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A profile of cardiac surgery-related acute kidney injury in adult patients at an academic hospital

Gontse Leballo

A research report submitted to the Faculty of Health Sciences,

University of the Witwatersrand, Johannesburg,

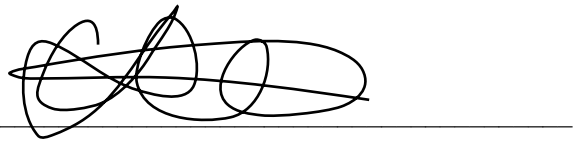
in the partial fulfilment of the requirements for the degree of

Master of Medicine in the branch of Anaesthesiology

Johannesburg, 2021

Declaration

I, Gontse Leballo, herewith declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Signed

On this 19th day of May 2021

Dedication

This project is dedicated to my family; my husband Kebalepile Mothibi and my children, Leago and Marang Mothibi. Thank you for your support and your love, especially when days were tougher than usual. Thank you to my parents Michael and Christinah Leballo; my sister, Naledi Leballo and my brother, Keorapetse Leballo. To Lisemelo Kolotsane, who is a second mother to my children, you are God sent. I am blessed to have you all in my life.

Presentations and publications from this research project

1. The MMED Article for this research project entitled: ***Factors associated with acute kidney injury and mortality during cardiac surgery***, has been accepted for publication in the CardioVascular Journal of Africa (CVJA), Ref.: Ms. No. CVJSA-D-20-00046, January 2021. Appendix 2.

2. A review article entitled: ***Cardiac surgery-associated acute kidney injury: pathophysiology, diagnostic modalities, and management***; has been accepted for publication in the CardioVascular Journal of Africa (CVJA), Ref.: Ms. No. CVJSA-D-19-00102, June 2020 Appendix 3 and 4.

3. A presentation at the South African Society of Anaesthesiology (SASA) Congress; 12th March 2020, Arcadia Pretoria, South Africa. The topic entitled; Cardiac surgery-associated acute kidney injury: *Tomorrow's leaders meet the Experts*. A topic presentation with Professor Michelle Chew from Linkoping University in Sweden. Appendix 5 and 6.

Abstract

Background

Cardiac surgery with cardiopulmonary bypass (CPB) is known to contribute towards the incidence of acute kidney injury (AKI) and perioperative morbidity and mortality. There are several patient, anaesthetic, and surgical factors that also contribute to its occurrence. It is imperative to know the profile of a patient that is likely to develop this complication and mitigate the modifiable risks. This study aimed at describing the profile of AKI in an adult (over the age of 18 years) patient following cardiac surgery on CPB. Factors associated with cardias surgery-associated acute kidney injury (CSA-AKI) are described, as well as the relationship between CSA-AKI and in-hospital mortality.

Methods

This was a contextual, descriptive, and retrospective single-centre study with data of 476 adult patients admitted post-cardiac surgery between January 2016 and December 2017. Data were collected from Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in South Africa. All adult patients who presented for elective cardiac surgery (coronary artery bypass graft), valvular, aortic, and other cardiac surgery on CPB were included. Peri-operative factors such as patient demographics, baseline renal functions, co-morbid factors, length of CPB and aortic cross-clamp time, degree of hypothermia, use of assist devices, and post-operative serum creatinine (SCr) levels were collected. Incomplete essential peri-operative data and data for patients who presented on renal replacement therapy (RRT) already were excluded. AKI was defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria.

Results

One hundred and thirty-five (28%) patients developed CSA-AKI and 20, 5 and 3% were in KDIGO 1, 2 and 3, respectively. Older age ($p = 0.024$), female gender ($p = 0.015$), high serum creatinine level ($p = 0.025$), and a lower estimated glomerular filtration rate (eGFR) ($p = 0.025$) were associated with the development of CSA-AKI, while a history of hypertension was predictive. Forty-six of the 476 patients died. Mortality rates were significantly higher in

those with AKI compared to those without [28 (21%) vs 18 (5%) p = 0.001], respectively. The incidence was significantly worse in those with severe kidney injury, as evidenced by mortality rates of 44 versus 5% between KDIGO 3 and KDIGO 1 (p < 0.001). pre-operative eGFR and CSA-AKI requiring RRT were significantly associated with mortality, while pre-operative eGFR was an independent predictor of mortality (hazard ratio 0.99, 95% confidence interval: 0.97 – 0.99, p = 0.019).

Conclusion

A history of hypertension was predictive of the development of CSA-AKI, and pre-operative eGFR was an independent predictor of mortality in this cohort. Both factors are modifiable.

Acknowledgements

To Dr Palesa Motshabi Chakane (PhD), you are one of a kind. Thank you for being an exemplary mentor. Your support and guidance exceeded my expectations. May God continue blessing your family and your life journey.

To Professor Michelle Chew, for your assistance and advise. Your guidance is valuable. Thank you for your time.

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LIST OF ABBREVIATIONS

AKI	acute kidney injury
CSA-AKI	cardiac surgery-associated acute kidney injury
CTICU	cardio-thoracic intensive care unit
ICU	Intensive care unit
KDIGO	Kidney Disease Improving Global Outcomes
CPB	cardiopulmonary bypass
CABG	coronary artery bypass graft
ECMO	extra-corporeal membrane oxygenator
IABP	intra-aortic balloon pump
VAD	ventricular assist device
BMI	body mass index
SCr	serum creatinine
eGFR	estimated glomerular filtration rate
RRT	renal replacement therapy
MDRD	modification of diet in renal disease

PUBLISHED RESEARCH ARTICLE

Cardiovascular Topics

Factors associated with acute kidney injury and mortality during cardiac surgery

Gontse Leballo, Hlamatsi Jacob Moutlana, Michel Kasongo Muteba, Palesa Motshabi Chakane

Abstract

Background: Cardiac surgery with cardiopulmonary bypass (CPB) is known to contribute towards the incidence of acute kidney injury (AKI) and peri-operative morbidity and mortality. There are several patient, anaesthetic and surgical factors that contribute to its occurrence. It is imperative to know the profile of a patient who is likely to develop this complication to mitigate for modifiable risks. This study aimed at describing a profile of AKI in an adult patient (over the age of 18 years) following cardiac surgery on CPB. Factors associated with the development of cardiac surgery-associated acute kidney injury (CSA-AKI) are described, as well as the relationship between CSA-AKI and in-hospital mortality.

Methods: This was a contextual, descriptive and retrospective single-centre study with data of 476 adult patients admitted post cardiac surgery between January 2016 and December 2017. Data were collected from Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in South Africa. All adult patients who presented for elective cardiac surgery (coronary artery bypass graft), valvular, aortic and other cardiac surgery on CPB were included. Peri-operative factors such as patient demographics, baseline renal function, co-morbid factors, length of CPB and aortic cross-clamp time, degree of hypothermia, use of assist devices, and post-operative serum creatinine (SCr) levels were collected. Incomplete essential peri-operative data and data for patients who presented on renal replacement therapy (RRT) already were excluded. AKI was defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria.

Results: One hundred and thirty-five (28%) patients developed CSA-AKI and 20, 5 and 3% were in KDIGO 1, 2 and 3, respectively. Older age ($p = 0.024$), female gender ($p = 0.015$), higher serum creatinine level ($p = 0.025$), and lower estimated glomerular filtration rate (eGFR) ($p = 0.025$) were associated with the development of CSA-AKI, while a history of hypertension was predictive. Forty-six of the 476 patients died. Mortality rates were significantly higher in those with AKI compared to those without [28 (21%) vs 18 (5%), respectively ($p = 0.001$)]. The incidence was significantly worse in those with severe kidney injury, as evidenced by mortality rates of 44 versus 5% between KDIGO 3 and KDIGO 1 ($p < 0.001$). Pre-operative eGFR and CSA-AKI requiring RRT were significantly associated with mortality, while pre-operative eGFR was an independent predictor of mortality (hazard ratio 0.99, 95% confidence interval: 0.97–0.99, $p = 0.019$).

Conclusion: A history of hypertension was predictive of the development of CSA-AKI, and pre-operative eGFR was an independent predictor of mortality in this cohort. Both factors are modifiable.

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Keywords: cardiac surgery-related acute kidney injury, cardiopulmonary bypass, adults, kidney disease improving global outcomes, renal replacement therapy

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Cardiac surgery-associated acute kidney injury (CSA-AKI) is a peri-operative complication that carries increased mortality rates,[1] as high as 50% in patients who require renal replacement therapy (RRT) following surgery.[1,2] The incidence of AKI is reported in up to 30% of patients who present for cardiac surgery, with risk factors in the peri-operative period.[3] An increase in pre-operative serum creatinine (SCr) level is significantly prognostic of morbidity and mortality following cardiac surgery.[4]

There are nearly two million cardiac surgeries performed globally per year.[5] There is a paucity of statistical data with regard to the incidence and mortality rate of CSA-AKI in sub-Saharan Africa. Studies that have reported on AKI in this region have been in non-surgical patients.[6,7] These reported on mortality rates of up to 43.5% from AKI. Insufficient resources such as RRT and renal transplant services in developing countries should encourage clinicians and scientists in developing approaches aimed at early recognition, diagnosis and the timeous management of AKI.

Peri-operative risk factors of CSA-AKI have been investigated and reported on extensively.[3,8,9] These are classified as modifiable and non-modifiable risk factors.[9] They include illnesses such as renal insufficiency, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, congestive cardiac failure, left main coronary artery disease and a left ventricular ejection fraction of less than 30%.[10] Procedure-related modifiable risk factors include surgical urgency, the length of cardiopulmonary

bypass (CPB) time, aortic cross-clamping time, off-pump surgery, non-pulsatile flow, haemolysis, haemodilution,[10] and the rewarming process following hypothermic arrest.[11] Knowledge of the risk factors allows for optimisation in the peri-operative period.

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a hospital affiliated to the University of the Witwatersrand in Johannesburg, South Africa, performs over 200 adult cardiac surgeries annually. The incidence of CSA-AKI and factors associated with it in this population are not known. This knowledge would allow for modifiable risk factors to be mitigated in the peri-operative period.

This research study aimed to describe a profile of AKI in adult patients post cardiac surgery on CPB. The primary objective was to identify the profile of a patient who is likely to develop AKI following cardiac surgery. The secondary objectives were to define factors associated with the development of CSA-AKI using logistic regression analysis to describe the relationship between CSA-AKI and in-hospital mortality using a Kaplan–Meier survival curve, and to determine factors associated with mortality with a Cox regression analysis.

Methods

This was a descriptive, retrospective cohort study. Data were collected from a single centre. The study population consisted of adult patients over the age of 18 years at CMJAH between January 2016 and December 2017 following cardiac surgery on CPB. Patient information was obtained from anaesthetic, intensive care unit (ICU) and perfusionist charts.

A total of 482 peri-operative patient data were retrospectively analysed during the study period. Six patients were excluded from the study due to incomplete essential data, which included SCr levels during the study period, age, gender and race/ethnicity. Patients on RRT pre-operatively were also excluded from the study. Fig. 1 represents a flow diagram of the study data.

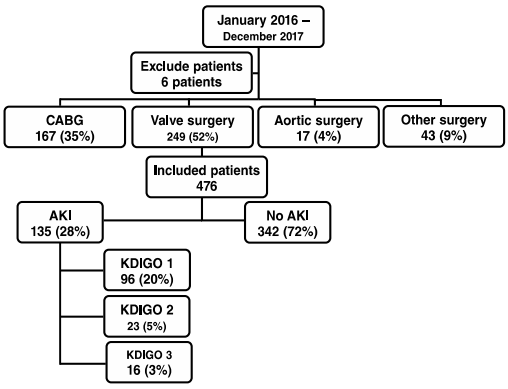


Fig. 1. A flow chart showing the derivation of the study cohort. CABG, coronary artery bypass graft; CSA-AKI,cardiac surgery-associated acute kidney injury; KDIGO, Kidney Disease Improving Global Outcomes.

Table 1. Definitions of diagnostic criteria[5,13,14]

Variables	*Definition*
AKI	An increase in SCr of > 0.3 mg/dl within 48 hours OR an increase in SCr of > 1.5 times baseline known or presumed to have occurred within the prior 7 days OR urine output < 0.5 ml/kg/h for 6 hours
eGFR	Normal: > 90 ml/min/1.73 m^2 Mild: 60–89 ml/min/1.73 m^2 Moderate to severe: < 60 ml/min/1.73 m^2 Renal failure: < 15 ml/min/1.73 m^2
KDIGO criteria	
Class 1	Increased SCr 1.5–1.9 times from the baseline OR urine output < 0.5 ml/kg/h for 6–12 hours
Class 2	Increased SCr 2.0–2.9 times from baseline OR urine output < 0.5ml/kg/h for ≥ 12 hours
Class 3	Increased absolute SCr to > 4.0 mg/dl OR initiation of RRT OR increased SCr 3.0 times from baseline OR 0.3 ml/kg/h for 24 hours OR anuria for 12 hours

AKI, acute kidney injury; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.

The current consensus for diagnosing and classifying AKI uses the Kidney Disease Improving Global Outcomes (KDIGO) criteria (Table 1).[4,8,12] In this study, the worst renal functional state within seven days post cardiac surgery was used to diagnose AKI and to grade into KDIGO classes. SCr levels were measured by the National Health Laboratory Service (NHLS), a national government laboratory. A rise of 0.3 mg/dl and higher was used to diagnose AKI. Baseline renal function was determined by calculating pre-operative estimated glomerular filtration rate (eGFR) levels using the Modification of Diet in Renal Disease (MDRD) equation. Pre-operative renal function severity was classified into mild, moderate to severe, and renal failure by eGFR levels (Table 1).[13] In-hospital mortality data post surgery were collected.

Ethics approval was attained from the Human Research Ethics Committee (Medical), the Graduate Studies Committee of the University of the Witwatersrand, and the National Health Research Committee (Gauteng). This retrospective analysis of patient records did not require informed consent. Patient information was collected by the primary author (GL), and patient confidentiality was preserved by the identification and assignment of numbers to subjects in the data. The principal investigator and the supervisors had access to patient information.

Statistical analysis

Data were collected on a Microsoft® Excel spreadsheet. Stata® 14 (StataCorp.2015, Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) was utilised for data processing and evaluation. Variables are presented as panel data analytics using absolute numbers, percentages, mean (SD), median (IQR) and categories. The occurrence of CSA-AKI on CPB was estimated with an overall 95% confidence interval and *p*-values less than 0.05 were statistically significant. Logistic regression analysis was used to determine factors associated with CSA-AKI, the relationship between CSA-AKI and mortality was assessed using a Kaplan–Meier survival curve, and factors associated with mortality with a Cox regression analysis.

Results

Demographic and pre-operative data for 476 patients are presented in Table 2. The total median (IQR) age was 53

(39–62) years. Patients were predominantly male 255 (53%), and the majority were of the African race [245 (52%)]. A total of 135 (28%) patients developed CSA-AKI within seven days following cardiac surgery on CPB (Table 3). These patients were older and predominantly female. Although they presented with significantly lower eGFR and higher SCr levels pre-operatively as a group compared to those without CSA-AKI, 32 (24%) had presented with normal renal function (eGFR levels) on admission.

Prolonged CPB time, peri-operative use of extracorporeal membrane oxygenator (ECMO), and intra-aortic balloon pump (IABP) were associated with the development of CSA-AKI ($p < 0.05$) (Table 3). History of hypertension was predictive of development of CSA-AKI ($p < 0.05$) in an adjusted model (Table 3). Ninety-six (71%) patients were classified as KDIGO 1, 23 (17%) KDIGO 2, and 16 (12%) KDIGO 3 (Table 4).

The mortality rate was 9.6% (46 out of 476 patients). Mortality rates were significantly higher in those with AKI compared to those without [28 (21%) vs 18(5%), respectively] ($p = 0.001$) (Table 5). The incidence was significantly worse in those with more severe kidney injury, as evidenced by mortality rates of 44 versus 5% between KDIGO 3 and KDIGO 1 ($p < 0.001$) (Table 4).

Causes of mortality for 21 patients were unclear and unspecific in the reports, while four were reported to be from septic shock with multi-organ failure, one from renal failure, one from left ventricular rupture, and one death on the table following relook surgery. The pre-operative eGFR status of the 28 patients who had developed AKI and died are as follows: five had normal renal function, 13 mild renal dysfunction, eight moderate-to-severe renal dysfunction and two had renal failure.

The Kaplan–Meier survival analysis (Fig. 2) showed the cumulative probability of dying on the first day to be higher for patients without AKI (15.8%, 95% CI: 5–41%) compared to patients with AKI (3.7%; 95% CI: 1–23.5%). The median (IQR) failure time (time to mortality) was 13 (1–40) days for patients without CSA-AKI and only 6 (3–16) days for patients with CSA-AKI. The difference was not statistically significant. Although mortality for patients with CSA-AKI seemed higher (Fig. 2) after the first week, with a shorter median (IQR) time to mortality, the overall in-hospital mortality rate was not statistically different (UHR = 1.51, 95% CI: 0.76–2.99, $p = 0.240$) between groups.

Table 2. Demographic and pre-operative data of patients who presented for cardiac surgery on CPB

Pre-operative variables	*All patients (n = 476) [median (IQR)/n (%)/mean (SD)]*
Age (years)	53 (39–62)
Male gender	255 (53)
Weight (kg)	70 (59.5– 83)
Height (m)	1.66 (1.6–1.73)
BMI (kg/m^2)	2 4 (21.5–29.8)
African race	245 (52)
Diabetes mellitus	67 (14)
Hypertension	126 (26)
Hypercholesterolaemia	77 (16)
Smoking	84 (18)
Pre-operative SCr (mg/dl)	1.03 (0.89–1.24)
Type of cardiac surgery	
CABG	172 (36)
Valve surgery	253 (36)
Aortic surgery	18 (4)
Other	43 (9)
eGFR (ml/min/1.73 m^2)	
< 15	4 (1)
15–60	97 (20)
60–90	(48)
> 90	148 (31)
KDIGO class	
0	342 (72)
1	96 (20)
2	23 (5)
3	16 (3)

BMI, body mass index; SCr, serum creatinine; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.

Table 3. Comparison of peri-operative/baseline parameters

Parameter	*CSA-AKI (n = 135) [mean (SD)/median (IQR)/n (%)]*	*No CSA-AKI (n = 342) [mean (SD)/median (IQR)/n (%)]*	p-*value*
Age (years)	56 (42–63)	52 (37.5–61)	0.024
Male gender	51 (37)	171 (50)	0.015
Weight (kg)	73 (60–85)	70 (59–83)	0.146
Height (m)	1.69 (1.64–1.74)	1.65 (1.59–1.72)	0.996
BMI (kg/m^2)	26 (21.6–30.3)	2 2 (21.5–29.8)	0.603
African race	76 (56)	157 (45)	0.441
Diabetes mellitus	24 (18)	42 (12)	0.120
Hypertension	34 (25)	91 (27)	0.724
Smoking	25 (19)	58 (17)	0.696
Cholesterol	20 (15)	56 (74)	0.666
Pre-operative eGFR (ml/min/1.73 m^2)	76.5 (58.3–89.9)	80.4 (61–98.35)	0.024
eGFR			
< 15	2 (2)	2 (0.5)	0.099
15–60	34 (25)	63 (18.5)	
60–90	66 (49)	160 (47)	
> 90	32 (24)	115 (34)	
Baseline SCr (mg/dl)	1.09 (0.92–1.3)	1.01 (0.87–1.21)	0.005
Type of cardiac surgery			0.319
CABG	56 (41)	111 (33)	0.319
Valves	56 (41)	186 (55)	
Aorta	5 (4)	12 (3)	
Other	11 (8)	32 (9)	
CPB time (min)	157 (121–203)	144 (113.5–179)	0.040
IABP	13 (10)	6 (2)	< 0.001
Cross-clamp time (min)	100 (81–133)	95 (71–120)	0.053
Lowest temperature on pump	30 (30–32)	32 (30–32)	0.200
ECMO	13 (10)	8 (2)	0.001
VAD	0	2 (0.6)	0.372
SCr difference from baseline (mg/dl)			
Day 1	0.10 (–0.05–0.27)	–0.09 (–0.19–0.01)	< 0.001
Day 2	0.35 (0.18–0.61)	–0.06 (–0.19––0.19)	< 0.001
Day 3	0.38 (0.08–0.74)	–0.14 (–0.27––0.02)	< 0.001
Day 4	0.25 (–0.02–0.67)	–0.18 (–0.36––0.06)	< 0.001
Day 5	0.08 (–0.11–0.62)	–0.21 (–0.42––0.09)	< 0.001
Day 6	0.09 (–0.20–0.57)	–0.25 (–0.61––0.10)	< 0.001
Day 7	0.05 (–0.24–1.26)	–0.20 (–0.50––0.05)	< 0.001
Mortality	28 (21)	18 (5)	< 0.001

BMI, body mass index; eGFR, estimated glomerular function; SCr, serum creatinine; CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenator; VAD, ventricular assist device.

Table 4. Demographic data of patients who underwent cardiac surgery on CPB, classified using KDIGO criteria

Parameter	*KDIGO 0* (n = 342) *[mean (SD)/median (IQR)/*n *(%)]*	*KDIGO 1* (n = 96) *[mean (SD)/median (IQR)/*n *(%)]*	*KDIGO 2* (n = 23) *[mean (SD)/median (IQR)/*n *(%)]*	*KDIGO 3* (n = 16) *[mean (SD)/median (IQR)/*n *(%)]*	p-*value*
Age (years)	52 (38–61)	57 (42.5–63.5)	60 (50–63)	49 (30.5–39.5)	0.0299
BMI (kg/m^2)	2 2 (21.5–29.8)	26 (21–30)	26.7 (21.5–32.7)	26.2 (22.8–31.2)	0.840
Male gender	172 (50)	35 (36)	9 (39)	7 (44)	0.094
Diabetes mellitus	42 (12)	19 (18)	4 (17)	1 (6)	0.206
Hypertension	91 (27)	26 (27)	4 (17)	4 (25)	0.798
Mortality	18 (5)	13 (14)	8 (35)	7 (44)	< 0.001
Hypercholesterolaemia	56 (16)	16 (17)	3 (13)	1 (6)	0.717
Smoking	58 (17)	16 (17)	5 (22)	4 (25)	0.795
Pre-operative eGFR (ml/min/1.73 m^2)	80.5 (6 1–98.1)	76.7 (57.3–89.9)	74.1 (48.8–89.9)	80.3 (66.6–92.6)	0.1278
eGFR					
< 15	2 (0.6)	2 (0.2)	Nil	Nil	0.0734
15–60	63 (18)	25 (27)	7 (30)	2 (12.5)	
60–90	160 (47)	45 (47)	11 (48)	10 (63)	
> 90	116 (34)	23 (24)	5 (22)	4 (25)	
Pre-operative SCr (mg/dl)	1 (0.87–1.2)	1.1 (0.95–1.29)	1 (0.87–1.32)	0.98 (0.89–1.26)	0.0338
Cross-clamp time (min)	95 (71–120)	100 (78–128)	119 (84–171)	95 (90–124)	0.1414
CPB time (min)	144 (114–178)	153 (121–192)	174 (124–239)	158.5 (118–250)	0.1554
IABP	6 (2)	10 (10)	2 (9)	1 (6)	0.001
VAD	2 (0.6)	Nil	Nil	Nil	0.851
ECMO	8 (2)	6 (6)	2 (9)	5 (31)	< 0.001
Lowest temperaure	32 (30–32)	30 (30–32)	32 (30–32)	31 (30–32)	0.6142
SCr change from baseline					
Day 1	0.94 (0.78–1.1)	1.2 (0.98–1.39)	1.24 (1–1.59)	1.4 (1.2–2.0)	0.0001
Day 2	0.97 (0.76–1.15)	1.4 (1.18–1.74)	1.69 (1.39–2.17)	1.76 (1.4–2.6)	0.0001
Day 3	0.87 (0.71–1.06)	1.4 (1–1.67)	1.79 (1.58–2.4)	2.6 (1.86–3.72)	0.0001
Day 4	0.81 (0.63–0.98)	1.2 (0.95–1.64)	1.5 (1.2–2.39)	3.0 (2.5–4.2)	0.0001
Day 5	0.78 (0.59–0.96)	1 (0.89–1.48)	1.6 (1–2.64)	3.0 (2.38–3.4)	0.0001
Day 6	0.78 (0.55–0.96)	1 (0.79–1.44)	1.6 (0.88–2.5)	2.8 (2–3.98)	0.0001
Day 7	0.8 (0.6–1)	1 (0.78–1.4)	1.3 (0.98–2)	2.8 (1.67–4.4)	0.0001
Type of cardiac surgery					
CABG	111 (66)	40 (24)	8 (5)	8 (5)	0.155
Valve	187 (75)	48 (19)	10 (4)	5 (2)	
Aortic	12 (70)	4 (24)	Nil	1 (6)	
Other	32 (74)	4 (9)	5 (12)	2 (5)	
RRT	Nil	3 (3)	Nil	Nil	0.007

BMI, body mass index; IABP, intra-aortic balloon pump; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; CABG, coronary artery bypass graft; RRT, renal replacement therapy.

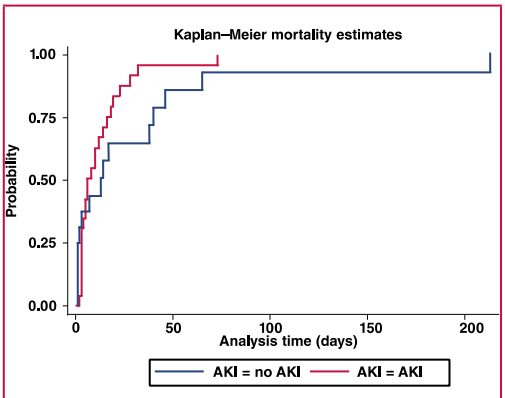


Fig. 2. Post-operative in-hospital survival probability curve in cardiac patients with and without cardiac surgery-associated acute kidney injury (CSA-AKI).

A univariable Cox regression analysis (Table 6) showed a significant relationship between in-hospital mortality and a history of smoking, coronary artery bypass graft (CABG)

Table 5. Logistic regression analysis of factors associated with CSA-AKI

Predictors of CSA-AKI (n = 135)	*Unadjusted logistic regression analysis*		*Adjusted logistic regression analysis*	
	UOR (95% CI)	p-*value*	*AOR (95% CI)*	p-*value*
Age	1.02 (1.00–1.03)	0.024	1.02 (0.99–1.03)	0.052
Female gender	0.60 (0.40–0.91)	0.017	0.58 (0.36–0.93)	0.025
African race	1.51 (1.01– 2.25)	0.044	1.12 (0.66–1.88)	0.676
ECMO	4.42 (1.79–10.93)	0.001	3.05 (1.11–8.39)	0.030
IABP	93 (2.21–1 95)	< 0.001	3.78 (1.29–11.03)	0.015
CPB time (min)	1.00 (1.00–1.01)	0.036	1.00 (0.99–1.04)	0.363
Baseline SCr	1.01 (0.89–1.15)	0.853	0.95 (0.77–1.19)	0.675
Pre-operative eGFR	0.99 (0.98–0.99)	0.010	0.99 (0.98–1.01)	0.253
Hypertension	0.92 (0.58–1.45)	0.724	0.53 (0.29–0.97)	0.041
Diabetes mellitus	1.54 (0.89–2.66)	0.122	1.69 (0.86–3.33)	0.126
Smoking	1.11 (0.66–1.86)	0.696	0.79 (0.43–1.45)	0.448

UOR, unadjusted odds ratio; AOR, adjusted odds ratio; SCr, serum creatinine; CI, confidence interval; ECMO, extracorporeal membrane oxygenator; IABP, intra-aortic balloon pump.

Table 6. Cox regression analysis of predictors of in-hospital mortality

Predictors of mortality (n = 46)	*Univariable regression analysis*		*Multivariable regression analysis*	
	UHR (95% CI)	p-*value*	*HR (95% CI)*	p-*value*
Age	1.02 (0.99–1.04)	0.115		
Male gender	0.86 (0.44–1.69)	0.667		
African race	1.34 (0.71–2.55)	0.368		
Valve surgery	0.54 (0.27–0.06)	0.073	0.60 (0.22–1.61)	0.309
CABG	2.02 (1.02–3.99)	0.043	1.16 (0.41–3.31)	0.775
Aortic surgery	22.56 (6.96–73.09)	< 0.001	0.54 (0.06–4.69)	0.575
Hypertension	0.89 (0.44–1.78)	0.742		
Cholesterol	0.97 (0.34–2.84)	0.962		
Diabetes mellitus	1.53 (0.77–3.02)	0.222		
Smoker	2.89 (1.21–6.91)	0.017	0.45 (0.17–1.23)	0.121
ECMO	1.20 (0.67–2.15)	0.540		
IABP	1.46 (0.74–2.89)	0.273		
Pre-operative eGFR	0.983 (0.97–0.99)	0.006	0.99 (0.97–0.99)	0.019
AKI	1.52 (0.72–3.23)	0.269		
RRT	0.64 (0.43–0.97)	0.034	2.64 (0.13–1.61)	0.223

UHR, unadjusted hazards ratio; HR, hazard ratio; CI, confidence interval; CABG, coronary artery bypass graft; ECMO, extracorporeal membrane oxygenator; IABP, intra-aortic balloon pump; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; RRT, renal replacement therapy.

surgery, aortic surgery, pre-operative eGFR and CSA-AKI requiring RRT ($p < 0.05$). Inclusion of those factors from the univariable Cox regression with $p \leq 0.1$ in a multivariable Cox regression model showed pre-operative eGFR to be the sole predictor of in-hospital mortality (HR 0.99, 95% CI: 0.97–0.99, $p = 0.019$).

Discussion

AKI is an important factor affecting outcomes following cardiac surgery. Its importance is emphasised in the Enhanced Recovery After Cardiac Surgery (ERACS) recommendations.[15] It is highlighted that 'early detection of kidney stress and interventions to avoid acute kidney injury after surgery' are necessary.[15]

This single-centre study was a retrospective records review of adult patients who presented for cardiac surgery. The cases included CABG, cardiac valve repair surgery, aortic surgery, and other cardiac-related surgeries on CPB. The prevalence of CSA-AKI, defined using the KDIGO criteria, at 28% in our study, is similar to that reported in previous reports that show the frequency of CSA-AKI to be up to 30%.[3,16] Thirty-two (24%) of these patients had presented with a normal pre-operative eGFR. This suggests a peri-operative and possibly modifiable factor in the development of their AKI. The majority had early kidney stress (KDIGO 1), which could have been improved with early detection and intervention.

The study highlights several modifiable factors that can be mitigated for better post-operative outcomes. Pre-operative eGFR and SCr levels, and long CPB times were three such factors associated with CSA-AKI. An elevated pre-operative SCr level was found to be an independent risk factor for the development of CSA-AKI and to contribute to mortality in one study.[4] Identifying patients with low eGFR and planning for renal rescue in the peri-operative period could lead to better outcomes, including in-hospital mortality rate.

Although a previous study[17] found no relationship between low cardiac output and need for IABP, duration of CPB and cross-clamping, we postulate that these factors were reflective of the peri-operative course and complications. Early identification of patients with these factors and planning for renal rescue in the peri-operative period could lead to better outcomes, including in-hospital mortality rate.[4]

Patients who developed AKI displayed a steady increase in SCr levels from baseline, notable on day one, the peak occurring on day three. The changes in SCr ranged from 1 (0.78–1.4) to 1.4 (1.18–1.74) over seven days. Patients in the non-AKI group, on the contrary, displayed a decline in SCr levels from day one, which continued over seven days. Although these changes seemed minor, Lassnigg *et al.*[18] in their study stated that 'even minor degrees of post-operative AKI, as manifest by only a 0.2 to 0.3 mg/dl rise in serum creatinine from baseline, predicted a significant increase in short-term mortality'. As part of a management strategy for CSA-AKI, the following recommendations have been made: prevention, optimisation pre-operatively, modification of risk factors, and peri-operative management using the KDIGO care bundle.[19]

In an attempt to detect early 'kidney stress', newer modalities of detection have been described and include the use of biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), cystatin C, insulin-like growth factor binding protein 7 (IGFBP-7) and tissue inhibitor of metalloproteinases-2 (TIMP-2).[20] These biomarkers have been investigated in line with the principles of the KDIGO care bundle.[21] Early biomarker-based prediction of imminent AKI followed by implementation of the KDIGO care bundle reduced AKI severity, post-operative creatinine increase, and length of ICU and hospital stay in patients after major non-cardiac surgery. Use of renal vascular ultrasound is one other modality being investigated.[22,23]

The mortality rate was 9.6% (46 out of 476 patients). Mortality rates were significantly higher in those with AKI compared to those without [28 (61%) vs 18 (39%), respectively] ($p = 0.001$). The incidence was significantly worse in those with more severe kidney injury. Similarly, a previous study has shown an association of increased 30-day mortality[24] with a higher KDIGO class. In a meta-analysis of 91 observational studies with 320 086 patients, Hu *et al.*[25] found pooled short- and long-term mortality rates of 10.7 and 30%, respectively, with increases along with the severity of stages.

The current study found pre-operative eGFR to be the sole predictor of in-hospital mortality. A Japanese study also found pre-operative eGFR to be predictive of all-cause mortality, cardiac mortality, and an increased risk of major adverse events (MACE) (HR 0.983, $p = 0.026$; HR 0.963, $p = 0.006$; HR 0.983, $p = 0.002$), respectively, in patients following cardiac surgery.[26] Due to the association with increased mortality rate and length of hospital stay, with mortality rates varying from 22 to 36%, and rates of 50 to 80% in severe AKI requiring renal replacement therapy, early detection of CSA-AKI is necessary to mitigate risk.[20] This is also emphasised in the ERACS recommendations.[15]

Limitations

Retrospective cohort studies rely on accurate record keeping, as errors related to bias and confounding factors are high, affecting the level of the evidence. Large sample sizes are required, as some

statistical analysis cannot be measured. Data were obtained from a single centre, therefore, results are contextual and may not be extrapolated to other population groups. The probable presence of unknown confounding factors affects the interpretation of the results. A multicentre study would be beneficial to permit larger sample sizes.

The mortality rate was low, making the regression models likely to be over-fitted. It also narrowed the scope of variables that could be included in the multivariable regression models. This may have confounded the results. Relationships were, however, apparent and echoed in other studies. This rapidly growing field with the novel use of biomarkers and ultrasound allows for further exploration. Pre-operative echocardiography information, together with data on the use of inotropes, diuretics, fluids and blood products intra-operatively, leaves the researchers with an opportunity to investigate such variables in a future prospective study.

Conclusion

Numerous modifiable factors including pre-operative renal dysfunction were found to be associated with the development of CSA-AKI and mortality. Identification of patients at risk of CSA-AKI, relying on serial SCr and/or urine output measurements may not be time sensitive and may delay timeous interventions. The use of novel biomarkers and renal vascular ultrasound promises the possibility of early diagnosis of renal injury. Kidney injury should be considered an important factor in post-operative outcomes in cardiac surgery. Those at risk of kidney injury should be identified and risk-modification strategies employed. Renal function is crucial for enhanced recovery after cardiac surgery, as evidenced by studies that show its association with adverse outcomes.

We thank Dr Katharina-Maria Vanderdonck for her assistance with data collection.

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APPENDICES

Appendix 1: Publishers guidelines

Journal: Cardiovascular Journal of Africa

Information for authors

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- South African and African Authors: ZAR 1000
- International Authors: ZAR 2000

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Basic Science publications related to clinical aspects either for elucidation, in-depth understanding or therapeutic approaches are accommodated. The Journal functions as official medium for other related societies which do not as yet have own Journals such as, Hypertension, Stroke, Nuclear Medicine and Magnetic Resonance in Cardiology, Paediatrics, Molecular and Cellular Cardiology, and Vascular disease in Diabetes and Obesity.

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All categories of manuscripts for the Cardiovascular Journal of Africa must be submitted on-line to Editorial Manager. You will be assigned your own password and username. This will allow complete interaction between the editor and authors. Internally, reviewers will be approached to review material in their field of expertise and assigned with similar interaction. All information will be entirely protected and confidential.

All submissions should be written in a clear and succinct manner, following the style of the Journal. Title page should include a descriptive title; authors' surname and forename, address

of each author and full address, telephone, fax and e-mail contacts for the corresponding author. In text: tables and figures are either inserted as part of sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (download off-line document). This must be provided to the Journal by fax or mail (fax number +27 21 976 8129 or PO Box 1013, Durbanville, 7551) or e-mail to info@clinicscardive.com

All images MUST be at or above intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi Image files also must be cropped as close to the actual image as possible.

Preferred Image Format		Alternative Image Format
Image Format	.tif	.jpg
Image Width	Greater than or equal to intended display size	Greater than or equal to intended display size
Colorspace	RGB	RGB
DPI	500+	500+
Alpha Channels	None	
Layers	Flattened	
Compression quality		Maximum

References numbered in the order of appearance in the text, according to Vancouver style. For articles: Author AB, Author C, Author M. The title of the article. Abbreviated journal title 1999; 14: 172–183. For book chapters: Author AB, Author CD. The title of the chapter. In: Editor A, Editor BC, ed. Title of the book, 2nd edn. Location: Publisher, 1999: 133 –139. DOI Numbers / PMID (Pubmed ID / PMC ID) must be added to all references to facilitate tagging for PubMed Central.

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within the context of current knowledge, leading to specific conclusions where possible. Acknowledgements. References, figures and tables as above.

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Title page as above. Abstract (150 words) setting out the scope, key messages and conclusions of the review. Body of text liberally partitioned with headings and subheadings leading to a synopsis with conclusions at the end. Key messages in a separate box itemising two to five short principal statements. Acknowledgements, references, tables and figures as above.

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Appendix 2: Letter of acceptance of the MMed article with original title

Ref.: Ms. No. CVJSA-D-20-00046R2

A profile of cardiac surgery-related acute kidney injury in adult patients at an academic hospital. A retrospective observational study.

CardioVascular Journal of Africa

Dear Dr Leballo,

We wish to inform you that your manuscript, A profile of cardiac surgery-related acute kidney injury in adult patients at an academic hospital. A retrospective observational study., has been accepted for publication in CardioVascular Journal of Africa.

Unfortunately, we are unable to tell you which Volume and on what pages at present as we rely on our set-out design & publishers for that information.

You will be contacted by our Production Editor when your article is ready for final proof reading before publication.

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We thank you for your interest and support in the Journal and we will be interested in any other material you may feel you would like to submit in this field.

Thank you for submitting your work to this journal.

With kind regards

Pat J Commerford, MBChB FCP(SA)
Editor-in-Chief
CardioVascular Journal of Africa

Appendix 3: Published review article from MMed literature review

Review Article

Cardiac surgery-associated acute kidney injury: pathophysiology and diagnostic modalities and management

Gontse Leballo, Palesa Motshabi Chakane

Abstract

Acute kidney injury is a disease spectrum that can present with from mild renal dysfunction to complete renal failure that would require renal replacement therapy. Cardiac surgery-associated acute kidney injury is a complication that carries a grave disease burden. Risk factors are identified as being either modifiable or non-modifiable. This literature review aims to define the pathophysiology of cardiac surgery-associated acute kidney injury, the current definition and classification of acute kidney injury and the available diagnostic modalities, especially the use of biomarkers.

Keywords: cardiac surgery-associated acute kidney injury, cardiopulmonary bypass, acute renal failure, renal replacement therapy, kidney disease improved global outcomes

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DOI: 10.5830/CVJA-2019-069

Cardiac surgery presents with postoperative complications, particularly when cardiopulmonary bypass (CPB) is utilised.[1] Acute kidney injury (AKI) is still one of the most common complications with deleterious effects following cardiac surgery.[2] Over two million cardiac surgical procedures are performed around the world each year.[3] A recent systematic review and a meta-analysis found the total incidence of AKI in adult patients after cardiac surgery to be 22.3%.[4] AKI is a broad clinical syndrome,[5] presenting small changes in renal function markers and progressing to a need for renal replacement therapy (RRT).[6] The incidence of AKI in patients undergoing cardiac surgery in the African population is not documented.

The risk of postoperative death in patients undergoing cardiac surgery ranges from 5 to 30% when serum creatinine levels are ≥ 1.5 mg/dl, which makes serum creatine an independent risk factor for morbidity and mortality following cardiac surgery.[7]

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Palesa Motshabi Chakane, MB ChB, BSc, DA (SA), FCA (SA)

In a retrospective evaluation of adult patients in a cardiac intensive care unit (ICU) following coronary artery bypass graft (CABG) or valvular surgery by Machado *et al.*,[7] using the Kidney Disease Improving Global Outcomes (KDIGO) criteria in a group of patients who presented with elevated serum creatinine levels pre-operatively, patients with an elevated serum creatinine in the pre-operative period associated with high EuroSCORE values and an increased length of CPB and ICU stay, developed cardiac surgery-associated AKI (CSA-AKI).[7] In this cohort of 918 patients, 391 (43%) developed CSA-AKI. The diagnosis of AKI using the KDIGO criteria was shown to be a powerful predictor of 30-day mortality.[7]

Using the AKIN criteria to diagnose CSA-AKI, Vellinga *et al.*[8] found 14.7% of patients to have developed AKI. These patients were of advanced age, had low pre-operative estimated glomerular filtration rate (eGFR), chronic kidney disease and presented for emergency surgery. The patients who developed AKI were also found to have received loop diuretics and had received blood transfusion in the postoperative period.[8]

Bastin *et al.*[9] assessed 1 881 patients using the Risk Injury Failure End Stage, Kidney Disease (RIFLE), Acute Kidney Injury Network (AKIN) and KDIGO criteria in defining the epidemiology of AKI following cardiac surgery and compared the outcome of patients requiring RRT in the same population. The AKIN and KDIGO criteria were found to be comparable in predicting the incidence and outcome of AKI. An increase in age, low pre-operative eGFR, longer duration of CPB, increased length of ICU and hospital stay, and repeat surgery correlated with an increased risk of CSA-AKI.[9] A total of 122 (6.5%) patients required RRT: 117 patients within seven days and five patients seven days after surgery.[9] Their hospital mortality rate decreased from 82.9% previously to 53.8%, and this was attributed to more patients being started on RRT before their serum creatinine level was > 30 mmol/l.[9]

In a review article by Rosner and Okusa,[10] the incidence of AKI correlated with the type of surgery. Combined CABG and valvular surgery had an AKI incidence of 4.6% with 3.3% of the patients requiring RRT.[10] CABG alone had the lowest incidence of AKI of 2.5%, while valvular surgery had an incidence of 2.8%.[10]

O'Neal *et al.*[11] divided risk factors into pre-, intra- and postoperative risks. An increase in age, female gender and co-morbid diseases such as hypertension, diabetes mellitus, chronic kidney disease, hyperlipidaemia, peripheral vascular disease, anaemia and smoking were contributing factors in the pre-operative period.[11] CPB was an intra-operative risk factor

that played a part in the pathophysiology of CSA-AKI.[10] Red blood cells were damaged by the CPB circuit, which resulted in the release of free haemoglobin, damaging the renal tubules by depleting plasma haptoglobin levels and promoting the production of free oxygen radicals.[11]

In sub-Saharan Africa, a 2016 systematic review by Olowu *et al.*,[12] assessing the outcome of AKI in children and adult patients identified 3 881 records between January 1990 and November 2014 of patients with AKI. Forty-one records met their inclusion criteria, with 1 403 adults and 1 937 paediatric patients. The incidence of mortality was found to be 32% in adults and 34% in the paediatric population, but had increased intensely to 82 and 73%, respectively, when RRT was required but not received. They concluded that the scarcity of resources in health centres, especially RRT, stressed the need to practice preventative approaches in the management of AKI in this continent.[12]

Pathophysiology

The development of AKI following cardiac surgery is a complex clinical phenomenon.[13] It was previously described as being secondary only to ischaemia and reperfusion injury.[2] The pathophysiology of CSA-AKI has however recently been seen to be multifactorial, [2,11,14] and the causes have been classified as pre-renal, renal and post-renal.[14] Bellomo *et al.*[13] described the pathophysiology as involving several mechanisms of injury. Genetic factors have also been described as contributors to CSA-AKI.[2]

Renal ischaemia and reperfusion injury

Ischaemia and reperfusion injury have been described as the most common cause of CSA-AKI.[15] The mechanisms of injury are related to a decrease in oxygen delivery, poor nutrient transport and poor removal of waste products in the renal tubular cells.[15] Research has demonstrated that it is not merely the decrease in GFR that leads to AKI, but also the regional differences in renal blood flow.[16] These are due to the high metabolic demands of the outer renal medulla with lower partial oxygen pressures (PaO_2) of 10–20 mmHg relative to other parts of the kidney, making it susceptible to hypoxic episodes.[2,11]

In the peri-operative period, renal ischaemia can be due to low cardiac output (CO) following cardiogenic shock.[2] Activation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS) due to a reduction in CO will cause systemic vasoconstriction, thus decreasing renal blood flow and leading to a low GFR.[2] The major factors associated with AKI post cardiac surgery are a reduced functional reserve and peri-operative renal ischaemia.[17]

Inflammation and oxidative stress

Renal tissue hypoxia that results from renal hypo-perfusion due to a decrease in CO and GFR is responsible for the inflammatory process and oxidative stress that follows.[15] Endothelial cellular injury as a result of ischaemia initiates tissue inflammation.[15] Selectins facilitate the adhesion of leukocytes to the injured endothelium.[16] This promotes the cascade of an inflammatory response.[18] Pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukins 6 and 8 (IL-6, IL-8) and chemotactic cytokines have been implicated in contributing to the response of local tissue ischaemia that results in maladaptive inflammatory tissue response.[18] Neutrophil and monocyte/lymphocyte ischaemia-induced kidney damage has also been described. This inflammatory cascade eventually results in dysfunction of the renal endothelium nitric oxide system, which is important in the renal oxygen supply.[16]

Nephrotoxins

Cardiac surgical patients are exposed to a variety of nephrotoxic agents in the peri-operative period. These may include drugs in the form of prescription medications such as antibiotics, antihypertensive agents, diuretics, non-steroidal anti-inflammatory agents (NSAIDS) and radiocontrast agents used during diagnostic medical procedures.[5,14]

Aminoglycosides and beta (β)-lactam antibiotics are the two groups of agents that have been implicated the most in causing acute interstitial nephritis, leading to drug-induced AKI.[2,5] These antibiotics can also cause direct injury to the kidneys.[2]

Hypertension has been shown to be one of the pre-operative risk factors of AKI in patients presenting for cardiac surgery.[11] Fuhrman and Kellum[2] have linked hypertension-related AKI to the use of angiotensin-2-receptor blocking agents (ARBs), which inhibit renal efferent arteriolar vasoconstriction in the pre-operative period.[2] Patients on ARBs and diuretic agents have an increased risk of hypovolaemia, which can worsen renal failure.[14]

Randomised control trials have shown the prophylactic use of loop diuretics, such as furosemide, to be ineffective and harmful when used in the peri-operative period in patients scheduled for cardiac surgery.[19-21] As part of their recommendations, Kellum,[2] Lameire[5] and the KDIGO AKI guideline work group[5] advised against the use of furosemide as a prophylactic agent in preventing AKI, and to avoid the use of diuretic agents in treating AKI.

NSAIDs have also been proven to worsen renal function in susceptible groups of patients.[14] Exposure to radiocontrast agents in the peri-operative period contribute to the risk of contrast-induced nephropathy and should ideally be avoided.[5,14]

Metabolic and neurohormonal activation

Cardiac surgery stimulates the SNS and the hypothalamic pituitary adrenal axis.[22] This activation results in the release of neurohormonal agents, including adrenaline and noradrenaline from the adrenal glands.[23] Zhang *et al.* reported that during cardiac surgery with CPB, plasma concentrations of adrenaline and noradrenaline reach peak levels.[24] The high plasma concentrations of these endogenous hormones give rise to erratic haemodynamic conditions that contribute to intra-operative renal injury.[22] This increase in sympathetic tone has led to the advocacy of the use of alpha-2-adrenergic agonists such as dexmedetomidine and clonidine to reduce the incidence of AKI.[22,25]

Genetics

A genome-wide association study (GWAS) for AKI after CABG surgery was performed in 2015 by Stafford-Smith and colleagues.[26] They discovered that other than the previously reported nine

loci of single nucleotide polymorphisms (SNP) related to renal function, there are two new loci that are specifically associated with an increased risk in AKI following cardiac surgery.[26] This discovery potentially increases the curiosity in researchers to further investigate the relationship between AKI and cardiac surgery at a genetic level.

Risk factors

The risk factors associated with AKI in this patient population can be grouped into patient-, surgery- and anaesthesia-related factors.[11] Risk factors associated with CSA-AKI can also be classified into non-modifiable and modifiable risks, enabling the identification of high-risk patients with modifiable risk factors that can be optimised for improved outcomes.[27] For the purposes of this review, the latter will be discussed.

Modifiable risk factors

The following modifiable risk factors will be discussed: the duration of CPB time, miniaturised extracorporeal circuit (mini-CPB), hypothermia, on-pump versus off-pump techniques, anaemia and blood transfusion, which contribute to the increased risk of AKI following cardiac surgery.[1,28]

Duration of CPB

CPB has been reported to induce systemic inflammatory response syndrome (SIRS), which is a mechanism related to the development of AKI in cardiac surgery patients.[1]

In a 2012 meta-analysis by Kumar *et al*.,[29] nine studies were included, resulting in a cohort of 12 466 patients, where a total of 756 patients developed AKI following cardiac surgery, correlating to longer durations of CPB.[29] Similarly, Mao *et al*.[1] had indicated a strong association between cardiac surgery-related AKI with longer CPB times. Mini-CPB has been found to offer benefits of improved renal function following cardiac surgery.[1] It led to a lesser inflammatory response with reduced haemodilution when compared to the standard CPB systems.[1] Benedetto *et al*.[30] investigated the occurrence of AKI when using the mini-CPB to that of the conventional CPB in patients for planned CABG surgery and showed that in patients where the mini-CPB was used, there were fewer reported cases of cardiac surgery-associated AKI compared to the conventional CPB.[30]

Hypothermia

During cardiac surgery, patients are often cooled down to systemic temperatures below 32°C allowing longer periods of decreased blood flow.[1] In a meta-analysis of 19 randomised, controlled trials with 2 218 patients, therapeutic hypothermia was not seen to prevent the development of AKI or the requirements for RRT.[31]

It has been postulated that the process of rewarming the patient post cardiac surgery could be one of the reasons related to increased ischaemia and reperfusion injury to the kidneys.[32] This hypothesis was tested in a study by Boodhwani *et al*.[32] on the effects of mild hypothermia and rewarming on renal function following CABG surgery. In this randomised control trial, patients undergoing elective CABG surgery were assigned to two groups. In the first group, patients were cooled down to a temperature of 32°C during CPB and then randomly assigned to be rewarmed to 34°C or 37°C. Results showed elevated serum creatinine levels in patients who were rewarmed to 37°C. They concluded that rewarming to 37°C should be avoided as it contributed to postoperative renal injury.[32]

On-pump versus off-pump technique

CPB is implicated in inducing a SIRS response that causes AKI related to cardiac surgery.[1, 33] Off-pump coronary artery bypass (OPCAB) induces less SIRS response when compared to on-pump CABG surgery.[34] Better renal perfusion and decreased systemic embolisation have been found.[1] There is still however conflicting evidence in the current literature when comparing these two techniques, with some authors showing that OPCAB is superior to the on-pump technique, while other authors have shown no variation.[35-37]

Anaemia

In AKI, peri-operative anaemia contributes to a decrease in oxygen delivery to the renal tubules, therefore promoting oxidative stress, especially in the already compromised renal medulla.[38] The oxidative stress is as a result of the reduction in red blood cells, which also have an antioxidant function.[39] Anaemia is further worsened by cardiac surgery as cardiac output is further decreased, influencing renal perfusion pressures.[38] CPB-related complications resulting in poor platelet function combined with anaemia, which requires blood transfusion, was seen as a factor that contributed to the additional risk of AKI.[38]

Blood transfusion

The transfusion of packed red blood cells is not without complications. Koch *et al*.[40] showed that the duration of red blood cell storage can contribute to complications following cardiac surgery. They concluded that the transfusion of red blood cells older than two weeks was associated with an increased risk of postoperative cardiac surgery complications.

Structural and functional changes to red blood cells were shown to include the depletion of adenosine triphosphate (ATP) and 2,3 diphosphoglyrecate (2.3 DPG) in the red blood cell.[41] Alterations in the structural proteins of red blood cells made them less deformable and contributed to pro-inflammatory cellular states.[41] This abnormal state of the red blood cells causes injury to target organs such as the kidneys and impairs the necessary oxygen delivery.[38] Poor oxygen delivery to the kidneys causes an insult to the renal tissue, a phenomenon termed 'kidney attack',[42] resulting in ischaemic injury.[16]

Hypovolaemia

Hypovolaemia has been recognised as a significant risk factor in the development of AKI following cardiac surgery.[5] A patient's volume status plays an important role in the peri-operative period as it is related to CO.[1] A low CO causes activation of the SNS which ultimately stimulates the RAAS, thus resulting in renal vasoconstriction.[1] The choice between crystalloids and colloids for intravascular volume expansion is still a topic of debate.[5]

Diagnosis of AKI

The kidneys receive 20% of the heart's CO.[43] A reduction in renal blood flow, whether generalised or localised, can cause a decrease in GFR, thus resulting in AKI.[15] GFR is used

commonly in the medical field as a surrogate measurement of global kidney functioning.

The diagnosis of CSA-AKI has evolved with time. Ronco[44] described what she calls the 'evolution of AKI diagnostic syntax', as shown in Fig. 1. She illustrated how between the years 1950 and 2016, the diagnosis of AKI had evolved from being a clinical finding to the development of molecular biomarker tests.[44] Studies have been performed that compare the differences in the diagnosis of AKI using serum creatinine levels to urine output volumes.

Criteria for diagnosis of AKI

In 2004, the Acute Dialysis Quality Initiative (ADQI) group described the RIFLE kidney disease criteria to classify the diagnosis of AKI.[45] An increase in a RIFLE score stage was shown to lead to an increase in the risk of death.[5] The RIFLE criteria utilised serum creatinine levels or GFR, and the patient's urine output to stratify them into risk, injury, failure and loss, or end-stage kidney disease grades according to the duration and loss of their renal function.[14] The RIFLE criteria are known to follow up the changes in renal function as observed over a period of seven days.[45]

The AKIN was subsequently developed as a modification of the RIFLE criteria by decreasing the threshold of serum creatinine levels in the first 48 hours of the diagnosis of AKI.[9] The AKIN further classified patients that require RRT into AKIN stage 3 and removed eGFR criteria as part of their work-up. Regardless of their differences, the RIFLE and AKIN classification criteria have proven to be useful in identifying patients with AKI.[9]

Table 1. The staging of AKI according to Kellum *et al.*[5]

Stage	*Serum creatinine*	*Urine output*
1	1.5–1.9 times baseline within 1 week or ≥ 0.3 mg/dl increase within 48 hours	< 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline or increase in serum creatinine to ≥ 4.0 mg/dl or the initiation of RRT or in patients < 18 years, a decrease in eGFR to < 35 ml/min/1.73 m^2	< 0.3 ml/kg/h for ≥ 24 hours or anuria for ≥ 12 hours

In 2013, the international AKI guideline work group brought together international experts from several medical specialities to produce a uniform definition and classification of AKI, as well as prevention strategies, pharmacological treatment and RRT guidelines.[5,46] This programme standardised the definition of AKI by bringing together the RIFLE and AKIN criteria and producing the KDIGO criteria for AKI.[46]

AKI by KDIGO is defined as an increase in serum creatinine of ≥ 0.3 mg/dl (or 26.5 µmol/l) for a period of ≤ 48 hours, or a rise in serum creatinine of ≥ 1.5-fold from the baseline, which is presumed to have occurred in the preceding seven days.[9] The diagnosis, evaluation and management of AKI, a KDIGO summary, divides AKI into three stages as illustrated in Table 1.[5] Table 2 demonstrates the differences in AKI diagnosis between the RIFLE score, and AKIN and KDIGO criteria.[7]

In the KDIGO criteria, patients with AKI can be diagnosed by solely using serum creatinine levels. This criterion has been shown to be a good predictor of 30-day mortality rate in patients undergoing cardiac surgery, who had displayed serum creatinine levels above the normal threshold pre-operatively.[7]

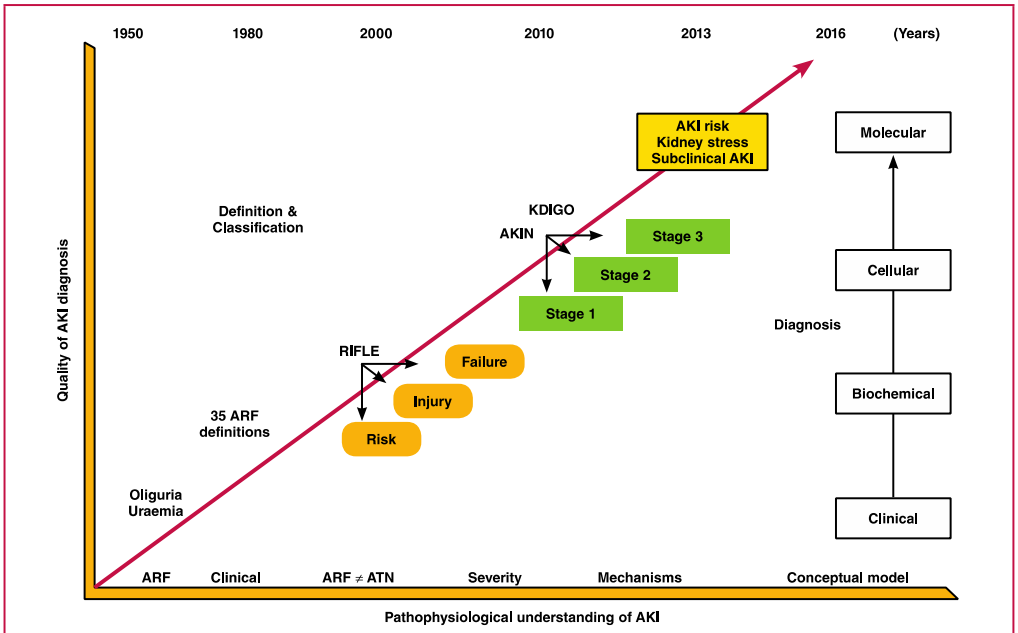


Fig. 1. The evolution syntax of AKI diagnosis by Ronco.[44]

Table 2. The classification and staging of the RIFLE, AKIN and KDIGO criteria as modified by Machado *et al*.[7]

Class	*RIFLE SCr or GFR*	*Stage*	*AKIN SCr*	*Stage*	*KDIG0 SCr*
Risk	Increases Scr X 1.5 or GFR decrease > 25% (within 7 days)	1	Increase in SCr ≥ 0.3 mg/dl or ≥ 150–200% (1.5–2-fold) from baseline (within 48 hours)	1	Increase in SCr by ≥ 0.3 mg/dl within 48 hours or increase in SCr 1.5–1.9 times baseline, which is known or presumed to have occurred within the previous 7 days
Injury	Increase Scr X 2.0 or GFR decrease > 50%	2	Increase in SCr to more than 200 to 300% (> 2–3-fold) from baseline	2	Increase in SCr to 2.0–2.9 times baseline
Failure	Increase Scr X 3.0 or GFR decrease > 75% or SCr ≥ 4.0 mg/dl or acute increase ≥ 0.5 mg/dl	3	Increase in SCr to more than 300% (> 3-fold) from baseline or SCr ≥ 4.0 mg/dl with an acute increase of at least 0.5 mg/dl or the initiation of renal replacement therapy	3	Increase in SCr to 3.0 times baseline or increase in SCr to ≥ 4.0 mg/dl or initiation of renal replacement therapy
Loss	Persistent acute renal failure = complete loss of kidney function > 4 weeks				
End-stage kidney disease	End stage of kidney disease (> 3 months)				

The use of serum creatinine levels in diagnosing AKI is not without its limitations. Inconsistencies still arise in the application of the diagnostic criteria and not only for the KDIGO criteria but also for the RIFLE score and AKIN criteria.[5] Creatinine measurements require many hours and days to identify any evidence of renal injury, and at the same time, mild renal injury can be missed as the kidneys might still maintain normal GFR.[11] It is therefore evident that AKI is a continuum from initial injury to the kidneys, to the development of the disease and then eventual kidney failure.[44]

In the hope of increasing awareness about the mortality and morbidity burden of AKI among clinicians, Kellum *et al*.[42] introduced a new concept known as 'kidney attack'. They proposed five steps that are important in improving outcomes in patients with AKI.[42] The first two steps offer a window period to intervene and possibly prevent further injury. They are known as the risk-assessment and early-detection steps. The other steps are early management, organ support and the recovery phase.[42]

When the initial attack occurs to the kidneys, molecular changes follow, which result in cellular damage. This leads to a variety of cellular markers known as biomarkers to be expressed and released by cells.[47] Clinical evidence has proven that biomarkers are present two days prior to the development of AKI,[48] therefore allowing for the subclinical diagnosis of renal injury.[44] This demonstrates that cellular and molecular biomarkers have the potential to be superior during the early diagnosis of AKI.[44]

Biomarkers in the diagnosis of AKI

The ADQI working group recommended the use of renal injury biomarkers in the diagnosis of AKI to supplement the RIFLE and AKIN scores.[49]

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a biomarker that can be measured in both the urine and plasma.[47] It is an acute-phase reactant protein released by inflammatory cells as well as leukocytes and epithelial cells of the loop of Henle and the collecting ducts of the renal tubules.[47] Urinary NGAL was shown to be superior to plasma NGAL in the early diagnosis of CSA-AKI.[1] Mishra *et al*.[50] found that urinary NGAL increased up to 25-fold within the first two hours following cardiac surgery, making it a highly sensitive and specific predictor of CSA-AKI.

It has however been shown that urinary NGAL levels can also be elevated in other inflammatory conditions, making it less specific.[47] In a study by Wagener *et al*.,[51] high levels of urinary NGAL correlated to the duration of CPB and aortic cross clamp.

Interleukin-18 (IL-18)

IL-18 is an inflammatory marker released by dendritic cells, monocytes and macrophages.[47] Urinary IL-18 was shown to peak six hours post cardiac surgery.[3] Urinary IL-18, together with NGAL and kidney injury molecule (KIM-1), are less sensitive and less specific in patients with co-morbid disease.[47]

Cystatin C

Cystatin C is a low-molecular weight protein released by all the nucleated cells of the body, and its levels can be measured in both the urine and plasma.[47] It is an inhibitor of cysteine proteases,[52] and an early diagnostic biomarker of AKI.[47] Cystatin C is freely filtered at the glomerulus, which renders it an appropriate marker for GFR.[52,53] This biomarker has been researched in the paediatric population admitted for cardiac surgery.[52,53] It was demonstrated by Hassinger *et al*.[53] to be a good early predicter of AKI after CPB in children.[53]

Plasma cystatin C was shown to be more specific and sensitive in the early diagnosis of AKI compared to serum creatinine in infants undergoing cardiac surgery under bypass.[52] Cystatin C has however also been shown to be less specific and sensitive in patients with co-morbid diseases and sepsis.[54]

Insulin-like growth factor binding protein 7 (IGFBP-7) and tissue inhibitor of metalloproteinases-2 (TIMP-2)

Urinary IGFBP-7 and TIMP-2 are cell cycle-arrest proteins.[47] In a study assessing the risk of AKI in 50 patients who had cardiac surgery on CPB, both IGFBP-7 and TIMP-2 showed specificity and sensitivity in predicting AKI as early as four hours following surgery.[55] In a systematic review and meta-analysis by Liu *et al*.,[34] it was shown that these two biomarkers are reliable in the early detection of AKI in adult patients.[34] IGFBP-7 and TIMP-2 have emerged as novel biomarkers of AKI compared to the others, as cell cycle arrest is considered the pathophysiological mechanism in the development of AKI.[47]

In 2014 the Food and Drug Administration (FDA) approved the marketing of the nephrocheck test, a laboratory instrument that detects the presence of IGFBP-7 and TIMP-2 proteins in the urine of patients at risk of developing AKI following cardiac surgery.[56] This apparatus is the first of its kind (Fig. 2). The amount of measured proteins provides an indication of



Fig. 2. Nephrocheck (TIMP-2*IGFBP7) test, an FDA-approved laboratory test that measures urinary levels of cell cycle-arrest proteins to identify patients at risk of developing AKI following cardiac surgery.[56]

renal tubular stress prior to tubular damage.[57] The results of the test provide a score that is based on the individual's risk of developing AKI within 12 hours of cardiac surgery.[56] In a prospective cohort study by Oezkur *et al*.,[57] the nephrocheck test was proven to be a strong predictor of postoperative CSA-AKI.[57]

Management of AKI

A reduction in the incidence and long-term renal outcomes of patients with CSA-AKI requires management that not only focuses on treating established disease, but to identify peri-operative risks as well.[58,59] This follows a complex route, given the multifactoral pathogenesis of the disease process. The hallmark in managing CSA-AKI is modifying risk factors.[13] Peri-operative fluid management influences renal perfusion. A positive fluid balance has been shown to increase incidence of mortality,[5] while haemodynamic stability optimises renal perfusion, thus preventing AKI.[59] Several trials have proven that the use of diuretics has unfavourable outcomes and loop diuretics are reserved for cases of fluid overload, especially in mechanically ventilated patients.[5,59,60] Vasodilators such as dopamine and fenoldopam are not effective in the prevention of AKI.[59]

The use of nephrotoxic agents such as aminoglycosides, contrast media, NSAIDs and ARBs should be avoided where possible.[5,59]

As part of their recommendations, the KDOGO group suggests maintaining an adequate nutritional status and normoglycaemia in the peri-operative management of CSA-AKI. A total energy intake of 20 to 30 kcal/kg per day at any KDIGO stage, as well as a glucose level of not more than 8.3 mmol/l (149 mg/dl) is recommended.[5] The timing of RRT has been a topic of debate; however a recent meta-analysis showed that early initiation of RRT has its benefits. It demonstrated a reduction in 28-day in-hospital mortality rates of up to 58% when RRT was initiated within 24 hours following the diagnosis of CSA-AKI.[61]

Conclusion

CSA-AKI is a complex disease spectrum. The identification, prevention and modification of patient and surgical risk factors can assist in reducing cases and thus the disease burden. The diagnosis remains an area of challenge and the use of novel biomarkers seems to be more promising in identifying at-risk patients earlier than conventional methods, such as the use of serum creatinine levels and urine output measurements.

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statistical analysis cannot be measured. Data were obtained from a single centre, therefore, results are contextual and may not be extrapolated to other population groups. The probable presence of unknown confounding factors affects the interpretation of the results. A multicentre study would be beneficial to permit larger sample sizes.

The mortality rate was low, making the regression models likely to be over-fitted. It also narrowed the scope of variables that could be included in the multivariable regression models. This may have confounded the results. Relationships were, however, apparent and echoed in other studies. This rapidly growing field with the novel use of biomarkers and ultrasound allows for further exploration. Pre-operative echocardiography information, together with data on the use of inotropes, diuretics, fluids and blood products intra-operatively, leaves the researchers with an opportunity to investigate such variables in a future prospective study.

Conclusion

Numerous modifiable factors including pre-operative renal dysfunction were found to be associated with the development of CSA-AKI and mortality. Identification of patients at risk of CSA-AKI, relying on serial SCr and/or urine output measurements may not be time sensitive and may delay timeous interventions. The use of novel biomarkers and renal vascular ultrasound promises the possibility of early diagnosis of renal injury. Kidney injury should be considered an important factor in post-operative outcomes in cardiac surgery. Those at risk of kidney injury should be identified and risk-modification strategies employed. Renal function is crucial for enhanced recovery after cardiac surgery, as evidenced by studies that show its association with adverse outcomes.

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Appendix 4: Letter of acceptance of the review article

Ref.: Ms. No. CVJSA-D-19-00102

Cardiac surgery associated acute kidney injury: pathophysiology, diagnostic modalities and management

CardioVascular Journal of Africa

Dear Dr Motshabi Chakane/ Leballo,

We wish to inform you that your manuscript, Cardiac surgery associated acute kidney injury: pathophysiology, diagnostic modalities and management, has been accepted for publication in CardioVascular Journal of Africa.

Unfortunately, we are unable to tell you which Volume and on what pages at present as we rely on our set-out design & publishers for that information.

You will be contacted by our Production Editor when your article is ready for final proof reading before publication.

On acceptance of a manuscript an Article Processing Fee will apply before the production team can finalise the paper for publication.

Please note that the online First Facility with full text availability via PubMed and the Journal's website which is accessible via Google and other search engines (www.cvja.co.za). This facility is also known internationally as E-publication, ahead of print and offers authors the opportunity to publish their research articles sooner for an international audience.

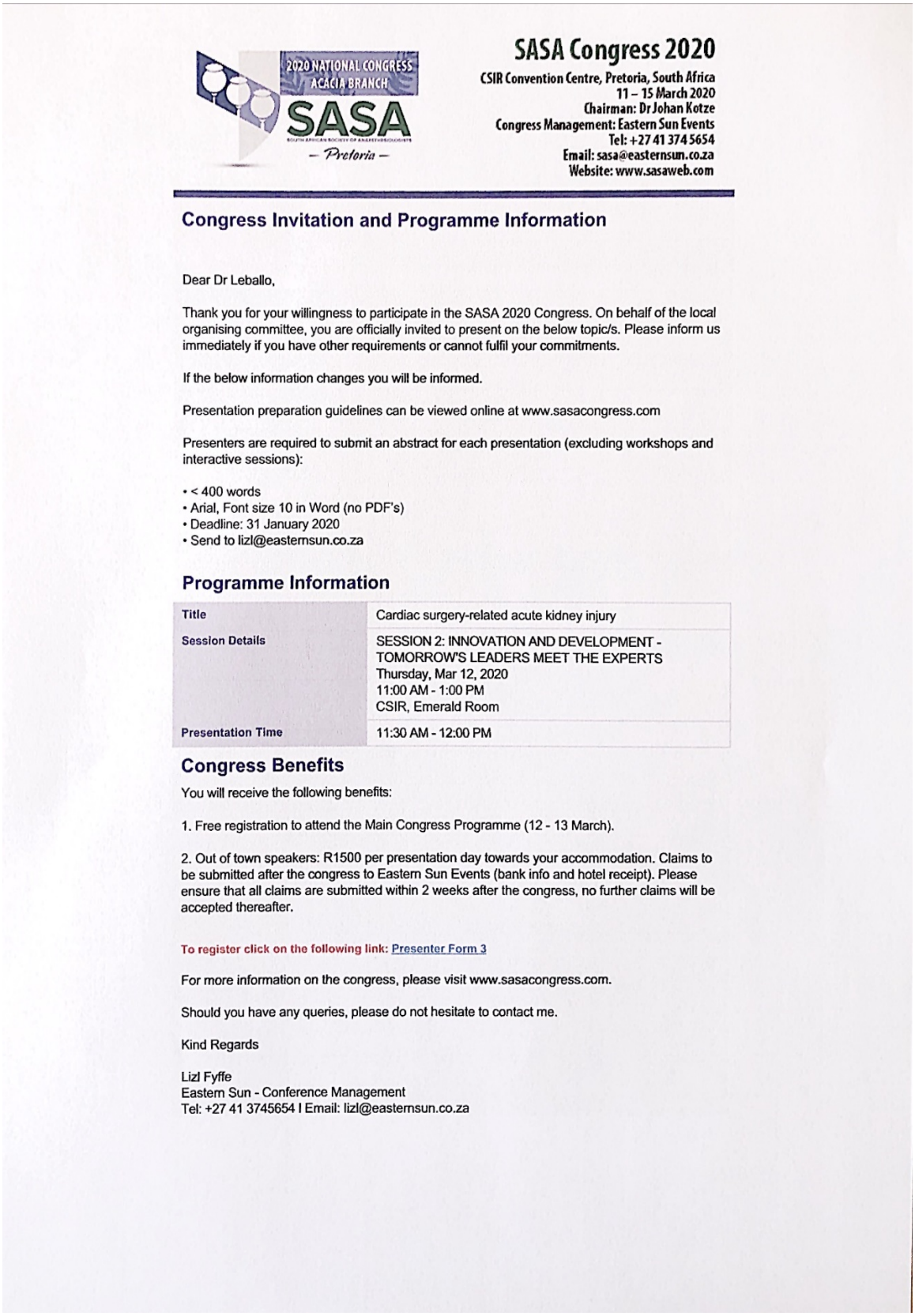
Articles published online with CVJA will be published with their unique DOI numbers, which ensures that the article can be cited using the date of the manuscript's first online posting and its DOI number. DOI's provided a persistent, permanent way to identify manuscripts in an electronic environment and are generated via our Editorial Management system and in accordance with the policy of the DOI foundation (www.doi.org).

We thank you for your interest and support in the Journal and we will be interested in any other material you may feel you would like to submit in this field.

Thank you for submitting your work to this journal.

With kind regards
Pat J Commerford, MBChB FCP(SA)
Editor-in-Chief

Appendix 5: Letter of invitation for presentation from SASA Congress 2020



2020 NATIONAL CONGRESS
ACACIA BRANCH
SASA
– Pretoria –

SASA Congress 2020
CSIR Convention Centre, Pretoria, South Africa
11 – 15 March 2020
Chairman: Dr Johan Kotze
Congress Management: Eastern Sun Events
Tel: +27 41 374 5654
Email: sasa@easternsun.co.za
Website: www.sasaweb.com

Congress Invitation and Programme Information

Dear Dr Leballo,

Thank you for your willingness to participate in the SASA 2020 Congress. On behalf of the local organising committee, you are officially invited to present on the below topic/s. Please inform us immediately if you have other requirements or cannot fulfil your commitments.

If the below information changes you will be informed.

Presentation preparation guidelines can be viewed online at www.sasacongress.com

Presenters are required to submit an abstract for each presentation (excluding workshops and interactive sessions):

- < 400 words
- Arial, Font size 10 in Word (no PDF's)
- Deadline: 31 January 2020
- Send to lizl@easternsun.co.za

Programme Information

Title	Cardiac surgery-related acute kidney injury
Session Details	SESSION 2: INNOVATION AND DEVELOPMENT - TOMORROW'S LEADERS MEET THE EXPERTS Thursday, Mar 12, 2020 11:00 AM - 1:00 PM CSIR, Emerald Room
Presentation Time	11:30 AM - 12:00 PM

Congress Benefits

You will receive the following benefits:

1. Free registration to attend the Main Congress Programme (12 - 13 March).

2. Out of town speakers: R1500 per presentation day towards your accommodation. Claims to be submitted after the congress to Eastern Sun Events (bank info and hotel receipt). Please ensure that all claims are submitted within 2 weeks after the congress, no further claims will be accepted thereafter.

To register click on the following link: Presenter Form 3

For more information on the congress, please visit www.sasacongress.com.

Should you have any queries, please do not hesitate to contact me.

Kind Regards

Lizl Fyffe
Eastern Sun - Conference Management
Tel: +27 41 3745654 I Email: lizl@easternsun.co.za

Appendix 6: Certificate of presentation at SASA Congress 2020



2020 NATIONAL CONGRESS
ACACIA BRANCH
SASA
SOUTH AFRICAN SOCIETY OF ANAESTHESIOLOGISTS
— Pretoria —

CERTIFICATE OF PRESENTATION

Presented to

Gontse

Leballo

2020 SASA Congress

CSIR Convention Centre
Pretoria - South Africa

12 - 15 March 2020

Date

Dr Johan Kotzé
Congress Chairman

EASTERN SUN
EVENTS
P. O. BOX 12612, CENTRAHIL
PORT ELIZABETH 6006
SOUTH AFRICA

Appendix 7: Proposal

A profile of cardiac surgery-related acute kidney injury in adult patients at an academic hospital

Gontse Leballo

Student number: 0105815e

Supervisor:	Dr Palesa Motshabi Department of Anaesthesiology
Co-supervisor:	Dr Jacob Hlamatsi Moutlana Department of Anaesthesiology

1. Introduction

The concept of "kidney attack" has been introduced to the medical fraternity by researchers such as Kellum et al. [1] with the expectation of creating a sense of urgency among clinicians and researchers. They expressed that a lack of understanding of acute injury to the kidneys has halted significant growth in clinical interventions and treatment in the affected patients.

Acute kidney injury (AKI) describes "a sudden decline in kidney function which can be reversible if detected early enough", [2] and if not reversed, can progress to chronic kidney disease (CKD) and end-stage renal disease that would require renal replacement therapy (RRT). [3] Studies have shown that AKI is an independent risk factor of mortality. [4] The Global Burden of Disease study of 2015 found a 16.3% increase, from 2005 to 2015, in CKD due to unspecified causes. [5]

AKI is classified in the literature using different criteria. In 2012, Kidney Disease: Improving Global Outcomes (KDIGO), a non-profit organization established by the National Kidney Foundation (NKF), put together clinical practice guidelines for AKI. [6] The authors standardised the definition of AKI by combining the Risk Injury Failure Loss and End-stage (RIFLE) and Acute Kidney Injury Network (AKIN) criteria to provide a uniform description. KDIGO defines AKI as an increase in serum creatinine of greater than or equal to 0.3 mg/dl from a baseline measurement (or greater or equal to 26.5 μmol/l) within 48 hours; or an increase in serum creatinine of greater than or equal to 1.5 times a baseline measurement in a period of seven days; or urine output of less than 0.5 ml/kg/hr for six hours. [7]

There are over two million cardiac surgeries performed every year globally. [8, 9] The occurrence of cardiac surgery-associated (CSA) AKI differs depending on the classification being used. A systematic review by Hu et al. [9] revealed the global incidence of AKI following cardiac surgery as 22.3% when they analysed multiple studies that used the RIFLE, AKIN, and KDIGO groups. Bastin et al. [10] compared the three criteria in cardiac surgery patients and found the incidence of AKI to be 2 9% when using both AKIN and KDIGO classifications. In a retrospective single-center study, Machado et al. [11] evaluated the

prognostic value of CSA-AKI according to the KDIGO criteria and found a higher incidence of 42%.

Serum creatinine measurements are more reliable when compared to urine output monitoring in the diagnosis of AKI. [12] KDIGO criteria allow for AKI diagnosis through monitoring of serum creatinine levels. This criterion is a good predictor of 30-day mortality in patients with elevated baseline serum creatinine levels following cardiac surgery. [13] Although easily accessible and useful to clinicians, serum creatinine levels may fail to detect early changes in subclinical renal injury. [14] The evolution of biomarkers is promising to offer improved results in the diagnosis of early kidney injury by detecting molecular and cellular changes that have occurred. [15, 16]

Modifiable risk factors have been identified that increase the risk of CSA-AKI. [17] Some modifiable risk factors include the length of cardiopulmonary bypass (CPB), on-pump versus off-pump techniques, hypothermia, [17] anaemia and blood transfusion. [18] Nonmodifiable risk factors can be grouped into patient, anaesthesia, and surgery-related factors. [12] Although factors such as age, gender and race cannot be directly modified, the related co-morbidities such can be appropriately managed, and patients can be optimised. [19]

2. Problem statement

AKI following cardiac surgery requiring CPB is the second most common cause of AKI in the intensive care unit. [17] AKI is a complex syndrome and is associated with adverse outcomes such as prolonged hospital stay, more extended periods of mechanical ventilation and increased mortality. [11, 20] In a study by Olowu et al., [2] it was concluded that the scarcity of resources in sub-Saharan Africa, such as RTT, emphasises the need to practice preventative approaches in the management of AKI on this continent.

A thorough understanding of the pathophysiology and profile of patients who are susceptible to postoperative AKI as modifiable risk factors associated with AKI can be addressed in the perioperative period. The profile of AKI post-cardiac surgery on CPB at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is not known.

3. Aim

The study aims to describe the profile of AKI in adult patients following cardiac surgery on CPB in the cardiothoracic intensive care unit (CTICU) at CMJAH.

4. Objectives

Are to describe**:**

the demographics of all adult patients presenting for cardiac surgery

the preoperative renal function

the intraoperative clinical information related to CSA-AKI

the postoperative clinical data

the occurrence of AKI.

5. Research assumptions

Adult: a person 18 years and older.

Acute kidney injury (AKI): in this study AKI will be defined according to KDIGO criteria. AKI will be defined as an increase in serum creatinine of equal to or greater than 0.3 mg/dl (or 26.5 μmol/l) from baseline for a period of less than or equal to 48 hours. [7]

Renal dysfunction: will be determined by looking at the patients' baseline serum creatinine measurement and calculating preoperative estimated glomerular filtration rate (eGFR). To calculate eGFR, the Modification of Diet in Renal Disease (MDRD) equation will be utilised. [21]

$$eGFR = 186 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African})$$

normal: > 90 ml/min/ 1.73 m^2

mild: 60 - 89 ml/min/1.73 m^2

moderate to severe: < 60 ml/min/ 1.73m^2

renal failure: < 15 ml/min/ 1.73 m^2

The National Health Laboratory (NHLS) reports serum creatinine measurements in µmol/l (SI unit). A factor of 88.4 will be used to convert the measurements into mg/dl (Metric unit) for the purposes of applying KDIGO criteria. [7]

Metric unit × conversion factor = SI unit

Hypothermia: in this study, the degree of hypothermia will be classified into four categories:

mild hypothermia: 32 ˚C – 35 ˚C

moderate hypothermia: < 32 ˚C – 28 ˚C

severe hypothermia: < 28˚ C – 20 ˚C

deep hypothermia: < 20˚C.

Patient records: will include ICU charts, perfusionist charts, anaesthetic records, and electronically captured patient data.

Incomplete data: records that will be excluded from the study will have the following information missing preoperative creatinine levels and creatinine levels within 48 hours (to diagnose AKI), patient age, gender, and race (required for MDRD equation).

6. Demarcation of the study field

The study will be conducted in the CTICU at CMJAH, which is affiliated to the University of the Witwatersrand in Johannesburg, South Africa. The CTICU at CMJAH is an eight-bed unit that admits, on average of 200 adult cardiac cases performed on CPB each year.

7. Ethical considerations

The approval to conduct this study will be obtained from the Human Research Ethics Committee (Medical), the Graduate Studies Committee of the University of the Witwatersrand and the National Health Research Committee (Gauteng). Permission to utilise ICU and anaesthetic data will be sought from the Heads of Department of Anaesthesiology and CTICU (Appendix A and B).

The study will be a retrospective record review. A list of patients' names and hospital numbers will be generated, and patients will be allocated a study number. This list will be kept separately from the raw data. No identifying patient information will be included on the data collection sheets, therefore, ensuring anonymity. To ensure confidentiality, only the researcher and the supervisors will have access to the raw data.

Data will be stored in a password protected database for six years after completing the study.

Principles of the Declaration of Helsinki, [22] and the South African Guidelines for Good Clinical Practice will be followed. [23]

8. Research methodology

8.1 Research design

A research design describes a structure that is produced to provide valid answers to research questions. [24] The research design in this study will be retrospective, contextual, and descriptive.

A retrospective study aims to find the relationship between variables measured in the past to the effects that have occurred. [25] In this study, clinical data of patient records between January 2016 until December 2017 will be used.

A contextual study focuses on a specific population or group of people. [26] This study will focus on adult patients who presented for cardiac surgery on CPB at CMJAH.

Brink et al. [25] define descriptive study designs as "study designs that may be used to identify problems with current practice; to justify current practice; make judgements or determine what other professionals in similar situations are doing, or to develop theories." In this study the profile of patients presenting for cardiac surgery on CPB will be described.

8.2 Study population

The study population consists of the records of all adult patients admitted to the CTICU at CMJAH following cardiac surgery on CPB.

8.3 Study sample

Sample method

A consecutive convenience sampling method will be used in this study. It is a sampling method whereby data of all accessible subjects is included. It is the most definite form of non-random sampling. [27]

This study will consist of the records of adult patients admitted to the CTICU post-cardiac surgery on CPB from January 2016 to December 2017.

Sample size

The justification of the sample size was determined in consultation with a biostatistician. To estimate the occurrence of AKI in adult patients following cardiac surgery on CPB, a two-year retrospective records review of a population of approximately 400 patients will be utilised. Based on a single-center study by Machado et al., the prevalence of AKI related to cardiac surgery is roughly 40%. The estimated prevalence has a precision of:

$$2\ x\ \sqrt{\frac{pq}{n}}$$

where p = prevalence = 40% = 0.4, q = (1 – p) = (1 – 0.4) = 0.6 and n is the number of patients,

$$2\ x\ \sqrt{\frac{0.4\ x\ 0.6}{400}} = \pm 4.5\%.$$

The sign and the magnitude of the coefficients of the independent variables will provide us with guidelines regarding their impact on the dependent variable. To detect factors that are associated with AKI in adult patients following cardiac surgery on CPB as being significant, suppose 40% of the patients have Diabetes Mellitus (DM). If among these patients the occurrence of AKI is 47% in patients who have DM and 33% to those who do not have it, the absolute difference is 14%. This study will have 80% power to detect this variable as statistically significant. This will apply to all categorical (dichotomous) factors. Continuous exposures such as BMI and time on CPB will give a greater power.

Inclusion and exclusion criteria

The inclusion criteria for this study are:

adult patients

presenting for cardiac surgery on CPB.

The exclusion criteria in this study are:

patients on RRT

incomplete data.

9. Data collection

9.1 Data collection sheet

The study by Machado et al. [13] was adapted for use in this research paper. A draft data collection sheet was developed and reviewed by three senior anaesthesiologists with interest in cardiac surgery. Their suggestions were incorporated, and a final data collection sheet was created.

The data collection sheet (Appendix 16) will include the following information:

patient demographics

age

weight

height

body mass index (BMI)

gender

race

co-morbidities

hypertension

diabetes mellitus

smoker

hypercholesterolaemia

other

type of surgery

coronary artery bypass grafting (CABG)

cardiac valve surgery (single/multiple)

aortic surgery

other

preoperative renal function

baseline creatinine levels

eGFR

intraoperative clinical data

CPB time

the lowest temperature on-pump

aortic cross-clamp time

postoperative clinical data

creatinine at 24 and 48 hours

mechanical haemodynamic support

extracorporeal membrane oxygenation (ECMO)

ventricular assist devices (VAD)

intra-aortic balloon pump (IABP)

renal replacement therapy (RRT)

mortality

9.2 Data capturing

Following the necessary approvals, data will be captured onto a Microsoft Excel® spreadsheet by the researcher. No records will be removed from the hospital premises.

9.3 Data analysis

Data analysis will be done in consultation with a biostatistician. This research study will be investigated employing panel data analytics, using categories and percentages. The occurrence of cardiac surgery-associated AKI on CPB will be estimated with an overall 95% confidence intervals. A descriptive table will be given summarizing baseline characteristics and prognostic factors by KDIGO criteria. Factors known to be clinically relevant will be kept in the model whether they are statistically significant or not.

10. Significance of the study

The pooled global incidence of AKI related to cardiac surgery in adult patients has been recorded as being up to 22.3% when all three criteria were studied. [9] The incidence CSA-AKI according to KDIGO criteria is between 24.2% [9] and 29%. [10] In a single-center study, however, Machado et al. reported a higher incidence of 42%. [11]

The occurrence of AKI in patients undergoing cardiac surgery in the South African population could not be identified in the literature. In a systematic review by Olowu et al., [2] the mortality in adult patients with AKI, not related to cardiac surgery, was found to be 32%. The authors concluded that the scarcity of resources on this continent emphasises the need to practice preventative approaches, where possible, to decrease the occurrence of AKI.

It is essential to know the profile of patients who are susceptible to postoperative AKI as modifiable risk factors can be addressed, allowing for patient optimisation and improved outcomes.

11. Validity and reliability of the study

Botma et al. [28] define validity of a study as a marker of how research methods and designs represent the actual findings of the research questions and reliability as the extent to which the produced results can be reproduced when the same research conditions are applied in a different population.

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

- selecting a suitable study design
- acquiring an appropriate sample size in consultation with a biostatistician
- using the standardized KDIGO criteria to diagnose AKI
- one researcher collecting all the data
- checking data for accuracy of entry
- analysing data in discussion with a biostatistician.

12. Potential limitations of the study

The following are limitations to this study.

Data will be acquired from a single-center, which makes it contextual. It means that the results obtained may not be extrapolated to other patients receiving cardiac surgery on CPB.

Although the European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a good predictor of mortality for patients undergoing cardiac surgery, it will not be possible to calculate it in this study because specific clinical data required for this risk stratification may not be found in the records.

13. Project outline

Activity	Nov 2017	Dec 2017	Feb 2018	March 2018	April 2018	May 2018	June 2018	July 2018	Aug 2018	Sep 2018
Proposal										
Proposal submission										
Ethics approval										
Postgrad approval										
Gauteng Health approval										
Data collection										
Data analysis										
Draft article										
Submission										

14. Financial plan

The University of the Witwatersrand's Department of Anaesthesiology will carry the cost of printing and paper.

Item	Price per page	Quantity	Total
Paper and printing	R1	800	R800
Binding	R100	2	R200
Total			R1000

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Appendix 8: Amended objectives

TO: Zanele Ndlovu
Administrative officer: Human Research Ethics Committee (Medical)
Biobanks and Biosafety Ethics Committees
Tel: 0117172700
E-mail: Zanele.ndlovu@wits.ac.za

FROM: Dr Gontse Leballo
Department of Anaesthesiology
E-mail: gleballomothibi@gmail.com

DATE: 15 May 2018
REF: *R14/49*

ETHICS CLEARANCE CERTIFICATE NO: M190129

PROJECT TITLE: A profile of cardiac surgery related acute kidney injury in adult patients at an Academic Hospital

A REQUEST TO ADD MORE OBJECTIVES TO THE CURRENT PROPOSAL

The objectives of my study are as follows:
to describe:

1. the demographics of all adult patients presenting for cardiac surgery
2. the preoperative renal function
3. the intraoperative clinical information related to cardiac surgery associated acute kidney injury
4. the postoperative clinical data
5. the occurrence of acute kidney injury.

I would like to add a sixth objective to the list by documenting the '***in-hospital mortality***' that occurred following cardiac surgery in adult patients. I am interested in

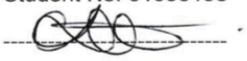
finding out if there is any relationship between the worsening renal function of the patient according to the KDIGO classification and patient mortality.

The fourth objective is describing postoperative clinical data. One of the clinical data includes serum creatinine levels at 24 and 48 hours following cardiac surgery (please see the data collection sheet attached). I would like to extend the collection of serum creatine levels to up to seven days following cardiac surgery. I believe this will provide me with a conclusive trend of the possible deterioration of renal functions in the susceptible group of patients.

Regards

Gontse Leballo

Student No. 0105815e



Appendix 9: Ethics approval for protocol amendments

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

10 July 2018

Dr Gontse Leballo
Department of Anaesthesiology

Sent by email to: gleballomothibi@gmail.com

Re: **Study no: M180129**
Study Title: A profile of cardiac surgery related acute kidney injury in adult patients at an Academic Hospital
Principal Investigator: Dr Gontse Leballo
Protocol amendments: Adding Sixth Objective

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the amendments as detailed in your letter dated 15 May 2018.

Thank you for keeping us informed and updated.

Yours Sincerely,

UNIVERSITY OF THE WITWATERSRAND OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH 10 JUL 2018 RESEARCH OFFICE HREC (Medical) JOHANNESBURG

Zanele Ndlovu
Administrative Officer
Human Research Ethics Committee (Medical)

Research Office Secretariat: Faculty of Health Sciences, Phillip Tobias Building, 3rd Floor, Office 301, 29 Princess of Wales Terrace, Parktown, 2193 Tel +27 (0)11-717-1252 /1234/2656/2700 Private Bag 3, Wits 2050, email: zanele.ndlovu@wits.ac.za Office email: hrec-medical.researchoffice@wits.ac.zaWebsite:

Appendix 10: Human research ethics committee clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr G Leballo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180129

NAME: (Principal Investigator)	Dr G Leballo
DEPARTMENT:	School of Clinical Medicine Department of Anaesthesiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A profile of cardiac surgery-related acute kidney injury in adult patients at an Academic Hospital
DATE CONSIDERED:	26/01/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr P. Motshabi, Ms H Perrie & Ms J Scribante
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/03/2018

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **January** and will therefore be due in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 11: Human Research Ethics Committee (Medical) approval for supervisor change

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

13/08/2018

Dr G Leballo
School of Clinical Medicine
Department of Anaesthesiology
Charlotte Maxeke Johannesburg Academic Hospital

Sent by e-mail to: gleballomothibi@gmail.co

Dear Dr Leballo

Re: **Protocol Ref No: M180129**
Protocol Title: *A profile of cardiac surgery-related acute kidney injury in adult patients at an Academic Hospital*
Principal Investigator: Dr G Leballo

Thank you for your letter of 07/05/2018. I apologise for the slow response.

I confirm that the amendments you propose to Protocol No. M180129 have been noted and approved.

For the record, the amendments are:

- replacement of Professor J Scribante and Ms H Perrie as co-supervisors by Dr J Moutlana

Thank you for keeping us informed and updated.

Yours Sincerely

J. Burns

.....
Mr I Burns
For the Human Research Ethics Committee (Medical)

Works2000/lain0007/Acknowledge.docx

Appendix 12: Charlotte Maxeke Johannesburg Academic Hospital CEO Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Tell: (011): 488-4812
Email: Nolwazi.Mzila@gautemg.gov.za
16 March 2018

GP_201803_030

Dear Dr. G. Leballo

STUDY TITLE: A Profile of Cardiac Surgery Related Kidney Injury in Adult Patients at an Academic Hospital

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~**not supported**~~

pp

Dr. M.L. Mofokeng
Clinical Director
DATE: 19/03/2018

Approved/not approved

Ms. G. Bogoshi
Chief Executive Officer
Date: 20.03.2018

Appendix 13: National Health Research Database (NHRD) Approval

APPLICATION DETAILS

TITLE OF RESEARCH PROJECT

A Profile of Cardiac Surgery Related Acute Kidney Injury in Adult Patients at an Academic Hospital

Type of Study

Academic

STATUS OF APPLICATION

Approved

STATUS OF PROJECT

On-Going

PROPOSAL SUBMISSION DATE

2018/03/13

You will find a list of all comments made on the selected research application. The list below displays comments visible to both the Applicant and Research Committee

COMMENTS

Comment	Comment Date	Comment By

PRIMARY INVESTIGATOR OF THE PROJECT/PROPOSAL

Title	Name	Surname	Role	Institution	E-Mail	Telephone No.	Mobile No.	CV/Resume
Dr	Gontse	Leballo	Lead Investigator	WITS	gleballomothibi@gmail.com	0119580766	0718904724	No File

RESEARCH STAFF ASSIGNED TO PROJECT/PROPOSAL

Title	Name	Surname	Role	Institution	E-Mail	Telephone No.	Mobile No.	CV/Resume

AIM AND OBJECTIVES

The aim of the study is to describe the profile of acute kidney injury (AKI) in adult patients following cardiac surgery on CPB in the cardiothoracic intensive care unit (CTICU) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The objectives of this study are to describe: • the demographics of all adult patients presenting for cardiac surgery • the preoperative renal function • the intraoperative clinical information related to cardiac surgery associated acute kidney injury (CSA-AKI) • the postoperative clinical data • the occurrence of AKI.

STUDY AREA(S)/FIELD(S)

Description
Clinical

STUDY DESIGN(S)

Description
Retrospective analysis

DATA COLLECTION METHOD(S)

Method Category	Method Description
-	Medical Records Audit

INTERVIEW REQUEST(S)

Position
No interview requests.

SAMPLE

A consecutive convenience sampling method will be used in this study. This study will consist of the records of adult patients admitted to the CTICU post cardiac surgery on CPB from January 2016 to December 2017. The justification of the sample size was determined in consultation with a biostatistician. To estimate the occurrence of AKI in adult patients following cardiac surgery on CPB, a two-year retrospective records review of a population of approximately 400 patients will be utilized. Based on a single-centre study by Machado et al., the prevalence of AKI related to cardiac surgery is roughly 40%. The estimated prevalence has a precision of: 2 x √(pq/n) where p = prevalence = 40% = 0.4, q = (1 – p) = (1 – 0.4) = 0.6 and n is the number of patients, 2 x √ ((0.4 x 0.6)/400)= ±4.5%.

DATA ANALYSIS TOOL(S)

Tool Description
Statistical software package (e.g., SPSS, STATA)

INFORMATION / DATA REQUEST?

No

INFORMATION / DATA REQUEST DETAILS.

No Data Requested

LOCATIONS(S) WHERE STUDY WILL BE CONDUCTED

Facility
---- Charlotte Maxeke Hospital

ANTICIPATED START DATE

2018/03/30

ANTICIPATED COMPLETION DATE

2018/05/31

INSTITUTION(S) WHICH GAVE ETHICAL APPROVAL

Institution
Wits - Human Research Ethics Committee (Medical), University of the Witwatersrand

ETHICS APPROVAL NUMBER

M180129

DATE OF ETHICAL APPROVAL

2018/03/13

DATE ETHICAL APPROVAL EXPIRES

2023/03/13

IF CLINICAL TRIAL, MCC APPROVED

No

NATIONAL CLINICAL TRIALS REGISTRY NUMBER

No Clinical Trial

FUNDING SOURCE

None

BUDGET (IN ZAR)

0 - 1 000

Appendix 24: Permission letter by the Cardiothoracic Surgery Head of Department

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

University
of the Witwatersrand
Johannesburg

Department of Cardiothoracic Surgery:

Charlotte Maxeke Johannesburg Academic Hospital

Post net Suite #235, Private Bag x2600, Houghton 2041 • Telephone +27 (0)11 488-3373 • Fax +27 (0)11 488-4322 • Email ramarhavhanal@gmail.com

07 February 2018

Dr Gontse Leballo

Registrar: Department of Anaesthesiology

University of the Witwatersrand

Dear Dr Leballo

RE: PERMISSION TO COLLECT DATA FOR MMED STUDY

This letter serves to confirm that approval is granted to collect data from cardiothoracic intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital, for your study titled: "A profile of cardiac surgery related acute kidney injury in adult patients at an academic hospital".

Yours Sincerely

Dr S.M Mogaladi

Head of Department (Cardiothoracic Surgery)

Charlotte Maxeke Johannesburg Academic Hospital

07/02/2018

Appendix 15: Permission letter by the Anaesthesiology Head of Department

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF ANAESTHESIA
Charlotte Maxeke Johannesburg Academic Hospital
University of the Witwatersrand
Tel: 011 488 4344
Fax: 011 488 4343

30 November 2017

Dr Gontse Leballo
Registrar: Department of Anaesthesiology
University of the Witwatersrand

Dear Dr Leballo

RE: PERMISSION TO COLLECT DATA FOR MMED STUDY

Your request for permission to collect data for an MMed study refers.

Approval is granted to collect data from anaesthesia records for your study titled: "A profile of cardiac surgery related acute kidney injury in adult patients at an academic hospital". This approval is subject to gaining the necessary clearances from other involved parties, including ethical approval.

I am looking forward to the results of your study.

Yours sincerely,

_____
Prof EE Oosthuizen
Clinical Head: Department of Anaesthesia
Charlotte Maxeke Johannesburg Academic Hospital

Appendix 16: Data collection sheet

8.1 Preoperative data

Patient demographics

Age	
Weight (kg)	
Height (m)	
BMI (kg/m^2)	

Gender	
Male	
Female	

Race	
Black African	
Non- Black African	

Co-morbidities	
Hypertension	
Diabetes Mellitus	
Smoker	
Hypercholesterolaemia	
Other	

Type of surgery	
CABG	
Cardiac valve surgery	
Aortic surgery	
Other	

Preoperative renal function	
Serum creatinine (µmol/l)	
Serum creatinine (mg/dl)	
Calculated eGFR	

8.2 Intraoperative data

Temperature	
32 ˚C – 35 ˚C	
< 32 ˚C – 28 ˚C	
< 28 ˚C – 20 ˚C	
< 20 ˚C	
CPB time	
Total	
< 90 minutes	
90 - 120 minutes	
> 120 minutes	

Aortic cross-clamp time	
minutes	

8.3 Postoperative data

Creatinine	24 hours	48 hours
(µmol/l)		
(mg/dl)		

Mechanical haemodynamic support	Yes	No
ECMO		
VAD		
IABP		

	Yes	No
RRT		
Mortality		

Appendix 37: Turn-it-in report

0105815e:CVJA-MmedARTICLE.pdf

ORIGINALITY REPORT

26%	22%	22%	10%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	academic.oup.com Internet Source	3%
2	issuu.com Internet Source	1%
3	www.tandfonline.com Internet Source	1%
4	journals.lww.com Internet Source	1%
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