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A retrospective study of the epidemiology, management and outcomes of patients with dialysis-requiring acute kidney injury, over a 24-month period, at Helen Joseph Hospital, Johannesburg, South Africa

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A research report submitted to the Department of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg

In fulfilment of the requirements for the degree of Master of Medicine

Co-authors

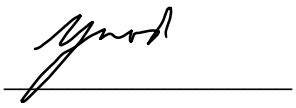
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Declaration

I, Yashika Naidu, Student number 445931, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine (Internal Medicine) at the University of the Witwatersrand, Johannesburg.
This research report is submitted in the submissible format as recognized by the Faculty of Health Sciences. It has not been submitted before for any degree or examination at any other University.



Yashika Naidu

April 2024, Johannesburg

The co-authors declare that the candidate has made the following contributions to this research paper:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.
- Drafting the work or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



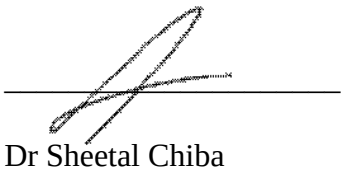
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It is said that one must "walk with the dreamers, the believers, the courageous, the cheerful, the successful people with their head in the clouds and their feet on the ground. Let their spirit ignite a fire within you to leave this world better than you found it…"

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List of Abbreviations

ABCC2: adenosine triphosphate binding cassette subfamily C member 2

ACE-I: angiotensin-converting enzyme inhibitors

ADQI: Acute Dialysis Quality Initiative

AKI: acute kidney injury

AKIN: Acute Kidney Injury Network

ANOVA: analysis of variance

APOL1: apolipoprotein L1

ARVS: antiretroviral drugs

ATN: acute tubular necrosis

ATP: adenosine triphosphate

CHBAH: Chris Hani Baragwanath Academic Hospital

CKD: chronic kidney disease

CRRT: continuous renal replacement therapy

CVVH: continuous veno-venous haemofiltration

CVVHD: continuous veno-venous haemodialysis

CVVHDF: continuous veno-venous haemodiafiltration

DM: diabetes mellitus

EDHF: extended daily haemofiltration

FSGS: focal segmental glomerulosclerosis

GFR: glomerular filtration rate

GSH: Groote Schuur Hospital

HICSs: high income countries

HIV: Human Immunodeficiency Virus

HIVAN: Human Immunodeficiency Virus associated nephropathy

HIVICK: Human Immunodeficiency Virus associated immune complex kidney disease

HJH: Helen Joseph Hospital

HUS: haemolytic uremic syndrome

ICU: Intensive Care Unit

IGFBP7: insulin-like growth factor-binding protein 7

IHD: intermittent haemodialysis

IL: interleukin

ISN: International Society of Nephrology

KDIGO: Kidney Disease: Improving Global Outcomes

KEH: King Edward V11 Hospital

KF: kidney failure

KIM-1: kidney injury molecule-1

L-FABP: liver-type fatty acid-binding protein

LLMICs: low-middle income countries

MACE: major adverse cardiovascular events

MRP2: multidrug resistant protein 2

NAC: N-acetyl cysteine

NCEPOD: National Clinical Enquiry into Patients Outcomes and Death

NGAL: neutrophil gelatinase-associated lipocalin

NSAIDS: non-steroidal anti-inflammatory drugs

PIRRT: prolonged intermittent renal replacement therapy

PLWH: people living with HIV

POC: point-of-care

PTC: proximal tubular cell

RAAS: renin-angiotensin-aldosterone system

RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney

RRT: renal replacement therapy

SCUF: slow continuous ultrafiltration

SLED: sustained low efficiency dialysis

TDF: tenofovir disoproxil fumarate

TIMP-2: tissue inhibitor of metalloproteinase 2 (TIMP-2)

TNF: tumor necrosis factor

TTP: thrombotic thrombocytopenia purpura

UMICs: upper-middle income countries

VL: viral load

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Submissible Article

Abstract

Background

Dialysis-requiring acute kidney injury (AKI) carries significant morbidity and mortality. A cohort of patients was reviewed at Helen Joseph Hospital (HJH) to contribute to local knowledge on the epidemiology, referral patterns, and outcome of dialysis-requiring AKI.

Methods

A retrospective review was conducted of patients receiving dialysis for AKI at HJH between 1 January 2019 and 31 December 2020. Patient demographics and aetiologies of AKI were described. Effects of baseline characteristics and aetiology of AKI on patient survival, duration of hospitalisation, and renal function recovery were analysed using Cox proportional hazards modelling and binomial regression analyses.

Results

Dialysis-requiring AKI occurred in younger median age. Human immunodeficiency virus (HIV) infection (38.7%), hypertension (27.4%) and diabetes mellitus (12.3%) were common comorbidities. Community-acquired AKI predominated with significant renal dysfunction at presentation. Leading causes of AKI were sepsis (51.9%) and hypovolaemia (26.4%). Mortality was high (56.6%). Age and diabetes increased mortality and reduced renal recovery. Sepsis (HR 1.48, 95% CI 1.37–1.60, $P < 0.001$) and cardiorenal syndrome (CRS) type 1 (HR 1.78, 95% CI (1.57–2.01, $P < 0.001$) increased mortality. HIV infection did not increase the risk of mortality and showed an increased likelihood of renal recovery (OR 1.71, 95% CI 1.51–1.95, $P < 0.001$). Chronic kidney disease was prevalent in survivors.

Conclusion

Results resemble that of other low- and middle-income countries. People living with HIV may be at increased risk of dialysis-requiring AKI. AKI carries a high mortality rate. Sepsis and CRS carry an increased risk of death; sepsis-associated AKI and comorbid diabetes are associated with reduced odds of renal recovery to dialysis-free levels.

Introduction

Acute kidney injury (AKI) is not uncommonly encountered in clinical practice, with an estimated incidence of 13.3 million cases per year, of which 85% occur in low- and middle-income countries (LMICs).[1] AKI contributes to 1.7 million deaths annually,[2] significantly increases medical costs,[3] and results in reduced quality of life in survivors.[4] The probability of survival and the cost of treatment increase as AKI stage progresses towards requiring dialysis.[4],[5]

The International Society of Nephrology 0by25 initiative aims to reduce preventable deaths from AKI by the year 2025.[1] Achieving this goal requires closing regional gaps in knowledge of the epidemiology, aetiology, management, and outcomes of AKI.[1]

Despite a high incidence, the presentation, management, and outcome of AKI remain underreported in LMICs.[1],[5] Available literature suggests regional variation in aetiological factors which may result in disparate outcomes.[1].[5] Lack of access to specialized nephrology care and kidney replacement therapies in the developing world results in a paucity of data on the outcomes of advanced-stage AKI from LMIC.[1] The available literature on dialysis-requiring AKI in the South African context is largely derived from intensive care unit (ICU) cohorts; rationing of access to this limited resource[6] is likely to have resulted in an incomplete picture of the disorder.

This study analyses the aetiology, referral patterns, and outcomes of dialysis-requiring AKI in an urban setting to characterize the effect of risk factors on mortality and renal recovery.

Methods

A retrospective review was conducted of all patients receiving dialysis at Helen Joseph Hospital (HJH) for AKI between 1 January 2019 and 31 December 2020. HJH is a tertiary-level facility that provides nephrology services to residents of the northern and western suburbs of Johannesburg; the community served by the hospital is ethnically and socio-economically heterogeneous.

The diagnosis of AKI was retrospectively confirmed as defined by the Kidney Disease Improving Global outcomes (KDIGO) 2012 definition, that is, by documented evidence of an absolute increase in serum creatinine of at least 0.3 mg/dL (26.5 μmol/L) within 48 hours, or

by a 50% increase in serum creatinine from baseline within seven days, or a urine volume of less than 0.5 mL/kg/h for at least six hours.[7] In cases where the premorbid renal function was not available, the contemporaneous diagnosis of AKI was retrospectively validated by subsequent improvement in glomerular filtration rate (GFR) to ≥ 60mL/min/1.73m^2, or where relevant investigations (normal-sized kidneys on ultrasound, absence of significant proteinuria, and suggestive laboratory parameters including calcium, phosphate and haemoglobin concentration, or histological examination) suggested the probability of AKI rather than established chronic kidney disease (CKD).

Anonymized data was extracted from clinical records of included patients to a Microsoft Excel (Microsoft Corp, USA) ® database and subsequently exported for analysis to Stata version 15 (StataCorp 2017, College Station, TX). Baseline characteristics (age, sex, comorbidities, renal function parameters) and ascribed AKI aetiology were described for the series as a whole and in consideration of referral patterns; where required these parameters were compared using the Mann Whitney U- and Fisher Exact tests as appropriate. Inpatient survival, duration of hospitalization, and kidney function recovery outcomes were described; the effect of baseline parameters and AKI aetiology categories on these outcomes were analyzed using Cox proportional hazards and logistic regression modeling respectively.

Approval for this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (protocol number M210221).

Results

The baseline characteristics of the 106 patients included in this study are shown in Table 1. The median age of patients living with HIV (PLWH) was not significantly different from those who were Human immunodeficiency virus (HIV) negative (39.0 years and 45.0 years respectively, P = 0.340). Hypertensives and diabetics were significantly older at presentation than those not affected by these comorbidities (61.0 versus 39.0 years, P < 0.001; and 61.0 versus 40.0 years, P = 0.001; respectively). Median age at presentation was not significantly different between males (40.0 years) and females (47.5 years), P = 0.652. Males comprised 58.5% of PLWH (P = 0.470); women were over-represented amongst hypertensives (62.1%, P = 0.048) and diabetics (69.2%, P = 0.079).

Table 1. Baseline characteristics of the sample cohort

Age (years)*	44.5 (33.0–61.0)
Sex**	
Male	58 (54.7%)
Female	48 (45.3%)
Comorbidity**	
HIV positive	41 (38.7%)
On ARV	28 (68.3%)
Viral load suppression	17 (41.5%)
TDF-containing regimen	28 (68.3%)
Hypertension	29 (27.4%)
Diabetes mellitus	13 (12.3%)
Known autoimmune disease	5 (4.7%)

*Values are *median (interquartile range) or **n (%). ARV, antiretroviral therapy; TDF, tenofovir disoproxil fumarate*

Patterns of referral are shown in Table 2. Patient age and sex showed were similar between Internal Medicine and surgical disciplines (P = 0.181 and P = 0.553, respectively). PLWH were more likely to be referred from Internal Medicine than from surgical disciplines (OR 6.4, 95% CI 2.4–17.1, P < 0.001); no such difference was observed for diabetes (P = 0.470) or hypertension (P = 0.0408). Patients presenting to Internal Medicine had poorer renal function on admission than those presenting to surgical disciples (median urea 23.4 versus 12.8 mmol/L, P < 0.001; median creatinine 413.5 versus 247 µmol/L, P = 0.003; median eGFR 13 versus 25 mL/min/1.73m^2, P = 0.002; respectively) and had commensurably poorer renal function on referral to nephrology services (urea 28.2 versus 17.4 mmol/L, P < 0.001; creatinine 640 versus 312 µmol/L, P < 0.001; respectively). Change in creatinine from admission and time to referral to nephrology services showed no significant difference between disciplines (P = 0.489 and P = 0.361, respectively). Dialysis was initiated at a median of 1 day after referral (interquartile range 0–2 days). Sepsis was the leading cause of AKI in this series, accounting for 51.9% of referrals; pneumonia (16 cases, 29.1% of sepsis-related cases of AKI) was the most common source of sepsis, followed by intra-abdominal sepsis (14 cases, 25.5%) and urogenital infections (seven cases, 12.7%). Tuberculosis accounted for 3 cases and malaria for 1 case; the source of septicaemia was retrospectively

unknown in 13 cases. Similar proportions of AKI ascribed to sepsis were observed between Internal Medicine and the surgical disciplines (P = 0.552). Absolute hypovolaemia caused by diarrhoeal illness was more frequent among medical referrals (P = 0.002) as was relative hypovolaemia caused by cardiac failure (P = 0.040).

No difference in the rate of nephrotoxin discontinuation or drug dose adjustment before referral to nephrology services was observed between Internal Medicine and surgical disciplines (P = 0.559 and P = 0.249, respectively), although numerical superiority was evident for both interventions in the referrals from Internal Medicine.

Table 2. Referral patterns to nephrology services

	All	Internal Medicine	General Surgery	OBGYN**	Urology	Orthopaedics
n (%)	106 (100%)	62 (58.5%)	34 (32.1%)	6 (5.7%)	3 (2.8%)	1 (0.9%)
Age (years)*	44.5 (33.0–61.0)	41 (34–55)	57 (39-68)	30 (26–32)	60 (58–65)	28
Sex						
Male	58 (54.7%)	32 (51.6%)	22 (64.7%)	-	3 (100%)	1 (100%)
Female	48 (45.3%)	30 (62.5%)	12 (35.3%)	6 (100%)	-	-
Urea on admission (mmol/L)*	18.3 (9.4–31.6)	23.4 (13.3–37.6)	11.3 (7.2–19.9)	13.5 (13.2–14.3)	37 (32–42)	6.8
Creatinine on admission (µmol/L)*	307 (140–697)	413.5 (210–947)	228 (97–366)	226.5 (211–313)	475 (408–1525)	286
eGFR on admission (mL/min/1.73m^2)*	17.5 (7.0–39.0)	13 (4–33)	27 (15–71)	25 (23–29)	11 (3–14)	26
Ascribed AKI aetiology						
Sepsis	55 (51.9%)	32 (51.6%)	22 (64.7%)	0	1 (33.3%)	0
Hypovolaemia	28 (26.4%)	17 (27.4%)	9 (26.5%)	2 (33.3%)	0	0
Diarrhoeal	11 (10.4%)	11 (17.7%)	0	0	0	0
Haemorrhage	6 (5.7%)	6 (9.7%)	0	2 (33.3%)	0	0
Cardiac failure	6 (5.7%)	0	4 (11.7%)	0	0	0
Distributive	5 (4.7%)	0	5 (14.7%)	0	0	0
Obstructive uropathy	5 (4.7%)	3 (4.8%)	0	0	2 (66.7%)	0
Glomerular disease	5 (4.7%)	5 (8.1%)	0	0	0	0
Malignant hypertension	4 (3.8%)	0	0	4 (66.7%)	0	0

Rhabdomyolysis	4 (3.8%)	0	3 (8.8%)	0	0	1 (100%)
Nephrotoxin exposure	3 (2.8%)	3 (4.8%)	0	0	0	0
Thrombotic microangiopathy	2 (1.9%)	2 (3.2%)	0	0	0	0
Time to referral from admission (days)*	1 (0–3)	1 (0–3)	1 (1–6)	0 (0–0)	0 (0–2)	0 (0–0)
Nephrotoxins were discontinued before referral	97 (91.5%)	57 (91.9%)	31 (91.2%)	5 (83.3%)	1 (100%)	1 (100%)
Medication dose adjusted before referral	92 (86.8%)	56 (90.3%)	28 (82.4%)	5 (83.3%)	2 (66.7%)	1 (100%)
Urea on referral (mmol/L)*	22.4 (14.3–36.5)	28.2 (19.4–41.5)	18.5 (12.1–26.2)	13.5 (13.2–14.3)	37.4 (32.8–42.0)	6.8
Creatinine on referral (µmol/L)*	399 (255–750)	640 (289–1064)	312.5 (187–433)	226.5 (211–313)	463 (408–1525)	286
Change in creatinine from admission (µmol/L)*	0 (0–70)	0 (0–34)	42 (0–123)	0 (0–0)	0 (-12–0)	0

*Values are *median (interquartile range); OBGYN, Obstetrics and Gynaecology*

The median duration of inpatient follow-up in this cohort was 13 days (interquartile range, 7–26 days). Sixty patients (56.6%) demised before discharge at a median of 4 days (interquartile range, 2–12 days) following dialysis initiation. Patients who demised during admission were significantly older than survivors (median age 60 years compared to 46 years in survivors, P < 0.001), and increasing age was independently associated with inpatient death (OR 1.05, 95% CI 1.03–1.08, P < 0.001). Age-adjusted Cox proportional hazard modeling revealed poorer survival for diabetics, patients with sepsis-associated AKI and those with cardiorenal syndrome (CRS); male patients, obstructive uropathy, glomerular disease-related AKI, AKI secondary to dehydration, and PLWH manifested lower risk of inpatient mortality (Table 3).

Table 3. Age-adjusted inpatient mortality

	HR (95% CI)	**P**
Male sex	0.92 (0.85–099)	0.019
Diabetes mellitus	1.34 (1.22–1.48)	< 0.001
People living with HIV	0.79 (0.73–0.87)	< 0.001
Sepsis-associated AKI	1.48 (1.37–1.60)	< 0.001
Cardiac failure (CRS)	1.78 (1.57–2.01)	< 0.001
Dehydration-related AKI (diarrhoeal illness)	0.87 (0.76–0.99)	0.040
Obstructive uropathy	0.68 (0.56–0.83)	< 0.001
Glomerular disease-related AKI	0.32 (0.25–0.43)	< 0.001

HR, hazard ratio; 95% CI, 95% confidence interval

The median duration of hospitalization in the 46 inpatient survivors of dialysis-requiring AKI was 21 days (interquartile range 12–28 days). Duration of hospitalization showed no significant difference by sex (P = 0.835), comorbid diabetes (P = 0.895), or HIV infection (P = 0.361) and was independent of patient age (b 0.24, 05% CI b -0.04 to 0.54, P = 0.101). The presence of dehydration as a causative factor in AKI did not affect the duration of hospitalization (P = 0.887); however, a trend toward a longer median duration of hospitalization was noted in patients with sepsis-associated AKI (25.5 days compared to 19 days, P = 0.051).

Amongst the 46 inpatient survivors of dialysis-requiring AKI, 12 (26.1%) demonstrated complete recovery of renal function, 29 (63.0%) manifested partial renal recovery, and 5

(10.9%) still required dialysis at discharge. Advancing age reduced the odds of renal recovery at discharge (OR 0.95, 95% CI 0.93–0.98, P < 0.001). Age-adjusted logistic regression demonstrated increased odds of recovery in PLWH and those with dehydration, obstructive uropathy, or glomerular disease-related AKI; comorbid diabetes mellitus, sepsis-associated AKI, and CRS-related AKI were associated with an unfavourable recovery prognosis (Table 4).

Table 4. Age-adjusted recovery of renal function

	OR (95% CI)	**P**
Male sex	0.99 (0.88–1.11)	0.886
Diabetes mellitus	0.68 (0.57–0.80)	< 0.001
People living with HIV	1.71 (1.51–1.95)	< 0.001
Sepsis-associated AKI	0.33 (0.29–0.37)	< 0.001
Cardiac failure (CRS)	0.45 (0.34–0.60)	< 0.001
Dehydration-related AKI (diarrhoeal illness)	2.27 (1.87–2.76)	< 0.001
Obstructive uropathy	1.45 (1.12–1.89)	0.005
Glomerular disease-related AKI	1.61 (1.17–2.22)	0.004

OR, odds ratio; 95% CI, 95% confidence interval

Of the 46 survivors of AKI, 19 (41.3%) defaulted subsequent outpatient follow-up, including 2 patients who still required haemodialysis on discharge; mortality outcomes in these patients after discharge are unknown. Twenty-seven patients were followed up after discharge at a median period of 71 days (interquartile range 21–119 days). Nineteen (70.3%) of these patients demonstrated complete renal recovery, 5 (18.5%) showed partial recovery, and 3 (11.1%) required ongoing dialysis.

Discussion

This first description of the patterns of dialysis-requiring AKI from HJH adds to the existing literature from South Africa and considers novel outcomes. Parameters including duration of hospitalization and recovery of renal function may assist in better contextualizing treatment costs.

The present series is concerning for the apparent preponderance of relatively youthful and potentially economically active patients developing dialysis-requiring AKI. Previous South African series from Chris Hani Baragwanath Academic Hospital in Johannesburg, [8] Groote Schuur Hospital in Cape Town,[9] King Edward VIII Hospital in Durban,[10] and Livingstone Hospital in Port Elizabeth,[11] have similarly reported higher proportions of younger patients diagnosed with more severe categories of AKI (Table 5). Whilst age-related disparities in accessing ICU-based care[12] may partially account for this phenomenon in the reports of Khuweldi[10] and Aylward[11] et al, analysis of the present cohort in whom institutional protocol provides for dialytic support for AKI irrespective of age supports the tendency for more severe forms of AKI to affect younger South Africans as noted by Variava[8] and Dlamini[9] et al.

The 0by25 Global Snapshot study revealed disparities in the age of patients developing AKI according to gross national income, with older patients being affected in higher-income countries, and younger patients being affected in low- and middle income countries (LMICs).[13] These disparities are reflective of differences in causative factors, with dehydration, infection, and pregnancy complications being important AKI aetiologies in LMIC,[14] whilst cardiac failure, surgical complications, and nephrotoxin exposure are more frequent factors in higher-income nations.[13] Additionally, the present study and those of Variava[8] and Aylward[11] et al show that PLWH contributes disproportionately to AKI series. HIV infection is known to increase individual risk of AKI for a variety of reasons, including increased risk of infection and diarrhoeal disease, exposure to nephrotoxic drugs, and the presence of underlying HIV-related CKD.[15] Higher prevalence rates of HIV in adults below the age of 50 years in the local context[16] may thus contribute to the preponderance of younger patients in the South African AKI series. It is perhaps instructive that in the present series, despite the majority (68%) of PLWH having been prescribed ARV, less than half (41%) had achieved virological control, and all patients on ARV were prescribed TDF, a drug with known nephrotoxic potential.[17]

Sepsis and dehydration due to diarrhoeal illness were the most commonly ascribed aetiologies of AKI in this series, consistent with previous reports from Dhlamini,[9] Khuweldi,[10] and Aylward [11] et al and with pooled experience from LMIC.[14] Subtle differences in the incidence of infective causes of AKI between the present series and those reported in the literature are however apparent.

Table 5. Recently reported South African acute kidney injury series

	Reference			
	Variava et al[8]	Dlamini et al[9]	Khuweldi et al[10]	Aylward et al[11]
Site	Chris Hani Baragwanath Academic Hospital, Johannesburg, 2009 - 2011	Groote Schuur Hospital, Cape Town, 2012 - 2013	King Edward VIII Hospital ICU, Durban, 2016	Livingston Hospital ICU, Nelson Mandela Bay Metropole, 2017 - 2018
N	324	366	178	497
Demographics				
Age (years)*	40 ± 13	44 (14–82)	35 (26–55)	43.7 ± 16.8
Sex	Male: 57%; Female: 43%	Male: 58.5%; Female: 41.5%	Male: 48.3%; Female: 51.7%	Male: 61.2%; Female: 38.8%
Comorbidities				
HIV	26%	20.6%	19.7%	35.1%
Hypertension	Not reported	41.5%	25.8%	32.2%
Diabetes	Not reported	17.8%	16.9%	16.1%
Aetiology of AKI	Decompensated CKD: 38.9% ATN: 38.3% HIV-related kidney disease: 13.6% GN**: 7.7%	Sepsis: 60.7% Toxins: 36.4% Surgery-related: 18% GIT-related dehydration: 12.8% Trauma: 11.2% Cardiovascular surgery: 8.2%	Sepsis: 32.6% Trauma: 15.7% Non-communicable: 51.7%	Hypovolaemic shock: 55.1% Sepsis: 40.6% Rhabdomyolysis: 24.8% Other: 6.6%

	Pregnancy-related: 7.4% Malaria: 5.9% Obstructive uropathy: 3.7% Malignancy: 3.4% Other: 3.4% Rhabdomyolysis: 3.1% Malignant hypertension: 3.1% Hypotension: 3.1% Drugs: 2.8% Unknown: 2.2% Metabolic acidosis: 1.2% HUS^{+}: 3.1%	Obstruction: 4.6% Pancreatitis: 4.4% Pre-eclampsia: 3.8% Obstetric haemorrhage: 1.1% Multiple myeloma: 0.8% ACS^{++}: 0.3% Renal infarction: 0.3%		
Percentage receiving dialysis	100%	55.7%	16.3%	10.4%
Outcomes				
Mortality	22.9%	30 days: 31.2%; 90 days: 38.8%	39.9%	31.8%
Renal recovery in survivors	34.6%	79.8%	Not reported	87.3%

**Values are mean ± SD or median (interquartile range); **GN, glomerulonephritis; $^{+}$HUS, haemolytic uraemic syndrome; $^{++}$ACS, abdominal compartment syndrome*

Gastrointestinal infections predominate in other series from LMIC [14] and some local series.[18] Environmental air quality is known to increase the risk of lower respiratory tract infections [19] and AKI [20]. Poorer air quality in Johannesburg compared to other urban centres in South Africa [21] may have increased the incidence of respiratory infection-associated AKI in this series relative to that of diarrhoeal infections.

Consistent with other non-ICU based AKI series reported from South Africa [9] and with LMIC experience [14], most patients in the current series who presented with community-acquired AKI, evidenced significant renal dysfunction at presentation and short time intervals between admission and on-referral to nephrology services. AKI in LMIC settings is associated with more severe renal dysfunction at presentation, which is thought to reflect poorer access to healthcare.[13] Higher rates of comorbidity, particularly HIV infection, may account for poorer renal function at presentation amongst referrals from Internal Medicine specialties in this series.

AKI carries significant mortality; the risk of death increases with the severity of AKI.[22] The significant mortality rate in the present series is therefore not unexpected. Advancing age is known to increase mortality risk in all stages of AKI.[13] Sepsis-associated AKI is known to be associated with poor survival outcomes.[13],[23] The high incidence of sepsis-associated AKI in the present series, combined with the increased mortality demonstrated in this aetiological category, are likely to have further contributed to the mortality rate observed in this cohort.

In the present study, AKI in the context of cardiac failure, equivalent to CRS type 1,[24] carried a poorer prognosis than even sepsis-associated AKI. Available literature confirms this observation, with CRS type 1 carrying an increased mortality and deteriorating prognosis with severity of AKI and requirement for dialysis.[25]

Despite the known association of AKI with HIV infection, AKI does not appear to show an increased risk of mortality in PLWH in most local series,[8],[9],[26] although Aylward et al have reported increased mortality in PLWH with critical illness.[11] In the latter study, HIV infection was associated with greater severity of illness, and the effect of HIV infection on mortality was ameliorated in multivariate models adjusting for these variables.[11] Although not specifically examined, we suspect that the association of HIV infection with readily reversible causes of AKI such as dehydration due to opportunistic gastrointestinal infections and nephrotoxin exposure may contribute to the reduced risk of mortality observed for this

patient group in the present study. This hypothesis is substantiated by the increased odds of renal recovery in PLWH who survive dialysis-requiring AKI observed in this cohort; similar findings have previously been reported for PLWH by Variava et al. [8]

Short-term kidney function recovery outcomes in survivors of dialysis-requiring AKI at HJH are satisfactory, with 89.1% achieving dialysis independence. Similar rates have been reported in other local series;[9],[11] the low recovery rate reported by Variava et al (34.6%) [8] may reflect bias occasioned by the inclusion of patients known with CKD in that study. Higher renal recovery rates have in general been reported for LMICs than for better-resourced countries.[13] Improved renal outcomes in the former countries may reflect a younger patient population with better kidney functional reserve and the contribution of rapidly remediable AKI causative factors such as dehydration as evidenced in the present study. Sepsis-associated AKI has the potential for profound and lasting injury, manifesting in an increased risk for CKD;[27] the longer duration of inpatient therapy observed in the present study may evidence the severity of this injury process in this group. Lower recovery rates in diabetics in this and other studies [11] are consistent with the described tendency for AKI to accelerate the progression of diabetic kidney disease.[28]

Although the proportion of complete recoveries increased at outpatient follow-up, a substantial proportion of patients in this cohort continued to manifest residual renal deficit (18.5%). The propensity of AKI to initiate CKD progression towards kidney failure is of particular concern in resource-constrained settings such as South Africa.[9],[29]

Limitations to this study include the small sample size and restriction to a single centre. The former arises as a result of the imposition of strict criteria for patient selection to include only AKI cases, since the inclusion of known CKD cases may have led to bias in analysis of renal function outcome parameters. Restriction to a single centre additionally ensured that patients receiving dialysis for AKI did so in consideration of a uniform selection protocol. We additionally acknowledge the paucity of outpatient follow-up data in this series, with only 25% of patients completing follow-up at variable times post-discharge. The lack of long-term outcomes data remains a significant challenge in the study of AKI and significantly affects the full understanding of the effects of the diagnosis on individual patients and the socioeconomic ramifications of the diagnosis on communities.

Conclusion

Dialysis-requiring AKI in the local context follows trends reported from LMICs, with a younger population being affected and sepsis and dehydration due to diarrhoeal illness being important causes; PLWH may be at increased risk of the disorder. Most cases of dialysis-requiring AKI are community-acquired, and late presentation with advanced AKI is common. The disorder carries a high mortality rate with sepsis-associated and cardiorenal causes being associated with an increased risk of death; sepsis-associated AKI and comorbid diabetes are associated with reduced odds of renal recovery to dialysis-free levels. Older patients are additionally at increased risk of mortality and are less likely to regain renal function. A true analysis of the burden of dialysis-requiring AKI is hampered by poor long-term follow-up amongst discharged survivors.

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Appendices

Approved Research Protocol with Extended Literature review

1.1 Introduction

1.1.1 Background and definition

Acute kidney injury (AKI) is a commonly encountered syndrome with various aetiologies, defined by an abrupt but usually reversible decline in glomerular filtration. [1] AKI carries significant morbidity and mortality, and imposes a not inconsequential financial burden on the healthcare system. [2] In November 2013, the International Society of Nephrology (ISN) launched the 0by25 initiative (zero preventable deaths from AKI by 2025) which advocates for the implementation of strategies that allow for prevention, early diagnosis and treatment of AKI. [3] The incidence of AKI has been estimated to be 13.3 million cases per year, with 85% of these cases occurring in low- and middle-income countries. [4] AKI has been shown to contribute to 1.7 million deaths annually. [4]

The epidemiology and management of AKI differs vastly between countries, and better insight into the patterns of AKI in different populations is vital in the development of AKI prevention strategies and in planning resource allocation to provide timeous and appropriate treatment of AKI. [1] A global perspective on the epidemiology of AKI has yet to be achieved, in part as a result of discrepancies which have occurred due to the lack of a standardized definition. [1] The latest classification of AKI by the Acute Kidney Injury Working Group of Kidney Disease: Improving Global Outcomes (KDIGO), 2012, is a combination of both the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) (2004) and Acute Kidney Injury Network (AKIN) classification (2007) (Table 1).

Table 1: Table comparing the RIFLE, AKIN and KDIGO criteria [Adapted from 5]

RIFLE		AKIN		KDIGO		
Criteria	**Creatinine definition**	**Criteria**	**Creatinine definition**	**Criteria**	**Creatinine definition**	**Urine output**
Risk	≥1.5-fold increase from baseline SCr or GFR decreased ≥25%	Stage 1	≥0.3 mg/dL increase or ≥1.5-fold increase from baseline SCr within 48 hours	Stage 1	≥0.3 mg/dL increase within 48 hours or 1.5-1.9 times baseline within 7 days	<0.5ml/kg/h for >6 hours
Injury	≥2-fold increase from baseline SCr or GFR decreased ≥50%	Stage 2	≥2-fold increase from baseline SCr	Stage2	2.0-2.9 times baseline within 7 days	<0.5ml/kg/h for 12 hours
Failure	≥3-fold increase from baseline SCr or GFR decreased ≥75% or SCr ≥4 mg/dL; acute rise ≥0.5 mg/dL	Stage 3	≥3-fold increase from baseline SCr or increase to ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL or initiation of KRT	Stage 3	≥3 times baseline within 7 days or increase to ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL or initiation of KRT	<0.3ml/kg/h for 24 hours or anuria for >12 hours

Joannidis *et al.* compared RIFLE and AKIN criteria in critically ill patients and found that RIFLE criteria failed to detect 9% of cases that were initially detected by AKIN criteria. [6] The AKIN criteria failed to diagnose 26.9% of cases detected by its predecessor. [6] AKI classified by either criterion was ultimately associated with an increased hospital mortality. [6] Evidence therefore supports the use of a combined RIFLE and AKIN criteria to optimize detection of AKI, namely the KDIGO classification of AKI. [6] As per the KDIGO definition, AKI is diagnosed by an absolute increase in serum creatinine of at least 0.3 mg/dL (26.5 μmol/L) within 48 hours, or by a 50% increase in serum creatinine from baseline within 7 days, or a urine volume of less than 0.5 mL/kg/h for at least 6 hours. [7]

AKI is staged for severity according to the following criteria:

Table 2: Table showing AKI Staging [Adapted from 7]

Criteria	Creatinine definition	Urine output
Stage 1	≥0.3 mg/dL (≥26.5μmol/l) or 1.5-1.9 times baseline	<0.5ml/kg/h for 6-12 hours
Stage2	2.0-2.9 times baseline	<0.5ml/kg/h for ≥12 hours
Stage 3	3 times baseline or increase in SCr to ≥4.0 mg/dL (≥353.6 μmol/l) or initiation of KRT	<0.3ml/kg/h for ≥24 hours or anuria for ≥12 hours

1.1.2 Epidemiology of AKI

The Global Snapshot Study of 2014 assessed differences in the recognition, management and outcomes of AKI across 72 countries over a 10-week period. [8] This study found that hypovolaemic shock was the most common cause of AKI in high-income (HICs) and upper-middle income countries (UMICs). [8] There was also a higher incidence of cardiac failure, post-operative AKI, use of nephrotoxic agents and older age groups in these settings. [8] In low-income and low-middle income countries (LLMICs), dehydration due to inadequate oral intake and diarrheal diseases was the most frequent cause of AKI. [8] Other important causes in lower-income settings included sepsis, pregnancy-related AKI and animal envenomation. [8]

Studies in Africa have previously suggested similar epidemiology of AKI to that observed in low- and low-middle income settings, with infections such as malaria, Human Immunodeficiency Virus (HIV) and diarrheal diseases being the main contributive factors. [9] Nephrotoxic agents and obstetric and surgical complications were also common causes. [9] There is, however, limited data available concerning the epidemiology of AKI in South Africa, and it is unclear whether local patterns follow those of higher- or lower-income settings.

A retrospective study conducted at Chris Hani Baragwanath Hospital (CHBAH) in Johannesburg over a 2-year period found similar AKI epidemiologies to that reported by other low-income countries. [10] In 324 cases of dialysis-requiring AKI included in this study, the major aetiologies reported included decompensated chronic kidney disease (CKD), sepsis, nephrotoxins including traditional herbal medications and radiographic contrast media, HIV and pregnancy-related kidney diseases, glomerulonephritis, and malaria. [10] Groote Schuur Hospital (GSH) in Cape Town has reported on the demographics and 3-month follow-up outcomes of 366 patients meeting the KDIGO definition of AKI. [11] In this study, hypertension, diabetes mellitus (DM) and HIV were the three most common comorbidities, [11] with sepsis and toxins being the leading causes of AKI. [11] A retrospective study of incidence and outcomes of patients with AKI within an Intensive Care Unit (ICU) at King Edward VIII Hospital in Durban, Kwa-Zulu Natal reported similar results; 119 out of a total of 178 patients (66.9%) were admitted with or developed AKI during their ICU stay. [12] The most common cause of AKI in this setting was sepsis, [12] with hypertension, diabetes and HIV being major risk factors as seen at both GSH and CHBAH. [12] Although only 29 patients (16.3%) required dialysis, these patients had a longer length of ICU stay and an increased mortality due to dialysis-related complications. [12]

1.1.3 Aetiology of AKI

There are numerous causes of AKI, all which lead to a common pathological pathway, namely reduction in renal blood flow resulting in a reduction in reduced glomerular filtration rate (GFR). [13] Clinically, it may be classified into three primary categories: pre-renal, intrinsic and obstructive causes. [13]

1.1.3.1 Pre-renal AKI:

The kidneys receive approximately 25% of cardiac output, any compromise of the systemic circulating blood volume has a significant impact on renal perfusion. [14] Renal hypoperfusion results in a reduced GFR without damage to the renal parenchyma. This an adaptive response to various extra-renal insults. [14]

1.1.3.2 Intrinsic AKI:

Aetiologies of intrinsic renal failure may be divided according to the four major structures within the kidney, namely the tubules, the glomeruli, the interstitium, and the intra-renal blood vessels. [15]

Tubular damage:

Acute tubular necrosis (ATN) results from direct damage to the tubules, commonly due to severe ischaemia or nephrotoxins. [15] Common nephrotoxins encountered include aminoglycosides, amphotericin B and radiocontrast media. [15]

Glomerular damage:

This is as a result of acute inflammation of blood vessels and glomeruli. Glomerulonephritis may be a part of a systemic illness or be due to a primary renal cause. [16]

Interstitial damage:

Interstitial damage is due to an inflammatory infiltrate in the kidney interstitium. [17] This is often secondary to drug therapies (such as beta-lactam antibiotics), infections (such as leptospirosis and legionella) or systemic diseases (such as systemic lupus erythematous, sarcoidosis, Sjogren's Syndrome). [17]

Vascular damage:

Any injury to the intra-renal vessels decreases renal perfusion as well as GFR. [16] Examples of vascular damage include malignant hypertension, atheroembolic disease, preeclampsia/eclampsia, and haemolytic uraemic syndrome (HUS) / thrombotic thrombocytopenia purpura (TTP). [16]

1.1.3.3 Obstructive AKI:

Acute urinary obstruction causes an increase in intra-tubular pressure thereby decreasing GFR. [16] Compromise renal blood flow may also develop thus contributing to a reduced GFR. [16] There are many causes of obstruction which can occur at any level along the urinary tract. [16]

Table 3: Table showing the causes of AKI [Adapted from 14]

CATEGORY	ABNORMALITY	POSSIBLE CAUSES
Pre-renal	Hypovolaemia	Haemorrhage
		Volume depletion
		Renal fluid loss (over diuresis)
		Third space (burns, peritonitis)
	Impaired cardiac function	Congestive heart failure
		Acute myocardial infarction
		Massive Pulmonary embolism
	Systemic vasodilation	Antihypertensive medications
		Gram negative bacteraemia
		Cirrhosis
		Anaphylaxis
	Increased vascular resistance	Surgery
		Anaesthesia
		Hepatorenal syndrome
		Drugs (NSAIDS, Cyclosporin)
Intrinsic	Tubular	Renal ischemia (shock, haemorrhage, trauma)
		Nephrotoxic drugs (antibiotics, antineoplastic drugs)
		Endogenous toxins (myoglobin, haemoglobin, uric acid)
	Glomerular	Acute post-infectious glomerulonephritis
		Lupus nephritis

		IgA glomerulonephritis
		Goodpasture syndrome
		Wegener disease
	Interstitium	Infections (viral, bacterial)
		Drugs (antibiotics, diuretics, NSAIDS)
	Vascular	Large vessels (bilateral renal artery stenosis, bilateral renal vein thrombosis)
		Small vessels (vasculitis, malignant hypertension, thrombotic thrombocytopenic purpura)
Post-renal	Extra-renal	Prostatic hypertrophy
		Improperly placed catheter
		Bladder, prostate, cervical cancer
		Retroperitoneal fibrosis
	Intra-renal	Nephrolithiasis
		Blood clots
		Papillary necrosis

1.1.4 Comorbidities associated with AKI

Patients over the age of 65 years have been shown to be at increased risk of developing AKI, due to the structural and functional deterioration of the kidneys associated with physiological aging. [18] Loss of functional tissue predisposes these patients to the development of AKI. [18] Other predisposing factors in this population group include the presence of comorbidities and an impaired ability to recover. [18] Most studies have identified pre-renal or ischemic causes to be the leading cause of AKI in the elderly. [18]

The risk of AKI has been shown to be increased in patients with diabetes mellitus (DM) due to associated comorbidities including cardiovascular disease and heart failure, as well as exposure to diuretics and other nephrotoxic agents, and pre-existing diabetes-related chronic injury. [19]

Diabetes may in addition increase the severity of AKI through pathways which link obesity and insulin resistance to inflammation. [19] Adipocytes produce pro-inflammatory cytokines

such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 which have been implicated in insulin resistance. [19] Upregulation of inflammatory cytokines in the kidney and urine have been shown in both rodent models of diabetes and diabetic humans. [19] These inflammatory cytokines play a role in long-term renal complications such as proteinuria and renal hypertrophy. [19] An experimental study by Gao *et al*. in Type 2 diabetic mice showed that pre- treatment of with TNF-α antibody was protective against renal ischemic injury, [19] suggesting that DM increases the susceptibility to ischemic AKI due to an elevated TNF-α-mediated inflammatory response. [20]

Hypertension has also been identified as a risk factor for AKI development. [21] Increased inflammation, overstimulation of the renin–angiotensin–aldosterone system (RAAS), increased oxidative stress, endothelial dysfunction, and genetic and epigenetic determinants which contribute to the mechanism of hypertensive injury may also serve to increase susceptibility to AKI. [22]

South Africa has the largest HIV epidemic in the world, with approximately 7.7 million people infected (2018 data). [23] AKI is common in HIV-infected individuals. [24] Dehydration secondary to gastroenteritis, opportunistic infections and sepsis, nephrotoxic medications and HIV –associated thrombotic thrombocytopenic purpura (TTP)- haemolytic uraemic syndrome (HUS) are the most common causes of AKI in HIV-infected patients. [25] High viral load (VL) (≥100,000 copies/ml) and low CD4 counts (< 200 cells/mm^3) are significant risk factors for the development of AKI. [24] Despite the national roll-out of antiretroviral treatment (ARVs), HIV-infected patients with AKI continue to have an increased risk of in-hospital mortality. [9]

Increased risk of chronic kidney disease in HIV-reactive patients reduces residual functional tissue and in turn increases risk of acute kidney injury from exposure both to nephrotoxins and opportunistic infections. [26]

Tenofovir disoproxil fumarate (TDF) is an important potential nephrotoxic agent. [27] Proximal tubular cells (PTCs) are the main site of toxicity due to its many cell membrane transporters that promote tenofovir accumulation. [28] PTCs are responsible for tubular reabsorbtion of molecules, activation of 25-dihydroxycholecalciferol by 1α hydroxylation and release of ammonia which is later needed for proton secretion into the urine by the distal segments. [28] Thus tenofovir-associated nephropathy often results in a partial or complete Fanconi syndrome, with or without a reduction in GFR. [28] Fanconi syndrome manifests in a renal tubular acidosis, glycosuria with normoglycaemia, aminoaciduria, hypophosphataemia,

hypouricaemia, and tubular proteinuria. [28] Lower CD4+ cell counts, pre-existing renal impairment, older age, concomitant nephrotoxins, especially the use of didanosine and boosted protease inhibitors, lower body mass and adenosine triphosphate (ATP)-binding cassette subfamily C member 2 (ABCC2) gene (which encodes the outward tenofovir transporter multidrug resistance-associated protein 2 MRP-2) polymorphisms are risk factors for renal toxicity. [28] Herlitz *et al*, examined the clinical and pathological findings in 13 cases of tenofovir nephrotoxicity. [29] In their study, patients received tenofovir therapy for a mean of 19.6 months. [29] Nine patients presented with acute kidney injury, and four had mild renal insufficiency with subnephrotic proteinuria and seven had documented glycosuria. [29] Renal biopsies of these patients revealed acute tubular necrosis, with proximal tubular eosinophilic inclusions representing giant mitochondria visible by light microscopy. [29] Significant renal recovery occurred in all patients after tenofovir discontinuation, showing that tenofovir nephrotoxicity is a reversible cause of acute tubular necrosis. [29]

1.1.5 Prevention and management

Early prevention, diagnosis and management are key to eliminate preventable deaths from AKI. Treating the underlying cause is as important as ensuring simple interventions such as rehydration, avoidance of nephrotoxins and controlling sepsis. [4] In 2009, The National Clinical Enquiry into Patients Outcomes and Death (NCEPOD) in the United Kingdom highlighted several shortcomings in the identification and management of AKI. The "Adding Insult to Injury" report revealed that a third of patients had received inadequate clinical assessments, investigations and monitoring. [30] It was also noted that there was poor assessment and recognition of risk factors. [30] Complications of AKI were missed in 13% of cases, avoidable in 17% and poorly managed in 22% of cases. [30] Furthermore, 21% of referrals to nephrology were delayed. [30] Such data is not available in South Africa but is urgently required in order to optimize patient care.

The 2012 KDIGO Clinical Practice Guideline for AKI, have suggested several recommendations for the prevention of patients at risk of AKI or with AKI. This includes the use of isotonic crystalloids as the initial fluid choice for intravascular volume expansion, the use of vasopressors in conjunction with fluids in patients with vasomotor shock and the use of a protocol-based management of hemodynamic and oxygenation parameters in the perioperative setting and in patients with septic shock [7]. Targeting a plasma glucose 6.1–8.3 mmol/L in the critically ill patient, as well as achieving a total energy intake of 20–30

kcal/kg/day in all patients with AKI are equally as important [7]. Aminoglycosides should be avoided in the setting of AKI [7]. Using the lowest dose, or either iso-osmolar or low osmolar iodinated contrast media together with oral N-Acetyl cysteine (NAC) and intravenous isotonic crystalloids to prevent contrast-induced nephropathy is recommended. [7]

Between 2016-2017, the ISN launched the 0 by 25 AKI Pilot Feasibility project. [31] The project evaluated the feasibility of the use of point-of-care (POC) serum creatinine and urine dipstick testing together with an education and training program to optimize the identification and management of AKI in the community, in three low-resource settings in Asia (Dharan, Nepal), Africa (Blantyre, Malawi), and Latin America (Cochabamba, Bolivia). [31] It concluded that was feasible to implement a comprehensive program and protocol-based management to improve the recognition and management of AKI. [31]

Delays in the identification of AKI, particularly in low-resource settings are associated with a 30% higher risk of mortality in hospitalized patients. [31] This is attributable to several factors such as inaccessibility of diagnostic tools, limited access to healthcare, as well as a lack of awareness of AKI and its outcomes. [31]

Prompt identification of AKI plays a major part in the management kidney dysfunction [31] and requires healthcare providers to be able to identify patients at increased risk, address these risk factors, and then implement the best evidence-based practices for prevention and management. [31]

The management of AKI is largely supportive but may require renal replacement therapy, in the form of haemodialysis. [32] The timing of dialysis initiation has been the source of long-standing debate [32] The STARRT-AKI trial provided strong evidence that an early RRT strategy in critically ill patients does not improve outcomes nor mortality [33].

There are various modalities available for RRT. Haemodialysis modalities may be continuous (continuous renal replacement therapy (CRRT)) or intermittent [32] CRRT consists of slow continuous ultrafiltration (SCUF), continuous veno-venous haemofiltration (CVVH, which uses convective clearance to remove toxins and solutes), continuous veno-venous haemodialysis (CVVHD, which relies on diffusive clearance) or a combination of convective and diffusive therapies, continuous veno-venous haemodiafiltration (CVVHDF). [34] Sustained low efficiency dialysis (SLED) or slow extended daily dialysis (SLEDD) and extended daily haemofiltration (EDHF) are characterised by a prolonged duration of dialysis between 6-12 hours per treatment. [35] Compared to IHD, continuous therapies allow for

slower solute clearance, lower blood flows and more gradual ultrafiltration thus is preferred in haemodynamically unstable patients. [35]

1.1.6 Outcomes

AKI is associated with poor patient outcomes. A South African study of critically ill adults with AKI has demonstrated an in-hospital mortality rate of 31.8% compared to 7.2% in those without AKI, [36] with the probability of death increasing with the severity of AKI. The highest mortality rate occurred in dialysis-requiring patients. [36] Morbidity has also been shown to correlate with AKI severity; for example, CKD has been reported as a long-term complication in 12.7 % of patients with stage 3 AKI. [36] The FUSION trial additionally demonstrated that major adverse kidney events are common in AKI survivors. [37] Repeated episodes of AKI may also accelerate the progression of CKD to KF. [38] Whilst CKD is a well-documented risk factor for cardiovascular events, studies have also shown that the risk of Major Adverse Cardiovascular Events (MACE) is higher in hospitalized patients with AKI than those without AKI. [39] The ASSESS AKI study reported higher adjusted risks of heart failure, but not major atherosclerotic events, among patients with AKI. [37]

1.1.7 Biomarkers and the future of AKI

Prevention of acute kidney injury requires early diagnosis to facilitate identification of risk factors and discontinuation of precipitating insults. Although changes in serum creatinine and urine output form the basis for the diagnosis of AKI as per the KDIGO definition, [7] other more sensitive and specific biomarkers are currently being studied. Serum creatinine is a late marker of kidney injury and is affected by age, gender, diet, muscularity, hydration status and medication. [40] Proposed biomarkers of AKI include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), interleukin-18 (IL-18), insulin-like growth factor-binding protein 7 (IGFBP7), tissue inhibitor of metalloproteinase 2 (TIMP-2), calprotectin and Cystatin C [41]. These molecules can be detected in urine or blood earlier than changes in serum creatinine and indicate structural damage to the kidney [41].

Biomarkers may be divided into 5 categories [42] according to the pathophysiology of the kidney injury at specific sites along the nephron:

Table 4: Table showing recently discovered biomarkers of AKI [Adapted from 42]

Biomarker category	Example
Functional biomarker	Cystatin C, proenkephalin
Urinary low-molecular-weight protein	α1-microglobulin, β2-microglobulin, retinol-binding protein, adenosine deaminase-binding protein, cystatin C
Cellular injury/stress-associated protein	Neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, liver-type fatty-acid-binding protein, tissue inhibitor of metalloproteinase 2, and insulin like-growth-factor–binding protein 7
Urinary tubular enzyme	Proximal renal tubular epithelial antigen, α-glutathione S-transferase, piglutathione S-transferase, γ-glutamyltranspeptidase, alanine aminopeptidase, lactate dehydrogenase, N-acetyl-beta-glucosaminidase, alkaline phosphatase
Inflammatory mediator	Interleukin-18

1.1.8 Rationale for Research

AKI has a significant impact on mortality, morbidity and imposes a financial burden on the economy. The management of AKI is largely supportive, with early detection being a key factor. The epidemiology and outcomes of AKI have not previously been analysed for Helen Joseph Hospital (HJH).

Better understanding of AKI allows for early identification, recognition of risk factors and implementation of prevention strategies, thereby reducing complications and improving patient outcomes.

1.2 Study Protocol

1.2.1 Definition of variables

- Acute kidney injury (AKI): defined by an absolute increase in serum creatinine, of at least 0.3mg/dL (26.5 µmol/L) within 48 hours or by a 50% increase in serum creatinine from baseline within 7 days, or a urine volume of less than 0.5ml/kg/hr for at least 6 hours. [7]
- Complete renal recovery: defined as a return to within 50% above baseline serum creatinine and dialysis independence as per the Acute Dialysis Quality Initiative (ADQI) Criteria [43].
- Partial renal recovery: defined as an improvement in creatinine and dialysis independence but not meeting the above criteria. [43]
- Chronic kidney disease (CKD): defined as per KDIGO as abnormalities of kidney structure or function, present for more than three months, with implications for health present for more than 3 months, and evidenced by:
    - Markers of kidney damage include the following:
        - Albuminuria (Albumin Excretion Rate ≥30 mg/24 hours; Albumin/Creatinine Ratio ≥30 mg/g [≥3 mg/mmol])
        - Urine sediment abnormalities
        - Electrolyte and other abnormalities due to tubular disorders
        - Abnormalities detected by histology
        - Structural abnormalities detected by imaging
        - History of kidney transplantation
    - Decreased glomerular filtration rate (GFR): < GFR 60 ml/min/1.73 m^2 [44]
- Kidney failure (KF): defined as a GFR <15ml/min/1.73m2 and /or the ongoing need for dialysis. [44]

1.2.2 Aim:

This study describes the epidemiology, management and outcomes of patients with dialysis-requiring acute kidney injury at Helen Joseph Hospital (HJH).

1.2.3 Objectives:

Primary Objective:

The primary objective of this study was to describe the epidemiology of patients with dialysis-requiring acute kidney injury.

Secondary Objectives:

Secondary objectives of this study included:

1. To assess the management of dialysis-requiring acute kidney injury prior to Renal Unit consult by evaluating the following:

a) Timing of referral to nephrology from documented development of AKI criteria (refer to Definition of Variables 1.2.1).
b) Evidence of discontinuation of nephrotoxic agents such as nonsteroidal anti-inflammatory agents (NSAIDS), angiotensin-converting enzyme inhibitors (ACE-I), aminoglycosides and tenofovir disoproxil fumarate (TDF) upon identification of AKI.
c) Evidence of renal dose adjustments of prescribed drugs such as antibiotics, urate lowering therapies, oral hypoglycaemic agents and enoxaparin upon identification of AKI.

2. To determine the outcomes of patients with dialysis-requiring acute kidney injury at discharge and over a 3-month follow-up period as determined by:

a) Patient survival
b) The presence of persistent significant renal dysfunction at follow-up, as defined by an ongoing need for dialysis or the presence of stage 3b CKD
c) The presence of mild residual renal dysfunction, as defined by the presence of albuminuria, or an improvement of GFR of less than 50% resulting in a residual GFR of less than 60ml/min/1.73m^2 but not meeting the above criteria for significant renal dysfunction, or hypertension diagnosed after AKI requiring treatment, otherwise defined as partial renal recovery
d) The presence of complete renal recovery as defined above

1.2.4 Methodology

Study Design:

A retrospective, observational study was conducted on patients with dialysis-requiring acute kidney injury who were referred to the Division of Nephrology at Helen Joseph Hospital, over a 24-month period between 01 January 2019 and 31 December 2020. Follow-up at 3 months was analysed to establish outcomes through review of renal outpatient files.

Study setting:

The study was undertaken at Helen Joseph Hospital, which is located in the city of Johannesburg, Gauteng, in South Africa. Helen Joseph Hospital is a large, public tertiary institution which is affiliated to the University of Witwatersrand's Medical School.

Inclusion criteria:

All patients with dialysis-requiring acute kidney injury who were referred to Nephrology during 01 January 2019 to 31 December 2020, from Internal Medicine, General Surgery and Obstetrics and Gynaecology at the Helen Joseph Hospital – Rahima Moosa complex were considered for inclusion if the following criteria were met:

- Age of 18 years or older
- Cases meeting the definition of acute kidney injury as per KDIGO definition. Alternatively, if a baseline serum creatinine was unavailable, patients who demonstrated a return to GFR$\geq$ 60ml/min/1.73m^2, or in whom relevant investigations (normal sized kidneys on ultrasound, absence of significant proteinuria, and suggestive laboratory parameters including calcium, phosphate and haemoglobin concentration, or histological examination) suggested the probability of AKI rather than established CKD were included.

Study Methods and Data Collection:

- A comprehensive data collection sheet was completed using information extracted from the online database which the Division of Nephrology maintained to facilitate outpatient follow-up. This system was used to identify patients enrolled in this study for the collection of follow-up data at 3-months after discharge. Access to the online database was obtained with permission from the Head of Nephrology at Helen Joseph

Hospital. Additional information was extracted through referral to patient hospital files. Follow-up information was obtained from the renal outpatient files.

- The following data was recorded on the data collection sheet:
    1. Patient demographics (age and gender)
    2. Patient comorbidities (diabetes mellitus (DM), Human Immunodeficiency Virus (HIV), hypertension, dyslipidaemia, obesity cardiovascular disease, autoimmune diseases and known history of CKD)
    3. Aetiology of AKI
    4. Time to referral to nephrology following the development of KDIGO-defined AKI
    5. Referral units
    6. Appropriate cessation of nephrotoxins and dosage adjustment of prescribed medications as required by GFR
    7. Creatinine and GFR on admission and at referral to the Division of Nephrology
    8. In the case of HIV positive patients, CD4 count, viral load and premorbid therapy with ARV (antiretroviral) drugs were also documented
    9. Time to the initiation of dialysis following referral, and duration of inpatient dialysis received
    10. Patient outcomes (inpatient death or survival) and the time to this outcome
- Data collection sheets was collected and uploaded onto the study Excel database.
- Standard protocol in the Division of Nephrology at Helen Joseph Hospital is to review discharged patients at 1 and 3 months after admission at the Renal Outpatients' Clinic, or weekly in the dialysis unit in the case of patients with ongoing dialysis requirements. Those who defaulted their appointment date were recorded as lost to follow-up. An attempt was made to check if the patient has demised before confirming as lost to follow-up through use of recorded contact details.
- The following data was collected at 3-month follow-up:
    1. Serum urea and creatinine and GFR
    2. Urine albumin: creatinine ratio (in non-oliguric patients)
    3. Brachial blood pressure and/or the presence of diagnosed hypertension
    4. Ongoing requirement for dialysis
- Once data collection is completed all identifying parameters were deleted to ensure

patient anonymity in final statistical analysis

1.2.5 Statistical Analysis

- The finalized anonymous Excel database was exported into Stata 15 for analysis. Confidential data was kept separate and only accessible by the researcher.
- Distribution of continuous variables was determined using the Shapiro Wilk W test and visual inspection of the histogram plot, and in consideration of the Central Limit Theorem. For normally distributed variables the central tendency and dispersal measurements were described using mean and standard deviation; for non-parametric data the median and interquartile range were employed. Categorical data were described using counts and percentages. The Student t-test or Analysis of Variance (ANOVA) were used for comparative testing between normally distributed continuous variables; in the case of non-parametric data the Mann-Whitney U test or Kruskall-Wallis ANOVA were deployed. The relative frequency of categorical parameters was compared using the Pearson Chi-square test; resort was made to the Fischer Exact test for binomial categories with less than 10 cases. Cox regression modelling was used to determine the contribution of analysed parameters to time-dependent outcomes such as duration of dialysis required; logistic regression was used to model the effect of identified parameters on outcomes such as residual renal dysfunction and ongoing need for dialytic support.

- In accordance with the aims of this study the following statistical analyses was undertaken:
  The epidemiology of AKI was described in consideration of the following parameters:

  1. Patient demographics (sex and age)
  2. Patient comorbidity
  3. Ascribed aetiology of AKI
  4. Presence of prescribed or administered nephrotoxins
  5. Referral units

Frequency tables and pie or histogram plots were used to represent this data; patient age was described using mean and standard deviation or median and interquartile range as dictated by the outcome of tests for normality of distribution.

The aetiology of AKI was further analysed in terms of patient demographics and co-morbidities using appropriate statistical testing as outlined above.

- Intervention prior to referral to the Renal Unit was described in terms of the frequency of appropriate dose reduction in prescribed drugs and in terms of discontinuation of potential nephrotoxins. This data was presented in frequency tables and using appropriate graphical illustration and compared between referral units using the Pearson Chi-square test. The time to referral to the Renal Unit following the development of AKI was described using appropriate measurements as dictated by normality of distribution. These parameters were compared between referral units using appropriate statistical testing as outlined above. Time to referral to the Renal Unit following development of AKI criteria was subjected to linear regression analysis in order to determine the effect of patient factors (patient age and comorbidities such as diabetes, hypertension, HIV infection, and pre-existing CKD), severity of renal dysfunction as evidence by creatinine and GFR, and referral unit on this parameter.
- Patient survival outcomes and renal recovery categories were described using frequency tables and illustrated using appropriate graphical techniques. In addition, the following analyses were undertaken in an effort to better understand factors involved in both patient and renal outcomes:

1. In-patient survival was modelled using Cox regression analysis for baseline demographic parameters, aetiology of AKI, time to dialysis initiation, and severity of renal dysfunction on referral
2. Cox regression analysis was deployed to determine the effect of the above parameters on duration of dialysis required before recovery of renal function
3. Logistic regression was used to model the effect of the above parameters on the combined outcome of significant residual renal dysfunction and on the outcome of partial renal recovery, as defined above.

- A p-value of less than 0.05 was statistically significant.

1.2.6 Ethics

- Permission for this study was obtained from the Wits Human Research Ethics Committee (Medical). Clearance certificate number M210221.
- Permission to conduct the study was also obtained from both the Head of Department of Internal Medicine and Head of Nephrology at Helen Joseph Hospital, as well as from the Research Committee of that hospital.
- Confidentiality was maintained by ensuring that all identifying parameters are deleted.

1.2.7 Timing

Gantt chart showing the timeline of the study:

	2020				**2021**	**2022**			**2023**	**2024**
	May	Jun-Aug	Sept	Oct-Dec	Jun-Dec	Jan-Apr	May-Sept	Oct-Dec	Jan-Dec	Jan-Feb
Literature review										
Protocol preparation										
Protocol assessment										
Ethics Application										
Data collection Sheet										
Data Analysis										
First draft										

Supervisor review & corrections										
Final write-up										
Submission										

1.2.8 Funding

Costs were minimal and included stationery and printing. All costs were incurred by the principal investigator.

1.2.9 Potential Limitations

- Patients who were lost to follow-up undermine the capacity of the study to assess outcomes.
- Hospital files were not always traceable thus limiting data collection.

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Data collection sheet

(Data to be recorded in Excel in the below format)

Patient Details	Study Number	
	Age	
Patient Demographics	Gender	
	Hypertension	
Patient Comorbidities	Dyslipidemia	
	Diabetes Mellitus	
	Obesity	
	HIV (specify regimen)	
	CVS disease	
	Autoimmune disease	
	CKD (Baseline eGFR)	
	Sepsis (specify source)	
Aetiology of AKI	Glomerulonephritis	
	Nephrotoxins	
	Hypovolaemia due to haemorrhage	
	Hypovolaemia due to acute gastroenteritis	
	Hypovolaemia due to decreased effective circulatory volume)	
	Post renal causes	
	Rhabdomyolysis	
	TTP	
	Other (specify)	
	Date of Admission	
Details of Referral	Date of Discharge	
	Date of renal referral	
	Time to referral to nephrology following the development of AKI	

	Referred from (specify medical unit)	
	Primary diagnosis & reason for renal referral	
	Has potential nephrotoxins been stopped prior to renal referral?	
	Has appropriate renal dosages adjustment of prescribed medications been done prior to renal referral?	

Investigations	**Baseline**	Urea (mmol/L)	
		Creatinine (umol/L)	
	Admission	Urea (mmol/L)	
		Creatinine (umol/L)	
	Referral	Urea (mmol/L)	
		Creatinine (umol/L)	
	Dialysis Initiation	Urea (mmol/L)	
		Creatinine (umol/L)	
	Discharge	Urea (mmol/L)	
		Creatinine (umol/L)	
	3 Month Follow-Up	Urea (mmol/L)	
		Creatinine (umol/L)	
		UPCR/ ACR	
		Ongoing need for Dialysis	
		BP (Brachial)	
		Diagnosed Hypertension	
	HIV +	CD4 (cells/mm^3)	
		VL (Copies/ml)	
	Renal Biopsy	Yes/ No	
		Result	
		Date	
	Renal Ultrasound	Result	
Plan		Date of Dialysis Initiation	

	Duration of Inpatient Dialysis	

Outcomes	**Patient Survival**	**Yes/ No**	
		Date of Demise (If No)	
	At Discharge	**Complete Renal Recovery**	
		Partial Renal Recovery	
		CKD	
		ESRD Requiring Dialysis	
		Mortality	
	3 Month Follow-Up	**Complete Renal Recovery**	
		Partial Renal Recovery	
		CKD	
		ESRD Requiring Dialysis	
		Mortality	
	Lost to Follow-Up	**Yes/ No**	

Ethical Considerations

Permission for this study was granted before data collection commenced by Dr Z Bayat (Head of Department of Internal Medicine, Helen Joseph Hospital), the Helen Joseph Hospital Ethics and Research Committee, and the Human Resource Ethics Committee (Medical) at the University of the Witwatersrand (Clearance Certificate No. M210221). The study was registered with the National Health Research Database website (Reference: GP_202201_022).

Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr Y Naidu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210221

NAME: (Principal Investigator)	Dr Y Naidu
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	*A retrospective study of the epidemiology, management and outcomes of patients with dialysis-requiring acute kidney injury over a 24-month period, at Helen Joseph Hospital, Johannesburg, South Africa* **Change of study title noted on 2021/12/07**
DATE CONSIDERED:	2021/02/26
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs M Davies and Z Cassimjee
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/06/07

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in February and therefore reports and re-certification will be due in the month of **February** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Y. NAIDU
Signature of Principal Investigator

09/12/2021
Date

Plagiarism and Turnitin Report

See attached full Turnitin Report.

