ONE YEAR SURVIVAL AND ITS ASSOCIATED FACTORS IN PATIENTS WITH END STAGE KIDNEY DISEASE UNDERGOING HAEMODIALYSIS AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

I certify that this book is my own original work and all resources used have been appropriately referenced. This work, to the best of my knowledge, has not been presented for the award of a degree in any other institution

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DEDICATION

I dedicate this work to my mother, who is now rested. A warrior through a battle with kidney disease. Even in death, I still strive to make you proud. I hope my contributions can make a small change for others like you.

ACKNOWLEDGEMENT

I have had the profound privilege of having: a supportive family (Tata, Oge, Sharon, Chebumbwo, Nonyot and Barchok) mentors and supervisors who have walked this journey with me. I am entirely grateful for their time and commitment to see this dissertation through.

LIST OF ABBREVIATIONS

CKD Chronic Kidney Disease

ESKD End Stage Kidney Disease

HD Haemodialysis

ISN International Society of Nephrology

KNH Kenyatta National Hospital

KRT Kidney Replacement Therapy

PTH Parathyroid Hormone

USRDS United States Renal Data System

KDIGO Kidney Disease Improving Global Outcomes

CRS Civil Registration Services

HIV Human Immunodeficiency Virus

HIVAN Human Immunodeficiency Virus Associated Nephropathy

OR Odds Ratio

IQR Interquartile Range

SD Standard Deviation

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ABSTRACT

Background: End Stage Kidney Disease is a growing public health concern. Haemodialysis, used in the management of ESKD, is now readily available. However, survival in patients with ESKD on haemodialysis is reduced compared to the general population with mortality nearing 7 times higher. This difference in survival is more pronounced in the first year of initiation of haemodialysis. Additionally, regional differences have been described in survival of patients with ESKD on haemodialysis. This information in our setup is lacking and this study aims at filling this knowledge gap on survival as well as its associations.

Objectives: To determine the one year survival and its associated factors in patients with ESKD undergoing HD at the KNH dialysis unit

Study design: This was a 5 year retrospective cohort study from January 2017 to December 2021 at KNH, dialysis unit.

Methodology: Files of adult patients with ESKD undergoing haemodialysis at the KNH were retrieved. Data on socio demographic, clinical and laboratory parameters was recorded in the data entry form. Information on vital status after one year of dialysis was documented. The outcomes of interest (survival and select clinical and sociodemographic characteristics) were analysed and strengths of association measured by hazard ratios. The Kaplan Meier curve was used to demonstrate cumulative survival and cox proportional hazard was used to calculate risk ratio and the impact of clinical and demographic variables on survival.

Results: Data from 189 files were analysed. The mean age of the patients was 47.8 years with 56.6% and 43.4% being males and females respectively. Age strata 40-59 years represented the majority of patients (41.8%). The commonest causes of ESKD were hypertension, diabetes, chronic glomerulonephritis and obstructive uropathy in order of frequency. At the end of 1 year, 76.2% patients were alive. A haemoglobin level of less than 6.5g/dl and albumin level of between 25-34.9g/l was associated with 3.9 and 2.3 fold risk of death.

Conclusion: Survival in our patient population at 1 year was at 76.2% with albumin of 25-34.9g/l and haemoglobin of <6.5g/dl being associated with reduced survival.

CHAPTER ONE

Introduction

End stage kidney disease is growing public health concern with implications on the burden to healthcare systems worldwide (1). As of 2010, globally, an estimated 4.9 to 9.7 million people required kidney replacement therapy, however only about 2.6 million people were on the same. In Africa, as at 2010, it was estimated that the number of people receiving Kidney replacement therapy was 83,000. This was a modest figure translating to an access of between 9-16 % for kidney replacement therapy (KRT). These figures are far worse in middle and eastern Africa where only 1-3% of patients in need of KRT actually receive it (2).

The causes of ESKD are diverse and range from inherited disorders to acquired disorders (3), with various studies within different geographical settings demonstrating differences in cause of ESKD. Data from the United States and countries in the gulf cooperation council have diabetes mellitus as the leading cause of ESKD (4,5) while that from Sub Saharan countries show chronic glomerulopathy and hypertension as the leading causes.

In the pathophysiology of ESKD, two mechanisms underlie the progression and symptomatology: the initial insult to the kidney and the maladaptive changes at the level of the nephron that result in reduction in the number of functioning nephrons and inability of the kidney to adequately perform its core functions (6). This results in a variety of systemic abnormalities not limited to fluid overload, electrolyte and acid base disturbances, hematologic abnormalities, cardiovascular disease and bone mineral disease.

It is in this background that KRT is an important modality in the management of ESKD in terms of improving quality of life for this subset of patients. However in this special population of patients, survival in comparison to the general population is reduced with mortality ranging from 6.1 to 7.8 times more (7). This disadvantage is replicated even in young patients with studies showing death from cardiovascular disease in the youthful population approaching that of the elderly (8). In addition to this, regional differences in survival of patients with ESKD have been demonstrated with 5 year survival rates of 39%, 41% and 60% in the United States, Europe and Japan respectively (9).

Mortality in patients with ESKD on haemodialysis has several associations both demographic and biochemical. When stratified by age, absolute risk of death is higher in the elderly population with (10) showing an increase in mortality with a 10 year increment in age, HR of

1.5 (1.43 - 1.56 95% CI). The elderly are more likely as well to die within 90 days of starting haemodialysis. Low albumin levels and anaemia have also been shown to predict mortality (11,12) however a causal association is not always the case.

Given the growing public health concern of ESKD, data on survival and its associations in this subset of patients in our population is important. This information in Kenya is largely lacking. This study therefore aims to fill this knowledge gap and spur optimal management of patients with ESKD on HD as well as discussions on prioritising adequate financing for KRT as well as kidney transplants as a means of improving outcomes in this subset of patients.

CHAPTER TWO

2.1 Literature review

ESKD: Definition and epidemiology

ESKD is the terminal stage of CKD defined as abnormality in kidney structure and function that is present for more than three months with a glomerular filtration rate of less than 15ml/min/1.73m2. It is a cause of reduced quality of life and premature mortality (13).

Two million, four hundred and fifty five thousand and four patients were managed for ESKD in 2016 according to data from all countries reporting to the United States Renal Data System (1). The prevalence of treated ESKD varies by countries with the United States of America having the most (709,501) representing 29% of the data by the international society of nephrology (ISN) Global Kidney Health Atlas survey 2019. This was followed by Japan (328,000: 13%), and Brazil (180,000: 7%) (14). Most of cases of ESKD in Africa remain undiagnosed and untreated leading to unreported mortalities. In view of this the prevalence of treated ESKD in Sub-Saharan Africa is less than 100 per million population (15) reflecting limited access to kidney replacement therapy (KRT) with studies demonstrating approximately 10% of incident ESKD patients sustaining dialysis for more than three months (7).

As of 2015, based on the United States Renal Data system, one hundred and twenty four thousand, four hundred and eleven new ESKD diagnoses were made with kidney disease ranking ninth as a cause of death. Rates of ESKD appeared to be higher in the black American and other racial/ ethnic minorities population in comparison to Caucasians with the disease being more common in males than in females. CKD is also common in the elderly population with a prevalence of 38.1% in ages greater than 65 and 6% in ages between 18 and 44 years (16, 17).

Similarly in Kenya, in a single centre cross sectional study, increasing age is associated with development of CKD as is the male sex with an OR191, 95% CI; 1.19,3.06 (18).

ESKD: Aetiology

The causes of ESKD are diverse and can range from inherited kidney diseases such as Alport's syndrome, autosomal dominant polycystic kidney disease or acquired diseases either due to primarily affection of the kidney disease or a systemic disease with impairment of kidney function (3). Ascertaining the common aetiologies of CKD and by extension ESKD is often compounded by lack of high quality population based studies in countries that have a high burden of the same and the lack of biopsy proven causes of CKD as this is the gold standard in terms of determining the cause of CKD. However in the latter case, the procedure is only advisable when diagnosis of the underlying cause is beneficial enough to outweigh the risks of the procedure (19). This being said, various studies in different geographical settings have demonstrated differences in the cause of ESKD.

In the United States, diabetes mellitus was found to be the commonest cause for ESKD followed by hypertension at 38.2% and 25.5% respectively between the years 2013 and 2014 (4). In comparison to data from countries in the gulf cooperation council where diabetes was the leading cause of ESKD followed by glomerulonephritis and then hypertension. In this set of patients diabetes and glomerulonephritis contributed to less than a third of the causes of ESKD (17% and 13 % respectively) (5). Data from Africa and specifically Sub Saharan Africa seems to differ as well. In a retrospective single centre study from Nigeria, the leading cause of ESKD was chronic glomerulopathy at 45.6% followed by hypertension at 29.7% and diabetes at 17.5% (20). Conversely (21) reports hypertension as the leading cause of CKD in Sub Saharan Africa ranging from 25%; 29.8%; 45.6% and 48.7% Senegal, Nigeria, South Africa and Ghana respectively.

ESKD: Pathophysiology

The mechanisms driving the pathophysiology of CKD involve;

1. The initial insult specific to the cause of kidney disease whether it be structural kidney disease, inflammatory conditions, toxins etc

2. The maladaptive changes at the level of the nephron involve hyperfiltration at the glomerulus and associated hypertrophy of the remaining viable nephrons. The sequelae of this is the inevitable reduction in kidney mass and function with the terminal stage 5 CKD where fluid, toxins and electrolytes usually excreted by the kidney accumulate and can lead to mortality if not removed by any form of kidney replacement therapy (22).

The term uraemic syndrome encompasses the constellation of symptoms that dominate in ESKD. It is more than just a failure in the excretory capacity of the kidneys and includes deficits in the metabolic and hormonal functions of the kidney. In addition to this, there is worsening inflammation with its consequences on both nutrition and the vascular bed.

Haematologic abnormalities

Abnormalities in haematologic parameters include but are not limited to anaemia and coagulopathy. The basic underlying mechanism of anaemia in ESKD is the reduced production of erythropoietin with a resultant normocytic, normochromic anaemia. Other compounding mechanisms of anaemia include bleeding secondary to bleeding diathesis, diminished red blood cell survival, deficiencies in iron folate and vitamin B12 etc. The resultant effect is reduction in oxygen delivery to the tissues, a subsequent increment in cardiac output with a downstream effect of ventricular hypertrophy and dilatation (22).

Coagulopathy in ESKD is an interplay between bleeding diathesis and thrombosis. In bleeding, intrinsic platelet dysfunction is due to reduction in thromboxane A_2 (23) with deficiency and alteration in platelet cytoskeleton (24,25). In addition to this thrombocytopaenia has been noted in patients with ESKD on HD due to complement activation when bioincompatible membranes are used (26). In thrombosis, HD is associated with increased aggregation of platelets especially towards the end of dialysis (27).

Electrolyte and Acid base disturbance

Given the key role of the kidneys in fluid, acid base and electrolyte homeostasis, ESKD results in abnormalities in these parameters. Among these are abnormalities in potassium excretion. Hyperkalaemia is the commonest and life threatening disorders encountered in ESKD (28). While reduced potassium excretion is one of the causes of hyperkalemia, transcellular shifts that accompany insulin deficiency, tissue breakdown, drugs and metabolic acidosis can contribute to the same. This can manifest as neuromuscular symptoms (muscular weakness and paraesthesia) and cardiac symptoms (cardiac arrest and arrhythmias). Hypokalemia, while less common, is no less threatening with symptoms ranging from ileus, paralysis and cardiac arrhythmias. Hypokalaemia can develop as a result of gastrointestinal losses (diarrhoea and vomiting), diuretic use (29) and use of low potassium dialysate (30,31).

With the notable role of the kidneys in management of acid base homeostasis in the body, it is not surprising that metabolic acidosis is a feature of ESKD. The ability of the failing kidney to conserve and generate bicarbonate reduces while the body's endogenous acid production remains unchanged. In addition, renal handling of ammonium is compromised (32). This leads to is activation of complement and tubulointerstitial inflammation (33), increased aldosterone and endothelin 1 production with these 2 effects further worsening CKD (34). Systemically, metabolic acidosis causes increased protein catabolism, with muscle wasting, endocrine abnormalities such as insulin resistance, compromised thyroid and growth hormone secretion and increased mortality (35).

Cardiovascular disease

The association between CKD and cardiovascular disease was first reported in 1836. Since then, it has been demonstrated that close to half of patients with CKD stage 4 and 5 have cardiovascular disease with cardiovascular mortality in 40-50% of all deaths in stage 4 and 5 CKD in comparison to 26% in controls with preserved kidney function. Cardiovascular risk factors account for the high burden of cardiovascular disease in CKD and include diabetes, hypertension and dyslipidaemia as well as inflammation, vascular calcifications and myocardial alterations (36).

The initiating event in development of left ventricular hypertrophy is myocardial stretch in response to increased volume or pressure load (37). In an attempt to adapt there is release of

vasoactive substances that results in myocyte growth (38) and if not abated progresses to maladaptation; where there's an imbalance in energy expenditure in the hypertrophied myocyte with an energy deficit leading to myocyte death and expansion of the cardiac interstitium with deposition of collagen and fibroblasts (39). Further some studies have shown parathyroid hormone (40), uraemia (41) and hypoalbuminaemia having a role in left ventricular hypertrophy as well as heart failure (42). Hypoalbuminaemia has been implicated in development of heart failure in ESKD through unclear mechanisms. It is thought that low albumin levels reflect a proinflammatory state (which is considered a risk factor for cardiovascular disease) and is associated with development of atheromatous plaques and endothelial dysfunction, both of which are drivers of cardiovascular disease (43).

ESKD: Survival

CKD and by extension ESKD is a known risk factor for mortality. Projections estimate that as at 2040, the disease spectrum will be the 5th leading cause of death (44). When comparing survival of patients with ESKD on HD to that of the normal population, mortality is 6.1 to 7.8 times more in this group of patients. This is more pronounced in the first year of treatment. The higher risk of death during this time can be explained in part by late diagnosis of CKD with the associated failure in mitigating some of the risk factors of mortality that accompany it. This delay in diagnosis is also compounded by the fact that patients are likely to initiate dialysis emergently rather than planned making it harder for the body to adapt to the physiological stress that accompanies dialysis (11).

Regardless of age, patients with ESKD on dialysis have increased mortality when compared to non dialysis patients with studies showing cardiovascular mortality in the youthful population with ESKD approaching that of the elderly in the general population (8).

However when patients with ESKD on dialysis are stratified by age, the absolute risk of mortality is higher in the elderly population partly due to more comorbidities (45). In a systematic review by (10) a 10 year increment in age resulted in an increase in mortality with a hazard ratio of 1.5 (1.43 - 1.56 95% CI). Early deaths are also observed in the elderly population. In (46) , at age groups >75 years, 65-74, 45-46, <45 the percentage of death within 90 days of starting haemodialysis was 11.6%, 9.5%, 4.6% and 2.3% respectively. Similarly, in a retrospective study in South Africa, patients older than 40 years of age had a higher mortality compared to those between 18 and 40 years of age (47). This finding has also been replicated by Watcherman et. al, in a retrospective study based on the united states renal data system where 1 year mortality for patients greater than 80 years of age was associated with a 1.8 times risk of death in a multivariate analysis (48)

Differences in epidemiology of CKD and ESKD in terms of sex exist. Global statistics show women are more likely to develop CKD. Data from the global burden of disease (GBD) study of 2016 demonstrated 417 million women with impaired kidney function vis a vis 335.7 million male. These findings were replicated at various stages of CKD save for ESKD where both sexes were afflicted equally. However when it came to KRT fewer women were on dialysis in comparison to males (1.3 million vs 1.7 million) (19). In Kenya a single centre cross sectional

study however had demonstrated a CKD prevalence of 62.7% (n=306) in males. This study was conducted among inpatients at Kenyatta National Hospital with an aim to determine the prevalence of CKD and its associated factors (18). Data on survival with regard to sex is varied. In a systematic review by (10) of studies done between 1985 and 2017, there was a higher risk of early deaths in females in 3 studies. In one of these studies the sample size approached half a million with overall risk of bias reported as low.

Various biochemical predictors of mortality in haemodialysis have been identified and while statistical significance is demonstrated with these risk factors, a direct causal association is not always the case (11). Hypoalbuminaemia, as a surrogate marker for both malnutrition and chronic inflammation has a role (12). With regards to survival, Ferreira et. al, demonstrated a HR of 0.23 (0.097-0.541 at 95% CI) with serum albumin of >4 (11). On the other hand, Msaad et.al showed that more than a third of deceased patients had a low albumin (49). Hypoalbuminaemia has also been associated with intradialytic hypotension and left ventricular remodelling, both of which have been shown to increase risk of death in this patient population (50)

As discussed before, patients with ESKD demonstrate a variety of haematologic abnormalities. Anaemia in ESKD has multiple aetiologies and is related to the risk of early death (11) . Whilst haemoglobin (Hb) levels of more than 12g/dl have no additional advantage on survival, Hb of <11g/dl has demonstrable increased risk of mortality HR 1.74 (95% CI range 1.24-2.43) (9). In a prospective study by Ko et. al in Korea, the impact of anaemia (Hb <10g/dl) was worse in the elderly population with increased overall mortality as well as cardiovascular disease related mortality. The reason behind this is postulated to be the effects of anaemia and the resultant tissue hypoxia with regards to cardiac remodelling specifically of the left ventricle (52)

The underlying cause of ESKD has also been shown to have an association with survival. In a 10 year retrospective study by Halle *et al*, in Cameroon, patients with underlying diabetes and hypertension as a cause of nephropathy had a higher overall and early mortality in comparison to ESKD secondary to diabetes or hypertension alone (87% higher risk of mortality in diabetes alone vs 127% in diabetes and hypertension) (53). These findings were replicated by Ferreira et.al where patients with chronic obstructive pyelonephritis fared much better in comparison to those with diabetic nephropathy (11)

Based on data from the Global Burden of Disease Study, as at 2013, CKD was 19th for global years of lost life (an indicator of premature deaths). Five year survival rates for ESKD

unadjusted was 39% , 41% and 60% in the United States, Europe and Japan respectively (9). These regional differences are partly attributed to comorbidities, demographic factors and dialysis practices (54). In a single centre retrospective study in Nigeria, around 25% of patients survived at 366 days after initiation of dialysis (55). Ferreira *et al* reported an 82.3% at year 1, and 49.1 % at year five in a retrospective single centre study in Brazil (11). In South Africa, Thabiet Jardine et. al reported a 1 year survival of 90.4%(58). Closer to home, a 1 year survival in a tertiary hospital in Tanzania was at 71.1% (47). All these countries have varied models of healthcare provision which may affect health care for the disadvantaged population with ESKD on haemodialysis (see table 1).

Table 1: Summary of the regional one and 5 year survival statistics in different regions

Region	**1 year survival (%)**	**5 year survival (%)**
Nigeria	25	
Brazil	82	
South Africa	90.4	
Tanzania	71.1	
United States of America		39
Europe		41
Japan		60
Brazil		49.1

2.2 Study Justification

ESKD is a growing epidemic and HD has played a role in improving quality of life for these patients. Globally, regional disparities have been demonstrated in terms of survival in patients with ESKD with patients in the United States, Europe and Japan fairing much better than those in Sub Saharan Africa. In our centre, data on these statistics are largely missing and the aim for this study is to fill this gap. In addition to this, knowledge of associations of survival in our centre will spur clinicians to actively address these factors in a bid to mitigate mortality in this group of patients.

2.3 Research Question

What is the proportion of patients with ESKD on HD at the KNH dialysis unit who are alive at 1 year of haemodialysis and are there any factors that portend a better survival?

2.4 Objectives

Broad Objective

To determine the one year survival rates and its associations in patients with ESKD on HD at the KNH dialysis unit

Specific Objectives

Primary Objectives

1. To estimate the proportion of patients with ESKD, on haemodialysis at the KNH dialysis, who are alive at 1 year.
2. To document select social, clinical and laboratory characteristics of patients with ESKD on haemodialysis at the KNH dialysis unit.

Secondary Objective

To explore factors associated with one year survival of patients with ESKD on haemodialysis at the KNH dialysis unit

CHAPTER THREE

Methodology

3.1 Study design

The study was a retrospective descriptive cohort study from January 2017 to December 2021

3.2 Study setting/site

The study was conducted at the Dialysis Unit in Kenyatta National Hospital using files of patients seen between January 2017 and December 2021. This is a busy unit at one of the largest teaching and referral hospitals in Kenya with close to 40 patients being dialysed per day. On average, patients receive twice weekly dialysis sessions.This facility is also unique in that patients have been reviewed by a nephrologist, a fellow in nephrology or a physician during their hospital visits since the hospital is the centre for training for the East Africa Kidney institute and one of the oldest medical schools in Kenya.

3.3 Study population

All files of adult patients with ESKD who had undergone haemodialysis at the KNH between January 2017 and December 2021 were included in the study.

3.4 Patient selection

3.4.1 Inclusion criteria

Files of patients greater than 18 years with ESKD, as defined by eGFR of <15ml/min, who had been on haemodialysis at KNH dialysis unit for at least 3 months or had a prior documentation of CKD that had resulted in ESKD necessitating HD.

3.4.2 Exclusion criteria

Files of patients with AKI on haemodialysis. Files with missing data that is pertinent to the study.

3.5 Sample size estimation

Using the Cochran formula below, a sample size of 139 was calculated. This was based on a study by Jardine et. al, in South Africa (47) where survival at 1 year from the debut of haemodialysis was found to be 90.4%.

$$n_0 = \frac{Z^2 pq}{e^2}$$

Where:

n_0 is the desired sample size

Z is the level of significance (1.96)

p is the estimated proportion of the population with the attribute (0.9)

q is 1-p (0.1)

e is the level of precision, in this case set at 0.05

3.6 Sampling method

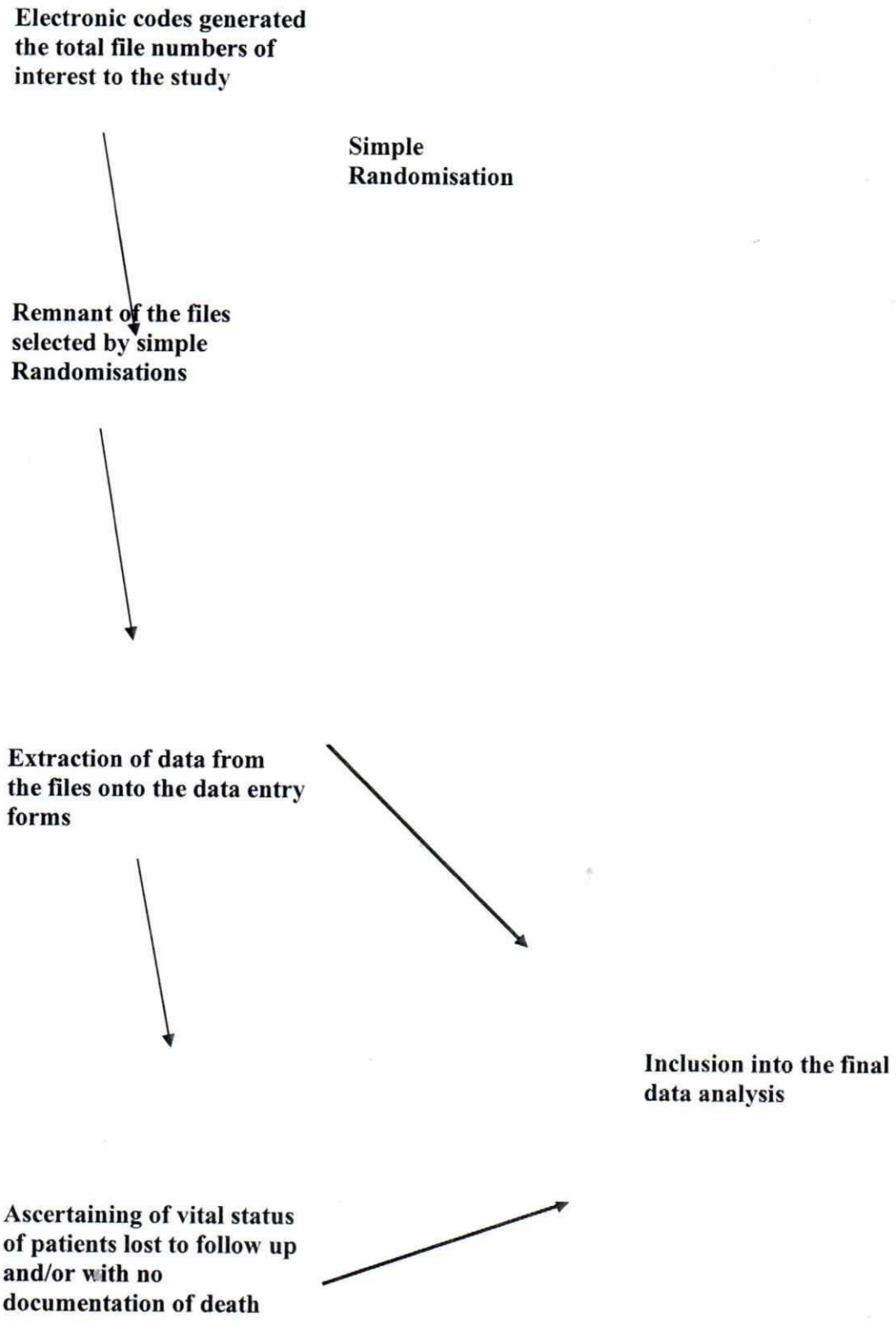
The electronic codes generated 1200 file numbers of interest to this study. From these, using simple randomisation method, the files that would eventually be included in the study were selected.

3.7 Data collection procedure

The files that were retrieved by the medical records officer after the simple randomisation were then reviewed by the investigator as well as two trained research assistants. Relevant information was extracted from the files and entered into a data entry form (See appendix 1). The data collection forms and files were counterchecked by the principal investigator for completeness and accuracy before the process was completed. During the process of follow up of the cohort for one year, if a patient was lost to follow up or information on their vital status (whether dead or alive) was missing, a follow up was made at the civil registration services to

obtain this information. CRS has an electronic compilation of all the death notifications in the country. (See figure 1 for summary of the data collection procedure)

Figure 1: Flow chart showing data collection procedure



3.8 Study variables and definitions

Entry point into the study was defined as a diagnosis of ESKD as defined by a eGFR of 15ml/min on maintenance haemodialysis. Exit from the study was documented if any of the following points were met:

1. Death as certified by the attending clinician or as ascertained in the registry of births and deaths.
2. End of the 1 year follow up period.
3. Kidney transplantation as documented by the attending clinician(s).
4. Point of termination of the study: defined as 31st December 2021.
5. Lost to follow up.

The variables of interest to this study include the

1. Sociodemographic characteristics of patients:
   a. Age as documented in the patient registration form
   b. Sex: either Male or Female
2. Causes of ESKD as documented by the clinician (s) reviewing the patient. These were grouped into the commonest causes of ESKD as enumerated:
   a. Diabetes
   b. Hypertension
   c. Glomerulonephritis
   d. Obstructive uropathy
   e. Others
3. Underlying comorbidities as documented by the clinician (s) reviewing the patient
   a. Infections: HIV, Hepatitis B
   b. Cancer
   c. Cardiovascular disease
   d. Others
4. Biochemical characteristics within the first month of initiation of haemodialysis specifically:
   a. Haemoglobin level grouped into >11g/dl, 10.1-11g/dl, 8-10g/dl, 6.5-7.9g/dl, <6.5g/dl
   b. Albumin level grouped as >/=35g/L, 25-34.9 <25
   c. Mode of entry into haemodialysis: Planned or Emergent haemodialysis

d. Type of access at the time of initiation of haemodialysis: Arteriovenous fistula, tunnelled cuffed dialysis catheter, non tunnelled non cuffed dialysis catheter

3.9 Ethical considerations

Approval was sought from the University of Nairobi/ Kenyatta National Hospital Ethics and research committee with regards to getting a waiver of consent in order to access patients records. Confidentiality was observed by ensuring that data entry forms did not have patient identifiers. Each form was identified using a unique study number and linked to patient records by the file's registration number. Hardcopies of data collection forms once filled were stored by the author in designated files and stored under lock and key. Electronic data for analysis were password protected and were only accessed by the principal investigator

3.10 Data management

Data from the data entry form was entered into Microsoft excel. Subsequent data cleaning, coding and statistical analysis was done using SPSS version 25. Continuous variables such as age and duration was represented using descriptive summary statistics such as median and corresponding IQRs depending on the distribution. Categorical data such as gender, comorbidities and cause of ESKD was summarised as percentages and frequencies. The outcomes of interest in this case survival and mortality plus relevant clinical and sociodemographic characteristics were analysed and strengths of association measured by hazard ratios. Kaplan Meier curves were used to demonstrate cumulative survival while the log rank test was used to extract factors impacting survival. The cox proportional hazard was then used to calculate risk ratio as well as the impact of clinical and demographic variables on survival. P values of <0.05 will be considered statistically significant.

CHAPTER FOUR

Results

Five hundred and seventy one files were retrieved using the sampling frame discussed under methodology. Of these, 382 files were excluded because of varied reasons: 27 files were of patients under the age of 18, 30 files were of patients on haemodialysis before January 2017, 67 files were of patients with other medical and surgical diagnoses, 54 files had missing relevant data, 56 and 84 files were of patients with acute kidney injury with the latter being on haemodialysis for less than 3 months while 64 files were of patients with chronic kidney disease but not on haemodialysis. One hundred and eighty nine files were eventually included having met the definition of the study population.

The mean age of the patients was 47.8 (SD 15.1) years, where the minimum age observed was 19.0 years, while maximum was 81.0 years. The median age was 48.0 (IQR 37.0 – 60.0) years. Majority of the patients were between the ages of 40 to 59 years (43.4%). There were 106 (56.1%) male patients and 83 (43.9%) female patients, a male to female ratio of 1.3:1.

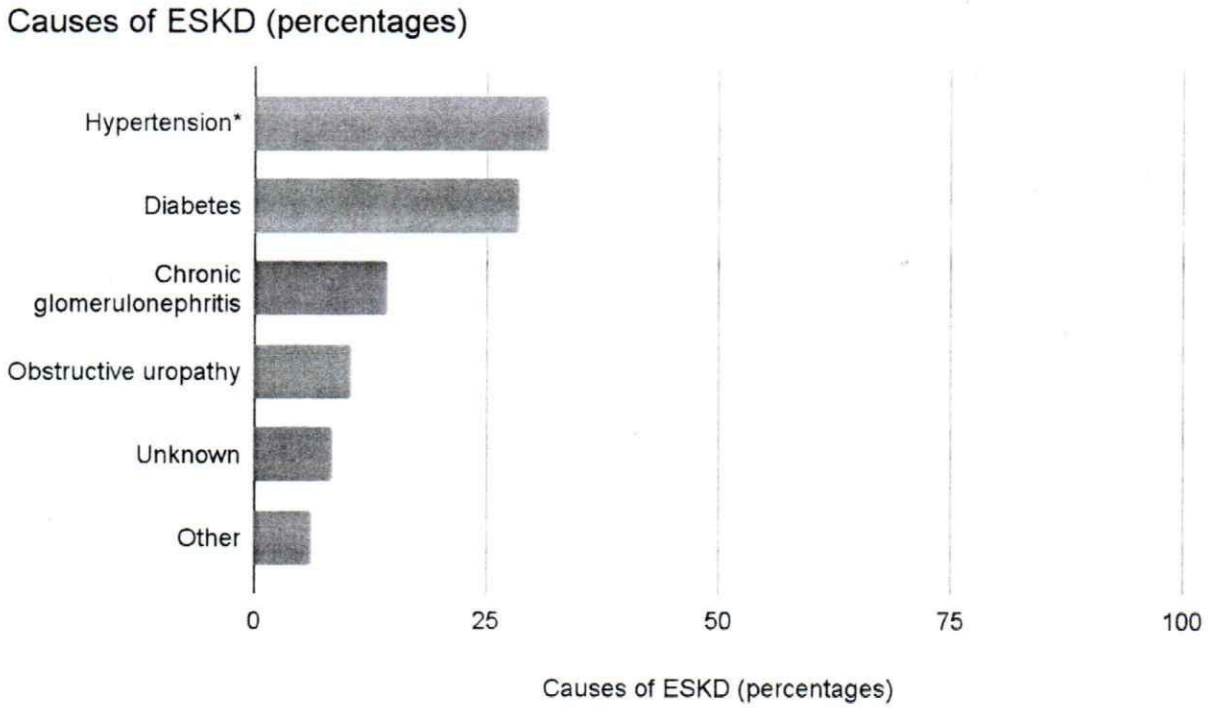
Table 2: Demographic characteristics

	Frequency, *(n=189)*	**Percent**
Age		
18 – 39	62	32.8
40 – 59	79	41.8
60 – 79	47	24.9
≥80	1	0.5
Sex		
Male	106	56.1
Female	83	43.9

The clinical characteristics of interest in this study were the cause of ESKD, associated comorbidities, dialysis access at the time of initiation of dialysis, mode of initiation of dialysis (whether planned or emergent) and the albumin and haemoglobin level at the time of dialysis initiation.

The causes of ESKD in this patient population were majorly from hypertension; 60, diabetes and hypertension; 54, chronic glomerulonephritis; 27, and obstructive uropathy (Figure 1) Other causes of ESKD accounting for 17 cases were ADPKD, HIVAN, Chronic graft dysfunction, congenital kidney abnormalities, drugs and multiple myeloma at 5, 3, 1, 3, 2 and 2 cases respectively.

Figure 2: Bar graph representing cause of ESKD

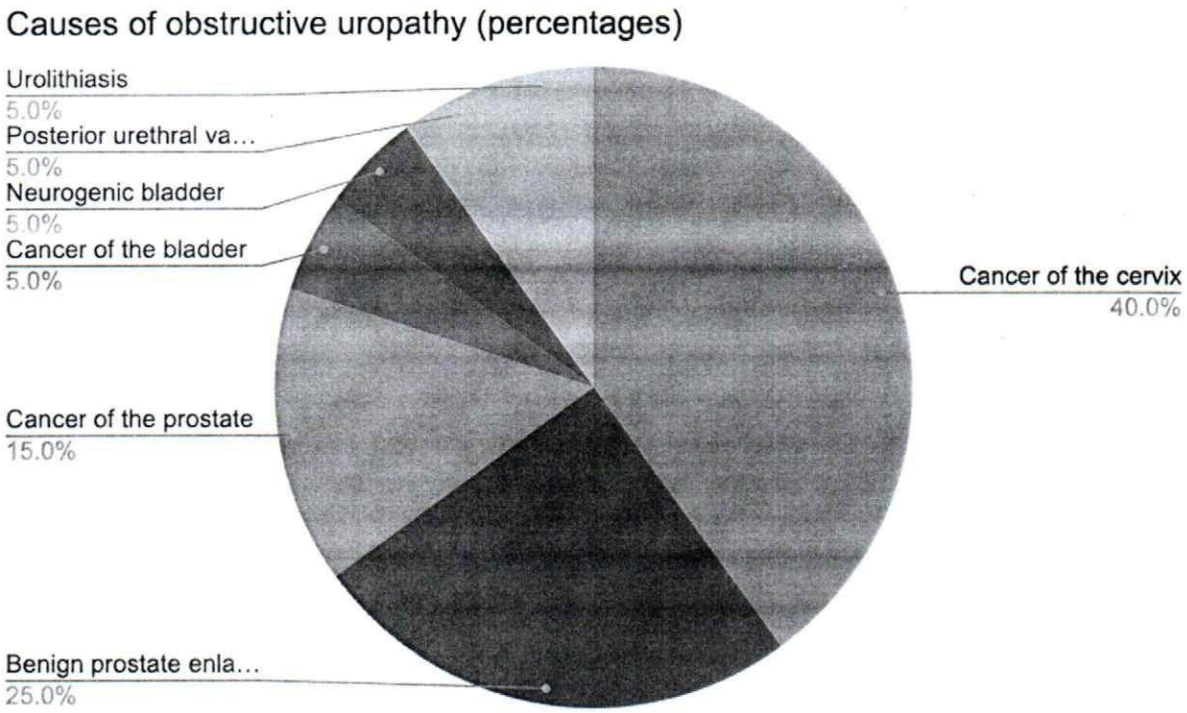


	Frequency, *(n=189)*	**Percent**
Hypertension*	60	31.7
Diabetes	54	28.6
Chronic glomerulonephritis	27	14.3
Obstructive uropathy	20	10.6
Other	16	8.5
Unknown	12	6.3

**Due to the younger age of study participants, most of the causes of hypertension likely reflect chronic glomerulonephritis as a cause of ESKD*

Of the 20 patients with obstructive uropathy, 8 of these had cancer of the cervix (40%), followed by 5 with benign prostatic enlargement and 3 with cancer of the prostate. Other causes of obstructive uropathy in this patient population included cancer of the prostate and bladder, neurogenic bladder, posterior urethral valves and urolithiasis. The frequencies of each of these as a cause of ESKD are delineated in Figure 2.

Figure 3: Pie chart representing causes of obstructive uropathy



	Frequency, *(n=20)*
Cancer of the cervix	8
Benign prostate enlargement	5
Cancer of the prostate	3
Cancer of the bladder	1
Neurogenic bladder	1
Posterior urethral valves	1
Urolithiasis	1

The commonest dialysis access at the time of initiation was the non tunnelled catheter followed by the tunnelled cuffed catheter at 74% and 10% respectively. Less than 2% of the patient population had an arteriovenous fistula as a dialysis access at the time of dialysis initiation. In terms of the mode of dialysis, more than half of the population (60%), had initiation of the same done as an emergency (table 2).

Table 3: Mode of dialysis and type of access for dialysis

	Frequency, *(n=189)*	Percent
Dialysis access		
Arteriovenous fistula	3	1.6
Tunnelled cuffed dialysis catheter	19	10.1
Non tunnelled dialysis catheter	141	74.6
Not documented	26	13.8
Dialysis type		
Planned	10	5.3
Emergent	120	63.5
Not documented	59	31.2

In terms of attendant comorbid conditions, infectious diseases and cardiovascular disease were most of the conditions documented in this patient population (tables 3).

Table 4: Comorbidity

	Frequency, *(n=189)*	Percent
Chronic infections*	20	10.6
Cardiovascular diseases**	13	6.9
Others	17	9.0
None	139	73.5

**These include HIV and hepatitis B*

***These include Heart failure, stroke, valvular heart disease, cardiomyopathy, ischaemic heart disease*

For the laboratory parameters, majority of the patients had hypoalbuminaemia of less than 35g/l while majority had a haemoglobin of less than 11g/dl (see table 4)

Table 5: Biochemical characteristics

Albumin	Frequency, *(n=189)*	Percent
<25.0	13	6.9
25.0 – 34.9	58	30.7
>35.0	55	29.1
Not documented	63	33.3
Hemoglobin		
>11.0	16	8.5
10.1 – 11.0	4	2.1
8.0 – 10.0	56	29.6
6.5 – 7.9	43	22.8
<6.5	22	11.6
Not documented	48	25.4

At the end of the one year follow up period, survival was at 76.2%. Of these patients, who were alive, only one had undergone a successful kidney transplant (table 5).

Table 6: Survival statistics and status of living patients

	Frequency, *(n=189)*	Percent
Status		
Living	144	76.2
Dead	45	23.8
Living	**Frequency, *(n=144)***	**Percent**
Transplant	1	0.7
End of 1 year follow-up	114	79.2
Termination of study	29	20.1

The overall Kaplan Meier survival curve estimated a mean survival time of around 10 months. The slope of the curve is steeper in the first 6 months and then subsequently plateaus.

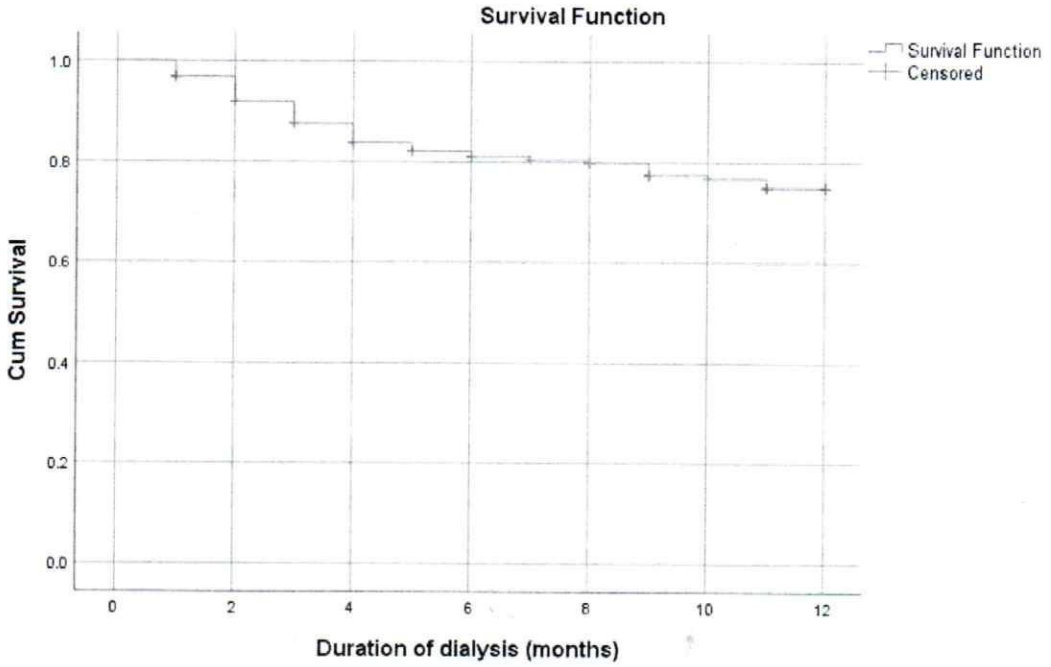


Figure 4 This is the overall Kaplan-Meier survival curve. The curve estimates the mean survival time at 10.1 (95% CI: 9.6 – 10.7) months

For the secondary analysis, the following factors, age, gender, cause of end stage kidney disease, albumin and haemoglobin levels were analysed for association with mortality. When stratified by age, the younger population appeared to have a worse survival though this difference was not statistically significant. Males were also less likely to die in comparison to females though this was also not statistically significant. When it came to causes of ESKD, patients with obstructive uropathy had an increased risk of death while those with hypertension had the least risk of death. These hazard ratios however were not statistically significant. Having a low albumin (25-34.9g/l) was also associated with reduced survival as was having

anaemia of less than 6.5g/dl with a 2.3 and 3.9 times higher risk of death and this was statistically significant (table 6)

Table 7: Factors associated with mortality amongst patients with ESKD. (The figures in brackets are in percentages)

	Dead	Alive	HR (95% CI)	p-value
Age	***n=45***	***n=144***		
18 – 39	16 (35.6)	46 (31.9)	1.2 (0.6 – 2.7)	0.612
40 – 59	19 (42.2)	60 (41.7)	1.2 (0.5 – 2.5)	0.718
≥60	10 (22.2)	38 (26.4)	Reference	
Gender				
Male	22 (48.9)	84 (58.3)	0.7 (0.4 – 1.3)	0.307
Female	23 (51.1)	60 (41.7)	Reference	
Cause of ESKD				
Diabetes				
Yes	12 (26.7)	44 (30.6)	0.9 (0.4 – 1.7)	0.678
No	33 (73.3)	100 (69.4)	Reference	
Hypertension				
Yes	11 (24.4)	47 (32.6)	0.7 (0.3 – 1.4)	0.278
No	34 (75.6)	97 (67.4)	Reference	
Chronic Glomerulonephritis				
Yes	7 (15.6)	20 (13.9)	1.1 (0.5 – 2.4)	0.881
No	38 (84.4)	124 (86.1)	Reference	
Obstructive uropathy				
Yes	6 (13.3)	14 (9.7)	1.5 (0.6 – 3.5)	0.373
No	39 (86.7)	130 (90.3)	Reference	
Albumin	***n=33***	***n=93***		
<25.0	4 (12.1)	9 (9.7)	2.0 (0.6 – 6.6)	0.241
25.0 – 34.9	20 (60.6)	38 (40.9)	2.3 (1.1 – 5.1)	**0.037**
≥35.0	9 (27.3)	46 (49.5)	Reference	
Hemoglobin	***n=37***	***n=104***		
>11.0	3 (8.1)	13 (12.5)	Reference	
10.1 – 11.0	1 (2.7)	3 (2.9)	1.3 (0.1 – 12.7)	0.811
8.0 – 10.0	9 (24.3)	47 (45.2)	0.8 (0.2 – 3.0)	0.769
6.5 – 7.9	12 (32.4)	31 (29.8)	1.4 (0.4 – 5.0)	0.587
<6.5	12 (32.4)	10 (9.6)	3.9 (1.1 – 14.0)	**0.034**

CHAPTER FIVE

Discussion

Chronic kidney disease and its progression to ESKD has been identified as a risk factor for death with global projections estimating that by the year 2040, this will be among the 5th leading causes of mortality. Haemodialysis, a modality in the management of ESKD, is also associated with the highest mortality (44). This study therefore set out to determine the one year survival in this population of patients at one of the largest dialysis centres in Nairobi as well as some of its associations in a bid to mitigate mortality in this group of patients.

This study analysed 189 files of patients with ESKD on HD at the KNH between January 2017 to December 2021. On follow-up at one year, the survival rate was 76.2%. These figures are lower than those of a retrospective study done earlier (1st January 2010 to 31st December 2019) by Kubo et.al, that reported one year survival at 79% (56). This difference could partly be attributed to the fact that the study was carried out in 2 centres, Kenyatta National Hospital and Nairobi Hospital (one of the largest private hospitals in Nairobi. These figures differ with select centres in Africa. In comparison to centres in some African countries, our centre has worse survival rates. Data from the Egyptian renal data system report from the year 2020, survival at one year was reported at 94.3% (22). This registry is a central database that collates data from several Egyptian dialysis units including both government and private funded centres. It is not surprising that the database demonstrates better survival statistics. Egypt, while facing similar challenges that low and middle income countries face, does have a higher nurse patient and nurse physician ratio. These figures are more or less at par with data from South Africa where Jardine et. al, reported a 90.4 % one year survival rate (47). In the South African study, data was similarly a collation of information from most dialysis units countrywide including both private and government funded facilities into the South African renal registry.

Conversely, survival rates from our centre fare better in comparison to data from several centres e.g Ethiopia, where survival probability at one year is 49.58% (57). In this retrospective study that was in a single centre done between March 2016 to March 2021, the survival figures were attributable partly to methodology as well as quality and access to healthcare. For starters, the study recruited patients with end stage kidney disease within 3 months of haemodialysis. In addition to this, patients likely presented late, received suboptimal dialysis compounded by financial constraints that could affect care. Similarly, survival at 1 year in a single centre retrospective study in Nigeria was at 25% (55). This largely reflects the financial constraints

that patients face as well inadequate health facilities and lack of a subsidy programme for medical management. While most of these constraints apply in our setup, the steps taken by the National Hospital Insurance Fund in Kenya to cover for at least two sessions of dialysis a week have gone a long way to mitigate early deaths in this patient population. The survival statistics from a tertiary hospital in Tanzania estimate one year survival at 71.1% which is more or less at par with our study (58). These numbers, as per the authors' postulations, reflect the recent investments in healthcare where facilities and caregivers providing medical attention to patients with ESKD on HD have increased dramatically over the recent years.

In our study, the overall Kaplan Meier survival curve estimated a mean survival time of ten months. In addition to this, the curve was steeper in the first 6 months after initiation of haemodialysis. Earlier deaths within the first year of haemodialysis have been shown to be as a result of haemodynamic strain that dialysis puts on the heart as well as the dramatic shifts of solutes and fluid during haemodialysis that are not in keeping with normal physiology (67). It is equally possible to postulate that most of our patients are diagnosed with ESKD at a later time and start haemodialysis emergently without the benefit of mitigating some of the deleterious effects of CKD earlier on in the disease progression. This particular finding has been explored by Ferreira et. al with the authors explaining that the higher mortality in the first year of initiation of haemodialysis is compounded by the difficulty of the body to adapt to the physiologic stress that accompanies haemodilaysis

With these numbers, it is apparent that more needs to be put in place to mitigate the high death rate in this patient population. Kidney transplantation is the only modality that's the best treatment option for ESKD (59). Kidney transplant recipients in comparison to their counterparts undergoing dialysis have an improved survival not to mention an improved quality of life (60). However, in our particular cohort of patients, only one had undergone a successful kidney transplantation during this follow up period. In a retrospective single centre study in Brazil by Ferreira et. al, out of 463 patients registered in the nephrology service, 22 were censored from the study after having undergone kidney transplantation (11). The figures in our centre may be a reflection of selection bias, the data was limited to patients dialysing in the KNH dialysis unit. However, being a national referral hospital, patients from all over the country can potentially access dialysis and transplant services at the facility. In addition to this, the study period cuts across the period of the coronavirus pandemic where most elective surgeries had been postponed due to the strain on the healthcare system at the time. That aside,

the cost of transplantation is out of reach for a large number of patients who access services for ESKD at KNH (61).

Several authors from different countries and centres have attempted to investigate associations between different clinical characteristics and survival in a bid to identify factors that can be altered in a bid to improve survival. Our study set out to evaluate select clinical parameters as well and as a secondary objective to determine if there was any association with survival. In our study, the patient population was predominantly male with a ratio of 1.3:1. This male predominance has also been described in other studies in Egypt, Brazil, South Africa (22, 11 47). This male predominance has been attributed to possible protective effects of oestrogen or the damaging effects of testosterone as well as an unhealthy lifestyle in men (62). Having said this though, survival in males in this population was better than females. This difference was however not statistically significant. In the spectrum of CKD, mortality predialysis tends to be worse in males but this trend is reversed in the context of ESKD and haemodialysis where mortality is worse in females (62). While these differences may be attributable to physiological reasons, social structures that disempower women and create inequities in accessing care for this subgroup of the population may contribute to this disparity (63, 19).

Age as a confounder for mortality has also been described widely in literature. In our study, the majority of the population (close to 75%) was under the age of 60 years. This finding was replicated in select studies in Africa (11, 55, 22). These differ with studies in Europe and United States of America where the proportion of patients greater than 65 years is more than 50% of the patients with ESKD on HD (54). In our study, the trend was higher risk of death in the younger population. This difference was however not statistically significant. Higher risk of death in the elderly population has been described in literature due to the attendant comorbidities (45). In addition, a systematic review by Hazara et. al, for every 10 year increment in age, there was an increased risk of death with a hazard ratio of 1.5 (1.43-1.56 95% CI) (10). These findings have been replicated in studies with a similar methodology as our current study (47), though this was data derived from a nationwide registry with multiple centres, and (55). It is easy to attribute the findings of this study to an inadequate sample size not powered to evaluate the association between age and survival. However, an alternative hypothesis could be the economic pressures at play that may influence health seeking behaviours in the young population. This, though, is beyond the scope of this study.

Hypertension was the leading cause of ESKD in our population, closely followed by diabetes, chronic glomerulonephritis and obstructive uropathy. This is consistent with studies from Sub Saharan Africa which show hypertension as a leading cause of ESKD (21). Conversely, data from the United States shows diabetes as the leading cause of ESKD (4) while in the gulf cooperative, chronic glomerulonephritis is the leading cause of ESKD (5). In the subanalysis on association with survival, there was a trend to better survival with hypertension as a cause of ESKD, followed by diabetes, chronic glomerulonephritis and obstructive uropathy in that order. This is similar to a retrospective study in Cameroon by Halle et.al, where compared to hypertension, having diabetes alone or diabetes and hypertension in combination was associated with a higher risk of death (53). This is not the case with other studies done elsewhere. In Brazil, having chronic obstructive pyelonephritis resulted in a lower risk of death compared to diabetic nephropathy. Conversely, hypertension and other causes of ESKD fared worse than diabetic nephropathy (11). The high risk of mortality associated with obstructive uropathy in our population is likely attributable to the fact that cancer accounted for slightly more than half of the causes of obstructive uropathy.

The laboratory parameters of interest in our study were albumin and haemoglobin level. Having an albumin of 25 - 34.9g/dl was associated with higher risk of death (2.3 times). This finding has also been noted by Msaad et. al, in a 10 year retrospective study in Morocco where an albumin of 38g/dl or less had a 1.85 times risk of death in patients with ESKD on HD (49). Ferreira et. al also observed that having an albumin of greater than 40 and between 35 and 40 was associated with a reduced risk of death (11). Hypoalbuminaemia has been used as an indicator of chronic malnutrition as well as chronic inflammation, both of which have an adverse bearing on survival (12). In addition to this, hypoalbuminaemia has also been associated with intradialytic hypotension and left ventricular remodelling, both of which have been shown to increase risk of death in this patient population (50)

More than a third of our patient population had a haemoglobin level of less than 10 g/dl. To put this in perspective, KDIGO practice guideline recommends a target haemoglobin of 10-11.5 g/dl for patients with ESKD on haemodialysis (64). The reason behind this is the increased risk of death and cardiovascular morbidity associated with anaemia (65, 66). The impact of anemia (Hb <10g/dl) has been shown to be worse in the elderly population with increased overall mortality as well as cardiovascular disease related mortality. The reason behind this is postulated to be the effects of anaemia and the resultant tissue hypoxia with regards to cardiac remodelling specifically of the left ventricle (52)

This increased risk of death was also noted in our study, and it worsened as the level of haemoglobin dropped with a haemoglobin of less than 6.5g/dl being associated with four and a half higher risk of death with reference to a level of between 10 and 11g/dl. This difference was statistically significant. This has similarly been reported in other studies (11, 9).

Conclusion

In our study, survival rate was at 76.2% and appeared to be significantly better than some of the neighbouring countries in Sub Saharan Africa (Ethiopia, Tanzania). There was a trend to better survival for males, those with hypertension as a cause of ESKD and being older.. In addition to this, having an albumin level of between 25-34.9g/dl and a haemoglobin of <6.5g/dl were associated with a higher risk of death. Further studies, perhaps with multiple centres involved and larger sample sizes are needed to elucidate some of these findings.

Study limitations and mitigation measures

1. This was a single centre study therefore generalisability and external validity is uncertain. However, our center is one of the national referral centers that serves patients from various parts of the country.
2. Our sample size was powered to assess for survival and may have been inadequate to measure some associations with survival. Perhaps some of the trends noted could serve as a basis for generating other hypotheses for future studies
3. This was a retrospective study and therefore the aspect of missing data and loss to follow up could not be avoided. We went further to access the civil registry to account for the vital status of some of the study participants.

Recommendations

1. A prospective study can be undertaken to evaluate for other circumstances that may contribute towards reduced survival in the first year of haemodialysis
2. For patients with ESKD, there should be routine assessment, close follow up and treatment of anaemia and malnutrition as this is a potentially modifiable risk factor to mitigate deaths in this patient population.

CHAPTER SIX

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CHAPTER FIVE

Appendix

1. Data entry sheet

Study number:			
Patient initials:			
Age			
Sex			
Cause of ESKD			
Initiation of dialysis (month/year)			
Censorship (month/year)	Dead	Living: 1.Lost to follow up 2. Transplant 3.Termination of study	
Duration of dialysis (months)			
Dialysis access	1.Arteriovenous fistula	2.Tunnelled cuffed dialysis catheter	3.Non tunnelled dialysis catheter
1.Planned dialysis		2.Emergent dialysis	
Comorbidity			
Albumin level 1. <25mg/dl			

2. 25-34.9mg/l 3. >/=35g/l			
Haemoglobin level 1. >11g/dl 2. 10.1-11g/dl 3. 8.0-10g/dl 4. 6.5-7.9g/dl 5. <6.5g/dl			

2. Dummy Tables

Gender	Number	Percentage
Male		
Female		
Age (years)		
18-39		
40-59		
>60		
Cause of ESKD		
Diabetes		
Hypertension		
Glomerulonephritis		
Obstructive uropathy		
Others		
Unknown		
Comorbidities		
HIV		
Cancer		
Cardiovascular		

Disease Ischaemic heart disease Cardiomyopathy Hypertensive heart disease Cerebrovascular accidents Other (specify)		
Hepatitis B		
Liver disease		
Albumin level		
<25g/l		
25-34.9g/l		
>/=35g/l		
Haemoglobin level		
>11g/dl		
10.1-11g/dl		
8-10g/dl		
6.5-7.9g/dl		
<6.5g/dl		

Associations of mortality

	Dead	Alive	HR (95% CI)	p-value
Age	*n*	*n*		
18 – 39				
40 – 59				
≥60				
Gender				
Male				
Female				
Cause of ESKD				
Diabetes				
Yes				
No				
Hypertension				
Yes				
No				
Chronic Glomerulonephritis				
Yes				
No				
Obstructive uropathy				
Yes				
No				
Albumin	*n*	*n*		
<25.0				
25.0 – 34.9				
≥35.0				
Hemoglobin	*n*	*n*		
>11.0				
10.1 – 11.0				
8.0 – 10.0				
6.5 – 7.9				
<6.5				

To

The director, Civil registration services,
Department of Civil Registration,
Hass Plaza,
P.O. Box 49178-00100, Nairobi.

Thro'
Chairperson, Prof Eratsus Amayo,
Department of Clinical Medicine and therapeutics,
University of Nairobi
P.O. Box 19657-00100, Nairobi.

Dear Madam,

RE: Request to access national registry on deaths

I am a postgraduate student in Internal Medicine, affiliated with the Department Of Clinical Medicine And Therapeutics At The University Of Nairobi. I am currently conducting research at the Kenyatta National hospital among patients with end stage kidney disease undergoing haemodialysis. In this study, one of my outcomes is death and it is for this reason that I request to be granted access to the national registry.

My study aims at determining one year survival in this subset of patients and it is my belief that this information can help clinicians to mitigate some of these deaths that occur in out set up.

Please find attached approvals to conduct this study at the Kenyatta National Hospital as well as a copy of my protocol.

I am looking forward to a favourable response.

Yours Sincerely,
Dr. Magoma Georgina
Senior House Officer, UoN/ KNH
+254724694369, georginamagomaedesa@students.uonbi.ac.ke

ONE YEAR SURVIVAL AND ITS ASSOCIATED FACTORS IN PATIENTS WITH END STAGE KIDNEY DISEASE UNDERGOING HAEMODIALYSIS AT KENYATTA NATIONAL HOSPITAL

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APPROVAL BY LEAD SUPERVISOR AND CHAIR OF THE DEPARTMENT

This dissertation is submitted with the approval of the lead supervisor and the chair of the department:

1. **Dr. Emma M. Karari**

Lecturer at the Department of Clinical Medicine and Therapeutics

Consultant Physician and Cardiologist

The University of Nairobi

Signature…… Date…16-11-2023……

2. **Prof E.O. Amayo**

Professor of Internal Medicine and Neurology,

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Signature…… Date…17/11/2023……