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Risk factors and outcomes of acute kidney injury among covid-19 patients at a tertiary hospital in Kenya

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RISK FACTORS AND OUTCOMES OF ACUTE KIDNEY INJURY AMONG COVID-19 PATIENTS AT A TERTIARY HOSPITAL IN KENYA

By

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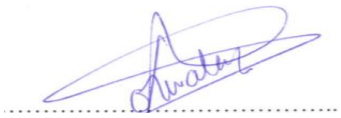

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ABSTRACT

Background

Corona Virus Disease 2019 (COVID-19), a novel infection caused by the SARS-Cov-2 virus, was declared a global pandemic on March 11, 2020. Three years later, 350,000 Kenyans had gotten the infection, with approximately 5,700 reported related deaths. Despite emerging research on the new virus, studies from the African continent on the impact of COVID-19 on the kidneys have been few.

Early studies suggest that up to 75% of patients with COVID-19 have a derangement in their kidney function as evidenced by new onset proteinuria and hematuria. That said, the prevalence of acute kidney injury has varied greatly across populations, ranging from nine to fifty five per cent depending on the geographical area, differences in COVID-19 infection severity, race, age, and the socioeconomic status of the patient population. Being of African descent in particular has been identified as an independent risk factor for AKI in many of these studies.

Acute kidney injury in hospitalized patients is associated with increased mortality risk and a prolonged duration of hospital stay, with higher odds seen among patients with COVID-19 infection. In addition, AKI-recovered patients are less likely to have complete recovery of their renal function, even after clearance of the infection, and have been shown to have a faster progression in chronic kidney disease on follow-up.

Aim and objectives

The study aims to determine the impact of COVID-19 infection on the kidneys. The primary objective is to determine the prevalence and risk factors of acute kidney injury in COVID-19 patients at a tertiary-level hospital in Nairobi, Kenya. The secondary objective is to assess the short-term outcomes of AKI in these patients at the time of hospital discharge. These outcomes include in-hospital mortality rate, the duration of hospital stay and the status of renal recovery.

Methods

In this retrospective cohort study, COVID-19 patients above the age of 18 years admitted between April 1st 2020 and October 31st 2021 were included. Patients without serial creatinine results and those with end-stage renal disease met the exclusion criteria. Data was collected on demographic and clinical characteristics. After determining the AKI period prevalence, bivariate analysis was carried out to determine statistically significant associations of these factors with AKI, with a p-value set at 0.05. A logistic regression model was then applied to determine independent associations with AKI, with results reported as an odds ratio with a 95% confidence interval, and adjusted for age and gender. The

outcomes of AKI were stratified based on the stage of AKI and reported as percentages, medians and interquartile ranges.

Results

The study included 1366 patients. The median age of study patients was 56 years (interquartile range [IQR] 45-68), with 67% of them being male (n=914). The AKI prevalence in the study period was 21.6% (n=295). Patients with AKI were older (median age 64 years vs 54 years; P<0.001) and more likely to be male (P<0.001). These patients were also more likely to have severe COVID-19 illness.

Comorbid conditions related to the development of AKI in COVID-19 patients in our setting include diabetes and hypertension, with an adjusted odds ratio of 1.75 (95% CI 1.34-2.30; P<0.001) and 1.68 (95% CI 1.27-2.23; P<0.001) respectively. COVID-19 patients with AKI were 11 times more likely to die (95% CI 7.56-17.03; P<0.001), with a mortality rate proportional to the severity of AKI. The median duration of hospital stay was 10 days for patients with AKI [IQR 5-18] vs 8 days for non-AKI patients [IQR 5-10]; P<0.001.

Conclusion

Acute kidney injury is a less recognized complication of COVID-19 infection. We found significantly higher odds of AKI with increasing age, gender, hypertension, diabetes and severity of COVID-19 illness. We also demonstrated a strong independent association between AKI in COVID-19 and mortality and an impact of AKI in COVID-19 on hospital duration and renal recovery.

Keywords; COVID-19, Acute kidney injury, African population, Risk factors, Prevalence, Outcomes

LIST OF ABBREVIATIONS USED

AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ART	Anti-Retroviral Therapy
COVID-19	Coronavirus Disease 2019
FGF	Fibroblast Growth Factor
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
HIV	Human Immunodeficiency Virus
IDF	International Diabetes Federation
IFNγ	Interferon-gamma
KDIGO	Kidney Disease Improving Global Outcomes
MERS	Middle East Respiratory Syndrome
PDGF	Platelet-Derived Growth Factor
RAAS	Renin Angiotensin Aldosterone System
RIFLE	Risk, Injury, Failure; End-Stage Renal Disease
RT-PCR	Reverse Transcription- Polymerase Chain Reaction
SARS-CoV	Severe Acute Respiratory Syndrome- Coronavirus
TMPRSS	Transmembrane Protease Serine Protein
TNFα -	Tumor Necrosis Factor Alpha
VEGF	Vascular Endothelial Growth Factor

DEFINITION OF TERMS

Acute kidney injury

Acute kidney injury is defined by the KDIGO classification as one of the following (KDIGO, 2012; Mehta et al., 2007);

- An increase in serum creatinine by 26.53 micromole/l (0.3 mg/dl) or more within 48 hours OR
- An increase in serum creatinine to 1.5 times the baseline or more within the last 7 days OR
- A urine output less than 0.5 mL/kg/h for 6 hours or more.

The severity of AKI is classified as stage 1, 2 or 3:

- Stage 1; a rise in serum creatinine by 1.5-1.9 times the baseline OR an increase in serum creatinine of ≥26.53 umol/l (0.3 mg/dl) OR a urine output < 0.5 mL/kg/h for at least 6 hours.
- Stage 2; a rise in serum creatinine 2-2.9 times the baseline OR a urine output < 0.5 mL/kg/h for at least 12 hours.
- Stage 3; rise in serum creatinine 3 times the baseline OR to ≥353.68 umol/l (4 mg/dl) OR the initiation of renal replacement therapy OR a urine output < 0.3 mL/kg/h for 24 h or anuria for ≥12 h

COVID-19 infection

The 2021 Kenyan guidelines on the case management of COVID-19 categorize severity of disease in adults as below (M. o. Health, 2020a);

- Mild illness; Patients presenting with fever, cough, sore throat, malaise, headache, and muscle pain BUT no shortness of breath and no abnormalities on chest imaging.

- Moderate illness; Patients with clinical features of pneumonia (fever, cough, dyspnea) AND/OR radiological features of pneumonia BUT sPO2 > or = 94% on room air.

- Severe illness; Patients with clinical and radiological features of pneumonia, tachypnea (respiratory rate >30 breaths/min) AND oxygen saturations of <90% on room air.

- Critical illness; Features of severe illness and any of the following; Respiratory failure, sepsis or septic shock, acute thrombosis or multiorgan dysfunction

Diabetes mellitus

The diagnosis of diabetes mellitus is based on the 2018 Kenya National Clinical Guidelines for the Management of Diabetes Mellitus, which was adopted from the 2017 IDF Clinical Practice Recommendations for managing type 2 diabetes (Association, 2019);

- A fasting plasma glucose level of 7 mmol/l (126 mg/dL) or higher, OR
- A 2-hour plasma glucose level of 11.1 mmol/l (200 mg/dL) or higher following ingestion of a 75-g glucose load OR
- A random plasma glucose of 11.1 mmol/L (200 mg/dL) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, OR
- A hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol) or higher

Hypertension

The definition and classification of hypertension in this study are based on the European Society of Cardiology (ESC)/ European Society of Hypertension (ESH) guidelines (Kjeldsen, Narkiewicz, Burnier, & Oparil, 2018) which have been adopted for the management of hypertension in Kenya;

- Optimal blood pressure; BP <120/<80 mmHg
- Normal blood pressure; BP <120-129/80-84 mmHg
- High normal; BP 130-139/85-89 mmHg
- Grade 1 hypertension; BP 140-159/90-99 mmHg
- Grade 2 hypertension; BP 160/179/100-109 mmHg
- Grade 3 hypertension; BP >180/>110 mmHg

Patients are classified as hypertensive if they have a BP >140/90 mmHg taken in two instances more than 4 hours apart.

Recovery of kidney function

Recovery of kidney function is defined by the KDIGO working group as independence from dialysis therapy, a decrease in serum creatinine to a level less than a defined threshold in patients older than 65 years or a return to baseline kidney function in patients younger than 65 years(KDIGO, 2012).

Complete recovery in kidney function is defined by consensus as a return to baseline pre-AKI creatinine levels (KDIGO, 2012). This may not however represent a 'true' complete recovery since patients with pre-AKI kidney values will likely have compensated kidney function to make up for the nephron loss. These patients are still at risk of progression to chronic kidney disease.

Partial renal recovery is defined by consensus as recovery in kidney function by >50% without a return to initial baseline values(KDIGO, 2012).

ACKNOWLEDGEMENT

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Thank you all.

DECLARATION

I declare this dissertation does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university and that, to the best of my knowledge, it does not contain any material previously published or written by another person except where due reference has been made in the text.

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(Signature of candidate)

3rd March, 2023

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Date

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CHAPTER 1: INTRODUCTION

1.1 Background

COVID-19 is a new infection caused by the SARS-CoV-2 virus of the coronavirus family. It was declared a global pandemic by the World Health Organization on March 11, 2020, three months after the first case of a 'pneumonia of unknown aetiology' was announced in the Wuhan area of China in December 2019 (Organisation, 2023). In Kenya, the first confirmed COVID-19-positive case was reported on 13th March, 2020. As of September 2021, approximately 340,000 people in Kenya had contracted the infection, with 5,700 reported COVID-19-related deaths (Worldometer, 2023).

Initial reports of the symptomatology of COVID-19 infection were synonymous with the respiratory system. Recent studies have however shown that receptors for the SARS-CoV-2 virus are present in kidney tubular cells, nerve cells, and cells of the small and large gut (Gagliardi et al., 2020; Sun, Lu, Xu, Sun, & Pan, 2020; Zou et al., 2020) Evidence suggests that up to 75% of patients with COVID-19 across the disease spectrum have a derangement in their kidney function, demonstrated in urinalysis and creatinine value changes (Gabarre et al., 2020; Gagliardi et al., 2020; Naicker et al., 2020).

Acute kidney injury (AKI) refers to a sudden decline in kidney function as evidenced by a reduction in the glomerular filtration rate and/or urine output over time, most recently defined by the 2012 Kidney Disease; Improving Global Outcomes (KDIGO) Classification (KDIGO, 2012). It is further categorized into pre-renal, renal and post-renal causes. In COVID-19 infected patients, AKI has been attributed to pre-renal and renal effects of the SARS-CoV-2 virus, either directly or indirectly (Gagliardi et al., 2020; Zou et al., 2020). AKI is a known independent risk factor for mortality in hospitalized patients, especially the critically ill, with the odds ranging from 2-3 (Uchino et al., 2005; H. E. Wang, Muntner, Chertow, & Warnock, 2012). It is also linked to longer hospitalization and increased medical costs. Kidney injury tends to occur more in patients with underlying comorbid conditions, including diabetes mellitus, cardiovascular disease and immunosuppressive states due to reasons ranging from underlying kidney damage to health-seeking behavior in these patients (Aylward et al., 2019; Schissler et al., 2013). Additionally, being of African descent has also been linked in some studies to be an independent factor for AKI development in COVID-19 patients, with the likelyhood ranging from 1.3 to 2.5 (Fisher et al., 2020; Hirsch et al., 2020; Nimkar et al., 2020; Nugent et al., 2021).

This single- center study aims to determine the prevalence of AKI in COVID-19 hospitalized patients and the clinical factors associated with AKI development. It also looks at the short-term outcomes of AKI in this cohort of patients, including in-hospital mortality rate, renal function status at the time of hospital discharge and the duration of hospital stay.

1.2 Problem statement

Recent studies have demonstrated that the prevalence of AKI is higher in patients with COVID-19 compared to other hospitalized patients (Arentz et al., 2020; Brill et al., 2020; L. Chan et al., 2021; Uchino et al., 2005; H. E. Wang et al., 2012). That said, this prevalence rate has varied greatly across populations, ranging from an average of nine per cent in earlier studies published in China, to 55% in US and European studies involving a bigger number of patients with varied COVID-19 infection severity, diverse races and age groups, differences in health facility size, geographical coverage, and the socioeconomic status of the patient population (Arentz et al., 2020; Brill et al., 2020; L. Chan et al., 2021; Chen et al., 2020; Fisher et al., 2020; Guan et al., 2020; Hirsch et al., 2020; Nimkar et al., 2020; Pelayo et al., 2020; Regina et al., 2020; Yang et al., 2020).

On outcomes , recent studies show that AKI is associated with even higher mortality risk in patients with COVID-19 infection, up to 13 times greater (L. Chan et al., 2021; Cheng et al., 2020; Fisher et al., 2020; Hansrivijit et al., 2020; Nimkar et al., 2020; Regina et al., 2020; Robbins-Juarez et al., 2020; Yang et al., 2020). In patients who are discharged from the hospital, COVID-19 patients with AKI are less likely to have complete recovery of their renal function, even after clearance of the infection, compared to other hospitalized patients with AKI, and are more likely to be discharged on dialysis (L. Chan et al., 2021; Fisher et al., 2020; Hirsch et al., 2020; Nugent et al., 2021; Pei et al., 2020; Robbins-Juarez et al., 2020).

Despite a rising prevalence of non-communicable diseases in our population (Ayah et al., 2013; Federation, 2021), studies from the African continent demonstrating the effect of COVID-19 infection on the kidneys have been few, and there have been no published papers from our region to the best of our knowledge. According to a 2017 economic analysis, about 10,000 Kenyans were dialysis dependent, with the annual cost of dialysis per patient in Kenya estimated at USD 16,000 (Mushi, Marschall, & Flessa, 2015). This patient number is expected to rise after the COVID-19 pandemic due to new cases of unrecovered kidney injury and the addition of previously undiagnosed chronic kidney disease patients.

1.3 Study rationale

The COVID-19 pandemic has been compared to the Spanish flu of the 1900s due to its global impact on health and the economy. As the world's focus shifts to the intermediate and long-term effects of the SARS-CoV-2 virus on the human body, studies from the developing world are emerging at a much slower pace. An analysis of the prevalence and factors associated with AKI in COVID-19 infection in our setting will add to this increasing evidence.

The study also assesses the degree of impact of known risk factors on acute kidney injury in COVID-19 patients at a hospital in Keny. Given the high burden and poor control of chronic illnesses in our setting, this study offers answers that are unique to our setting. In addition to known risk factors, the study also assesses the impact of HIV, a potential and less-studied risk factor, on AKI in COVID-19 patients. The burden of HIV in sub-Saharan Africa is high and the disease has been shown to contribute to kidney injury, thus the need to be included as a potential risk factor.

Lastly, the study looks at the short-term impact of AKI in COVID-19 patients up to the time of hospital discharge. It will form a foundation for further studies on the intermediate and long-term effects of COVID-19 infection. Information on renal status and the progression of kidney disease is important in health system planning. Health care in Kenya is primarily supported through government expenditure(M. o. Health, 2020b). Understanding the impact of COVID-19 infection on increased dialysis dependence rate and chronic kidney disease care will aid with health expenditure planning.

1.4 Research question

What are the associated factors and outcomes of acute kidney injury in patients hospitalized with COVID-19 infection?

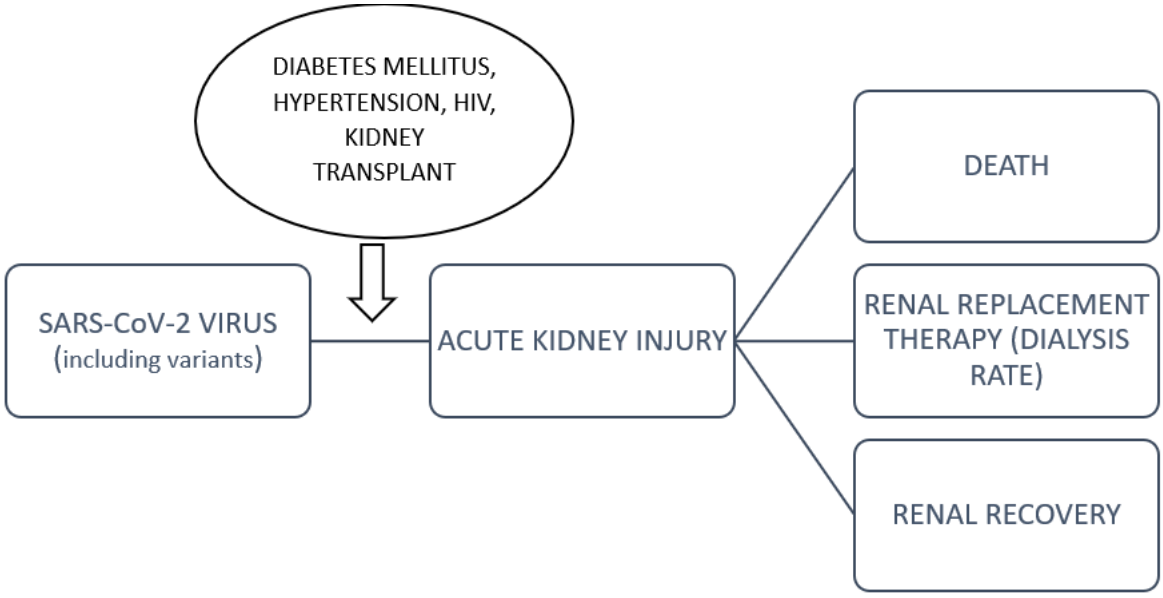
1.5 Aim and objectives

The study aims to determine the relationship between COVID-19 infection and the kidneys.

The study has two objectives. The primary objective is to determine the prevalence and risk factors of acute kidney injury in COVID-19 patients admitted to Aga Khan University Hospital, Nairobi, between April 1st 2020 and October 31st 2021. The secondary objective is to assess the outcomes of AKI in these patients. These outcomes include the in-hospital mortality rate, renal function status at hospital discharge and the duration of hospital stay.

1.6 Conceptual framework

See below the theoretical and conceptual framework



CHAPTER 2: LITERATURE REVIEW

The literature review covers the pathophysiology of COVID-19 infection and acute kidney injury. The structure of SARS-CoV-2 is explained in detail, including its attachment to receptors of the kidney cells. Variants of concerns and their effect in altering the diseases course and prevalence of kidney injury is covered appropriately. Risk factors for acute kidney injury include chronic illnesses and genetic reasons that may account for population differences in AKI prevalence. The impact of these factors on AKI causation, particularly in our population, is expounded. Lastly, the outcomes of AKI are described, including renal replacement therapy and timing, mortality rates and renal recovery, with reasons.

2.1 COVID-19

The coronavirus family of viruses is a group of single-stranded RNA viruses that have been responsible for emerging respiratory disease outbreaks over the years in humans and animals across the globe. Examples of coronavirus outbreaks in humans include the SARS-CoV-1 pandemic of 2002-2004 which began in Asia and spread to countries in Europe, and North and South America, and the MERS-CoV epidemic which originated in the Middle East in 2012 (Y. Wang, Grunewald, & Perlman, 2020). Both viruses cumulatively infected about 10,000 people globally and caused approximately 1,500 deaths. In comparison, the SARS-CoV-2 virus has infected approximately 620 million human beings across the globe so far, with reported related deaths at 6.5 million people as at November 2022 (Worldometer, 2023).

SARS-CoV-2 virus differs from other viruses in the coronavirus family in that it has a mutation in the gene coding for the receptor binding domain (RBD), which is a segment of the spike protein found on the cell surface of the SARS-CoV-2 virus (Gagliardi et al., 2020; Y. Wang et al., 2020; Zou et al., 2020). This mutation increases its binding affinity to receptors in human cells, making it more infective (spread from one person to another) and more symptomatic (increased disease severity).

Since the first reported infections in early 2020, different variants of the SARS-CoV-2 virus have been reported emerging from certain parts of the world between December 2020 and mid-2021, namely the alpha, beta, gamma, omicron and delta variants among others. All these variants of concern are associated with missense mutations in the gene coding for parts of the spike protein, resulting in a greater increase in infectivity, disease severity and of greater concern, immune evasion in the background of vaccine development (Hadj Hassine, 2022). Of particular note is the delta variant of the

SARS-CoV-2 virus, first detected in May 2021 in India, which has been shown to have a uniquely high infectivity and disease severity rate, and reduced vaccine effectiveness (Hyams et al., 2022).

The SARS-CoV-2 virus attaches to Angiotensin Converting Enzyme 2 (ACE2) receptors that are found in cells of various organs including the lung, cardiac muscle cells, renal cells, vascular endothelial cells and enterocytes of the small and large gut. With the assistance of the TMPRSS2 receptor protein on the host cell surface, the virus enters the cell to trigger cell lysis and an immune response that culminates in tissue injury, a dysfunctional coagulation cascade and a cytokine response syndrome with multiple organ dysfunction (Gabarre et al., 2020; Gagliardi et al., 2020; Kuppalli & Rasmussen, 2020; Y. Wang et al., 2020; Zou et al., 2020).

In the kidney, ACE-2 receptors are expressed mainly by proximal tubular cells and, to a lesser extent, by renal distal tubular cells, glomerular parietal epithelial cells, and the principal and intercalated cells of the collecting duct (Gabarre et al., 2020; Gagliardi et al., 2020; Zou et al., 2020). Coreceptors including TMPRSS2 protein that aid in virus entry, are present on the surface of podocytes and renal proximal tubular cells, which could explain why acute kidney injury in COVID-19 infection is often preceded by proteinuria, hematuria and hypokalemia (Gabarre et al., 2020; Gagliardi et al., 2020; Naicker et al., 2020; Sun et al., 2020; Y. Wang et al., 2020).

Early studies have shown that approximately 80% of COVID-19 infection cases are mildly symptomatic while 20% range from moderate to severe illness requiring hospital admission (Gagliardi et al., 2020). The severity of the disease varies based on the virus variant, the human unique physiology and the demographic characteristics of the patients. COVID-19 infection spreads from human to human via respiratory droplets.

2.2 Acute kidney injury

Acute kidney injury(AKI) is defined as a sudden rapid decline in kidney function as evidenced by a drop in the glomerular filtration rate, with or without a reduction in urine output (KDIGO, 2012).

The KDIGO (Kidney Disease: Improving Global Outcomes) classification system was proposed in 2012 and is used to define and classify AKI based on severity (2). It is currently preferred over other AKI criteria for two reasons. First, the KDIGO criteria is a more sensitive indicator for acute kidney injury. This has been demonstrated in multiple trials that show a higher AKI prevalence in the same study population when compared to the use of previous AKI classification criteria. In the BAKIT trial, the KDIGO criteria identified more patients with acute kidney injury (51%) in comparison with the RIFLE (46.9%) and AKIN (38.4%) criteria (3).

Secondly, the KDIGO criteria for AKI takes into account time changes in creatinine values by incorporating both time limits used previously in the AKIN and RIFLE criteria i.e., a change in creatinine value in 48 hours as per AKIN criteria AND/OR changes in estimated glomerular filtration rate within seven days as per RIFLE criteria. This also makes the KDIGO criteria easier to employ in the diagnosis of AKI.

2.3 Pathophysiology of AKI in COVID-19

COVID-19 infection causes acute kidney injury in the following pre-renal and intrarenal ways (Gabarre et al., 2020; Gagliardi et al., 2020; Kuppalli & Rasmussen, 2020; Naicker et al., 2020; Sun et al., 2020; Y. Wang et al., 2020; Zou et al., 2020);

2.3.1 Pre-renal causes

Infection with the SARS-CoV-2 virus causes a systemic hypotension due to a dysregulation of the host immunoregulatory system, leading to the release of cytokines with accompanying changes in vascular permeability. The result is a circulatory collapse with reduced blood flow through the glomerular cells, causing a rise in creatinine levels. Other pre-renal causes of AKI include idiopathic hypotension and vasopressor-induced renal vasoconstriction, especially in critically ill patients on mechanical ventilation.

2.3.2 Intrarenal causes

At the kidney level, the SARS-CoV-2 virus binds to renal tubular cells and surrounding interstitial cells and causes cell death by a direct cytopathic effect. This results in glomerular leakage and acute tubular necrosis, which presents early on as hematuria, proteinuria and electrolyte disturbances.

Activation of the immune system then occurs as a result of cell damage and virus recognition, accompanied by the release of cytokines involved in triggering inflammation, for instance, interleukin-6 and 11. In addition, regulatory T cell activity is reduced. These actions promote tissue inflammation, increase renal vascular permeability and cause changes in the microcirculation culminating in reduced blood flow to the nephrons and ischemic/hypoxic cell damage. Further dysregulation of the host immune response can occur, with recent renal pathology studies indicating a similarity in inflammatory pathways and markers between AKI in COVID-19 and AKI in sepsis.

Chronic proteinuria as a result of podocyte and glomerular cell damage has a toxic effect on renal tubular cells, promoting inflammation and renal fibrosis with time. This has been proposed as a long-term renal effect of COVID-19 infection, which may explain the ongoing decline in glomerular function with time in patients already recovered from COVID-19 infection.

Excessive activation of the renin-angiotensin-aldosterone system (RAAS) has been shown to contribute to renal dysfunction in COVID-19 infection. The attachment of SARS-Cov-2 virus to ACE2 receptors results in a downregulation of these receptors as the body's protective response to the viral infection. Angiotensin Converting Enzyme 2 normally functions in the body to convert angiotensin II to its inactive form angiotensin. As a result of the downregulation of these receptors, angiotensin II is not inactivated; it accumulates and causes efferent arteriolar vasoconstriction, raising the glomerular filtration pressure. Prolonged raised pressure causes glomerular cell damage with activation of the immune system and eventually healing with glomerular and tubular fibrosis.

Rhabdomyolysis with myoglobinuria causes acute tubular necrosis. Muscle breakdown results from SARS-CoV-2 virus entry into myocyte cells with accompanying inflammation and triggered cell death. Other plausible reasons include tissue hypoxia from vascular changes in sepsis and as an adverse effect of medication used in the treatment of COVID-19-infected patients e.g., propofol. Tissue hypoxia can also cause renal medullary hypoxia with cell death.

A disruption in intra-renal blood flow due to a hypercoagulable state and microangiopathy is another cause of intra-renal AKI. SARS-CoV-2 virus infection activates the immune system with the release of tissue factors that then trigger the coagulation cascade. Additionally, erythrocyte aggregates and fibrin deposits in glomerular and peritubular capillaries as a result of cytokine release and coagulation pathway activation interfere with blood flow within the kidneys causing acute cortical necrosis.

Lastly, AKI can be triggered by medication, ranging from over-the-counter self-medication like non-steroidal anti-inflammatory drugs, to antibiotics in an outpatient setting that patients with mild to moderate illness may take as a symptom-mitigating treatment. Medication contributes to kidney injury either as a direct toxic effect or via disruptions in renal blood flow.

2.4 Prevalence of Acute Kidney Injury in COVID-19 patients

The prevalence of acute kidney injury in hospitalized patients has varied across populations based on health facility type and size, demographic differences, diagnosis and severity of illness. In a meta-analysis study based on the KDIGO criteria and published in 2013, Susantitaphong et al demonstrated a pooled AKI worldwide prevalence rate of 23.2% (Susantitaphong et al., 2013). Of note, this study included 312 publications, most of them from high-income countries with good healthcare resource allocation, and none from the African continent. In a UK population-based cohort study (GLOMMS-II), the incidence of hospital-acquired AKI in the Calgary health care system in 2003 was 19.4 % (Sawhney, Marks, Fluck, Levin, Prescott, et al., 2017).

Local studies have indicated a lower AKI incidence rate in both community-acquired and hospitalized patients. A cross-sectional study on the point prevalence of AKI in hospitalized patients carried out by Munyu et al at a Kenyan private tertiary-level hospital in 2008 demonstrated a period prevalence rate of 1.05% (Munyu, 2008). A similar study by Mohamed et al in 2016 at a Kenyan public tertiary-level hospital yielded a period prevalence rate of 8.1% (Mohammed, 2017). The difference in AKI prevalence in these two Kenyan studies could be explained by the different AKI criteria used (RIFLE vs KDIGO criteria respectively), and differences in health facility services (public vs private) which reflect the socio-economic characteristics of the patient population that influences health-seeking behaviour. In both Kenyan studies, identified risk factors for acute kidney injury included local genitourinary infections, sepsis, gastrointestinal fluid and electrolyte losses, the unintentional or iatrogenic use of nephrotoxic medication and the contribution of poorly controlled comorbid conditions like diabetes, pulmonary disease and malignancies(Mohammed, 2017; Munyu, 2008).

The prevalence of acute kidney injury is noted to be higher in COVID-19 patients in comparison studies where analysis was done versus non-COVID-19 hospitalized patients. Fisher et al assessed the prevalence of AKI in COVID-19 patients versus AKI in non-COVID-19 patients hospitalized in the same time period and found that in COVID-19 patients, the rate was 1.5 times higher in COVID-19 patients, at 56.9% versus 37.2% (Fisher et al., 2020). In recent studies from the US and Europe, AKI prevalence in COVID-19 patients has ranged between 18-54 %, reflecting an increased risk effect of COVID-19 on acute kidney injury of 2.5-6.8 (Arentz et al., 2020; Brill et al., 2020; L. Chan et al., 2021; Chen et al., 2020; Fisher et al., 2020; Guan et al., 2020; Hirsch et al., 2020; Nimkar et al., 2020; Nugent et al., 2021; Pelayo et al., 2020; Regina et al., 2020; Yang et al., 2020).

2.5 Risk Factors for Acute Kidney Injury in COVID-19 patients

Identified factors associated with acute kidney injury in COVID-19 disease include age, race, comorbid conditions and COVID-19 disease severity. That said, the extent to which these risk factors exist and contribute to the outcomes in this subset of patients has varied greatly based on the population's clinical and demographic characteristics.

2.5.1 Critical illness

Of all probable risk factors for acute kidney injury, the severity of COVID-19 disease is possibly the greatest contributor to the prevalence and poor outcomes of acute kidney injury (Arentz et al., 2020; Hirsch et al., 2020; Regina et al., 2020; Robbins-Juarez et al., 2020). The severity of COVID-19 disease is linked to a higher likelihood of intensive care unit (ICU) care, the need for mechanical ventilatory support and the use of vasopressors.

According to a multi-centre retrospective study involving 5449 COVID-19 patients in the US, almost 90% of critically ill ventilated COVID-19 patients developed AKI, versus 22% of non-ventilated COVID-19 patients(Hirsch et al., 2020). A meta-analysis study by Robbins-Juarez et al that assessed 14 studies from the US, Europe and China, with a focus on critically ill COVID-19 patients, indicated a 77% AKI prevalence rate in this sub-group of patients (Robbins-Juarez et al., 2020).

2.5.2 African race

Patients of African descent have higher odds of an acute kidney injury when exposed to renal insults, especially so with COVID-19 infection. US studies assessing the relationship between AKI and COVID-19 demonstrated an increased AKI risk in the African American population, with adjusted odd ratios of 1.3-2.1 of AKI (Hirsch et al., 2020; Nimkar et al., 2020; Nugent et al., 2021; Pelayo et al., 2020). Pelayo et al looked at COVID-19 factors at a hospital in inner-city New York serving a predominantly black population, and demonstrated a period prevalence of 49.3%, higher than the AKI average reported in other similar US studies (Pelayo et al., 2020). A similar study by Hirsch et al with a population of over 5000 patients in a large US health system had an adjusted odds ratio for AKI of 1.01-1.5 for African Americans (Hirsch et al., 2020).

Reasons for the higher incidence of AKI in the African population have been postulated to include genetic mutations which increase the chances of progressing kidney injury (Bhatraju et al., 2015; Friedman & Pollak, 2011; Parsa et al., 2013), socioeconomic disadvantages that reduce African Americans' access to medical care, the higher incidence of poorly controlled comorbid conditions,

poor health seeking behaviour and increased exposure to over-the-counter nephrotoxic drugs as self-medication (Nimkar et al., 2020; Pelayo et al., 2020).

Health data in the US shows that African Americans have a higher prevalence of certain comorbid conditions like type 2 diabetes mellitus, hypertension and cardiovascular disease compared to other population groups ((CDC), 2020; Association, 2019; Effoe et al., 2017; Federation, 2021). According to the 2020 National Diabetes Statistics Report, the disease burden for diabetes is higher in the African American population; 13% of African Americans above the age of 18 years have type 2 diabetes mellitus compared to a 9% population prevalence in the white non-Hispanic population ((CDC), 2020).

Mutations in the APOL1 gene contribute to the argument that being of African descent is a factor associated with the development of acute kidney injury, especially when other chronic medical conditions co-exist (Bhatraju et al., 2015; Friedman & Pollak, 2011; Parsa et al., 2013).

Studies have looked at the presence of variants of the APOL1 gene, found almost exclusively in people of African descent, as a possible physiological explanation for the higher AKI incidence in the black population. The presence of this gene variant imparts an increased risk of acute kidney injury and the kidney disease progression especially in patients with hypertensive renal disease, HIV-associated nephropathy, and diabetes related renal pathology (Friedman & Pollak, 2011; Grams et al., 2014).

That said, this gene variant as a contributor to kidney disease progression in a certain sub-group of patients is more prevalent in West Africans as compared to Sub-Saharan Africa. It is also present in 70-80% of the African American population, likely explained by our political history and migration patterns in past centuries (Friedman & Pollak, 2011; Parsa et al., 2013).

2.5.3 Poorly controlled chronic medical illnesses

Recent studies have shown a conflicting relationship between the incidence of AKI in COVID-19 and comorbid conditions like hypertension and diabetes. Two studies carried out in the US in a mixed population demonstrated an increased risk of AKI in diabetics and hypertensive patients, ranging from 1.1- 2.7 greater odds (Hirsch et al., 2020; Nimkar et al., 2020). In contrast, Pelayo et al concluded that diabetes and hypertension were not significantly associated with an increased risk of AKI in COVID-19 patients (Pelayo et al., 2020). Poorly controlled diabetes and hypertension are associated with chronic kidney damage which, histologically, presents as focal segmental glomerulosclerosis. The effect of chronic kidney disease on AKI incidence in COVID-19 is unclear (KDIGO, 2012).

In developing countries, non-communicable diseases including hypertension, diabetes mellitus, and malignancies has been on an upward trend, with recent data from the International Diabetes Federation indicating that 4 in 5 patients with diabetes live in low and middle-income countries (Federation, 2021). According to Kenyan population-based studies, the prevalence of diabetes ranges from 3.5-5% in persons above the age of 18 (Ayah et al., 2013; Azevedo & Alla, 2008; Mohamed et al., 2018). In a 2015 Kenyan National Diabetes Survey, 57% of the patients found to have diabetes were unaware of their diagnosis (Mohamed et al., 2018). Of the population who were aware of their condition, only half were on treatment, and of these, less than 10% had achieved glycemic control.

The rising cases of chronic kidney disease and other non-communicable diseases in Kenya, has necessitated the prioritization of the management of non-communicable diseases as documented in the Kenya Health Policy document 2014-2030 (K. M. o. Health, 2014). Recognizing and gathering data on the relationship between chronic illnesses, acute kidney injury and COVID-19 infection in our population is therefore important in healthcare policy planning.

2.5.4 Human Immunodeficiency Virus (HIV)

Antiretroviral therapy (ART) in HIV patients was shown to impart a 1.6 times increased risk for acute kidney injury according to a South African study by Aylward et al (Aylward et al., 2019). In the same study, patients with HIV but not on treatment did not have an increased risk for acute kidney injury, implying that ART use is an independent risk factor for AKI.

HIV as a risk factor for the development or progression of acute kidney injury in COVID-19 patients is unclear. There has been a scarcity of studies assessing this disease in AKI in patients with SARS-CoV-2 virus infection.

Patients with HIV may have pre-existing kidney disease that results from infection by the virus or other opportunistic infections or may develop kidney damage as an adverse effect of antiretroviral medication. The pathophysiology of HIV-associated nephropathy includes podocyte effacement, tubulointerstitial disease, focal segmental glomerulosclerosis and an immune-complex mediated kidney injury. Antiretroviral medication use contributes to kidney damage via acute tubular necrosis (tenofovir disoproxil fumarate) and interstitial nephritis (atazanavir and indinavir) (Choi, Li, Parikh, Volberding, & Shlipak, 2010; Swanepoel et al., 2018).

The burden of HIV in Sub-Saharan Africa is high, with 54% of all persons living with HIV globally, residing in East and Southern Africa (UNAIDS). In Kenya, according to 2018 HIV prevalence

estimates, 1.3 million adults between the age of 15 and 64 years are living with HIV, reflecting a 4.9% population prevalence rate, with 30,000 new HIV infections reported annually (KENPHIA, 2020). Of the known HIV-positive patients, 20% are not on treatment. Current Kenyan guidelines recommend the use of tenofovir, lamivudine and dolutegravir as first-line treatment for HIV.

2.6 Outcomes of AKI in COVID-19 patients;

2.6.1 Recovery of Renal Function

Historically, studies have shown that 64-87% of hospitalized patients with acute kidney injury will recover either partial or complete renal function by the time of hospital discharge or in the early weeks after discharge (Bagshaw et al., 2005; Hoste et al., 2015; Prescott et al., 2007; Uchino et al., 2005). The degree of recovery of the renal function determines the prognosis and progression of kidney disease. Patients with complete renal recovery were shown to have a slower progression but were still at higher risk for kidney dysfunction compared to non-AKI patients.

According to a prospective study by Liano et al that followed up patients with AKI secondary to acute tubular necrosis for a median 7.2 year period, the patients that had complete recovery in their kidney function at hospital discharge had better long-term survival rates, in addition to slower disease progression than patients with partial recovery of their renal function (Liano et al., 2007). Sawhney et al in a 10-year prospective study that followed patients discharged from the Calgary Health System showed that 14% of patients with recovered AKI had a greater than 30% decline in estimated glomerular filtration rate compared to 10% of non-AKI hospitalized patients.

Patients with COVID-19 and acute kidney injury are less likely to recover complete kidney function at the time of hospital discharge, with more patients being dialysis-dependent at discharge (L. Chan et al., 2021; Lili Chan et al., 2021; Gupta et al., 2021; Pei et al., 2020; Robbins-Juarez et al., 2020). Pei et al in their study indicated that only 45% of AKI patients attained renal recovery at hospital discharge (Pei et al., 2020). Two large studies that included more than 4000 patients with COVID-19 infection demonstrated that about 30% of COVID-19 patients with AKI were dialysis-dependent at hospital discharge (Lili Chan et al., 2021; Gupta et al., 2021)

Newer studies looking at the acute kidney injury prognosis in COVID-19 patients discharged after partial or complete renal recovery are similarly grim. Nugent et al followed up COVID-19 patients who had recovered from acute kidney injury and concluded that these patients had a steeper decline in renal function six months after discharge when compared to other hospitalized patients with AKI in

the same period (Nugent et al., 2021). Additionally, COVID-19 patients with partial or no recovery in kidney function are less likely to recover renal function in the outpatient follow-up period (Lili Chan et al., 2021; Kant et al., 2020; Kooman & van der Sande, 2021; Robbins-Juarez et al., 2020). .

2.6.2 Renal Replacement Therapy

Indications for renal replacement therapy by consensus include intravascular volume overload unresponsive to diuretic therapy, hyperkalemia refractory to medical management, metabolic acidosis refractory to medical management, overt uremic symptoms like encephalopathy, pericarditis and coagulopathy, and progressive azotemia in the absence of specific symptoms (KDIGO, 2012).

The timing of renal replacement therapy initiation in hospitalized patients has been debatable over time, and the same applies to COVID-19 patients. Earlier studies, including a systematic review published in May 2020 concluded that the timing of initiation of renal replacement therapy did not have an impact on the outcomes in AKI patients (Gaudry et al., 2020). The STARRT-AKI trial, a multinational multicenter study involving 3019 patients whose aim was to compare outcomes, including mortality rate, in patients on early renal replacement therapy (RRT) versus late initiation concluded no difference in outcome between the two groups (Investigators et al., 2020).

Not all stage 3 AKI patients will require RRT, with the incidence of RRT in stage 3 AKI patients ranging between 5-30% according to recent studies (Bagshaw et al., 2005; Hoste et al., 2015; Uchino et al., 2005). This incidence is expectedly higher in critically ill patients. A large prospective multicenter study in the UK with 29,269 patients with critical illness reported an AKI incidence of 5.7%, of whom 72% required RRT (Uchino et al., 2005). In a systematic review of the worldwide incidence of RRT in patients with AKI, defined using the KDIGO criteria, 23.5% of critically ill patients AKI patients required RRT (Hoste et al., 2015).

In COVID-19 patients, the renal replacement therapy rate is higher than that reported for hospitalized patients, although this has varied greatly depending on the population characteristics and the study sample size. Two US studies reported an RRT rate of 14.3% and 19% in COVID-19 patients with AKI (L. Chan et al., 2021; Hirsch et al., 2020). Earlier studies from China, however, show a much lower RRT rate of 0.1-5% (Lili Chan et al., 2021; Chen et al., 2020; Guan et al., 2020). A meta-analysis study with a pooled renal replacement therapy rate in COVID-19 patients from 14 mostly China-based studies summed up their findings with a 3.6% rate of renal replacement therapy (Robbins-Juarez et al., 2020). These differences in RRT rates could be explained by a smaller sample size in studies from

China, the COVID-19 disease severity and emerging variants, demographic and health system disparities.

According to a US comparison study by Fisher et al analysing the RRT rate incidence in COVID-19 patients with AKI against a similar cohort of patients admitted the year before, the rate of RRT in COVID-19 patients with AKI was three times that of hospitalized AKI patients the year before (Fisher et al., 2020).

Renal replacement therapy options include hemodialysis and, rarely, peritoneal dialysis. Modalities of hemodialysis are three; Slow Low-Efficiency Dialysis (SLED), Continuous Renal Replacement Therapy (CRRT) and Intermittent Hemodialysis (KDIGO, 2012). SLED is generally preferred to other modalities, and particularly in COVID-19 patients since it minimizes the chances of hypotension.

Guidelines for effective RRT in COVID-19 patients are daily emerging based on new evidence. Acceptable evidence-based adjustments to RRT in COVID-19 patients include the use of full-dose anticoagulation therapy during dialysis to reduce the chances of clotting, the consideration for early central venous access in high-risk patients likely to require RRT and, if possible, the avoidance of numerous typical investigations in COVID-19 patients requiring RRT e.g. a renal ultrasound unless the investigation will alter management (Rudd et al., 2021).

2.6.3 Mortality Rate

Acute kidney injury is an independent risk factor for mortality in hospitalized patients, with a relative risk ranging from 2-10 according to several published studies over the years (Lins, Elseviers, & Daelemans, 2006; Uchino et al., 2005; H. E. Wang et al., 2012). In patients with AKI and COVID-19, this risk increases greatly.

Susantitaphong demonstrated, in a meta-analysis study, a worldwide pooled AKI-associated mortality rate of 21.6% in hospitalized patients(Susantitaphong et al., 2013). In a cross-sectional study comparing 19,249 hospitalized patients with AKI and without AKI, the mortality rate was 10.8% in patients with AKI vs 1.5% in non-AKI patients (Sawhney, Marks, Fluck, Levin, Prescott, et al., 2017). The relationship between AKI and the mortality rate is ever more crucial in critically ill patients, imparting a 30-60% mortality rate (Aylward et al., 2019; Uchino et al., 2005).

Infection with the SARS-CoV-2 virus is associated with a higher risk of mortality in hospitalized patients with and without acute kidney injury. A meta-analysis on the relationship between AKI, COVID-19 and mortality rate involving mostly studies from China concluded that COVID-19 patients

with AKI were 13 times more likely to die compared to non-AKI COVID-19 positive patients (Hansrivijit et al., 2020). The odds of mortality increased to 15 in critically ill patients with AKI and COVID-19 in a different meta-analysis study focused on this sub-group of patients (Robbins-Juarez et al., 2020). In a different population, Chan et al reviewed 3993 COVID-19 patients in a US Health System and concluded that COVID-19 patients with AKI had a 9 times increased risk of mortality compared to non-AKI patients, with the odds of mortality increasing to 11 in critically ill patients (L. Chan et al., 2021).

When assessing the impact of COVID-19 infection on AKI outcomes, Fisher et al demonstrated 3.8 times odds of mortality in AKI and COVID-19 compared to non-COVID patients with AKI admitted the previous year (Fisher et al., 2020).

CHAPTER 3: MATERIALS AND METHODS

3.1 Research design

This is a retrospective cohort study where data was collected from patient files on COVID-19 patients hospitalised between 1st April 2020 and 31st October 2021.

The start period was selected after the publication of guidelines from the Kenya Ministry of Health on the management of COVID-19 (M. o. Health, 2020a). The duration of the study was guided by the presence of COVID-19 waves in the country characterized by changes in virus infectivity and disease severity, driven by the emergence of SARS-CoV-2 variants of concern (see **Figure 1** below).

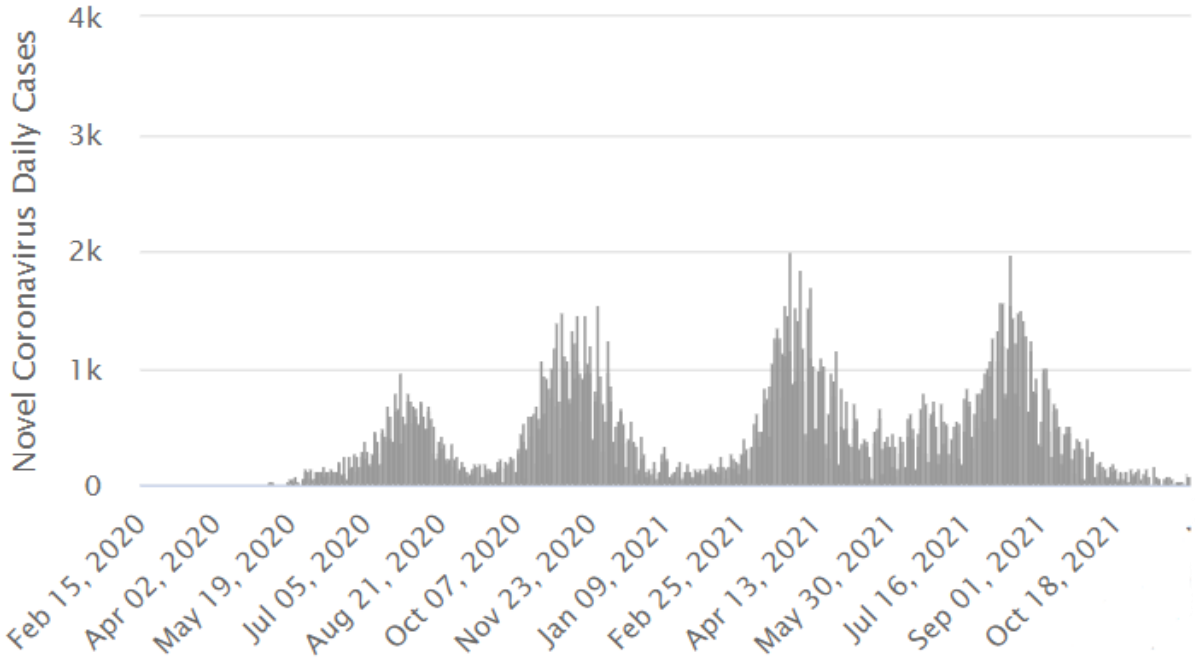


Figure 1: Average daily new COVID-19 cases in Kenya (April 2020-October 2021)

Source; https://www.worldometers.info/coronavirus/country/kenya/

3.2 Study location

The study location is the Aga Khan University Hospital, Nairobi (AKUHN). AKUHN is a tertiary-level teaching hospital located in Nairobi, the capital city of Kenya. The hospital admits patients from many parts of Kenya and sub-Saharan Africa, with patient numbers increasing during the COVID-19 pandemic.

The hospital has a bed capacity of 260, with an Intensive Care Unit (ICU) and High Dependency Unit (HDU) capable of accommodating approximately thirty patients at any given time. At the height of the COVID-19 pandemic in Kenya, additional wards were created and dedicated to the management of COVID-19 patients. Approximately 1,900 patients have been admitted with a COVID-19 diagnosis between 1st April, 2020 and 31st October, 2021, with 250 of these patients requiring ICU and/or HDU care.

All patients with severe and critical illness presenting at the hospital were admitted based on the availability of beds. Patients with mild to moderate illness were admitted if they required oxygen supplementation to maintain oxygen saturations above 94%, and/or if they were stable, with an incidental finding of COVID-19 infection, but required in-patient care for other medical or surgical reasons.

3.3 Study population and sampling

Data was collected from the files of all patients above the age of 18 years admitted with a COVID-19 diagnosis. Because of varying AKI prevalence rates in COVID-19 patients from previous studies around the world and a paucity of studies from similar patient populations in sub-Saharan Africa, we proposed to include all admitted patients who met the inclusion criteria in the period stated above.

3.3.1 Inclusion criteria

All patients >=18 years old with confirmed COVID-19 diagnosis via a positive Reverse Transcription Polymerase Chain Reaction (RT PCR) test and/or features suggestive of COVID-19 infection on HRCT of the chest.

3.3.2 Exclusion criteria

Patient files lacking serial creatinine values and patients with end-stage renal disease

3.4 Diagnostic tests

The diagnosis of COVID-19 infection was based on RT-PCR testing of nasopharyngeal swabs. The laboratory utilizes two analyzer machines that identify two of the genes within the SARS-CoV-2 virus (Allplex^{TM} SARS-CoV-2 assay, Seegene Realstar® SARS-CoV-2 RT-PCR kit 1.0, Altona Diagnostics) . The RT PCR test for COVID-19 infection has been shown to have a 99% specificity (Teymouri et al., 2021; Zitek, 2020).

In addition to PCR testing, some patients admitted with a preliminary COVID-19 diagnosis underwent High-Resolution Computed Tomography Scans (HRCT) of the chest. The hospital uses a 256 slice multi-detector dual energy and dual source CT scan machine, with chest images reviewed and validated by qualified hospital radiologists.

3.5 Data collection

Hospital electronic health records were initially reviewed, and patients admitted with the medical code for COVID-19 diagnosis in the selected period were identified. After screening for duplicate records, 1964 patient records were selected for analysis. Out of these patients, 90 were excluded for lack of a confirmatory COVID-19 test i.e., absent or negative COVID-19 PCR test and/or a negative CT scan of the chest. 1 patient was admitted twice within the study period, both times with a confirmed COVID-19 diagnosis.

Out of the 1874 records, 508 patients met the exclusion criteria; 487 patients did not have serial creatinine levels and 21 patients had pre-existing end-stage renal disease. 1366 patient files were included in the final analysis (see **Figure 2** below)

Data were collected on patient demographic characteristics including age and gender. Clinical characteristics included current pregnancy and comorbid conditions; Diabetes mellitus, Hypertension, HIV, and renal transplant. The severity of COVID-19 disease was documented in three categories; mild to moderate disease, severe disease and critical illness.

The diagnosis of AKI was made using the KDIGO criteria as previously discussed. In patients without preadmission baseline creatinine values, the baseline creatinine was taken to be the median of values during the entirety of the hospital stay. Urine output was not used in the diagnosis of AKI since very few patients had this measurement documented in their hospital records. The stage of AKI was documented based on the KDIGO criteria. The outcomes of AKI including mortality, renal function status at hospital discharge and the duration of hospital stay were documented and stratified according to the severity of AKI.

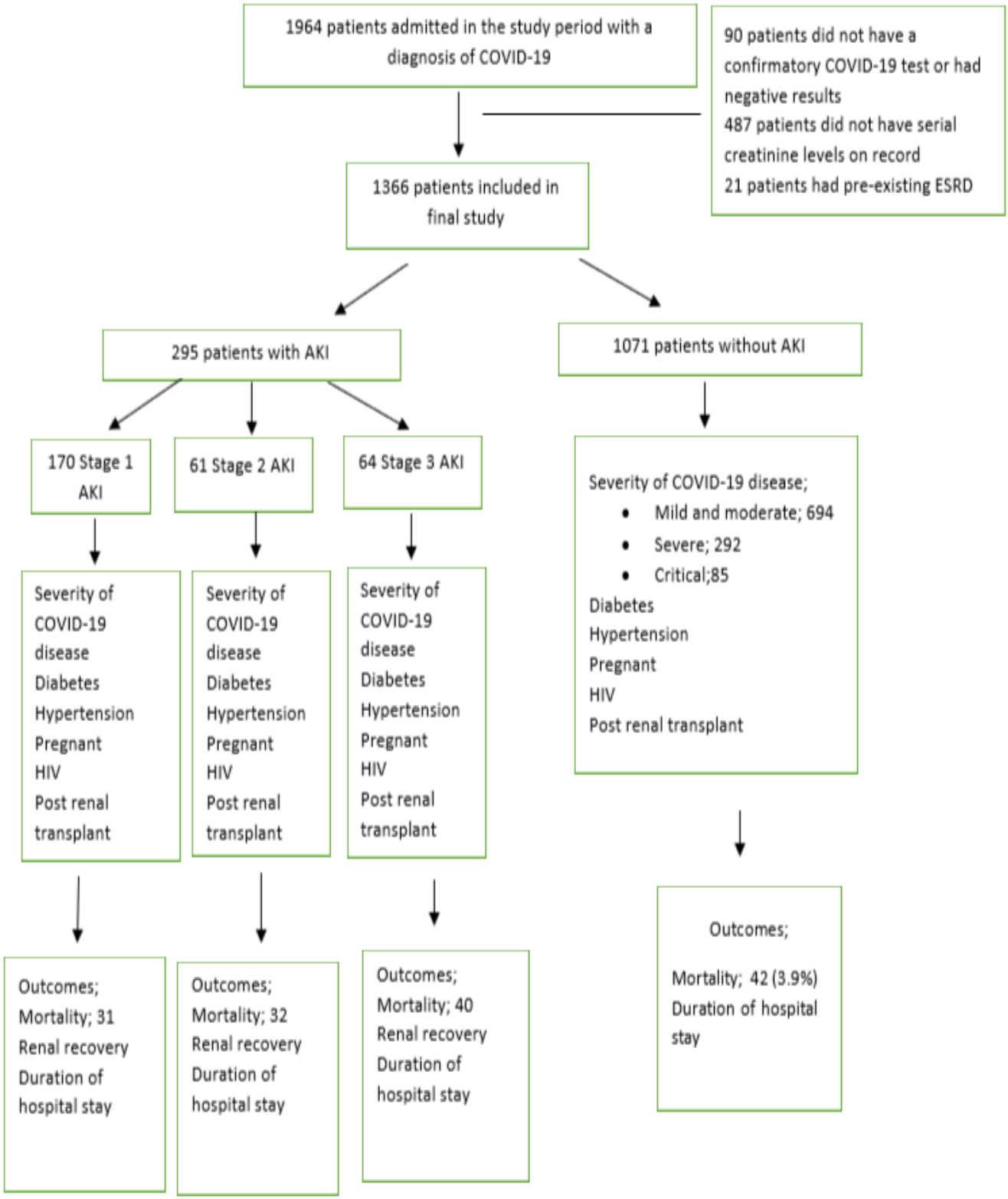


Figure 2: Patient Flow Chart

3.6 Data analysis

We performed descriptive statistics on patient demographic and clinical data, including medians and interquartile ranges for skewed continuous measures and proportions for categorical measures.

The period prevalence of acute kidney injury was calculated as the fraction of patients with AKI to all admitted COVID-19 patients and stratified according to the severity of COVID-19 disease.

Univariate analysis was performed using the Chi square test and Fisher Exact test to look for associations between demographic and clinical factors and AKI. To determine independent associations between these factors and AKI incidence, logistic regression models were used. The results were presented as odds ratios (ORs) with a 95% confidence interval, and adjusted for demographic covariates. Covariates to be adjusted were chosen based on univariate testing and included age and gender.

To assess the primary outcome of in-hospital mortality, a logistic regression model was again applied, with results reported as odds ratios with a 95% confidence interval, and adjusted for age and gender. The secondary outcomes of the status of renal recovery at hospital discharge and duration of hospital stay were calculated and presented as percentages, and stratified based on the severity of COVID-19 disease.

Statistical analysis was performed using SPSS (IBM version 20).

3.7 Ethical consideration

Consent for the study was sought from the Aga Khan University Institutional Scientific Ethics Review Committee (ISERC) and the National Commission for Science Technology and Innovation (NACOSTI) before the commencement of the study.

Data was collected from the hospital information management system by the primary researcher only. The collected data was then coded and entered into an MS Excel form. Patient-unique identification numbers used in the initial search were excluded in the analysis. Access to the Excel form was password protected and limited to the research personnel only.

3.8 Expected application of results

Results of the study will be presented to the Aga Khan University Faculty Academic Rounds for initial feedback. The final results will be submitted to applicable peer-reviewed journals for publication. These study results will also be presented at conferences nationally and internationally on related themes. A copy of the final dissertation will be stored in the AKUHN university library for use and reference.

CHAPTER 4: RESULTS

4.1 Patient characteristics

Patient characteristics are outlined in **Table 1** below.

Most patients included in the study were between the age of 31 and 80 years, with 34 patients aged 30 years and below and nine patients above the age of 90. Two-thirds of all the patients were male (n= 914). Fifteen patients had a confirmed pregnancy on admission (3.3% of females).

Of the 1366 admitted patients, most patients had mild to moderate disease (58 %) patients, while 200 patients had critical illness requiring mechanical ventilation. Two-thirds of all admitted patients were hypertensive and 40% had diabetes (n=548). Five patients admitted with COVID-19 illness had undergone a kidney transplant in the past. Approximately 50% of all admitted patients were not tested for HIV, either due to lack of provider-initiated testing and counselling or due to test decline. Of the twenty-four patients with an HIV-positive diagnosis, seven were newly diagnosed (0.01% of all tested). Of the seventeen patients already on treatment, fifteen were virally suppressed.

Table 1:Study characteristics

Demographics of the popn		**n**	**%**
Age (years) (median [IQR])		56.0 [45.0, 68.0]	
Gender	Females	452	33.1%
	Males	914	66.9%
Outcome	Alive	1215	88.9%
	Dead	151	11.1%
Received contrast	Yes	444	32.5%
	No	922	67.5%
COVID-19 Severity	Mild to Mod	791	57.9%
	Severe	376	27.5%
	Critical	199	14.6%
Hypertension	Yes	441	32.3%
	No	925	67.7%
Diabetes	Yes	548	40.1%
	No	818	59.9%
HIV	Positive	24	1.8%
	Negative	669	49.0%
	Not Tested	673	49.3%
ARVs	Yes	17	70.8%
	No	7	29.2%
Viral Suppression	Yes	15	62.5%
	No	9	37.5%
Pregnant	Yes	15	3.3%
	No	437	96.7%
Post Renal Transplant	Yes	5	0.4%
	No	1361	99.6%
AKI	Yes	295	21.6%
	No	1071	78.4%
Stage AKI	1	170	57.6%
	2	61	20.7%
	3	64	21.7%
Outcome AKI	Complete Recovery	165	55.9%
	Partial Recovery	24	8.1%
	Ongoing RRT	3	1.0%
	Death	103	34.9%
Hospital Duration (days) (median [IQR])		8.0 [5.0, 13.0]	

4.2 Prevalence of AKI in COVID-19

The period prevalence of acute kidney injury was 21.6% (n=295); 170 patients (57.6%) had stage 1 AKI, 61 (20.7%) had stage 2 AKI and 64 (21.7%) had stage 3 AKI.

The incidence of AKI rose by five percentage points in the fourth COVID-19 wave 27haracterized by the presence of the Delta SARS-CoV-2 variant, as shown in **Table 2** below.

12% of patients with mild to moderate COVID-19 had AKI. The AKI prevalence increased with increasing disease severity, with 22% of patients with severe COVID-19 and 57% of those with critical illness having AKI.

Table 2; Comparison of COVID-19 waves and AKI incidence

ADMISSION PERIOD	ADMISSIONS	AKI CASES	AKI PREVALENCE
May-September 2020	278	55	**19.78%**
October 2020-January 2021	317	63	**19.87%**
February-June 2021	461	100	**21.69%**
July-October 2021	310	77	**24.84%**
	1366	**295**	**21.60%**

4.3 Risk factors for AKI in COVID-19

Statistically significant risk factors for AKI included increasing age, the male gender, the severity of COVID-19 illness, hypertension and diabetes as outlined in **Table 3** below. Being HIV positive or on antiretroviral treatment was not associated with an increased risk for AKI in COVID-19 patients. Pregnancy and a renal transplant history were also not associated with AKI.

Table 3*:* Univariate analysis of demographic and clinical characteristics

		Acute Kidney Injury				P Value
		Yes (N = 295)		No (N = 1071)		
Age (years) (median[IQR])		64.0	[53.0, 75.0]	54.0	[44.0, 65.0]	<0.001
Gender	Females	62	21.0%	390	36.4%	<0.001
	Males	233	79.0%	681	63.6%	
Outcome	Alive	186	63.1%	1029	96.1%	<0.001
	Dead	109	36.9%	42	3.9%	
use of contrast	Yes	97	32.9%	347	32.4%	0.956
	No	198	67.1%	724	67.6%	
COVID-19 Severity	Mild to Mod	97	32.9%	694	64.8%	<0.001
	Severe	84	28.5%	292	27.3%	
	Critical	114	38.6%	85	7.9%	
Hypertension	Yes	141	47.8%	300	28.0%	<0.001
	No	154	52.2%	771	72.0%	
Diabetes	Yes	160	54.2%	388	36.2%	<0.001
	No	135	45.8%	683	63.8%	
HIV	Positive	2	0.7%	22	2.1%	0.111
	Negative	293	99.3%	1049	97.9%	
ARVs	Yes	1	50.0%	16	72.7%	0.507
	No	1	50.0%	6	27.3%	
Viral Suppression	Yes	1	50.0%	14	53.6%	0.999
	No	1	50.0%	8	36.4%	
Pregnant	Yes	2	3.2%	13	3.3%	0.999
	No	60	96.8%	377	96.7%	
Post Renal Transplant	Yes	2	0.7%	3	0.3%	0.296
	No	293	99.3%	1068	99.7%	
Hospital Duration (Days) [median		10.0	[5.0, 18.0]	8.0	[5.0, 12.0]	<0.001

Being female was associated with a 63% reduction in risk for acute kidney injury in COVID-19. Increasing age was also related to higher AKI incidence.

After adjustment for age and gender, patients with severe COVID-19 disease were 1.92 times more likely to get an acute kidney injury compared to patients with mild to moderate disease (95% CI 1.38-2.68, P<0.001), with the odds increasing to 8.03 with critical disease (95% CI 5.56-11.60, P<0.001). The odds ratio for AKI in a hypertensive patient was 1.68 (95% CI 1.27-2.23, P<0.001) and in diabetes, 1.75 (95% CI 1.34-2.30, P<0.001) as shown in **Table 4** below.

Table 4: Adjusted odds ratio for AKI risk factors

		OR	95% CI	p value
COVID19 Severity	Severe	1.92	[1.38, 2.68]	<0.001
	Critical	8.03	[5.56, 11.60]	<0.001
Hypertension	Yes	1.68	[1.27, 2.23]	<0.001
Diabetes	Yes	1.75	[1.34, 2.30]	<0.001
**Adjusted for Age and Gender*				

4.4 Outcomes of AKI in COVID-19

The outcomes of AKI in COVID-19 patients, including death and renal recovery, are outlined in **Figure 3** below.

The mortality rate of AKI in COVID-19 patients in our study was 34.9% (n=103). Patients with AKI had 11.35 higher odds of mortality compared to non-AKI patients (95% CI 7.56-17.03, P<0.001). The odds of death increased with the rising severity of AKI; 18% of patients with stage 1 AKI (n=31) died compared to 51% of patients with stage 2 (n=32) and 64% of stage 3 AKI (n=40).

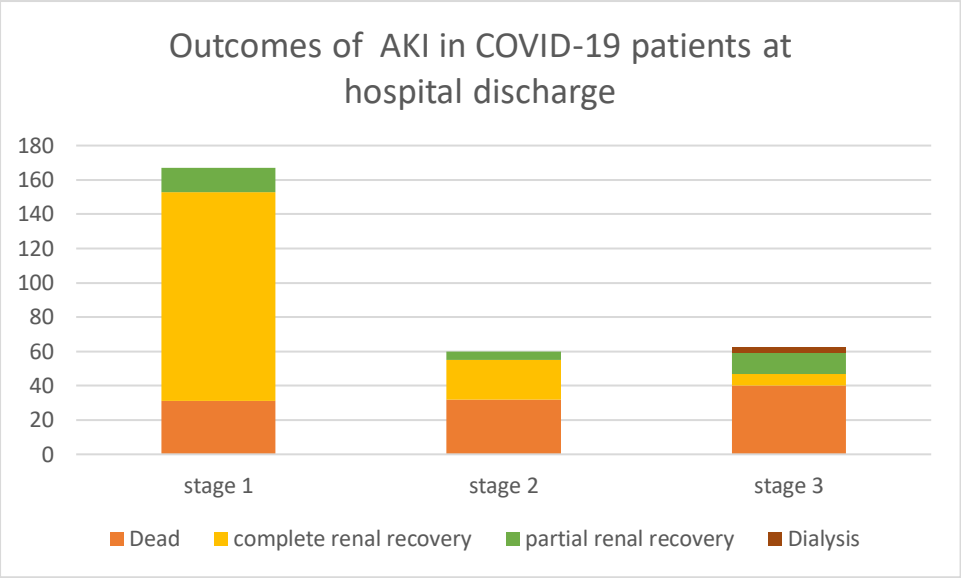


Figure 3: Review of outcomes of AKI in COVID-19; death, renal recovery and dialysis

10 out of 64 patients with stage 3 AKI underwent hemodialysis (representing 3.4% of all patients with AKI). Out of these, 4 were discharged alive; 3 of the 4 patients required ongoing dialysis after hospital discharge.

The impact of acute kidney injury on the duration of hospital stay is outlined in **Figure 4** and **Table 5** below. The median hospital duration increased in patients with AKI compared to non-AKI patients (8 days versus 10 days, P<0.001). Median hospital duration was longer with increasing severity of AKI; 9 days for stage 1 AKI (IQR 6-13 days), 11 days for stage 2 AKI (IQR 7-9 days) and 12 days for stage 3 AKI (IQR 8-18 days).

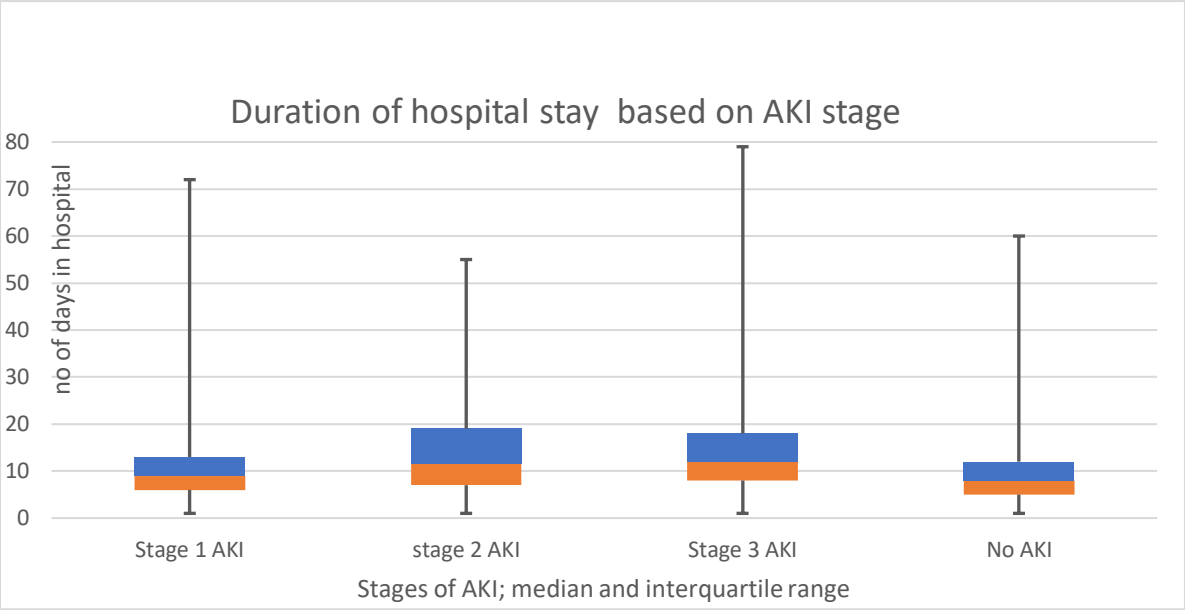


Figure 4: Median duration of hospital stay with interquartile ranges; AKI versus non-AKI COVID-19 patients

Table 5: Duration of hospital stay

DURATION OF HOSPITAL STAY		
	Median (days)	IQR
No AKI	8	5.0, 12.0
AKI	10	5.0, 18.0
Stage 1 AKI	9.0	6.0, 13.0
stage 2 AKI	11.5	7.0, 19.0
Stage 3 AKI	12.0	8.0, 18.0

CHAPTER 5: DISCUSSION

In our study, the prevalence of AKI in COVID-19 patients was 21.6%. This is lower than reports from previous studies with a similar socio-demographic population and health system strains that reported prevalence rates of 40-60%, although in these studies, most cases were stage 1 AKI (Hirsch et al., 2020; Nimkar et al., 2020; Pelayo et al., 2020). That said, the prevalence is still higher than reports from China that showed an average AKI prevalence of 8.4% (Chen et al., 2020; Yang et al., 2020). Compared to pre-COVID Kenyan studies assessing the AKI prevalence in hospitalized patients(Mohammed, 2017; Munyu, 2008), the prevalence in COVID-19 patients is significantly high by up to 5 times. The higher AKI prevalence of AKI in COVID-19 is in keeping with other studies and can be explained by the pathological effects of the virus on the kidneys directly and, indirectly, on the immune system and cardiovascular stability.

The difference in AKI prevalence between our study and related studies may also be explained by the exclusion of patients without serial creatinine levels, who may have had a stage 1 AKI i.e., serial creatinine tests were more likely to be performed on sicker older patients in our facility. Additionally, the hospital admission criteria excluded 'well' patients on symptomatology, which may mean that some patients with early onset kidney injury were missed.

Demographic factors like male gender and increasing age were associated with an increased risk of AKI in COVID-19. This is similar to a study by Fisher et al that showed a higher risk of AKI in men with COVID-19 infection (Fisher et al., 2020). The higher risk may be attributable to more men presenting with comorbid conditions and, by extension, a higher COVID-19 disease severity compared to women. In our study, 70% of patients with diabetes and hypertension were male. In addition, the male gender constituted 68% of patients with severe and critical COVID-19.

Increasing age was also found to be a risk factor for AKI in our study. In a study by Hirsch et al, age above 50 years was associated with increased odds for AKI (Hirsch et al., 2020). A probable explanation is that age is accompanied by a higher incidence of chronic illnesses, which are risk factors for AKI in COVID-19 infection.

Diabetes and hypertension were shown to increase the risk of AKI in this study, similar to what was found in two previous studies, although the impact of hypertension on AKI risk was higher in our study (Hirsch et al., 2020; Nimkar et al., 2020). We could then infer that a higher prevalence of poorly controlled comorbid conditions in the country may account for that difference (Mohamed et al., 2018).

Further analysis of patients with comorbid conditions to assess their level of sugar and blood pressure control may help strengthen the association between AKI risk and comorbidities.

In our study, the overall mortality rate for patients with AKI in COVID-19 was almost 35%, related to that reported in two studies with similar socio-demographic characteristics (Cheng et al., 2020; Hirsch et al., 2020), but higher than the mortality rate noted in a meta-analysis that included most studies from China (Hansrivijit et al., 2020). When compared to studies on the mortality rate in AKI in the pre-COVID era (Lins et al., 2006; Uchino et al., 2005; H. E. Wang et al., 2012), the current rates in AKI patients with COVID-19 have been on average three times higher. This higher rate can be attributable to increased virus infectivity, a strain in the health system attributed to the COVID-19 pandemic, admission of rather sick patients who met the hospital admission criteria, and late presentation of critically ill patients to the hospital. The mortality rate in our study was also noted to be higher with increasing severity of AKI, with a 63% mortality rate in patients with stage 3 AKI. Two-thirds of the patients with stage 3 AKI had critical COVID-19 illness, a risk factor for AKI identified in our study.

The rate of dialysis in stage 3 AKI patients with COVID-19 in our study was lower than that reported from similar studies, which have ranged from 4.9%-20% (Arentz et al., 2020; Lili Chan et al., 2021; Fisher et al., 2020; Gupta et al., 2021; Hirsch et al., 2020; ICNARC, 2021). Although there is no definite timing for the initiation of renal replacement therapy as shown by the STARRT-AKI trial (Investigators et al., 2020), delayed initiation may play a role in poor outcomes. Of the four patients who were discharged alive after dialysis, three required continued renal replacement therapy. This incidence is high compared to previous studies on COVID-19 patients who underwent RRT, where only approximately 30% of patients required ongoing dialysis (Lili Chan et al., 2021; Gupta et al., 2021). Additionally, renal recovery after dialysis is lower in COVID-19-recovered patients compared to other non-COVID-19 hospitalized patients, as demonstrated in our study and in previous studies (Lins et al., 2006; Sawhney, Marks, Fluck, Levin, McLernon, et al., 2017; Uchino et al., 2005), including in a comparison study of patients admitted during the same period (Fisher et al., 2020).

5.1 Strengths of the study

The strengths of our study include a large sample size of 1366 patients admitted to a tertiary-level referral facility. This is also one of the few studies from sub-Saharan Africa evaluating the impact of COVID-19 infection on the kidneys.

5.2 Study limitations

Limitations to the study are explained below.

First, this study assessed the impact of COVID-19 on the kidneys in patients who were hospitalized at one private-care facility based on a preset admission criteria to ensure only sick priority patients would get admitted; hence the results cannot be generalizable to the population.

Second and equally important, this study excluded 487 patients who did not have serial creatinine results (a diagnosis of AKI relies on at least two creatinine results on record), amounting to 25% of all COVID-19 patients admitted in the study period. This exclusion may contribute to a higher AKI prevalence rate than would typically be expected.

In addition, the impact of HIV and pregnancy on AKI in COVID-19 could not be accurately assessed due to the small sample size of patients.

Lastly, patients who were transferred out of the hospital to continue care at other facilities were said to be discharged alive, and the outcomes of AKI were assessed at the point of hospital transfer, which may not be the ultimate outcome after recovery from COVID-19 disease.

CHAPTER 6: CONCLUSION

This study demonstrated the relationship between acute kidney injury and COVID-19 infection in patients admitted to a hospital in Kenya. It assessed the AKI prevalence and the association between AKI and demographic and clinical risk factors, with age, gender, hypertension and diabetes being significantly associated with increased AKI risk in COVID-19 infection. Additionally, the outcomes of AKI in COVID-19 infection were determined and noted to be more pronounced in AKI patients compared to non-AKI patients and other non-COVID-19 hospitalized patients. These included a longer hospital stay, higher mortality rates, and lower renal recovery rate after dialysis.

CHAPTER 7: RECOMMENDATIONS

This study demonstrates that certain chronic illnesses increase the risk of development and progression of kidney injury when exposed to particular triggers; in this case, the SARS-CoV-2 virus. Future studies on the impact of well managed diabetes and hypertension on kidney injury and other outcomes may add to this knowledge.

Evaluation of early versus late RRT on outcomes in patients with stage 3 AKI and COVID-19 infection can add to the knowledge of RRT timing.

This study also forms a foundation for further research on the intermediate and long-term outcomes of COVID-19 infection on the kidneys.

Currently, approximately 10,000 Kenyans are dialysis dependent, with most health care costs catered for by the Government of Kenya via the National Health Insurance Fund (NHIF) and out-of-pocket payments. Information on dialysis rates, renal recovery and progression in kidney disease after the COVID-19 pandemic is necessary to guide health financing and infrastructure policies as countries across the globe shift focus to the longterm consequences of the COVID-19 pandemic.

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