There is a scarcity of data to quantify the incidence of AKI in South African ICU's, however, it is likely to be higher than that of the developed world as a result of the burden of disease associated with AKI in this region (8)

Prior to 2004 there was no clear consensus for the definition and classification of AKI. In 2004 the acute dialysis and quality initiative group consisting of experts in nephrology and intensive care developed the RIFLE criteria to standardise the definition and classification of AKI (14). The RIFLE classification takes into consideration changes in serum creatinine values or glomerular filtration rate (GFR) from baseline along with urine output to determine the diagnosis and stage of disease. If any of the criteria are fulfilled the patient is then classified accordingly in terms of severity as either risk, injury, failure or clinical outcome as either loss or end stage (15). The RIFLE classification was identified as having shortcomings. The major problem identified was that the classification relies on a baseline serum creatinine which is not always available and thus an estimate is used (16). As a result, the scoring system does not always detect the presence of acute renal impairment. In an attempt to improve on the classification for AKI the Acute Kidney Injury Network (AKIN) proposed revised guidelines in order to increase sensitivity and reliability. Four main adjustments were applied to the RIFLE criteria including (7,16):

- adding an increase in serum creatinine equal to or greater than 0.3mg/dl to define AKI
- applying a time frame of 48 hours instead of from baseline when considering the rise in creatinine
- if RRT was required to immediately classify as stage three
- Risk, Injury, and Failure have been replaced with stage 1, 2, and 3 respectively and the outcome categories Loss and End stage renal disease have been eliminated.

In 2012, the Kidney Disease - Improving Global Outcomes (KDIGO) published clinical Practice Guidelines for AKI in which the important advances in knowledge surrounding AKI are presented as well as the numerous deficits that still require further research and validation (17). AKI is defined as any of the following (7);

- An increase in serum creatinine by ≥0.3mg/dl (≥26.5µmol/l) within 48 hours
- An increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
- Urine output volume <0.5ml/kg/hr for 6 hours,

and staged for severity according to criteria which is similar to that of the AKIN classification. The RIFLE, AKIN and KDIGO classifications are summarised in table 4.1(7,12).

Table 4.1: RIFLE, AKIN and KDIGO classifications for AKI

	S_{Cr} and GFR Criteria	Urine Output Criteria
RIFLE Category		
Risk	S_{Cr} increase by 1.5 fold or GFR decrease by >25% from baseline	<0.5 ml/kg/h for ≥6 hours
Injury	S_{Cr} increase by 2 fold or GFR decrease by >50% from baseline	<0.5 ml/kg/h for ≥12 hours
Failure	S_{Cr} increase by 3 fold or GFR decrease by >75% from baseline or S_{Cr} ≥354µmol/L with an acute increase of at least 44µmol/L	Anuria for ≥12 hours
Loss	Complete loss of function (RRT for > 4 weeks)	
ESRD	RRT >3 months	
AKIN Criteria		
Stage 1	S_{Cr} increase ≥27 µmol/L or 1.5-2 fold from baseline	<0.5 ml/kg/h for ≥6 hours
Stage 2	S_{Cr} increase >2-3 fold from baseline	<0.5 ml/kg/h for ≥12 hours
Stage 3	S_{Cr} increase > 3 fold from baseline or S_{Cr} ≥354 µmol/L with an acute increase of least 44 µmol/L or Need for RRT	<0.3 ml/kg/h for ≥24 hours or anuria for ≥12 hours
KDIGO Criteria		
Stage 1	S_{Cr} increase ≥27 µmol/L or 1.5-1.9 fold from baseline	<0.5 ml/kg/h for 6-12 hours
Stage 2	S_{Cr} increase >2-2.9 fold from baseline	<0.5 ml/kg/h for ≥12 hours
Stage 3	S_{Cr} increase > 3 fold from baseline or S_{Cr} ≥354 µmol/L or need for RRT	Anuria for ≥12 hours

Patients who are diagnosed with AKI within the ICU setting have been supported with various forms of haemodialysis for several decades. There are many studies that have attempted to decipher the conundrum of the optimal timing for treatment to be initiated. As a result of the high morbidity and mortality associated with AKI it was postulated that initiating dialysis prior to the classical or absolute indications (life threatening fluid overload, refractory hyperkalaemia, refractory or worsening metabolic acidosis) for renal replacement therapy (RRT) might confer better outcomes. The risks associated with RRT need to be balanced against the possible benefits of early RRT, especially considering that some patients with severe AKI may have spontaneous recovery of renal function (18,19). Early initiation of RRT prior to the onset of severe AKI could potentially prevent kidney specific damage whilst promoting greater kidney recovery, and remote organ injury resulting from fluid overload, electrolyte and metabolic imbalance and systemic inflammation (20,21). Early initiation of RRT was first investigated in 1960 in a prospective study of 15 patients with AKI where the entity of prophylactic haemodialysis was introduced (22). This study prompted further research into the merits of early initiation of RRT. Despite a large body of data, results are not easily comparable as a result of wide variations in definitions used both for the diagnosis of AKI and for what constitutes early initiation (14). Poor research methodology including retrospective design, small sample size and poor generalisability further compounded the short comings (18,23).

In 2008, a systematic review and meta-analysis was carried out to determine whether early versus late initiation of RRT in critically ill patients is associated with a survival benefit (24). The study included five RCT, one prospective cohort and 17 retrospective cohorts. Meta-analysis of the RCT studies showed a 36% mortality reduction with early initiation of RRT, however, this was not statistically significant (RR, 0.64; 95% CI, 0.4 to 1.05; p=0.08). In contrast, the meta-analysis of the cohort studies showed a 28% mortality risk reduction with early initiation of RRT which was statistically significant (RR, 0.72; 95% CI, 0.64-0.82; p <0.001). The authors concluded that early RRT may confer improved survival in patients with AKI.

Similarly, in 2011 a systematic review and meta-analysis which included two RCT, four prospective and nine retrospective cohorts was conducted (21). This study showed a 28-day mortality reduction with early RRT which was significant (OR 0.45; 95% CI 0.28-0.72). Like the previous study, the authors concluded that there may be benefit in terms of mortality reduction to early initiation of RRT in critically ill patients. In 2016, a further meta-analysis was performed which included 36 studies (25). This included seven RCT, seven prospective and 19 retrospective studies. Of these studies, only nine (six RCT, one prospective and two retrospective cohorts) were deemed to be of high enough quality to be included for analysis. This study concluded that there is no benefit to early initiation of RRT (OR 0.665; 95% CI 0.384-1.1153, p=0.146).

Subsequently three large prospective RCT have been conducted. The artificial kidney initiation in kidney injury (AKIKI) trial (26), the early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury (ELAIN) trial (27), and the initiation of dialysis early versus delayed in the intensive care unit (IDEAL-ICU) trial (28). The results of the AKIKI and IDEAL-ICU found that there is no mortality benefit in early initiation of RRT (p=0.79 and p=0.38 respectively), whereas the ELAIN trial found that there was with a mortality rate of 39.3% versus 53.7% in the late group (hazard ratio [HR], 0.66, 95% CI 0.45-0.97). However the ELAIN trial has been found to have multiple methodological flaws. There is currently a large well designed study, the Standard Versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial underway. The results of which will likely be very informative.

Although haemodialysis has been adopted internationally for many years there remains a wide variation in its application. The timing of initiation, modality, dose, and length of treatment remains controversial (2). Current recommendations for initiation of RRT in the setting of AKI are not graded due to a lack of high quality evidence. The recommendations by the KDIGO guidelines are that the broader clinical context should be assessed for conditions which can be modified by RRT, and trends in laboratory data should guide decision making rather than using isolated laboratory thresholds alone (14). A wide variation in interpretation and implementation of RRT amongst clinicians has resulted.

Currently there are no definitive guidelines worldwide for the optimal timing for the initiation of RRT. Some evidence to date has suggested that initiation of dialysis prior to the development of classical indications may confer better outcomes with respect to morbidity and mortality (21,24,27,29–33). A wide variation in implementation amongst clinicians has been observed (15). In the literature reviewed no data was found to provide information on current practices in South Africa or Africa with regard to the timing of RRT. These areas are resource constrained, thus evidence based practices may assist with equitable access to RRT.

4.2. Aim and objective

4.2.1. Aim

The aim of this study is to describe current practices with regards to the indications and the timing of RRT in patients with AKI, at the Chris Hani Baragwanath Academic Hospital (CHBAH).

4.2.1. Objectives

The primary objectives of this study are to:

- describe the indications for RRT in patients with AKI admitted to the ICU
- describe the timing of RRT in patients with AKI with reference to the KDIGO classification for the diagnosis of AKI

The secondary objectives are to:

- describe the characteristics of patients diagnosed with AKI who receive RRT
- describe severity of illness scoring of patients on admission and on day of RRT commencement
- estimate and describe possible delays in the implementation of RRT in patients with AKI
- describe the staging (KDIGO) of patients with AKI at the time at which RRT is initiated
- describe early patient outcome at ICU discharge

4.3. Research assumptions

This section clarifies definitions that will be used in this study.

Renal Replacement therapy (RRT): will refer to haemodialysis therapy. Haemodialysis can either be continuous or intermittent. Prolonged intermittent haemodialysis (IHD) included sustained low efficiency dialysis (SLED) and extended daily dialysis (EDD).

Intensive Care Unit (ICU): The specialised unit which offers organ support to critically ill patients at the CHBAH.

Adult: A person aged 18 and above.

Acute Kidney Injury: Acute kidney injury is defined as any of the following (7):

- An increase in serum creatinine by ≥0.3 mg/dl (≥27 µmol/l) within 48 hours
- An increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
- Urine output volume <0.5 ml/kg/hr for 6 hours.

Timing of RRT: will refer to the time at which a decision to dialyse a patient is made.

Initiation of RRT: will refer to the time at which dialysis is commenced.

4.4. Demarcation of study field

The study will be conducted in the adult ICU at the Chris Hani Baragwanath Academic Hospital, which is affiliated to the Faculty of Health Sciences of the University of the Witwatersrand.

The Chris Hani Baragwanath Acaedemic Hospital is the third largest hospital in the world and has approximately 3200 beds. It is located in Soweto, Johannesburg and serves a large population with over 150 000 inpatients per year. (34)

The ICU is a multidisciplinary adult and paediatric unit. It has 9 paediatric beds, 18 adult beds (9 trauma and 9 surgical/medical) and 9 adult high care beds.

The adult unit is staffed by a number of qualified intensivists as well as fellows in training. Each week the unit is covered by two clinicians who make decisions regarding patient care. There is no protocol for the initiation of RRT, the decision is made by either of the two clinicians covering the unit.

4.5. Current treatment regimens include

4.5.1. Fluid therapy

The 2 isotonic crystalloids used currently are Balsol and Ringers lactate(R/L) 0.9% Normal saline is not used unless specifically to treat a hyponatremia, hypochloraemia patient.

4.5.1. Renal replacement therapy

Continuous veno-venous haemodiafiltration (CVVHDF) is predominantly used, whilst IHD is used infrequently.

Indications for dialysis

- Hyperkalaemia
- Persistent or worsening metabolic acidosis
- Fluid overload
- Oliguria/anuria
- Persistently rising urea /creatinine
- Specific toxin removal
- Other: e.g temperature etc

4.6. Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Post Graduate Committee of the University of the Witwatersrand.

Permission to conduct the study in the adult ICU at CHBAH will be requested from the hospital CEO via the CHBAH Medical advisory committee. (Appendix 1)

Furthermore, additional permission will be requested from the Head of Department of the ICU Unit (Appendix 2).

As the proposed study will be a retrospective chart review with no patient impact and patient details will be kept separately, no informed consent will be sought. The gatekeeper of the records will be asked permission to access the data.

Anonymity will be ensured at all times with the use of a coded subject number associated with each patient. A document linking the participant's personal details to the subject number will be stored securely on a computer belonging to the principal investigator. Only the principal investigator and supervisors will have access to the matched coded subject number and access to the raw clinical data. Data will be stored securely for six years after the completion of the study. The data will be stored on an external hard drive with password protection.

The study will be conducted according to the principles of the Declaration of Helsinki (35).

4.7. Research methodology

4.7.1. Research design

A retrospective, contextual, descriptive research design will be followed in this study.

A retrospective study looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is established at the start of the study (36). In the proposed study, the information gathered will be used to describe events surrounding the decision to initiate haemodialysis and the time at which it is implemented, both of which have already occurred.

The study is contextual because the context of a single South African intensive care unit is the centre of interest.

4.7.1. Study population

The study population will consist of the records of adult patients admitted to the critical care unit who are diagnosed with AKI and are subsequently dialysed.

4.7.1. Study sample

Sample method

Convenience sampling will be used whereby all patients admitted during the period 1 January 2014 – 31 December 2015 who fulfil inclusion criteria will form part of the study. Patient charts from 2016 will not be included as some may be missing from archive owing to their need in other departments for example, forensic medicine. Convenience sampling is a non-probability sampling method that samples a number of patients present at the hospital, in this case in the past, which is easy for the researcher to sample (37). This type of sampling allows for collection of data within a relatively short period of time.

Sample size

Calculation of sample size was based on an estimated incidence of RRT of 5-10%, 95% confidence and a precision of 5%. The minimum required sample size was 33 patients. The study period from 1 January 2014 until 31 December 2015 was used to ensure this minimum sample size.

Inclusion and exclusion criteria

The inclusion criteria for this study will be:

- all adults (≥18 years old) admitted to the ICU
- patients with established AKI on ICU admission
- patients developing AKI during ICU admission
- Patients who receive supportive haemodialysis whilst admitted to the ICU

The exclusion criteria in this study will be:

- patients with established chronic kidney disease
- patients with transplanted kidneys

4.8. Data collection

4.8.1. Data collection method

Chart reviews of all adult patients admitted for the period of 1 January 2014 and 31 December 2015 will initially be assessed for patients who meet the inclusion criteria. Once patients have been identified for inclusion, data will be entered into an Excel ® spreadsheet. The data collected is shown in Figures 2-8. All data points will be collected on the day of admission as well as the day of RRT (if they differ) unless otherwise specified.

DEMOGRAPHICS		
Age (years)		
Mass (kg)		
Gender	Male	
	Female	
Diagnostic Criteria	Medical	
	Surgical	General
		Trauma
		Obstetrics and Gynaecology
	Other	
Presence of Co-morbidities	HIV	
	Hypertension	
	Diabetes Mellitus	
	Coronary Vascular Disease	
	Malignancy	
	Haematological Malignancy	
	Other	
Surgical Status	No Surgery	
	Emergency Surgery	
	Elective Surgery	

Figure 2: Demographics

METABOLIC AND RENAL CHARACTERISTICS	
Arterial Blood Gas (ABG)	pH
	HCO_3^- (mmol/L)
	Base Excess (BE) mmol/L
	Lactate mmol/L
Serum	Na^+ mmol/L[#]
	K^+ mmol/L
	Cl^- (mmol/L)[#]
	CO_2 (mmHg)
	Urea (Ur) (mmol/L)
	Serum Creatinine (S_{Cr}) µmol/L
	Corrected Calcium (Ca^{2+}) mmol/L
	Magnesium (Mg^{2+}) (mmol/L)
	Albumin g/L
	PO_4^- mmol/L
	Total Bilirubin mmol/L
Diagnosis and Severity of AKI according to KDIGO classification	See Table 1.1
Input/Output	UO in first 24 hours (ml)[#]
	Total fluid in first 24 hours (ml)[#]

Figure 3: Metabolic and Renal Characteristics

[#]Data points collected on the day of admission only

VENTILATION, OXYGENATION and HAEMODYNAMICS	
Vitals	Respiratory rate (breaths per minute)
	Heart rate (beats per min)
	Systolic Blood Pressure (mmHg)
	Diastolic Blood Pressure (mmHg)
	Temperature (°C)
Arterial Blood Gas	Mean Arterial Pressure (mmHg)
	PaO2 (mmHg)
Ventilator	PaCO2 (mmHg)
	Invasive ventilation (n)
Calculations	Peak ventilator pressure (mmHg)
Vasopressor/Inotrope use	FiO2 (mmHg)
	PF ratio (PaO2/ FiO2¥)
	(Adrenaline/Phenylephrine/Dobutamine)
	(mcg/kg/min)

Figure 4: Ventilation, Oxygenation and Haemodynamic

¥ F_iO_2 expressed as a fraction

SEPTIC MARKERS
White cell count (x10^9/L)
C Reactive protein (mg/L)
Procalcitonin (µg/L)
Beta D glucan (pg/ml)
Temperature °C

Figure 5: Septic Markers

ON THE DAY OF RRT	
ICU day	
SOFA score	
Delta SOFA score	
Urine Output	6 hours preceding timing of RRT
	24 hours preceding timing of RRT
Cumulative Fluid Balance	
Indication for dialysis	Worsening Acidosis
	Refractory Hyperkalaemia
	Oliguria/Anuria
	Fluid Overload
	Worsening Creatinine/Urea
	No indication
Delay in Initiation of RRT (hours)	

Figure 6: Additional data points captured at the timing of RRT

HAEMATOLOGICAL MARKERS
Haemoglobin (g/dL)
Platelet (Plt) ($x10^9$/L)
International normalised ratio (INR)
Activated Partial Thromboplastin Time (sec)

Figure 7: Haematological markers

OUTCOME AT ICU DISCHARGE	
Mortality	Alive
	Deceased
Dialysis Dependent	
Diuretic Dependent	
Total Days dialysed	

Figure 8: Outcome at the time of ICU discharge

In addition to the discrete data points collected three scores were captured for each of the patients. The first is the Glasgow Coma Scale (GSC). This score was calculated as part of the admission examination for each patient and recorded. The components of this score are shown in Figure 9. This score was initially developed for use in patients with traumatic brain injury (38), however it has gained widespread use in clinical practice. The Sequential Organ Failure Assessment (SOFA) (39) is a useful tool to stratify and compare patients in terms of their degree of organ dysfunction or failure on admission and the delta SOFA score can give information on the degree worsening of the organ dysfunction or failure. The SOFA score was calculated using the data points collected for the day of admission as well as on the day of RRT if this differed. The maximum number of points is 24 with a higher score correlating to a greater severity of disease. The components of the score are show in Figure 10. The Simplified Acute Physiology Score (SAPS) II is a severity of disease classification system (40). Similarly it was calculated using the data points collected on the day of admission. The maximum number of points is 163 with a higher score correlating to a greater severity of disease. The components of the score are shown in Figure 11.

GLASGOW COMA SCALE	
Eye opening response	
No eye response	1
Eye opening in response to painful stimulus (peripheral)	2
Eye opening to speech	3
Eye opening spontaneously	4
Verbal Response	
No Verbal Response	1
Incomprehensible sounds (moaning but no words)	2
Inappropriate words (random or exclamatory articulated speech, no conversational exchange)	3
Confused (patient responds coherently but there is some disorientation and confusion)	4
Orientated (patient responds coherently and appropriately to questions)	5
Motor Response	
No motor response	1
Extension to pain (extensor posturing: abduction of the arm, external rotation of shoulder, supination of the forearm, extension of the wrist, decerebrate response)	2
Abnormal flexion to pain (flexor posturing: Adduction of arm, internal rotation of shoulder, pronation of forearm, flexion of wrist, decorticate response	3
Flexion/withdrawl to pain	4
Localises painful stimulus	5
Obeys Commands	6

Figure 9: Glasgow coma scale

SEQUENTIAL ORGAN FAILURE ASSESSMENT	
P_a0_2/F_i0_2	
>400	0
300-399	1
200-299	2
100-199 with respiratory support	3
<100 with respiratory support	4
Platelet Count (x 10^3/µL)	
≥150	0
100-150	1
50-99	2
20-49	3
<20	4
Glasgow Coma Scale (See figure 9)	
15	0
13-14	1
10-12	2
6-9	3
<6	4
Bilirubin (mg/dL/µmol/L)	
<1.2/<20	0
1.2-1.9/20-32	1
2.0-5.9/33-101	2
6.0-11.9/102-204	3
≥12.0/>204	4
Mean Arterial Pressure (mmHg) OR Administration of Vasoactive Agents (mcg/kg/min)	
No hypotension	0
MAP <70	1
Dopamine <5 or dobutamine (any dose)	2
Dopamine >5, adrenaline ≤0.1 or noradrenaline ≤0.1	3
Dopamine >15, adrenaline >0.1 or noradrenaline >0.1	4
Creatinine (mg/dL/µmol/L) OR Urine Output (mL/day)	
<1.2/<100	0
1.2-1.9/110-170	1
2.0-3.4/171-299	2
3.5-4.9/300-440 OR <500	3
≥5.0/>440 OR <200	4

Figure 10: Sequential Organ Failure Assessment (SOFA)

SIMPLIFIED ACUTE PHYSIOLOGY SCORE II (SAPS)	
Age (years)	
<40	12
40-59	15
60-69	16
70-74	18
Heart Rate (beats/min)	
<40	11
40-69	2
70-119	0
120-159	4
≥160	7
Systolic Blood Pressure (mmHg)	
<70	13
70-99	5
100-199	0
≥200	2
Temperature ≥39°C	
Yes	3
No	0
GCS(See figure 9)	
14-15	0
11-13	5
9-10	7
6-8	13
<6	26
Pa02/Fi02	
No mechanical ventilation	0
<100	11
100-199	9
≥200	6
BUN (mg/dL) or serum Urea mmol/L	
BUN <28 or urea <10	0
BUN 28-83 or urea 10-29.6	6
BUN ≥84 or urea ≥30	10
Urine Output (ml/day)	
<500	11
500-999	4
≥1000	0
Sodium (mmol/L)	
<125	5
125-144	0
≥145	1
Potassium (mmol/L)	
<3.0	3
3.0-4.9	0
≥5.0	3
Bicarbonate (mmol/L)	
<15	6
15-19	3
≥20	0
Bilirubin (mg/dL/µmol/L)	
<4.0/68.4	0
4-5.9/68.4-102.5	4
≥6/≥102.6	9
White Blood Cell (x10^3/mm^3)	
<1	12
1-19.99	0
≥20	3
Chronic Disease	
None	0
Metastatic Cancer	9
Haematologic malignancy	10
AIDS	17
Type of Admission	
Scheduled Surgical	0
Medical	6
Unscheduled surgical	8

Figure 11: Simplified Acute Physiology Score II (SAPS)

4.8.1. Data analysis

The data will be analysed together with a biostatistician using the data entered in to the Microsoft Excel® spreadsheet using Statistica® version 13.3. Descriptive and inferential statistics will be used to analyse the data. For categorical data, frequencies and percentages will be used.

4.9. Significance of the study

Acute kidney injury is common in patients admitted to the ICU. There are currently no national or international guidelines as to the optimum timing for initiation of RRT. The ICU of interest has a number of clinicians who use their clinical judgement in making the decision to initiate RRT in patients with AKI. It is expected that this will result in a variation in practice which will be described. In addition, the ICU of interest functions on limited resources and thus, it is expected that there will be delays in initiation of RRT from the point at which a decision to provide RRT is made. Delays in initiation of RRT may result in deterioration of a patient's clinical condition. Poor clinical condition may impact on the effectiveness of the RRT once initiated. Results from the study may inform current policy within the CHBAH ICU.

4.10. Validity and reliability of the study

Validity and reliability will be used to ensure that the study's conclusions are in keeping with the study design. Validity as defined by Botma et al (41) "indicates whether the conclusions of the study are justified by the design and interpretation." The reliability of the study is a representation of the consistency of the measure achieved, i.e. if a valid measuring instrument is applied to a different group under different circumstances, it should produce the same results (41).

The validity and reliability of this study will be ensured by:

- The use of an appropriate study design and data collection techniques
- Charts reviewed with inadequate data will be reported upon and possibly excluded from the study
- The use of an internationally validated classification system for AKI
- A single investigator will be responsible for data

4.11. Potential limitations of the study

Convenience sampling will be used which incurs sampling error that may result in selection bias. The contextual design limits the study results in that they may not be applicable to other centres. As the data will be obtained from retrospective chart review, incomplete or poorly completed charts will impact on the accuracy and completeness of the data collected.

4.12. Project outline

4.12.1. Time frame

The proposed time frame for the process is outlined in Table 4.1.

Table 4.2: Project Outline

	2017										2018		
Activity	March	April	May	June	July	August	Sept	Oct	Nov	Dec	Jan	Feb	March
Chapter 1-3	■	■	■										
Proposal	■	■	■										
Ethics committee Assessment				■	■								
Postgraduate committee Assessment				■	■								
Data collection						■	■						
Data analysis								■	■				
Chapter 4-5										■	■		
Edit final draft												■	
Submit													■

4.12.1. Financial plan

The primary investigator will bear the cost of printing and paper for the proposal, ethics and postgraduate approvals. A cost estimate is show in Table 4..

Table 4.3: Proposed budget for the study

Description	Price per item	Number of items	Total
Printing of Proposal	60c per page	±400	R240.00
Printing data collection sheets	60c per page	±50	R30.00
Binding of final research report	R150	3	R450.00
Total			R720.00

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APPENDICES

Appendix A: Permission from the Medical advisory Committee

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 1 June 2017

TITLE OF PROJECT: The indications and timing of haemodialysis in critically ill patients with acute kidney injury admitted to ICU

UNIVERSITY: Witwatersrand

Principal Investigator: P Brown

Department: Anaesthesiology

Supervisor (If relevant): S Omar, L Redford

Permission Head Department (where research conducted): Yes

Date of start of proposed study: June 2017
Date of completion of data collection: Dec 2018

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

Recommended
(On behalf of the MAC)
Date: 01 June 2017

Approved/Not Approved
Hospital Management
Date: 03/06/17

Appendix B: Permission from Head of Department of ICU

health and
social development
Department: Health and Social Development
GAUTENG PROVINCE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
Intensive Care unit

Dr JM Brown
Jacqui.Brown@wits.ac.za
Tel: 0119381596
Fax:0119381595

25th May 2017

To whom it may concern

Re: Permission to conduct research for MMed in Chris Hani Baragwanath Hospital Intensive Care unit

Title of research project:
The indications and timing of haemodialysis in critically ill patients with acute kidney injury admitted to ICU

Investigator: Dr Patricia Brown

Permission is hereby granted for Dr P Brown to access ICU files for the purpose of her data collection. The data collected will be used for her MMed. Permission is subject to ethics approval.

Regards

Dr JM Brown
Deputy Head: Intensive Care Unit
Chris Hani Baragwanath Hospital
Soweto
Affiliated to University of the Witwatersrand

Appendix C: Ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Patricia Mary Brown

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170684

NAME: (Principal Investigator)	Dr Patricia Mary Brown
DEPARTMENT:	Anaesthesia Chris Hani Baragwanath Academic Hospital - Main ICU
PROJECT TITLE:	The Indications and Timing of Haemodialysis in Critically ill Patients with Acute Kidney Injury in Johannesburg
DATE CONSIDERED:	30/06/2017
DECISION:	Approved unconditionally
CONDITIONS:	Change of title 18/11/2019
SUPERVISOR:	Dr S Omar and Dr L Redford
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	26/07/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year. Unreported changes to the application November invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature   Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D: Approval of title

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

01 November 2019
Person No: 0317431P
TAA

Dr PM Brown
30 Fifth Road
Greymont
2195
South Africa

Dear Dr Patricia Brown

Master of Medicine: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Medicine** has been approved:

From:

To: **The indications for and timing of haemodialysis in critically ill patients with acute kidney injury in Johannesburg**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix E: Turnitin report

0317431p:PM_BROWN_MMED_TURNITIN_FORMAT.docx

ORIGINALITY REPORT

29%	22%	14%	16%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	ccforum.biomedcentral.com Internet Source	2%
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17	Paul M Palevsky. "Clinical review: Timing and dose of continuous renal replacement therapy in acute kidney injury", Critical Care, 2007 Publication	<1%

12 February 2020

Turinit in report Mmed in Anaesthesiology

RE: Patricia Brown- 0317431p

<u>Title: The indications for and timing of haemodialysis in critically ill patients with acute kidney injury in Johannesburg</u>

To whom it may concern,

The turnit in analysis was shown to have a 29% match overall, however, the high match rate is largely due to the use of common phrases and classification systems (RIFLE, AKIN, KDIGO etc). Furthermore, the use of the names of trials and quotation of the figures from the relevant trials, which are discussed and compared further in the literature review, have contributed to the percentage match.

The third resource where there is a match of 2% (*Abstracts of scientific presentations at the 2019 National Annual Congress of the Critical Care Society of Southern Africa in Cape Town, South Africa - Brenda Morrow*) is due to the publication of scientific abstracts that are available on the internet following presentation of the research at the CCSSA last year.

Both the student and supervisors has reviewed the turnit in report and we are satisfied that there is no evidence of plagiarism.

Kind Regards

Dr Lindsey Redford

MBChB (UCT), DA (SA), FCA (SA), Mmed (Anaes)
Private Practice
083 383 6988

Professor Shahed Omar

University of Witwatersrand, School of Clinical Medicine, Chris Hani Baragwanath Academic Hospital, Intensive Care Unit