PREVALENCE OF URINARY TRACT INFECTIONS, ASSOCIATED FACTORS, AND ANTIMICROBIAL SUSCEPTIBILITY PATTERNS OF THE UROPATHOGENS ISOLATED FROM HEART FAILURE PATIENTS ON SODIUM-GLUCOSE TRANSPORTER 2 INHIBITORS AT JAKAYA KIKWETE CARDIAC INSTITUTE.

Julieth Michael Kaaya, B. Pharm

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Department of Clinical Pharmacy and Pharmacology

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By

Julieth Michael Kaaya

A Dissertation Submitted in (Partial) Fulfillment of Requirement for the Degree of Master of Hospital and Clinical Pharmacy of

Muhimbili University of Health and Allied Sciences
October, 2024

CERTIFICATION

The undersigned certifies that they have read and hereby recommends for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled; **"Prevalence of Urinary Tract Infections, Associated Factors, and Antimicrobial Susceptibility Patterns of the Uropathogens Isolated from Heart Failure Patients on Sodium-glucose Transporter 2 Inhibitors at Jakaya Kikwete Cardiac Institute"** in (partial) fulfillment of the requirements for the Degree of Master of Pharmacy (Hospital and Clinical Pharmacy) of Muhimbili University of Health and Allied Sciences.

_____

Dr. Ritah Mutagonda

(Supervisor)

Date: _____

_____

Dr. Deus Buma

(Co-Supervisor)

Date: _____

_____

Hamu Mlyuka

(Co-Supervisor)

Date: _____

DECLARATION AND COPYRIGHT

I, **Julieth Michael Kaaya**, declare that this **dissertation** is my original work. It has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature…… **Date**……

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DEDICATION

To my beloved son Meshack Gervas, my mother Emily Samson, my aunt Anande Samson, my grandmother Ngasalia, my brothers, and Millambo's family.

ABSTRACT

Background: Urinary tract infections (UTIs) are among the most encountered infectious diseases, with a global incidence of at least 150 million annually. UTI can occur because of a variety of risk factors, including the administration of certain drugs. Sodium-glucose transporter 2 inhibitors (SGLT2i) have recently emerged as a standard therapy for heart failure patients, and evidence has shown the drug to confer mortality benefits and reduce hospital readmission. Despite its undeniable benefits, previous studies have reported an association between SGLT2 inhibitors and a high risk of UTI. The management of UTI can be complicated due to the resistance of the uropathogens towards the commonly used antibiotics. Therefore, urgent information is required on the prevalence of UTIs among patients using SGLT2 inhibitors and the antibiotic susceptibility pattern of the isolated uropathogens.

Broad objective: This study aimed to investigate the prevalence of UTI, associated factors and evaluate the antimicrobial susceptibility patterns of the isolated uropathogens among heart failure patients using SGLT2 inhibitors at Jakaya Kikwete Cardiac Institute (JKCI).

Methodology: This cross-sectional study was conducted among heart failure patients using SGLT2 inhibitors at JKCI. A structured questionnaire was used to collect participant socio-demographic characteristics, and a case report form was used to record medical and medication history, together with laboratory result data. UTI was defined by positive cultures with significant bacteriuria of $\geq 10^5$ CFU/ml as a gold standard, and urinalysis parameters including pyuria, and positive or negative nitrites. Antimicrobial susceptibility test (AST) was performed for the isolated uropathogens using the Kirby Bauer disc diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines and susceptibility patterns were recorded based on tested antibiotics, Statistical data analysis was performed by Statistical Product and Service Solution (SPSS) software version 26 (IBM SPSS Statistics, IBM Corp, Armonk, NY, USA). For analytical statistics, univariable and multivariable as well as Poisson robust regression models were used to assess the association between positive UTI and the risk factors such as age, sex, comorbidities, previous history of UTI, type of SGLT2 inhibitor, and duration of use of SGLT2 inhibitors. Moreover, the Pearson Chi-square test was also used to

establish an association. The 95% confidence intervals were obtained, and p values <0.05 were considered statistically significant.

Results: Out of 141 patients, more than half were males (55.3%) and individuals aged ≤60 years (53.9%). Empagliflozin (53.2%) and dapagliflozin (46.8%) were the main SGLT2 inhibitors used, with most patients using them for less than 4 months (87.0%). The prevalence of UTI among study participants was 15.6%. Compared to the culture and sensitivity test used for diagnosis, urinalysis showed a high sensitivity (100%) and lower positive predictive value (46.8%). Advanced age (>60 years) significantly increased UTI risk (aPR 3.77, 95% CI: 1.42-10.01), also the female sex (aPR 2.92, 95% CI: 1.19-7.15) was a risk for UTI. Moreover, a longer duration of SGLT2 inhibitor use (≥4 months) was also associated with a higher likelihood of UTI (aPR 3.19, 95% CI: 1.70-5.96). Uropathogens isolated included *Escherichia coli* (50%), *Klebsiella pneumoniae* (13.6%), *Klebsiella oxytoca* (9.1%), *Pseudomonas aeruginosa* (9.1%), *Candida spp* (9.1%), *Staphylococcus aureus* (4.5%), *Staphylococcus saprophyticus* (4.5%). High resistance of the uropathogens was noted for Ampicillin (99.9%), Tetracycline (69.2%), Ceftazidime (53.8%), Ceftriaxone (46.2%), and Gentamicin (46.2%). In contrast, the uropathogens were more susceptible to Nitrofurantoin (84.6%) and Meropenem (100%).

Conclusion: This study has shown UTIs are prevalent by 15.6% among heart failure patients who were on SGLT2 inhibitors This study highlights significant socio-demographic and clinical factors associated with UTIs among heart failure patients using SGLT2 inhibitors. Advanced age, female sex, prolonged medication use, and post-menopausal status are key risk factors. Commonly isolated uropathogens included *Escherichia coli*, *Klebsiella* spp, *Pseudomonas aeruginosa*, *Staphylococcus* spp, and *Candida* spp. The bacterial uropathogens were highly resistant to Ampicillin, Tetracycline, Ceftazidime, Ceftriaxone, and gentamicin. While more susceptible to Nitrofurantoin and Meropenem. These study's findings therefore inform clinical practice and show the importance of targeted monitoring and preventive strategies to mitigate UTI risk in this vulnerable population. Continued research and clinical vigilance are essential to optimize heart failure patient management on SGLT2 inhibitors and reduce the burden of UTIs.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AMR	Antimicrobial Resistance
CFU	Colony Forming Unit
CLSI	Clinical and Laboratory Standards Institute
CPL	Central Pathology Laboratory
DAPA-HF Trial	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DELIVER Trial	Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure
EMPEROR Reduced Trial	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction
EMPEROR Preserved Trial	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction
HF	Heart failure
HFmrEF	Heart Failure with mildly reduced Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HPF	High power field
JKCI	Jakaya Kikwete Cardiac Institute
NYHA	New York Heart Association
RCTs	Randomized Clinical Trials
SGLT2i	Sodium-glucose cotransporter 2 Inhibitor
TMDA	Tanzania Medicines and Medical Devices Authority
UPEC	Uropathogenic Escherichia coli
UTI	Urinary Tract Infections

DEFINITION OF KEY TERMS

Antimicrobial Susceptibility Test (AST)	Is an in vitro measure to assess the likelihood that a particular antimicrobial agent will treat an infection caused by a particular organism.
Class 1 of recommendation	Evident and general agreement that a given treatment or procedure is beneficial, useful, effective (is recommended or is indicated)
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Heart Failure (HF)	HF is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood.
Urinary Tract Infections (UTIs)	Is an infection in any part of your urinary system: kidneys, bladder, ureters, and urethra.
Uropathogens	Microorganisms that can cause Urinary tract infection
Sensitivity	The ability of a test to correctly identify patients with a disease.
Specificity	The ability of a test to correctly identify people without the disease
True positive	The person has the disease, and the test is positive.
True negative	The person does not have the disease, and the test is negative.
False positive	The person does not have the disease, and the test is positive.
False-negative	The person has the disease, and the test is negative.
Positive predictive value	It is a measure of how often someone tests positive for the disease and truly has the disease.
Negative predictive value	It is a measure of how often someone who tests negative for the disease does not have the disease.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Urinary tract Infections (UTIs) are among the common infectious diseases that are mostly encountered in developing countries, with an estimated incidence of 150million people per year globally (1).UTI is described as the presence of microbial pathogens in the urinary tract that can be symptomatic or asymptomatic. Clinically, UTIs can be categorized as complicated and uncomplicated. An uncomplicated UTI generally affects healthy individuals with no abnormalities in the urinary tract either structurally or neurologically, the non-pregnant and the ones with no urinary catheter (2).All the other forms of UTI are considered complicated. These infections are further categorized based on where they occur, that is the upper UTI (pyelonephritis) affecting the kidney and the lower UTI (cystitis) affecting the bladder(2).

Both gram-negative and gram-positive, as well as certain fungi are responsible for causing most UTIs, both complicated and uncomplicated(2). However, the most common microorganisms are gram-negative including the Enterobacteriaceae family majorly being Uropathogenic *Escherichia coli* (UPEC) and others like *Klebsiella pneumoniae, Proteus mirabilis*, *Pseudomonas aeruginosa.* The gram-positive bacteria include *Staphylococcus aureus* and *Staphylococcus saprophyticus*(3,4). The fungi causing UTI include *Candida* spp (5).

Among others, one of the etiological causes of UTI is an adverse drug reaction from a particular group of drugs based on their mechanism of action, or because most medications and their metabolites are eliminated through urine keeping the urinary tract at risk(6).Sodium-glucose transporter 2 inhibitors (SGLT2i) including the common Dapagliflozin, Empagliflozin, Canagliflozin, and Sotagliflozin, this group of drugs was primarily an antihyperglycemic agent, with an ability to reduce the reabsorption of glucose at the proximal convoluted tubule where up to 90% of glucose gets reabsorbed thus causing glucosuria (7).This increased glucose in urine can favor bacterial growth and proliferation thus a risk to UTI (8)

Apart from the sugar control of SGLT2 inhibitors, this class of drug has demonstrated beneficial cardiac protection, this was proved by the randomized clinical trials that focused on patients with type 2 diabetes mellitus (T2DM) and marked significant protection against major adverse cardiovascular events and all-cause of mortality for heart failure(9,10).SGLT2i involves both molecular and cellular mechanisms at a vascular, systemic, and cardiac level to offer its cardiovascular benefit. The vascular benefits are related to blood pressure reduction, osmotic diuresis and natriuresis, and the improvement of endothelial function by different mechanisms (11,12).

SGLT2i cardio protection advantages have recently been further demonstrated in the landmark randomized clinical trials that targeted heart failure patients with common primary endpoints of cardiovascular death or hospitalization for heart failure (13–17)These studies demonstrated the benefit of SGLT2i in all ranges of left ventricular ejection fraction despite their diabetic status. However, in most of these trials, UTI was not labeled as an event of important safety concern, therefore it is possible that the events were underreported (18).

Heart failure (HF) poses a significant health burden in Tanzania, primarily affecting younger adults compared to high-income countries. The main etiological factors are hypertension, cardiomyopathies, rheumatic heart disease, and congenital heart disease(19) .The introduction of SGLT2 inhibitors for HF management in Tanzania marks a significant shift, with evidence supporting their efficacy in reducing HF hospitalizations, mortality, economic and social burden.

Therefore, based on these approved cardiovascular benefits of SGLT2i, it has been regarded as with level A of evidence and Class 1 of recommendation as part of the add-on therapy in heart failure management in European and American guidelines (20,21).As these recommendations were recently published, the regimen for managing HF that includes the SGLT2i is not yet included in the Tanzania National Treatment Guideline (STG), but it is used and included in hospital formulary in some clinical settings. Dapagliflozin and Empagliflozin are registered and approved for use by the Tanzania Medicines and Medical Devices Authority (TMDA)(22)

1.2 Problem statement

UTI is associated with increased morbidity, mortality, and treatment costs with more than 50% of all women and at least 12% of men experiencing an episode of UTI in their lifetime (2).Patients with heart failure are usually frail and have other comorbidities that render them vulnerable to different infections due to their impaired immune system(23).

Infections, including UTIs, are typically considered one of the common and yet under-recognized medical conditions that can result in rapid deterioration among heart failure patients leading to increased morbidity and mortality.

Among the potential adverse effects of SGLT2i that has recently been included in the medication pillars for Heart failure management is UTI. In many studies investigating the benefit of SGLT2i in heart failure patients, this event was not designated as an event of interest with safety concerns. Yet this population group is at high risk of infections due to other causes that could impact their quality of life.

Despite this known risk, there is a gap in knowledge of the extent to which this specific population is affected by UTI, specifically in developing countries and our local ethnic group, where there is a risk of poor hygiene.

Moreover, UTI being common in most settings, it is empirically treated with no data that supports the choice of antibiotics that leads to antimicrobial resistance that induces a major problem in the treatment of infectious diseases(24)

While SGLT2 inhibitors show promise, challenges remain in their accessibility and integration into standard care practices in Tanzania. The evolving landscape of HF management necessitates ongoing research and adaptation to local healthcare needs.

1.3 Conceptual framework

Several studies have clearly shown a relationship between socio-demographic characteristics such as age, sex, poor hygiene, and clinical characteristics as a risk for the growth of the uropathogens causing UTI(25). Moreover, some drugs can also be a risk for UTI by a different mechanism(6). For this study, SGLT2i either Dapagliflozin or Empagliflozin used as part of management of HF has a risk for UTI due to its mechanism of action that supports microorganism proliferation in the urinary tract. On the other hand, infection is a risk for decompensated heart failure. Again, heart failure lowers patient immunity and thus the risk of infection. (Figure 1)

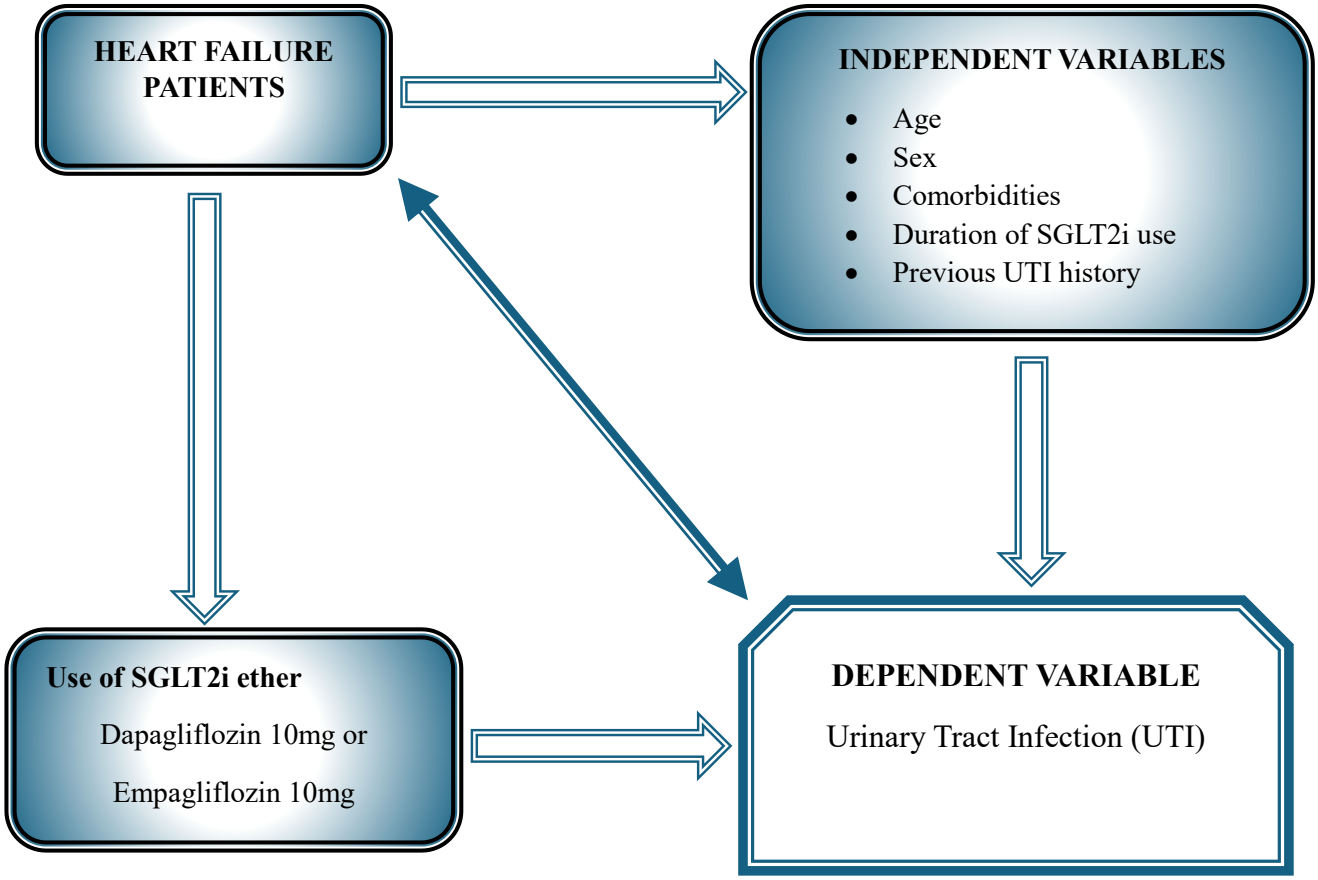


Figure 1: Conceptual framework

1.4 Rationale of the Study

This study's findings will provide a crucial insight into the prevalence of UTI in this specific population that was not yet studied, as infections can be a risk for decompensation of heart failure and frequent hospitalization.

The burden of heart failure (HF) is significant, with high morbidity and mortality rates impacting the quality of life both socially and economically, the study aims to show the safety extent of using SGLT2 inhibitors as an add-on therapy in the management of HF.

Moreover, the knowledge of the prevailing uropathogens and their susceptibility patterns has determined the important pathogens and specific antibiotics susceptible to a particular isolated microorganism.

The findings add isolates and antibiotic susceptibility patterns data to the institute's and national cumulative antibiogram. This gives an evidence-based decision in selecting empirical treatment for UTI before the culture and sensitivity results for patients suspected of UTI.

This rational use of antibiotics will then impact reducing antimicrobial resistance and complications of UTIs that arise from resistant antibiotics.

1.5 Research Questions

1.5.1 Broad Research Questions

What is the prevalence of UTI, associated factors, and antimicrobial susceptibility pattern of isolated uropathogens among heart failure patients using SGT2 inhibitors?

1.5.2 Specific Research Questions

1. What is the prevalence of UTIs among heart failure patients using SGLT2 inhibitors at JKCI?
2. What potential risk factors are associated with UTIs in heart failure patients on SGLT2 inhibitors at JKCI?

3. What are the common uropathogens responsible for UTIs in heart failure patients on SGLT2 inhibitors at JKCI?
4. What are the antimicrobial susceptibility patterns of the uropathogens isolates causing UTI in heart failure patients on SGLT2 inhibitors at JKCI?

1.6 Research Objectives

1.6.1 Broad Objectives

To assess the prevalence of UTIs, associated factors, and antimicrobial susceptibility pattern of isolated uropathogens among heart failure patients on SGLT2i at JKCI.

1.6.2 Specific objectives

1. To determine the prevalence of UTI among heart failure patients using SGLT2 inhibitors at JKCI.
2. To investigate the potential risk factors associated with UTI in heart failure patients on SGLT2 inhibitors at JKCI.
3. To identify the common uropathogens responsible for UTI in heart failure patients on SGLT2 inhibitors at JKCI.
4. To evaluate the antimicrobial susceptibility patterns of the uropathogens causing UTI in heart failure patients on SGLT2 inhibitors at JKCI.

1.7 Literature review

1.7.1 Prevalence of UTIs among Heart failure on SGLT2 inhibitors

Heart failure (HF) is a growing public health concern in Tanzania, contributing significantly to morbidity and mortality. The prevalence of HF in sub-Saharan Africa is estimated to be between 1% to 4% of the adult population, with higher rates reported in urban areas due to lifestyle changes and increased prevalence of risk factors (26).

A study conducted at tertiary hospitals in Tanzania revealed that HF accounts for a significant proportion of hospital admissions, with an increasing trend attributed to factors such as hypertension, ischemic heart disease, and rheumatic heart disease(19). The standard treatment includes diuretics, ACE inhibitors, beta-blockers, and mineralocorticoid receptor antagonists. However, access to these medications can be limited, particularly in rural areas.

Recent guidelines have included SGLT2 inhibitors as a vital component in managing HF. While they have shown efficacy in reducing hospitalizations and mortality, their association with UTIs poses a new challenge that requires further investigation in local settings.

So far, there is little literature and publications regarding the use of SGLT2 inhibitors specifically for heart failure patients and their safety impacts, including UTI. A pooled analysis of the five landmark randomized clinical trials analyzed the safety endpoints of SGLT2 inhibitors against the placebo in heart failure patients and demonstrated that among all combined patients who received SGLT2 inhibitors 585 UTI events were recorded compared to 529 UTI events for the patients that received placebo (18). In most of these trials, UTI was not documented as an event of attention, thus most of the events might have been underreported, therefore creating bias also since these trials were conducted on standardized conditions, most of the other risk factors for UTI such as poor hygiene must have been eliminated (18).

In another meta-analysis for the safety outcomes of SGLT2 inhibitors for ten RCTs that enrolled high-risk patients of cardiac disease, significant findings of increased risk trend of UTI compared to placebo were reported (9.08% vs 7.10%). These findings were clinically substantial

but statistically insignificant (27). These trials had a black representative population of <5.1% and no participants were from sub-Saharan Africa (18,27).

Due to the scarcity of data on UTIs regarding this population group, further studies may be warranted to monitor a broader range of safety outcomes of SGLT2i especially in Africa where patients are exposed to more risk factors for UTIs.

1.7.2 Potential Risk Factors Associated with Urinary Tract Infections

Multinational studies have generally shown the common risk factors that can predispose to UTIs in different population groups.(25). Fewer data is available for specifically Heart failure patients. Among the reported risk factors for UTI includes the socio-demographic such as female gender, this can be explained by the anatomical difference where the female urethra is shorter and near to the perineum thus more risk of UTI compared to the male gender (25).

UTI prevalence in older people was significantly higher than that in teenagers in the study done in Tanzania (28)However, most studies are difficult to compare due to differences in the number of people in different age groups.

Moreover, other risks leading to recurrent UTI are reduced by fluid intake, delayed urination, wiping from back to front after defecation, douching and wearing occlusive underwear as well as irregular bowel (29).

Again, some drugs based on their mechanism of action can compromise the immune system and impair the urinary tract leading to a risk of UTI(6).SGLT2i risk to UTIs has been studied more among diabetic patients than in its use in heart failure patients and there have been varying results(8,30). Furthermore, comorbidities such as uncontrolled diabetes, and kidney diseases promote bacterial growth increasing the risk of UTI(31).

1.7.3 Common Uropathogens Responsible for Urinary Tract Infections

According to most international and national studies and reviews, the most identified uropathogens responsible for UTIs both complicated and uncomplicated are *Escherichia coli, Klebsiella pnemouniae, Klebsiella oxytoca, Proteus mirabilis, Staphylococcus saprophiticus*, *Pseudomonas aeruginosa*, *Acinetobacter* spp (32–35). However, Uropathogenic Escherichia

coli (UPEC) is the most prevalent and responsible for 50% of the community-acquired and 80% of the hospital-acquired infections (36).

UPEC isolates prevalence is higher in developing countries compared to developed countries ranging from 50%-85% versus 3%-40% respectively(36).

According to the study conducted in East Africa (Kenya, Uganda, and Tanzania) in 2019-2020 among the symptomatic patients with a predominance of resistance bacteria causing UTI the predominant bacteria was *Escherichia coli* (37.0%), *Staphylococcus* spp (26.6%), *Klebsiella* spp (5.8%) and *Enterococcus* spp (5.5%) (37)Moreover compared to Tanzania and Uganda, Kenya showed a higher proportion of *Staphylococcus* spp. Uganda in contrast showed a higher level of *Escherichia coli* compared to Kenya and Tanzania (37).

These study findings align with the number of recent studies carried out in Tanzania such as a study on the prevailing uropathogens, a study done in Morogoro found the common bacteria to be UPEC (47%) of all isolated uropathogens and *Pseudomonas aeruginosa* (17%), *Klebsiella pneumoniae* (11.4%), *Proteus mirabilis* (14.2%) (28)This is also the same as the study done in Dar es Salaam and Mwanza, which focused on the prevalence of UTI. This study found some pathogens that are rarely associated with UTI.(38).

1.7.4 Antimicrobial Susceptibility Patterns of the Uropathogens Responsible for Urinary Tract Infections

A nine-year study in a tertiary hospital in central Europe showed the isolated pathogens including Escherichia coli, were resistant to most of the antibiotics in the case of Ampicillin, both fluoroquinolones exceeding 30%, and 10% resistance for Amoxicillin/Clavulanic acid, Piperacillin/tazobactam, cefuroxime and cefepime. A susceptibility was higher for third-generation cephalosporin, gentamicin, and nitrofurantoin. On the other hand, amikacin, carbapenems, and colistin showed nearly no resistance (33).

Moreover, the same study reported an alarming rate of up to 90% resistance to penicillin, fluoroquinolones, Nitrofurantoin, gentamycin, and co-trimoxazole by *Klebsiella* spp. The only suitable antibiotic in this case of UTI caused by *Klebsiella* spp were Amikacin and carbapenems (33).

In a study done in East Africa, patients showed a difference in the resistance pattern despite being in the same region. There was an MDR prevalence of 60.3%, with the isolates from Tanzania showing a high proportion of MDR.(37).Escherichia coli from Kenya were less likely to be resistant to ampicillin, amoxicillin/clavulanic acid, ciprofloxacin, ceftriaxone, and ceftazidime than those from Tanzania and Uganda.(37).

A recent study in Tanzania has isolated pathogens showing a marked high resistance to common antibiotics, including cotrimoxazole and ampicillin. *Escherichia coli* was the predominantly isolated microorganism that had shown resistance to ceftriaxone (34%), ciprofloxacin (37%), and nitrofurantoin (37%) which are among the first-line recommended antibiotics for UTI in Tanzania Standard Treatment Guideline thus giving an alert in the selection of empirical treatment of UTI. (28). This is like the study conducted in Uganda.(39)

Moreover, this study found significant differences in resistance between the biofilm-forming and non-biofilm-forming isolates, thus creating a need to perform biofilm tests whenever possible beyond culture and sensitivity. Again, dipstick urinalysis was shown to be less sensitive in this study.(28).

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study design

This was a cross-sectional study conducted for three months, from March to June 2024.

2.2 Study Site

This study was conducted at JKCI, a super-specialized hospital offering evidence-based cardiovascular care, training, and research services. The institute has a 157-bed capacity and attends over 1800 outpatients and 100 inpatients weekly. It serves referred patients from all over Tanzania for super-specialized cardiovascular care. Moreover, the institute also receives patients from nearby countries (40).

2.3 Study population

Inpatients and Outpatients with a diagnosis of heart failure at JKCI.

2.3.1 Study inclusion and exclusion criteria

Inclusion criteria

Inpatients and outpatients aged 18 and above on either Empagliflozin or Dapagliflozin as part of their heart failure treatment regimen.

Exclusion criteria

- Patients on SGLT2i for heart failure on antibiotics or were on antibiotics in the previous 7 days
- Patients who did not provide informed consent
- Urethral catheterized inpatients who were on SGLT2i for heart failure

2.3.2 Sample Size and Sampling Technique

Sample size

Since this was a cross-sectional study design, the sample size calculation formula for estimating a single proportion was used (41).

$$n = (Z^2 * p * (1 - p)) / (E^2)$$

Where:

- n is the required sample size
- Z is the Z-score corresponding to the desired confidence level (e.g., Z = 1.96 for a 95% confidence level)
- p is the expected prevalence of urinary tract infections
- ε is the desired level of precision (margin of error)

Based on the available recent literature, the prevalence of UTI among heart failure patients on SLGT2i is approximately 9.08% (27).

n = (Z^2 * p * (1 - p)) / (E ^2)

Using a Z-score of 1.96 for a 95% confidence level:

n = (1.96^2 * 0.0908 * (1 - 0.0908)) / (0.05^2)

n ≈ 127

By considering a 10% non-response rate

127/0.9=141 patients

Therefore, a sample size of approximately 141 heart failure patients on SGLT2is at the JKCI, which includes the 10% non-response, was used to achieve a 95% confidence level with a margin of error of 5%.

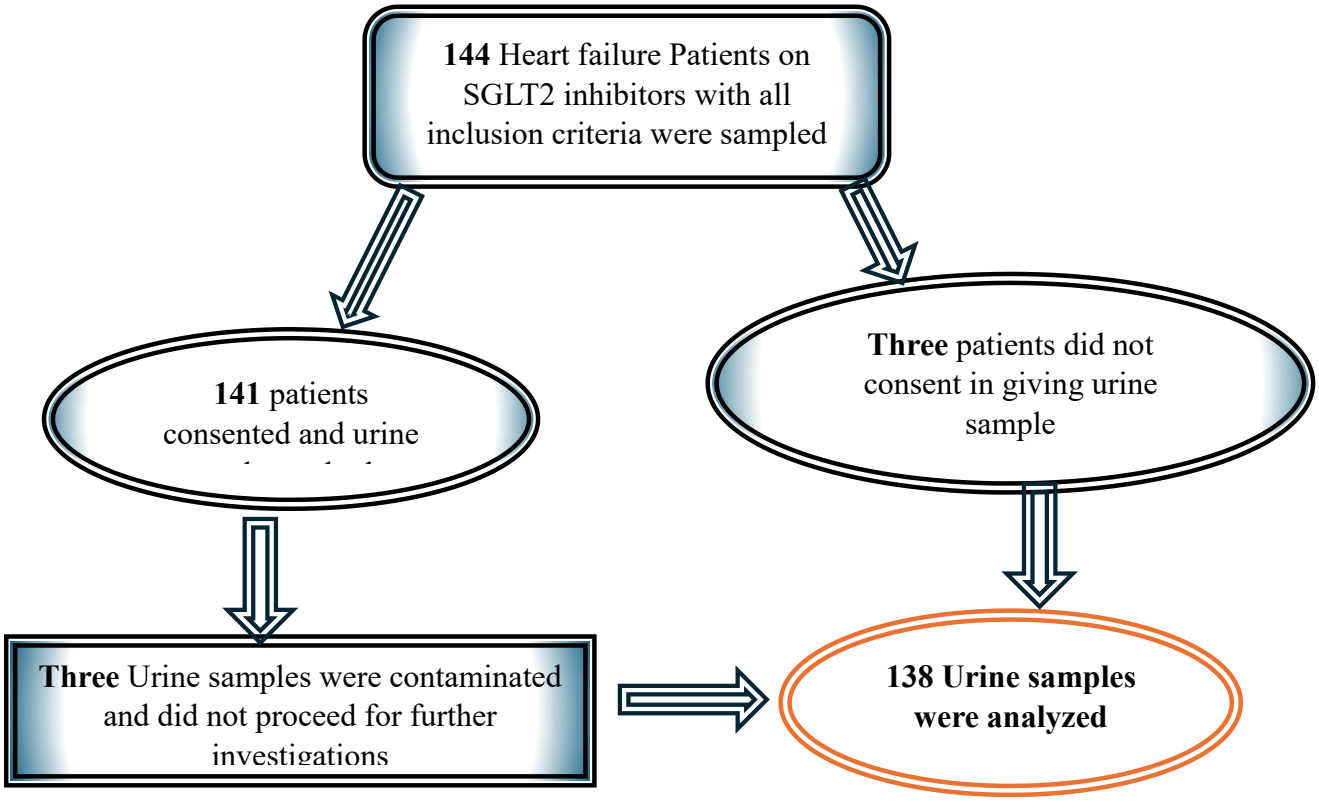


Figure 2: Sample flowchart

2.4 Data Collection

2.4.1 Data Collection Tools

A semi-structured questionnaire was used to collect patient socio-demographic information. In contrast, a case report form was used to collect and document the patient medical and medication history, vital signs, and laboratory results.

2.4.2 Data Collection Methods

Participant Recruitment and Data collection.

Patients already diagnosed with Heart failure were sampled while collaborating with other healthcare providers in the follow-up clinics and wards at JKCI. Upon consenting and being given relevant information, the principal investigator recorded the patient's specific socio-

demographic characteristics, possible risk factors associated with UTI history, medical and medication history, and vital signs on respective data collection tools**.**

Collection, Handling, and Transport of Urine Sample.

Recruited patients were instructed on the proper collection of the urine sample to avoid contamination; clean voided 10-20 milliliters of midstream urine specimens were collected in two separate wide screwed mouth containers and transported within 10 minutes in a cool box to the Central Pathology Laboratory (CPL) at microbiology and parasitology department for culture and sensitivity and urinalysis investigation respectively.

All the samples were collected between 0800 and 1200hrs, specimen containers were labeled with identification number, time, and date for sample collection.

Laboratory Investigation Procedures

Urinalysis

At the pathology laboratory, the urine sample was investigated both macroscopically and microscopically. The urine chemistry results, including protein, glucose, nitrites, leukocytes, and urine pH, were evaluated and recorded at the macroscopic level. White blood cells, red blood cell levels in High Power Field (HPF), urine specific gravity, cast cells, and crystals were recorded at the microscopic levels.

Culture, Isolation, and Identification of uropathogens

The urine sample was inoculated at the microbiology laboratory using a calibrated 1 microliter disposable loop in a Cysteine, lactose electrolyte-deficient (CLED) agar, and blood agar media. After 24 hours of incubation at 35-37 °C, significant growth was further analyzed, and specific bacteria were isolated and identified through colony morphology, gram reaction, and biochemical tests.

A growth of $\geq 10^5$ Colony-forming units (CFU)/ml was required for statistical significance. Contamination was defined by the mixed growth of up to $\geq 10^4$ more than two species.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility test was conducted on each isolated uropathogen using the Kirby Bauer disk diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (2024) for performing the Antimicrobial Susceptibility Test (42).

Bacterial suspensions were prepared by emulsifying one pure colony into a tube containing 2-5ml sterile normal saline (0.9% NaCl) and mixing gently until a homogeneous suspension formed. The suspension's turbidity was then adjusted to 0.5 McFarland standards to standardize the inoculum size. A sterile cotton swab was then dipped into the suspension and swabbed on the surface of the Mueller-Hinton agar plate. Standard antimicrobial-impregnated discs based on the uropathogen isolated were then aseptically placed on the culture.

The inoculated agar plates were incubated at 37 °C for 18-24 hours. The diameter of the zones of inhibition was measured in millimeters. The interpretation breakpoints were based on whether the bacteria were Susceptible (S), Intermediate (I), or resistant (R) to the tested antibiotic according to CLSI recommendations (42).Based on the type of isolated microorganism and CLSI recommendations, the antibiotics discs that were used with their respective concentrations include Amikacin 30µg (AK), Ampicillin 10 µg (AMP), Amoxy-clavulanate 20/10 µg (AMC), Cefepime 30 µg (FEP), Ceftazidime 30 µg (CAZ), Ceftriaxone 30 µg (CRO), Cefoxitin 30 µg (FOX), Ciprofloxacin 5 µg (CIP), Gentamicin 10 µg (GE), Meropenem 10 µg (MEM), Nalidixic acid 30 µg (NA), Nitrofurantoin 300 µg (F), Penicillin G 10 units, Piperacillin-tazobactam 100/10 µg (TZP), Trimethoprim-sulfamethoxazole 1.25/23.75 µg (SXT), Tetracycline30 µg (TE), Tobramycin 10 µg (TM).

Operational definition.

The diagnosis of UTI, regardless of the symptoms, was based on True positive for both positive culture as a gold standard and urinalysis parameters, including pyuria and positive or negative nitrites.

2.5 Variables

2.5.1 Dependent Variables

Prevalence of UTIs among heart failure patients who are on SGLT2 inhibitors as part of their treatment regimen.

2.5.1 Independent Variables

- Age
- Sex
- Comorbidities and other medical conditions
- Type of SGL2 inhibitor
- Duration of SGLT2 inhibitor use
- Previous UTI history

2.6 Data Analysis

Data was analyzed using the Statistical Product and Service Solution (SPSS) software version 26 (IBM SPSS Statistics, IBM Corp, Armonk, NY, USA). For analytical statistics, univariable and multivariable as well as Poisson robust regression models were used to assess the association between positive UTI and the risk factors such as age, sex, comorbidities, previous history of UTI, type of SGLT2 inhibitor, and duration of use of SGLT2 inhibitors. Moreover, the Pearson Chi-square test was also used to establish an association. The 95% confidence intervals were obtained, and p values <0.05 were considered statistically significant.

The susceptibility pattern results for the isolated microorganisms were analyzed using the proportion. Moreover, the diagnostic accuracy of urinalysis was evaluated using sensitivity and sensitivity, calculating the positive and negative predictive values using Culture as a gold standard.

2.7 Ethical Considerations

The MUHAS Institutional Review Board granted ethical approval to conduct this study with approval number DA.282/298/01.C/2049 9(Appendix V). Permission to perform this study was also obtained from JKCI (Appendix VI) and Muhimbili National Hospital for the laboratory investigations at CPL (Appendix VII). Consent to participate in this study was obtained from the patient by signing a written informed consent form (Appendix I & II). This study caused no harm to the study participants**.** Results were communicated to the primary care physician for management for the participants who had positive UTI tests, and all other participants' information was confidential.

CHAPTER THREE

3.0 RESULTS

3.1 Patient's Socio-demographic Characteristics

Out of 141 participants, more than half were aged ≤ 60 years (53.5%). The sex distribution showed that 55.3% were male and 44.7% were female. Regarding menopausal status among female participants, 44.4% were post-menopausal. Most participants (70.2%) were married. Occupational status revealed that 56% of participants were self-employed. Health insurance coverage was present in 61% of the participants, while 39% relied on general cash payments. The majority resided within Dar es Salaam (53.2%). Nearly all participants used flashing latrines (98.6%), and alcohol consumption was reported by only 9.2% of participants. (Table 1)

Table 1: Socio-demographic characteristics of the study participants

Variables	Frequency (n)	Percent (%)
Age (Years)		
≤60	76	53.9
>60	65	46.1
Sex		
Male	78	55.3
Female	63	44.7
Menopausal status		
Pre-menopausal	35	55.6
Post-menopausal	28	44.4
Marital status		
Married	99	70.2
Widow/Widower	26	18.4
Cohabiting	6	4.3
Single	5	3.5
Divorced	5	3.5
Occupational status		
Self-employed	79	56.0
Retired	37	26.2
Government/Private employed	22	15.6
Unemployed	2	1.4
Student	1	.7
Bills coverage		
Health insured	86	61.0
Cash	55	39.0
Permanent Residence		
Within Dar es Salaam	75	53.2
From other regions	61	43.3
From other countries	5	3.5
Alcohol drinking habits		
Yes	13	9.2
No	128	90.8

3.2 Clinical characteristics and medication history of the study participants

Most of the study participants (56%) were outpatients. The use of SGLT2 inhibitors was even between Empagliflozin 10mg (53.2%) and Dapagliflozin 10mg (46.8%). SGLT2 inhibitor use was predominantly less than 4 months (87%).

The patient's vital statistics indicated a median systolic blood pressure (SBP) of 112 mmHg, a median diastolic blood pressure (DBP) of 83 mmHg, and a median pulse rate of 88 bpm. The left ventricular ejection fraction (LVEF) showed that 32.6% had HFrEF and 41.1% had HFmrEF. Most participants (40.4%) had a normal weight. According to the New York Heart Association (NYHA) classification, 70.9% were in Class I & II, and 29.1% in Class III. Other chronic diseases were present in 58.9%. A previous history of UTI was reported by 12.8% of participants. (Table 2)

Table 2: Clinical Characteristics and Medication History of the Study Participants

Variables	Frequency (n)	Percent (%)
Patient admitted as		
Outpatient	79	56.0
Inpatient	62	44.0
Type of SGLT2 inhibitor used		
Empagliflozin 10mg	75	53.2
Dapagliflozin 10mg	66	46.8
Duration of SGLT2 inhibitor use		
< 4 months	123	87
≥ 4 months	18	12.8
Patient vitals		
Median SBP (IQR) (mmHg)	112 (112, 134)	
Median DBP (IQR) (mmHg)	83 (78, 88)	
Median Pulse rate (IQR) (bpm)	88 (83, 92)	
Left ventricular ejection fraction (LVEF) %		
≤ 40 (HFrEF)	46	32.6
41-49 (HFmrEF)	58	41.1
≥ 50 (HFpEF)	37	26.2
BMI status Kg/m^2		
Underweight (≤18.5)	8	5.7
Normal weight (18.5-24.9)	57	40.4
Overweight (25.0-29.9)	44	31.2
Obese ≥30	32	22.7
New York Heart Association Class (NYHA)		
I&II	100	70.9
III	41	29.1
Other Chronic Diseases		
Yes	83	58.9
No	58	41.1
Other Chronic Diseases		
Other Cardiovascular diseases	53	63.9
Diabetes Mellitus	16	19.3
HIV/AIDS	3	3.6
Diabetes and other cardiovascular diseases	8	9.6
HIV/AIDS and other cardiovascular diseases	3	3.6
Previous history of UTI		
Yes	18	12.8
No	86	61.0
Unknown	36	26.2
UTI symptoms		
Asymptomatic	116	82.3
Symptomatic	25	17.7

As pillars for managing heart failure, almost all patients were on mineralocorticoid receptor antagonists (97.2%), and beta-blockers (92.9%). Either ACEI (70.9%), ARB (22.0%), or Sacubitril/Valsartan (7.1%). About 4.3 % of other drugs were used based on co-morbidities and 17.0% of the drugs were used by diabetic patients. (Figure 3)

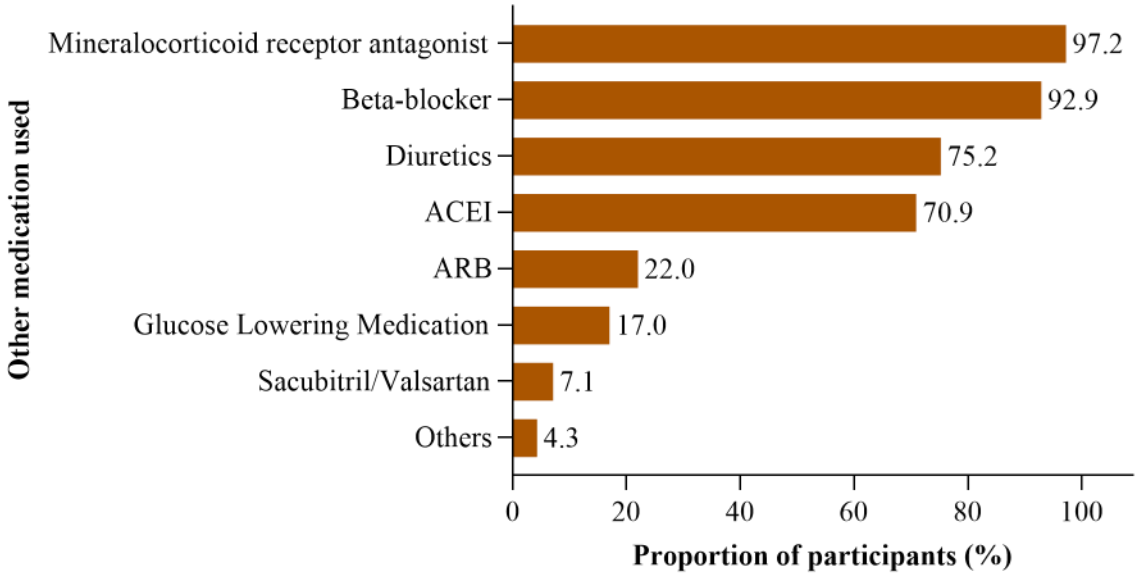


Figure 3: Other medications used by the study participants

3.3 Laboratory findings

Laboratory findings of the study participants are presented in Table 3. Based on urinalysis, glucose levels were moderate +2 (100 mg/dl) in (39%), and high +3 (300mg/dl) in (44%). Blood in urine was negative in 99.3% of participants, nitrites were positive in 12.8%, and leukocytes were positive in 28.4%. The median white blood cell (WBC) count in high power field (HPF) was 1 (range 0-120), and the median red blood cell (RBC) count in HPF was 0 (range 0-100). Yeast cells were positive in 2.8% of the study participants, and uric acid was positive in 3.5%. Fastidious culture results were positive in 21.3% and negative in 76.6% significant bacterial growth was noted in 15.6% of the participants. (Table 3)

Table 3: Laboratory findings of the study participants

Variable	Frequency (n)	Percent (%)
Glucose		
+1	24	17.0
+2	55	39.0
+3	62	44.0
Blood		
Positive	1	99.3
Negative	141	.7
Nitrites		
Positive	18	12.8
Negative	123	87.2
Leucocytes		
Positive	40	28.4
Negative	101	71.6
Median WBC (HPF) (Range)	1 (0, 120)	
Median RBC (HPF) (Range)	0 (0, 100)	
Yeast cells		
Positive	4	97.2
Negative	137	2.8
Uric acid		
Positive	5	3.5
Negative	136	96.5
Fastidious culture		
Positive	30	21.3
Negative	108	76.6
Contamination	3	2.1
Significant bacteria growth		
$\geq 1\times10^5$ CFU	22	15.6
$\leq 1\times 10^5$ CFU	8	5.7

Key: HPF: High power field, CFU: Colony Forming Units

3.4 Prevalence of UTI among heart failure patients using SGLT2 inhibitors at JKCI.

Based on urinalysis parameters and positive culture results with significant growth, the prevalence of UTIs among heart failure patients whose urine samples (n=138) were 34.06% and 15.94% respectively (Figure 4). Three samples revealed contamination by mixed growth and did not undergo further investigations.

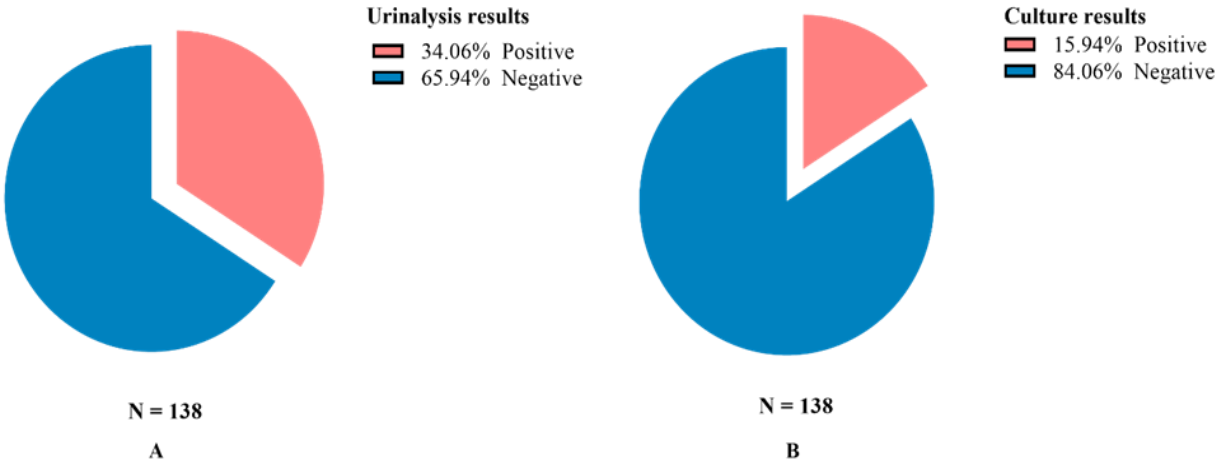


Figure 4: Prevalence of UTI among study participants using urinalysis and culture

3.5 Performance Characteristics of Urinalysis in Detecting UTI

The performance characteristics of urinalysis in detecting urinary tract infections are detailed in (Tables 4 and 5). The test sensitivity was 100% (95% CI: 84.6% - 100%), and the specificity was 78.4% (95% CI: 69.9% - 85.5%). Diagnostic accuracy was reported at 81.9% (95% CI: 74.4% - 87.9%). The positive predictive value was 46.8% (95% CI: 32.1% - 61.9%), and the negative predictive value was 100% (95% CI: 96.0% - 100%).

Table 4: Performance characteristics of urinalysis in detecting urinary tract infection

	Culture results		
Urinalysis	**Positive**	**Negative**	**Total**
Positive	22 (TP)	25 (FP)	47
Negative	0 (FN)	91 (TN)	91
Total	22	116	138

Key: TP (True positive), FP (False positive), FN (False negative), TN (True Negative

Table 5: Performance characteristics of the urinalysis in detecting urinary tract infection

		95% Confidence Interval	
Decision Statistics	**Estimate**	**Lower**	**Upper**
Test sensitivity	100.0 %	84.6 %	100.0 %
Test specificity	78.4 %	69.9 %	85.5 %
Diagnostic accuracy	81.9 %	74.4 %	87.9 %
Positive predictive value	46.8 %	32.1 %	61.9 %
Negative predictive value	100.0 %	96.0 %	100.0 %

3.6 Potential risk factors associated with UTIs in heart failure patients on SGLT2 inhibitors at JKCI

Univariable and multivariable analyses were conducted to identify factors associated with UTI (Table 6). In the univariable analysis, age >60 years (cPR 5.36, 95% CI: 1.91–15.01, p = 0.001) compared those with those aged ≤60 years, and female sex (cPR 4.05, 95% CI: 1.58–10.35, p = 0.004) were significantly associated with UTI compared to male. The duration of SGLT2 inhibitor use for ≥4 months was also significantly associated (cPR 6.67, 95% CI: 3.40–13.07, p < 0.001) compared to the patients that used either of the drug for less than four months.

In the multivariable analysis, age >60 years (aPR 3.77, 95% CI: 1.42–10.01, p = 0.008) and female sex (aPR 2.92, 95% CI: 1.19–7.15, p = 0.019) remained significantly associated with

UTI. Additionally, the duration of SGLT2 inhibitor use for ≥4 months (aPR 3.19, 95% CI: 1.70–5.96, $p < 0.001$) continued to show a significant association.

The history of UTI was significant in the univariable analysis (cPR 3.78, 95% CI: 1.74–8.23, $p = 0.001$) compared to those who had no history of UTI, but in the multivariable analysis, there was no significant association (aPR 1.58, 95% CI: 0.90–2.79, $p = 0.113$).

Table 6: Univariable and multivariable analysis of the factors associated with urinary tract infection

		Univariable analysis			Multivariable analysis		
Variable	**Category**	**cPR**	**95% CI**	**p-value**	**aPR**	**95% CI**	**p-value**
Age group	≤ 60	Ref					
	>60	5.36	1.91 – 15.01	0.001	3.77	1.42 – 10.01	**0.008**
Sex	Male	Ref					
	Female	4.05	1.58 –10.35	0.004	2.92	1.19 – 7.15	**0.019**
BMI Status	Underweight	0.57	0.09 – 3.83	0.566			
	Overweight	0.85	0.38 – 1.90	0.697			
	Obese	0.14	0.02 – 1.05	0.056			
	Normal weight	Ref					
Alcohol	Yes	0.46	0.07-3.13	0.426			
	No	Ref					
Admitted as	Outpatient	1.11	0.51 – 2.43	0.791			
	Inpatient	Ref					
SGLT2 inhibitor	Empagliflozin 10mg	Ref					
	Dapagliflozin 10mg	0.66	0.30 -1.47	0.311			
Duration of	< 4 months	Ref					
SGLT2i use	≥ 4 Months	6.67	3.40 – 13.07	**<** 0.001	3.19	1.70 – 5.96	**< 0.001**
Chronic diseases	Yes	1.55	0.68 - 3.57	0.299			
	No	Ref					
DM	Yes	1.47	0.60 – 3.59	0.396			
	No	Ref					
NYHA Classes	I & II	Ref					
	III	1.70	0.79 – 3.65	0.177			
History of UTI	Yes	3.78	1.74 – 8.23	**0.001**	1.58	0.90 – 2.79	0.113
	Unknown	0.97	0.33 – 2,89	0.958	0.85	0.37 – 1.99	0.713
	No	Ref					

Key: cPR: crude Prevalence Ratio, aPR: adjusted Prevalence Ratio, Ref: Reference, DM: Diabetes mellitus, NYHA: New York Heart Association, BMI: Body Mass Index

3.7 The proportion of uropathogens responsible for UTIs in heart failure patients on SGLT2 inhibitors at JKCI.

Although gram-positive and gram-negative bacteria and fungi were isolated, the predominant uropathogens isolated among the heart failure patients on SGLT2 inhibitors were *Escherichia coli,* with an isolate rate of 50.0% (Figure 5).

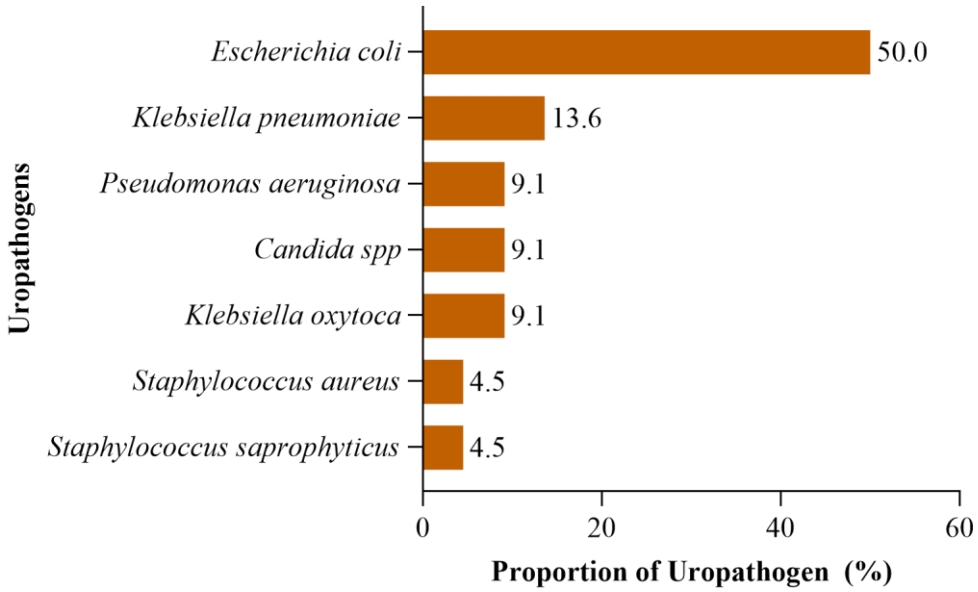


Figure 5: Proportion of isolated uropathogens among study participants inhibitors with a positive culture

3.8 The proportion of resistance of the isolated uropathogens causing UTI among Heart failure patients at JKCI

The overall proportion resistance of gram-negative uropathogen was high in Ampicillin (100%) for *Klebsiella* spp and (90.9%) in *Escherichia coli. Pseudomonas aeruginosa* showed resistance of (100%) to Amikacin and Piperacillin/tazobactam. The low proportion of resistance of gram-negative organisms was in Nitrofurantoin (0%) in *Escherichia coli* and (33.3%) for *Klebsiella pneumoniae*. Ciprofloxacin (0%) for *Klebsiella Oxytoca* and *Pseudomonas aeruginosa.*

Piperacillin/Tazobactam also had a (0%) resistance to Klebsiella spp and (30.0%). Meropenem was highly sensitive to *Escherichia coli* and *Klebsiella spp.* (Table 7)

For gram-positive bacteria, they all had a (100%) resistance to Tetracycline while showed a (0%) resistance to Nitrofurantoin. *Staphylococcus saprophyticus* showed high resistance (100%) to Gentamicin, Penicillin G, and Sulfamethoxazole-trimethoprim. (Table 8)

Table 7: Antimicrobial resistance pattern of gram-negative bacteria isolated from urine culture

Bacterial Isolates	n	Antimicrobial agents resisted (%)														
		AK	AMP	AMC	FEP	CAZ	CRO	CIP	GEN	MEM	NA	F	TZP	SXT	TE	TM
Escherichia Coli	11	27.3	90.9	45.5	54.5	70.0	54.5	36.4	36.4	0	54.5	0	30.0	54.5	40.0	-
Klebsiella pneumoniae	3	33.3	100	33.3	33.3	33.3	33.3	33.3	33.3	0	33.3	33.3	0	66.7	66.7	-
Pseudomonas aeruginosa	2	100	-	-	0	100	-	0	-	50.0	-	-	100	-	-	0
Klebsiella oxytoca	2	0	100	50.0	0	0	0	0	50.0	0	0	50.0	0	50.0	0	-

Key: (-) Not applicable, AK: Amikacin, AMP: Ampicillin, AMC: Amoxicillin-Clavulanic acid, FEP: Cefepime, CAZ: Ceftazidime, CRO: Ceftriaxone, CIP: Ciprofloxacin, GE: Gentamycin, MEM: Meropenem, NA: Nalidixic acid, F: Nitrofurantoin, TZP: Piperacillin/tazobactam , SXT: Trimethoprim/Sulfamethoxazole, TE: Tetracycline: Tobramycin.

Table 8: Antimicrobial resistance pattern of gram-positive bacteria isolated from urine culture

Bacterial Isolates	n	Antimicrobial agents resisted (%)						
		FOX	CIP	GE	F	Pen G	SXT	TE
Staphylococcus aureus	1	0	100	0	0	0	0	100
Staphylococcus saprophyticus	1	-	0	100	0	100	100	100

Key:(-) Not applicable, FOX: Cefoxitin, CIP: Ciprofloxacin, GEN: Gentamycin, F: Nitrofurantoin, Pen G: Penicillin G, SXT: Sulfamethoxazole-trimethoprim, TE: Tetracycline.

CHAPTER FOUR

4.0 DISCUSSION

The study found a UTI prevalence of 15.6 % among heart failure patients using SGLT2 inhibitors. Though UTI prevalence for this specific population has not been extensively studied, these findings were higher compared to meta-analysis studies on the safety of SGLT2 inhibitors, these studies involved clinical trials in a controlled environment (18,27), a possible reason for this higher prevalence could have been due to the study site, water scarcity that limits proper hygiene, again, Tanzania is a tropical developing country with most of the summer season, and most warm weather leads to dehydration and decreased urine output leading to increased risk of UTI(43,44). All these studies have reported an increased risk, this is due to the mechanism of increased glucosuria, which creates an environment conducive to bacterial growth (45).

A lower positive predictive value of urinalysis (46.8%) almost like the study on the utility of dipstick urinalysis (46), this suggests that false positives are of concern and a confirmatory test, is required to avoid the misuse of antibiotics (47).

Age older than 60 significantly increases the risk of UTI. The most likely contributors to this risk are age-related changes in immune function, urinary tract anatomy, and comorbidities. (25). This is similarly reported in previous studies that investigated both diabetic and non-diabetic patients using SGLT2 inhibitors (48,49). Moreover, sex was also significantly associated with UTIs, female sex being at more risk, this finding aligns with known anatomical factors such as the urethra being closer to the anus and the urethral opening being near the bladder, together with the hormonal factors that predispose women to UTI more than men (50). Among women post-menopause women had a more increased risk of UTIs compared to pre-menopause this is due to changes in estrogen levels that eventually lead to changes in the urinary tract making it more susceptible to UTIs (50). These results are like the ones that were done in a follow-up study (51).The other study didn’t find any significance in menopausal status due to the few representatives in the group (48).

Furthermore, the duration of SGLT2 inhibitors use was also a significant factor for UTIs among patients, those who had been on the medication for four months had markedly higher risk of UTIs. This is due to persistent glucosuria, which increases the risk of bacteria proliferation and subsequent infection(6). This finding is similar to the study that studied the incidence of UTI among patients on SGLT2 inhibitors, which found that the occurrence of UTI was within three and six months of treatment (51). The observed late occurrence of UTI events of up to three months can be explained by initial polyuria caused by the SGLT2 inhibitors, the diuresis acts to prevent the expected glucosuria and the increased flow of urine through the tract decreases the urine bacterial load, therefore, preventing the proliferation of both bacteria and fungi (52)In this study there was no difference in the risk of UTIs in patients taking either Dapagliflozin 10mg or Empagliflozin, however, there is a study that showed an increased risk of UTI with Dapagliflozin compared to Empagliflozin(53) .

The study identified several uropathogens responsible for UTIs in this population, with Escherichia coli being the most frequently isolated pathogen (50%). This finding is consistent with global trends, where *E. coli* is the predominant uropathogen in both community-acquired and healthcare-associated UTIs (1).Other significant pathogens included *Klebsiella pneumoniae* (13%), *Pseudomonas aeruginosa* (9.1%), *Candida* spp. (9.1%), and *Klebsiella oxytoca* (9.1%). *Staphylococcus aureus* and *Staphylococcus saprophyticus* were responsible for 4.5% of the infections of Gram-positive organisms. The diversity of pathogens highlights the need for comprehensive diagnostic approaches to identify the causative organisms accurately and guide effective treatment.

Based on the isolated uropathogens, high resistance was noted that 100% and 90.9% of *Klebsiella* spp and *Escherichia coli* were resistant to Ampicillin like other studies in Tanzania (28,54), this persistent absolute resistance of Ampicillin even to other East African countries has led to the revocation of this product as a monotherapy in Tanzania by TMDA (22). The least resistance to no resistance was observed in Meropenem and Ciprofloxacin. *P. aeruginosa*, an alert micro-organism, has shown resistance to Amikacin, Piperacillin/tazobactam and is susceptible to Ciprofloxacin. The gram-positive bacteria are more resistant to tetracycline,

Staphylococcus saprophyticus is resistant to gentamycin, penicillin G, and Sulfamethoxazole/trimethoprim that is susceptible to *Staphylococcus aureus*, these gram-positive bacteria have shown a high susceptibility to nitrofurantoin which is also among the first-line treatment of UTIs.

This resistance pattern is consistent with other studies (33,37,39)and shows the importance of culture and sensitivity testing to tailor antibiotic therapy effectively, thereby improving treatment outcomes and mitigating the development of antibiotic resistance.

CHAPTER FIVE

5.0 LIMITATION, CONCLUSION AND RECOMMENDATIONS

5.1 Study limitations

This study had some limitations, the cross-sectional design limits the establishment of causality. Moreover, this study was single centered which may limit the generalizability of the findings to other settings. Fewer individual isolates fail to meet the criteria for generating an antibiogram and a conclusion on the susceptibility patterns.

To mitigate these, patients who were exposed to more risk factors, such as catheterized patients, were excluded, and the clear residence places of the patients were collected to observe the coverage of the patients from different regions.

5.2 Conclusion

This study has shown UTIs are prevalent by 15.6% among heart failure patients who were on SGLT2 inhibitors. Commonly isolated uropathogens included Escherichia coli, Klebsiella spp, Pseudomonas aeruginosa, Staphylococcus spp, and Candida spp. The bacterial uropathogens were highly resistant to Ampicillin, Tetracycline, Ceftazidime, Ceftriaxone, and gentamicin. While more susceptible to Nitrofurantoin and Meropenem. This study further highlights significant socio-demographic and clinical factors associated with UTIs among heart failure patients using SGLT2 inhibitors. Advanced age, female sex, prolonged medication use, and post-menopausal status are key risk factors. These study's findings therefore inform clinical practice and show the importance of targeted monitoring and preventive strategies to mitigate UTI risk in this vulnerable population. Continued research and clinical vigilance are essential to optimize heart failure patient management on SGLT2 inhibitors and reduce the burden of UTIs.

5.3 Recommendations

Regular vigilant monitoring and tailored preventive strategies for UTIs, especially in high-risk patients at baseline and follow-up clinics, should be mandatory.

Whenever possible, a culture confirmatory test should be implemented after a positive urinalysis to avoid misuse of antibiotics that create resistance.

Further studies with a different design are recommended to confirm these findings and provide a more comprehensive insight into the prevalence, management, and more effective intervention of UTIs in this population group.

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APPENDICES

Appendix I: Informed consent form (English Version)

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

SCHOOL OF PHARMACY

DEPARTMENT OF CLINICAL PHARMACY AND PHARMACOLOGY

ID no:……..

TITTLE: PREVALENCE OF URINARY TRACT INFECTIONS, ASSOCIATED FACTORS, AND ANTIMICROBIAL SUSCEPTIBILITY PATTERNS OF ISOLATED UROPATHOGENS AMONG THE HEART FAILURE PATIENTS ON SODIUM GLUCOSE TRANSPORTER 2 INHIBITORS (SGLT2i) JAKAYA KIKWETE CARDIAC INSTITUTE (JKCI).

PRINCIPLE INVESTIGATOR**:** JULIETH MICHAEL KAAYA

CONTACT: EMAIL**:** juliethmichael77@gmail.com

MOBILE NO: 0756437262/0786346868

Before joining, read and comprehend this form; asking for clarification is allowed.

Purpose of study: You are asked to participate in a research study. Before you decide to participate in this study, you must understand why the research is being done and what it will involve. Please read the following information carefully and ask the researcher if anything is unclear or if you need more clarification.

The purpose of this study is to assess the prevalence of urinary tract infections (UTIs) and evaluate the antimicrobial susceptibility patterns of the uropathogens among patients with heart failure diagnosis and are using either Dapagliflozin 10mg or Empagliflozin10mg as part of their management.

The study seeks to answer the following questions:

1. What is the prevalence of urinary tract infections (UTIs) among heart failure patients using Sodium Glucose Transporter 2 Inhibitors (SGLT2 inhibitors) at Jakaya Kikwete Cardiac Institute (JKCI)?
2. What potential risk factors are associated with UTIs in heart failure patients on SGLT2 inhibitors at JKCI?
3. What are the common bacterial isolates responsible for UTIs in heart failure patients on SGLT2 inhibitors at JKCI?
4. What are the antimicrobial susceptibility patterns of the uropathogens causing UTIs in heart failure patients on SGLT2 inhibitors at JKCI?

Study procedures: You shall meet with the researcher/ research assistant to complete a questionnaire involving your demographic information and Urine sample collection for laboratory analysis. All the necessary information will be documented, kept in your file, and used for further management.

Study protocol review and participant safety: The study protocol has been carefully reviewed by the MUHAS Institutional Ethical Review Board (IRB), whose role is to protect your rights, assess potential risks, and guarantee that the study is conducted ethically.

Voluntary participation

Your participation is voluntary, and you can withdraw from this study anytime. Your decision to participate or not to participate in this study will not impact the care and services provided at JKCI.

Risks: No risks or harm are associated with participating in this study.

Benefits: Your participation in this study will help to provide accurate data on whether there is a risk of developing UTI with the use of Dapagliflozin or Empagliflozin so that proper care and prevention interventions can be used along with these medications**.**

Privacy: The information and results of this research will be kept confidential except in cases where the researcher is legally obligated to report specific incidents.

Contact information: If you have questions about this study or experience adverse effects because of participating, you may contact the researcher whose contact information is provided on the first page.

If you have questions regarding your rights as a research participant or if problems arise that you do not feel you can discuss with the Primary Investigator, please contact the Institutional Review Board at +255 022 2152 489, drp@muhas.ac.tz.

Participation: Participation in this study is voluntary, and you will continue to receive any treatment to which you are entitled, regardless of your choice.

Consent: I have read and understand the provided information and have had the opportunity to ask questions. I know that my participation is voluntary and that I can withdraw at any time without giving a reason or cost. I understand that I will be given a copy of this consent form. I voluntarily agree to take part in this study.

Participant's signature _____ Date _____

Investigator's signature _____ Date _____

Appendix II: Informed consent form (Swahili Version)

CHUO KIKUU CHA AFYA NA SAYANSI SHIRIKISHI MUHIMBILI

SHULE YA FAMASI

IDARA YA FAMASI TIBA NA FAMAKOLOJIA

Namba ya uwakilishaji……...

FOMU YA UTOAJIIDHINI

Tafiti: UENEAJI WA MAAMBUKIZI YA NJIA YA MKOJO NA UPIMAJI WA DAWA SANIFU DHIDI YA VIJIDUDU SABABISHI KATI YA WAGONJWA WA MATATIZO YA MOYO WANAO TUMIA DAWA ZA VIZUIA SODIAMU GLUKOZI KATIKA USAFIRISHAJI (SGLT2i): UTAFITI KATIKA TAASISI YA MOYO YA JAKAYA KIKWETE (JKCI).

Mtafiti mkuu: JULIETH MICHAEL KAAYA

TAASISI: CHUO KIKUU CHA AFYA NA TIBA SHIRIKISHI MUHIMBILI (MUHAS)

SLP 65001 DAR ES SALAAM.

Mawasiliano: Baruapepe: juliethmichael77@gmail.com

Simu: 0756437262/0786346868

Ndugu mshiriki,

Unaombwa kushiriki kwenye utafiti.

Tafadhali shiriki baada ya kusoma na kulielewa vizuri dodoso hili. Kama kuna kitu chochote hautakielewa au unahitaji maelezo zaidi unaweza kuuliza.

Madhumuni ya utafiti: Dhumuni la utafiti huu ni kujua hali ya uenezi wa maambukizi ya njia ya mkojo na upimaji wa dawa sanifu dhidi ya vijidudu sababishi kati ya wagonjwa wa matatizo ya moyo wanao tumia dawa za vizuia sodiamu glukozi katika usafirishaji (SGLT2i): utafiti katika taasisi ya moyo ya Jakaya Kikwete (JKCI).

Utafiti huu unalenga kutoa majibu Kwa maswali yafuatayo:

1. Uenezi wa maambukizo ya njia ya mkojo (UTIs) miongoni mwa wagonjwa wa matatizo ya moyo wanaotumia vizuizi vya usafirishaji wa Sodiamu Glukosi 2 (SGLT2 inhibitors) katika Taasisi ya Moyo ya Jakaya Kikwete (JKCI)?
2. Ni vitisho vipi vinavyohusishwa na Maambukizi ya njia ya mkojo kwa wagonjwa wa matatizo ya moyo wanaotumia SGLT2 inhibitors katika JKCI?
3. Ni aina gani za bakteria mara kwa mara zinazosababisha UTIs kwa wagonjwa wa matatizo ya moyo wanaotumia SGLT2 inhibitors katika JKCI?
4. Ni Antibiotiki gani sanifu dhidi ya viini vya maambukizo ya njia ya mkojo inayosababisha Kwa wagonjwa wa matatizo ya moyo wanaotumia SGLT2 inhibitors katika JKCI?

Utaratibu wa utafiti: Utakutana na mtafiti/msaidizi wa utafiti kwa ajili ya kujaza dodoso ambalo linajumuisha taarifa zako binafsi na ukusanyaji wa sampuli ya mkojo kwa ajili ya uchambuzi wa maabara. Taarifa zote muhimu zitahifadhiwa na kumbukwa katika faili lako na kutumiwa kwa ajili ya usimamizi zaidi.

Ukaguzi wa itifaki ya utafiti na usalama wa mshiriki: Itifaki ya utafiti imepitiwa kwa makini na Bodi ya ukaguzi wa Taasisi ya chuo cha Muhimbili (IRB), ambalo jukumu lao ni kulinda haki zako, kutathmini hatari zinazoweza kutokea, na kuhakikisha kuwa utafiti unafanyika kwa maadili**.**

Ushiriki wako ni hiari

Ushiriki wako katika utafiti huu ni hiari na unaweza kujitoa katika utafiti huu mda wowote ukitaka. Na kutokushiriki katika utafiti huu hakutokuwa na madhara yoyote kwenye huduma za kimatibabu zitolewazo na hospitali kwa mgonjwa**.**

Madhara: Hakuna madhara yoyote au athari zozote zitakazo ambatana na ushiriki wako katika utafiti huu.

Faida: Ushiriki wako utasaidia kujua tathmini ya maambukizi ya njia ya mkojo (UTI) yatokanayo na matumizi ya Dapagliflozin au Empagliflozin, tathmini hii itasaidia kutoa huduma na elimu ya kuzuia na matibabu Sahihi kwa kipindi utakachokua unatumia dawa hizi.

Mawasiliano: Ikiwa una maswali wakati wowote kuhusu utafiti huu, au ukapata athari mbaya kutokana Na kushiriki katika utafiti huu, unaweza kuwasiliana na mtafiti ambaye maelezo yake ya mawasiliano yametolewa kwenye ukurasa wa kwanza.

Ikiwa una maswali kuhusu haki zako kama mshiriki wa utafiti, au kama matatizo yatatokea ambayo hujisikii unaweza kujadili Na Mpelelezi Mkuu, tafadhali wasiliana Na Bodi ya Uthibitishaji wa Taasisi kupitia namba +255 022 2152 489, drp@muhas.ac.tz.

Ushiriki: Ushiriki wako katika utafiti huu ni wa hiari na utaendelea kupokea matibabu yoyote unayostahiki bila kujali chaguo lako.

Ridhaa: Nimesoma na kuelewa taarifa zilizotolewa na nimepata fursa ya kuuliza maswali. Naelewa kwamba ushiriki wangu ni wa hiari na naweza kujiondoa wakati wowote, bila kutoa sababu yoyote na bila gharama. Naelewa kwamba nitapewa nakala ya fomu hii ya ridhaa. Kwa hiari yangu mwenyewe, nakubali kushiriki katika utafiti huu.

Sahihi ya Mshiriki _____ Tarehe _____

Sahihi ya Mtafiti _____ Tarehe _____

Appendix III: Structured questionnaire

TITTLE: PREVALENCE OF URINARY TRACT INFECTIONS, ASSOCIATED FACTORS AND ANTMICROBIAL SUSCEPTIBILITY PATTERNS OF THE ISOLATED UROPATHOGENS AMONG THE HEART FAILURE PATIENTS ON SODIUM GLUCOSE TRANSPORTER 2 INHIBITORS (SGLT2i) AT JAKAYA KIKWETE CARDIAC INSTITUTE (JKCI).

ID NO: …….

PART A: PARTICIPANT DEMOGRAPHIC INFORMATION

1. Age ……. (Years)

2. Sex
    a) Female
    b) Male
3. Marital Status
    a) Single
    b) Married
    c) Divorced
    d) Widow/Widower
    e) Co-habiting
4. What is your current occupation Status
    a) Government Employed
    b) Self Employed
    c) Unemployed
    d) Home job
    e) Student
5. How do you cover your medical bills?
    a) Health Insurance
    b) Cash

6. Where do you reside permanently
    a) Within Dar es Salaam
    b) Other Regions
    c) From a border country.

PART B: MEDICAL AND MEDICATION HISTORY

7. Do you have any other chronic comorbidities besides heart failure?
    a) Yes
    b) No
8. If yes for Response 9, What other comorbidities do you have
    a) Other Cardiovascular Diseases, Diabetes
    b) Others
    c) HIV/AIDS

PART C: LIFESTYLE AND OTHER RISK FACTORS

9. What type of toilets do you use at home?
    a) Pit latrines
    b) Flashing Latrines
    c) Others
10. Do you have any idea about UTI prevention strategies?
    a) Yes
    b) No
11. Do you know any symptoms of UTI (Fever, chills, Nausea, Vomiting, lanky pain, dysuria)
    a) Yes
    b) No
12. Have you ever been diagnosed with a urinary tract infection (UTI)?
    a) Yes
    b) No

Appendix IV: Case report form

SECTION A: PATIENT MEDICAL MEDICATION HISTORY

Patient attendee at jkci as	TICK/Record	ANY COMMENT
✓ Inpatient		
✓ Outpatient		
Patient vital signs		
SBP		
DBP		
HR		
Type of SGLT2 Inhibitor the patient has been taking		
✓ Empagliflozin		
✓ Dapagliflozin		
1. Duration since started on SGLT2 inhibitor		
✓ 1month		
✓ 2-4months		
✓ 5-7 months		
✓ More		
2. Other heart failure drugs the patient is taking		
✓ Beta blocker		
✓ Loop Diuretics		
✓ Spironolactone		
✓ ACEI /ARNI)/ARB		

Others (specify)		
3. Left Ventricular Ejection Fraction		
✓ <40%		
✓ 41-49%		
✓ >50%		
4. The patient has urinary tract infection symptoms		
✓ YES		
✓ NO		

SECTION B: URINE SAMPLE COLLECTION AND LAB RESULTS

5. Urine sample aseptically collected and labeled		
✓ YES		
✓ NO		
6. Urine samples timely sent to a laboratory		
✓ YES		
✓ NO		
7. Bacteriuria		
✓ Negative		
✓ No significant growth		
✓ A colony count of $\geq 10^5$ CFU/ml		

8. Uropathogens isolated		
9. Antimicrobial susceptibility test results		
10. Urinalysis results		

Appendix V: Approval for ethical clearance

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION

Ref. No.DA.282/298/01.C/2049 Date: 19/02/2024

MUHAS-REC-02-2024-2049
JULIETH MICHAEL KAAYA
MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: PREVALENCE OF URINARY TRACT INFECTIONS AND ANTIMICROBIAL SUSCEPTIBILITY PATTERNS OF UROPATHOGENS ISOLATED FROM HEART FAILURE PATIENTS ON SODIUM GLUCOSE TRANSPORTER 2 INHIBITORS AT JAKAYA KIKWETE CARDIAC INSTITUTE

Reference is made to the above heading,

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 19/02/2024
EXPIRATION DATE OF APPROVAL: 19/02/2025

STUDY DESCRIPTION:
Purpose:

The purpose of this study is to assess the prevalence of UTI and evaluate the antimicrobial susceptibility patterns of the isolated uropathogens among heart failure patients using SGLT2 inhibitors at Jakaya Kikwete Cardiac Institute (JKCI).

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided: https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2014554.pdf and in the MUHAS archives.

The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain Data Transfer Agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain Material Transfer Agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country.
8. Apply for and obtain permission to publish the results from National Institute for Medical Research. The application should be before submitting to a publisher and not concurrently through the email publications@nimr.or.tz.
9. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
10. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
11. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.



Dr. Nahya Salim Masoud,
CHAIRPERSON, MUHAS RESEARCH AND ETHICS COMMITTEE

Appendix VI: Permission letter to collect data at Jakaya Kikwete Cardiac Institute.

UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

JAKAYA KIKWETE CARDIAC INSTITUTE
(JKCI)

JAKAYA KIKWETE CARDIAC INSTITUTE

In reply please quote;
Ref No: AB.123/307/01K/20 12/03/2024

Julieth Michael Kaaya
HD/MUH/T.422/2022
MPharm Hospital and Clinical Pharmacy
MUHAS

RE: PERMISSION TO CONDUCT RESEARCH AT JKCI

Reference is made to your letter requesting to do a research study entitled **"Prevalence of Urinary Tract Infections And Antimicrobial Susceptibility Patterns of Uropathogens Isolated from Heart Failure Patients on Sodium Glucose Transporter 2 Inhibitors at Jakaya Kikwete Cardiac Institute."** here at JKCI.

This letter serves as an official document that permits you to do the above-mentioned task as requested. However, the institution also requires you to have JKCI local co-supervisor.

It is our sincere hope that you will abide by the rules and regulations of good clinical practice. We wish you the best and hope your stay at JKCI will be fruitful.

Best Regards,

JAKAYA KIKWETE CARDIAC INSTITUTE P. O. Box 65141 Dar-es-Salaam JKCI

Dr. Pedro Pallangyo
Head of Research, Training and Consultancy.
CC: ALL DIRECTORATES & Head of Units

Jakaya Kikwete Cardiac Institute (JKCI); Upanga East Plot No. 1048, Kalenga Street, Malik Road, P. O. Box 65141 - Dar es Salaam; Telephone Number + 255 -22- 2152392Email:info@jkci.or.tz, Website: ww.jkci.or.tz.

Appendix VII: Permission to conduct research at CPL -(MNH)

THE UNITED REPUBLIC OF TANZANI

MINISTRY OF HEALTH

MUHIMBILI NATIONAL HOSPITAL

In reply please quote;

Ref. No.: MNH/CRTCU/Perm/2024/141 Date: 18th March, 2024

Head of Department,
Central Pathology Laboratory,
Muhimbili National Hospital

RE: PERMISSION TO COLLECT DATA AT MNH

Name Student	**Julieth Michael Kaaya**
Title	**"Prevalence of Urinary Tract Infections and Antimicrobial Susceptibility Patters of Uropathogens Isolated From Heart Failure Patients on Sodium Glucose Transporter 2 Inhibitors at Jakaya Kikwete Cardiac Institutional".**
Institution	Muhimbili University of Health and Allied Sciences
Supervisor	Dr. Ritah Mutagonda (MUHAS)
Co – Supervisor	Albert Ntukula (MNH)
Period	18th March, 2024 to 30th May, 2024

Approval has been granted to the above principal investigators to collect data at MNH. Dissemination of study findings at MNH shall be overseen by **Albert Ntukula** (MNH) supervisor.

Kindly ensure the named principal investigator abide to the ethical principles and other conditions of the research approval.

Sincerely,

Dr. Charles K. Pallangyo
For: Head of Clinical research, Training and Consultancy Unit

TEACHING, RESEARCH & CONSULTANCY UNIT
P.O. Box 65000
DAR ES SALAAM
MUHIMBILI NATIONAL HOSPITAL

c.c DCSS
c.c Albert Ntukula
c.c **Julieth Michael Kaaya**

Upanga West, Kalenga Street, Plot No. 10480/3, P.O. BOX 65000, Dar es Salaam, Tanzania.
Telephone: +255-22-2151367-9, Telephone: +255-22-2151351-2
Email: info@mnh.or.tz, Website: www.mnh.or.tz