PREVALENCE, SEVERITY AND OUTCOMES OF COMMUNITY ACQUIRED ACUTE KIDNEY INJURY IN MEDICAL PATIENTS AT KENYATTA NATIONAL HOSPITAL

DISSERTATION SUBMITTED IN PART FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE (INTERNAL MEDICINE), THE FACULTY OF MEDICINE, UNIVERSITY OF NAIROBI.

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DEDICATION

I dedicate this work to my beloved parents who have always been my source of inspiration and encouragement throughout my life and to my lovely wife Farida and my beautiful daughter Tasneem who have been a strong pillar of support throughout this study.

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LIST OF ABBREVIATIONS

ACE-1	Angiotensin converting enzyme inhibitors
ADQI	Acute dialysis quality initiative
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ARBs	Angiotensin receptor blockers
ARVs	Anti retrovirals
ATN	Acute tubular necrosis
BUN	Blood urea nitrogen
CIN	Contrast induced nephropathy
CKD	Chronic kidney disease
DPT	Diphtheria-pertussis-tetanus
E.g	Example
GFR	Glomerular filtration rate
GN	Glomerulonephritis
HRS	Hepatorenal syndrome
KDIGO	Kidney disease improving global outcomes
KNH	Kenyatta national hospital
LOHS	Length of hospital stay
NSAIDs	Non steroidal anti-inflammatory drugs
RBC	Red blood cell
RCT	Randomized control trial
RIFLE	Risk, injury, failure, loss of kidney function, end stage kidney disease

ABSTRACT

Introduction

Acute kidney injury (AKI) results in a decline in the glomerular filtration rate. It has a high prevalence both in the developed and developing countries and is frequently encountered in hospitalized patients; it has a negative impact on mortality and morbidity.

Objectives

This study was designed to determine the prevalence of community acquired acute kidney injury in all patients admitted to the medical wards at Kenyatta National Hospital during the study period, to determine the severity of acute kidney injury based on the KDIGO criteria and to elucidate the associated risk factors of acute kidney injury. The management modalities were described as well as their outcomes at the point of discharge or after 2 weeks.

Method

A longitudinal study was carried out on acute kidney injury at Kenyatta National Hospital. All patients over the age of 13 years admitted to the general medical wards were followed up prospectively for 2 weeks and those diagnosed to have AKI were assessed daily for severity, risk factors and outcome

Results

A total of 136 patients were enrolled from August 20th 2016 to November 22nd 2016. The period prevalence was found to be 8.1% at admission. Most of the patients had stage 1 AKI (51.5%) while the rest had stage 2 and stage 3 AKI (48.6%). Only 2 patients underwent RRT. The median length of stay was 9 days, 11 days and 10 days in stages 1, 2 and 3 respectively. There was no association between AKI severity and length of hospital stay. 60% had non-recovery while 21 patients (18.6%) recovered fully and the more severe the AKI, the lesser the chances of recovery with a p value of 0.045. The in-hospital all- cause mortality during the study period was 23 patients (16.9%). The severity of AKI increased the chances of mortality with a p value of 0.012. The commonest cause of AKI was pre-renal, followed by intrinsic then obstructive.

Conclusion

AKI is common in our environment. Similar findings have been noted in developed countries. Prevalence and mortality in patients with AKI is high. The severity of AKI was associated with non- recovery, mortality and need of renal replacement therapy with no association in the length of hospital stay.

1. Introduction

Acute kidney injury (AKI) is a widespread problem of epidemic status and the new consensus term for acute renal failure. It is a clinical syndrome characterized by a rapid (hours to days) decrease in renal excretory function (1).The replacement of the term acute renal failure to acute kidney injury is to emphasize that a continuum of kidney injury exists that begins long before sufficient loss of excretory kidney function can be measured with standard laboratory tests. Acute kidney injury also suggests a continuum of prognosis, whereby even small rises in serum creatinine leads to increasing mortality, and a further increase in mortality as the serum creatinine continues rising (2).

Most of the epidemiological data on AKI comes from developed world settings. In these settings AKI is predominantly hospital acquired and up to 22% of adult patients are affected during an inpatient stay(3,4). These patients develop adverse outcomes, even in its mildest forms, with mortality across all stages of AKI estimated at 21%, increasing with AKI severity(3,5). Moreover, it can lead to other organ dysfunction and the development or progression of chronic kidney disease (CKD)(6).

AKI has been thought to have a vast global burden. 85% of the world's population lives in developing world settings and assuming the same incidence and outcome of AKI to high-income countries, this equates to an estimated 13 · 3 million cases of AKI per year worldwide with a potential 1 · 7 million deaths (7). The greatest impact of AKI may therefore be in the poorest parts of the world. However, in these regions the epidemiological data on AKI is most limited and where adverse outcomes from AKI may be preventable with relatively cheap and simple interventions (8,9).

There had been no consensus on the diagnostic criteria or clinical definition of AKI, resulting in multiple different definitions until recently when the risk, injury, failure, loss, end stage renal disease (RIFLE), acute kidney injury network (AKIN) and kidney disease improving global outcomes (KDIGO) criteria came about. Because of this confusion, there has been wide variability in the reporting of incidence and clinical significance (10).

2. Literature Review

2.1 Epidemiology of AKI

The epidemiology of AKI has changed over the years. This may partly be caused by change in patient characteristics, but more importantly, by change in definition of the disease (11). Pameena Susantitaphong et al did a meta-analysis study on the world incidence of AKI in 2013 and found that 21.6% adults and 33.7% children experience AKI worldwide using the KDIGO definition. Higher rates of AKI were observed in critical care settings and after cardiac surgery (4).

In developed countries, hospital acquired AKI is more common as the disease burden is dominated by lifestyle- related chronic diseases and degenerative disorders in the elderly. It usually occurs as part of multiple organ involvement in an already hospitalized elderly patient or after surgical or diagnostic interventions, and iatrogenic factors have an important role (12,13). Trauma, surgery and sepsis contribute to a majority of the cases of AKI in developed countries(14)

The prevalence of AKI in the developed world has increased in the last decade because of the availability of standardized criteria for diagnosis and staging of AKI (15). Kaufman et al. reported that community-acquired AKI was responsible for 1% of all hospital admissions, with a great proportion presenting pre-renal etiology and a low mortality (7%)(16) . A study done in the United Kingdom by Finlay et al. showed that acute kidney injury was present in 55/316 (17.7%) patients, with sepsis, hypovolaemia, chronic kidney disease (CKD) and diabetes mellitus identified as the major risk factors (17). In USA there has been an average of 23.8 cases per 1000 discharges with an 11% yearly increase between 1992 and 2001 (18,19). In Spain incidences have increased from 61 to 288 per 100,000 population from 1998 to 2002 (20). Ali et al reported an incidence of 1811 cases of AKI per million population in Scotland with sepsis as the most frequent precipitating factor (47%) followed by hypovolemia (32%).They also found a mortality of 56% and full renal recovery from the AKI at 68% (21).

Community acquired acute kidney injury

Despite improvements in preventive and diagnostic facilities, community acquired acute kidney injury (CAAKI) is still one of the main reason for admissions to nephrology units. The etiology of CAAKI in the tropics is different from that seen in other countries.

The incidences from some of the countries are as follows:

- Kuwait: 4.1 per 100,000 population per year (22)
- North India: 6.4 cases per 1000 admissions (23)
- Brazil: 7.9 cases per 1000 hospital admissions (24)

In the developing countries, especially in rural areas or smaller cities in the countryside, AKI is usually a community-acquired disease, affecting younger and previously healthy individuals (14). In Africa, CAAKI is a challenging problem because of the disease burden especially HIV related AKI, malaria, nephrotoxins mainly from herbal remedies and diarrheal diseases, late presentation of patients to health facilities, lack of resources to support AKI patients and paucity of data on the epidemiology (25).

Some studies have been done in Africa to look at the number of cases of AKI. In Nigeria, 11.7 cases of AKI per year in children in a hospital that serves more than 1 million children was reported by Anochie et al.(26). A study done by Emmanuel Effa et al. showed an AKI prevalence of 3.6% in hospitalized patients at the University of Calabar Teaching Hospital in Nigeria (27). In South Africa the incidence of AKI is 20 cases per year per million population (25,28).

In Kenya, there is no nationwide data on the prevalence of AKI but there are some center based studies which have tried to look at the prevalence and outcomes of AKI. Peter Munyu looked at prevalence, risk factors and outcomes of AKI at a private facility in Nairobi and found a period prevalence of 1.05% with higher values found in the critical care areas (29)

2.2 Etiology of AKI

Fry et al in a review of AKI has classified the causes into 3 groups (30).

1. **Prerenal AKI** represents the most common form of kidney injury and often leads to intrinsic AKI if it is not promptly corrected. It accounts for approximately 70% of all community acquired cases of AKI (31). The causes can be attributed to:

I. **Volume depletion** which can be caused by the following: **renal losses** - Diuretics, polyuria , **gastrointestinal (GI) losses** - vomiting, diarrhea, **cutaneous losses** - burns, Stevens-Johnson syndrome, hemorrhage and pancreatitis

II. **Decreased cardiac output** secondary to: heart failure, pulmonary embolus, acute myocardial infarction, severe valvular disease, abdominal compartment syndrome - tense ascites

III. **Systemic vasodilation** which can be caused by the following: Sepsis, anaphylaxis, anesthetics, drug overdose

IV. **Afferent arteriolar vasoconstriction** secondary to: hypercalcemia, drugs - NSAIDs, amphotericin B, calcineurin inhibitors, norepinephrine, radiocontrast agents, hepatorenal syndrome

V. **Diseases that decrease effective arterial blood volume** include the following: hypovolemia, heart failure, liver failure, sepsis

VI. **Renal arterial diseases** that can result in AKI include renal arterial stenosis, septic embolic disease (eg, from endocarditis) or cholesterol emboli.

2. **Intrinsic AKI:** It accounts for approximately 20% of community acquired AKI cases (31). Structural injury in the kidney is the hallmark of intrinsic AKI; the most common form is ATN, either ischemic or cytotoxic. Causes of intrinsic AKI can be divided into vascular, glomerular, tubular and intrinsic.
3. **Obstructive AKI:** Accounts for approximately 15% of non-ICU AKI cases and around 10% of community acquired AKI cases (20,32). Diseases causing urinary obstruction from the level of the renal tubules to the urethra include the following:
   - Tubular obstruction from crystals - Eg, uric acid, calcium oxalate etc.
   - Ureteral obstruction - Retroperitoneal tumor, urolithiasis, or papillary necrosis etc.
   - Urethral obstruction - Benign prostatic hypertrophy; prostate, cervical cancers etc.

2.3 Diagnosis of AKI using serum creatinine

The glomerular filtration rate (GFR) is the best overall index of kidney function in health and disease. However, it is difficult to measure and is commonly estimated from the serum level of endogenous filtration markers, such as creatinine. Chertow et al. found that an increase of serum creatinine (SCr) of more than 26.5 µmol/l was independently associated with mortality (13). Similarly, Lassnigg et al. found out that in a cohort of patients who underwent cardiac surgery,

an increase SCr by 44.2 μmol/l was associated with worst survival (33). Therefore, small changes in kidney function in hospitalized patients are important and associated with significant changes in short and long-term outcomes.

In March 2012, The Kidney Disease Improving Global Outcomes (KDIGO) work group combined the RIFLE and AKIN classifications in order to establish one classification of AKI for practice, research and public health. The rationale of coming up with KDIGO classification was based on a study done by Joaniddis et al. (34). In this study they directly compared the RIFLE and the AKIN criteria. What they found out was that when using the RIFLE criteria, it failed to detect 9% of cases that were detected by the AKIN criteria. However, the AKIN criteria missed 26.9% of cases detected by RIFLE. These data provide strong rationale for use of both RIFLE and AKIN criteria to identify patients with AKI. Therefore, for KDIGO criteria, definition and staging of AKI is based on a combination of the RIFLE and AKIN criteria (35,36). Both criteria rely on GFR, and its proxy serum creatinine, and urinary output as the most useful overall indices of acute changes of kidney function.

Definition of AKI by KDIGO is an increase in SCr by 26.5 μmol/L within 48 h; or an increase in SCr to more than or equal to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or a urine volume of less than 0.5 mL/kg/h for 6 h (1).

AKI has been staged in severity. Staging of AKI is important because, with increased stage of AKI, the risk for death and need for RRT increases (2,37–39). Furthermore, there is now accumulating evidence of long-term risk of subsequent development of cardiovascular disease or CKD and mortality, even after apparent resolution of AKI (40–42).

For staging purposes, patients should be staged according to the criteria that give them the highest stage. Thus when creatinine maps to different stages, the patient is staged according to the highest (worst) stage. The staging of AKI as per KDIGO is as follows:

Table 1: Staging of AKI

STAGE OF AKI	PARAMETERS
Stage 1	Serum creatinine 1.5-1.9 times above baseline, or A rise in serum creatinine of 26.5µmol/l or more, or A urine output of less than 0.5ml/kg/hour for 6-12 hours
Stage 2	Serum creatinine 2-2.9 times above baseline, or A urine output of less than 0.5ml/kg/hour for 12 hours
Stage 3	Serum creatinine 3 times of the baseline, or Increase in creatinine above 353.6µmol/l, or Initiation of dialysis, or Urine output of less than 0.3ml/kg/hr for more than 24 hours, or Anuria for more than 12 hours

Therefore, the KDIGO criteria rely on the rise in serum creatinine or a decrease in urinary output to make a diagnosis of AKI. Reduction in GFR remains the standard for clinical diagnosis of AKI. GFR is estimated by measuring the clearance of exogenous filtration markers such as iothalamate, iohexol, and inulin. However, these are expensive and require exposure to radiation, thus have limited use in the routine laboratory settings. On the other hand, creatinine is freely filtered, has minimal tubular secretion and absorption, is simple and inexpensive to measure from random blood samples, and has relatively good accuracy. It has therefore become a valuable clinical tool for estimating GFR.

However, Scr too has got its own shortfalls. Its use limited by its biological variability, medication effects, nutrition, and by the alterations in circulating serum creatinine produced by non-renal disease states. In healthy people and CKD patients, the estimation of GFR by serum

creatinine differs because of differences in GFR range and creatinine production between these two populations. As a result of this, there is a risk of overestimating the GFR, and the magnitude of the overestimation is not predictable (43).

2.4 Ancillary evaluation

2.4.1 Urinalysis

Urinalysis is the most important noninvasive test in the initial workup of acute kidney injury especially intrinsic AKI.

ATN will show granular, muddy brown casts on urine microscopy and may also show the presence of tubular cells or tubular cell casts also supports the diagnosis of ATN.

Reddish brown or cola-colored urine suggests the presence of myoglobin or hemoglobin, especially in the setting of a positive dipstick for heme and no red blood cells (RBCs) on the microscopic examination. Tubular injury may reveal significant proteinuria on a dipstick assay.

RBCs presence in the urine is always pathologic. Eumorphic RBCs suggest bleeding along the collecting system. Dysmorphic RBCs or RBC casts suggest glomerulonephritis.

Pyelonephritis suggested by the presence of white blood cells (WBCs) or WBC casts. The presence of urine eosinophils is helpful in establishing a diagnosis but is not necessary for allergic interstitial nephritis to be present as they can also be seen in urinary tract infection, glomerulonephritis, and atheroembolic disease.

Uric acid crystals may represent ATN associated with uric acid nephropathy. Calcium oxalate crystals are usually present in cases of ethylene glycol poisoning.

Proteinuria may be seen in patients with CKD in diabetics and hypertensives.

2.4.2 Renal ultrasonography utility

Renal ultrasonography should be performed in most patients with acute kidney injury, particularly in older men, to rule out a post renal cause and chronic kidney disease. Post renal AKI may be considered when the post void residual urine is greater than 100 mL and this requires renal ultrasonography to detect hydronephrosis or outlet obstruction (44,45).

Hydronephrosis will be found in approximately 95% of patients with obstruction and sensitivity approaches 100% in patients with moderate to severe hydronephrosis (46,47). Increased echogenicity of the kidneys and size of less than 90mm will be seen in seen in chronic kidney disease.

2.5 Prevention

The fundamental principle of prevention of acute kidney injury is to treat the cause or trigger. Use crystalloid solutions instead of colloids for the management of hypovolemic shock, in the absence of hemorrhagic shock as initial management for expansion of intravascular volume in patients at risk for AKI or with AKI and the resuscitation should begin immediately (1,48)

Maintenance or immediate restoration of adequate oxygenation and haemoglobin concentration (at least 70 g/L) should be sought (49).Some patients will remain hypotensive (mean arterial pressure of less than 65–70 mm Hg) despite restoration of intravascular volume. In such patients, auto-regulation of renal blood flow can be lost, contributing to acute kidney injury (50).
To treat the low cardiac output, inotropic drugs or the application of ventricular assist devices might be necessary (51).

Loop diuretics might protect the loop of Henle from ischaemia by decreasing its transport-related workload. However, no double-blind, randomised controlled studies have shown that these agents reduce the incidence of acute kidney injury (52). The usefulness of diuretics remains confined to the control of fluid status.

No established pharmacotherapy exists for acute kidney injury. Drugs such as theophylline, urodilatin, fenoldopam, bicarbonate, and atrial natriuretic peptide have been studied in different subgroups of patients and clinical contexts (53–56).

2.6 Outcome

2.6.1 Need for renal replacement therapy

AKI requiring renal replacement therapy occurs in 5%–6% of ICU patients, with an extremely high in-hospital mortality rate of 60% (57).

Renal replacement is required in some patients with severe acute kidney injury. No one set of criteria exists to guide such intervention. But most clinicians use the conventional criteria:

- Anuria (negligible urine output for 6 h)
- Severe oliguria (urine output of less than 200 mL over 12 h)
- Hyperkalaemia (potassium concentration higher than 6·5 mmol/L)
- Severe metabolic acidosis (pH less than 7·2 despite normal or low partial pressure of carbon dioxide in arterial blood)
- Volume overload (especially pulmonary oedema unresponsive to diuretics)
- Pronounced azotaemia (urea concentrations greater than 30 mmol/L or creatinine concentrations more than 300 μmol/L)
- Clinical complications of uraemia (eg, encephalopathy, pericarditis, neuropathy)(2)

The best time to start renal replacement therapy is controversial because the only studies linking timing with outcome are observational (58,59). One randomized controlled trial (RCT) has evaluated the effect of timing of initiation of RRT on outcome. Bouman et al. randomized 106 critically ill patients with AKI to early vs. late initiation of RRT. The early initiation group started RRT within 12 hours of oliguria (less than 30 ml/h for 6 hours, not responding to diuretics or hemodynamic optimization), or CrCl of less than 20 ml/min. The late-initiation group started RRT when classic indications were met. The study did not find differences in ICU or hospital mortality, or in renal recovery among survivors, but was clearly too small to allow for definitive conclusions (60).

2.6.2 Mortality

There is increased long-term mortality in those with AKI surviving hospitalization, with adjusted mortality risk of 1.4, which augmented with increasing severity of AKI (61). It is estimated that about two million people die of AKI every year (58,62).Those who survive AKI have a higher risk for later development of CKD (42).

AKI affects the fate of other organs and overall mortality (63). Although therapy for AKI has improved in recent years, AKI is still highly prevalent, especially in critically ill patients in the intensive care unit (ICU) (64). AKI in the ICU has high mortality rates, reaching 80%; these rates have remained largely unchanged despite improvements in therapies (65,66).

AKI occurred in over 1 of 5 hospitalized patients and was associated with an over fourfold increased mortality in a study done by Wang H et al in Alabama, USA (67).

The overall in-hospital mortality rate in the BEST Kidney cohort study was 60.2% (58). As with PICARD, mortality varied widely across centers. Among countries contributing more than 100 patients to the cohort, in-hospital mortality ranged from 50.5% to 76.8% (68).

The mortality rate in severe AKI is almost 50%, depending on the type of AKI and comorbidities of the patient. In the Madrid study, patients with ATN had a mortality rate of 60%, whereas those with prerenal or postrenal disease had a 35% mortality rate. Most deaths are not caused by the AKI itself but rather by the underlying disease or complications. In the same Madrid study, 60% of deaths were caused by the primary disease and the remaining 40% were caused by cardiopulmonary failure or infection (32).

Mortality rates in Africa are no different. Effa et al. in Nigeria found a mortality of 31 % in patients with AKI (27). A study done by Bagasha et al. in Uganda found an in-hospital mortality of 21% among patients with sepsis related AKI and 59% of patients who were discharged alive or were still on the wards, after 2 weeks, had persistent kidney injury (69).

In Kenya, studies done at Kenyatta National Hospital have shown varied mortality rates. Anthony Were et al, in 1986, found a mortality rate of 40.4% in patients with acute renal failure (70). Peter Gatuma study on hypovolemia associated acute renal failure in the medical wards found a mortality of 10.6% (71) while Brenda Kiiru's study in ICU patients found a very high mortality of 52% (72).

Even when dialysis is initiated, the mortality has shown to be high particularly with higher blood urea nitrogen (BUN) as shown in the Program to Improve Care in Acute Renal Disease (PICARD) study where dialysis was initiated in 243 patients from five geographically and ethnically diverse clinical sites. Initiation of RRT at higher BUN (blood urea of more than 27.1mmol/l]) was associated with an increased risk of death (RR 1.85; 95% CI 1.16–2.96) (68).

2.6.3 Length of stay and degree of renal recovery

The severity of AKI affects the length of hospital stay meaning that the more severe the AKI, the longer the length of stay in the hospital. The degree of biochemical renal recovery has also been shown to be affected by the severity, that is, the more the severe the AKI, the more slowly the recovery process.

A study done by Meier et al in Switzerland found that Hospital Acquired Acute Kidney Injury (HA-AKI) was associated with a longer hospital stay compared with no HA-AKI. Moreover, increasing severity of HA-AKI according to the AKIN classification was associated with an increasing length of hospital stay for all patients (73).

Another study carried out in South Korea by Yoo et al. showed that the proportion of patients who recovered from AKI was significantly different between the two duration groups: 98% recovered in the 1 to 5-day group, while only 44% recovered in the ≥ 6-day group ($p < 0.0001$). Also, long-term survival was significantly better for those who recovered than those who did not ($p < 0.0001$) (74).

In Turkey, Magden et al. looked at recovery process in patients followed-up due to acute kidney injury and found out that BUN and creatinine levels went down to the basal values only in the prerenal AKI group and remained higher in the postrenal and renal groups on the 7th day of treatment. BUN levels decreased to the normal values on average 7th day in the postrenal, while remained higher in the renal group (75).

In a population based study by Ali et al. full renal recovery was achieved in 321 (68%) of those in the AKI group; 24 (5%) partially recovered, and in 127 (27%), recovery could not be determined because the patient died in the acute phase. Recovery in the severe category was significantly lower. After exclusion of the 127 patients in whom it was not possible to determine the recovery because they died in the acute phase of their illness, 92.5% had full renal recovery, 7% had partial recovery, and 0.6% had no recovery. Thirty-seven (8%) patients with AKI received RRT and twenty one (57%) of those who received RRT died. The median duration of stay for AKI was 17 days; this was significantly shorter in the mild form and longer in severe AKI (21).

The Uganda study by Bagasha et al. showed 20 of 62 patients were discharged with resolved kidney injury, while 29 had persistent kidney injury at the time of discharge from hospital or from the study (after 2 weeks of follow up (69).

3. Study Justification

Acute kidney injury (AKI) is increasingly prevalent in developing and developed countries and is associated with severe short term and long term morbidity and mortality.

AKI can be preventable if risk factors are identified early and if managed early it can be reversible.

Currently the International Society of Nephrology (ISN) has made AKI a priority issue and come up with a 0 by 25 initiative (no deaths by 2025) and therefore its importance.

The KDIGO criteria are one of the recently described classification methods for renal injury. So far, this has not been applied in a study in our setting to assess its applicability and reliability in predicting prognosis.

The last study done to look at acute kidney injury in Kenya was carried out in a tertiary hospital and that was almost 10 years ago and using a different AKI definition. It is possible that our epidemiology is different from that seen in that hospital.

4. Objectives

4.1 Study question

What was the prevalence, severity and outcomes of patients with community acquired acute kidney injury in the general medical wards at Kenyatta National Hospital?

4.2 Study objectives

4.2.1 Broad Objective

To determine the prevalence, severity and outcomes of patients with AKI

4.2.2 Primary objectives

1. To determine the prevalence of AKI as seen in the general medical wards
2. To grade severity at presentation of AKI according to KDIGO criteria
3. To determine the two week outcomes of patients with AKI in form of need of RRT, LOHS, degree of recovery of renal function and all-cause mortality.

4.2.3 Secondary objectives

To document the risk factors associated with AKI

5. Methodology

5.1 Study setting

The study was carried out in the general medical wards at Kenyatta National Hospital. It is a tertiary referral hospital located in the capital city of Kenya, Nairobi. It was established in 1968 and is the largest hospital in Eastern and Central Africa. It has a capacity of 2000 beds. It serves as the teaching hospital for the University of Nairobi, College of Health Sciences, both for the undergraduate and the post graduate programs. There are 7 general medical wards in total in the hospital with approximately 400 to 550 admissions monthly. These admissions are from the accident and emergency department and out of these approximately 55 to 85 patients are admitted with AKI monthly.

5.2 Study population

Patients with AKI admitted to the general medical wards at Kenyatta National Hospital who fulfilled the KDIGO criteria.

5.3 Case definition

i. Acute kidney injury was defined, according to KDIGO, as any of the following:

- Increase in serum creatinine (Scr) by ≥ 26.5 µmol/L within 48 hours
- Increase in Scr by ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.

For all patients with deranged creatinines, we used the known baseline for patients whose baseline creatinine has been established and for the rest of the patients whose baseline was unknown used an estimated baseline creatinine. The baseline creatinine was estimated by using the simplified modification of diet in renal disease (MDRD) formula, assuming a GFR of 75ml/min per 1.73m2. This was as recommended by KDIGO (45).

$$epCr = \left(\frac{GFR}{Sex \times Race \times 186 \times Age^{-0.203}} \right)^{-\frac{1}{1.154}} (\text{mg/dl})$$

Where *GFR* was the assumed GFR (ml/min); *Sex* = 1 if male and 0.742 if female; *Race* = 1.21 if black, otherwise *Race* = 1; and *Age* was in years. To convert from mg/dl to µmol/L we multiplied by 88.5

ii. The severity of AKI was defined according to the different stages as follows:

Stage 1: Serum creatinine 1.5-1.9 times above baseline, or a rise in serum creatinine of 26.5µmol/l or more

Stage 2: Serum creatinine 2-2.9 times above baseline

Stage 3: Serum creatinine 3 times of the baseline, or increase in creatinine above 353.6µmol/l, or initiation of dialysis

iii. Risk factor categorization and definition were as follows:

The patients were clinically categorized into 3 categories namely: pre renal, renal and post renal/obstructive following history, clinical and file evaluation. Though, patients were categorized into 3 distinct categories, it was possible that a patient could have two or more risk factors from the same category or from the other two categories and so they were not mutually exclusive.

Pre-renal failure was suggested by a history of any risk factors that increased the risk of volume and blood pressure reduction resulting in poor perfusion to the kidneys. These factors included:

- **Gastrointestinal losses** which was either secondary to diarrhea or vomiting. The persistent diarrhea and vomiting can lead to dehydration which was defined as any patient with either of the two: sunken eyes, dry mucous membranes, delayed skin turgor, capillary refill time of > 2 seconds, hypotension, tachycardia or altered mental status.
- **Significant bleeding** - overt bleeding followed within 24 hours by a decrease in systolic blood pressure, rise in pulse rate, a 2g/dL fall in hemoglobin, or a definite transfusion requirement of 2 units of blood.
- **Left heart failure** – was clinically defined as any patient with symptoms of dyspnea associated with orthopnea and paroxysmal nocturnal dyspnea and oedema, increased jugular venous pressure, coarse crepitations and/or hepatomegaly on examination.
- **Sepsis –** was based on the diagnosis in the file 24 hours within admission.
- **Skin losses –** was defined as those patients with excessive sweating or more than 5% burns or those patient with an adverse skin drug reaction (Steven Johnsons syndrome, toxic epidermal necrolysis).
- **3rd space losses –** were those patients with oedema states like massive ascites

Renal causes was defined as those risk factors that affected the renal parenchyma. The risk factors were divided into tubular, glomerular, interstitial or vascular.

- **Tubular** damage will lead to **acute tubular necrosis** and this was defined as any patient with a history of receiving nephrotoxic medications (including over-the-counter, illicit, and herbal), hypotension, trauma or myalgias suggesting rhabdomyolysis, recent exposure to radiographic contrast agents (within 24-72 hours of admission) and the urine analysis showing brown 'muddy' casts.
- **Acute Glomerulonephritis** - was defined as the sudden onset of hematuria, proteinuria, and red blood cell (RBC) casts. The clinical picture is often accompanied by hypertension, edema, decreased glomerular filtration rate [GFR]), and renal salt and water retention.
- **Interstitial causes** was defined as those patients with recent medication use (e.g., antibiotics, NSAIDs), rash, arthralgias, fever, infectious illness
- **Vascular causes** was suggested in those patients diagnosed as malignant hypertension, nephrotic syndrome, trauma, flank pain, anticoagulation (atheroembolic disease), recent vessel catheterization or vascular surgery

Obstructive uropathy – was defined as those risk factors that caused mechanical obstruction of the urinary collecting system. This was based clinically on lower urinary tract symptoms (irritative and obstructive symptoms), physical examination and ultrasonography (showing the cause of the obstruction and even suggested by bilateral hydronephrosis)

iv. CKD was defined as any patient with either a known history of kidney disease for at least 3 months or with laboratory findings of normocytic normochromic anemia, hypocalcemia and hyperphosphatemia or proteinuria or with a renal ultrasound showing small, shrunken, hyperechoic kidneys.

v. The outcomes were defined as follows:

Degree of biochemical recovery was categorized as either full, partial or non-recovery within the two weeks, or at discharge or death. Each of them were defined according to ADQI definitions as below:

1. Full recovery of renal function as defined by return of creatinine to within 50% of baseline serum creatinine.
2. Partial recovery of renal function as defined by failure to return to 50% of baseline serum creatinine.

3. Non recovery as defined by no change in serum creatinines since admission in the 2 weeks

Need for RRT was defined as any patient who required dialysis within the two weeks as indicated by any of the conventional indications as described earlier in the literature review. Some of the definitions were as follows:

- Pulmonary oedema was defined clinically as a patient with tachypnea, tachycardia and fine crackles mainly as the lung bases bilaterally not responding to diuretics.
- Metabolic acidosis was defined by Kussmaul respiration and supported by an arterial blood gas analysis showing a pH of less than 7.2

Death was defined as any patient certified by a medical officer as being dead in the file.

5.4 Study design

This was a longitudinal study to determine the point prevalence in 3 months' time of AKI with follow up of the patients to record their outcomes over 2 weeks.

5.5 Sampling method

Consecutive sampling

5.6 Sample size calculation

According to KNH medical records, approximately 2 patients with acute kidney injuries were seen daily. This implies that an estimated 60 AKI patients were seen monthly. Using data for 6 months which translates into 360 patients, a representative sample was drawn from the population in the period. The sample size calculation was obtained using the formula for finite population (Daniel, 1999). The calculation was as follows:

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

Where

n' = sample size with finite population correction,

N = size of the target population = 360

Z = Z statistic for 95% level of confidence = 1.96

P = Estimated mortality rate of patients admitted in the ward = 17% (Munyu et al, 2008)

d = margin of error = 5%

$$= \frac{360 \times 1.96^2 \times 0.17 \times 0.83}{0.05^2 (360-1) + 1.96^2 \times 0.17 \times 0.83}$$

Substituting into the formula,

n = 136

This study sampled 136 AKI patients to estimate mortality rate within 5% level of precision.

5.7 Inclusion criteria

1. Any patient with AKI fulfilling the KDIGO criteria
2. Patients who are 13 years and older
3. Provide an informed consent
4. Written informed assent for those less than 18 years

5.8 Exclusion criteria

Any chronic kidney disease patient

5.9 Screening and recruitment

The principle investigator (PI) with the help of 2 study assistants (registered clinical officers) looked out for any newly admitted patient aged 13 years and older with a file diagnosis of AKI or any patient with a deranged creatinine in the general medical wards. Any patient with findings suggestive of chronic kidney disease (CKD) as evidenced by history of kidney disease for more than 3 months, anaemia, low serum corrected calcium with high serum phosphate levels and small, shrunken and hyperechoic kidneys on renal ultrasound were excluded. After CKD was excluded, patients who fit the KDIGO criteria for AKI were enrolled in the study. The urine output criteria was excluded as it was not measured routinely in the wards. The patients were then given all the relevant information about the study and those who gave written informed consent were recruited.

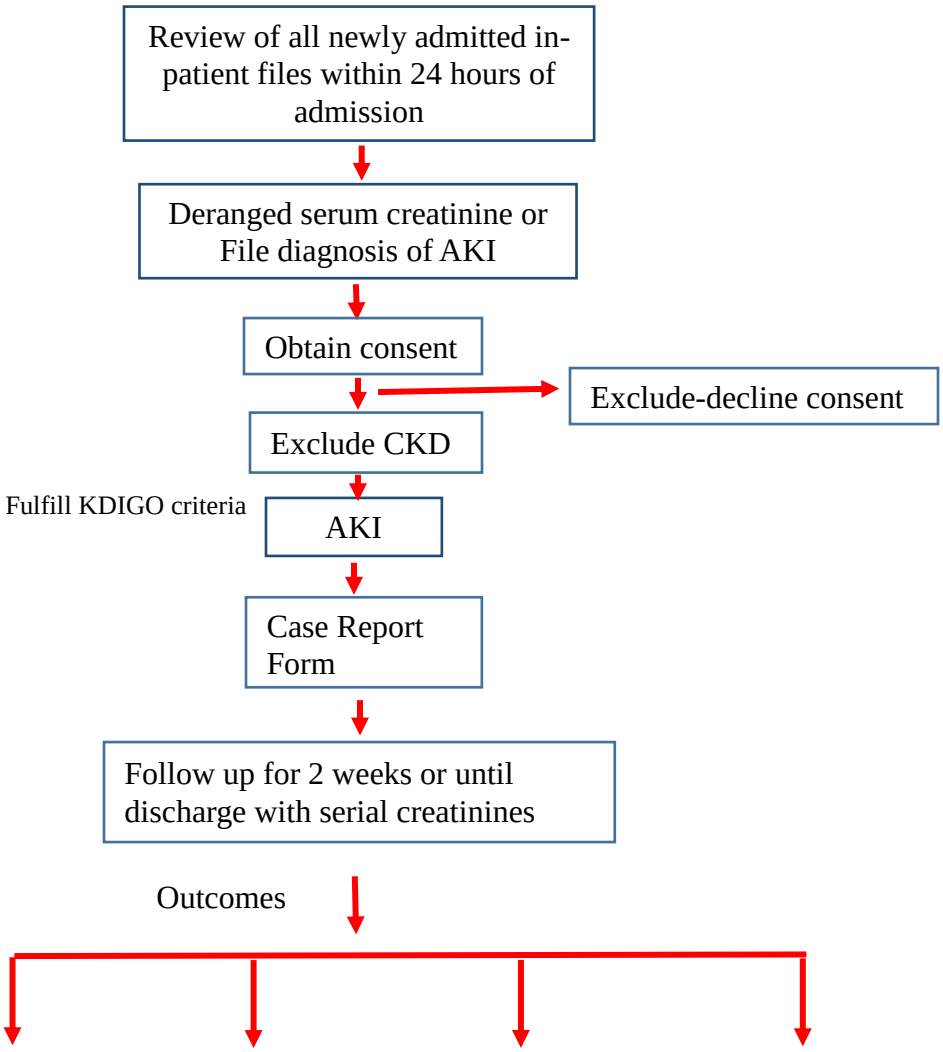
Once written informed consent was acquired a case report form was administered and appropriate investigations carried out. Those who declined consent were excluded.

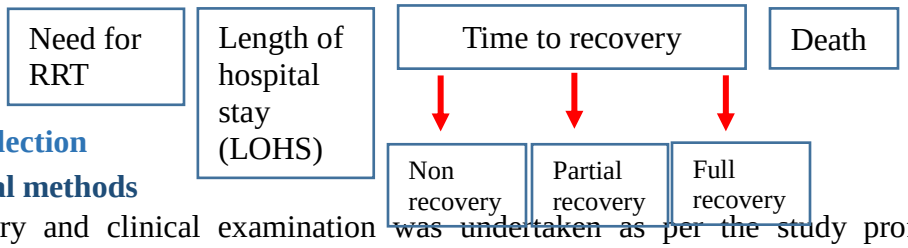
A copy of the consent form was included as appendix 2.

Clinical data included date of admission, date of discharge, a previous history of chronic kidney disease and possible risk factors for AKI like age, diabetes, hypertension, heart failure, sepsis/systemic inflammatory response syndrome (SIRS), nephrotoxic drugs in the past 2 weeks (including intravenous contrast dye, aminoglycosides, amphotericin B, ARVs, NSAIDs, ACE-I, and ARBs), hypotension or shock, use of vasopressors and/or inotropes. Patient management and course of renal dysfunction data was collected during the patients stay in the hospital. The above data was filled in a case report form.

The investigations that were done included a complete blood count, renal function tests, corrected serum calcium and phosphate levels, spot urinalysis and renal ultrasound. The serum creatinine, corrected calcium with phosphate levels and spot urinalysis was done by the study investigators. The complete blood count was done as routine as a standard management practice. The renal ultrasound was done in the renal unit by an ultra-sonographer.

5.10 Patient flow-chart





5.11 Data collection

5.11.1 Clinical methods

A brief history and clinical examination was undertaken as per the study proforma. Data collection was done using a case report form designed to pick the parameters relevant to the study. Information was obtained through patient interviews, care giver interviews, clinical notes and the laboratory. Data was collected by the investigator. All information was kept confidential and no names written on the case report forms to ensure anonymity. Subjects' medical record numbers were written on the forms to allow review of clinical charts in case of errors or missing data.

5.11.2 Laboratory methods

5.11.2.1 Specimen collection, transportation

Patients were asked to provide blood sample for serum calcium with phosphate levels within 24 hours of admission and serum creatinine after every three days until discharge or at the end of 2 weeks. 2mls of blood was drawn aseptically and collected in plain vacutainers. The patients was also asked to provide a urine sample in a container. Both the blood and urine samples were transported at room temperature within 2 hours of collection to the renal laboratory in KNH for analysis. Results obtained were recorded immediately in the study proforma.

5.11.2.2 Specimen analysis

The serum creatinine, calcium with phosphate levels were done in the renal laboratory using a well calibrated BioLis 50i superior machine. It had been validated for precision, accuracy, linearity, sensitivity and specificity in the measurement of creatinine. Urine analysis was performed by the laboratory technician at the renal laboratory. This was done in 2 parts: by doing a dipstick test using the URIT 10V kit and then observing the sample under the microscope for casts and cells.

5.11.2.3 Follow up

Subsequently, the patients were reviewed after every 72 hours by the principal investigator or the research assistant to establish the modalities of management applied, the degree of renal dysfunction reached as well as outcome. In addition, patients were reviewed daily by the registrars in the ward and incase of any indication of dialysis which came up, the principal

investigator or the assistant was informed. A clinical examination was then done to assess for pulmonary oedema and signs of uremia. An arterial blood gas was done when deemed necessary to rule out metabolic acidosis.

The duration during which the subjects were in hospital was determined and subject's outcome assessed at 2 weeks of recruitment or at discharge or death.

There were six possible outcomes for any patient at the end of hospital stay:-

1. Full recovery of renal function
2. Partial recovery of renal function
3. Non recovery of renal function
4. Need for renal replacement therapy
5. Duration of hospital stay
6. Death as another possible outcome of the subjects.

5.11.2.4 Quality assurance

Standard operating procedures for specimen collection and transport were followed with timely deliver to the laboratory to minimize pre-analytical errors. The blood and urine specimen were taken to the renal laboratory. This laboratory undergoes both internal and external quality control measures.

5.12 Study Variables

Independent variables

- Age, sex, co-morbidities, medications, laboratory parameters, severity of AKI

Dependent variables

- In-hospital mortality, degree of renal recovery, LOHS, initiation of RRT

5.13 Data analysis

Data was collected by the PI and research assistant and entered into a password protected Microsoft Access database managed by the statistician. Once data entry was complete, entries in the database were compared to the hard copies to ensure accuracy. Inconsistencies were detected by use of simple frequencies and correlations and those identified were rectified before data analysis began. Data was analyzed using SPSS software version 21 for windows.

The population was described using mean/medians and percentages for continuous and categorical data respectively. Point prevalence of AKI was calculated as the percentage number of patients admitted with AKI out of all the admissions in the period of the study i.e 3 months.

Severity, risk factors, treatment modalities and outcomes of AKI was analyzed and presented using percentages with 95% confidence intervals. Outcomes were associated with severity of AKI using chi square test of associations. Statistical tests was performed at 5% level of significance. Findings were presented in tables and graph.

5.14 Data Grouping

Parameters that necessitated data grouping included:

Age - the age was grouped in intervals of 10 years

Causes –These was grouped as follows:

1. Pre renal
2. Renal/Intrinsic
3. Post renal/Obstructive

5.15 Study administration

It was the responsibility of the PI to inform AKI patients about the study. The PI then recruited those willing to participate in the study and obtained their informed consent. The research assistants worked with the PI to ensure that data was collected efficiently, on time and that it was recorded accurately. All recorded data was verified by the PI, who ensured that all relevant forms were completed. The supervisors offered guidance to the PI throughout the process. The statistician offered guidance during proposal development, data entry, analysis and presentation of the final statistical analysis.

5.16 Ethical consideration

This study was undertaken after approval by the Department of Clinical Medicine and Therapeutics, University of Nairobi (UoN) and the KNH/UoN Scientific and Ethical Review Committee. Patients eligible to participate in the study were recruited after going through the consent process as outlined below:

The patients or their legal guardians were informed that the study involved research.

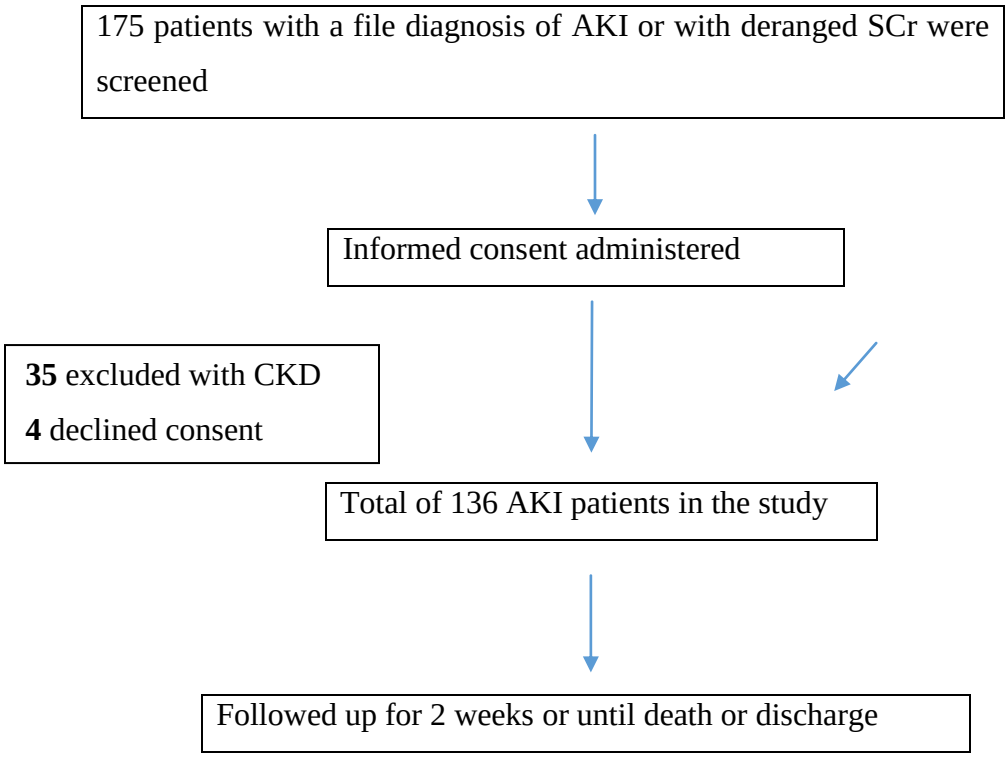
They were given a detailed explanation of the purpose, the nature of the study and any laboratory tests to be reviewed. The patients were assured that participation was voluntary and that medical attention would not be denied if they were to decline participation in the study.

Confidentiality was strictly maintained and all data gathered was securely stored and only revealed upon a need to know basis.

Following full explanation and acceptance, the patient or legal next of kin was requested to sign the consent form.

6. Results

This study was carried out between August 2016 and November 2016. One hundred and seventy five patients were screened for the presence of acute kidney injury .We excluded thirty nine patients who did not meet the study criteria.



Baseline Characteristics

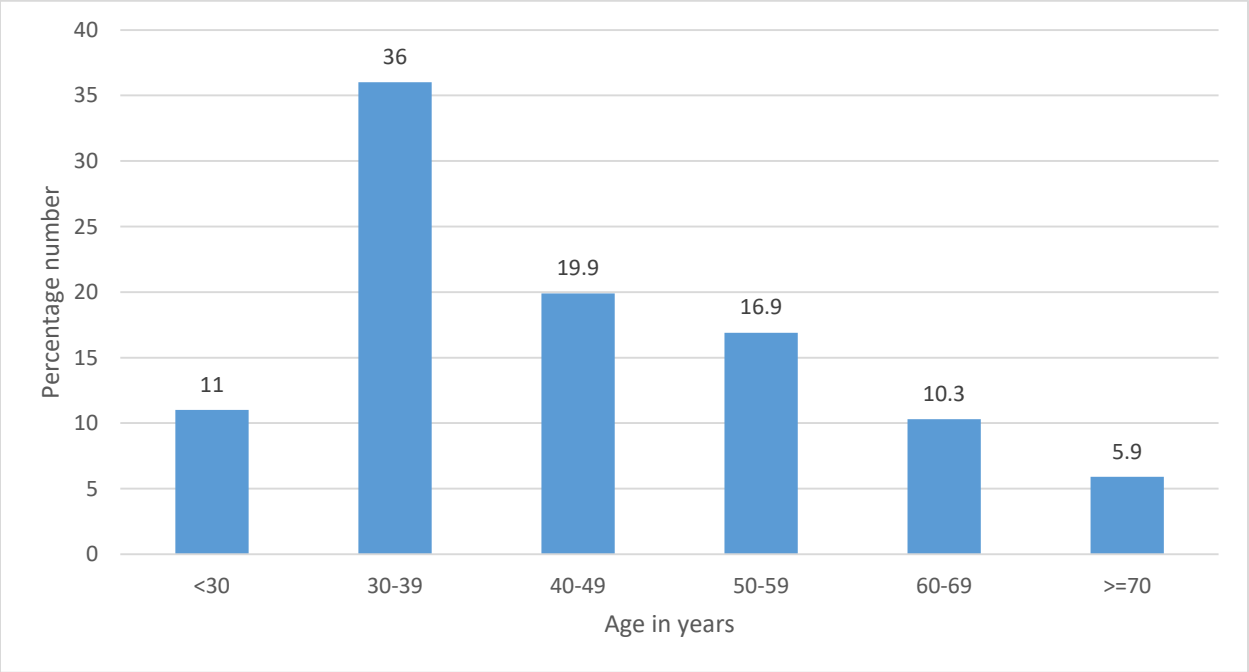
A total of 136 patients were recruited during the study period. There was equal distribution between the sexes at 50% each. The mean age was 44.7 years. Most of the patients were from rural areas at 63.2%.

Table 2: Socio-demographic characteristics

Variable	**Range mean ± SD**
Mean age (SD)	44.7 (13.8)
Sex	
Male	68 (50.0)
Female	68 (50.0)
Area of residence	
Urban	50 (36.8)
Rural	86 (63.2)

67% of the patients were less than 50 years of age and from those, most of them were between the ages 30-39 as shown in figure 1.

Figure 1: Age distribution histogram



Prevalence of AKI

The total number of medical admissions during the study period between August 2016 and November 2016 was 1687. The admission period prevalence of AKI in the general wards was 8.1%.

Severity at presentation of AKI

Most of the patients had mild (stage 1) AKI. Table 3 depicts the severity of AKI at presentation.

Table 3: Severity of AKI

Variable	Frequency (%)	95% CI
Severity of AKI		
Stage 1	70 (51.5)	43.4-59.6
Stage 2	33 (24.3)	17.6-31.6
Stage 3	33 (24.3)	17.6-31.6

2 week outcome in form of need of RRT, LOHS, degree of and time to renal recovery and death

a) Need of RRT

14 patients had either one or multiple indications for renal replacement therapy. From those fourteen patients, ten patients had stage 3 AKI, three patients had stage 2 AKI and one had stage 1 AKI. Only 2 patients (14%) from our study population underwent hemodialysis and both the patients were in stage 3 disease with uremic encephalopathy. For the first patient, the dialysis was started 48 hours after admission while for the second patient it was started after 72 hours of admission. The most common indications for dialysis in our study were pronounced azotemia and uremic complications. The indications which warranted RRT are summarized in the table 4.

Table 4: Indications of RRT

Indications	No. of patients
Hyperkalemia	4
Severe metabolic acidosis	2
Volume overload	3
Pronounced azotemia	7
Uremic complications	5

b) Length of hospital stay

The median length of hospital stay was 9 days in patients with stage 1 AKI, 11 days with stage 2 AKI and 10 days with stage 3 and thus the severity did not affect the LOHS.

Table 5: Length of hospital stay

Variable	Severity of AKI			P value
	Stage 1	Stage 2	Stage 3	
Length of hospital stay, median (IQR)	9.0 (7.0-11.0)	11.0 (8.0-14.0)	10.0 (9.0-14.0)	0.233

c) Degree of renal recovery

At 2 weeks, 60% had not recovered from AKI while 21 patients (18.6%) recovered fully.

Table 6: Degree of renal recovery

Variable	Frequency (%)
Degree of recovery	
None	60 (53.1)
Partial	32 (28.3)
Full	21 (18.6)

From our study, the more severe the AKI, the lower the chances of recovery with a p value of 0.045 as shown in table 7.

Table 7: Degree of renal recovery and severity of AKI

Variable	Stage 1	Stage 2/3	P value
Degree of recovery			
None	20 (46.5)	40 (57.2)	0.045
Partial	14 (32.6)	18 (25.7)	
Full	9 (20.9)	12 (17.1)	

d) Death

The in-hospital all- cause mortality during the study period was 23 patients (16.9%).

The more severe the AKI, the higher chances of mortality i.e there were 11 patients (33.3%) with severe AKI who died and that was statistically significant with a p value of 0.012. Most of the patients who were given a discharge had stage 1 AKI.

Table 8: Mortality and severity of AKI

Variable	**Severity of AKI**			**P value**
	Stage 1	**Stage 2**	**Stage 3**	
In-hospital mortality				
Dead	7 (10.0)	5 (15.2)	11 (33.3)	0.012
Discharged/alive in 2 weeks	63 (90.0)	28 (84.8)	22 (66.7)	

Risk Factors

The risk factors were categorized into 3 groups: pre-renal, renal (intrinsic) and post renal (obstructive).

a) <u>Pre renal</u>

We found 74.3% (101 out of the 136) of patients with pre-renal causes. The pre renal risk factors were any of those that increased the risk of volume and blood pressure reduction resulting to poor perfusion of the kidneys. They were sub classified into gastro-intestinal losses which included anyone with diarrhea, vomiting or dehydration, significant bleeding, left heart failure, sepsis, skin losses and 3rd space losses. The summary of findings of the causes of pre-renal AKI have been depicted in table 9.

Table 9: Pre-renal causes

Pre-renal factors	N=136 Frequency (%)
Gastro-intestinal losses	58 (42.6)
Significant bleeding	9 (6.6)
Left heart failure	20 (14.7)
Sepsis/infections	70 (51.5)
Skin losses	0 (0)
3rd space losses	2 (1.5)

b) Intrinsic

24 out of the 136 patients had an intrinsic cause of AKI. This accounted to 17.6% of the total patients with AKI. The renal factors were those risk factors that may have affected the renal parenchyma and were divided into tubular which included some of the drugs, herbal medicines and contrast media, glomerular, interstitial which mainly included some drugs and lastly vascular. A urinalysis with microscopy was done on all the patients to further assist in categorizing the patients in this particular into the different categories mentioned above.

Table 10 shows the number of patients on medications a week prior to admission, herbal medications and toxins. These risk factors may have contributed to intrinsic AKI.

Table 10: Intrinsic AKI risk factors

Drugs used before admission	
Number of patients on medications	62 (45.6)
Aminoglycosides	8 (5.9)
NSAIDS	14 (10.3)
ACE-1	19 (14.0)
ARVs	25 (18.4)
Sulfonamides	23 (16.9)
Diuretics	19 (14.0)
Amphotericin B	1 (0.7)
Penicillin	16 (11.8)
Herbal medications	
Yes	6 (4.4)
No	130 (95.6)
Contrast within 5 days	
Yes	2 (1.5)
No	134 (98.5)

The urinalysis findings are summarized below:

- Blood in 44 patients
- White blood cells in 35 patients
- RBCs in 16 patients
- Nitrite in 22 patients
- Albumin in 28 patients
- Urinary sediments

- Bland in 3 patients
- RBC casts in 4 patients
- White blood cell casts in 11 patients
- Eosinophils in 1 patient
- Coarse brown casts in 1 patient

Table 11 shows the different causes of intrinsic/renal causes of AKI

Table 11: Intrinsic AKI causes

Renal factors	N=136 Frequency (%)
Tubular	18 (13.2)
Acute glomerulonephritis	5 (3.6%)
Interstitial	1 (0.7)
Vascular	0

c) Post renal (obstructive)

There were 11 patients (8.1%) with obstructive features on the renal ultrasound. Nine out of those patients had features of benign prostatic enlargement, one had metastatic cervical cancer while one had renal stones.

7. Discussion

We got an admission period prevalence of 8.1%. This may not reflect the true prevalence as we may have missed some patients in the accident and emergency department who could have been discharged as out -patient. The prevalence was much higher than what Peter Munyu got from his study done at a private facility in Nairobi with prevalence of 1.05% (29) and similarly Kaufman et al. reported CA-AKI prevalence of 1% of all hospital admissions (16). However, a much higher prevalence of 17.2% was seen in a study done by Evans et al. (76). The possible reason in the differences may be due to the different criteria used to define AKI. Munyu et al. used the RIFLE criteria for their AKI definitions as compared to our KDIGO criteria. Evans et al used the same KDIGO criteria but got a higher prevalence possible because he used a different study design (prospective observational).

The severity was classified per different stages using the KDIGO criteria. Most of the patients had mild (stage 1) disease while the rest had moderate to severe disease at 48.6%. Similarly a study done by Wei et al. in China found 46.1% with stage 1, 25.0% with stage 2 and 28.9% with stage 3 AKI. This was in contrast to what Evans et al. found in his study where there were 33 patients in stage 1 (21·6%), 27 in stage 2 (17·7%), and 93 in stage 3 (60·8%) (77). This may signify our patients seeking healthcare earlier.

The most common indication for RRT from our study was pronounced azotemia followed by uremic complications with uremic encephalopathy being the most common. We found three patients with uremic encephalopathy. From a total of 14 patients who needed RRT, only 2 patients (14.3%) underwent it. This was similar to what Munyu et al found in his study. The number of patients who underwent RRT in his study were 13.73% (29). Ogiator et al. in Nigeria found 61 patients (58.7%) in need of dialysis and out of those 56 (53.8%) were dialyzed. The reason as to why we may had fewer patients having been dialyzed would have been that our study was focused in the medical wards while the study by Ogiator et al. included the critical patients as well.

The severity of AKI in our study was not associated with the length of hospital stay (p-value = 0.233). The median length of stay was 9 days in stage 1 disease, 11 days in stage 2 and 10 days in stage 3 disease. This was different from other studies which showed a significant association between severity of AKI and LOHS. A study done by Bedford et al. found that the more severe the AKI, the longer the length of hospital stay. They used the AKIN criteria for defining AKI and at stage one disease the median length of stay was 5 days and at stage 3 AKIN it was 9 days (80). Another study by Chertow et al. also found the severity of AKI to be consistently associated with an independent increase in LOHS (13). In another study done by Ali et al., the median duration of stay for AKI was 17 days; this was significantly shorter in the mild form and longer in severe AKI (21). The reason as to why this study did not find an association between length of hospital stay and severity was possibly due to fact that our study was not powered enough to assess effect of severity on LOHS and secondly we did not look at possible confounders and this may have given us the non-association. This may have affected the length

of hospital stay. The other difference may have been due to the fact that our study was a short term study for just two weeks while the studies quoted above were for at least 3 months.

Full recovery was observed in 21 patients, partial recovery in 32 and non-recovery in 60 (53%) individuals. There was no statistical difference among the three groups. The severity of AKI affected the rate of recovery, that is, the more severe the AKI, the less chances of recovery and this was statistically significant with a p value of 0.045. This was similar to what Evans et al. found in their study done in Malawi. The non-recovery was comparable to what Bagasha et al. found in their study. They found that 47% had non recovery but 32% recovered fully as compared to our study where only 21% had a full recovery (69). In another study done by Ali et al., full renal recovery was achieved in 321 (68%) of those in the AKI group and 24 (5%) partially recovered and recovery in the severe category was significantly lower (21). Most of our patients had non recovery and fewer had full recovery. This non recovery may have been high in our setup due to a delay in managing these patients as supported by a comparison study done by Gatuma et al which found that patients with AKI secondary to hypovolemia who were intervened in earlier stages as compared to those that were not had higher chances of renal recovery and reduced mortality (71).

The overall mortality in our patients with CA-AKI was 16.9% and of note was that with increasing severity, the mortality increased and this was statistically significant. This was similar to what Munyu et al got; an overall mortality of 16.6 (29). Higher mortalities were observed in the BEST and PICARD studies at 60.2% and 64% respectively and by Brenda Kiiru at 52% and Were at 40.4% (58,70,72). In another study done on the medical admissions by Evans et al. in a Malawi hospital, hospital mortality was 44.4% in patients with AKI overall and almost half of patients with stage 3 AKI died (76). Ogiator found a mortality of 25% in a retrospective study done in Nigeria on medical admissions (78).

The higher mortalities observed in the above studies maybe due to the fact that they some of them were carried out in critical care units while our study was carried out in the general wards while the study done by Were et al and Ogiaotr et al. involved the other non-medical wards as well and this may have given a higher mortality percentage. The Malawi study done on medical

admissions also had a high mortality rate and this may have been due to more patients with severe disease (stage 3). A study done by Peter Gatuma at Kenyatta National Hospital in the medical wards and found a mortality of 10.6% (71). The lower mortality may be because he only looked at one aspect of AKI i.e on hypovolemia while our study looked at all the possible causes and this may have given us a bigger number of deaths. When we compare the mortality with other 2 week outcome studies done in different set of patients, more people died from AKI. A study done by Karanga et al in 2016 found a mortality rate of 13.5% in heart failure patients with hyponatremia (79). This was lower than what we found thus showing the burden AKI carries.

Mortality was also seen to increase significantly with increasing severity of AKI in our study as the most deaths were observed in stage 3 disease at 33.3%. Similarly, in a study by Thakar et al. the risk of death increased with the increasing severity of AKI: AKIN stage 1, odds ratio (OR) 2.2; stage 2, OR 6.1 and stage 3, OR 8.6 (80). Another study by Bagshaw et al. also showed a significant relationship between crude mortality and increasing severity of AKI (30.4% for risk, 72.7% for injury, 90% for failure, $P < 0.001$) while using the RIFLE criteria (81). Evans et al. in Malawi found that the crude mortality in patients with AKI was higher with increasing AKI severity [n = 18 (30 · 0%) in stage 1 and 2 vs. n = 46 (49 · 5%) in stage 3; p = 0 · 017] (76).

Pre-renal causes accounted for the most cases of AKI, followed by renal and lastly obstructive causes. This was similar to what Turner et al found in their study (31). The three most common risk factors for CA-AKI which we found in our study was sepsis at 50.5%, followed by nephrotoxic medications at 45.6% and lastly gastrointestinal losses at 42.6%. .This was comparable to what Munyu Peter found in his study done at AKUH. The commonest risk factor was drug use with most common associated findings including a history of vomiting and diarrhea. The most common underlying diagnoses were sepsis (50%) in his study which was closely related to what we found in our study (29). An important observation from our study was that we found AKI being multifactorial for example a patient would be on nephrotoxic medications, have gastroenteritis and have heart failure in the same instance. It's a known fact that AKI is a multifactorial disease and sometimes establishing a single cause proves to be a daunting task.

Nephrotoxic medications which are commonly implicated in causing intrinsic renal failure particularly acute tubular necrosis were the most common attributed risk factor of AKI in our study. In particular, there was a high use of antibiotics (penicillins, aminoglycosides, sulfonamides) known to cause nephrotoxicity as well as the use of ACE I and non-steroidal anti-inflammatory drugs reported in 14% and 10% of patients. This highlights the need for clinicians to closely monitor and adjust patient's prescriptions to prevent adverse effects.

Sepsis is associated with high morbidity and mortality and therefore requires timely empirical antibiotics within an hour of seeing the patient with proper fluid management and control of fevers.

Gastrointestinal losses were the third most common risk factor. The vomiting and diarrhea may have led to dehydration, hypotension and renal dysfunction. It is therefore important to target patients with these symptoms for prompt and proper fluid status management.

The mean age in our cohort was 44.7 years with 36% of patients between the ages of 30 to 39. This was almost similar to what was reported by Munyu et al which was 50.14 (29). This was slightly higher than that reported by Hadidy S et al from Syria which was 39.8 years in males and 35.9 years in females (82). However, studies from the developed countries have a higher mean age like a study done in Korea reported a mean age of 68 years and another one by Chertow et al. done in the USA had a mean age between the ranges of 52.8 to 58.8 (13,83). This difference in age could be due to the fact that developing countries have a relatively younger population than that seen in the developed countries.

We found an equal distribution between male and females. This was in contrast to a study done by Munyu et al who reported a male preponderance of around 70% (29). Other similar studies both from the developed and developing countries have also found a slightly high male preponderance like a study by Wang et al in USA reporting a male representation of 51% (84). This may have been a chance finding in our study.

8. Conclusion

This study showed a high prevalence of CA-AKI in patients admitted in the general wards at KNH and the severity of AKI was associated with non- recovery, mortality and need of renal replacement therapy with no association with the length of hospital stay. The most common risk factors were sepsis, nephrotoxic drug use and gastrointestinal losses.

9. Recommendations

1. All AKI patients should be evaluated for possible manageable/correctable risk factors which should be attended to with restoration of volume and removal of nephrotoxins or drugs with adverse renal outcomes.
2. Multicenter studies should be done in the developing countries to elucidate the epidemiology better.
3. Long term studies need to be done to assess the recovery rates of AKI in our circumstances. Health related quality of life assessment in those who have AKI should be done to elucidate the best ways to manage them.

10. Study Limitations

Some of the limitations to this study were as follows:

1. Obstructive uropathy is mainly a surgical admission and therefore missed.

2. Some CKD patients have a normal sized kidneys on an ultrasound and may have been included in the study.

3. Inherent worldwide AKI study problem of no previous known baseline renal function and therefore most of our baseline creatinine were based on estimation

4. Pulmonary oedema as an indication for dialysis was based on clinical judgement only and we may have missed some patients.

Appendices

Appendix IV: References

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Appendix II: Consent Form

INFORMATION SHEET

Introduction

I, Mohammed M. Taiyebali, am a postgraduate student at the University of Nairobi, currently doing a masters' degree in Internal medicine. I am conducting my research project for which I request your participation. As you read this form you may ask any questions on what you do not understand.

Purpose of the study

I am carrying out a study on patients with acute kidney injury to see how many of these patients we admit to our medical wards, what are the main causes and how it relates to the length of time. The study is part of my university requirements but the results of the study will be used to offer recommendations which, if implemented, may lead to improved management and quality of life of patients with acute kidney injury.

Procedures to be followed in the study

Once you agree to participate in the study, you will have to answer questions of a personal nature as outlined in the study questionnaire, undergo a physical examination and provide a blood and urine sample.

Confidentiality

All the information you provide will be handled in a confidential manner and will not be divulged to any other person without your consent. Your individual responses will be stored in a locked place under my control and will only be seen by my statistician and I.

Voluntariness of participation

Your participation in this research is voluntary and in the event that you refuse to participate in this study, your treatment will not be affected. If you choose to participate and not answer certain questions, you are free to do so. You are free to terminate the interview and withdraw from the study at any time. You are free to ask questions before signing the consent form.

Benefits

Your participation in the study and the tests will be used for your individual benefit. Information obtained will improve knowledge to health care givers at Kenyatta National hospital.

Risks

You may feel slight pain/ discomfort when the blood sample is drawn. There may be slight swelling at the site of the needle prick, but this will disappear on its own after a few days. The amount of blood that will be drawn will not affect your health.

Rights

You may choose to withdraw from the study at any time whatsoever with no consequences to your treatment.

PATIENT CONSENT FORM

I, _____, have read and fully understood the explanation given to me regarding this study. All my questions have been answered satisfactorily by the investigators. I hereby consent to participation in this study.

Signature: _____

Date: _____

Thumbprint: _____

Witness (PI/Research assistant): _____

Date: _____

Signature: _____

CONTACTS

For further information, you may contact any of the following:

1. Dr. Mohammed M Taiyebali. (Principal investigator)

P.O Box 82485 – 80100, Mombasa.

Tel: 0720 366543

2. Professor A. N. Guantai,

Chairman of Kenyatta National Hospital/University of Nairobi Ethics and Research Committee,

P.O Box 20723, Nairobi.

Tel 020-2726300, extension 44102.

PATIENT ASSENT FORM

I, _____, have read and fully understood the explanation given to me regarding this study. All my questions have been answered satisfactorily by the investigators. I hereby assent to participation in this study.

SIGNED (Patient): _____

PARENT / GUARDIAN: _____

WITNESS (PI / Research assistant): _____

DATE: _____

CONTACTS:

For further information, you may contact any of the following:

1. Dr. Mohammed.M.Taiyebali (Principal investigator)

P.O Box 82485 – 80100, Mombasa.

Tel 0720 366543

2. Professor A. N. Guantai,

Chairman of Kenyatta National Hospital/University of Nairobi Ethics and Research Committee,

P.O Box 20723, Nairobi.

Tel 020-2726300, extension 44102.

2. FOMU YA MAELEZO YA UTAFITI

Utangulizi

Mimi, Mohammed M Taiyebali, ni mwanafunzi katika chuo kikuu cha Nairobi. Ninatarajia kufanya uchunguzi kuhusu ugonjwa wa figo na ningependa wewe uhusike. Fomu hii ni ya maelezo yote utakayohitaji ukiamua kama utajiunga na utafiti huu. Unapoisoma na baada ya kusoma fomu hii, uko huru kuuliza maswali yoyote kama kuna sehemu hujaelewa vyema.

Je,utafiti huu unalenga kutambua nini?

Ninafanya utafiti kwa wagonjwa wenye figo ili kujua wangapi kati yao wana matatizo ya figo na kulinganisha matatizo hayo na muda wa ugonjwa.

Utafiti huu unahitajika kama sehemu ya masomo yangu lakini matokeo yatakayopatikana yatatumika kutoa nasaha, ambayo ikiwa itatumika inaweza kuleta manufaa katika matibabu na hali ya maisha ya wagonjwa wa figo.

Utaratibu wa utafiti:

Utakapokubali kujiunga na utafiti huu, utahitajika kujibu maswwali ya kibinafsi kama yalivyodokezwa katika karatasi ya maswali, utapimwa kimwili na utahitaji kutoa damu na mkojo. Tutahitaji kuondoa mililita tano au kijiko kimoja kidogo cha damu.

Hatari na gharama inayohusika

Unaweza hisi uchungu kidogo damu inapoondolewa. Mahali unapodungwa panaweza fura kidogo, lakini itaisha yenyewe baada ya siku chache. Damu itakayoondolewa ni kidogo na haitakudhuru.

Haki zako

Kujiunga na utafiti huu ni kwa hiari yako. Hutabaguliwa kimatibabu ukikataa kujiunga na utafiti huu. Ukijiunga na utafiti huu na ushindwe kujibu mojawapo au maswali mengine tutakayouliza, ni sawa. Una uhuru wa kutoka kwenye mahojiano na kujitoa kwa utafiti huu wakati wowote. Una uhuru wa kuuliza maswali yoyote uliyo nayo kabla ya kutia sahihi fomu ya makubaliano. Maelezo yako yote yatawekwa pahali pa siri. Ni mtafiti mkuu na mwanatakwimu wake pekee ambao wataangalia maelezo yako.

Manufaa ya utafiti huu

Kujiunga na utafiti huu na vipimo vya maabara vitatumika kwa manufaa yako. Matokeo ya utafiti yatasaidia wauguzi katika hospitali ya Kenyatta.

Cheti cha ridhaa

Nimesoma, au nimesomewa maelezo yaliyopewa. Nimepata fursa ya kuuliza maswali kuhusu utafiti na maswali yote niliyouliza yamejibiwa vyema. Ninakubali kuhusika katika utafiti huu.

Jina la mhusika:……

Sahihi/Alama ya kidole gumba cha kushoto :……....

Tarehe:……

KAULI YA MTAFITI:

Mimi, mtafiti mkuu, nimemweleza mhusika vilivyo kuhusu utafiti huu.

Sahihi (mtafiti mkuu/msaidizi): _____ Tarehe: _____

MAWASILIANO

Ukiwa na maswali yoyote ya ziada, unaweza kuwasiliana na wafuatao:

1. Dkt. Mohammed M. Taiyebali (Principal investigator)

SLP 82485-80100, Mombasa.

Simu: 0720 366543

2. Prof. A.N. Guantai

Kamati ya Maadili ya Hospitali ya Kenyatta na Chuo kikuu cha Nairobi

SLP 20723 NAIROBI

Simu: 020 726300

Appendix III: Case Report Form

Acute Kidney Injury As Seen At Kenyatta National Hospital

DATE: _____

CODE NO. _____

AGE _____

GENDER: MALE ☐ FEMALE: ☐

URBAN…… RURAL …….

DATE OF ADMISSION: _____

DATE OF DISCHARGE: _____

DATE OF AKI DIAGNOSIS: _____

PRESENTING COMPLAINTS

DIARRHOEA	YES……	NO……
VOMITING	YES……	NO……
SIGNIFICANT BLEEDING		
(Leading to hypotension)	YES……	NO……
OTHER (SPECIFY)	YES……	NO……

DRUGS USED BEFORE ADMISSION

(WITHIN A WEEK OF DIAGNOSIS)	TICK IF USED
AMINOGLYCOSIDES	.....
NSAIDS	…..
ACE-I	…..
ACYCLOVIR	…..
ARVs	…..
SULFONAMIDES	…..
DIURETICS	…..
AMPHOTERICIN B	…..
DON'T KNOW	…..

TOXINS	YES……	NO……
CONTRAST WITHIN 5 DAYS	YES……	NO……

CLINICAL ASSESSMENT WITHIN 24 HOURS OF ADMISSION

BP _____

PULSE RATE (BPM) _____

TEMPERATURE _____

RESPIRATORY RATE _____

DEHYDRATION YES ☐ NO ☐

LEFT HEART FAILURE YES ☐ NO ☐

OTHERS (SPECIFY) _____

INITIAL DIAGNOSIS _____

ASSOCIATED DIAGNOSIS _____

LABS

CREATININE (umol/L) (at days 1,4,7,10 & 14) D1 ____, D4____, D7____, D10____, D14____

UREA (mmol/L) at admission _____

PARAMETER		FINDING
SPECIFIC GRAVITY		
OSMOLARITY		
BLOOD		
WBC		
RBC		
NITRITE		
PROTEINS		
URINARY SEDIMENT	BLAND	
	RBC CASTS	
	WBC CASTS	
	EOSINOPHILS	
	COARSE BROWN CASTS	

RENAL ULTRASOUND

KIDNEY SIZE: SMALL < 9.0 CM ☐ NORMAL ☐ LARGE > 13CM ☐

OBSTRUCTION YES ☐ NO ☐

OUTCOME AT DISCHARGE OR DEATH

FULL RECOVERY ☐

PARTIAL RECOVERY ☐

NON RECOVERY IN 2 WEEKS ☐

DEATH ☐

RENAL REPLACEMENT THERAPY ☐

Indications of RRT	TICK IF ANY
Hyperkalaemia	…….
Severe metabolic acidosis	……..
Volume overload	…….....
Pronounced azotaemia	……..
Clinical complications of uraemia	……..

Appendix IV: Data collection tool

A structured case report form was used to collect data relevant to the study. It had both open ended and closed questions depending on the variable being assessed.

The questionnaire had 8 parts which were:

1. Patient's characteristics – hospital number, age, gender, date of admission, discharge or death.
2. The presenting complaints of the patients which included: diarrhea, vomiting, significant bleeding and the symptoms which included orthopnea, paraoxsymal nocturnal dyspnea, seizures, alcohol and drug abuse, fevers, recent blood transfusion.
3. Enquiry of exposure to nephrotoxins – radiocontrast agents, drugs such as aminoglycosides, NSAIDS, ACE-I, acyclovir, ARVs, sulfonamides, diuretics, amphotericin B and other toxins such as herbal therapies.
4. Clinical findings which may have been relevant to the AKI like low blood pressures, high temperatures, change in heart rate, dehydration.
5. Diagnoses was based on the file diagnosis within 24 hours of admission.
6. Laboratory and imaging findings including serial serum creatinines, urea on admission, renal ultrasound and urinalysis.
7. Outcome of renal failure at discharge, death or after 2 weeks in hospital.