

**STUDY OF EPIDEMIOLOGY, MANAGEMENT AND OUTCOME OF ACUTE
KIDNEY INJURY POST NONCARDIAC SURGERY OVER 12 MONTHS AT
GROOTE SCHUUR HOSPITAL, CAPE TOWN.**

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***THIS IS PART OF A LARGE PROSPECTIVE STUDY OF EPIDEMIOLOGY,
MANAGEMENT AND OUTCOME OF ACUTE KIDNEY INJURY
CONDUCTED BY RENAL UNIT AT GROOTE SCHUUR HOSPITAL***

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(Mmed-mini dissertation)**

Faculty of Health Science

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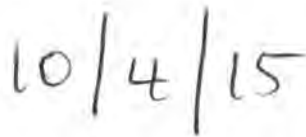
DECLARATION

This research is my own original work neither the whole work nor any part of it has been or being submitted for another degree to any University. None of this work has been published in any format prior to the registration for the above mentioned degree.

Signature

A handwritten signature in black ink, appearing to read 'Muzni'.

Date

A handwritten date in black ink, '10/4/15'.

DATE OF SUBMISSION: 20/01/2015

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ABSTRACT

INTRODUCTION: Acute kidney injury (AKI) is a disorder that is defined by rising serum creatinine and reduced urine output. It occurs in approximately 1-7% of hospitalized patients and is a major predictor of morbidity and mortality. It increases the costs and duration of hospital stay. AKI has been extensively studied post cardiac surgery, but there has been little attention on AKI occurring after non cardiac surgery. There have been few studies on AKI from developing countries and a paucity of data of post non cardiac surgery AKI.

OBJECTIVE: To identify which known risk factors for AKI are commonly encountered at Groote Schuur Hospital, to document 30 and 90 day mortality, length of hospital stay, recovery of renal function at 90 days and identify factors associated with outcome post non-cardiac surgery.

DESIGN: Prospective observational study.

SETTING: Surgical Wards and ICU.

PARTICIPANTS: Patients with AKI post non-cardiac surgery admitted between July 2012 and July 2013, who were 18 years and above without underlying stage 5 chronic kidney disease.

OUTCOME MEASURES: Mortality, identification of risk factors, length of hospital stay and recovery of renal function.

RESULTS: Of 367 patients referred to renal unit with AKI, 60 patients met inclusion criteria. Patients had an average age of 52.8 years (standard deviation 16.6) and 70% (42/60) were male. 61.7% (37/60) were Coloured, 20% (12/60) were White and 18.3% (11/60) were Black. These patients were exposed to the following risk factors: 80%(48/60) had emergency surgery, 66.7%(40/60) had sepsis, 65%(39/60) had perioperative contrast exposure, 53.3%(32/60) had hypotension that required inotropic support in 50%(30/60). Mortality was 33.3% (20/60) at 30 days and 45% (27/60) at 90 days. Of the 33 patients who did not die, 81.8% (27/33) recovered their renal function to normal baseline creatinine at 90 days. Of the 6 patients, whose renal function did not return to baseline, none required long term dialysis. Perioperative contrast exposure was associated with a longer median length of hospital stay compared to patients not exposed to contrast (21 vs 16 days respectively, $p < 0.05$). Sepsis and age > 60 years was associated with poor recovery of renal function ($p = 0.005$, $p = 0.01$ respectively). No risk factor was identified to be associated with mortality.

CONCLUSION: Risk factors for post non cardiac surgery AKI commonly encountered at Groote Schuur Hospital were emergency surgery, sepsis, hypotension, perioperative use of inotropes and perioperative contrast exposure. The latter was identified as a modifiable risk factor

which significantly prolonged hospital stay. Sepsis and age > 60 years were associated with poorer recovery of renal function.

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ABBREVIATIONS

ACEI- ANGIOTENSIN CONVERTING ENZYME INHIBITOR

ADQI- ACUTE DIALYSIS QUALITY INITIATIVE

AKI – ACUTE KIDNEY INJURY

AKIN –ACUTE KIDNEY INJURY NETWORK

APACHE 11 SCORE- ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION

ARF–ACUTE RENAL FAILURE

ASA PS-AMERICAN SOCIETY OF ANESTHESIA PHYSICAL STATUS

CKD–CHRONIC KIDNEY DISEASE

DM–DIABETES MELLITUS

GFR-GLOMERULAR FILTRATION RATE

GIT-GASTRO INTESTINAL TRACT

HTN–HYPERTENSION

KG-KILOGRAMS

ICU-Intensive Care Unit

NSAIDs-NON STEROIDAL ANTI-INFLAMMATORY DRUGS

RIFLE–RISK INJURY FAILURE LOSS ENDSTAGE RENAL DISEASE

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Study of epidemiology, management and outcome of acute kidney injury post non-cardiac surgery at Groote Schuur Hospital

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CHAPTER 1:

INTRODUCTION AND LITERATURE REVIEW

Acute renal failure is a syndrome characterized by rapid decline in glomerular filtration rate, retention of nitrogenous waste products and disturbance of extracellular fluid, electrolytes and acid base status (1). Recently the use of the word acute renal failure has been changed to the term acute kidney injury (AKI) which is thought to represent the spectrum of kidney dysfunction ranging from minor changes in serum creatinine or urine output to severe AKI requiring dialysis. In 2004 the Acute Dialysis Quality Initiative (ADQI) established a new definition and staging of AKI. The definition encompassed both changes in urine output and reduction in glomerular filtration rate. Essentially this involved a decline in urine output to less than 0.5ml/kg/hour over a period of 6 hours despite adequate fluid challenge, more than 25% decline in glomerular filtration rate and an increase in creatinine by more than 1.5 times the baseline. AKI is then staged into Risk- Injury-Failure-Loss-End stage renal disease (RIFLE) as shown in table 1 (2). It was thought that this definition would improve detection of early changes of renal dysfunction so as to prompt early action to prevent further progression. This definition of AKI by ADQI was subsequently modified by the AKI Network (AKIN) in 2007 to help improve the sensitivity of the RIFLE criteria as shown in table 1 (3). The AKIN definition included changes in serum creatinine as small as 0.3mg/dl (26.5mmol/L) if this change occurred in 48 hours, creatinine rise by 1.5-2 times the baseline that is known to have occurred within 7days and urine output of less than 0.5ml/kg/hour for 6 hours despite fluid challenge. They also reduced the number of stages of AKI to 3 instead of 5 originally suggested by the RIFLE criteria. Stage 4, 5 of RIFLE criteria and patients with AKI requiring dialysis were incorporated into stage 3 of AKIN. Despite the modification the AKIN criteria sensitivity was not improved in cardiac surgery patients compared to RIFLE (4, 5). One of the short comings of AKIN criteria is that the change in serum creatinine must be within 48 hours, which means if serum creatinine rises slowly such as 0.1mg/dl per day, AKI would not be identified. Both RIFLE and AKIN criteria are considered relevant to use when identifying cases of AKI (6). To avoid the complexity of using both RIFLE and AKIN criteria in practice (6), Kidney Disease Improving Global Outcome (KDIGO) recommended the following guidelines using the following criteria in a single definition (7):

Increase in serum creatinine by 1.5 times baseline within seven days.

Increase in serum creatinine by >0.3mg/dl (26.5mmol/L) within 48 hours.

Urine output \leq 0.5ml/kg/hour for 6hours.

TABLE 1-COMPARISON BETWEEN RIFLE AND AKIN CRITERIA IN IDENTIFYING AND CLASSIFYING AKI

AKIN STAGING	COMMON FEATURES OF RIFLE & AKIN CRITERIA (urine output)	RIFLE CLASS
Stage 1: increase of creatinine by 0.3mg/dl(26.5mmol/L) or by 1.5-2 times baseline	Urine output<0.5ml/kg/hour for 6 hours despite fluid challenge	RISK: increase in serum creatinine by 1.5 times baseline or GFR decrease>25%
Stage 2: increase of creatinine by 2-3 times baseline	Urine output<0.5ml/kg/hour for 12 hours	INJURY: 2 fold rise in serum creatinine 2 or GFR decrease>50%
Stage3: increase of creatinine by 3 times baseline or 4mg/dl(354mmol/L) or acute rise of at least 0.5mg/dl(44mmol/L) or on renal replacement therapy	Urine output<0,3 ml/kg/hour for 24 hours or anuria for 12 hours	FAILURE: increase in serum creatinine by 3 fold or >354mmol/L or acute rise of 44mmol/L or GFR decrease>75%
		LOSS: persistent acute renal failure with complete loss of renal functions >4 weeks
		END STAGE-ESRD >3 months

EPIDEMIOLOGY AND DISEASE IMPACT

The incidence of AKI among hospitalized patients may vary considerably depending on the criteria used to define AKI. In one study the incidence was reported to be 4.9% (9) but when the same data was analyzed some years later it was 7.2% (10). Among surgical patients with previous normal renal function undergoing major non-cardiac surgery using glomerular filtration rate to define cases of AKI, the incidence was 0.8% (12). In another study using AKIN criteria the incidence was 7.5% (11). These findings underlie the poor sensitivity of glomerular filtration rate to define AKI and need for criteria like RIFLE, AKIN or KDIGO. Treatment of AKI is expensive due to high cost directly related to the management of acute kidney disease and its associated complications, and the prolonged duration of hospital stay (8,13). In addition the mortality is high which is attributed to AKI and its complications rather than other postoperative complications and comorbidities (14,15,16). Post cardiac surgery even a small increase in serum creatinine as low as 0,5mg/dl is associated with increased mortality (17,18). Patients with previous normal renal function undergoing major non-cardiac surgery have a 1% risk of developing acute kidney injury which carries 8 fold rise in mortality within a space of 30 days (12,19). In addition AKI that has required dialysis is known to be an independent risk factor for mortality (20). Even after hospital discharge, patients with postoperative AKI are prone to

develop chronic kidney disease that sometimes requires long term chronic dialysis and reduced long term survival even after initial recovery of their renal function (14).

Published data regarding AKI in the post non-cardiac surgery population is scarce and only reported in high risk aortic procedures (21, 22). Our view is that the pathophysiological changes expected in non-cardiac surgery are different from those that occur in cardiac surgery patients and as a result we cannot assume that the risk factors and outcome of AKI after non-cardiac surgery are the same as those after cardiac surgery which support need for more studies to be conducted in non-cardiac surgery population as well.

A number of publications have addressed the incidence and risk factors for AKI after non-cardiac surgery (11, 12, 23, 27) though little is known about the prevalence and risk factors in developing countries.

RISK FACTORS AND CAUSES OF POSTOPERATIVE AKI

A number of studies have been conducted to establish risk factors associated with postoperative AKI with varying results as shown below. Abelha and colleagues studied determinants of AKI post major non-cardiac surgery, and found age, emergency surgery, high risk surgery, higher American Society of Anaesthesiology physical status (ASA-PS), congestive heart failure, ischemic heart disease and total revised cardiac risk index (RCRI) to be important risk factors (11). In addition the incidence of AKI has been reported to be increasing and black patients are reported to be at higher risk (8). In a study of predictors of postoperative acute renal failure after non-cardiac surgery in patients with previously normal renal function, old age, emergency operation, presence of liver disease, obesity, peripheral arterial disease, severe chronic obstructive pulmonary disease, intra-operative vasopressor use and diuretic administration were identified (12). Contrary to prior reports there is no association between perioperative use of a statin and the incidence of AKI post non-cardiac surgery provided the statin was used at a dose routinely used to treat hypercholesterolemia (24). In an AKI study after lung surgery, older age, higher BMI, higher ASA PS classification, lower preoperative haemoglobin, higher baseline creatinine, lower estimated glomerular filtration rate, CKD, hypertension, ischemic heart disease, diabetes mellitus, peripheral vascular diseases, intraoperative use of crystalloids, red blood cell transfusion, invasive surgery and duration of surgery and anaesthesia were identified as risk factors for postoperative AKI (23). Non-steroidal anti-inflammatory drugs, ACEI and ARB used preoperatively especially in patients with low blood pressure were additional risk factors (23).

Several studies have identified that fluid therapy with hydroxyethyl starch or red cell transfusion were also associated with AKI (25,27). Elevated intra-abdominal pressure whether caused by oedematous bowel in the setting of a noncompliant abdominal wall or accumulation

of blood (fluid) in the abdominal cavity is associated with postoperative AKI, multi-organ failure and high mortality (26).

TABLE 2: ETIOLOGY, EXPOSURE AND SUSCEPTIBILITY TO AKI (7).

EXPOSURE TO	SUSCEPTIBILITY(AT RISK FOR AKI)
Sepsis	Dehydration
Critical illness(multi-organ disease)	Old age
Shock(circulatory)	Female
Burns	Black race
Trauma	CKD
Cardiac surgery	Comorbidity
Major non-cardiac surgery	DM
Nephrotoxicity	Cancer
Radio-contrast agents	Anaemia

TABLE 3: RISK FACTORS FOR DEVELOPMENT OF POSTOPERATIVE AKI (11, 12, 23, 28)

Preoperative risk factors	Preoperative renal dysfunction Increasing age Heart disease (ischemic or congestive) Smoking Diabetes mellitus American Society of Anaesthesiology Physical Status class 4 or 5 (high anaesthetic risk)
Intraoperative factors	Emergency surgery or intraperitoneal, intrathoracic, supra-inguinal vascular surgeries Erythrocyte transfusion Inotrope use Aortic cross-clamp time Cardiopulmonary bypass, furosemide use
Postoperative factors	Erythrocyte transfusion Vasoconstrictor use Diuretic use Antiarrhythmic drugs

TABLE 4: COMMON CAUSES OF POSTOPERATIVE AKI (1).

DIFFERENTIAL	PRERENAL	RENAL	POSTRENAL
DIAGNOSIS			
	HYPOTENSION: Absolute Relative	ACUTE TUBULAR NECROSIS: Ischemia reperfusion Radiocontrast	URINARY CATHETER OBSTRUCTION: catheter kinking debris
	HYPOVOLEMIA absolute Relative such as Intra-abdominal pressure	ACUTE INTERSTITIAL NEPHRITIS	Prostate hypertrophy with urinary retention

PREVENTION OF AKI

During initial evaluation of a patient, it is important to assess for presence of known risk factors for AKI as shown in (table 2) and do frequent monitoring of renal functions in those individuals found to be at risk of AKI (20).

WAYS TO PREVENT AKI POSTOPERATIVELY ARE: (7).

1. Assessment and monitoring of hemodynamics.
2. Administration of fluid
3. Inotropic support
4. Protect against development of intra-abdominal hypertension
5. Protect against development of contrast induced nephropathy
6. Pharmacological intervention

MONITORING

Postoperative AKI is associated with systemic hypovolaemia, hypotension or decreased cardiac output that results in renal hypoperfusion. On the other hand, fluid resuscitation resulting in a positive fluid balance causes increased risk of death after 60 days (29). It is therefore important to monitor haemodynamics to optimize patient outcome. A meta-analysis has demonstrated that AKI risk is reduced by optimization of haemodynamics whether it is done before, during and after operation (30). It is unclear which instrument to use in monitoring as there is no benefit found in using pulmonary catheters though these catheters are still being used to

monitor cardiac output in high risk patients (32). The noninvasive cardiac monitoring techniques that are used are pulse pressure variation and esophageal Doppler probes during perioperative period to assess fluid status (31). At our institution we use clinical assessment of blood pressure response to tilt testing, intra-arterial line, Doppler probe to assess venous filling and pulse pressure variation, and ultrasonic cardiac output monitoring.

FLUID THERAPY

The use of fluid therapy to prevent postoperative AKI is the recommended method of prevention, though the amount of fluid to be given is not clear. It has been shown that fluid accumulation in very sick patients is associated with high risk of death and was not associated with improvement of renal function (45). Fluid accumulation was associated with cardiopulmonary complications and reduced tissue healing post colorectal surgery (33). Fluid boluses given according to the changes in mean systemic arterial pressure improve postoperative outcome (34). This Goal Directed Fluid Therapy is associated with fewer complications and reduced mortality (35). Early Goal Directed Fluid Therapy is therefore recommended in patients at high risk of developing AKI such as patients with sepsis and shock (30). There is still a debate regarding which type of fluid to be used in resuscitation because colloids have been demonstrated to increase the filling of the heart but the overall advantage of colloids in terms of mortality in comparison to the crystalloids has not been shown (36). Cochrane review (37), found that there is no evidence from randomized controlled trials that resuscitating with colloids instead of crystalloids reduces mortality risk in patients with trauma, burns and following surgery. Several studies have shown that hydroxyethyl Starch is nephrotoxic (25). The mechanisms of colloid induced renal injury are poorly understood though it could involve direct molecular effect or elevated oncotic pressure (38). It is thought hypertonic hydroxyethyl Starch causes osmotic nephrosis that eventually leads to renal dysfunction (39). Guidelines advise using isotonic crystalloids rather than colloids as initial management for expansion of intravascular volume in patients at risk of AKI or with AKI in the absence of hemorrhagic shock though colloids might still have a role in patients requiring additional fluid (7). Blood used in resuscitation is also associated with increased risk of AKI as described in cardiothoracic surgery (27). Urinary alkalization is protective for the kidneys in patients undergoing cardiopulmonary bypass (40) but it has not been studied in patients undergoing post non-cardiac surgery.

VASOPRESSOR THERAPY

The indication for vasopressor therapy use is persistent hypotension despite adequate fluid resuscitation that threatens organ function (41). Sepsis and septic shock remains among the leading causes of AKI (42) and once there is sepsis and requirement for vasopressor therapy, the risk for AKI also increases in these patients. The target is to maintain a mean arterial

pressure that suffices all organ functions which ranges from at least 60mmHg to even higher mean arterial pressures in patients with chronic hypertension (43).

PREVENTION OF INTRA-ABDOMINAL HYPERTENSION

Some patients develop renal dysfunction as a result of intra-abdominal hypertension, discussed in previous section as one of the causes of decreased urine output and AKI.

The causes of elevated abdominal pressure could be blood accumulation in the abdominal cavity, fluid accumulation in the abdominal cavity, distension of the bowel and closure of abdomen when the bowel is edematous (26).

A widely used method of measuring abdominal pressure is through bladder transduction, and if it is high then the procedure to decrease abdominal pressure must be done such a therapeutic paracentesis or exploratory laparotomy that may prevent AKI (43).

GLUCOSE CONTROL:

Earlier studies showed that tight control of glucose was associated with good results in patients treated in the intensive care unit and reduced need for renal replacement therapy (44) but subsequent studies did not show this positive outcome which requires further studies to clear this contradiction(46, 47). Current guidelines do not recommend strict glucose control in intensive care unit in critically ill patients (69).

AVOIDANCE OF CONTRAST INDUCED NEPHROPATHY (CIN)

Contrast induced nephropathy can be defined as development of new AKI following contrast exposure. CIN can be prevented by intravenous fluids given before and after the administration of contrast and this has been demonstrated to minimize the risk of contrast induced nephropathy (48), though the type of fluid remains controversial. In one study it was shown that intravenous sodium bicarbonate in patients for coronary angiography minimizes the risk of contrast induced nephropathy compared to those receiving only normal saline though there was no improvement in outcome such as length of hospital stay and mortality (49). Though initial studies assessing the effect of N-acetyl-cysteine in prevention of CIN showed inconclusive results (49) current guidelines recommend use of N-acetyl-cysteine and intravenous isotonic crystalloids in patients at increased risk for contrast induced nephropathy.

There is strong correlation between the volume of contrast media administered and risk of contrast induced AKI (50). Multiple studies suggest that the risk of contrast induced AKI is low in patients with few risk factors even after use of high osmolar contrast. In contrast in high risk patients such as diabetics or patients with chronic kidney disease, high osmolar contrast increases the risk and it is recommended to use low osmolar contrast (51,52).

PHARMACOLOGICAL INTERVENTION

There are several drugs that must be avoided or used with caution in patients at risk of AKI such as contrast, aminoglycosides, amphotericin B, cyclooxygenase inhibitors and immunosuppression such cyclosporin (57). Fenoldopam has not been fully studied in the management of AKI patients as in some experimental work it showed some benefit but large studies are required (62). Current practice does not recommend use of fenoldopam to treat or prevent AKI. There are not sufficient numbers of studies on the use of atrial natriuretic peptide in AKI but on a systemic review of existing literature atrial natriuretic peptide appears to be associated with beneficial effects when used in patients undergoing major surgery (53). Atrial natriuretic peptide use is not recommended to treat or prevent development of AKI in current practice. Furosemide therapy in patients with AKI is not associated with better outcome (54; 55). It was shown that furosemide given in the intra-operative period was associated with renal dysfunction (60) so furosemide use in these patients is not recommended. When using aminoglycosides such as gentamicin, a once daily dosing has been associated with reduced nephrotoxicity compared to multiple dosing (56). It is important to stress the importance of avoiding use of these drugs if it is possible, but if it is really necessary in the use of them, then it is better to use a once daily dose with close monitoring of drug levels.

PROPHYLACTIC RENAL REPLACEMENT THERAPY:

Prophylactic dialysis in patients at high risk of AKI who are undergoing major surgery such as coronary bypass surgery was associated with reduced mortality although it is not clear whether there is same benefit in patients who are not at high risk (58). Similarly in patients with chronic renal failure undergoing percutaneous coronary intervention, peri-procedural dialysis was associated with reduction in contrast induced worsening of renal function and appears to improve outcome (59). However current guidelines do not recommend use of prophylactic dialysis in patients undergoing general contrast exposure (7).

MANAGEMENT OF DECREASED URINE OUTPUT AND AKI

The fundamental principle in treating all AKI is to treat the underlying cause. If the cause is unknown or cannot be reversed immediately then avoidance or minimizing use of nephrotoxins and assessment of fluid deficit is important to the management of AKI.

Renal perfusion is maintained by fluid therapy or inotropic support when it is necessary. Goal directed fluid therapy is advised. There has been growing interest to use diuretics in the management of AKI with oliguria and this has resulted in increased risk of death in patients with AKI (61) and diuretic use is ineffective in treatment of AKI itself. In hypovolaemic state diuretics

use must be avoided so as not to precipitate AKI (62). Other drugs such as dopamine and atrial natriuretic peptide have not been shown to improve outcome in AKI (62). The management of AKI includes monitoring of body weight, maintenance of fluid intake to match fluid output and monitoring of serum chemistries and acid base status with a view to initiate renal replacement therapy if refractory hyperkalemia or refractory metabolic acidosis or refractory volume overload or systemic uraemia is noted (63).

DIALYSIS:

There is general agreement that dialysis must be started if there is fluid overload, systemic uraemia, refractory hyperkalemia and refractory metabolic acidosis (7). Studies have suggested an early dialysis improves outcome (67,68). Although there are no controlled trials comparing the types of dialysis, it is recommended to use continuous renal replacement therapy in patients with haemodynamic instability (low blood pressure). It has an advantage of avoiding complications such as cerebral disequilibrium syndrome though it is associated with high rate of venous clotting and immobilization. Intermittent haemodialysis is preferred in patients where rapid fluid, electrolytes or toxin removal is required as in patients with pulmonary oedema, hyperkalemia and poisoning though it has a disadvantage of cerebral disequilibrium syndrome (7). Low efficiency haemodialysis (SLED) has advantages of both continuous renal replacement therapy and intermittent haemodialysis with little disadvantage of each (7). Peritoneal dialysis is no longer commonly used these days except in children and poorly resourced areas. Its advantages are that no vascular access problems are involved, no associated venous thrombosis, no bleeding risk, no disequilibrium syndrome and is not associated with haemodynamic instability. Disadvantages are low effectiveness (as in splanchnic hypoperfusion), the risk of peritonitis and respiratory compromise that occurs by development of acute hydrothorax. The studies have failed to show the benefit of using high dose of hemodialysis compared to standard dose (64, 65, 66). Timing of stopping dialysis has not been studied but the current practice guidelines suggest that it is influenced by initial indications for dialysis. Although AKI post non-cardiac surgery have been studied with most studies conducted in developed countries, we know little about epidemiology, management, outcome and factors influencing the outcome in developing countries.

There is therefore an important need to study the epidemiology, management and outcome of AKI post non-cardiac surgery in South Africa to help establish prevention and treatment protocols relevant to developing countries and allocation of scarce health care resources.

OBJECTIVES

To identify which known risk factors for AKI post non-cardiac surgery are commonly encountered at GROOTE SCHUUR HOSPITAL

To document mortality at 30 days and 90 days.

To document length of hospital stay.

To document recovery of AKI after 90 days.

To identify factors associated with recovery of renal function, mortality and length of hospital stay

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CHAPTER 2

PUBLICATION READY MANUSCRIPT

STUDY OF EPIDEMIOLOGY, MANAGEMENT AND OUTCOME OF AKI POST NON-CARDIAC SURGERY.

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Key words: Acute kidney injury, non-cardiac surgery, risk factors and outcome.

Authors contribution: L Mzingeli and T Dlamini designed the study.

Professor B Rayner supervised the study

Katya Mauff (statistician) and Mzingeli analyzed data

K.Ncwana and D. Blanckenberg both assisted with patient follow up.

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ABSTRACT

INTRODUCTION: Acute kidney injury (AKI) is a disorder that is defined by rising serum creatinine and reduced urine output. It occurs in approximately 1-7% of hospitalized patients and is a major predictor of morbidity and mortality. It increases the costs and duration of hospital stay. AKI has been extensively studied post cardiac surgery, but there has been little attention on AKI occurring after non cardiac surgery. There have been few studies on AKI from developing countries and a paucity of data of post non cardiac surgery AKI.

OBJECTIVE: To identify which known risk factors for AKI are commonly encountered at Groote Schuur Hospital, to document 30 and 90 day mortality, length of hospital stay, recovery of renal function at 90 days and identify factors associated with outcome post non-cardiac surgery.

DESIGN: Prospective observational study.

SETTING: Surgical Wards and ICU.

PARTICIPANTS: Patients with AKI post non-cardiac surgery admitted between July 2012 and July 2013, who were 18 years and above without underlying stage 5 chronic kidney disease.

OUTCOME MEASURES: Mortality, identification of risk factors, length of hospital stay and recovery of renal function.

RESULTS: Of 367 patients referred to renal unit with AKI, 60 patients met inclusion criteria. Patients had an average age of 52.8 years (standard deviation 16.6) and 70% (42/60) were male. 61.7% (37/60) were Coloured, 20% (12/60) were White and 18.3% (11/60) were Black. These patients were exposed to the following risk factors: 80%(48/60) had emergency surgery, 66.7%(40/60) had sepsis, 65%(39/60) had perioperative contrast exposure, 53.3%(32/60) had hypotension that required inotropic support in 50%(30/60). Mortality was 33.3% (20/60) at 30 days and 45% (27/60) at 90 days. Of the 33 patients who did not die, 81.8% (27/33) recovered their renal function to normal baseline creatinine at 90 days. Of the 6 patients, whose renal function did not return to baseline, none required long term dialysis. Perioperative contrast exposure was associated with a longer median length of hospital stay compared to patients not exposed to contrast (21 vs 16 days respectively, $p < 0.05$). Sepsis and age > 60 years was associated with poor recovery of renal function ($p = 0.005$, $p = 0.01$ respectively). No risk factor was identified to be associated with mortality.

CONCLUSION: Risk factors for post non cardiac surgery AKI commonly encountered at Groote Schuur Hospital were emergency surgery, sepsis, hypotension, perioperative use of inotropes and perioperative contrast exposure. The latter was identified as a modifiable risk factor

which significantly prolonged hospital stay. Sepsis and age > 60 years were associated with poorer recovery of renal function. 418/500

INTRODUCTION:

Acute kidney injury may be defined as a metabolic disorder that is characterized by a rise in serum creatinine and a decrease in urine output. Its incidence varies from 1 -7% depending on the criteria used to define AKI (4,5,10,11). AKI is predictor of morbidity and mortality and it increases cost and duration of hospital stay (12,13). It also occurs as a complication following surgery. According to the available literature, there are few studies on AKI post non-cardiac surgery in comparison to post cardiac surgery AKI. In addition there is a paucity of data on AKI in developing countries.

There is therefore an important need to study epidemiology, risk factors, management, the timing of dialysis and outcome of AKI in South Africa to help establish preventative and management protocols relevant to developing countries.

AIM:

To establish the epidemiology, management and outcome of AKI post non-cardiac surgery.

METHODS:

The Faculty of Health Science Research Ethics Committee at University of Cape Town approved the study (303/2012).

All patients referred to Renal Unit by Surgical Wards and ICU with AKI post non-cardiac surgery between 1 July 2012 and 30 June 2013 were assessed with documentation of demographics, comorbidity, chronic medication and toxins, and full physical examination.

Patient were excluded if they were younger than 18 years, post cardiac surgery, had no surgical procedure and had pre-existing CKD stage 5.

The indications for admission and surgery, complications post-surgery (such as sepsis, hypotension), intra and postoperative data (such as inotrope, colloids, blood transfusion, nephrotoxic drugs) were recorded and calculation of Apache II Score was done (6).

AKI was defined using AKIN and RIFLE criteria, and staging of AKI as shown in table 1, whether patients were dialyzed or not was recorded.

Risk factors for AKI post non-cardiac surgery were documented (3,4,5). Mortality was observed at 30 days and 90 days as well as length of hospital stay and recovery of renal function.

Factors associated with recovery, mortality and length of hospital stay were analyzed. Subject confidentiality was ensured through removal of patient identifiers in data collection and analysis.

FINANCIAL ASSISTANCE: the study was funded by a MMed Research Grant from the University of Cape Town.

STATISTICAL ANALYSIS

All variables were described using tables. Continuous variables (for example the length of hospital stay or Apache II score) were described using summary statistics, specifically: the number of subjects for whom the value was not missing, the range (minimum to maximum), median and interquartile range (IQR: 25th to 75th percentile). Means and standard deviations were not used, as none of the continuous variables were symmetrically distributed.

Associations between continuous variables and categorical variables (for example between the Apache II Score and the binary recovery to normal baseline creatinine variable) were assessed using Mann-Whitney Tests (aka the Wilcoxon Rank Sum test). The null hypothesis of this test is that the median values or distribution of the continuous variable is the same for each value of the categorical variable. Nonparametric tests were used instead of T-tests because of the skewed underlying distributions of the continuous variables. Tests were assessed for significance at the 5% level. Differences in the median values of the continuous variables between categories were described and graphically presented using Box and Whisker Plots. These plots show the median, interquartile range, range and outlying values, where outliers are determined to be any value more than 2.5 times the IQR.

Associations between categorical variables were assessed using contingency tables, Chi-squared tests of association, and Fisher's Exact tests where appropriate (where the numbers in the contingency tables were small). Contingency tables (cross-tabulations of the two variables being investigated) were done. The Chi-squared test of association assumes as its null hypothesis that the variables of interest are independent of one another. P-values less than 5% indicate that this hypothesis should be rejected.

Finally, associations between continuous variables are determined using the Spearman Rank Correlation, and graphically illustrated with scatter plots. Significance is again assessed at the 5% level.

RESULTS

A total number of 367 patients were referred to renal unit with acute kidney injury between July 2012 and July 2013.

307 patients were excluded because AKI was not associated with post non cardiac surgery.

60 patients met inclusion criteria.

The following data could not be accounted for:

Missing data:

- Comorbidity: 7
- Perioperative drugs: 1
- Perioperative Inotrope: 7
- Perioperative blood transfusion: 1
- Perioperative colloids : 1
- Apache II score: 9
- AKIN Stage: 7

TABLE 5: Patient demographics, mortality, recovery of renal functions and length of hospital stay.

Variables	N =60	Recovery to baseline creatinine (%)	Mortality (%)		Development of CKD (%)	Length of hospital stay Median(IQR)
			30 DAYS	90 DAYS		
AGE(YEARS)						
<60	36	21(35%)	10(16.7%)	14(23.3%)	1(1.7%)	21 (14)
>60	24	6(10%)	10(16.7%)	13(21.7%)	5(8.3%)	21(17.5)
GENDER						
Male	42	18(30%)	13(21.7%)	19(31.7%)	5(8.3%)	21(11)
Female	18	9(15%)	7(11.7%)	8(13.3%)	1(1.7%)	15(14)
RACE						
Coloureds	37	14(23.4%)	14(23.3%)	18(30%)	5(8.3%)	21(14)
White	12	5(8.3%)	5(8.3%)	6(10%)	1(1.7%)	21(7)
Black	11	8(13.3%)	1(1.7%)	3(5%)	0%	21.5((27)
COMORBIDITY						
Diabetes	9	4(6.67%)	3(5%)	5(8.3%)	0%	21(19)
No diabetes	46	20(33.3%)	16(26.7%)	20(33.3%)	6(10%)	14(21)
HTN	25	8(13.3%)	11(18.3%)	14(23.3%)	3(5%)	21(14.5)
No HTN	28	10(16.7%)	8(13.3%)	15(25%)	3(5%)	21(14)
CKD	3	2(3.3%)	0(0%)	0(0%)	1(1.7%)	21(56)
No CKD	50	21(35%)	18(30%)	23(38.3%)	5(8.3%)	21(16)

TABLE 6: Patient demographics, mortality, recovery of renal function and length of hospital stay.

Variables	N=60	Recovery to baseline creatinine (%)	Mortality (%)		Development of CKD (%)	Length of hospital stay Median(IQR)
			30 DAYS	90 DAYS		
TYPE OF SURGERY						
Emergency	48	20(33.3%)	19(31.7%)	22(36.7%)	6(10%)	21(14)
Elective	12	7(11.7%)	4(6.7%)	5(8.3%)	0%	21(17.5)
RISK factors						
Inotropes	30	11(18.3%)	13(21.7%)	16(26.7%)	3(5%)	21(14)
No inotropes	23	11(18.3%)	7(11.7%)	9(15%)	3(5%)	21(14)
Colloids	12	5(8.3%)	4(6.7%)	5(8.3%)	2(3.3%)	21(33.5)
No colloids	47	22(36.7%)	16(26.7%)	21(35%)	4(6.7%)	21(19)
Blood transfusion	22	8(13.3%)	6(10%)	11(18.3%)	3(5%)	21(11)
No blood transfusion	37	19(31.7%)	15(25%)	15(25%)	3(5%)	21(15)
Contrast	39	17(28.3%)	15(25%)	18(30%)	4(6.7%)	21(11)
No contrast	21	10(16.7%)	6(10%)	9(15%)	2(3.3%)	16(15)
NEPHROTOXINS						
Polymixin E	5	1(1.7%)	2(3.3%)	4(6.7%)	0%	21(43.5)
NSAIDs	2	2(3.3%)	0%	0%	0%	21(14)
Gentamicin	4	1(1.7%)	3(5%)	3(5%)	0%	16.5(14.5)
COMPLICATIONS						
Hypotension	32	16(26.7%)	11(18.3%)	13(21.7%)	3(5%)	21(15)
No hypotension	28	11(18.3%)	9(15%)	14(23.3%)	3(5%)	21(14)
Sepsis	40	13(21.7%)	15(25%)	21(35%)	6(10%)	21(14)
No sepsis	20	14(23.3%)	6(10%)	6(10%)	0%	21(18.5)
APACHE II SCORE						
<20	25	13(21.7%)	9(15%)	10(18.3%)	2(3.3%)	21(14)
>20	26	8(13.3%)	10(16.7%)	14(21.7%)	4(6.7%)	21(11.5)
AKIN STAGE						
Stage 1	4	3(5%)	0%	0%	1(1.7%)	21(8)
Stage 2	11	4(6.7%)	4(6.7%)	5(8.3%)	2(3.3%)	21(21)
Stage 3	38	17(28.3%)	15(25%)	19(31.7%)	2(3.3%)	21(14)
DIALYSIS (acute)						
Yes	43	16(26.7%)	15(25%)	21(35%)	6(10%)	21(14)
No	17	10(16.7%)	6(10%)	7(11.7%)	0%	21(16.5)

TABLE 7: Summary of selected AKI variables

Variable	N	Min	Max	Mean	Std Dev.	Median	25th Percentile	75th Percentile
Apache II Score	51	10	39	21.8	7.1	20	17	27
Urine Output	60	9	3740	676.0	799.7	365	169	938
Duration of dialysis days	42	1	77	10.6	12.9	7	2	14
No of days between AKI and dialysis	42	0	20	3.3	4.2	2	1	3
Length of hospital stay	60	3	90	24.4	20.0	21	14	28

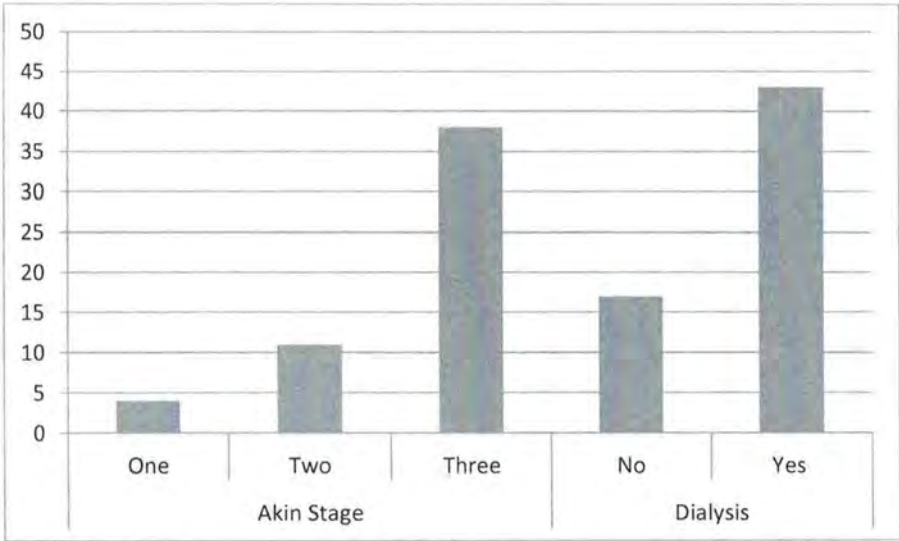


FIGURE 1: AKIN staging and number of patients who received and did not receive acute dialysis.

Out of 60 patients, 70% (42/60) were male and 30% (18/60) were female with a mean age of 52.8 years (standard deviation 16.6). 61.7% (37/60) were Coloured, 20% (12/60) were White and 18.3% (11/60) were Black. 80% (48/60) had emergency surgery and 20% (12/60) had elective surgery. Patient demographics are shown in table 5 and table 6. AKIN staging and number of patients who received and did not receive acute dialysis is shown in figure 1. Known perioperative risk factors that were common in our study population were sepsis in 66.7% of patients, contrast exposure in 65% of patients, hypotension in 53.3% of patients, inotrope use in 50% of patients and emergency surgery in 80% of patients. Other perioperative risk factors that were found but not common in our study population were colloid exposure in 20% of patients, blood transfusion in 36.7% of patients. Very few patients had perioperative nephrotoxins such as aminoglycosides in 6.7% of patients, polymixin E in 8.3% of patients and NSAIDs in 3.3% of patients. Important comorbidities were CKD in 5% of patients, diabetes mellitus in 15%, and hypertension in 41.7%. The mortality was 33.3% (20/60) in 30 days and 45% (27/60) in 90 days. 55% (33/60) of patients were alive in 90 days and out of this number 81.2% (27/33) had recovery of renal function to baseline while 18.2% (6/33) had no recovery of renal function though no chronic dialysis was required. There was poorer recovery of renal function to baseline in patients with sepsis ($p=0.005$) and age older than 60 years ($p=0.011$).

The calculated median length of hospital stay was 21 days. An association was found between patients who were exposed to contrast and length of hospital stay. The individuals that did not receive contrast had a median length of hospital stay of 16 days (IQR: 9-21), compared to those that did have contrast, who had a median length of hospital stay of 21 (IQR: 17-28, $p<0.04$) as shown in table 6. No association between length of hospital stay and colloids, blood transfusion, inotrope use and Apache II Score as shown in table 6.

RECOVERY TO NORMAL BASELINE RENAL FUNCTION

The total number of patients alive at 90 days were 55%(33/60) and recovery of renal function to normal baseline occurred in 45% (27/60) of patients at 90 days while (10%) 6/60 had no recovery of renal function to baseline. Recovery of renal function in relation to baseline demographics, comorbidities and risk factors is shown in table 5 and 6. Statistical association was noted between recovery of renal function to normal baseline and patients with no sepsis 70% (14/20) versus patients with sepsis 32.5% (13/40) with $p=0.005$ and patients who were 60 years or younger 58.3% (21/36) versus older than 60 years 25% (6/24) with $p=0.01$. No other variables were found to have statistical association with recovery of renal function to normal baseline though certain trends were noted. For instance recovery of renal function was lower in diabetic patients 66.7% (4/9, $p=0.96$), in hypertensive 32% (8/25, $p=0.78$), in patients with CKD 66.7% (2/3, $p=0.36$), those undergoing emergency surgery 41.7% (20/48, $p=0.30$), receiving blood transfusion 36.4% (8/22, $p=0.26$) and in patients exposed to colloids 41.7% (5/12,

p=0.75). Contrary to expectations, recovery of renal function was better in patients receiving contrast 43.6% (17/39, p=0.76), in patients with hypotension 50% (16/32, p=0.41) and in patients with higher APACHE II Score 30.8% (8/26, p=0.12). The number of patients receiving other nephrotoxins was too few to be meaningful.

DEVELOPMENT OF CKD

Development of CKD occurred in 10% (6/60) of patients at 90 days though none of these patients required chronic dialysis. All the patients who developed CKD had emergency surgery, sepsis and acute dialysis as shown in table 5 and 6. Most of these patients were older than 60 years 8.3% (5/60), coloured 8.3% (5/60), males 8.3%(5/60), had APACHE II Score>20 in 6.7% (4/60) and exposure to contrast in 6.7% (4/60). This association between variables and CKD was not statistically meaningful due to fewer numbers of patients who developed CKD. No other factors were noted to be associated with development of CKD. Among patients who developed CKD, 16.7% (1/6) had baseline CKD.

MORTALITY

Overall mortality was 33.3% (20/60) at 30 days and 45% (27/60) at 90 days. The relationship between the variables and mortality is shown in table 5 and 6. No mortality was observed in patients who had baseline CKD. No statistical association between variables and mortality was shown for example mortality at 90 days in patients with APACHE II Score>20 or \leq 20 was statistical insignificant (p=0.12), in patients exposed to sepsis, mortality was 52.5% (21/40, p=0.099), exposed to contrast, mortality was 46.2% (18/39, p=0.76), with emergency surgery, mortality was 45.8% (22/48, p=0.30), with acute dialysis, mortality was 48.8% (21/43, p=0.59), exposed to inotrope, mortality was 53.3% (16/30, p=0.30) and with hypotension, mortality was 40.6% (13/32, p=0.41). Mortality in patients on nephrotoxic drugs and patients with important comorbidity was few to be meaningful.

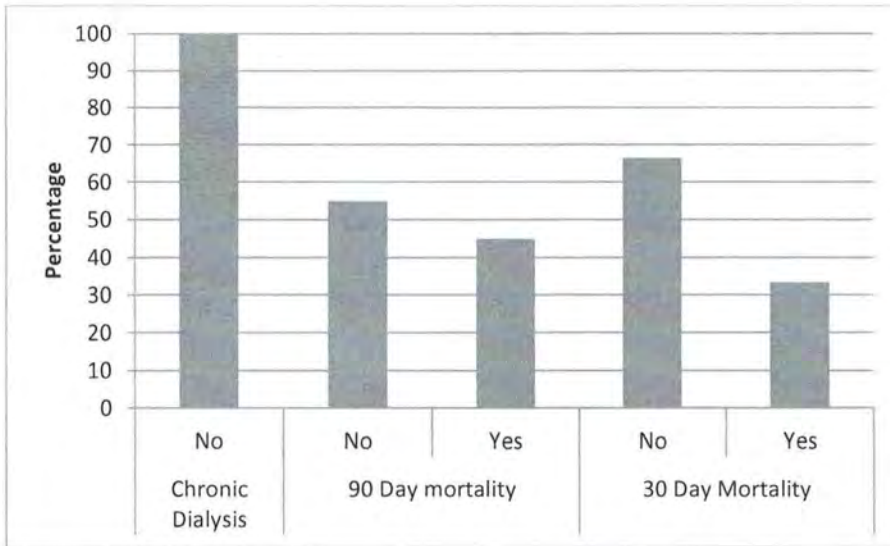


FIGURE 2: Mortality at 30 and 90 days and chronic dialysis.

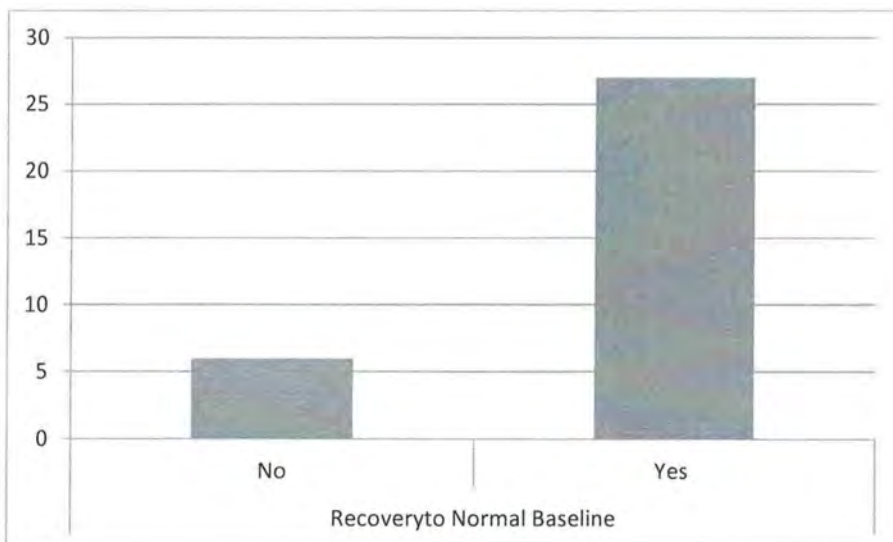


FIGURE 3: Recovery to normal baseline.

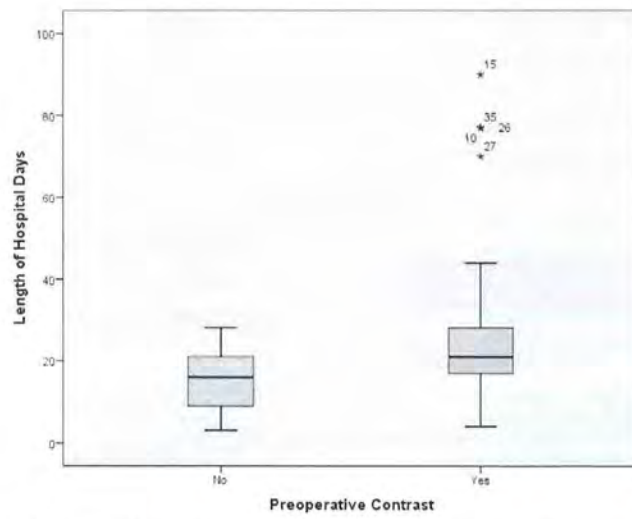


FIGURE 4: The relationship between perioperative contrast use and length of hospital stay.

DISCUSSION AND CONCLUSIONS

Recognized risk factors for AKI were common in our study population at Groote Schuur Hospital. For example 80% had emergency surgery, 66.7% had sepsis, 65% had contrast, 53.3% had hypotension and 50% had inotropic support. Other perioperative risk factors that have been identified in other studies (4,5) were not common in our study population. For instance 20% were exposed to colloids, 36.7% to blood transfusion, 8.3% to Polymixin E, 6.7% to aminoglycosides, 3.3% to NSAIDs. Some important comorbidities previously described to be associated with AKI post non-cardiac surgery (4,5) were noted as 5% had CKD, 15% had DM and 41.7% had hypertension.

The importance of identifying these risk factors is that occurrence of postoperative AKI can be prevented or minimized by appropriate interventions. These risk factors can be divided into modifiable and non-modifiable. In our study, the modifiable risk factors were perioperative sepsis, perioperative contrast use, hypotension, inotrope use, nephrotoxin use, blood transfusion and colloid use. The non-modifiable risk factors were emergency surgery, age and presence of comorbidity. Sepsis has been identified as the leading cause of AKI which is difficult to control once it is present (8). It can be prevented by frequent hand washing to avoid the spread of infection among patients, use of contact precautions, maintenance of sterility during surgical procedures, isolation of infectious patients and early appropriate treatment of index cases. Contrast is known to be associated with prolonged hospital stay and high mortality (7). All high risk patients for AKI should have rehydration before, during and after contrast exposure. Use of low osmolality contrast is associated with low risk of developing AKI in a high risk patients and N-acetyl-cysteine before and after contrast exposure. Hypotension requires high level of haemodynamic monitoring, identification and treatment of the cause of hypotension such as sepsis, hypovolemic shock and neurogenic shock. Haemodynamic monitoring is also important for identifying patients with fluid overload as it is associated with poor outcome in critical ill patients. The ideal method to use in monitoring remains unclear (10) as the recommended invasive pulmonary catheters have not been found to be the best tool. Haemodynamic assessment in our patients was done by combination of clinical assessment of blood pressure response to tilt testing, intra-arterial line, use of Doppler probes to assess the venous filling and pulse pressure variation and ultrasonic cardiac output monitoring. Aggressive treatment of shock with fluids using goal directed fluid therapy (11) and inotropic support where it is necessary is recommended according to the available evidence (24,25) and this therapy was applied to our patients. Fluid type to be used in patients with AKI or at risk of AKI is not known (9). Though colloids have been found to be nephrotoxic (1), no studies have compared the colloids and crystalloids or showed benefit of crystalloids over colloids. Current guidelines advise initial resuscitating with crystalloids but if additional fluid is needed then colloids could be used. In our study 20% of patients received colloid and the remainder of our patients were

given crystalloids. No association was identified between fluid type and outcome in this study which could be related to small sample size. Inotrope use must be limited to patients who remain hypotensive despite adequate fluid resuscitation as in septic shock or neurogenic shock (24,25). 50% of patients received inotropic support for different forms of shock (mainly septic and hypovolemic). No other pharmacological agents other than vasopressor therapy were used to prevent AKI as recommended on the practice guidelines. Red blood cell transfusion has been described to be associated with AKI in other studies (3). About 36.7% of patients received perioperative blood transfusion in this study.

In patients with non-modifiable risk factors such as emergency surgery, old age and comorbidities, AKI can be prevented by identifying patients at high risk of AKI during initial assessment and doing frequent monitoring of renal function. This risk stratification is not commonly practiced in our environment except in those patients who are admitted to intensive care unit. In this study with the exception to 41.7% of patients with hypertension, there were relative few patients with comorbidities as shown that only 15% had diabetes mellitus and 5% had CKD. This could be due to the fact that most of our patient had emergency surgery which is related to trauma involving fit and young patients.

In this study population, nephrotoxins (18,19,20) were not common as shown that only 6.7% patients were exposed to aminoglycosides, 8.3% of patients were exposed to Polymixin E and 3.3% were exposed to non-steroidal anti-inflammatory drugs. This minimum use of nephrotoxins is probable related to increasing awareness about disadvantages of using these drugs. NSAIDs are generally avoided in patients at high risk of AKI, whereas polymixin E and aminoglycosides would only be given if no alternative drug. Aminoglycosides are best avoided but if they have to be given then a once daily dosing should be used (21) and monitoring of drug levels is advised.

33.3% (20/60) mortality at 30 days and 45% (27/60) mortality at 90 days after non-cardiac surgery was noted. This high mortality has been described to vary from 45% to as high as 89.1% in cardiovascular surgery and 84.6% in non-cardiac surgery (2). Various factors were associated with increased mortality, but none were statistically significant presumably due to small sample size. In patients older than 60 years the mortality rate was higher compared to patients \leq 60 years (54.2% versus 38.9%, $p=0.24$). This difference could be related to old age associated frailty and underlying comorbidities. There was also low mortality in Blacks (27.3%) compared to Whites (50%) and Coloured (48.6%). This could be due to the fact that some of these patients especially Whites were transferred as complicated cases following surgery at private hospitals whereas most Blacks had first surgery at our hospital. The mortality was high in patients with diabetes mellitus with 55.6% compared to patients without diabetes with 43.5% ($p=0.96$). Diabetic patients with poor control are prone to infections (22) which eventually lead to death

if it is not treated aggressively. Death was significant in patients who were on inotropic support (53.3%) compared to patients who required not inotropic support (39%, $p=0.30$). This high mortality was probable related severity of underlying disease such as septic shock. There was also high mortality in patients who received blood transfusion (50%) compared to patients who had no blood transfusion (40.5%, $p=0.26$). The number of patients who had transfusion did not correlate with number of patients with high Apache II Score (Apache II Score >20). Red blood transfusion is associated with impairment of immune function, increased risk of infections, acute lung injury and volume overload. Mortality could also be attributed to the fact that patients who bleed tend to be transfused. So patients who receive blood transfusion are at increased risk of multiple organ failure due to these factors (23). There was a higher mortality in patients with APACHE II Score >20 (53.8%) compared to patients with APACHE II Score ≤ 20 (40%, $p=0.12$). Most patients with high APACHE II Score have multi-organ failure which predisposed them to death. In one study, factors associated with high mortality were multi-organ failure, perioperative hypotension, oliguria, need for dialysis and emergency surgery (2), but we did not find any of this association on statistical analysis in our study probable due to the fact that our sample size was too small. Death was not statistically significant ($p=0.47$) in patients with hypotension (40.6%) compared to patients with no hypotension with mortality of 50%. Emergency surgery had 45.8% mortality compared to elective surgery with mortality of 41.7% which was found to be insignificant, $p=0.79$. Patients who required dialysis had 48.8% mortality compared to those who needed no dialysis who had 41.2% mortality ($p=0.59$). No other variables associated with mortality were found.

Recovery to normal baseline renal function occurred in 45% (27/60) of patients. This recovery was significant in patients who were 60 years or younger (58.3%) compared to patients who were older than 60 years (25%) $p=0.01$. This poor recovery of renal function associated with advanced age has been described in other studies (15). Elderly patients are predisposed to development of renal dysfunction due to age associated decline in glomerular filtration rate and therefore minor insult to the kidney easily results in AKI. Recovery of renal function is also impaired due to poor reserve in renal function when compared to younger patients. Interestingly in patients with sepsis the recovery of renal function was observed in 32.5% compared to patients with no sepsis with renal function recovery in 70%, $p=0.005$. Sepsis can affect kidneys in many ways such as immune complex deposition, acute tubular necrosis secondary to hypotension and sepsis in the kidney itself and the likelihood of renal recovery would depend on the underlying mechanisms. There was no other statistical observation partly due to sample size. However there were interesting trends. For instance there was increased recovery to baseline renal function in female (50%) in comparison to males (42.9%, $p=0.61$). This recovery could be related to the fact that our study population included young females 27.8% (5/18) who had caesarian section who tend to have excellent overall prognosis due to their age and lack of comorbidity. Recovery was also observed in patients with elective surgery (58.3%)

compared to emergency surgery patients (41.7%), $p=0.30$. Patients operated on emergency bases are likely to be complicated by multiple factors such as hypotension and sepsis therefore they are likely to have poor recovery of renal function. Interestingly recovery to normal renal function in patients with hypotension (50%) was higher than those without hypotension (39.3%, $p=0.41$). Some patients with no hypotension could have had positive fluid balance which is also associated with increased risk of death after 60 days (13). Patients receiving inotropic support showed statistically insignificant less recovery of renal function (36.7%) when compared with patients who were not on inotropic support (47.8%) $p=0.41$. Inotropes are known to be associated with poor renal perfusion and recovery would depend on the duration of inotropic support and underlying etiology. Blood transfusion patients had less recovery of renal function (36.4%) compared with patients with no blood transfusion (51.4%), $p=0.26$. Red blood transfusion is associated with impairment of immune function, increased risk of infections, acute lung injury and volume overload as described above. There was poorer recovery of renal function recovery in patients with acute dialysis (37.2%) versus patients without acute dialysis (58.8%) $p=0.12$. Patients with no acute dialysis had better recovery which could be related to absence of complications such metabolic acidosis, hyperkalemia, fluid overload and systemic uraemia. No other variables were associated with recovery of renal function to normal baseline.

Incomplete recovery of renal function was observed in 10% (6/60) of patients. Most of these patients had emergency surgery 10% (6/60), diabetes mellitus (10%), sepsis (10%), acute dialysis (10%) and patients were older than 60 years (8.3%) but this data was too small to make statistical significance. Again this was related to small sample size.

Median Length of hospital stay was 21 days. There was an association found between length of hospital stay and perioperative contrast use with $p=0.04$. It has been described in other studies that contrast induced AKI is associated with prolonged hospital stay and high hospital mortality (7). The method used to prevent contrast induced nephropathy in our patient was rehydration, use of N-acetyl cysteine though this measure was not applied to all our patients probably due to lack of protocols. As part of prevention of CIN, there is a need to identify patients who are at high risk of developing AKI such as dehydration, old age, female gender, Black race, CKD, DM, anaemia and cancer patients as shown in table 2. These patients when undergoing procedure involving contrast, they need to have proper rehydration, treatment with Acetyl Cysteine, use of lower osmolality contrast and frequent monitoring of renal function. It must be emphasized that there is conflicting results in available clinical trials and met-analysis examining the effectiveness of acetyl-cysteine in prevention of CIN (16,17) though its use is still recommended

by KDIGO 2012 guidelines because it has potential benefit, is cheap and well tolerated. No other factor was found to be associated with prolonged hospital stay.

General management:

Glucose was managed with insulin infusion as recommended in the guidelines (12).

No prophylactic dialysis was used on these patients as recommended by the current guidelines.

Dialysis was offered to 71.7% of patients according to the known indications for acute dialysis such as refractory metabolic acidosis, refractory hyperkalemia, systemic uremia, fluid overload and persistent oliguria. The earliest dialysis was started within a day of surgery and longest duration of dialysis was 77 days. Mortality was not different between early dialysis (on day 0 to day 1 after AKI) and late dialysis (beyond day 2 after AKI), $p=0.66$. Recovery to normal baseline renal function was not different between early dialysis (on day 0 to day 1 after AKI) and late dialysis (beyond 2 days after AKI), $p=0.94$. The mode of dialysis was determined by individual haemodynamic status and indication for dialysis on that specific day. The available forms of dialysis were intermittent haemodialysis, low efficiency haemodialysis and continuous haemodialysis. The factors determining discontinuation of dialysis were recovery of patient or lack potential benefit of continuing dialysis due to irreversibility of underlying disease process. Death among dialyzed patients was 48.8% (21/43) compared to 41.2% (7/17) in patients who were not dialyzed which was not statistically different between these two groups ($p=0.59$). This is contrary to previous studies reporting high mortality among dialyzed patients compared to patients who were not dialyzed. This reduced difference in mortality between the two groups could be due to multiple reasons such high mortality in patients who were not dialyzed or reduced mortality in dialyzed patient related to early initiation of dialysis, and successful management of underlying disease and its complications. Our study followed these patients only for a period of 90 days and reduced long term survival and development of CKD has been described even after initial recovery of renal functions and discharge from hospital (14).

Our study was limited by length of follow up. The sample size was small limiting the power of the study. All the referred cases of AKI were referred to Renal Unit because they had renal dysfunction requiring intervention which means that there might be cases of AKI which were not referred, so this sample size might not be true reflection of total number of AKI cases post non cardiac surgery that occurred. Urine output was not always recorded accurately to define cases of AKI.

The fact that it was conducted in one hospital makes it difficult to generalize the results.

Loss of patient data during follow up of these patients affected the validity of the study.

The observational nature of the study makes difficult to comment on the causative factors and the lack of control group makes it difficult to determine the prevalence of AKI.

Despite these limitations the study offers insight to the presence of emergency surgery, sepsis, hypotension, vasopressor use and perioperative contrast use as commonly encountered risk factors for postoperative AKI in our population.

We also document 33.3% mortality at 30 days and 45% mortality at 90 days, the recovery of renal function to normal baseline in 45% of patients after 90 days. It was also observed that patients older than 60 years and patients with sepsis were associated with significant poor recovery of renal function. The median length of hospital stay of 21 days in patients exposed to contrast compared to those patients who had no exposure to contrast with length of hospital stay of 16 days which is significant.

Given the lack of resources in our environment and the impact of AKI in our population, we suggest prevention of AKI by assessment of risk factors for AKI as part of initial assessment along with appropriate biochemistry and this biochemistry must be repeated on regular basis in high risk individuals. Haemodynamic monitoring using clinical assessment, intra-arterial line, Doppler probes and electronic cardiac output monitoring in the absence of gold standard tool is recommended. Fluid therapy using goal directed therapy is recommended. Crystalloid must be used as initial fluid for resuscitation but colloids could be added if additional fluid is needed. Avoidance of nephrotoxic drugs in high risk patients for AKI if possible or if nephrotoxins are to be given, a high level of monitoring of biochemistry and drug levels in high risk patients is necessary. We also recommend strict infection control. Contrast exposure prophylaxis in high risk patients undergoing contrast exposure.

The future study on this topic is required but large sample size will be of value.

A trial on fluid type to be used in patient with high risk factors for AKI is required.

Best tool for hemodynamic monitoring is needed.

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APPENDIX

DATA COLLECTING SHEET

Name & GSH Reference

Date of birth

M/F

Date

Hospital Admission Date

Referral Date

Reason For Referral

Baseline Creatinine & Date

Current Creatinine

Past History:Med/Surgery/Obste & Gynae

Family History

Medication/Toxins/Drug Sensitivity/Allergy

Habits

BP	HR	RR	Temp	Sat	Vent/FIO2	Inotrope dose	Visidex/glucose

ABG/VBG

General examination

Derm/MSK/Endo

Respiratory System

CVS

Abd/GUS

Neuro

ABG

Fluid State(hypovol/euvol/hypervol)

Urine Volume

24hours

48hours

Fluid Intake Past 24 hours & Type(enteral/intrav/medication/blood products)

Peri-operation contrast exposure

Intra-operation medication

Post operation medication use

Complication of surgery

APACHE 11 SCORE

Investigations-baseline creatinine

Complete flow chart overleaf

Urine dips	Urine vol	CXR	ECG	Rena u/s	Hep B	Hep C	HIV
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Assessment

Plan:dialysis-Y/N

Renal Required Y/N Changes

Dialysis mode	Dialysis reason	Blood pump speed	UF first Y/N	Duration	Heparin Y/N minimal or citrate	UF goal
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FOLLOW UP SHEET

FOLLOW UP FOR DIALYSIS (need for dialysis, duration of dialysis and type of dialysis)

FOLLOW UP FOR MANAGEMENT (nephrotoxic drugs and nephrotoxic agents)

FOLLOW UP FOR RECOVERY (normalizing of renal functions and development of CKD)

FOLLOW UP FOR MORTALITY (mortality at 30 days and 90 days)

RESULTS FLOW SHEET

DATE									
Na									
K									
Urea									
Creat									
Cal.cor									
Mg									
PO4									
Hb									
MCV									
Wcc									
PLT									
INR									
Alb									
ALT									
Glucose									
PH									
PCO2									
PO2									
SBC									
Lactate									
Upr									
Druglevel									

HIV Results

if positive CD4

HBSAg

Hep C

Micro Results

DATE: 12 September 2013

Dr L Mzingeli

Student Number: MZNLUV001

BY EMAIL

Dear Dr Mzingeli

Approval of Change of Title

Degree	MMed in Medicine
Old Title	Incidence of AKI post non-cardiac surgery
New Title	Study of epidemiology, management and outcome of AKI post non-cardiac surgery of Groote Schuur Hospital
Department	Medicine
PhD Supervisor	Prof B Rayner
Ethics approval	303/2012

I am pleased to advise that the Chair of the Doctoral & Master's Committee has approved your candidature for the above degree on behalf of the Committee. Formal approval was obtained via Dean's Circular PG-Med June 2013.

Yours sincerely

Jackie Cogill

