COLLEGE OF MEDICINE AND HEALTH SCIENCES, SCHOOL OF MEDICINE AND PHARMACY, INTERNAL MEDICINE DEPARTMENT

# Incidence and risk factors of acute kidney injury in malaria patients; case of Nyagatare and Nyanza District hospitals

Final project submitted in partial fulfillment of the requirements for the award of the Masters of medicine in internal medicine

**By**

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## DECLARATION

I, DUFATANYE Erhard, to the best of my knowledge hereby declare and certify that the work presented in this dissertation entitled "INCIDENCE AND RISK FACTORS OF ACUTE KIDNEY INJURY IN MALARIA PATIENTS; CASE OF NYAGATARE AND NYANZA DISTRICT HOSPITALS." is entirely my original work and it has never been presented or submitted in a whole or in part to any other university.

DUFATANYE Erhard Signature: …… Date: ……

Supervisor:

I, hereby declare that this dissertation has been submitted with my approval as the supervisor.

DUSABEJAMBO Vincent, MD Signature: …… Date: ……

Kailani Leway, MD Signature…….. Date…….

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## DEDICATION

To God the Almighty

To my Parents

To my sisters and brothers

To my relatives and friends

To my classmates and other people who contributed to my studies

I dedicate this work

## ACKNOWLEDGEMENT

This dissertation for the award of a Masters` degree would not have been successful if there were not joint efforts in terms of moral, intellectual, and financial support and guidance of various people to whom I give thanks. I would like to extend my sincere gratitude and heart-felt appreciation firstly, to the Almighty God father, my Savior Jesus Christ, my redemptory Holy Spirit, and the Virgin Mary for abundant blessings, guidance, protection, and intercession during my work and studies.

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My thanks are finally presented to all my colleagues, friends and relatives for their endurance and charity throughout my life, and particularly to my studies “May the Almighty God bless you“.

DUFATANYE Erhard

## ACRONYMS

CHUK: Centre Hospitalier Universitaire de Kigali

CMHS: College of Medicine and Health Sciences

WHO: World Health Organization

MOH: Ministry Of Health

AKI: Acute kidney injury

CKD: Chronic kidney disease

KIDGO: Kidney disease improving global outcome

NSAIDs: Non-steroidal anti-inflammatory drugs

ACE: Angiotensin converting enzyme

ARF: Acute renal failure

MARF: Malaria acute renal failure

WBCs: white blood cells

DIC: Disseminated intravascular coagulation

## ABSTRACT

**Background**: Acute kidney injury is a frequent complication of malaria. There is no data about this problem in Rwanda. The purpose of this study was to determine the incidence and risk factors of acute kidney injury in malaria patients presenting to 2 rural district hospitals located in malaria endemic areas in Rwanda.

**Methods:** After excluding patients with concurrent infectious diseases, pregnant women, children under 15 years of age, people who refused to sign consent, and those with one or no serum creatinine measurement, we included 100 patients in the analysis. AKI was defined as an increase in serum creatinine by $\geq$ 0.3 mg/dl from the baseline within 48 hours. Malaria was diagnosed by either thin, thick smear or rapid test.

We studied those 100 consecutive patients presenting with a primary diagnoses of malaria to NYANZA and NYAGATARE district hospitals, in a 10 months period within the period from April 2018 to January 2019.

**Results:** AKI occurred in 40(40%)patients. significant risk factors for AKI were: late consultation[RR:2.1(1.3-3.4,p=0.002)],hypotension at presentation[RR:1.7(1.1-2.7,p=0.02)],inability to drink[RR:2.8(1.6-4.9,p<0.001)],patients with diarrhea[RR:2.1(1.3-3.5,p=0.004)],altered mental status at presentation[RR:2.0(1.3-3.1,p=0.002)],and the presence of underlying chronic diseases[RR:1.7(1.0-2.8,p=0.04)].

The incidence density calculated for our patients during 10 months of our study period was 48.2 person years (40/0.83 year).

**Conclusion:** In malaria endemic area in Rwanda, a cohort study conducted in 10 months period including all malaria peak seasons in Rwanda, the incidence of AKI was 40%, the incidence density was 48.2 person years. Identified important risk factors were: inability to drink, late referral, concurrent chronic diseases, altered mental status at presentation, hypotension or diarrhea at presentation.



**Keywords**: Malaria, acute kidney injury, plasmodium falciparum

# Chapter I: Introduction

## I.1: Background

Acute kidney injury is a frequent complication of many infectious diseases. Malaria is one of the common infectious diseases in sub-Saharan Africa, and in Rwanda particularly, and it seems to be frequently complicated with acute kidney injury[1].

It is not known how many patients will develop acute kidney injury as a complication of malaria in Rwanda and what the comorbidities that will influence this are. Moreover, elsewhere, a lot of studies have been done many years ago, when the incidence of acute kidney injury in malaria was still low, and most of them were calculating the incidence of AKI(acute kidney injury) in general, not specifically in malaria patients[2].

In the period between Jan. 1995 and Dec. 1999, a study was conducted in India, where MARF (malaria acute renal failure) accounted for 15.5% of all cases of ARF (acute renal failure) hospitalized in the Hemodialysis Unit during this period[3]. There was an alarming rise in the incidence of MARF from 6.66% in 1995 to 27% in 1999[4].A lot of other studies confirmed that this incidence have been increasing recently[5].

No explanation, however, is available for the consistent increase in the incidence of malaria acute renal failure in some areas[6].This study is aimed at determining the incidence of acute kidney injury and associated risk factors in malaria patients in 2 rural district hospitals in Rwanda, during the study period of 10 months.

Many patients will develop acute kidney injury as a complication of malaria, some of these patients may recover completely if well managed, some others will progress to chronic kidney disease, others will have worsening and progression of their chronic kidney disease if they were already having CKD(chronic kidney disease), others will develop acute renal failure requiring renal replacement therapy or die from complications of overt acute renal failure[1].

Patients who have developed acute kidney injury will have worse outcomes comparing to those who didn't, and may stay longer in the hospital and it will increase the cost both for them, the hospital and for the country in general[7].

Risk factors for high mortality include late referral; short acute illness; high parasitemia; and presentation with oliguria, hypotension, severe anemia, or significant jaundice[8].

### I.2: Problem statement

Many patients with Malaria develop renal impairment and it's costly and makes the management of these patients very difficult. There is no data about the incidence of acute kidney injury in malaria patients in Rwanda. This study aimed at determining the incidence of acute kidney injury in malaria patients and factors that are associated with occurrence of AKI.

### I.3: Research hypothesis

There is high incidence of acute kidney injury complicating malaria in Rwanda and different factors seem to play a role.

### I.4: Objectives of the study

#### I.4.a: General objective

To determine the incidence of acute kidney injury and associated factors in patients with malaria presenting at NYAGATARE and NYANZA district hospitals, during the period from April 2018 to January 2019.This is the period that includes all malaria peaks in Rwanda.

#### I.4.b: Specific objectives

-To determine the incidence of AKI in patients with malaria presenting to NYANZA and NYAGATARE district hospitals.

-To determine the factors associated with high incidence of acute kidney injury in malaria patients presenting to NYAGATARE and NYANZA district hospitals.

-To determine the relationship between parasitemia and the development of AKI

## I.5. Research question

What is the incidence and risk factors of acute kidney injury, among patients with malaria in 2 rural district hospitals in RWANDA?

## I.6. Study rationale

Having these results, we will raise awareness to all health facilities treating malaria patients; to recognize people at risk and take preventive measures accordingly. We will also give recommendations of how to prevent acute kidney injury as it is easily preventable, but if already installed, it's very difficult to handle.

## Chapter II: Literature review

### II.1. Definition and profile of Malaria

Malaria is a life-threatening infectious disease caused by plasmodium parasites that are transmitted to human through the bites of infected female Anopheles mosquitoes, Occasionally malaria can be transmitted by blood transfusion, rarely the disease can also be transmitted from a mother to her fetus[9].

It is an acute preventable and curable febrile illness. In a non-immune individual, symptoms usually appear 10–15 days after the infective mosquito bite, this incubation period can extend to 30 days[10]. The shorter incubation periods are observed mostly with *P. falciparum* and the longer ones with *P. malariae*[10].

The first symptoms, including fever, headache, and chills may be mild and difficult to recognize as malaria. A person remains infectious to mosquitoes as long as the parasites are present in his blood. This may take several years if adequate treatment is not given [10].

In *P. vivax* and *P. ovale* infections, patients having recovered from the first episode of illness may suffer from several subsequent relapses after months or even years without symptoms. Relapses occur because *P. vivax* and *P. ovale* have dormant liver stage parasites (hypnozoites) that may reactivate[11].

Children with severe malaria frequently develop one or more of the following symptoms: severe anemia, respiratory distress in relation to metabolic acidosis, or cerebral malaria. In adults, multi-organ involvement is also frequent. In malaria endemic areas, people may develop partial immunity, allowing asymptomatic infections to occur[11]. Travelers to endemic area can develop malaria symptoms a long time after returning to their non-endemic area; this is due to the prophylaxis taken before going to the endemic area. As a consequence, clinicians may not think of malaria initially, as the history is not consistent with the usual natural course of the disease[11].

Malaria is caused by five species of the genus Plasmodium namely, Plasmodium vivax, P. falciparum, P. malariae, P. ovale, and P.knowlesi[12].Plasmodium falciparum is more found in tropical Africa including Rwanda[12]. Common clinical presentations of infection with all five

Plasmodia species are periodic paroxysm of fever, chills, rigors, sweating, body aches, headache, nausea, general weakness and prostration[13].

Severe life threatening complications such as cerebral malaria (CM), severe anemia, acidosis, respiratory distress, jaundice, acute renal failure (ARF), acute respiratory distress syndrome (ARDS), etc…occur mostly with P. falciparum infection[14]. Some population groups are at higher risk of contracting malaria, and developing severe disease, than others. These include infants, children under 5 years of age, pregnant women and patients with HIV/AIDS, as well as non-immune migrants, mobile populations and travelers[13].

Besides Plasmodium falciparum, other species can causes severe complications of malaria, in a study from Karachi, Pakistan, 3 out of 124 cases of malarial ARF had P. vivax infection while the remaining 121 had P. falciparum infection[14]. Recently, life threatening complications with P. knowlesi infection has been reported in humans[13]. Renal involvement has been reported not only in P. falciparum infection ,but also with P. malariae, and recently in P. vivax infections[13]. P. malariae associated nephropathy was reported mainly from Africa. Malarial acute kidney injury is commonly found in non- immune (to malaria) adults and older children with falciparum malaria.

### II.2. Disease burden

According to the latest World malaria report, released in November 2018, there were 219 million cases of malaria in 2017, up from 217 million cases in 2016. The estimated number of malaria deaths stood at 435 000 in 2017.

The World Health Organization African Region continues to carry a high share of the global malaria burden. In 2017, the region was home to 92% of malaria cases and 93% of malaria deaths.

WHO 2019 report reveals that, in 2017, five countries accounted for nearly half of all malaria cases worldwide: Nigeria (25%), the Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%).The 2018 WHO report recognizes an important reduction of malaria burden in Rwanda, with 436,000 fewer Malaria cases recorded in 2017 compared to those of 2016. This reduction is attributed to different strategies taken and they have reduced severe malaria cases by 40% and deaths due to malaria by 43% between 2015 and 2018. Those strategies include: the management of Malaria at community level by community health workers, distribution of long lasting insecticide nets (LLINs) and, Indoor Residual Spraying in high burden areas[15]. From November 2016, people with limited resources access malaria diagnosis and treatment free of

charge to address their financial barriers[15]. Despite that reduction, there is still a lot to do in Rwanda, as there are still many cases of malaria and its complications.

### II.3. Management

Mainstay of treatment consists of appropriate antimalarial drug therapy, fluid replacement, and renal replacement therapy. Loop diuretics can convert an oliguric kidney injury to non-oliguric kidney injury without affecting outcome of the disease though the conversion reduces the risk of volume overload and can indicate patients who are more likely to recover from the renal impairment. Nephrotoxic drugs such as ACE inhibitors, NSAIDs, aminoglycosides, cephalosporins should be avoided as they may accelerate the renal impairment[14].

### II.4. Definition of acute kidney injury

Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function, resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes, it is a syndrome that commonly presents with more than one pathophysiology[16]. The term AKI has largely replaced acute renal failure (ARF), reflecting the recognition that smaller decrements in kidney function that do not result in overt organ failure are of substantial clinical relevance and are associated with increased morbidity and mortality[16].

Several consensus definitions of AKI have been developed in order to provide a uniform definition of AKI. These definitions are based exclusively on the serum creatinine and urine output and are used primarily to identify patients with AKI in epidemiologic and outcome studies. The Kidney Disease Improving Global Outcomes (KDIGO) definition and staging system is the most recent and preferred definition[17]. AKI is defined by KIDGO as any of the following:

1: Increase in Serum creatinin by $\geq$ 0.3 mg/dl ($\geq$ 26.5 µmol/l) within 48 hours; or

2: Increase in Serum creatinin to $\geq$ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or

3: Urine volume<0.5ml/kg/hour for 6 hours.

### II.5.Pathophysiology of acute kidney injury in malaria

The features of acute kidney injury in malaria are not well-known, however; several mechanisms have been hypothesized:

1. Dehydration and hypovolemia can lead to renal hypo perfusion, but this is reversible with adequate rehydration. High-grade fever, profuse sweating, lack of adequate intake, vomiting and diarrhea contribute to dehydration[13].

2. Increase in blood viscosity due to dehydration and hyperparasitemia also results in renal hypo perfusion.

3. Intravascular hemolysis and clogging of the tubules by the products of hemolysis is another important cause for renal dysfunction. Severe falciparum malaria results in hemolysis of parasitized as well as non-parasitized red cells. Although hemoglobin itself is not nephrotoxic, other products of hemolysis can cause acute tubular necrosis, particularly in the presence of dehydration and acidosis.

4. Effect of parasitized RBC on the microcirculation, the entry of parasite into the RBC produces changes in the surface of the parasitized RBC causing formation of knob-like processes, which helps in anchoring the endothelium and adhesion between RBCs[18]. Parasites developing inside red blood cell transport P. falciparum erythrocyte membrane protein 1(pfEMP1) to the red blood cell membrane functioning as a key ligand for cytoadherence .pfEMP1 is expressed on red cell protrusions, or 'knobs', that confer point of attachment to the endothelium[19] .This tight pack of RBCs impedes the microcirculation to various vital organs including the kidney. There occurs cytoadherence due to thrombospondin formation from vascular endothelium. This is specifically seen in P. falciparum and not in other species. Hence, acute kidney injury is seen more in falciparum malaria cases[18].

In addition, there is rigidity of parasitized and non-parasitized red blood cells and clumping of infected red blood cells (platelet mediated auto agglutination) and uninfected red blood cells adhering to infected red blood cells (rosette formation). This inability of parasitized red blood cells to deform according to the need of microcirculation leads to sluggish blood flow and consequently to renal ischemia[19].

5. Non-specific effects of inflammation: There may be leakage of fluid from intravenous compartment due to increased vascular permeability.

6. Intravascular coagulation (DIC) also occurs in some cases.

7. Release of cytokines and NO that result in systemic vasodilatation, this leads to activation of sympathetic nervous system, renin-angiotensin-aldosterone axis, and release of vasopressin for keeping the falling blood pressure. Unfortunately, these compensatory mechanisms continue worsen the renal pathology leading to overt renal failure[13].

8. Hepatic dysfunction in malaria will cause acute kidney injury through hyperbilirubinemia and cast nephropathy[20].

9. AKI can also occur as hepato-renal syndrome in case of remarkable liver failure

10. Hemolytic uremic syndrome has also been observed in malaria, but its mechanism is not yet well understood (high serum levels of cytokines are thought to play a role)[20].

11. Direct effect of plasmodium antigen to the glomeruli causing glomerulonephritis[20].

12. Exaggerated host immune response mediated through cytokines and reactive oxygen and nitrogen species, immune complex deposition to the glomeruli also cause AKI[13].

The above pathophysiology cause kidney injury through different mechanisms including: prerenal azotemia, acute tubular necrosis, acute interstitial nephritis, and glomerulonephritis or rarely, renal cortical necrosis depending on the degree of renal injury[20]. In children, the disease manifests as steroid resistant nephritic syndrome[18].These histologic findings have been described either alone or in a combination.

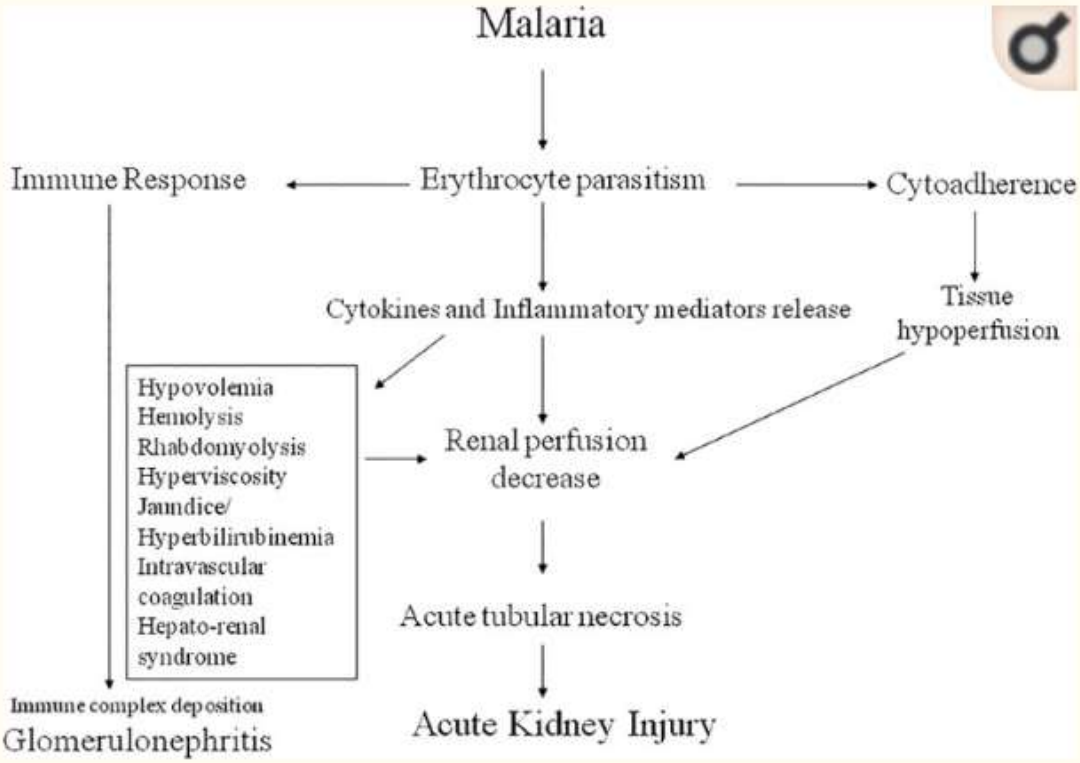


Figure 4

**Pathophysiology of kidney involvement in Malaria**

[20]. (Image courtesy from G. B. Da Silva et.al)

### II.6.Incidence of acute kidney injury in previous researches

Previous researches have shown that acute kidney injury complicates falciparum malaria in less than 1 to 4.8% of native patients in endemic areas, yet it is much more frequent in non-immune Europeans; reported incidence usually is 25 to 30%[18]. Reported contribution of malaria infection to the overall hospital admissions for acute kidney injury varies from 2 to 39%[18].

Note that almost all the previous studies have used the definition of 2006 from world health organization (WHO), defining acute renal failure as increase of serum creatinine to 3mg/dl, this

definition consists of patients who already have criteria for severe malaria. It can miss patients with AKI who don't meet the definition of severe malaria.

These data are from western countries and Asia; our study is giving data on Rwandan population, the definition used for acute kidney injury is by KIDGO, using serum creatinin. Acute kidney injury was defined as increase of serum creatinine by 0.3 mg/dl (26.5µmol/l) or more from the baseline within 48 hours[17]. Using this definition, we were able to detect all cases of AKI, including those who are otherwise fit without any other end organ involvement.

## Chapter III: Methodology

### III.1: Study design

It was an observational analytical prospective cohort study, to determine the incidence and risk factors of acute kidney injury in malaria patients presenting to NYAGATARE and NYANZA district hospitals. These 2 district hospitals are located in malaria endemic areas in east and south Rwanda respectively.

### III.2: Study population

Patients with confirmed malaria by thick, thin smear or rapid serological test, presenting to the above mentioned health facilities who consented for the study.

### III.3: Selection criteria

#### III.3.a: Inclusion criteria

-patients with confirmed malaria by thick or thin smear; or rapid test

-patients who have signed consent

#### III.3.b: exclusion criteria

-Concurrent illnesses (other acute infectious diseases, acute liver failure, acute decompensated heart failure)

-pregnant women

-Pediatric patients (cutoff age was: less than 15 years old)

### III.4: Sampling technique

We used purposive sampling (judgment sampling), which is a non-probability sampling method where a researcher chooses appropriate method according to the objectives of the study[21].We have chosen participants consecutively on the field, on daily basis for 10 months within the period from April 2018 to January 2019.This is the period that includes all malaria peaks in Rwanda. In fact, there are 2 rainy seasons that are; from February to April, and from October to November, sometimes extending into December. Malaria peaks are observed in periods following rainy

seasons that are; may to June and November to December. So this study has included both seasons with malaria peaks.

### III.5: Data collection

A pretested and pre-coded questionnaire was used to obtain the data. We trained nurses to help us in data collection at respective district hospitals. The questionnaire did not reveal the name of participant. In our study, acute kidney injury was defined as increase of serum creatinine by 0.3 mg/dl (26.5µmol/l) or more from the baseline within 48 hours according to KIDGO. Malaria was diagnosed with either thick, thin smear or rapid test.

Hyperparasitemia was defined as results expressed with 3+ or 4+ on malaria smear, note that parasites count is not expressed quantitatively(in number of parasites per microliter of blood) in the district hospitals where our study was conducted, rather a qualitative method is used. The number 4+ means that the technician has counted 100 and more malaria parasites per field, the number 3+ means 30-99 parasites per field, the number 2+ corresponds with 11 to 29 malaria parasites per field, and finally 1+ indicating parasites less than 10 in 1 field. The technician has to read 100 fields on 1 sample, meaning that 10 parasites per field corresponds to 100 parasites in the whole sample.

The commonest method used in many centers is the method where parasites are counted on a thick film. Parasites are counted with white blood cells (WBCs), when the technician has counted 200 white blood cells, he stops to count and reports the number of parasitized red blood cells per 200 white blood cells. To calculate the parasite density, we consider a whole thick film as containing 8000 WBCs and do the calculation using the formula below[22]:

$$Parasites/\mu\mathbf{l} = \frac{\text{No of parasitized red cells } \times 8000 \text{ WBCs}/\mu\mathbf{l}}{\text{No WBCs counted}}$$

The technician decides when to stop counting by following these rules: If he has counted ≥ 100 parasites in 200 white blood cells, he stops counting, and records the results as the number of parasites per 200 white blood cells. If he has counted ≤ 99 parasites in 500 white blood cells, he stops counting, and records the results as the number of parasites per 500 white blood cells[22].

We enrolled all patients presenting with malaria to NYAGATARE and NYANZA district hospitals. Every patient presenting to these health facilities with suspicion of malaria, blood sample was collected for creatinine; after fulfilling the inclusion criteria and sign consent. The samples were analyzed by laboratory technologist at the district hospital. Creatinin was measured twice within the 1rst week of presentation to the hospital with the interval of at least 48 hours between 2 measurements. The researcher was doing follow-up of the results. Patients with an increase in serum creatinin of 0.3mg/dl (26.5µmol/l) or more from baseline within 48 hours were considered as having acute kidney injury. Data were stored in a secure cupboard.

Every patient who was found to have increased creatinine, was called by the principal investigator to be followed up for the renal impairment at the district hospital by the hospital treating team, and if needed ,they were transferred to CHUK or RMH accordingly through normal referral system regardless whether he/she is included in the study or not. The principal investigator was responsible to reintroduce the patient in the system and present him/her to the treating team for appropriate management of the acute kidney injury.

### III.6: Data analysis and management

Data were collected using a well-structured and pre-checked questionnaire and entered in Epidata version 3.1 then exported to IBM SPSS statistics version 25. Logistic regression was used to compare the presumed risk factors of AKI where the Relative risk was used as a measure of associations to measure the risk of developing AKI in groups for categorical variables and Mann Whitney U test was used to measure the association between continuous variables and the risk of developing AKI. The statistically significance of associations (significance level) was set at P value $<0.05$.

## III.7. Ethical consideration

Approval to conduct the study was sought from the School of Medicine, Research and Ethics Committee of University of Rwanda; as well as from the health facilities involved in the study.

Written informed consent was signed from participant patients or care takers of all the study participant patients, management of the patient who did not consent was not affected and the participants had the freedom to withdraw from the study at any point and there was no any consequence to them.

## Chapter IV. Results and interpretation

A total of 100 participants met the inclusion criteria and enrolled from Nyagatare and Nyanza district hospitals according to the flow chart below.

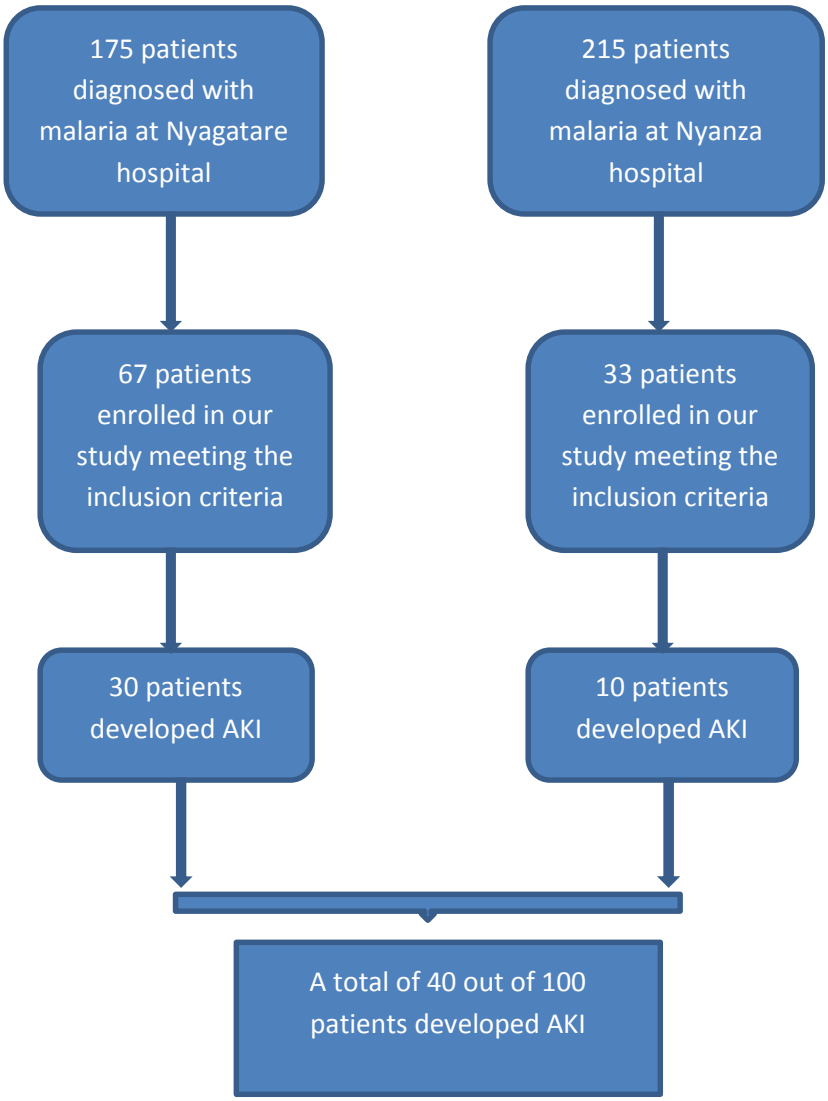

**Table 1 : Risk of developing AKI according to sociodemographic characteristics**

| characteristics | | AKI | | RR (95% CI) | P value |
|---|---|---|---|---|---|
| | | Yes | No | | |
| Age in years | Median (Min-Max) | 26.5 (15-74) | 22.5 (15-70) | - | 0.104 |
| Age categories | ≤65 years | 37 (39.4%) | 57 (60.6%) | 1.2 (0.5-2.9) | 0.576 |
| | >65 years | 3 (50.0%) | 3 (50.0%) | | |
| Gender | Male | 26 (49.1%) | 27 (50.9%) | 1.6 (0.9-2.9) | 0.058 |
| | Female | 14 (29.8%) | 33 (70.2%) | | |
| Home address | Nyagatare | 30 (44.8%) | 37 (55.2%) | 1.4 (0.8-2.6) | 0.188 |
| | Nyanza | 10 (30.3%) | 23 (69.7%) | | |

*AKI: acute kidney injury; RR: relative risk; CI: confidence interval*

Elderly people were prone to develop AKI (RR=1.2 and 95%CI: 0.5, 2.9 with p=0.576) but we can't conclude based on this, as elderly people were only 6 in our study (half developed AKI, half didn't) and the p value is not really significant. In general, our population was younger, as we see the median age is around 25 years of age. This is due to the life expectancy that is still low in Rwanda, and the majority of the population is the youth. Male patients were more affected than females (RR=1.6 and 95% CI: 0.9, 2.9 with p=0.058).Note that there is no statistically significant difference among these sociodemographic parameters. There is no statistically significant difference between the incidence of AKI in NYANZA and NYAGATARE

**Table 2: Observed overall incidence of AKI in malaria patients**

| Serum creatinine (mg/dl) | AKI | | P value |
|---|---|---|---|
| | Yes (n=40) | No (n=60) | |
| Baseline creatinine [Median (Min-Max)] | 0.8 (0.7,16) | 0.7 (0.5,3.3) | <0.001 |
| Repeat creatinine [Median (Min-Max)] | 1.45 (1,16) | 0.8 (0.2,3.4) | <0.001 |
| **Incidence of AKI** | **40/100=0.4 (40%)** | | |

The observed overall incidence of AKI was 40%. The median repeat creatinine was 1.45 mg/dl in group who developed AKI compared to 0.8 mg/dl in the group who didn't develop AKI (Mann Whitney U test used, with p <0.001). The incidence density calculated for our patients during 10 months of our study period was 48.2 person years (40/0.83 year).

The total number of patients diagnosed with malaria at Ntagatare hospital during the period of our research was 175(total number of patients at risk) and among them, 30 patients developed AKI. Calculated incidence of developing AKI in Nyagatare hospital, the denominator being all patients diagnosed with malaria positive was 0.17 (17%). The total number of patients diagnosed with malaria at Nyanza hospital was 215 and among them 10 patients developed AKI. Calculated incidence of developing AKI in Nyanza hospital was 0.046 (4.6%).

**Table 3 : Relationship between clinical presentation and developing AKI**

| Signs and symptoms | | AKI | | RR (95% CI) | P value |
|---|---|---|---|---|---|
| | | Yes | No | | |
| Inability to drink | Yes | 21 (61.8%) | 13 (38.2%) | 2.8 (1.6-4.9) | <0.001 |
| | No | 19 (28.8%) | 47 (71.2%) | | |
| Urine reduced in amount | Yes | 13 (76.5%) | 4 (23.5%) | 2.3 (1.5-3.5) | <0.001 |
| | No | 27 (32.5%) | 56 (67.5%) | | |
| Diarrhea | Yes | 4 (80.0%) | 1 (20.0%) | 2.1 (1.3-3.5) | 0.004 |
| | No | 36 (37.9%) | 59 (62.1%) | | |
| Altered mental status | Yes | 16 (64.0%) | 9 (36.0%) | 2.0 (1.3-3.1) | 0.002 |
| | No | 24 (32.0%) | 51 (68.0%) | | |
| Hypotension | Yes | 11 (61.1%) | 7 (38.9%) | 1.7 (1.1-2.7) | 0.022 |
| | No | 29 (35.4%) | 53 (64.6%) | | |
| Vomiting | Yes | 24 (49.0%) | 25 (51.0%) | 1.6 (0.9-2.6) | 0.065 |
| | No | 16 (31.4%) | 35 (68.6%) | | |
| Cough | Yes | 13 (56.5%) | 10 (43.5%) | 1.6 (1.0-2.5) | 0.046 |
| | No | 27 (35.1%) | 50 (64.9%) | | |
| Difficult of breathing | Yes | 6 (54.5%) | 5 (45.5%) | 1.4 (0.8-2.6) | 0.245 |
| | No | 34 (38.2%) | 55 (61.8%) | | |
| Seizures | Yes | 5 (45.5%) | 6 (54.5%) | 1.15 (0.6-2.3) | 0.683 |
| | No | 35 (39.3%) | 54 (60.7%) | | |

*AKI: acute kidney injury; RR: relative risk; CI: confidence interval*

Inability to drink was a risk to development of AKI (RR=2.8 and 95% CI: 1.6, 4.9 with p<0.001)

Diarrhea was associated with the development of AKI (RR: 2.1 and 95%CI: 1.3, 3.5and p=0.004).Hypotension was a risk for AKI (RR: 1.7 and 95%CI: 1.1, 2.7 and p=0.022).Altered mental status was also an important risk factor (RR: 2with 95%CI: 1.3, 3.1 and p=0.002).All of these factors are potent as we see that their association with AKI is statistically significant.

**Table 4: Relationship between different clinical characteristics and the development of AKI**

| | | AKI | | RR (95% CI) | P value |
|---|---|---|---|---|---|
| | | Yes | No | | |
| Onset of symptoms | ≤3 days | 17 (27.9%) | 44 (72.1%) | 2.1 (1.3-3.4) | 0.002 |
| | >3 days | 23 (59.0%) | 16 (41.0%) | | |
| Any chronic disease | Yes | 8 (61.5%) | 5 (38.5%) | 1.7 (1.0-2.8) | 0.048 |
| | No | 32 (36.8%) | 55 (63.2%) | | |
| IVF given before sample collection | Yes | 25 (43.9%) | 32 (56.1%) | 1.2 (0.7-2.1) | 0.372 |
| | No | 15 (34.9%) | 28 (65.1%) | | |
| Parasitemia quantification | Low | 24 (37.5%) | 40 (62.5%) | 1.1 (0.7-1.9) | 0.49 |
| | High | 16 (44.4%) | 20 (55.6%) | | |
| Gentamycin given | Yes | 1 (16.7%) | 5 (83.3%) | 0.4 (0.06-2.4) | 0.322 |
| | No | 39 (41.5%) | 55 (58.5%) | | |
| NSAIDs given during illness | Yes | 0 (0.0%) | 3 (100%) | 0.3 (0.02-4.1) | 0.368 |
| | No | 40 (41.2%) | 57 (58.8%) | | |

*AKI: acute kidney injury; RR: relative risk; CI: confidence interval; IVF: intravenous fluid; NSAIDS: nonsteroidal anti-inflammatory drugs.*

Patients who presented late were more likely to get AKI RR: 2.1[95%CI: 1.3-3.4 and p=0.002].

Rehydration was not found to reduce risk of developing AKI, but there was no quantification of the amount of fluid given, some of the patients were under hydrated, we also note that, some patients were sampled just at the beginning of IVF.

People with chronic diseases were at risk of AKI with RR: 1.7 [95%CI: 1.0-2.8 and p=0.048].

Only 3 patients were given NSAIDS before sample collection, none of them developed AKI.

6 patients were given gentamycin, one of them developed AKI, but its association with the incidence of AKI is not statistically significant. Parasitemia was not associated with the development of AKI

**Table 5: Final model on the predictors of AKI among study participants**

| Signs and symptoms | | AKI | | Adjusted RR (95% CI) | P value |
|---|---|---|---|---|---|
| | | Yes | No | | |
| Inability to drink | Yes | 21 (61.8%) | 13 (38.2%) | | |
| | No | 19 (28.8%) | 47 (71.2%) | 0.34 (0.14-0.87) | 0.025 |
| Urine reduced in amount | Yes | 13 (76.5%) | 4 (23.5%) | 4.6 (1.3-16.4) | 0.018 |
| | No | 27 (32.5%) | 56 (67.5%) | | |

From the multivariable analysis model, inability to drink and reduced urine amount were found to be the significant predictors in developing acute kidney injury.

## Chapter V. Discussion

We extended upon previous epidemiological studies, confirming the high and continuously increasing incidence of acute kidney injury in malaria patients[4], [5]. The overall incidence of AKI in our study population from NYANZA and NYAGATARE district hospitals during the study period of 10 months was 40% that coincides with the findings in a study done in 2015 by Liese C.Koopmans et al and was published in malaria journal [23] .

The highest incidence of AKI was found in NYAGATARE patients where the incidence was 30% ,while that of NYANZA patients was 10%;but there is no statistically significant difference between the two figures across those 2 population RR:1.4[95%CI:0.8-2.6,p=0.18].We identified a spectrum of factors that are associated with high incidence in AKI, including the inability of the patients to drink, oliguria at presentation, cerebral and lung involvement, late consultation, concomitant chronic diseases(Diabetes mellitus, or Chronic hypertension), and hemodynamic instability at presentation.

Furthermore, the relative risks vary across those factors. Our study found same association between hypotension and occurrence of AKI as found in a study done by J Prakash et al[4].Older age influenced the occurrence of AKI in our study as it was found in a study done in America in 2014 by kavitha saravu et al[24]. But in another study from India by J. Prakash et.al published in 2002, there was no significant difference considering age as a risk of developing AKI[4].

From our study, findings concerning age categories and the development of AKI were not powerful to conclude on that as a separate risk factor, as median age in people with AKI was almost the same as in people without AKI (26.5 versus 22.5)and the p value was not significant(p=0.104). Furthermore, we only analyzed 6 elderly patients with more than 65 years of age, and a half developed AKI with a half being safe(i.e:3 patients with AKI and 3 patients without AKI) ,again the p value was not significant(p=0.57). Considering the above 2 conflicting studies, one from India, another from America, older age is not considered as really a risk factor for the development of AKI.

Being a male was a risk of developing AKI in our study, with almost a half of male patients with malaria developing AKI(49.1% versus 50.9%),this was not the same finding in a study by J. Prakash et.al[4]. Oliguria, diarrhea and pulmonary involvement were found to be risks for AKI, which coincides with the findings in a study done by RACHAD S.BARSUM and was published

in journal of American society of nephrology in 2000[18]. Late referral or late consultation was found to be a risk for the development of AKI as in the study done by J. Prakash et .al 2002[4].

In our study, heavy parasitemia was not found to be a risk factor for developing acute kidney injury, contrary to a study done in India in 1996 by J. Prakash et .al ,where hyperparasitemia among other factors influenced the development of AKI in 30.8% of patients[3]. In the cited study, heavy parasitemia was thought to induce AKI by causing renal ischemia through blood viscosity. Our study didn't find the same association most probably due to the definition of heavy parasitemia used.

In our study, heavy parasitemia was defined as any parasite count expressed by 3+ and above. Note that this is a qualitative method which is an estimation that categorizes parasitemia according to how many parasitized red blood cells the technician has seen on a field, it is not a fixed number, it is a range, meaning that one expression can mean different parasites load. Parasite density counting should not be generalized, every endemic area should have its own definition. All of this also depends on the experience of the technician.

We also note that, what is called heavy parasitemia in our study, may be a normal parasitemia especially in malaria endemic areas, where it requires a high number of parasites to define hyperparasitemia (around 250 000 parasites per $mm^3$). All of these make our parasite density counting not accurate and may be the reason to find different findings from the previous studies.

These observations are important because the prevention and management of AKI will depend on individual risk factor, and the emphasis in prevention and aggressive management will be directed toward the most powerful risk factor.

## Chapter VI. Conclusion

We studied 100 consecutive patients diagnosed with malaria in a 10 months period. AKI occurred in 40(40%) of patients with confirmed malaria. The incidence density calculated for our patients during 10 months of our study period was 48.2 person years (40/0.83 year). Significant contributing factors to the development of AKI were; inability to drink, malaria complicated with diarrhea, late consultation (more than 3 days of symptoms onset), concurrent chronic diseases (i.e. Diabetes mellitus, hypertension), severe malaria presenting with other end organ damage (i.e.: altered mental status, hypotension, and pulmonary involvement with cough). Inability to drink and reduced urine amount were found to be the most significant predictors of AKI. High Parasitemia was not found to influence the occurrence of AKI in this study.

## Chapter VII. Recommendation

Our recommendations go to the ministry of health and Rwanda biomedical center, to recognize the high incidence of acute kidney injury among malaria patients, recognizing that late referral, poor fluid resuscitation have been independent risk factors of AKI. Strict guidelines should be elaborated addressing all levels of health care from the community, where community health workers should recognize early, patients who are unable to drink and feed, patients who are very weak and be transferred quickly to the health post or health center.

People at health center should know to take a good history and start adequate fluid resuscitation even before transfer to the district hospital, aggressive fluid resuscitation for patients who are unable to feed orally, those with diarrhea and/or vomiting.

Doctors at district hospital should continue fluid resuscitation, monitoring input and output as well as serum creatinine and electrolytes where possible. They should recognize early, patients who are developing oliguria, anuria and/or edema, cough and/or lung crackles following adequate fluid resuscitation. These are patients who are probably developing acute kidney injury and possibly going into acute tubular necrosis. They should be transferred without delay to a center with the possibility of renal replacement therapy as they may need it soon.

Lastly, the general population should be sensitized through media: Radio, television, newspapers, and during their meeting after "UMUGANDA". They should be instructed about common symptoms of malaria, and they should be sensitized to consult early as they develop those symptoms, as late consultation has been shown to be a risk factor for acute kidney injury. Further studies should be done at population level in the community, to calculate the incidence based on the total population at risk.

## Chapter VIII .Study limitations

We described patients who developed acute kidney injury in the hospital setting but did not describe those patients who had already developed renal impairment from any cause prior to hospital admission or consultation. We note that the subsequent course of these patients may be variable, with some patients improving and others exhibiting additional increases in serum creatinine and eventually progress to chronic kidney disease, but no follow-up done for those patients due to budget issue. However, we helped patients with AKI to get in the health system that will manage them.

Our data originating from few medical centers, extrapolation to the entire Rwandan population should be made with caution. There was no detailed information on the care received prior to the hospital presentation (for example, from health center, community health workers,…)[7].Due to budget limitation again, no urinalysis was done for those patients, no renal biopsy, so we couldn't differentiate clearly Renal impairment caused by malaria infection from that caused by medications and other insults, though malaria itself is associated with different mechanisms in kidney injury.

We also note that cases that come to the district hospital are already cases of complicated malaria, most simple malaria cases being treated at the level of health centers, with the exception of people using other insurances than "community health insurance" who can bypass the health center and consult immediately the hospital without transfer.

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## ANNEXES

### Annex 1. Data collection tool

QUESTIONNAIRE FOR INCIDENCE AND RISK FACTORS OF ACUTE KIDNEY INJURY IN MALARIA

Questionnaire

1. Identification

a. Numeric number..... Initials: .....

b. IP number.....

C. Date of enrolment.....

2. Social Demographics

a. AGE (years).....

b. SEX 1.M..... 2.F.....

Marital status:

Length of stay in the hospital or any other health facility if applicable:

-Home address.....

-Sector.....

Referral status; ……..

Telephone contacts 1.....

3. Presenting complaints and findings on exam:

1. Fever [ ] yes [ ] No. Seizures [ ] yes [ ] no.

2. Present hypotension SBP<90mmHg [ ] yes [ ] no

3. Altered mental status [ ] yes [ ] no.

4. Cough [ ] yes [ ] No. Difficulty in breathing [ ] yes [ ] no.

5. Passing tea colored urine [ ] yes [ ] no.

6. Urine amount reduced [ ] yes [ ] no

7. Able to drink [ ] yes [ ] no. Vomiting [ ] yes [ ] no. Diarrhea [ ] yes [ ] no.

8. Yellow discoloration of eyes [ ] yes [ ] No. Flank pain [ ] yes [ ] no.

9. Onset of symptoms [ ] less than 3 days, [ ] more than 3 days ago.

10 .Able to feed orally [ ] yes [ ] no

11. Has pitting edema [ ] yes [ ] no

4. past medical history;

Intravenous fluid given before sample collection [ ] yes [ ] no

NSAIDs given during this illness [ ] yes [ ] no. Gentamycin given [ ] yes [ ] no.

Any chronic disease [ ] yes [ ] no

History of hospitalization in the past [ ] yes [ ] no

5. Laboratory findings:

Serum creatinine----------

parasitemia high[ ]low[ ]

## Annex 2. Informed consent form (English version)

DUFATANYE Erhard is carrying out a study, to determine the incidence of acute renal failure in malaria. This study will look at how many patients, who have malaria, will develop acute renal failure as a consequence of the malaria infection.

You are invited to participate in this study by giving blood on a voluntary basis, but no more than twice within a week and it will be enough for the study.

All blood draws will be performed by qualified technicians at the hospital, few mls of blood will be withdrawn from a vein in your arm.

During the collection of blood, you may experience discomfort and bruising at the site of collection .To minimize these risks, you will be asked to be down while an experienced technician collects the blood sample. You may feel light-headed after having blood drawn. If you feel faint, you should not get up and should notify a nurse.

Although you will not be given money for the study, you will make a major contribution to the information known about acute renal failure in malaria in the future. Others may benefit because we will know the burden malaria can cause and raise awareness including advocacy to the Ministry of Health and RBC, so that appropriate preventive measures can be taken to save a lot of lives and money in the future. In other hand, you may benefit because we may discover your kidney impairment and advise you and your treating medical team, to follow up your disease and if needed, to be transferred to the tertiary level.

A research assistant will keep a record of all blood draws in a secure database. Only the professional staff at the hospital will know the identity of study participants.

Your signature on this form means that you understand the information presented, and that you want to participate in the study, you understand that participation is voluntary and you may withdraw from the study at any time.

N.B: You have all the rights to refuse the participation in this study, without any condemnation either about your treatment here or any other consequence. Even after enrollment, you also have right to withdraw your consent at any point without any consequence.

_____

Signature of participant

Contact information for DUFATANYE Erhard

Email:erhardufatanye@gmail.com

Cell phone: 0786686820

In case of any concern about the study, feel free to contact the UR/CMHS ethics committee:

Chairperson of the CMHS IRB: 0788490522

Deputy Chairperson: 0783 340 040

## Annex 3. Informed consent form (Kinyarwanda version)

Kwemera gukorerwaho ubushakashatsi

Muganga DUFATANYE Erhard arimo gukora ubushakashatsi,kureba abantu bangirika impyiko biturutse ku burwayi bwa malaria.

Tukaba tugusaba ngo ube muri bamwe bakorerwaho ubushakashatsi,turagufata amaraso tujye kuyapima turebe uko impyiko zawe zikora.Birasaba kuzagufata amaraso inshuro ebyiri mu cyumweru kugirango tubashe kubona amakuru akenewe.Ibi ni ku bushake bwawe,ntabwo utegetswe kuza muri ubu bushakashatsi.

Amaraso azajya afatwa n'umukozi ubifitiye ubushobozi n'uburambe,azajya afatwa mu mutsi hakurwemo nka mililitiro 100.

Ushobora kumva ububabare mu gihe bagufata amaraso,ushobora no kubona amaraso akomeje kuva aho bateye urushinge cyangwa akipfundika(imfunira).kugirango twirindi ibi bivuzwe haruguru,urasabwa kuba uryamye igihe bagufata amaraso.Ushobora kumva isereri nyuma yo gufatwa amaraso,icyo gihe uzirinda kubyuka,hanyuma ubimenyeshe umuforomo.

Nubwo nta gihembo uzabona kubera ubu bushakashatsi;uzaba ufashije cyane kuko amakuru azava muri ubu bushakashatsi azadufasha kumenya umutwaro uburwayi bwa malariya bushobora guteza,cyane cyane mu kwangiza impyiko.Ibi bizatuma dukora ubuvugizi mu nzego bireba nka Minisiteri y'ubuzima ndetse n'ikigo cy'igihugu cy'ubuzima,kugirango hafatwe ingamba zo kwirinda ko malariya yakwangiza impyiko.

Ariko kandi,igihe twasanga impyiko zawe zangiritse,twakumenyesha ndetse tugasaba n'abaganga bagukurikirana ko bakwita kuri icyo kibazo,byaba na ngombwa bakaba bakwohereza ku bitaro bifite ubushobozi bwisumbuye .

Amaraso tuzaba twagufashe azajya apimwa n'abakozi b'ibitaro babishinzwe,nta handi azajyanwa.Nta n'undi muntu uzamenya ibijyanye n'ibizamini twagukoreye kuko ni ibanga hagati yawe n'abaganga.

Niba wemeye gukorerwaho ubu ubushakashatsi,urasinya kuri uru rupapuro,bivuga ko wasobanukiwe neza ibijyanye n'ubu bushakashatsi,ko winjiyemo ku bushake bwawe nta gahato, kandi ko nta gihembo uzahabwa.Igihe cyose waba utagishaka gukomeza muri ubu bushakashatsi,wabitumenyesha tukagukuramo,kandi nta ngaruka n'imwe bizakugiraho.

*Icyitonderwa:* ufite uburenganzira busesuye bwo kwanga gukorerwaho ubu bushakashatsi,kandi ibyo nta ngaruka n'imwe byakugiraho haba mu bijyanye n'uburyo uzavurwa cyangwa indi ngaruka iyo ariyo yose.Igihe kandi waba wabyemeye,wagera nyuma ugashaka kwisubiraho,ufite uburenganzira bwo kuvamo kandi nabwo nta ngaruka n'imwe byakugiraho.

umukono w'ukorerwaho ubushakashatsi

Ukora ubushakashatsi DUFATANYE Erhard

Email:erhardufatanye@gmail.com

Telefoni: 0786686820

Ugize ikibazo muri ubu bushakashatsi, wahamagara Uhagarariye iby'ubushakashatsi muri Kaminuza y'u Rwanda

Kuri tel: 078849052/0783340 040

## Annexe 4.IRB Approval

UNIVERSITY OF RWANDA — COLLEGE OF MEDICINE AND HEALTH SCIENCES

*CMHS INSTITUTIONAL REVIEW BOARD (IRB)*

Kigali, 3rd /04/2018

**Dr DUFATANYE Erhard**
**School of Medicine and Pharmacy, CMHS, UR**

**Approval Notice: No 075 /CMHS IRB/2018**

Your Project Title ***"Incidence Of Acute Renal Failure In Malaria Patients; Case Of Nyagatare And Nyanza District Hospitals"*** has been evaluated by CMHS Institutional Review Board.

| | | Involved in the decision | | |
|---|---|---|---|---|
| | | | No ( Reason) | |
| **Name of Members** | **Institute** | Yes | **Absent** | **Withdrawn from the proceeding** |
| Prof Kato J. Njunwa | UR-CMHS | | X | |
| Prof Jean Bosco Gahutu | UR-CMHS | X | | |
| Dr Brenda Asiimwe-Kateera | UR-CMHS | X | | |
| Prof Ntaganira Joseph | UR-CMHS | X | | |
| Dr Tumusiime K. David | UR-CMHS | X | | |
| Dr Kayonga N. Egide | UR-CMHS | X | | |
| Mr Kanyoni Maurice | UR-CMHS | X | | |
| Prof Munyanshongore Cyprien | UR-CMHS | X | | |
| Mrs Ruzindana Landrine | Kicukiro district | | X | |
| Dr Gishoma Darius | UR-CMHS | X | | |
| Dr Donatilla Mukamana | UR-CMHS | X | | |
| Prof Kyamanywa Patrick | UR-CMHS | | X | |
| Prof Condo Umutesi Jeannine | UR-CMHS | | X | |
| Dr Nyirazinyoye Laetitia | UR-CMHS | X | | |
| Dr Nkeramihigo Emmanuel | UR-CMHS | X | | |
| Sr Maliboli Marie Josee | CHUK | X | | |
| Dr Mudenge Charles | Centre Psycho-Social | X | | |

After reviewing your protocol during the IRB meeting of where quorum was met on 23rd March 2018, **Approval has been granted to your study.**

EMAIL: researchcenter@ur.ac.rw P.O. Box: 3286, Kigali, Rwanda WEBSITE: http://cmhs.ur.ac.rw/ www.ur.ac.rw

Please note that approval of the protocol and consent form is valid for **12 months**.

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 3rd April 2018

Expiration date: The 3rd April 2019

Professor Kato J. NJUNWA
**Chairperson Institutional Review Board,**
**College of Medicine and Health Sciences, UR**

Prof. JB Gahutu
Vice Chair

**Cc:**

- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR