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Outcomes and prognostic factors of Malaria-associated acute renal failure requiring haemodialysis at Chris Hani Baragwanath Academic Hospital

Moja, Lebogang

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Outcomes and Prognostic Factors of Malaria-associated acute renal failure requiring haemodialysis at Chris Hani Baragwanath Academic Hospital

Lebogang Moja

0402113X

A research report submitted to the University of the Witwatersrand, Johannesburg in fulfillment for the requirements of the degree of Master of Medicine 2017.

DECLARATION

I, Lebogang Moja, declare that this research report is my own work, which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at this or any other university

……

…….Day of ……2017

ACKNOWLEDGEMENTS

A most heartfelt thank you to my impeccable supervisors

Professor Menezes, thank you for your patient tutelage and guidance throughout this process, your words of encouragement, constantly overseeing the progress and inspiring as well as pushing me to strive for and do better. I could never fully convey my gratitude for your selfless dedication and time spent mentoring me on this journey, thank you.

Dr Mashabane, thank you for inspiring the topic and subject matter concerned and your support, time and dedication throughout this entire process and for allowing me access to the database in the department.

Last but certainly not least to my family, friends and my significant other. Thank you for your patience, understanding and support throughout this process. I am blessed to have you in my world and forever grateful.

ABSTRACT

Background

Plasmodium falciparum malaria is common in Sub-Saharan Africa. Acute kidney injury (AKI) is a complication of this infection. There are currently no studies that have been done in South Africa examining the outcomes in patients with AKI secondary to malaria infection who received acute haemodialysis.

Objectives

To describe the outcomes of malaria-associated AKI in patients treated with haemodialysis at Chris Hani Baragwanath Academic Hospital.

Methods

Clinical data from patients with confirmed *P. falciparum* malaria and AKI was analyzed to assess the demographics, initial clinical presentations, survival and predictors of mortality resulting in death. All patients presented to the Dumisani Mzamane Institute of Kidney Disease at Chris Hani Baragwanath Academic hospital from 01/01/2005 to 31/12/2014.

Results

Our study showed that 77 (56 male, 21 female) cases of AKI were secondary to malaria. The majority (98.7%) were black, with a median age of 37 years (IQR: 19-69). Fever (93.5%), nausea and vomiting (92.2%), metabolic acidosis (74.7%) and anuria (58.4%) were the commonest clinical presentations. The overall mortality rate was 30%, with anuria and shock being the main predictors of mortality**.** Approximately 47/54 (87%) of patients who survived had improvement of the renal function with a serum creatinine dropping to less than 265micromol/l.

Conclusion

The initiation of haemodialysis combined with effective antimalarial therapy for the treatment of AKI in patients with *P. falciparum* malaria results in the improvement of renal function in majority of patients in this study.

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ABBREVIATIONS

AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
ACT	Artemisinin Combination Therapy
BART	Bara Active Renal Tracking
CNS	Central Nervous System
DDT	Dichlorodiphenyltrichloroethane
DIC	Disseminated Intravascular Coagulopathy
GFR	Glomerular Filtration Rate
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HRP-II	Histidine Rich Protein 2
ICAM-1	Intracellular adhesion molecule 1
IL-6	Interleukin 6
INR	International Normalized Ratio
KZN	KwaZulu-Natal
LDH	Lactate Dehydrogenase
NHLS	National Health Laboratory Service
PCR	Polymerase Chain Reaction
PfEMP1	Plasmodium Falciparum Erythrocyte Membrane Protein 1
pLDH	Parasite Lactate Dehydrogenase
TNF alpha	Tumour Necrosis Factor alpha
WHO	World Health Organization

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1.1 EPIDEMIOLOGY

Malaria remains an important global cause of morbidity and mortality, with an estimated 252 million cases attributed to Sub-Saharan Africa (1). The highest incidence and prevalence of malaria is noted in Sub-Saharan Africa, Southeast Asia and the South American Amazon basin (2, 3). This region accounts for approximately 88% of the global malaria disease burden and 90% of the related deaths (2, 3). In South Africa, malaria is known to be endemic in parts of Kwazulu-Natal (KZN), Limpopo and Mpumalanga provinces, these border on neighbouring Mozambique, a country with endemic and prevalent malaria (3, 4).

There has been a noted decline in the burden of the disease in African countries, particularly South Africa due to strengthening of vector control programs such as, indoor spraying of dichlorodiphenyltrichloroethane (DDT), the use of insecticide treated nets in these “malaria risk” areas and the introduction of effective treatments in the form of artemisinin combination therapies (3, 4). In recent years “imported malaria” has increasingly become an important contributor of overall malaria cases in South Africa, this is due to increased travel by non-immune South African citizens to malaria endemic countries in the subcontinent (4, 5). There has also been a noted increase in the number of economic migrants and refugees coming into South Africa from malaria endemic countries, thus increasing both the prevalence and burden of disease in South African provinces and the health care sector generally (4, 5).

1.1.2. THE LIFECYCLE OF PLASMODIUM AND VECTORS

Malaria is a parasitic disease caused by the protozoa *Plasmodium* (2*).* There are four main species which have been implicated with causing disease in humans, *Plasmodium falciparum*, the commonest subtype in Sub-Saharan Africa accounting for the majority of cases in severe and complicated malaria, *Plasmodium vivax*, *Plasmodium malariae, Plasmodium ovale* and a fifth relatively newly described species *Plasmodium knowlesi* which has been described as causing malaria in parts of South-east Asia (6). The vector implicated in the spread of the disease is the female *Anopheline* mosquito, which infects the human host with sporozoites while feeding on a blood meal (2, 7). The inoculated sporozoites are taken up by the hepatocytes, where they mature and develop over a 7 to 10 day period into hepatic schizonts (2, 7). The schizonts rupture and release merozoites into the host bloodstream, which go on to infect human red blood cells forming trophozoites, which then mature into erythrocytic schizonts over a 24 to 72-hour period (2, 7, 8). The erythrocytic schizonts then rupture, releasing merozoites to infect further red blood cells, thus perpetuating and replicating the cycle of infectivity (2, 7, 8). Disease in humans is primarily caused by these asexual stages (2, 8). Female and male gametocytes develop, which are then taken up by the female *Anopheles* mosquito during a blood meal (2). These multiply and develop in the mid-gut, giving rise to sporozoites and migrate to the salivary glands of the mosquito to be inoculated into the human host during a bite (2). The incubation period from the time of mosquito inoculation with sporozoites to the appearance of the parasitaemia, as well as the signs and symptoms of

the infection varies from 6 to 14 days and may be slightly prolonged in non-*falciparum* species (2).

The virulence factors aiding in the infectivity of *P. falciparum* include, *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1), which is located on the surface of the erythrocytes, this protein aids in the binding of infected red blood cells to the vascular endothelial wall and the consequent sequestration in the tissue capillary beds (7-10). This membrane protein allows protozoal evasion of host defenses through antigenic variation as well as impaired immune responses (7, 8). The release of inflammatory cytokines such as Tumour necrosis factor alpha (TNF α) and Interleukin 6 (IL-6) result in upregulation of other endothelial receptors such as intracellular adhesion molecule 1(ICAM-1), which further worsens the sequestration, resulting in obstruction of the tissue capillary vascular bed, leading to hypo perfusion and lactic acidosis (8, 9). The adherence of infected red blood cells to non-infected cells in a process called rosetting aggravates this microcirculatory occlusion (7, 8). The splenic clearance of infected red blood cells is also adversely affected by this prevalent capillary sequestration (7, 8, 9).

1.1.3 SYMPTOMS AND CLINICAL PRESENTATION

The clinical presentation and severity of malaria infection is the result of a complex interplay between host factors such as patient immune status as well as *Plasmodium* related factors, including the type of infecting species and the degree of parasitaemia (2, 9). The initial symptoms of malaria infection are

very non-specific and may mimic a viral prodrome (2, 9, 10)**.** These include fever, malaise, abdominal pain, nausea and vomiting (2, 10). The hallmark symptom in malaria infection is the fever, which is initially irregular and then becomes periodic after a few days, coinciding with the rupture of schizonts and the release of the merozoites (8, 9). Due to the non-specificity of the signs and symptoms associated with malaria, there may be delays in diagnosis and treatment as patients may attribute them to a flu-like illness (2, 9, 10).

1.1.4 DIAGNOSIS OF MALARIA

The gold standard for the diagnosis of malaria infection is the direct microscopic evaluation of thick and thin peripheral blood smears by trained laboratory personnel to confirm the presence of asexual stages of the life cycle of the malaria parasite as well as quantifying the degree of parasitaemia, which aids in prognostication and the assessment of degree of severity, various stains can be performed on the blood specimen including the Giemsa, Leishman or rapid field staining method (2, 11)**.** The thick films are used for the detection of the malaria parasite whereas the thin films are useful for recognition of the exact *Plasmodia* species causing disease (2, 11). Rapid diagnostic tests have been developed to aid in quick diagnosis of malaria infection, these immunochromatographic tests assess the presence of malaria specific antigens in the blood such as histidine-rich protein II (HRP-II) and parasite lactate dehydrogenase (pLDH) (11). These tests are relatively quick to perform and have a high sensitivity (11). The quantitative buffy coat blood

parasite detection method is a relatively new test used primarily as a screening method, the performance of the test still needs to be followed by thick and thin peripheral blood smears and the prohibitive high cost as well as restricted availability has limited the use of this test to mainly a laboratory setting where it has been shown to be both beneficial and time saving (11).

Nucleic acid amplification tests have been shown to be more sensitive than traditional microscopy in both the diagnosis of malaria as well as speciation of the exact causative species especially in cases of mixed infection (11). The use of polymerase chain reaction (PCR) based tests is hampered by the expense and limited availability**.** However, it is envisaged that the use of these tests will further increase from experimental use to diagnosis of malaria especially in resource rich settings (11). These tests can also be used for monitoring response to drug therapy by assessing the reduction in the degree of parasitaemia on treatment (11).

1.2 ACUTE KIDNEY INJURY IN MALARIA

1.2.1 DEFINITION

The World Health Organization (WHO) defines malaria associated AKI as a serum creatinine of >256micromol/L**,** a blood urea of >20mmol/L or a urine output of <400ml/24hrs (6, 7). It is mainly associated with *P. falciparum* infection though a small minority has been described with *P. vivax* (7, 8). It may occur in the initial phase of the illness as part of multiple organ involvement where it carries a grave prognosis or alternately in the recovery

phase of the infection (8). AKI complicates 1-5% of cases with *falciparum* malaria with a mortality rate as high as 15-45% (8, 12).

The 2010 WHO criteria for severe malaria in patients with *P. falciparum* infection are defined as the presence of 1 or more of the following clinical or laboratory parameters (6), see table 1 below.

Table1: 2010 WHO criteria for severe malaria (6)

Clinical features	***Laboratory findings***
• Impaired consciousness or unarousable coma with a Glasgow coma score <11 • Prostration, i.e. generalized weakness with the patient unable to walk, sit up or stand without assistance • Multiple convulsions: more than 2 episodes in 24hours • Respiratory distress and acidotic breathing • Circulatory collapse or shock with a systolic blood pressure <80mm Hg in adults and <70mm Hg in children • Clinical jaundice • abnormal spontaneous bleeding • anuria	• hypoglycaemia (blood glucose <2.2mmol/l) • metabolic acidosis (plasma bicarbonate <15mmol/l) • severe normocytic anaemia (Hb < 5g/dl or a haematocrit of <15%) • haemoglobinuria • hyperparasitaemia (*P. falciparum* parasitaemia >10%) • hyperlactaemia (lactate >5mmol/l) • renal impairment (serum creatinine >265micromol/l

• acute respiratory distress syndrome and acute pulmonary oedema	• pulmonary oedema (radiological)

1.2.2 PREDICTORS OF MORTALITY

Conjugated hyperbilirubinaemia has been shown to predispose to the development of AKI in patients with severe malaria (8, 12, 13). The jaundice results in toxicity to the renal tubules and subsequent development of acute tubular necrosis with declining Glomerular filtration rate (GFR). It was previously shown that AKI associated with clinical jaundice had a higher mortality in comparison with non-jaundiced patients (14, 15).

It was noted that AKI associated with the concurrent development of cerebral malaria carried an adverse prognosis, as demonstrated in a study conducted by Mishra et al (16), where 28.9% of the 526 patients with cerebral malaria in the study developed AKI. The mortality rate was 39.5% when cerebral malaria was associated with AKI, while it was only 13.9% when not complicated by renal failure. The association of cerebral malaria and AKI was also shown in studies conducted in Southeast Asia where half of the patients had biochemical evidence of renal impairment (17, 18)

Previous studies conducted in children showed DIC associated with severe malaria and AKI resulted in increased mortality (19, 20). Similar findings have not been conclusively established in adults. The complications of severe

malaria infection such as septic shock, haemolysis and dehydration have all been shown to contribute to the development of AKI (12, 17, 20).

1.2.3 THE MECHANISM OF AKI IN MALARIA

The pathophysiological mechanisms that have been implicated in the aetiology of AKI in severe *P. falciparum* malaria include increased sympathetic nervous system activation with the release of catecholamines, resulting in renal microvasculature vasoconstriction (21-24). This is evidenced by the decreased urine sodium concentration, decreased urine volume and decreased glomerular filtration rate (GFR) owing to the reduced renal blood flow in these patients (21-24).

The direct changes in the erythrocyte cell surface structure due to entry of the malaria merozoite by binding of the cell surface thrombospondin glycoprotein receptor allows the expression of certain protrusions on the erythrocyte cell surface resulting in reduction of cell deformability and increased adhesion to the endothelial cells (8, 10). The adherence to the vessel wall causes occlusion of the microcirculation which then results in ischemia of the renal peritubular vessels (24, 25). There is also an increase in blood viscosity in patients with severe *P*. *falciparum* malaria which impairs renal blood flow and contributes to the AKI in these patients (8, 24, 25).

Hypovolaemia in patients with AKI is mainly due to the release of vascular permeability factors, which result in leaky capillaries and the release of protein and water molecules (23, 24). This is further compounded by activation of the

sympathetic nervous system resulting in compromised renal blood flow, renal ischemia and AKI (24). The hypovolaemia may also be due to insensible fluid losses associated with the systemic infection, fever, reduced fluid intake and associated nausea and vomiting. This coupled with the increased capillary permeability results in decreased renal perfusion and ischemia causing the acute tubular necrosis (24, 25).

Metabolic acidosis is commonly seen in patients with severe malaria. The cause for this is multifactorial. This includes decreased tissue perfusion due to the occluded microvasculature by the parasite, reduction in liver lactate clearance due to reduced blood flow, the inhibition of gluconeogenesis owing to circulating TNFα, severe anaemia decreasing the delivery of oxygen to the cells and tissues, reduced levels of 2,3-biphosphoglycerate, hypotension, hypovolaemia and inhibition of mitochondrial glucose oxidation (24, 25, 26). The increase in anaerobic metabolism at cellular level with accumulation of both lactic and 3-hydroxybutyric acid accounts for the metabolic acidosis frequently found in patients with severe *P. falciparum* malaria (27). The uraemia frequently found in patients with AKI also contributes to the metabolic acidosis (24-27).

DIC has been implicated as a possible mechanism of AKI (19, 20). The increase in fibrinogen degradation products, thrombocytopaenia due to both splenic pooling of platelets, platelet agglutination and the decreased survival of cells in the blood circulation contribute to the intravascular coagulation which further compromises the renal blood flow in these patients (12, 19, 20**).**

There is a strong correlation between conjugated hyperbilirubinaemia and AKI in patients with *Falciparum* malaria (8, 12, 13, 20, 28). This is due to the toxic effect of the bile acids on the renal tubular cells (28). Jaundiced plasma has been shown to increase the sensitivity of the vascular endothelial cells to the effects of the catecholamines, therefore resulting in vasoconstriction of the renal microcirculation (28).

1.2.4 TREATMENT OF MALARIA

1.2.4.1 Dialysis

AKI in malaria is often transient and in the majority of patients can be treated with adequate intravenous fluid replacement coupled with antimalarial therapy (28). Severe renal failure with certain clinical and laboratory indications however requires renal replacement therapy in the form of either peritoneal or haemodialysis, with the latter being the preferred mode of treatment particularly when initiated early in the course of infection (21, 28). In a study conducted in Vietnam, it was shown that mortality amongst patients with malaria associated AKI receiving haemodialysis was 26%, which is significantly lower than 75% mortality noted in the group who did not get dialyzed (18). Peritoneal dialysis in the treatment of malaria associated AKI is limited by the impaired microcirculation and peritoneal dysfunction occurring in these patients which then results in poor clearance (17, 21). The indications for haemodialysis include anuria with a urine output of <50ml/24hrs, intractable hyperkalaemia not responding to medical treatment,

the presence of severe high anion gap metabolic acidosis and the uraemic syndrome which comprises either encephalopathy in a previously recovering patient, the presence of uraemia related gastrointestinal bleeding and pericarditis (7, 17).

1.2.4.2 Drug therapies

The antimalarial drug quinine is the most widely used and available drug for the treatment of *P. falciparum* malaria. Treatment involves the use of an initial intravenous loading dose of 20mg/kg followed by a maintenance dose of 10mg/kg, which should ideally be given by slow intravenous infusion in order to minimize the hypotension and cardiac related side effects such as prolonged QT interval, supraventricular and ventricular tachyarrhythmias (2, 17, 23)**.** In severe renal failure, the loading dose can be given at a similar dose but it is advised to reduce the maintenance dose by 30 to 50% and to administer the quinine dose after haemodialysis for patients receiving renal replacement therapy (2). Artemisinin based derivatives such as artesunate are not as readily available as quinine but have been shown to be beneficial in parasite clearance, being 20% faster and more effective than quinine based therapy (2, 23). Artesunate has a better side effect profile and a shorter duration of treatment compared to quinine (2, 23).

It has been shown in prior studies that prognosis of AKI in *P*. *falciparum* infection is heavily dependent on the severity of the infection, complicating extra-renal associations such as jaundice and the prompt initiation of effective antimalarial therapy coupled with dialysis support (18, 28). AKI-related

complications and further worsening of renal function can be prevented by cautious and targeted intravenous fluid therapy, avoidance of complicating nephrotoxic agents and if required, the early institution of renal replacement therapy (18, 28).

1.3 STUDY AIMS AND OBJECTIVES

1.3.1 AIMS

The aim of this study is to describe the clinical outcomes and prognostic factors of malaria-associated AKI in patients treated with haemodialysis at Chris Hani Baragwanath Academic Hospital, to our best knowledge no such study has been conducted in South Africa.

1.3.2 OBJECTIVES

Primary objectives

1. To describe the clinical outcomes and survival in patients with confirmed malaria-associated AKI who received haemodialysis.
2. To determine the predictors of mortality according to the WHO clinical criteria.

Secondary objectives

1. To describe the demographics of patients with malaria-associated AKI.
2. To describe the initial clinical presentations in the study population.

1.4 METHODOLOGY

1.4.1 STUDY DESIGN AND SAMPLE POPULATION:

A retrospective record review of adult patients with AKI secondary to malaria infection who received acute haemodialysis at the Chris Hani Baragwanath Academic Hospital Dumisani Mzamane Institute of Kidney Disease over a 10 year period from 01/01/2005 to 31/12/2014 comprising approximately 70 to 100 patients.

1.4.2 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

- Adult patients ≥ 18 years of age
- Confirmed malaria infection with either a positive peripheral blood smear and/or *P. falciparum* antigen positive.
- Concomitant AKI (with a serum creatinine >265micromol/l) (6).
- Received acute haemodialysis at Chris Hani Baragwanath Academic Hospital Dumisani Mzamane Institute of Kidney Disease.

Exclusion criteria:

- Paediatric cases < 18 years of age.
- Patients never referred to and treated by the adult nephrology unit (including those admitted to and dialyzed in the intensive care unit at Chris Hani Baragwanath Academic Hospital).

- Patients who demised prior to receiving haemodialysis.
- Patients with confirmed malaria and renal failure but did not receive dialysis.

1.4.3 DATA COLLECTION

The data collection will be done retrospectively utilizing the Bara Active Renal Tracking electronic file-keeping database available at the Dumisani Mzamane Institute of Kidney Disease for the period of 01/01/2005 to 31/12/2014. The physical copies of the files will be sought from the medical records department to aid in data collection. Data from the files will be collected using the prepared collection sheet (Appendix A). This will be the principal method utilized to collate the most relevant patient information for purposes of this study. These include: patient demographics, presenting clinical features, predictors of mortality and ultimately the outcome in the study population. Permission to access as well as utilize the clinical records for purposes of this study will be sought from the Head of Department of Internal Medicine as well as the hospital administration at Chris Hani Baragwanath Academic Hospital.

1.4.4 DATA ANALYSIS

Data will be analyzed using SPSS® version 22.0 (Armonk, NY: IBM Corp, 2013). Baseline demographics such as age, gender and race will be analyzed as medians with interquartile ranges (IQR) and proportions. The presenting clinical, laboratory parameters and co-morbidities will also be assessed as proportions. The significant predictors of mortality will be analyzed as means

with standard deviations and the t-test to compare the means between both the survived and demised group of patients. Binary logistical regression will be used to assess the prognostic factors associated with mortality. A statistician will be sought to assist with the data analysis process.

1.5 STUDY LIMITATIONS

- The study is retrospective in design and thus the quality of the data collected is entirely dependent on the preexistent quality of record keeping. Therefore, some information may be absent or incomplete.
- Patients who were never referred to or did not receive acute haemodialysis in the adult nephrology unit at Chris Hani Baragwanath Academic Hospital are excluded from the study.
- Patients with severe AKI admitted to the intensive care unit are not included in the study.
- The absence of a discernible control group comprising patients with malaria-associated AKI but did not receive haemodialysis will weaken the study findings.

1.6 STUDY TIMING AND OUTLINE

Progress	Sep-14	Oct-14	Nov-Dec 14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15
Literatur review														
Protocol Prep submission														
Ethics submission														
Protcol assessment aproval														
Data collection														
Data analysis														
Thesis write up														
Paper write up														

1.7 FUNDING

Description	Cost
Photocopying, printing, binding	R1500
Stationery	R500
Total costs	R2000

The researcher will incur the total costs of the research

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CHAPTER 2: SUBMISSIBLE ARTICLE

Title: Outcomes and prognostic factors of malaria-associated acute renal failure requiring haemodialysis at Chris Hani Baragwanath Academic Hospital

Authors:

Lebogang Moja [1,3]

Colin N Menezes [2,3]

Mduduzi J Mashabane [1,3]

Affiliations:

[1] Division of Nephrology, Department of internal medicine, Chris Hani Baragwanath Academic Hospital Johannesburg, South Africa.

[2] Division of Infectious Diseases, Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa.

[3] Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Short title: Outcomes of malaria-associated renal failure in South Africa

Conflict of interest: Nil

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Corresponding Author:

Lebogang Moja

E-mail: lebogang.moja@yahoo.com

Mobile: 0724277605

Postal Address: P.O Box Karen Park, Pretoria 0182

Word Count: 2619

Abstract:

Background:

Plasmodium falciparum malaria is common in Sub-Saharan Africa. Acute kidney injury (AKI) is a complication of this infection. There are currently no studies that have been done in South Africa examining the outcomes in patients with AKI secondary to malaria infection who received acute haemodialysis.

Objectives:

To describe the outcomes of malaria-associated AKI in patients treated with haemodialysis at Chris Hani Baragwanath Academic Hospital.

Methods

Clinical data from patients with confirmed *P. falciparum* malaria and AKI was analyzed to assess the demographics, initial clinical presentations, survival and predictors of mortality resulting in death. All patients presented to the Dumisani Mzamane Institute of Kidney Disease at Chris Hani Baragwanath Academic hospital from 01/01/2005 to 31/12/2014.

Results

Our study showed that 77 (56 male, 21 female) cases of AKI were secondary to malaria. The majority (98.7%) were black with a median age of 37 years (IQR: 19-69). Fever (93.5%), nausea and vomiting (92.2%), metabolic acidosis (74.7%) and anuria (58.4%) were the commonest clinical presentations. The overall mortality was 30% with anuria and shock being the main predictors of mortality. Approximately 47/54 (87%) of patients who survived had improvement of the renal function with a serum creatinine dropping to less than 265micromol/l.

Conclusion:

The initiation of haemodialysis combined with effective antimalarial therapy for the treatment of AKI in patients with *P. falciparum* malaria results in the improvement of renal function in majority of patients in this study.

Abstract Word Count: 235

Introduction:

Malaria remains a major health problem in many parts of the developing world such as Southeast Asia, South America and Sub-Saharan Africa (1).

Acute kidney injury (AKI) is one of the most dreaded complications of severe *P. falciparum* malaria complicating approximately 1-4% of cases, with a mortality rate as high as 15-45%, if adequate treatment with effective parenteral antimalarial agents and renal replacement therapy in the form of haemodialysis is not instituted early in the course of the disease (1-3).

Conjugated hyperbilirubinaemia has been shown to be a common association with AKI carrying a poor prognosis with a high mortality rate in this group of patients (2-6).

Cerebral malaria is rarely associated with *P. falciparum* induced AKI, its presence however signals severe parasitic infestation and disease (2). This has been demonstrated in a prior study conducted by Mishra et al (7) where 28.9% of patients with cerebral malaria developed AKI as a complication of the infection (7)**.** A mortality rate of 39.5% was shown in these patients with a combination of cerebral malaria and AKI whereas it was only 13.9% when cerebral malaria was not complicated by AKI (7). It was found in previous studies done in children that the presence of DIC with falciparum malaria was associated with increased mortality (8, 9).

The other risk factors associated with increased mortality of AKI in *falciparum* malaria include: advanced age, oligo-anuria, leukocytosis and hyperkalemia (10)

Our study aimed to describe the baseline demographics, presenting clinical, laboratory features and predictors of mortality associated with outcomes in patients with AKI complicating severe malaria infection.

Methods

This retrospective study was carried out at the Chris Hani Baragwanath Academic Hospital Dumisani Mzamane Institute of Kidney Disease in Soweto, Johannesburg, a 3200-bedded hospital, which serves as a tertiary referral center for the southern part of the Gauteng as well as the North West Province of South Africa. Patients were from the general medical, surgical, and obstetric units in the hospital. Patients with severe malaria infection and AKI admitted to and dialyzed in the intensive care unit were not included in the study**.** Cases over a 10-year period from January 2005 to December 2014 were reviewed for inclusion in the study. The inclusion criteria were confirmation of *P. falciparum* infection through either a positive rapid antigen test or the demonstration of the asexual parasite stages on peripheral blood smears and AKI coupled with confirmed malaria infection requiring haemodialysis. Study patients included those who were diagnosed with malaria in one of the referral units in the hospital and either presented with AKI complicating the presentation or developed the AKI during the course of

the disease or treatment. The definition of AKI is based on the latest WHO criteria for severe malaria with a serum creatinine of >265 micromol/L or urine output less than 400ml/24hrs despite adequate fluid rehydration (6).

Data collection

The collection of data was done retrospectively through the review of patient medical records utilizing the Bara Active Renal Tracking (BART) electronic file-keeping database in the Division of Nephrology over the period of 01/01/2005 to 31/12/2014. Additional data was obtained from the medical records department. The information captured included patient demographics, the presenting clinical features, predictors of mortality based on the World health organization (WHO) criteria of severe malaria infection and the clinical outcomes.

The WHO criteria for severe malaria in patients with *P. falciparum* infection are defined as the presence of at least 1 or more of the following clinical or laboratory parameters (11). The clinical parameters are an impaired consciousness with a Glasgow Coma Scale score of <11, the presence of multiple convulsions (>2 seizures) within a 24hour period, severe prostration with the patient unable to sit, walk or stand without assistance, acidotic breathing and respiratory distress, acute pulmonary oedema with acute respiratory distress syndrome, shock with a systolic blood pressure of less than 80mmHg in adults, clinically evident jaundice, the presence of anuria or oliguria with a urine output <400ml/24hrs and abnormal bleeding (11).

The laboratory findings in severe malaria include hypoglycaemia with a blood glucose of less than 2.2mmol/l, severe metabolic acidosis with a serum bicarbonate level of <15mmol/l or lactate level of >5mmol/l, normocytic normochromic anaemia with a haemoglobin of <5g/dL, a high parasite count (>10% parasitized red blood cells) and a plasma or serum creatinine >265micromol/l or blood urea >20mmol/l (11). Thrombocytopaenia was defined as platelet count of <100 $x10^9$/L (11).

Blood results were obtained from the National Laboratory Health Services (NHLS). Peripheral blood smears were available for all the patients in the study; however, the quantification of the degree of parasitaemia was not done for all in the study population and thus was not analyzed. The blood investigations, which were analyzed as part of evaluating the prognostic factors associated with outcomes included the haemoglobin, white cell and platelet count, the evaluation of the blood urea and the serum creatinine concentration and electrolytes. Liver function tests, comprising alanine transaminase and total bilirubin as well as INR were analyzed if the results were available. Age and gender based reference ranges provided by the NHLS but further classified according to the set WHO criteria for severe malaria infection was utilized to stratify into normal or abnormal results.

Haemodialysis was the preferred method of renal replacement therapy utilized in all patients in the study population who had one or other indications for dialysis. The indications include a severe high anion gap metabolic acidosis,

intractable hyperkalemia not responding to conservative treatment, the presence of uraemia related complications such as encephalopathy, bleeding and pericarditis and a rising creatinine level with or without oliguria despite adequate intravenous fluid replacement therapy. Vascular access in the form of temporary double lumen dialysis catheters inserted into either the femoral or internal jugular veins were used for dialysis. The duration of treatment as well as frequency of dialysis sessions was determined by the clinical and biochemical response based on decisions by the responsible treating physician which is usually based on improvement in urine output and a reduction in the urea, creatinine and correction of electrolyte abnormalities.

Statistical analysis

Retrospective study data was collected and managed using REDCap electronic data capture tools hosted at the University of the Witwatersrand. The data was then downloaded into an Excel spreadsheet, which was later exported into SPSS® version 22.0(Armonk, NY: IBM Corp, 2013).

The baseline characteristics of the study population were analyzed using percentages and medians with interquartile ranges (IQR). The presenting clinical and laboratory parameters, and co-morbidities were assessed as proportions. The significant predictors of mortality were analyzed as means with standard deviations and the t-test to compare the means between both the survived and demised group of patients. Binary logistical regression was used to assess the prognostic factors associated with mortality. A statistician

was sought to assist with the data analysis process. The use of data for the purposes of the study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

Results:

Baseline characteristics of the study population

A total of 77 patients with confirmed *P. falciparum* malaria complicated by AKI were included in the study. Approximately fifty-six (73%) of the patients were male; the majority (98.7%) were black. The median age of the study population was 37 (IQR 19-69 years).

Presenting clinical features

Fever (93.5%) was noted to be the commonest clinical presentation in both the survived and demised groups of patients, followed by nausea and vomiting (92.2%), metabolic acidosis (74.7%), thrombocytopaenia (72.7%) and anuria (58.4%). The presenting clinical features associated with death in our study group were anuria *(P*=0.028) and the presence of shock (*P*=0.002). The presenting clinical and laboratory features of the study population are summarized in Tables 1 and 2.

Patient clinical outcomes

The overall mortality in our study was 30%. At the time of death 17/23 (74%) of patients still had a documented serum creatinine of >265micromol/l**.** Approximately 47/54 (87%) of survivors had improvement of renal function

(with a serum creatinine of <265micromol/l) based on the last recorded blood test results available.

Predictors of mortality and comorbidities

The characteristics of the 23 patients who died were compared with the 54 survivors to determine the factors associated with increased risk of mortality. There was a statistically significant difference in the GFR between the two groups with the GFR in the survived group higher (18.32) compared to (12.14) in those who demised (*P*=0.000). Interestingly, the mortality rate was also noted to be higher in patients with a white cell (*P*=0.037) and platelet count (*P*=0.006) on the upper limit of normal, when compared to survivors.

There were no statistically significant differences in terms of race *(P*= 0.123) and gender (*P*=0.879). Similarly, there were no statistically significant differences in terms of the haemoglobin, total bilirubin, alanine transaminase and the INR (*P*=0.230, 0.470, 0.886 and 0.077 respectively).

Though HIV co-infection was present in more than two-thirds, 16/23 (69.6%) of those that died, there was no statistically significant difference between the survived and demised group (*P*=0.641). Similarly, there was no difference for hypertension and diabetes mellitus (*P*=0.727 and 0.640 respectively). The prognostic factors and co-morbidities associated with outcome are shown in Table 3.

Treatment of malaria

The majority of patients in our study 57/77 (74%) received quinine for the treatment of *P. falciparum* malaria. The remaining 20/77 (26%) received artesunate.

Discussion:

AKI is a dreaded complication of *P. falciparum* malaria and is associated with a high mortality rate if not timeously and effectively treated. It remains an important cause of morbidity and mortality in Southern Africa (1). Majority of patients in our study were male (73%) and consequently more males died compared to female subjects. This male predominance has been observed and demonstrated in previous similar studies conducted in South East Asia, which also have a high prevalence of malaria infection (3, 6, 12, 13). The exact reasons for this are poorly understood, however it is postulated that males engage in outdoor activities more frequently than females and thus have an increased risk of exposure to infecting mosquitoes (6, 13). The possibility of genetic susceptibility to the development of AKI with *Falciparum* malaria infection has been postulated but not extensively investigated (6).

All 77 patients in our study had *P. falciparum* as the causative species**.** This finding has been observed in a number of other studies where it was shown that *P. falciparum* is more frequently associated with complicated severe malaria (6, 13).

The commonest presenting clinical features with AKI in our study were fever, nausea and vomiting, anuria and jaundice, with the commonest laboratory findings being thrombocytopenia and metabolic acidosis**.** AKI associated with jaundice has been shown to have a higher mortality compared to its occurrence in non-jaundiced patients and it has been previously shown that the simultaneous occurrence of both jaundice and AKI is associated with a poor outcome and increased mortality (2, 3, 4).

In our study 33/77 (42.9%) of patients had documented jaundice and 9/23 (39.1%) of patients who died were jaundiced. The majority of patients in our study 45/77 (58.4%) presented with anuria. This is similar to the 60-70% prevalence reported in other similar studies (3, 14). It was shown that patients with anuria had a poor outcome as 17/23 (73.9%) of these patients demised (see table 1). It is known that AKI in *Falciparum* malaria is mainly oligo-anuric and hyper catabolic (3, 14).

The mortality in our study was 23/77 (30%) which corresponds with similar studies conducted in other parts of the world where renal replacement therapy as a modality of treatment is available. The mortality in other studies ranges between 15 to 45% (3, 7, 15). In a similar retrospective study conducted in Pakistan between 1990 and 1999 with a sample size of 99 patients, the mortality rate was 26% (3). CNS involvement in the form of cerebral malaria in patients with AKI has been shown to be strongly associated with mortality (3, 16, 17). In our study however, the prevalence of suspected cerebral malaria

was relatively low, with only 7/77 (9.2%) of the study subjects and 8.7% of those who died being diagnosed with suspected cerebral malaria.

All patients in our study received haemodialysis, it has been shown to be more effective than peritoneal dialysis, the effectiveness of which is hampered by the impaired microcirculation in malaria infection and the complicating peritoneal dysfunction (2, 3, 6, 10). Renal replacement therapy has been shown to dramatically improve outcomes in patients with AKI secondary to malaria infection (3, 6, 18). In this study, the majority of survivors 47/54 (87%) had improvement of renal function as evidenced by a serum creatinine of <265micromol/l. Antimalarial drugs to treat the infection remain the backbone of treatment in patients with AKI secondary to f*alciparum* malaria. The clear majority of patients in our study were treated with quinine whilst a smaller proportion received artesunate. The safer option of intravenous artesunate is still not readily available in South Africa as the standard of treatment for complicated malaria as it is yet to be registered by the South African Medicines Control Council (MCC). Most patients with AKI do not require the institution of renal replacement therapy and respond well to the effective combination of anti-malarial treatment with careful intravenous fluid resuscitation in those who are fluid depleted (14). The excessive and aggressive administration of intravenous fluids in patients who are fluid replete may result in fluid overload and adult respiratory distress syndrome (ARDS) due to the inherent increased vascular permeability found in these patients (14).

Previous studies have demonstrated that the predictors of mortality most frequently associated with a poor clinical outcome include conjugated hyperbilirubinaemia, cerebral malaria, DIC, oligo-anuria and anaemia (3, 13, 19). In our study the presenting clinical features and predictors of mortality associated with a poor outcome were the presence of anuria and shock complicating the clinical presentation. Patients who are noted to have any of the afore-mentioned poor prognostic factors should be treated timeously and watched closely to prevent further worsening of the AKI. These measures include the timeous institution of parenteral anti-malarial therapy, avoidance of nephrotoxic agents which may further worsen the kidney function and if indicated, careful and measured fluid resuscitation. These measures need to be instituted early during treatment to avoid the need for dialysis if not indicated. However, for those patients with explicit indications the commencement of renal replacement therapy should not be delayed as it has been shown to result in a good outcome as seen in our study.

In terms of limitations, the lack of a comparative control group, comprising patients with AKI secondary to malaria infection but treated conservatively without the institution of haemodialysis is a limitation of our study, as is the non-inclusion of patients admitted to and dialyzed in the intensive care unit of the hospital. The small sample size also slightly weakens the study, however similar studies carried out in other parts of the world also have small sample sizes as many of the patients with malaria AKI respond well to supportive treatment and antimalarial therapy without the need for haemodialysis.

To the best of our knowledge, this is the first study conducted in South Africa documenting clinical outcomes and predictors of mortality in patients with AKI and malaria, a common disease in this part of the world. Further prospective studies are required to assess the predictors of mortality in *Falciparum* malaria to better understand outcomes in patients with complicated infection.

Conclusion

P. falciparum malaria is an important cause of morbidity and mortality in Sub-Saharan Africa and accounts for a significant number of global malaria related deaths. A high index of clinical suspicion resulting in early diagnosis and the prompt initiation of effective antimalarial drugs, coupled with supportive treatment and haemodialysis for the treatment of AKI improves survival and the recovery of renal function.

Acknowledgements

REDCap

Disclosure statement: The authors have no conflict of interest to declare

Table 1: Presenting clinical features of Malarial AKI

Clinical features	**Malaria with AKI** ***(N***=77)	**Survivors** (*N*=54)	**Non-survivors** (*N*=23)	***P* value**
Fever	72 (93.5)	50 (92.6)	22 (95.7)	0.642
Jaundice	33 (42.9)	24 (44.4)	9 (39.1)	0.845
Oliguria	25 (32)	18 (34)	7 (27.3)	0.669
Anuria	45 (58.4)	28 (51.9)	17 (73.9)	0.028
Nausea/vomiting	70 (92.2)	48 (90.7)	22 (95.7)	0.104
Impaired consciousness	12 (15.6)	9 (16.7)	3 (13.0)	0.733
Cerebral malaria	7 (9.2)	5 (9.4)	2 (8.7)	0.825

Data is expressed as proportions with the absolute values and corresponding percentages**.**

P value of <0.05 is significant.

Table 2: Presenting laboratory features of Malarial AKI

Laboratory features	**Malaria with AKI** (*N*=77)	**Survivors** (*N*=54)	**Non-survivors (***N*=23)	***P* value**
Anaemia	8 (10.4)	3 (5.6)	5 (21.7)	0.230
Thrombocytopaenia	55 (72.7)	39 (72.2)	16 (73.9)	0.879
Shock	12 (15.6)	4 (7.4)	8 (34.8)	0.002
Disseminated intravascular coagulopathy (DIC)	15 (19.7)	8 (15.1)	7 (30.4)	0.061
Metabolic acidosis	57 (74.7)	39 (71.7)	18 (81.8)	0.359
Acute respiratory distress syndrome (ARDS)	2 (2.6)	2 (3.7)	0	0.642
Hyponatraemia	19 (25)	15 (28)	4 (18.2)	0.381

Data is expressed as proportions with the absolute values and corresponding percentages

P value of <0.05 is significant.

Table 3: Prognostic factors and co-morbidities

Characteristic	**Survived (*N*=54)**	**Demised (*N*=23)**	**P-value**
Haemoglobin (g/dl)	8.55± 2.28	8.02± 2.16	0.350
White Cell count ($x10^9$)	7.67± 4.78	11.19± 7.05 *	0.037
Platelets ($x10^9$)	233.52± 112.31	139.30± 170.60*	0.006
Serum urea (mmol/L)	9.91± 7.96	33.80±17.92*	0.000
Serum creatinine (μmol/L)	201.47±177.15	856.17± 676.83*	0.000
Glomerular filtration rate (GFR)	45.45±18.32	11.87±12.14*	0.000
Total Bilirubin (μmol/L)	77.85±111.882	101.17±124.61	0.470
Alanine transaminase (U/L)	97.51±143.83	103.06±124.28	0.886
International normalized ratio (INR)	1.37± 0.421	1.75± 0.971	0.077
Duration of illness (days)	21.04±16.11	10.91±20.85*	0.024
Co-morbidities			
Hypertension	13.2%	17.4%	0.727
Diabetes mellitus	1.9%	0.0%	0.640
HIV	70.4%	69.6%	0.641

Data is expressed as means with standard deviations except for the co-morbidities, which are expressed as proportions.

*P value of <0.05 is significant.

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CHAPTER 3: APPENDICES

3.1. DATA COLLECTION SHEET: APPENDIX A

PARTICIPANT NUMBER:

AGE:

GENDER:

MALE	FEMALE

RACE:

BLACK	WHITE	INDIAN	COLOURED	OTHER

PRESENTING CLINICAL FEATURES:

FEATURE	**YES**	**NO**
FEVER		
JAUNDICE		
OLIGURIA		
ANURIA		
NAUSEA/VOMITING		
IMPAIRED CONSCIOUSNESS		
CEREBRAL MALARIA		
ANAEMIA		
THROMBOCYTOPAENIA		
SHOCK		
DISSEMINATED INTRAVASCULAR COAGULOPATHY		
METABOLIC ACIDOSIS		
HYPONATRAEMIA		
CONFIRMED MALARIA		
ACUTE RESPIRATORY DISTRESS SYNDROME		
OTHER		

PREDICTORS OF MORTALITY:

	FIRST RECORDED	LAST RECORDED
DATE		
HAEMOGLOBIN		
WHITE CELL COUNT		

PLATELET COUNT		
BLOOD UREA		
SERUM CREATININE		
SERUM SODIUM		
SERUM POTASSIUM		
SERUM BICARBONATE		
TOTAL BILIRUBIN		
ALANINE TRANSAMINASE		
INTERNATINAL NORMALISED RATIO		
DURATION OF ILLNESS (DAYS)		
OTHER		

CO-MORBIDITIES:

DISEASE	YES	NO
HYPERTENSION		
DIABETES MELLITUS		
HUMAN IMMUNE DEFICIENCY VIRUS		

TREATMENT OF MALARIA:

Treatment used	**YES**	**NO**	**DURATION OF TREATMENT (DAYS)**
Quinine			
Artemisinins			

CLINICAL OUTCOMES:

	YES	**NO**
SURVIVED		
DEMISED		
RECOVERY OF RENAL FUNCTION		
WORSENING OF RENAL FUNCTION		

FOLLOW UP:

YES	**NO**

3.2. ETHICS CLEARANCE

R14/49 Dr Lebogang Moja and Prof Colin Menezes

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150602

NAME: (Principal Investigator)	Dr Lebogang Moja and Prof Colin Menezes
DEPARTMENT:	Internal Medicine CHBAH
PROJECT TITLE:	Outcomes and Prognostic Factors of Malaria-Asscociated Acute Renal Failure requiring Haemodialysis at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	26/06/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Mduduzi Mashabane
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/06/2015

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 Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES