PREVALENCE AND TYPES OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN DIALYSIS NAÏVE CHRONIC KIDNEY DISEASE PATIENTS AT KENYATTA NATIONAL HOSPITAL

Dr. ANTHONY MUGUIYI MUTURI
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SUPERVISORS

1. Prof. Elijah S. N. Ogola
   MBChB(NBI), CTM, MMED-Int. Med(NBI), FACC
   Associate Professor
   Consultant Physician and Cardiologist
   Department of Clinical Medicine & Therapeutics
   University of Nairobi

   Signed: _____

   Date: _____

2. Prof. Joshua Kyateesa Kayima
   MBChB(Makerere), MMED-Int. Med(NBI)
   Associate Professor
   Consultant Physician &Nephrologist
   Department of Clinical Medicine & Therapeutics,
   University of Nairobi

   Signed: _____

   Date: _____

DECLARATION

I understand the nature of plagiarism, and I am aware of the University's policy on this. I certify that this dissertation is my original work and has not been submitted to any other university for the award of any degree.

Signature: _____

Date: _____

ABBREVIATIONS

ACC	-	American College of Cardiology
AF	-	Atrial Fibrillation
AHA	-	American Heart Association
AV	-	Atrio-Ventricular
AVB	-	Atrio-Ventricular Block
BMI	-	Body Mass Index
CKD	-	Chronic Kidney Disease
CVD	-	Cardiovascular Disease
ECG	-	Electrocardiograph
eGFR	-	Estimated Glomerular Filtration Rate
ESRD	-	End Stage Renal Disease
ESC	-	European Society of Cardiology
HF	-	Heart Failure
HIV	-	Human Immunodeficiency Virus
KDIGO	-	Kidney Disease: Improving Global Outcomes
KNH	-	Kenyatta National Hospital
KNH/UON-ERC	-	Kenyatta National Hospital/University of Nairobi – Ethics & Research Committee
LAF	-	Lone Atrial Fibrillation
LAFB	-	Left Anterior Fascicular Block
LBBB	-	Left Bundle Branch Block
LPFB	-	Left Posterior Fascicular Block
LVH	-	Left Ventricular Hypertrophy
MDRD	-	Modification of Diet in Renal Disease
MI	-	Myocardial Infarction
NCD	-	Non-Communicable Diseases
NSVT	-	Non-sustained Ventricular Tachycardia
PCI	-	Percutaneous Intervention
PVC	-	Premature Ventricular Contractions
QTc	-	Corrected QT Interval
RBBB	-	Right Bundle Branch Block
SCD	-	Sudden Cardiac Death

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THE PREVALENCE AND TYPES OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN DIALYSIS NAÏVE CHRONIC KIDNEY DISEASE PATIENTS AT KENYATTA NATIONAL HOSPITAL.

ABSTRACT

Background: Chronic non-communicable diseases (NCDs) contribute to more than 60% of all deaths worldwide and approximately 80% of these deaths occurred in low and middle income countries, a category where Kenya belongs. Chronic Kidney Disease (CKD) is a risk multiplier and is associated with an eight- to tenfold increase in cardiovascular mortality. The presence of cardiac arrhythmias and other electrocardiographic abnormalities is high in CKD patients and this increases the risk for sudden cardiac death which is the single greatest contributor to mortality in advanced renal disease. There is paucity of data in Kenya on the prevalence of ECG abnormalities in dialysis naïve CKD patients.

Objectives: The primary aim of this study was to determine the prevalence and types of ECG abnormalities in dialysis naïve CKD patients at Kenyatta National Hospital. The secondary objective was to correlate the ECG abnormalities with the CKD stage

Methods: This was a cross-sectional descriptive study carried out at the Kenyatta National Hospital. Patients aged 30 years and above who had a file documented diagnosis of CKD and were dialysis naïve were recruited consecutively. The study was carried out from November 2013 to February 2014. A standard 12 lead resting ECGs was recorded and interpreted by the principal investigator as per the *"AHA/ACC recommendations for the standardization and interpretation of the electrocardiogram"* and the readings were subsequently confirmed by a consultant cardiologist. Estimation of serum creatinine was done so as to establish the CKD stage.

Results: A total of 212 patients were recruited. The mean age of the patients was 54.2 years and 58% were male. Hypertension and diabetes were the main aetiological factors for CKD in more than 80% of the participants. Overall, 64% of the patients had at least one form of ECG abnormality. The proportion of patients who had atrial fibrillation was 16%; premature ventricular contractions at 8%; left ventricular hypertrophy at 29.7%; repolarisation changes at 18.9%; prolonged QT interval at 14.6%. Advanced CKD was associated with abnormal ECG findings and the prevalence of ECG abnormalities increased proportionately to the severity of CKD.

Conclusion: The prevalence of ECG abnormalities in our dialysis naïve CKD patients is high and this includes ECG abnormalities that predict adverse cardiovascular morbidity and mortality such as left ventricular hypertrophy, prolonged QT interval and repolarisation changes.

Recommendations: An ECG should be recorded and evaluated in all CKD patients and a multi-disciplinary approach to these patients is crucial. There is need for more studies to establish the role of serial ECGs in the long term follow-up of CKD patients which may be crucial in the early detection of new ECG changes. In order to establish the prognosis and therapeutic effects of treatment given to CKD patients who have various ECG abnormalities, more follow-up studies are needed.

1 BACKGROUND

In 2005, more than 35 million deaths (60% of all deaths worldwide) were due to chronic non-communicable diseases (NCDs). Approximately 80% of these deaths occurred in low and middle income countries, a category where Kenya belongs. Chronic kidney disease, cardiovascular disease, cancer, chronic respiratory diseases, and diabetes were the main culprits. The morbidity and mortality from these diseases was projected to rise exponentially over the years if measures to curb this pandemic were not implemented. This necessitated the World Health Organisation to reaffirm the importance of these diseases as a neglected global health issue.[1]

Chronic kidney disease is a risk factor for adverse outcomes of chronic disease. Among patients with diseases such as cardiovascular disease, diabetes, or cancer, the presence of chronic kidney disease is associated with an increased risk of complications related to those diseases when compared to those patients with normal kidney function. In diabetes mellitus and hypertension, it is a risk multiplier which confers an eight- to ten-fold increase in cardiovascular mortality.[2]

Chronic kidney disease is a major public health problem in sub-Saharan Africa due to the fact that most patients who develop renal disease in Africa do not have access to quality medical care due to the shortage of physicians, nephrologists, and infrastructure such as dialysis machines.[3] Nephrologist to general population ratios in Africa are among the lowest in the world making comprehensive delivery of renal care in this continent extremely challenging.[4] This is further complicated by the high incidence of late presentation to specialised care.[5]

The presence of cardiac arrhythmias and other electrocardiographic abnormalities is high in CKD patients and this increases the risk for sudden cardiac death which is the single greatest contributor to mortality in end stage renal disease. Sudden cardiac death accounts for approximately 25% of all-cause mortality in end-stage renal disease patients and hence prevention of disease progression through modification of risk factors should be of priority.[6]

CKD patients have the unique propensity to develop cardiovascular disease with associated electrocardiographic abnormalities. The progressively declining renal function itself represents a continuum of cardiovascular risk, and in those individuals who survive to reach ESRD, the risk of suffering a cardiac event such as sudden cardiac death is high.

2 LITERATURE REVIEW

2.1 Chronic Kidney Disease And Its Impact on Cardiovascular Morbidity and Mortality

CKD is defined by the ***Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group*** as abnormalities of kidney structure or function, present for three months, with implications for health. Chronic kidney disease is classified based on the cause, glomerular filtration rate category, and albuminuria category.[7]

For one to diagnose CKD, either of the following should be present for more than three months:

- Markers of kidney damage (one or more) which include;
    - Albuminuria (Albumin excretion rate ≥30 mg/24 hours; Albumin-to-creatinine ratio ≥30 mg/g [≥3 mg/mmol])
    - Urine sediment abnormalities
    - Electrolyte and other abnormalities due to renal tubular disorders
    - Histological abnormalities in renal biopsies
    - Structural abnormalities detected by imaging
    - History of kidney transplantation
- Decreased Glomerular Filtration rate (GFR)
    - GFR <60 ml/min/1.73m^2

Table I: Classification of CKD based on GFR categories (KDIGO 2012)[7]

Stage	Description	Estimated GFR (ml/min/1.73m^2)
1	**Kidney damage with normal or increased GFR**	**≥90**
2	**Kidney damage with mild reduction in GFR**	**60-89**
3a	**Mildly to moderately decreased GFR**	**45-59**
3b	**Moderately to severely decreased GFR**	**30-44**
4	**Severe decrease in GFR**	**15-29**
5	**Kidney failure**	**<15(or dialysis)**

Table 2: Albuminuria categories in CKD (KDIGO 2012)[7]

Albuminuria in CKD				
Category	**Albumin Excretion Rate (AER)**	**Albumin-to-creatinine ratio (mg/mmol)**	**Albumin-to-creatinine ratio (mg/g)**	**Terms**
A1	**<30**	**<3**	**<30**	**Normal to mildly increased**
A2	**30-300**	**3-30**	**30-300**	**Moderately increased**
A3	**>300**	**>30**	**>300**	**Severely increased**

Leading of aetiologies of CKD in Kenya and internationally include;[8,9,10,11,12,13]

- Hypertension
- Diabetic mellitus
- Glomerulonephritis
- HIV Nephropathy
- Obstructive uropathy
- Renal parenchymal disease

When compared with age-matched counterparts in the general population, patients with CKD have an increased incidence of cardiovascular morbidity and mortality. There are strong associations between non-dialysis dependent CKD patients and outcomes such as coronary events and heart failure. A study that was done at the Kenyatta National Hospital in Nairobi by Nadeem *et al* showed that traditional cardiovascular risk factors, such as hypertension with or without left ventricular hypertrophy, smoking history, diabetes, dyslipidaemia and older age, were prevalent in this population.[12]

In a large, community based population study to assess the increased cardiovascular risk associated with renal disease, data from over 1 million patients in a single large integrated health care system who had not undergone dialysis or kidney transplantation was evaluated and analysed. The median follow-up was 2.84 years, the mean age was 52 years, and 55% of the patients were women. The adjusted risk of death increased as the GFR decreased. The adjusted hazard ratio for cardiovascular events also increased inversely with the estimated GFR and the same trend was observed with the adjusted risk of hospitalization. This therefore showed an independent, graded association between a reduced estimated GFR and the risk of death, cardiovascular events, and hospitalization.[14]

In CKD patients, the risk of cardiovascular mortality is much higher than the risk of eventually requiring any form of renal replacement therapy. This was observed in a longitudinal follow-up study of nearly 30,000 patients with estimated GFRs of less than 90mL/min/1.73m2. The rate of renal replacement therapy and death was reported at five years. The results showed that the rate of renal replacement therapy was 1.1%, 1.3%, and 19.9%, respectively, for the CKD stages 2, 3, and 4, while that the mortality rate was 19.5%, 24.3%, and 45.7%. This showed that the rate of death was higher than the rate of renal replacement therapy at all stages.[15]

Albuminuria is an important marker of kidney damage that can be detected before any noticeable decline in glomerular filtration rate and is an independent risk factor for the development of cardiovascular disease. The presence of albumin in urine may be present in 4% of men and 2% of women aged above 45 years in the general population and it is present in about 25% of patients with an estimated glomerular filtration rate of <30mL/minute/1.73m^2.[16] The PREVEND study which sampled over 40,000 individuals found that a doubling of the albumin-to-creatinine ratio equated to approximately 30% increase in the risk for cardiovascular mortality.[17] The HOPE study found that proteinuria of any amount increased the risk of cardiovascular events in individuals with or without diabetes mellitus and the risk increased proportionately to the level of proteinuria. The study also demonstrated that screening for albuminuria was important in patients with a high risk of developing cardiovascular events.[18]

There is therefore strong evidence that subjects with CKD have increased cardiovascular morbidity and mortality and this further emphasises the public health implications of this disease.

2.2 The Electrocardiogram

Electrocardiography is a non-invasive procedure for recording of the electrical impulses of the heart. It is a cheap and readily available. These impulses are generated by the polarization and depolarization of cardiac muscles, and they are translated into a waveform. The impulses are detected using electrode leads placed on the upper limbs, lower limbs and the anterior aspect of the chest. The ECG recorder presents these waveforms on a graph with time represented on the x-axis and voltage represented on the y-axis.

The waveform generated is used for the diagnosis of various cardiac conditions such as myocardial ischaemia, conduction abnormalities, cardiac chamber enlargement, electrolyte disturbances and effects of various therapeutics agents on the heart. It is also used in the diagnosis of various infective and inflammatory conditions of the heart such as endocarditis, myocarditis and pericarditis. It is useful in the preoperative assessment of patients undergoing cardiac or non-cardiac surgery. It is also used to screen individuals in high-risk occupations and those who participate in rigorous sports such as long distance marathon runners.[19]

For the sake of consistency and accurate ECG interpretation, various international committees have come up with recommendations for the standardisation of the interpretation of the electrocardiogram. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures has come up with comprehensive guidelines for electrocardiography. The guidelines contain recommendations on the processing of the ECG signal, standardisation of placement of limb and precordial leads, standardisation of diagnostic terminology use and standardisation of diagnostic criteria for various ECG abnormalities such as conduction abnormalities, myocardial ischaemia/infarction and chamber enlargement.[20,21,22,23,24,25]

2.3 Electrocardiographic Abnormalities in Chronic Kidney Disease

The association between electrocardiographic abnormalities and CKD has been assessed in various studies.

In a study to assess electrocardiographic abnormalities and their impact on cardiovascular mortality in elderly patients with CKD, 5888 participants with a mean age of 74.7 years were enrolled and 1192 were found to have CKD at baseline. Of the patients who had CKD, 38.8% had major ECG abnormalities, 29.7% had minor abnormalities and 31.5% had no abnormalities. Major ECG abnormalities were those that were independent predictors of cardiovascular and overall mortality, and nonfatal cardiovascular events in patients with CKD. Patients with estimated GFR <60 mL/min/1.73m^2 were more likely to have ECG abnormalities at baseline than those with GFR >60mL/min/1.73m^2. During the mean follow-up period of 10 years, 68.3% of the participants died. Participants who had major ECG abnormalities had the highest risk for cardiovascular events and death as compared to those who had minor ECG abnormalities. This showed that major ECG abnormalities were prevalent in this population and they signified a higher risk for death and other adverse cardiovascular outcomes.[26]

In a study done in Ilorin, Nigeria to assess the prevalence of electrocardiographic abnormalities among dialysis naïve chronic kidney disease patients, 86% of the patients had abnormalities. Left ventricular hypertrophy and left atrial enlargement were the most common ECG abnormalities.[27]

In a population-based, longitudinal study to assess whether electrocardiogram abnormalities were predictors of cardiovascular death in CKD, 3238 participants were analysed. Participants with CKD had longer PR and corrected QT intervals as compared to those without CKD. It was found that for each 10 millisecond increase in the QRS interval, there was an associated 15% greater risk for incident heart failure, a 13% greater risk for coronary heart disease, and a 17% greater risk for mortality. For each 5% increase in the QT interval, there was an associated 42%, 22%, and 10% increased risk for heart failure, coronary heart disease and mortality, respectively. There was a high prevalence of major ECG abnormalities in patients with CKD and they predicted a significantly higher risk for death and adverse cardiovascular outcomes.[28]

Therefore, ECG abnormalities that predict adverse cardiovascular outcomes are highly prevalent in CKD.

2.4 Pathogenesis of Electrocardiographic Abnormalities in Chronic Kidney Disease

The pathogenesis of cardiovascular complications in CKD can be attributed to atherosclerosis which predisposes these patients to coronary artery disease which is likely to be at least in part responsible for arrhythmias in CKD. The pathophysiological conditions associated with chronic kidney disease that may be involved in the genesis of arrhythmias include uraemia, inflammation, autonomic imbalance, electrolyte disturbances and endothelial dysfunction. These pathological processes that cause coronary disease are also likely to lead to CKD.[6]

2.4.1 Endothelial Dysfunction in CKD

Endothelial dysfunction is one of the main factors involved in the pathogenesis of atherosclerosis. The endothelium ensures normal vascular tone, normal blood viscosity, with minimal expression of pro-inflammatory cytokines. Cardiovascular risk factors such as diabetes, smoking, alcohol intake, dyslipidaemia, and hypertension, are all associated with endothelial dysfunction. These factors result in chronic inflammation which results in the loss of antithrombotic qualities of the endothelium. There is also an increase in vasoconstrictors and pro-thrombotic cytokines which cause vessel narrowing and thrombotic events. The reduction of the bioavailability of nitric oxide is one of the main pathological factors associated with endothelial dysfunction in CKD. Nitric oxide is a vasodilator and the lack of it causes vasoconstriction.[29]

In uremic patients, there is an increase in oxidative stress which occurs because of the loss of residual renal function, and may be exacerbated by dialysis. Oxidative stress is associated with acute phase inflammation, endothelial dysfunction and eventual atherosclerosis. Microalbuminuria, which is a marker of glomerular hyperfiltration, has been correlated with and may be a marker of endothelial dysfunction.[30]

Endothelial dysfunction therefore leads to coronary artery disease which in turn causes multiple electrocardiographic abnormalities such as ST segment and T-wave abnormalities, conduction abnormalities, supraventricular arrhythmias and ventricular arrhythmias.

2.4.2 Uraemia and Inflammation

CKD is associated with marked inflammation with a state of chronic leucocyte activation. There is also retention of pro-inflammatory metabolites, cytokines and chemotactic factors.

Uraemia is a marker of a multitude of oxidative and pro-inflammatory metabolites that are not routinely measured but that are likely to contribute to this. Biochemical tests of inflammation such as C reactive protein are associated with adverse cardiovascular outcome in CKD.

Long-standing uraemia leads to uremic cardiomyopathy, with typical changes of diffuse myocardial fibrosis, which could impede electrical conduction and cause arrhythmias.[31]

2.4.3 Myocardial Ischaemia/Infarction

Chronic renal disease is an independent risk factor for coronary artery disease. It is also associated with an adverse effect on prognosis from cardiovascular disease. When CKD patients are compared to non-CKD patients, they are at an increased risk for more severe coronary heart disease. They are more likely to die after an acute coronary syndrome even after reperfusion.[32] Coronary artery calcification correlates with the extent of coronary atherosclerosis and, consequently, with an increased risk for cardiovascular events. This is more frequent in uremic patients than in the general population and may be linked to hyperphosphataemia. In a study to assess the extent of coronary artery calcification in patients who had CKD but were not on dialysis, showed that coronary artery calcification was found in 40% of patients with CKD and 13% of controls.[33]

Myocardial ischaemia and infarction are associated with various ECG changes mainly in the ST-segments and T-waves. Arrhythmias are also common. The development of cardiac arrhythmias seen in myocardial ischaemia could be attributed to generalised autonomic dysfunction which results in increased automaticity of the myocardium and conduction system. The damaged myocardium also causes re-entrant circuits to be generated due to the refractoriness of the myocardium by the pathological changes such as fibrosis. This causes arrhythmias such as ventricular fibrillation and ventricular tachycardia, which may be lethal.

Unrecognized MI is defined as MI that initially is undetected and is eventually discovered by surveillance electrocardiography, myocardial imaging techniques, or pathologic findings on

autopsy.[34] The precise course of events that leads to unrecognized myocardial infarction is not known.[35] Unrecognized myocardial infarctions in chronic kidney disease are commonly seen among individuals with an eGFR <60 mL/min/1.73m2 and albuminuria and are associated with an increased mortality risk.[36] In a study to identify whether chronic kidney disease is associated with unrecognised myocardial infarctions, a total of 2,656 consecutively hospitalized patients with acute myocardial infarctions were sample over a study period of four years. In conclusion, it was found that a lower eGFR was a strong, independent predictor of presentation with painless acute myocardial infarction versus painful acute myocardial infarction.[37]

2.4.4 Electrolyte Imbalance

Many electrolyte disturbances are seen in CKD. The ones associated with specific ECG changes are mainly the ones involving sodium and potassium levels.

2.4.4.1 Potassium

Hyperkalemia and hypokalemia are common electrolyte disturbances in CKD.

Hyperkalemia in renal disease is caused by multiple factors. Reduced GFR with reduced urine flow leads to decreased renal excretion of potassium. Drugs that can interfere with urinary potassium excretion include potassium-sparing diuretics, cyclosporine, trimethoprim, non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Hypoaldosteronism in chronic renal failure also results in hyperkalemia.[38]

Hyperkalaemia is associated with ventricular arrhythmias via the inactivation of sodium-gated channels which leads to the broadening of the depolarisation complexes, and also the direct activation of potassium-gated channels. This results in rapid ventricular repolarisation and the resultant ‘tented’ T waves.

Hypokalaemia on the other hand, causes an increased resting membrane potential and the prolongation of repolarisation. The ECG change seen is the U wave. Hypokalaemia is however more arrhythmogenic than hyperkalemia.[39]

2.4.4.2 Calcium

Hypocalcaemia in advanced CKD is common mainly due to increased serum phosphorus and reduced renal hydroxylation of 25-hydroxy-vitamin D to 1'25-dihydroxy-vitamin D.

Hypocalcaemia prolongs the action potential of the myocardium and this can lead to heart block and torsade's de pointes. But, hypocalcaemia-induced sudden cardiac death is very rare due to the fact that skeletal muscular manifestations of hypocalcaemia usually manifest before the cardiac ones.

Hypocalcaemia manifests in the ECG recording as a prolongation of the QT or PR interval. QT prolongation is caused by the prolongation of the plateau phase of the cardiac action potential which results in the calcium ion channels opening for a prolonged period and hence permitting late calcium inflow and subsequent early after-depolarisations.[40] Hypercalcaemia however, is not a risk factor for SCD. It is not associated with significant arrhythmias other than occasional bradycardia.

2.4.5 Cardiovascular Autonomic Dysfunction

In CKD, autonomic dysfunction confers an increased risk of cardiovascular morbidity and mortality and it is more common in diabetics with CKD than non-diabetics.[41] This is associated with an increased risk of cardiac arrhythmias and sudden cardiac death.

Studies done to assess the autonomic function in CKD patients have demonstrated abnormalities in up to 60% of the patients.[42] The level of dysfunction is assessed via the parasympathetic function with tests such as the heart rate response to deep breathing, induced hypotension, and the valsalva manoeuvre. Most male patients with CKD may complain of impotence which is a common symptom of autonomic dysfunction. Others symptoms include bowel and bladder dysfunction, impaired sweating, and orthostatic hypotension.[43]

The sensitivity of baroreceptors in the arterial walls that are necessary for the control of blood pressure is affected by arterial calcification which may occur in CKD. This may be a contributing factor to autonomic dysfunction. This predisposes these patients to cardiac arrhythmias and possible sudden cardiac death.[44]

2.5 Major Electrocardiographic Abnormalities in CKD

2.5.1 Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is the thickening of the myocardium of the left ventricle of the heart which may be accompanied chamber enlargement.[45]

Patients with electrocardiographic evidence of LVH have a higher prevalence of ventricular premature beats and other arrhythmias than patients without LVH or normotensive subjects and this is independent of the etiology of the left ventricular hypertrophy.[46,47] Ventricular arrhythmias are also more in patients with echocardiographically demonstrated left ventricular hypertrophy compared with normal subjects or hypertensive patients without LVH.[48] The presence of echocardiographic LVH, even in the absence of a history of hypertension, is associated with increased rates of ventricular arrhythmia. This was demonstrated in a study in elderly men aged 70 years and above.[49]

Left ventricular hypertrophy is strongly associated with atrial fibrillation and this is well established. The Framingham study provided evidence of an increased prevalence of atrial fibrillation among patients with hypertensive cardiovascular disease as compared with control subjects with a risk ratio of about 2.0.[50] Left ventricular hypertrophy was shown to increase the development atrial fibrillation in a study of 2482 subjects with essential hypertension followed for up to 16 years. Multivariate analysis revealed that age and left ventricular mass to be the only independent predictors of developing atrial fibrillation. For every one standard deviation increase on left ventricular mass, the risk of atrial fibrillation was increased 1.20 times.[51]

The prevalence of LVH in CKD patients is high and it increases proportionately to the severity of renal disease. In a case-control study where the study subjects were divided into three groups of healthy normal controls, subjects with mild to moderate CKD and subjects with severe CKD, a progressive rise in prevalence of LVH was observed with the severity of kidney disease from 64% (mild/ moderate CKD group) to 96% (severe CKD group) and higher prevalence of LVH in females than males in the severe CKD group.[52]

In a study that was done to assess the prevalence of echocardiographic left ventricular hypertrophy in the pre-dialysis CKD patients who were about to commence dialysis, LVH was present in over 70% of the patients, and it was an independent risk factor for cardiovascular death.[53] Another study done in Nigeria to determine the prevalence of

electrocardiographic LVH among end-stage renal disease patients who were about to commence dialysis showed that LVH was detected in 82.9% of the study population.[54] In a prospective follow-up study of 1249 elderly subjects with relatively mild CKD, the presence of electrocardiographic LVH was associated with a higher cardiovascular risk of death than that associated with smoking, diabetes and hypertension.[55]

The electrocardiographic diagnosis of LVH is quite reliable when very prominent voltage is seen in conjunction with left atrial and ST-T abnormalities, leftward axis, or widening of the QRS. Patients with LVH may fail to show voltage criteria, especially if they have only mild hypertrophy or underlying obstructive lung disease. The sensitivity is also reduced in women and in subjects with obesity. Right bundle branch block, when associated with decreased S waves in leads V1 and V2, may decrease the sensitivity of some voltage criteria for LVH. Increased voltage is a common normal variant in young adult males.[56] Left anterior fascicular block can simulate LVH in the limb leads. Hypertension is one of the most common causes of left anterior fascicular block and also a major cause of LVH and these can co-exist.[57]

The following are the major criteria used in the electrocardiographic diagnosis of LVH:

a) Sokolow-Lyon indices
b) Cornell voltage criteria
c) Romhilt-Estes point score system

The Sokolow-Lyon index detects LVH by calculating the sum of the height of the S wave in lead V1 and that of the R wave in V5 or V6 whichever is higher. If the sum is 35 millimetres or more, it indicates the presence of an LVH. The sensitivity is 22% whereas the specificity is 100%.[58] Sokolow-Lyon Criteria = S in V1 + R in V5 or V6 (whichever is larger) $\geq$ 35 mm

In the Cornell voltage criteria, the ECG diagnosis of LVH involves the measurement of the sum of the R wave in lead aVL and the S wave in lead V3. If the sum is >28 millimetres in males or >20 millimetres in females, it indicates the presence of LVH. The sensitivity is 42%, whereas the specificity is 96%.[58]

Cornell voltage criteria = S in V3 + R in aVL > 28 mm (men) or > 20mm (women)

The Romhilt-Estes point score system as the name suggests is a point-score system for the ECG diagnosis of left ventricular hypertrophy. It takes into account the voltages, ST-T

abnormalities, QRS duration among other factors in the scoring system. A sum of five points is diagnostic. The sensitivity is about 20% whereas the specificity is >90%.[59]

None of these criteria are perfect, though by using multiple criteria sets, the sensitivity and specificity may be increased. Most of these criteria have a low sensitivity of but a high specificity.

2.5.2 Atrial Fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia.

The American College of Cardiology (ACC), American Heart Association (AHA), and the European Society of Cardiology (ESC) classification atrial fibrillation as follows:[60]

- First detected - only one diagnosed episode
- Paroxysmal - recurrent episodes that self-terminate in less than 7 days.
- Persistent - recurrent episodes that last more than 7 days
- Permanent - an ongoing long-term episode

The ACC/AHA/ESC further describes AF based on other characteristics.

- Lone atrial fibrillation (LAF) – absence of clinical or echocardiographic findings of other cardiovascular disease
- Non-valvular AF
- Secondary AF – associated with conditions such as thyrotoxicosis, pulmonary thromboembolism etc.

The incidence increases with age.[61] The prevalence of atrial fibrillation in CKD is approximately 2-3 times higher than that in the general population.[62,63] The pathogenesis of atrial fibrillation is multifactorial.[64]

The most common and devastating complication of atrial fibrillation is thrombus formation and embolization which may be asymptomatic or may present with syncope, palpitations, chest pains, or heart failure.[65] In the prospective follow-up study of the original Framingham Heart Study cohort, atrial fibrillation was associated with an increased adjusted mortality risk.[66]

2.5.3 Atrioventricular Block

Atrioventricular (AV) block is caused by the delayed transmission of the electrical impulse from the atria to the ventricles due to dysfunction conduction system. This may be temporary or permanent and multiple factors may cause this such as, myocardial ischaemia, increased vagal tone and degeneration of the conducting fibres by calcification and fibrosis. AV blocks cause prolongation of the PR interval. They are classified as first degree AV block, second degree AV block (Mobitz I or II) or third degree AV block[67]

Most patients are asymptomatic but, the ones with a complete heart block may present with heart failure, syncope and even sudden cardiac death. 7575 individuals from the Framingham Heart Study, which was a prospective, community-based cohort with a mean age 47 years and 54% being women, underwent routine 12-lead electrocardiography and were followed up. Prolongation of the PR interval was associated with increased risks of AF, pacemaker implantation, and all-cause mortality.[68]

The prevalence of AV blocks in patients with CKD is increased by the presence of myocardial fibrosis and calcification of the atrioventricular conduction system. This increases the incidence of permanent pacemaker insertions in dialysis patients.[69] Several other factors in CKD can contribute to the pathogenesis of atrioventricular blocks and include ischemic heart disease, hyperkalaemia, medications, infiltrative malignancies, cardiac instrumentation and hyperthyroidism. [67]

2.5.4 Intraventricular Conduction Defects

2.5.4.1 Left bundle branch block (LBBB)

Left bundle branch block (LBBB) is associated with progressive conducting system disease. Causes of LBBB include; dilated cardiomyopathy, acute myocardial infarction, aortic stenosis, long standing hypertension, aortic regurgitation and primary disease of the cardiac electrical conduction.[70]

The incidence increases with age and it is rare in young healthy people. In a study of 237,000 airmen under the age of 30, the incidence of LBBB was only 0.05%. 90% of the subjects who had LBBB had no apparent heart disease and their prognosis was benign.[71] In a prospective study, 855 Swedish men in the general population who were 50 years of age were followed

up for 30 years. The incidence of LBBB showed a gradual increase with age. The incidence was 0.4% at 50 years and increased to 5.7% by the age of 80 years.[72]

The prospective Framingham Heart Study illustrated that new onset LBBB was a marker for advanced heart disease and it occurred mostly in people with underlying heart disease such as coronary heart disease, hypertension and cardiac enlargement. As mentioned earlier, all these predisposing conditions are highly prevalent in CKD patients. 48% of the participants developed clinical coronary disease or congestive failure for the first time. Only 11% remained free of clinically apparent cardiovascular abnormalities. 50% died from cardiovascular diseases within 10 years of the onset of LBBB. Male sex was a poor prognostic factor.[73] Also, it has been shown that patients with type 2 diabetes mellitus and concomitant LBBB have more severe and extensive coronary artery disease and advanced left ventricular dysfunction compared with those with diabetes but without LBBB and those with isolated LBBB.[74] During long-term follow-up of myocardial infarction patients, new LBBB is an independent predictor of all major adverse cardiovascular outcomes.[75]

2.5.4.2 Right bundle branch block (RBBB)

Similar to LBBB, the prevalence of RBBB also increases with age.[71] Aetiology includes; chronically increased right ventricular pressure, as in cor-pulmonale and pulmonary embolism, myocardial ischemia/infarction and in myocarditis. Other causes include hypertension, cardiomyopathies, and congenital heart disease. RBBB can also result from idiopathic progressive cardiac conduction disease. Iatrogenic RBBB can also be caused by procedures and interventions such as right heart catheter insertions e.g. Hemodialysis catheter insertion. Nonsurgical septal reduction therapy with ethanol ablation has been used with increasing frequency in patients with obstructive hypertrophic cardiomyopathy. In a study of 70 patients undergoing this procedure, 62% developed RBBB.[76]

RBBB is an independent predictor of all-cause mortality in patients with known or suspected coronary heart disease. This was shown in a study of 7073 adults referred for nuclear exercise testing: at a mean follow-up of 6.7 years, the 190 patients with complete RBBB had a greater mortality than those without this finding. An incomplete RBBB was not associated with an increased mortality.[77] The presence of a RBBB following an acute myocardial infarction is associated with a significant increase in mortality, even when revascularisation therapy has been done. However, the long-term outcomes are generally excellent in patients without any apparent heart disease. In a study in which 394 airmen who presented with

complete RBBB, 94% had a normal cardiovascular examination and a benign course, with only one requiring a pacemaker in 10 years.[71] CKD patients are predisposed to coronary artery disease and hence RBBB.

2.5.5 Premature Ventricular Contractions and Non-sustained Ventricular Tachycardia

Premature ventricular complexes (PVCs) are early ventricular depolarizations that are commonly asymptomatic. They are caused by an increase in the automaticity of the ventricles. Non-sustained Ventricular Tachycardia is a situation where three or more consecutive PVCs occur at a rate greater than 100 beats-per-minute. PVCs and NSVT are usually considered clinically insignificant but they may be a sign for increased risk for cardiac disease.[78]

A prospective study was done to assess whether the presence of PVCs at study baseline influenced the risk of incident stroke among middle-aged men and women. In participants who did not have hypertension and diabetes, PVCs were associated with the risk of incident stroke. However, among participants with either diabetes or hypertension, the presence of any PVCs did not increase the risk of stroke. This suggests that PVCs may be a risk factor for incident stroke.[79]

A study done in Nigeria showed that 6% of dialysis naïve chronic kidney disease patients have premature ventricular complexes.[27]

2.5.6 Acquired QT Syndrome

Corrected QT interval prolongation is an independent risk factor for sudden cardiac death. The QT interval is a measurement of the duration of ventricular depolarization and repolarization.

QT prolongation predisposes to polymorphic ventricular tachycardia (torsade de pointes), ventricular fibrillation and sudden cardiac death. [80]

Corrected QT interval prolongation and torsade de pointes are associated with severe renal disease and is most commonly found in ESRD.[81] In fact, the prolonged QTc is further increased by hemodialysis and hence multiplying the risk for cardiovascular mortality.[82]

3 THE STUDY

3.1 Study Justification

Chronic non communicable diseases (NCDs) are the most common cause of morbidity and premature deaths worldwide.

CKD is a key determinant of the poor health outcomes of major NCDs.

Only a small fraction of CKD patients in Kenya has access to dialysis and therefore, knowledge about electrocardiographic abnormalities in dialysis naïve CKD patients is important because these abnormalities are prevalent and they significantly increase the risk of death and other adverse cardiovascular outcomes.

Electrocardiography is a cheap and efficient tool which can predict cardiovascular outcomes.

There is paucity of data in Kenya on the prevalence of ECG abnormalities in dialysis naïve CKD patients.

3.2 Research Question

What are the ECG abnormalities in dialysis naïve CKD patients at KNH?

3.3 Primary Objectives

i. To determine the prevalence of ECG abnormalities among the dialysis naïve CKD patients at Kenyatta National Hospital
ii. To determine the types of ECG abnormalities in dialysis naïve CKD patients at Kenyatta National Hospital.

3.4 Secondary Objective

i. To determine the possible relationship between the prevalence of ECG abnormalities and the clinical stage of CKD.

4 THE METHODOLOGY

4.1 Study Design

This was a hospital based cross-sectional study

4.2 Study area

The study was carried out at the nephrology outpatient clinic and the medical outpatient clinic in KNH, Nairobi. The nephrology outpatient clinic runs every Friday from 8.00am to 2.00pm. About sixty patients are attended to and most of them have a diagnosis of chronic kidney disease. Majority of these patients are dialysis naïve. The medical outpatient clinics run every weekday from 9.00am to 2.00pm. This clinic caters for all medical cases and only a fraction have a diagnosis of chronic kidney disease. An average of thirty patients is seen on each day.

4.3 Sampling Technique

Consecutive sampling procedure was utilized for the enrolment of patients in this study

4.4 Sample size calculation

$$n = \frac{Z^2 \times P\,(1-P)}{d^2}$$

n – Sample size

Z – 1.96 (95% confidence interval)

P – Estimated proportion of CKD patients with at least one form of ECG abnormality = 86%

d – Margin of error (precision error) = ±5%

Substituting into the formula, **n = 185**

Sample size calculation was based on a study done in Nigeria titled, **"*Electrocardiographic abnormalities among dialysis naïve chronic kidney disease patients in Ilorin, Nigeria.*"** [27]

4.5 Case Definition

A patient attending the nephrology and medical outpatient clinics with a file documented diagnosis of chronic kidney disease by the attending physicians, with laboratory or imaging evidence of the same, and had never undergone dialysis.

4.6 Inclusion and Exclusion Criteria

4.6.1 Inclusion criteria

- Willingness to provide a written consent
- A file documented diagnosis of CKD
- Patients who were dialysis naïve
- 30 years of age and above

4.6.2 Exclusion criteria

- Documented or self-reported prior history of history of myocardial infarction, angina, congestive heart failure, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty or stenting
- Presence of permanent pacemakers

4.7 Study Variables

4.7.1 Patient Variables

i. Age
ii. Sex
iii. Aetiology of kidney disease
iv. Body Mass Index (BMI)
v. Smoking – current smoker, former smoker, non-smoker
vi. Alcohol use
vii. Chronic Kidney Disease Stage

4.7.2 ECG Variables

The presence of ECG abnormalities was defined as the presence of at least one abnormality. ECG abnormalities were defined as per the *"American Heart Association/American College of Cardiologists (AHA/ACC) recommendations for the standardization and interpretation of the electrocardiogram"* [20,21,22,23,24,25]

The ECG recordings were reviewed through the creation of descriptive reports and determination of the following variables:

- Cardiac axis
- Heart rate
- Presence, amplitude and duration of the P wave
- PR intervals
- QRS duration
- The Cornell voltage criteria – This was used for the ECG diagnosis of LVH. It involves the measurement of the R wave in lead aVL and the S wave in lead V3. LVH is diagnosed if;
    - S in V3 + R in aVL > 28 mm (men)
    - S in V3 + R in aVL > 20 mm (women)
- Corrected QT interval duration (milliseconds)
- ST segment changes
- T wave changes

The above parameters aided in the determination of the following **ECG variables**;

i. Arrhythmias
    a) Supraventricular
        - Atrial fibrillation
        - Sinus tachycardia
        - Sinus bradycardia
        - Atrial flutter
        - Premature atrial contractions
    b) Junctional rhythm
    c) Ventricular rhythm
        - Premature ventricular contractions

ii. Electrical conduction delays
    a) Atrioventricular (AV) blocks

- First degree AV block
- Second degree AV block
- Third degree AV block

b) Intraventricular conduction defects

- Left Bundle Branch Block (LBBB)
- Right Bundle Branch Block(RBBB)
- Left anterior fascicular block (LAFB)
- Left posterior fascicular block (LPFB)
- Bi-fascicular block

iii. Chamber enlargement

- Left ventricular hypertrophy
- Right ventricular hypertrophy
- Right atrial enlargement
- Left atrial enlargement

iv. Prolonged QT interval

v. Repolarisation changes

- ST segment changes
- T wave changes
- Pathological Q waves

4.7.3 Operational definitions

i. CKD was defined as per the "***Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group"*** definition as abnormalities of kidney structure or function, present for three months, with implications for health.[7]

ii. Aetiology of CKD was derived from documented clinical features and the results of relevant investigative procedures which included urinalysis, blood biochemistry, imaging studies and tissue histology.

iii. The definition of cigarette smoking was based on the smoking status definition of the United States of America Centres for Disease Control and Prevention(CDC)[83]

a) Non-smoker – Respondents who reported that they have never smoked 100 cigarettes in their lifetime.

b) Former smoker – Respondents who reported smoking at least 100 cigarettes in their lifetime and who, at the time of the study, did not smoke at all for at least one year.

c) Smoker – Respondents who reported smoking at least 100 cigarettes in their lifetime and who, at the time of study, smoked either every day or some days.

iv. Body mass index (BMI) – defined as weight of the patient in kilogrammes divided by the square of his/her height in metres (kilogrammes/metre^2) and classified as per the World Health Organisation (WHO) classification.[84]

v. Alcohol Use – defined as consumption of alcohol in the last one year.

vi. Chronic kidney disease stage – was estimated using the Cockcroft-Gault formular as shown:

$$\textbf{Estimated GFR(eGFR)} = \frac{\textbf{\{140-Age(years)\} x Mass(Kilogrammes) x (0.85 if Female)}}{\textbf{Serum Creatinine(in } \textit{m}\textbf{mol/l}}$$

The estimated glomerular filtration rate (eGFR) was used to define the stage CKD stages as per the KDIGO- CKD classification.

4.8 Screening and Recruitment

Records of patients attending the nephrology and medical outpatient clinics were perused for a documented diagnosis of chronic kidney disease. The principal investigator and his research assistant then interviewed the patients who met the above requirement and perused their files to ensure that they met the rest of the inclusion criteria. The nature of the study was explained to the patients verbally and via the written study explanation form. Informed consent was then obtained from the participants who were then asked to duly sign the consent form.

Other patient details were then obtained in the interview and recorded. A resting ECG was recorded after which, five millilitres of venous blood was collected from the median cubital vein to ascertain the levels of serum creatinine.

4.9 ECG Methods

A 12-lead resting ECG was recorded by the principal investigator at a paper speed of 25mm/s with a gain setting of 10 millivolt by the principal investigator using a **Bionet CardioCare 2000** ECG machine. It was ensured that the patients had rested for a minimum of five minutes before the ECG recording. The patient was prepared as follows;

i. Unrestricted access to the skin on the chest area, upper and lower limbs was ensured to allow correct placement of the electrodes.
ii. The patients were placed in supine position.
iii. Once the electrodes were positioned and the connecting wires appropriately attached, the patients were covered with a gown to preserve their dignity during the procedure.
iv. The principle investigator ensured that the sensitivities of the patient were respected so as to minimise embarrassment. A chaperone was used when necessary.
v. A comfortable couch was used so as to ensure the patient was relaxed so as to facilitate accurate recordings with minimal artefact.
vi. Skin preparation was done to eliminate artefacts by minimising the skin-to-electrode impedance. This was be done by removal of excess chest hair and cleansing using alcohol swabs. This was done after consent was obtained from the patient.
vii. Electrodes were placed on the body as per the standard American Heart Association recommendations.

The American Heart Association recommendations of electrode placement are as follows:-

Limb leads:

- Right arm limb lead - Right forearm proximal to wrist
- Left arm limb lead - Left forearm proximal to wrist
- Left leg limb lead - Left lower leg proximal to ankle
- Right leg limb lead - Right lower leg proximal to ankle

Precordial chest leads:

- V1 - Fourth intercostals space, right sternal edge
- V2 - Fourth intercostals space, left sternal edge
- V3 - Midway between V2 and V4
- V4 - Fifth intercostals space, mid-clavicular line.

- V5 - Left anterior axillary line, same horizontal line as V4
- V6 - Left mid-axillary line, same horizontal level as V4 and V5

The ECG recordings were done in duplicate. One copy was placed in the patient's file while the principal investigator handled the second one. All ECGs were recorded and interpreted by the principal investigator as per the *"American Heart Association/American College of Cardiologists (AHA/ACC) recommendations for the standardization and interpretation of the electrocardiogram"*[20,21,22,23,24,25] and the findings were subsequently confirmed by a consultant cardiologist.

4.10 Quality Assurance

The ECGs were recorded and interpreted as per **"American Heart Association/American College of Cardiologists (AHA/ACC) recommendations for the standardization and interpretation of the electrocardiogram."**[20,21,22,23,24,25] Resting standard 12-lead ECGs were recorded at study entry using a **Bionet CardioCare 2000** ECG machine manufactured by **Bionet America Incorporated** which was pre-programmed in accordance with the American Heart Association specifications.

All ECGs were recorded and interpreted by the principal investigator as per the *"American Heart Association/American College of Cardiologists (AHA/ACC) recommendations for the standardization and interpretation of the electrocardiogram"*[20,21,22,23,24,25] and the findings were subsequently confirmed by a consultant cardiologist.

During the collection of blood for estimation of serum creatinine, standard procedures of specimen collection, handling and storage were followed to avoid pre-analytical errors. The laboratory equipment was calibrated according to the manufacturer's specifications. Serum creatinine assay was performed at the KNH Renal laboratory using the **Technicon fully automatic clinical chemistry analyser (RA-1000)** manufactured by **Technicon Instruments, USA.** Results were accepted only if they were within expected reference ranges.

The research assistant was a qualified Clinical Officer who underwent training to ensure competence in data collection.

4.11 Ethical Considerations

Approval to carry out the study was sought from the Department of Clinical Medicine and Therapeutics at the University of Nairobi and the Kenyatta National Hospital/University of Nairobi -Ethics & Research Committee (KNH/UON-ERC).

Patients were enrolled into the study only after giving informed consent. Those found to have electrocardiographic and biochemical abnormalities were be referred to the appropriate care givers.

Results of the findings were communicated to the patients. Those who gave consent were not exposed to any unnecessary risks. Full confidentiality with each patient was maintained. Freedom to withdraw from the study without prejudice was observed.

4.12 Data management and analysis

At the end of data collection, data was coded, entered and managed using SPSS software version 21.

The patients were described using baseline characteristics. Continuous variables such as age and BMI were summarized into means and standard deviations (SD). Categorical variables such as sex, aetiology of kidney disease, smoking, alcohol use and CKD stage were presented as proportions. ECG abnormalities were presented as percentage of patients with abnormal ECG findings and overall prevalence of ECG abnormalities was calculated as the proportion of patients with at least one abnormal ECG finding.

The prevalence of ECG abnormalities was analysed against the stage of CKD. Categorical variables were analysed using Chi square test while continuous variables were analysed using Student's t test. Odds ratios were used to estimate the risk of an abnormal ECG. Independent factors associated with ECG abnormalities were determined via the logistic regression model. All statistical tests were performed at 5% level of significance (95% confidence interval).

5 RESULTS

The study was carried out in ambulatory patients at the medical outpatient clinic and the nephrology outpatient clinic at Kenyatta National Hospital from November 1st 2013 to February 14th 2014. A total of 358 patient files were screened and 122 patients were excluded. Among the excluded patients, 88 of these had received hemodialysis while 34 had incomplete records. Out of the 236 patients who satisfied the inclusion criteria, 212 were recruited while 24 declined to give consent.

The flow chart below summarises the patient recruitment.

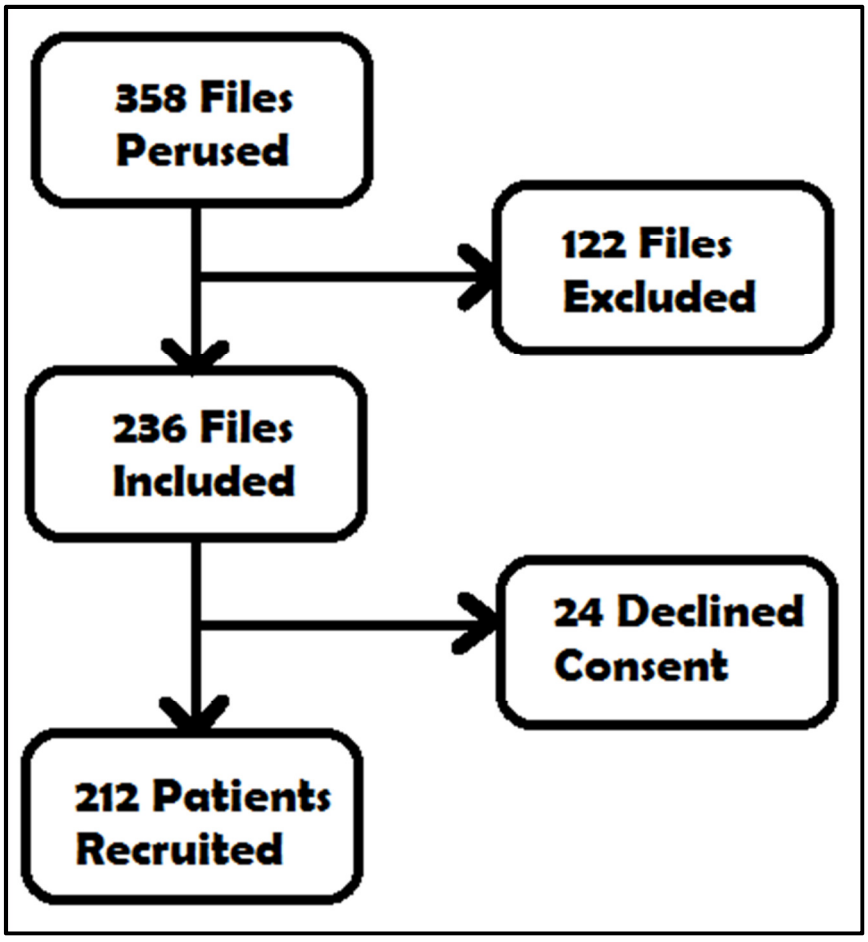

Figure 1: Flow Chart

5.1 Baseline characteristics

Of the 212 patients sampled, 123 were male who made up 58% of the study population. (**Figure 2**)

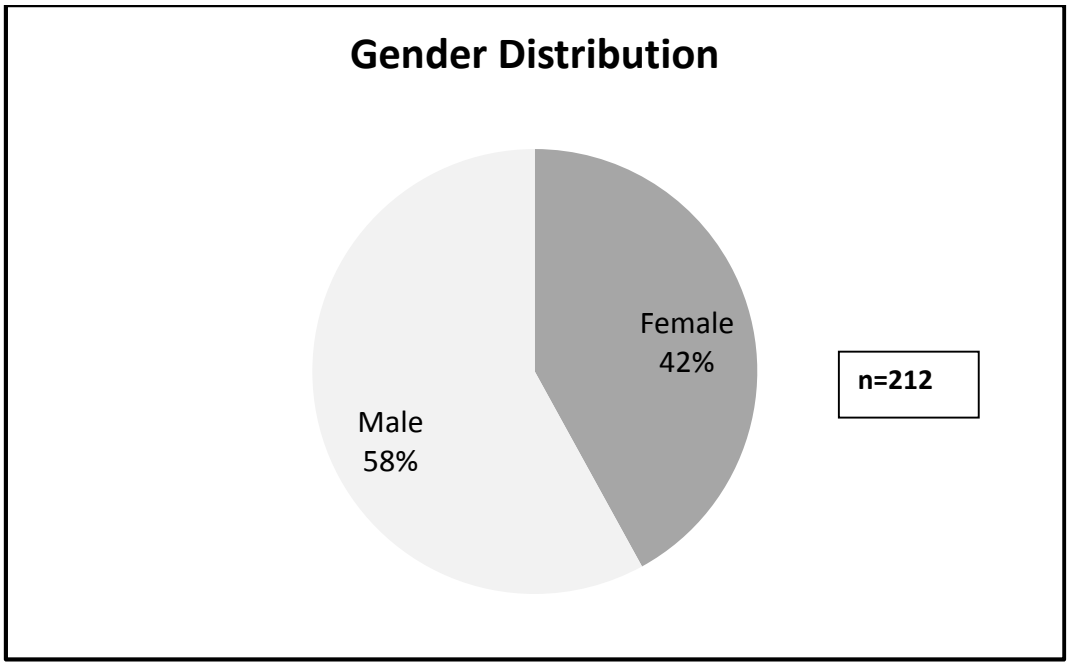

Figure 2: Gender Distribution

The mean age was 54.2 years ± 15 SD ranging between 30 and 87 years. The peak age group was the 40-49 years age group which made up 25.9% of the study population. **(Figure 3)**

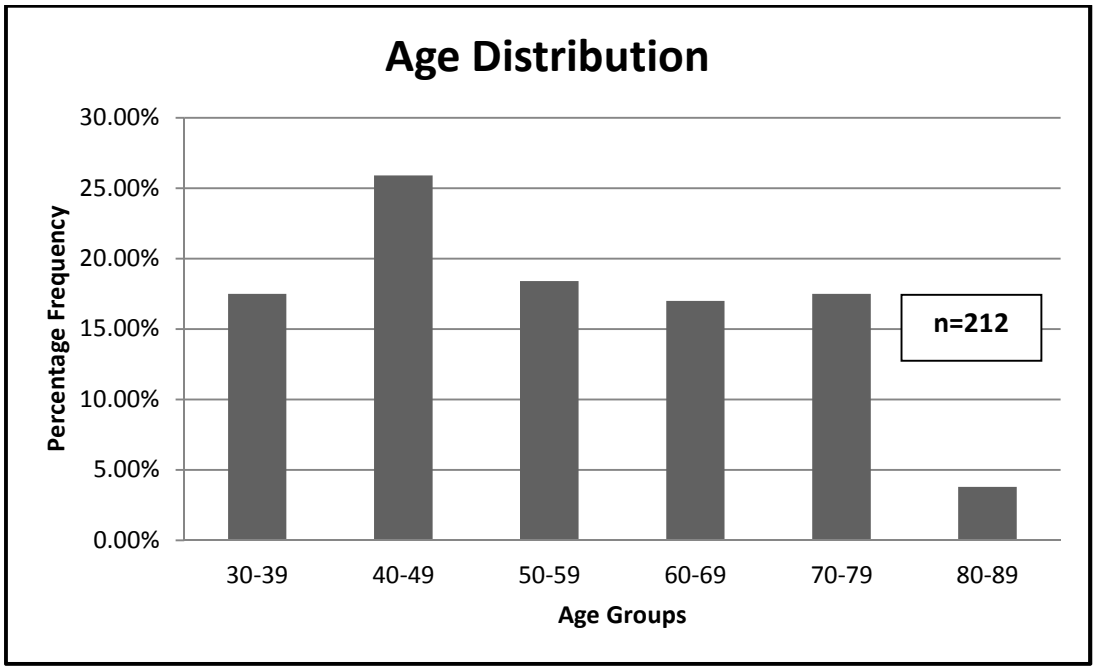

Figure 3: Age Distribution

In this study, 55 patients (25.9%) had a history of alcohol intake while 142 of them (67%) were non-smokers. Among the patients who consumed alcohol, 87.3% were male whereas 95.8% of the current smokers were male. The mean BMI was 26.5kg/m^2 and more than 60% of the patients were either overweight or obese. Diabetes and hypertension were the major causes of chronic kidney disease and they both contributed to more than 80% of the CKD cases. The mean estimated glomerular filtration rate was 29.9ml/min/1.73m2. The number of patients who had Stage 5 disease (end-stage renal disease) was 78 (36.8%) whereas the ones who had Stage 1 disease were 6 (2.8%). The baseline characteristics for the study population are shown in **Table 3**.

Table 3: Baseline characteristics of the entire study population

CHARACTERISTICS	**PROPORTION (n=212)**
Age - Years	
• Mean (SD)	54.2 (± 15)
• Range(min-max)	57(30-87)
• Mode	46
• Median	52
Males — no. (%)	123(58)
Alcohol use — no. (%)	55(25.9)
Cigarette Smoking — no. (%)	
• Current	24(11.3)
• Former	46(21.7)
• Non-smoker	142(67)
BMI - kg/m^2	
• Mean (SD)	26.5 (3.9)
• Range(min-max)	17.7(17.3-35.0)
• BMI Distribution **— no. (%)**	
○ Underweight	9(4)
○ Normal	72(34)
○ Overweight	89(42)
○ Obese	42(20)
Aetiology of CKD — no. (%)	
• Diabetes	75(35.4)
• Hypertension	50(23.6)
• Diabetes and Hypertension	47(22.2)
• Chronic Glomerulonephritis	18(8.5)
• Obstructive Nephropathy	19(9)
• Polycystic Kidney Disease	3(1.4)
CKD Stage — no. (%)	
• Stage 1	6(2.8)
• Stage 2	14(6.6)
• Stage 3	52(24.5)
• Stage 4	62(29.2)
• Stage 5	78(36.8)

5.2 Prevalence of ECG abnormalities

In this study, 135 patients [63.7% (95% confidence interval [CI], 56.6 to 69.8)] had at least one form of ECG abnormality.

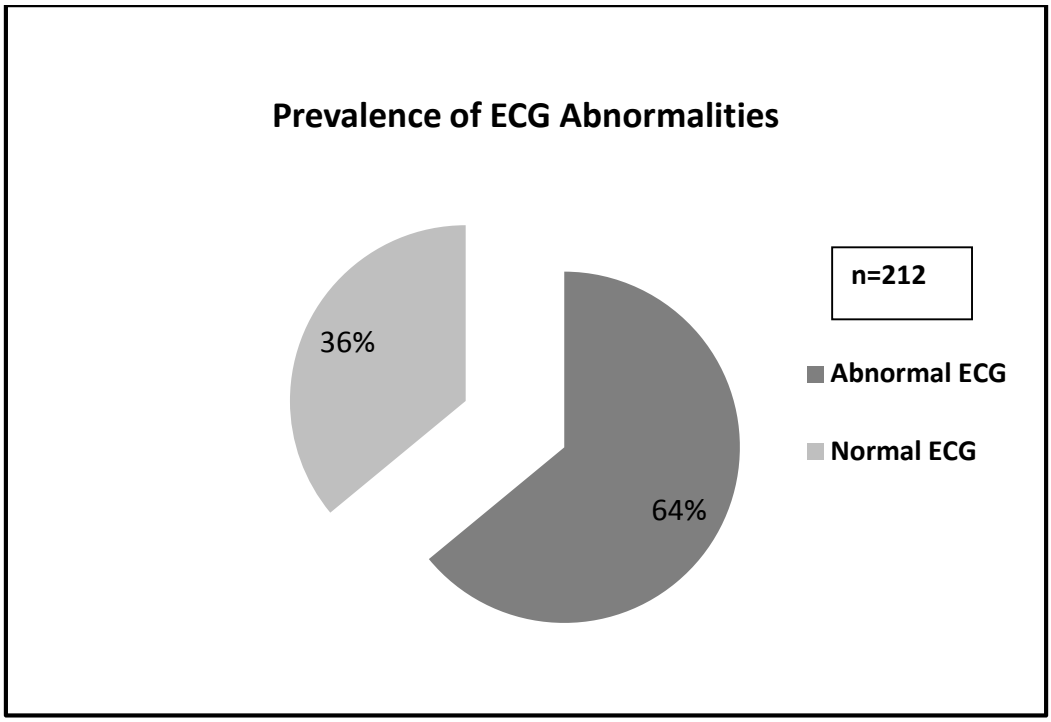

Figure 4: Prevalence of ECG Abnormalities

The most prevalent abnormalities were left ventricular hypertrophy (29.7%), left atrial enlargement (15.1%), atrial fibrillation (16%) and repolarisation changes (18.9%).

The various abnormalities are summarised in **Table 4.**

Table 4: Summary of ECG abnormalities

ECG ABNORMALITIES	FREQUENCY (%) n=212	95% Confidence Interval
Any Arrhythmia — no. (%)	**96(45.3)**	**38.7 - 51.4**
Sinus Tachycardia	13(6.1)	
Sinus Bradycardia	14(6.6)	
Atrial Fibrillation	**34(16)**	**11.3 – 21.2**
Atrial Flutter	0(0)	
Premature atrial contractions	0(0)	
Premature Ventricular Contractions	17(8)	
Junctional Arrhythmias	3(1.4)	
Atrio-Ventricular Blocks	**10(4.7)**	**2.4 – 7.5**
First degree AV block	7(3.3)	
Second degree AV block	0(0)	
Third degree AV block	3(1.4)	
Intra-Ventricular Blocks	**19(9)**	**5.2 – 13.2**
Left bundle branch block	5(2.4)	
Right bundle branch block	6(2.8)	
Left anterior fascicular block	6(2.8)	
Left posterior fascicular block	0(0)	
Bi-fascicular block	2(0.9)	
Prolonged QT Interval	**31(14.6)**	**10.4 – 19.8**
Any Chamber Enlargement — no. (%)	**64(30.2)**	**24.1 – 36.3**
Left Ventricular Hypertrophy	63(29.7)	
Left Atrial Enlargement	32(15.1)	
Right Ventricular Hypertrophy	3(1.4)	
Right Atrial Enlargement	0(0)	
Repolarisation Changes — no. (%)	**40(18.9)**	**13.2 – 24.1**
ST Segment Changes	**17(8)**	**4.2 – 11.8**
• Depressed ST segment	15(7.1)	
• Elevated ST segment	2(0.9)	
T-Wave Abnormalities	**35(16.5)**	**11.3 – 21.7**
• Inverted T waves	29(13.7)	
• Hyperacute T waves	6(2.8)	
Pathological Q Waves	**2(0.9)**	**0.0 – 2.4**

5.3 Prevalence and Types of Arrhythmias

The most common ECG abnormalities were arrhythmias which were found in 45.3% (95% confidence interval [CI], 38.7 to 51.4) of the patients. Atrial fibrillation was the most common arrhythmia at 16% (95% confidence interval [CI], 11.3 to 21.2).

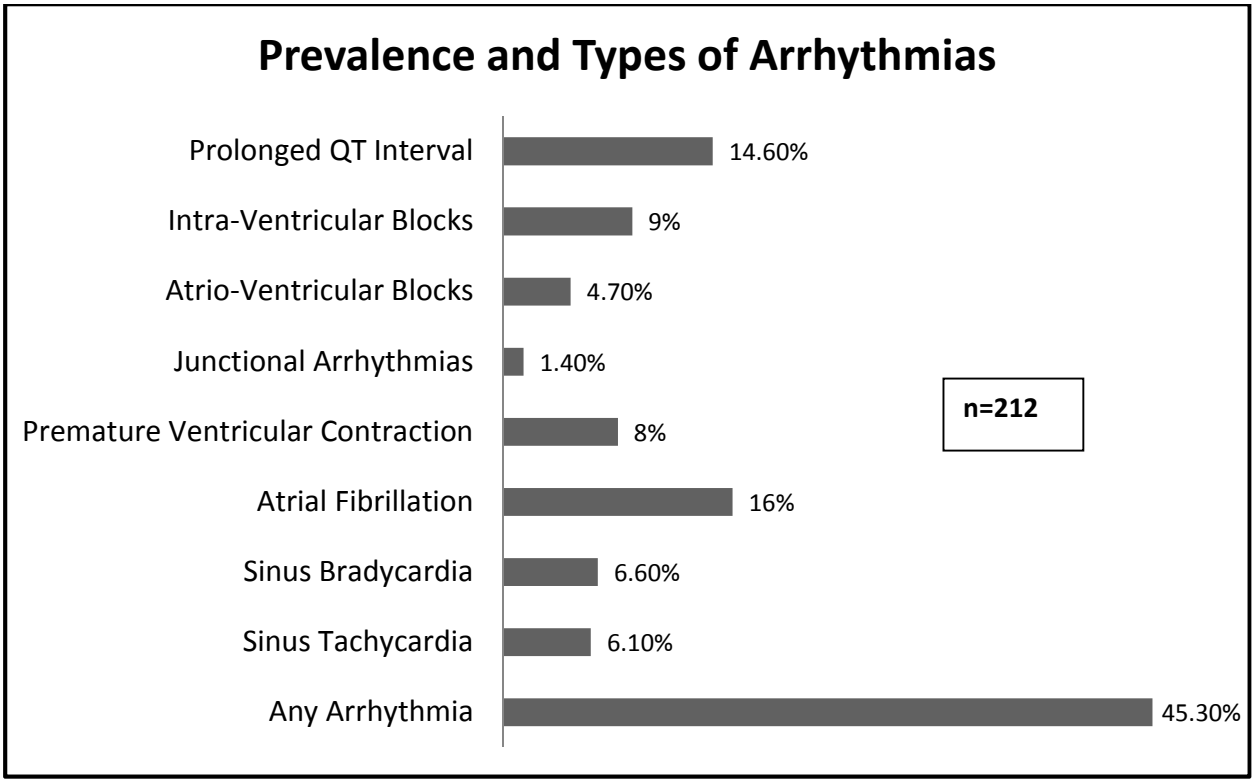

Figure 5: Prevalence and Types of Arrhythmias

5.4 Prevalence of Chamber Enlargement

Chamber enlargement was found in 30.20% (95% confidence interval [CI], 24.1 to 36.3) of the patients with left ventricular hypertrophy and left atrial enlargement being the most common chamber enlargement abnormalities.

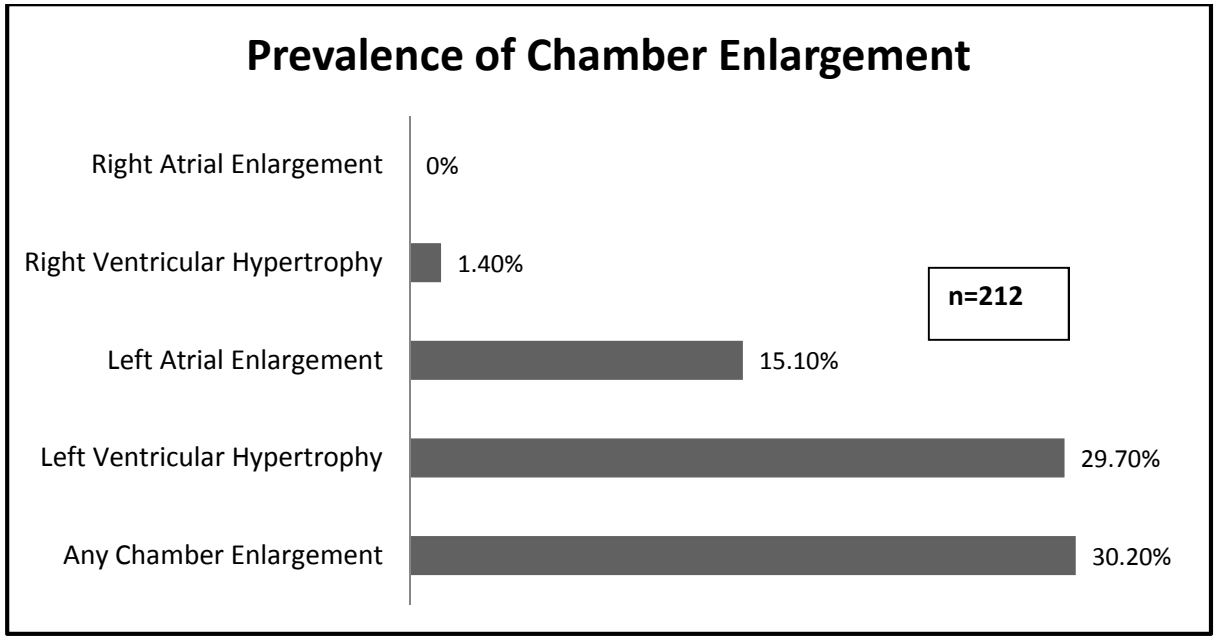

Figure 6: Prevalence of Chamber Enlargement

5.5 Repolarisation Changes

In the study population, repolarisation changes were found in 40 patients [18.9% (95% confidence interval [CI], 13.2 to 24.1)]. T-wave abnormalities were the most common repolarisation changes with a prevalence of 16.5% (95% confidence interval [CI], 11.3 – 21.7).

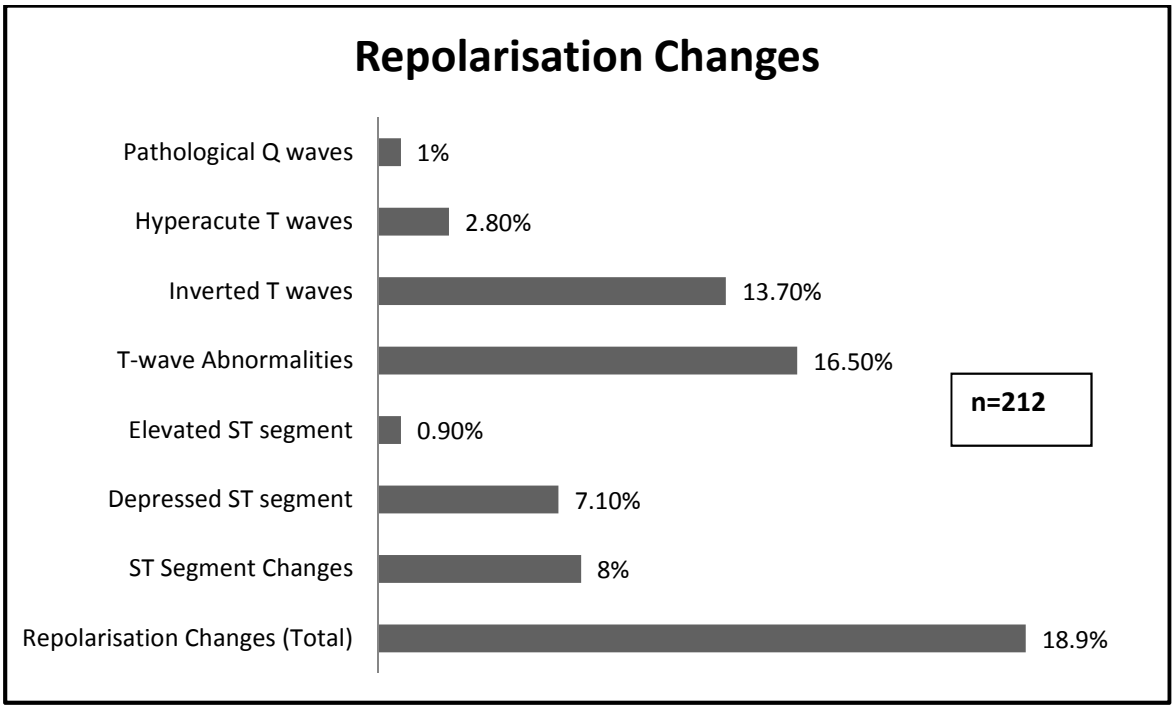

Figure 7: Repolarisation changes

5.6 ECG abnormalities as per the CKD stage

Stages 4 and 5 of CKD were shown to confer an increased risk for the development of abnormal ECGs. Stage 4 CKD increased the risk by nine times whereas stage 5 CKD increased by nineteen times. **(Table 5)**

Table 5: ECG abnormalities as per the CKD stage

CKD STAGE	PATIENTS WITH ABNORMAL ECGs (n=135)	PATIENTS WITH NORMAL ECGs (n=77)	OR(95% CI)	P-value
CKD Stage — no. (%)				
Stage 1	1(16.7)	5(83.3)	1.0	
Stage 2	5(35.7)	9(64.3)	2.8 (0.3-30.9)	0.406
Stage 3	27(51.9)	25(48.1)	5.4 (0.6-49.5)	0.136
Stage 4	40(64.5)	22(35.5)	9.1 (1.0-82.8)	0.050
Stage 5	62(79.5)	16(20.5)	19.4 (2.1-177.7)	0.009

6 DISCUSSION

This cross-sectional study of dialysis naive chronic kidney disease patients showed that they have a high prevalence of electrocardiographic abnormalities in the resting electrocardiogram exam. The overall prevalence was 64% and the most prevalent abnormalities were atrial fibrillation, left ventricular hypertrophy, left atrial enlargement and repolarisation changes. Advanced CKD increased the risk for abnormal ECG findings.

A similar cross-sectional study done in Ilorin, Nigeria by Chijioke *et al*[27] showed an overall prevalence of ECG abnormalities in dialysis naïve CKD patients of 86%. However, the Nigerian study sampled patients with stage 4 and 5 CKD only and this could have contributed to the higher prevalence. In a population-based longitudinal study in Ohio, USA by Dobre *et al*, a total of 1192 elderly participants who had CKD at baseline were found to have a prevalence of 68.5%.[24] The Ohio study, which had a prevalence that was in keeping to our study, recruited patients with all stages of CKD.

Among the abnormal ECG findings, left ventricular hypertrophy was found in 30% of the patients and this was an interesting finding when we consider that the screening test that was used for the diagnosis was the ECG. The ECG has a low diagnostic sensitivity and a high specificity in the detection of LVH. We used the Cornell voltage ECG criteria for the diagnosis of LVH which has a sensitivity of 42% and specificity is 96%.[58] The low sensitivity of the ECG could suggest that the prevalence of LVH could have been much higher. LVH is present even in early CKD and these patients have an increased risk for the development of coronary artery disease and is a strong predictor of future cardiovascular mortality.[85,86]

The prevalence of atrial fibrillation was 16% and it was most prevalent among the patients with stage 5 of CKD. Most of these patients were not on any form of treatment for atrial fibrillation during sampling and this could suggest a low detection rate in our population. Atrial fibrillation is associated with significant morbidity and mortality since it increases the risk for stroke, dementia, heart failure and overall mortality. [87] In the Rotterdam study, a population-based prospective cohort study among subjects aged ≥55 years, the baseline prevalence of AF in 6808 healthy participants was 5.5%.[88] The prevalence of atrial fibrillation in our study was therefore high as compared to the general population and hence our group had an increased risk for adverse cardiovascular outcomes.

A significant proportion of patients were found to have repolarisation changes which are markers of myocardial ischaemia or electrolyte disturbance such as hyperkalemia. We found a prevalence of 16.5% for T-wave changes and 8% for ST-segment changes. These are important indicators of underlying coronary heart disease which could suggest myocardial ischaemia and hence increases the cardiovascular mortality risk in our study poplation.[26]

Of the patients sampled in our study, 14.6% had prolongation of the QT interval segment which is associated with an independent increased risk of sudden cardiac death. Prolongation of the QT interval could lead to polymorphic ventricular tachycardia, or torsade de pointes, which itself may lead to ventricular fibrillation and eventual sudden cardiac death.[80] Prolonged QT intervals tend to be associated with severe renal disease and it is in fact more prevalent in the patients undergoing hemodialysis.[89]

The proportion of patients in this study who had premature ventricular contractions was 8% and this did not vary much from the study by Chijioke *et al*[27] in Nigeria which found a prevalence of 6%. Premature ventricular contractions are common arrhythmias with an estimated prevalence of 1% to 4% in the general population and ranges from <1% in children to 69% in subjects aged more than 75 years. These arrhythmias are often indolent but frequent premature ventricular complexes may predispose to, or exacerbate left ventricular dysfunction due to premature ventricular contraction-induced cardiomyopathy.[90]

7 CONCLUSION

In conclusion, this was the first study in Kenya to describe the prevalence of ECG abnormalities in dialysis naïve CKD patients and it highlights the various ECG abnormalities such as atrial fibrillation, left ventricular hypertrophy, prolonged QT interval and repolarisation changes that increase the risk for adverse cardiovascular outcomes and death.

We were also able to demonstrate a link between advanced CKD with the presence of ECG abnormalities in dialysis naïve CKD patients.

8 RECOMMENDATIONS

An electrocardiogram should be recorded and evaluated in all CKD patients and this also suggests that a multi-disciplinary approach to these patients is crucial.

There is need for more longitudinal follow-up studies to establish the role of serial ECG recordings in the long term follow-up of CKD patients which may be crucial in the early detection of new electrocardiographic changes.

In order to establish the prognosis and therapeutic effects of treatment given to CKD patients who have various ECG abnormalities, more follow-up studies are needed.

9 STUDY LIMITATIONS

Being a hospital based study, the results cannot be generalised to the population.

Due to the study design, we could only describe the associations and prevalence but not the cause and effect of the electrocardiographic abnormalities.

Only a resting ECG was done and hence some electrocardiographic abnormalities which require Holter monitoring could have been missed out.

The diagnosis of CKD only relied upon the file documented diagnosis by the attending physicians at the KNH Nephrology and Medical outpatient clinics.

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APPENDIX

APPENDIX I

STUDY PROFORMA

SERIAL No. _____

DATE: _____/_____/_____

BIODATA

1. **AGE:** ☐

2. **SEX:** ☐ **1=MALE** **2=FEMALE**

3. **BMI** _____

4. **SMOKING:** ☐

1=CURRENT SMOKER **2=FORMER SMOKER** **3=NON-SMOKER**

5. **ALCOHOL:** ☐

1=YES 2=NO

6. **AETIOLOGY OF CKD** ☐

1=DIABETIC NEPHROPATHY **2=HYPERTENSIVE NEPHROPATHY**

3=CHRONIC GLOMERULONEPHRITIS **4=OBSTRUCTIVE UROPATHY**

5=POLYCYSTIC KIDNEY DISEASE **6=OTHER (Specify) _____**

7. STAGE OF CKD

Estimated GFR: _____ CKD Stage ☐

1=CKD Stage 1 **4=CKD Stage 4**
2=CKD Stage 2 **5=CKD Stage 5**
3=CKD Stage 3

8. ELECTROCARDIOGRAPHIC ABNORMALITIES

IS THE ECG NORMAL? ☐ **1=YES 2=NO**

IF NO, PROCEED…….

(a) DOES IT SHOW AN ARRHYTHMIA? ☐ **1=YES 2=NO**

IF YES, ☐

1=SUPRAVENTRICULAR **2=JUNCTIONAL**
3=VENTRICULAR **4=NONE**

(b) IF SUPRAVENTRICULAR, PLEASE SPECIFY:

☐ **1=ATRIAL FIBRILLATION 2=SINUS TACHYCARDIA 3=SINUS BRADYCARDIA 4=ATRIAL FLUTTER 5=PREMATURE ATRIAL CONTRACTIONS 6=OTHERS 7=NONE**

(c) DOES IT SHOW PREMATURE VENTRICULAR CONTACTIONS?

☐ **1=YES 2=NO**

(d) DOES IT SHOW <u>OTHER</u> VENTRICULAR ARRHYTHMIAS?

☐ **1=YES 2=NO**

IF YES, PLEASE SPECIFY:_____

(e) DOES IT SHOW CHAMBER ENLARGEMENT? ☐

1=YES 2=NO

YES=1 NO=2 ☐ **LEFT VENTRICULAR HYPERTROPHY**

YES=1 NO=2 ☐ **RIGHTVENTRICULAR HYPERTROPHY**

YES=1 NO=2 ☐ **LEFT ATRIAL ENLARGEMENT**

YES=1 NO=2 ☐ **RIGHT ATRIAL ENLARGEMENT**

(f) DOES IT SHOW ATRIO-VENTRICULAR (AV) CONDUCTION ABNORMALITIES?

☐ **1=YES 2=NO**

IF YES, PLEASE SPECIFY: ☐

1=First degree AV block **2=Second degree AV block type I**

3=Second degree AV block type II **4=Third degree AV block**

5=None

(g) DOES IT SHOW INTRAVENTRICULAR CONDUCTION ABNORMALITIES? ☐ **1=YES 2=NO**

IF YES, PLEASE SPECIFY: ☐

1= Left Bundle Branch Block (LBBB) **2= Right Bundle Branch Block (RBBB)**

3= Left anterior fascicular block (LAFB) **4= Left posterior fascicular block**

5=Bifascicular Block **6=None**

(h) DOES IT SHOW A PROLONGED QT INTERVAL?

☐ **1=YES 2=NO**

(i) DOES IT SHOW ST SEGMENT CHANGES?

☐ **1=YES 2=NO**

IF YES, PLEASE SPECIFY: ☐ **1=ELEVATED 2=DEPRESSED 3=NORMAL**

(j) DOES IT SHOW T WAVE ABNORMALITIES? ☐

1=YES 2=NO

IF YES, PLEASE SPECIFY:

☐ **1=INVERTED 2=HYPERACUTE**
3=FLATTENED 4=NONE

(k) ARE THERE PATHOLOGICAL Q WAVES? ☐

1=YES 2=NO

APPENDIX II

Consent Explanation Form

Electrocardiographic abnormalities in dialysis naïve Chronic Kidney Disease patients in KNH

I am Dr Anthony Muguiyi Muturi. I am a postgraduate student of Internal Medicine in the Department of Clinical Medicine and Therapeutics at the University of Nairobi.

I would like to inform you that I am conducting a hospital based study on the ***"Prevalence and Types of Electrocardiographic abnormalities in dialysis naïve Chronic Kidney Disease patients in KNH".***

An ECG (electrocardiogram) is a test that measures the electrical activity of the heart. The heart is a muscular organ that beats in rhythm to pump the blood through the body. In an ECG test, the electrical impulses made while the heart is beating are recorded and usually shown on a piece of paper. This is known as an electrocardiogram, and records any problems with the heart's rhythm, and the conduction of the heart beat through the heart which may be affected by underlying heart disease. Patients with kidney disease may present with these problems.

Joining the study is voluntary and no payments will be charged to you due to participation in the study. Participation in the study will not delay your treatment in any way and may even be beneficial to you in case you are found to have any ECG abnormalities. Appropriate management will be given to you in accordance with the available hospital facilities.

You may decline to participate in the study or drop out at will and this will not lead to any denial of treatment or any form of care in the hospital.

The study will entail that I obtain an ECG and following that, collect some blood for the following tests: Serum creatinine

This blood test is used to assess the severity of your kidney disease.

Any results will be communicated to your primary physician for the appropriate therapy to be instituted.

The information collected from you will be treated with utmost confidentiality. Any publications arising from the study will not identify you, or your next of kin in person.

If you have understood the information that we have given you and you are willing to participate in the study, you will be required to sign a form indicating your willingness to be recruited.

If you have any questions about this study, you may contact Dr. A. Muguiyi Muturi using the following contacts: 0722-614585 or antomuturi@yahoo.com

APPENDIX III

CONSENT FORM

Electrocardiographic abnormalities in dialysis naïve Chronic Kidney Disease patients in KNH

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐ (Tick)

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason ☐ (Tick)

3. I confirm that I have agreed to have a five millilitres blood sample be drawn from my vein to ascertain the level of serum creatinine ☐ (Tick)

4. I confirm that I have agreed to have an electrocardiogram (ECG) be recorded from me. ☐ (Tick)

5. I agree to take part in the above study ☐ (Tick)

Name of Participant:_____ Signature: _____

Date: _____

Name of Investigator: _____ Signature: _____

Date:_____

APPENDIX IV

Consent Explanation Form (KISWAHILI)

Electrocardiographic abnormalities in dialysis naïve Chronic Kidney Disease patients in KNH

Jina langu ni Dr. Anthony Muguiyi Muturi. Mimi ni mwanafunzi wa somo la udaktari wa shahada ya uzamili katika Chuo Kikuu cha Nairobi.

Ningependa kukujulisha kuwa ninafanya utafiti juu ya idadi na aina ya magonjwa inayoathili umeme wa roho kwa wagonjwa wanaougua ugonjwa wa figo katika hospitali kuu ya Kenyatta, ama kwa lugha ya kiengereza, ***"Prevalence and Types of Electrocardiographic abnormalities in dialysis naïve Chronic Kidney Disease patients in KNH".***".

"Electrocardiogram (ECG)" ni aina ya picha ya roho inayokagua umeme wa moyo. Moyo ni kiungo cha mwili ambacho ni bomba la damu inayoenea kwenye viungo vyote vya mwili. ECG ni kifaa ambacho hupima umeme unaosaidia roho kupiga. Wagonjwa wanaugua ugonjwa wa figo wanaweza kuwa na magonjwa yanoyoathili umeme wa roho.

Kujiunga kwa utafiti huu ni kwa hiari yako na hakuna malipo yeyote itakayolipwa kutokana na kushiriki katika utafiti huu. Kushiriki kwenye utafiti huu hakutachelewesha matibabu yako kwa njia yoyote na kunaweza kuwa na manufaa kwako kama uko na ugonjwa wa roho ambao haujagunduliwa. Kama utagunduliwa kuwa na ugonjwa wowote katika utafiti huu, matibabu mwafaka yataanzishwa.

Unaweza kukataa kushiriki katika utafiti huu ama kujiondoa wakati wowote bila ya hofu ya kubaguliwa ama kunyimwa tiba au aina yoyote ya huduma katika hospitali hii.

Utafiti utahusisha kupigwa kwa picha la ECG na kukusanya damu kidogo ili kutathmini kiwango cha ugonjwa wa figo zako.

Matokeo yoyote itawasilishwa kwa daktari wako kwa ajili ya kuanzisha matibabu sahihi. Taarifa zitakazokusanywa katika utafiti huu zitahifadhiwa vizuri ili kulinda faragha yako. Machapisho yoyote ambayo yatatokana na utafiti huu hayatachapisha majina yako ama yale ya jamaa yako.

Kama umeelewa juu ya utafiti huu na ungependa kushiriki, utahitajika kuweka sahihi kwenye fomu ya ridhaa.

Kama una maswali yoyote kuhusu utafiti huu, unaweza kuwasiliana na Dr A. Muguiyi Muturi kutumia nambari ya simu: **0722-614585** ama barua pepe kwa anwani ifuatayo; **antomuturi@yahoo.com**

APPENDIX V

FOMU YA RIDHAA

Electrocardiographic abnormalities in dialysis naïve Chronic Kidney Disease patients in KNH

1. Ninathibitisha ya kwamba nimesoma na nimeelewa karatasi linaloeleza kuhusu utafiti huu na nimepewa nafasi ya kuuliza maswali ☐ (Weka Alama)

2. Naelewa kwamba kushiriki kwangu kwa huu utafiti ni kwa hiari yangu na kwamba nina uhuru wa kujiondoa wakati wowote, bila ya kutoa sababu ☐ (Weka Alama)

3. Ninathibitisha ya kwamba, nimekubali sampuli ya mililita tano damu za damu kutolewa kwa mshipa wangu ili kuthibitisha kiwango cha kreatini*(creatinine)* ☐ (Weka Alama)

4. Ninathibitisha kuwa nimekubali roho yangu kupigwa picha ya *Electrocardiogram (ECG).* ☐ (Weka Alama)

5. Ninathibitisha ya kwamba, nimekubali kushiriki katika utafiti huu. ☐ (Weka Alama)

Jina la Mshiriki: _____ Sahihi: _____

Tarehe: _____

Jina la Mchunguzi: _____ Sahihi: _____

Tarehe: _____2