Determination of Concordance between Bio-Impedance Analysis and a Clinical Score in Fluid Status Assessment of Patients on Maintenance Haemodialysis

A thesis submitted in part fulfilment of the requirements for the award of Master of Medicine degree in Internal Medicine

University of Nairobi

By

Dr. Kamiti Muchiri

Reg. No. H58/87308/2016

DECLARATION OF ORIGINALITY

Name of Student: Kamiti Muchiri

Registration Number: H58/87308/2016

College: College of Health Sciences

Faculty/School: School of Medicine

Department: Department of Clinical Medicine and Therapeutics

Course Name: Master of Medicine in Internal Medicine

Title of the Work: Determination of Concordance between Bio-Impedance Analysis and a Clinical Score in Fluid Status Assessment of Patients on Maintenance Haemodialysis

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This thesis has been submitted as part fulfilment for the award of a degree of Master of Medicine in Internal Medicine with the full approval of the following supervisors:

1. Prof. J. K. Kayima

   Department of Clinical Medicine and Therapeutics

   University of Nairobi

   Signed……Date……..

2. Prof. E. N. Ogola

   Department of Clinical Medicine and Therapeutics

   University of Nairobi

   Signed……Date…….....

3. Prof. S. O. McLigeyo

   Department of Clinical Medicine and Therapeutics

   University of Nairobi

   Signed……Date…….

ACKNOWLEDGEMENT

The Almighty God

This would not have been possible without my wife, Dr. Sally Wambui, whose support throughout the process of this research has been invaluable.

I would like to thank my supervisors for their tireless dedication and guidance throughout the process of conducting this research.

I would also like to thank Dr. Samuel Kabinga for his advice and assistance during various stages of the research.

I am also indebted to Dr. Marshal Mweu who graciously advised on and performed the statistical analysis for this thesis.

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List of Abbreviations

ACR	Albumin-to-Creatinine Ratio
AER	Albumin Excretion Rate
BIA	Bio-impedance Analysis
BIS	Bio-impedance Spectroscopy
BMI	Body Mass Index
BP	Blood Pressure
CKD	Chronic Kidney Disease
CS	Clinical Score
DBP	Diastolic Blood Pressure
DDFQ	Dialysis Diet and Fluid Questionnaire
ECV	Extracellular Volume
eGFR	estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
FO	Fluid Overload
FPR	False Positive Rate
GFR	Glomerular Filtration Rate
HD	Haemodialysis
IDWG	Inter Dialytic Weight Gain
IQR	Inter Quartile Range

IVC	Inferior Vena Cava
KDIGO	Kidney Disease: Improving Global outcomes
KNH	Kenyatta National Hospital
MTRH	Moi Teaching and Referral Hospital
NaCl (0.9%)	0.9% normal saline
NT Pro BNP	N-Terminal Pro Brain Natriuretic Peptide
NYHA	New York Heart Association
OH	Over hydration
OR	Odds Ratio
PD	Peritoneal Dialysis
PI	Principal Investigator
ROC curve	Receiver Operating Characteristic Curve
RRT	Renal Replacement Therapy
SBP	Systolic Blood Pressure
SSA	Sub-Saharan Africa

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ABSTRACT

Background: The burden of chronic kidney disease (CKD) is rising rapidly globally. Fluid overload (FO), an independent predictor of mortality in CKD, must be quantified accurately to enable maintenance of normohydration. Clinical assessment is widely used to determine FO but its individual elements may not be precise and could result in underestimation of FO. Conversely, bio-impedance analysis (BIA) has been shown to be accurate and reproducible in determining fluid status of CKD patients on haemodialysis (HD). However, it is unclear which of the two methods is more sensitive in assessing volume status in our population.

Objective: To assess the hydration status of maintenance HD patients using BIA and assess the level of agreement between BIA and a clinical score (CS) in fluid status assessment.

Methodology: This was a single centre hospital based cross-sectional analytic study that recruited a sample of 80 CKD patients at the renal unit of Kenyatta National Hospital. Included patients were 18 years of age or older, on maintenance HD, without a pacemaker, metallic implant or bilateral limb amputation. Data on the patients' clinical history, physical examination and chest radiography findings were filled into a predesigned questionnaire. Using the same questionnaire, data on determinants of fluid overload was collected. Bio-impedance analysis for fluid status was then performed on each of the study participants.

Bio-impedance analysis was used as the reference to which the CS was compared. The sensitivity and specificity of the CS was computed and used to plot a receiver operating characteristic (ROC) curve that was used to ascertain the ideal cut-off point for the CS. McNemar's chi-square was used to check for association between fluid overload status by BIA and CS. Logistic regression was used to analyse the factors associated with FO.

Results: A high proportion of patients on maintenance HD have FO (88.75%) with mean excess extracellular volume being 3.02 L $\pm$ 1.79 L.

There was a statistically significant difference in the proportion of patients diagnosed to have FO using BIA and the CS (p-value <0.0001, 95% CI 0.1758 – 0.4242). The best cut-off point identified for the CS was four with values >4 indicating FO and values $\leq$ 4 indicating no FO. At this cut-off point, the CS had a sensitivity of 63% and a specificity of 78%. None of the factors assessed had a statistically significant association with FO on multivariable logistic regression analysis.

Conclusion: In this population, BIA was able to diagnose FO more frequently than the CS.

Further studies need to be done to determine the consistency of these findings.

1 INTRODUCTION

According to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on evaluation and management of chronic kidney disease (CKD), CKD is the presence of abnormal structure and function of the kidney present for more than 3 months with an impact on the health of a person. The diagnosis of CKD is based on either a reduction in estimated glomerular filtration rate (eGFR) or the presence of one or more markers of kidney damage such as an abnormal urine sediment, albuminuria or histological abnormalities after biopsy (1).

Chronic kidney disease is associated with increasing age, diabetes, hypertension and primary renal disorders such as glomerulonephritis (2). A rise in diabetes prevalence worldwide has led to an increase in CKD, indeed the prevalence of diabetic kidney disease has risen by 39.5% over the past 5 years (3). Chronic kidney disease is considered a cardiovascular risk accelerator and is an independent risk factor for occurrence of cardiovascular events (2).

With progression of CKD, complications such as uraemia, disorders of fluid and electrolyte balance including sodium and potassium abnormalities, metabolic acidosis and disorders of calcium and phosphate metabolism may occur. In addition, there are wide ranging complications in various systems such as: cardiovascular abnormalities that include ischemic heart disease, hypertension, heart failure and pericardial disease; hematologic abnormalities like anaemia and disordered haemostasis; neurologic abnormalities like peripheral neuropathy; gastrointestinal abnormalities like gastritis and mucosal ulceration; endocrine abnormalities like abnormalities in glucose and oestrogen levels and dermatologic abnormalities like pruritus can occur.

In the advanced stages of CKD, there is a reduction in the ability to excrete sufficient amounts of sodium resulting in water retention and development of fluid overload (FO). In end stage renal

disease there is a need to assess accurately the fluid status of patients. This can be done in various ways including: dilution techniques, relative plasma volume monitoring, natriuretic peptides, various imaging modalities like chest radiography and ultrasound, clinical judgement and bio-impedance analysis (BIA). Patients who are fluid overloaded require renal replacement therapy (RRT) that may be of various forms including haemodialysis (HD), peritoneal dialysis (PD) and renal transplantation. However, this is not always available and conservative estimates suggest that over half those who require RRT worldwide die due to lack of access to the same. In Africa the situation is worse with less than 3% of those requiring RRT in Central and Eastern Africa receiving it (4).

In view of the rising prevalence of CKD and the importance of accurately determining the fluid status of patients with end stage renal disease (ESRD), this study seeks to determine the level of agreement between fluid status assessment using BIA and a clinical score (CS) in ESRD patients on maintenance haemodialysis. We also seek to determine the fluid status of this same population of patients using BIA.

2 LITERATURE REVIEW

2.1 Diagnosis of CKD

The diagnosis of CKD is based on either a reduction in eGFR or the presence of one or more markers of renal damage such as an abnormal urine sediment, albuminuria (e.g. as detected by albumn creatinine ratio [ACR] or albumin excretion rate [AER]) or histological abnormalities after biopsy as illustrated in table 1 (1).

Table 1: Criteria for Diagnosing Chronic Kidney disease

Criteria for CKD (either of the following present for >3 months)	
Markers of kidney damage (one or more)	Albuminuria (AER>30 mg/24 hours; ACR>30 mg/g [>3 mg/mmol])
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation

Adapted from KDIGO Guidelines for the Evaluation and Management of CKD, 2012 (1)

The reduction in Glomerular Filtration Rate (GFR) is based on estimating the GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and classifying the

kidney disease into 6 stages from 1 to 5 with stage 3 split into 3a and 3b as demonstrated in table 2 (1).

Table 2: GFR categories in CKD

GFR Stage	**GFR (ml/min/1.73m^2)**	**Terms**
G1	≥90	Normal or high
G2	60 – 89	Mildly decreased
G3a	45 – 59	Mildly to moderately decreased
G3b	30 – 44	Moderately to severely decreased
G4	≤15 – 29	Severely decreased
G5	<15	Kidney failure (End stage renal disease)

Adapted from KDIGO Guidelines for the Evaluation and Management of CKD, 2012 (1)

2.2 Epidemiology of CKD

Chronic kidney disease has been noted to be a global public health issue of enormous concern. According to the 2015 Global Burden of Disease Study (3), CKD is currently the 17th most common cause of death worldwide. Worryingly this has risen by 31.7% over the past decade to its current position, such a rapid rise matched only by diabetes mellitus and dementia. This has resulted in a rise of 18.4% of the global years of life lost.

The global prevalence of CKD has been estimated at 13.4% in a pooled meta-analysis that was published in 2016 (5). In addition, mean population age, diabetes and hypertension were significantly associated with CKD.

In Africa, the pooled prevalence is 10.1% with that of Sub-Saharan Africa (SSA) being 14.02%. The commonest causes of CKD in Africa were reported as hypertension, diabetes and chronic glomerulonephritis. Furthermore, CKD is less common in men but they have more severe disease with a higher risk of cardiovascular and all-cause mortality (6). Similarly, a meta-analysis of renal disease in SSA reported that the prevalence of CKD was 13.9%. In SSA, CKD primarily affects adults 20 to 50 years old compared to the western world where it primarily affects the elderly. In addition most of the patients present late with 3 out of 4 patients requiring dialysis at presentation (7).

In Nigeria the prevalence of CKD has been reported at 7.8% (8), while a study done in South African teachers in Cape town reported a prevalence of 6.1% (9). Closer home, a study in Tanzania noted that the prevalence was 7% (10) while in Uganda a community based survey reported the prevalence of CKD was 15.2% (11).

To the best of the author's knowledge, no studies have been carried out to assess the population prevalence of CKD in Kenya.

2.3 Fluid status of CKD patients

In CKD, the inability to excrete adequate amounts of sodium causes sodium and water retention. This leads to increased capillary hydrostatic pressure, dilution of intravascular albumin and increased fluid flux from intravascular to the interstitial compartment resulting in isotonic FO. In healthy subjects the extracellular volume (ECV) may vary by $\pm$ 1 L depending on salt intake (12).

Fluid overload is defined as the volume of extracellular fluid that exceeds the range observed in healthy subjects with normally functioning kidneys (12). In ESRD, more patients are fluid overloaded than dehydrated. The hydration status of ESRD patients on chronic HD is an

important independent predictor of mortality secondary only to the presence of diabetes (13). With sustained FO there is associated left ventricular dilation, left ventricular hypertrophy associated with arterial hypertension, congestive cardiac failure and a resultant increase in mortality (14).

Furthermore, with systolic and diastolic dysfunction, the patient is at risk of intradialytic hypotension and sudden cardiac death. With oedema, there is a risk of skin infections, especially in diabetic patients, that can result in sepsis with a resultant increase in mortality and limb amputations. Congestion in the gastrointestinal tract leads to nutrient malabsorption while in the lungs it leads to an increased risk of bronchitis and pneumonia (15).

Relative over-hydration (OH) greater than 15%, corresponding to greater than 2.5 L FO, is an independent predictor of mortality after adjustment for left ventricular mass and left ventricular ejection fraction (16). In addition, this level of OH carries an 8.5% increased risk of mortality even in a relatively healthy group of CKD patients on dialysis (13).

On the other hand with dehydration there is an increased frequency of intradialytic symptoms such as cramps and hypotension, cardiac stunning and depletion of any residual renal function (14).

The fluid status of patients on HD is variable and determines the post dialytic weight and inter-dialytic weight gain (IDWG). The post dialytic weight, a marker of the patient's dry weight, may be defined as the lowest tolerated weight of a patient attained by a gradual alteration in weight to where they seldom have signs or symptoms of hyper or hypovolemia (17). Currently there is no measure of the adequacy of fluid removed during dialysis (18).

An analysis of more than 1500 European haemodialysis patients from 22 centres revealed that 25% were 2.5 L above normohydration target before treatment (19)). According to the Renal

Research Institute based in New York 51% of their CKD patients on HD are fluid overloaded with 7% being fluid depleted (12).

While looking at the time averaged fluid overload in CKD patients on dialysis for more than 6 months, in Barcelona, Moissl *et al* found that out of a study population of 56 patients 31% were fluid overloaded, 46% normohydrated and 22% dehydrated at baseline (14).

In a German study involving 5 dialysis centres, out of 234 patients, 63% had FO greater than 1.1L with 5% being dehydrated. The investigators determined that there was a significant correlation between pre-dialysis FO and pre-dialysis systolic blood pressure (SBP) in patients without diabetes. They also noted that in 26% of the patients a more active management of dry weight would be beneficial (20).

A study done in South Africa using bio impedance spectroscopy (BIS) showed that 63% of 160 HD and PD patients were fluid overloaded (21). In this study, investigators assessed patients with stage 3 CKD and had healthy controls to determine the usefulness of bio-impedance in evaluation of fluid status.

In a study done at the Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya, between January and March 2012 that assessed 51 patients on HD, 69% of the patients had FO when assessed by BIA (22).

These studies suggest that most ESRD patients on HD are fluid overloaded with a higher risk of mortality as the degree of FO worsens. It is therefore important to assess the fluid status using the most sensitive tools available to ensure that patients attain their dry weight.

2.4 Fluid assessment techniques

Various methods are used to assess the fluid status of ESRD patients on HD including relative plasma volume monitoring, dilution techniques, natriuretic peptides, BIA, clinical and radiological assessment. Radiological assessment may involve use of chest radiographs or various ultrasound modalities. Dilution techniques are considered the gold standard but are not feasible for routine clinical use. Currently BIA is considered the best alternative for day-to-day clinical use. However, in the Kenyan setup most facilities are unable to afford it necessitating the use of clinical and radiologic assessment due to their low cost nature and relatively easier availability.

2.4.1 Chest radiographs

Chest radiographs have been used to detect FO with changes such as dilated pulmonary veins, enlarged cardiac shadow, interstitial oedema, distended pulmonary artery, pleural effusion, alveolar oedema, prominent superior vena cava and Kerley lines being apparent to various degrees with FO (23). These radiographic changes may only become apparent after clinical symptoms have started reducing their utility in acute presentations. Furthermore, the sensitivity of radiographs in detecting cardiomegaly is not satisfactory. It has also been reported that they are of less value in dehydration and that portable radiographs are poorly sensitive for FO (24).

The measurement of vascular pedicle width may improve the sensitivity of radiographs in determining fluid status. A vascular pedicle width less than 70 millimetres and a cardiothoracic ratio less than 0.55 are considered normal. However, this is affected by many factors such as patient position, height and build of the patient, diseases of the mediastinum, prior surgery, chest irradiation and technical factors in taking the radiograph (25).

The radiologic signs of FO have a temporal evolution and have been grouped into three stages. In stage 1, there is cardiomegaly and distention of upper lobe veins in an erect radiograph. With

progression into stage 2, there is leakage of fluid into the interstitial space because of increased capillary pressure resulting in Kerley B lines and peri-bronchial haziness. With continued leakage of fluid into the interstitium, the ability of lymphatics to clear it is overwhelmed leading to leakage of fluid into the alveoli and pleural space resulting in alveolar oedema and pleural effusions that are typical of stage 3 (26).

Due to the widespread availability of chest radiographs, despite being less sensitive in detecting some aspects of FO, they may be one of the tools that can be routinely utilized in determining FO.

2.4.2 Clinical judgement

Patients with dysvolemia may have clinical signs and symptoms that guide the clinician in determining their fluid status. Indeed, clinical judgement, guided by a systematic clinical approach, has been noted by some to be the most important factor in assessing OH. Furthermore integration of clinical judgement with routine laboratory and imaging techniques (such as chest radiographs) makes it a valuable and precise tool in the assessment of hydration status of HD patients (27). A systematic clinical approach is based on input from the patient in terms of a history, input from a clinician in terms of a clinical examination and the consideration of additional data from laboratory and radiological studies. Sole reliance on patient reports can be misleading, however, patient reported symptoms of OH become more specific as the level of FO increases (28).

Clinical judgement may be confounded by factors such as vascular stiffness, hypoalbuminemia, cardiac dysfunction and the presence of multiple comorbidities in a patient. Most fluid overloaded HD patients based on BIA may not have the classic signs such as pitting oedema, lung crepitation’s and elevated jugular venous pressure or added heart sounds on auscultation (29).

In a meta-analysis of studies using heart failure as a diagnostic model that assessed the history and physical examination findings for assessing fluid status of patients, exertional dyspnoea was the most sensitive finding whereas paroxysmal nocturnal dyspnoea, orthopnoea and oedema were the most specific findings (30).

Other symptoms that may be assessed when determining the presence of FO include a nocturnal cough and the number of antihypertensive medications required to control blood pressure (BP).

When performing a physical examination, the signs to be assessed include checking the extent of peripheral oedema, jugular venous distention, the presence of hepatojugular reflux and auscultating for the presence of extra heart and lung sounds. Jugular venous distention is an indirect measure of right atrial pressure. It has however been noted to have an inconsistent relationship with objective measures of right atrial pressure. Nevertheless, some still consider it a valuable tool in assessing moderate to severe levels of OH (31).

The presence of a third heart sound has been noted to have high specificity for ventricular dysfunction and has a high positive likelihood ratio for FO. It however has poor sensitivity as a negative predictor owing to the difficulty of hearing it in those with confounding illnesses such as obesity and chronic obstructive pulmonary disease (30).

The assessment of a patient's BP needs to be informed by various perspectives derived from previous research. Hypotensive symptoms may occur even when fluid overloaded when the rate of ultrafiltration exceeds the rate at which plasma is refilling. Additionally excess fluid is considered by some as the most important factor causing hypertension in HD patients and the control of hypertension without medication the single best predictor of survival in HD patients (32). To put it in perspective, 80% of hypertension in HD patients is considered to be due to chronic FO (18).

In addition, paradoxical hypertension (increase in BP during dialysis) is also thought to indicate the presence of FO despite its mechanism not being well understood (33). With hypertension that has a neuro-hormonal component, it may take several months after achieving normovolemia before resolution (34). However, patients may have normal BP despite being overhydrated as demonstrated by an analysis of more than 1500 patients in 22 HD centres in Europe in which 38% had normal BP despite being fluid overloaded (19). On average every litre of fluid lost may be worth 6.6 mmHg (35) to 9.9 mmHg (14) reduction in SBP. Furthermore, the reduction in dry weight as determined by clinical signs and symptoms results in reduction in BP equivalent to the addition of a thiazide diuretic (35).

Weight is also regularly used in assessment of fluid status. However, its use may not be very objective and may be affected by other factors like a change in diet with increased caloric intake or adopting a weight loss regimen. An underappreciated source of variation in weight is the presence or absence of food contents in the gastrointestinal tract and the water-glycogen content of liver and muscle that can acount for up to 2 to 3 kilograms (36).

Age, left ventricular mass and body mass index (BMI) are the most important determinants of oedema. However, oedema has not been correlated to NT pro BNP, Inferior vena cava (IVC) diameter, IVC collapsibility index, ejection fraction, pressures in the right atrium, diameter of the left atrium or changes in blood volume. Although oedema might not be a good marker of intravascular volume in stable long-term HD patients, it signals the possibility of existence of risk factors for FO that should be identified and managed. In addition, increasing the number of observers and the use of a constellation of physical signs may improve its value in assessment of fluid status (37).

The use of a clinical scoring system has been used by some to assess the hydration status of patients. Though it is attractive because of its ease of documentation, regularity of reviews and

recording and early detection of shifts in symptoms, the use of a scoring system is limited by being subjective, incomplete, nonspecific and dependent on the observer. Scoring only symptoms that appear de novo and disappear after correction of the fluid status may however improve specificity. Such an approach was used by *Wizemann et al* who grouped together symptoms of hypovolemia and those of hypervolemia and scored them as shown in table 3 (28).

Table 3: Clinical score of volume state

Symptoms		**Score**
Scored as hypovolemia	Symptomatic dialysis hypotension	-1
	Symptomatic dialysis hypotension treated by normal saline (NaCl) (0.9%) infusion – for every 100 ml of 0.9% NaCl	-1
	Muscle cramps, graded	-1 to -4
Scored as normohydration	Absence of symptoms given in this table	0
Scored as hypervolemia	Dyspnoea during exercise (>50 watts)	+1
	Dyspnoea during exercise (<50 watts)	+2
	Dyspnoea during recumbence	+3
	Dyspnoea during sitting or standing	+4
	Oedema (ankles, tibial, graded)	+1 to +4

Adapted from Wizemann et al., 1995 (28)

In a study done in Canada in 2015 that assessed the relationship between clinical and bio-impedance parameters in assessing the fluid status of patients on HD, clinical assessment was reported as neither sensitive nor specific enough to be utilized to robustly assess fluid status. In this study 194 patients were assessed by use of BIS and compared to several clinical and biochemical parameters including pre- and post-dialysis BP while sitting for the same session and 5 previous sessions, intradialytic hypotension, paradoxical hypertension during or after dialysis, pedal oedema, IDWG and dry weight from patient charts. The biochemical parameters included sodium, potassium, albumin, white cell count, urea reduction ratio and cholesterol level. Although several clinical parameters had increased prevalence in their HD patients with fluid expansion, none had the required sensitivity or specificity to robustly assess fluid status. Of the clinical parameters, oedema, a lower BMI and SBP were significant predictors of volume expansion. In addition, it was noted that despite frequent clinical assessment, up to 50% of patients had moderate to severe OH. This study concluded that clinical assessment lacks precision and it may underestimate severe FO when compared to BIS (38).

An article in the Renal Society of Australia Journal has suggested a framework for assessing fluid status that begins with a history of the general well-being of the patients and screening for symptoms related to their fluid status including their tolerance of their last dialysis session. Additionally, a medication history is also taken before doing a head to toe physical examination where an assessment of facial oedema and the jugular venous pulse are undertaken. In the chest, a detailed respiratory system assessment is undertaken and the abdomen is assessed for ascites. The vital signs, weight and height are also assessed as illustrated in the table 4 (39).

Despite the individual limitations of the various parameters of clinical assessment, being the tools we readily have access to in determining whether HD patients have FO, we have to utilize them to the best possible effect. Furthermore, a constellation of symptoms and signs in addition

to basic laboratory and radiographic parameters may improve their sensitivity and specificity in detection of patients with FO.

Table 4: Framework for fluid assessment

FRAMEWORK FOR FLUID ASSESSMENT	
History	General well being
	Symptoms relating to fluid status
	Tolerance of previous dialysis sessions
	Medication history including antihypertensive and diuretic agents
Weight	
Vital signs	Blood pressure
	Pulse rate
	Respiratory rate
Face	Oedema
Neck	Jugular Venous Pulse
Chest	Oxygen saturation
	Basal crackles
	Pleural effusion

Peripheries	Oedema
Recent biomarkers	Sodium
	Albumin
Radiography	Chest radiograph

Adapted from Campbell S., 2006 (39)

2.4.3 Bio-impedance analysis

Bio-impedance was originally proposed by Thomasset in 1963 (40). The basic principle behind it is that electrical impedance of a cylinder is directly proportional to its length and indirectly proportional to its cross sectional area multiplied by its specific sensitivity (18). It relies on the passing of an alternating current through the body, if it is a low frequency current it preferentially passes extracellularly while higher frequencies traverse both intra and extra cellular spaces (12).

It has been validated against several methods including isodilution methods, conventional reference body composition methods, techniques using relative change in fluid volume and extensive clinical assessment of the hydration state with some sources reporting much better reproducibility than clinical assessment. The prediction error of BIS has been reported as 3.5 – 6.9% in a 70 kilogram adult (41) with an inter-observer error of less than 2% (29). Prediction equations for populations of African descent have been developed and validated such as in the Modelling the Epidemiologic Transition Study (METS) (42). This study used 5 populations (rural Nkwanta Kese, Ghana; urban Cape Town, South Africa; urban Kingston, Jamaica; Island of Mahe, Seychelles and suburban Maywood, Illinois, United States) that consisted primarily of

people of African descent that were chosen to correspond to a wide range of both economic and social development as defined by the United Nations Human Development Index. The researchers used a single frequency bio-impedance analyser from RJL systems to get resistance values. The equations developed had comparable error, bias and concordance when compared to a sample of selected equations currently in use.

There are two main factors determining the impedance to an alternating current: resistance and capacitance. Resistance is affected by the size, shape, length and type of materials while capacitance is the ability of a non-conducting system to store energy and discharge it once fully saturated (43).

An alternating current comprises of the current wave and the voltage wave which have the same frequency but different amplitudes. When their 2 peaks collide, they are said to be in phase. However, on passing through a system with capacitance, the voltage wave is delayed and the peaks become non-simultaneous and thus out of phase. Their difference is expressed as a phase angle that has been proven as a good predictor of prognosis and mortality in HD patients (44).

Broadly, bio-impedance can be categorized into the single frequency devices, the multi-frequency devices and BIS. The multi-frequency modalities can assess either the whole body or a segment of the body such as the calf, trunk, arms or legs.

The multi-frequency approach has a better theoretical foundation than the mono-frequency one by using the Cole-Cole model and Hanai principle when converting resistance and reactance into fluid volumes. Currently there are two models used to compute ECV namely the Xitron equations and Moissl equations. The Moissl equations provide a better estimation of fluid volumes (12).

The computation of ECV by whole body bio-impedance has been validated by tracer methods, currently considered the gold standard, with an average difference of 1.01 L $\pm$ 1.63 L. Its accuracy is however based on the obviously erroneous presupposition that the human body can be modelled as one cylinder with identical conductivity in all its segments. The cross sectional area of the limbs differs significantly from that of the trunk and the total resistance from the limbs is about 90% of the whole body while accounting for only about 30% in terms of volume (12).

Because of this, segmental analysis is potentially more accurate than whole body assessment but has yet to be linked to better clinical outcomes (29). The limitation of segmental analysis is the subject should not move during the assessment or be subjected to multiple assessments (45).

Whole body bio-impedance has been reported to be in excellent concordance with all gold standard comparisons for HD patients and healthy volunteers (46). However, its precision is insufficient in children, pregnant women and those with pacemakers or metallic prosthesis; it is affected by morbid obesity, intense physical activity and ingestion of food or fluids before evaluation. It has also been noted not to accurately estimate fluid changes during HD (47).

In a meta-analysis published in 2018, bio-impedance defined OH was an independent predictor of mortality in CKD patients with its predictive value based on its ability to identify an absolute or relative expansion of extracellular fluid as an independent risk (16).

Bio-impedance analysis is advantageous in many ways such a being non-invasive and convenient. It is also portable and easy to use.

However, BIA cannot differentiate extra cellular water in plasma from that in the extra vascular compartment such as oedema. This leads to a risk of compromising residual renal function with bio-impedance driven dry weight in the setting of progressive tissue OH with muscle wasting

seen in patients on chronic HD (29). In addition, accurate measurement of intracellular volume is confounded by temperature and ion effect while that of ECV is confounded by effect of recumbence. Pre-dialysis measures often underestimate ultra-filtrate volume and bio-impedance underestimates the volume of fluid removed from the trunk (18).

On the other hand, BIS takes advantage of the dielectric theory of electrical conduction through mixed emulsified bodies (18). It differs fundamentally from BIA in that it provides a more direct and individualized measure of body compartments with a BMI corrected equation that allows for differentiation of normally hydrated tissue from excess fluid (43). It was proposed because a significant proportion of errors in measurement are due to the impact of adiposity on intracellular water estimates. It extrapolates values for resistance at very high (infinity) and very low (0) frequencies from resistance values in the frequency range that can be reliably measured (1 – 500 KHz). From these values, total body water and extracellular water can be determined and intracellular volume calculated from the two. Its use in guiding dry weight assessment has been shown to lead to regression of left ventricle mass index, BP reduction, improved arterial stiffness and improved survival (48).

Bio-impedance is not appropriate when measuring small changes in volumes (<1 L) occurring during fluid intake or sweating. To improve on accuracy and reliability of measurements, care must be taken to place electrodes at the correct site. Other factors that may affect the measurements are the skin temperature, skin blood flow, posture of the patient and changes in plasma osmolality or sodium concentration (49) in addition to other factors mentioned above.

In a study done in Israel that looked at patients with stages 1 to 4 of CKD without any clinical evidence of OH, the use of BIS revealed subclinical OH in 58.3% of those in stage 4, 39.3% of those in stage 3, 18.5% of those in stage 2 and 3.3% of those in stage 1 CKD (50). Subclinical OH was associated with elevated BP and higher C-reactive protein levels.

Due to its sensitivity, benefits in identifying patients at high risk for mortality and validation against a variety of methods across multiple populations, bio-impedance analysis is an ideal tool for assessing fluid status of CKD patients on HD. However, the cost involved in purchase of the equipment limits its availability in a resource-limited setting such as ours.

2.4.4 Summary of fluid assessment methods

There are many methods of fluid assessment each with its various advantages and disadvantages, as shown in the table 5, making them uniquely suited to different clinical scenarios.

Table 5: Summary of methods of assessing fluid status of CKD patients

Method	Principle	Advantages	Disadvantages
Relative plasma volume monitoring	Use of optical absorbance to measure intradialytic change in protein and haematocrit.	Non-invasive	Significantly underestimates blood volume change, affected by ultrafiltration and vascular filling, relies on uniform mixing of plasma proteins
Dilution techniques	Determination of tracer mass within a compartment.	Accurate measurement of fluid compartments.	Impractical for routine clinical use.

BNP and NT Pro BNP	Increased blood levels with ventricular stretch.	Predictive of cardiac events and mortality.	Weak correlation with ECV, levels affected by renal and dialysis clearance, not specific, levels do not reduce with restoration of normovolemia.
Atrial Natriuretic Peptide	Increased serum levels with increased transmural atrial pressure.		No clear relation with OH, not specific or sensitive.
Chest radiographs	FO may present with various observable features.	Cheap, widely available.	Lags behind clinical abnormalities by hours, less useful for dehydration, portable radiographs poorly sensitive for OH.
Chest ultrasound	Assessing the number and strength of sonographic lung comets present.	Easy to use, can be used intra-dialysis.	Limited specificity, difficult to differentiate fibrosis and fluid, operator dependent.
IVC Ultrasound	Determines the absolute diameter of the IVC and the level of collapse with respiration. FO leads to distention of the IVC.	Easy to use, widely available.	Wide variation in normal people, operator dependent, affected by various medical conditions like right heart dysfunction.

Clinical judgement	FO produces typical clinical signs and symptoms such as oedema, elevated jugular venous pressure, and third heart sound.	Widely available, minimal equipment required.	Confounded by comorbidities, requires training and experience to reliably pick up the signs and symptoms.
Bio-impedance analysis	Electrical impedance of a cylinder is directly proportional to its length and indirectly proportional to its cross sectional area multiplied by its sensitivity.	Validated against standard methods, accurate, simple to use, non-invasive.	Affected by extreme obesity, intense physical activity, intake of food or fluid before evaluation, expensive, cannot adequately measure small changes in volume (less than 1 litre).

2.5 Factors associated with fluid overload

When considering factors associated with FO one of the most important to consider is BP. Excess fluid is considered by some as the most important factor causing hypertension in HD patients and the control of hypertension without medication the single best predictor of survival in HD patients (32). It has also been reported that there is increased mortality with SBP greater than 130 mmHg (51). Volume overload leads to hypertension by causing a combination of increased cardiac output and increased systemic vascular resistance.

Mean arterial pressure, SBP and diastolic blood pressure (DBP) are higher with FO. With improvements in volume status, control of hypertension improves and less patients will require antihypertensive agents. Hypertension also leads to left ventricular hypertrophy that is a predictor of mortality (51).

On the other hand, intradialytic hypotension and orthostatic hypotension are significant and independent factors associated with mortality in HD patients with those having hypotension having an increased 2-year mortality (52). Similarly, Iseki et al who followed up about 1250 patients over a mean period of 62 months in Okinawa reported that low DBP was associated with increased mortality especially in diabetic patients (53). Furthermore, in another study on diabetic patients on HD, those dying from a myocardial infarction had repetitive severe episodes of hypotension during dialysis (54).

According to *Tapolyai et al*, the number of antihypertensive agents used is positively correlated with FO, with increasing FO with an increase in the number of agents used. They also found a positive correlation between the use of diuretics and the presence of OH. They postulated that use of diuretics leads to a false sense of security in patients resulting in increased fluid intake. Because BP may be well controlled, medical practitioners tend to be less aggressive with their ultrafiltration. In addition, these patients tend to achieve normotension faster when on dialysis and the ultrafiltration is stopped earlier leading to FO. However, they found no relationship between OH and residual renal function, BMI or dialysis vintage with IDWG having little association with OH (55).

According to *Ozdogan et al*, increase in IDWG by 1% leads to 22% increase in mortality (56). However, other studies report that IDWG has no association with FO (57). IDWG is primarily due to salt and water intake. With an increased salt intake, patients develop osmometric thirst that leads to increased water intake due to increased osmotic pressure resulting in increased

intravascular volume and thus hypertension. Post dialysis, patients may develop volumetric thirst due to hypovolemia because of the volume of water removed by ultrafiltration (51).

In CKD the kidneys ability to excrete sodium is limited, leading to sodium retention that results in fluid retention. Every gram of salt consumed leads to 100 – 120 ml of fluid gained (51). According to WHO, the gold standard method for evaluating salt consumption is repeated 24-hour urine collections. However, this is tedious and costly and may not be practical for routine clinical use. Often, questionnaires such as the Dialysis Diet and Fluid Questionnaire (DDFQ) are used but they frequently underestimate actual intake.

Guidelines currently recommend the intake of 500 to 1000 ml of fluid in addition to the estimated urine output from the previous day (58). However, distribution of water ingested depends on concomitant ingestion of salt. If no salt is ingested with water, water is evenly distributed among the fluid compartments but when salt is ingested more of the ingested water remains in the extra cellular compartment resulting in ECV expansion. A reduction in sodium intake results in marked reductions in thirst and weight loss in HD patients (59). Limiting fluid intake to 1000 ml per day translates to a daily weight gain of about 1 kg in HD patients.

Because of the importance of salt in contributing to volume status, KDIGO recommends that optimal intake should be less than 2 g per day (1). According to the Global Burden of Disease survey the mean intake of salt worldwide is 3.95 g daily with adults in 51 countries ingesting double the recommended amount daily (60). Control of total body sodium leads to improved hypertension control and reduction of its deleterious effects. This can be done by controlling the input through dietary restriction and reduction of dialysate sodium and increasing the output through ultrafiltration by convection (61). Limiting dietary sodium intake also leads to reduction in proteinuria, oedema, number of antihypertensive agents required and IDWG (62).

In practice, patients are frequently non-adherent to guidance provided by healthcare workers in fluid and salt intake. In a study that evaluated 916 patients in Germany and Belgium using the DDFQ, 81% of patients were non adherent to diet recommendations and 75% were non adherent to fluid restriction with increased IDWG reported in those who were non adherent (63). In a study done in India that evaluated 100 CKD patients using the DDFQ, 20% of the participants reported mild deviation from the recommendations with 22% of them having mild FO and 67% reported moderate deviations from recommendations with 69% of them having moderate FO (64).

During the initial stages of HD, use of antihypertensive agents in addition to HD leads to progressive weight loss with patients becoming euvolemic initially over the first 3 months. Over the next year, they gradually gain weight with increased muscle and fat but after this period there is a gradual decline of the BMI (65). A BMI of greater than 30 is associated with significantly lower FO with lower BMI associated with higher N-Terminal Pro Brain Natriuretic Peptide (NT Pro BNP) values. Lower BMI is associated with higher mortality with the highest risk in those with a BMI less than 20 (57). In a study that evaluated almost 7000 patients, weight loss resulted in increased mortality with weight gain improving survival in patients with lower BMI. However, the mortality benefit was attenuated in obese patients with them also not having any benefit of gaining weight (66).

A lower BMI has been reported to be a significant predictor of FO. It has been postulated that patients with higher BMI appear fluid overloaded due to their physique and thus tend to be misclassified to a higher hydration group even when they are normohydrated or dehydrated leading to persistent dry weight reduction. However, this is not the case with lean patients; they are more likely to be classified correctly according to their volume status. Furthermore, lower BMI has been associated with a higher NT pro BNP which has been used as a biochemical

marker for FO (57).Increased duration of dialysis has been associated with increased mortality up to 6 to 8 years after initiating HD with a reduction in mortality thereafter (53).

The Frequent Haemodialysis Network Trials reported that frequent HD leads to reduced BP, with daily HD there is reduced SBP by 7.7 mmHg and DBP by 3.9 mmHg (67). Their nocturnal trial also resulted in similar BP reductions when compared to thrice-weekly haemodialysis (68). It may thus be necessary to increase the frequency or duration of HD sessions to control BP in HD patients (51). Missing HD sessions leads to increased IDWG, depression and malnutrition with a reduction in quality of life (69).

In summary, according to the evidence presented above various factors may be associated with FO including BP, use of antihypertensive medication, BMI, fluid and salt intake, compliance to fluid and salt restriction, number of dialysis sessions, missed sessions of dialysis and duration of dialysis (dialysis vintage).

2.6 Justification

As the global prevalence of CKD rises, despite the paucity of local data, it is reasonable to expect that the prevalence of CKD locally will similarly be rising. The government, through the National Hospital Insurance Fund, has been improving the availability of RRT to the populace with at least 68 centres currently approved to provide HD under this scheme (70). These centres are distributed throughout the country and have led to the provision of dialysis services at grassroots level.

The hydration status of ESRD patients on chronic HD is an important independent predictor of mortality secondary only to the presence of diabetes (13). On the other hand with dehydration there is an increased frequency of intradialytic symptoms such as cramps and hypotension, cardiac stunning and depletion of any residual renal function (14).

Dilution techniques considered as the gold standard in fluid assessment are impractical for day-to-day use and more suited to controlled environments such as in a laboratory setting. Currently BIA is considered the best alternative for day-to-day assessment of fluid status of ESRD patients on HD. However, it is not widely available locally due to the high initial cost of purchase.

Locally, most centres use clinical assessment as the main tool for assessing fluid status. Though individual signs and symptoms lack adequate sensitivity to be used as stand-alone measures of FO, the use of graded symptoms and signs of FO in addition to radiographs may improve their sensitivity. Integrated clinical and radiographic information is readily available in most, if not all, dialysis units.

This study seeks to determine whether a graded CS based on a detailed clinical history and examination and a chest radiograph can be concordant with fluid status as assessed by BIA.

This CS utilizes elements of history, physical examination and investigations that are widely available locally.

If sensitive, the CS would provide a low cost alternative to reliably diagnose FO accurately even in low-resource settings at grassroots level. In addition, such a study has not been done in our setup. This study will provide information that would be useful for day-to-day clinical practice and can help shape health policy in our country.

Furthermore, it also seeks to determine the fluid status of patients undergoing HD at the renal unit in Kenyatta National Hospital (KNH) and looks into the factors associated with FO in ESRD patients on HD.

2.7 Research Question

Is there agreement in fluid status assessment between bio-impedance analysis and a clinical score in chronic kidney disease patients on maintenance haemodialysis at the renal unit in Kenyatta National Hospital?

2.8 Objectives

2.8.1 Broad Objective

To assess the level of agreement between bio-impedance analysis and a clinical score in fluid status assessment of chronic kidney disease patients on maintenance haemodialysis at the renal unit in Kenyatta National Hospital

2.8.2 Specific Objectives

i. To determine the level of agreement between bio-impedance analysis and a clinical score in fluid status assessment of chronic kidney disease patients on maintenance haemodialysis at the renal unit in Kenyatta National Hospital
ii. To assess the hydration status of chronic kidney disease patients on maintenance haemodialysis at the renal unit in Kenyatta National Hospital using bio-impedance analysis

2.8.3 Secondary Objectives

1. To determine the factors associated with fluid overload in chronic kidney disease patients on maintenance haemodialysis at the renal unit in Kenyatta National Hospital including:
    I. Duration of dialysis
    II. Having received education about and practice of fluid restriction
    III. Having received education on salt restriction
    IV. Body Mass Index
    V. Number of antihypertensive or diuretic medication

2.9 Hypothesis

There is no difference in the proportion of patients diagnosed to have fluid overload by bio-impedance analysis and the clinical score.

3 METHODOLOGY

3.1 Study Site

This study was performed at the renal unit in KNH, a national teaching a referral hospital located in the capital of Kenya, Nairobi. The hospital was established in 1901 and has a capacity of 1800 beds with over 6000 members of staff, and is the largest teaching and referral hospital in the country. It has 50 wards, 22 outpatient clinics, 24 theatres (16 specialised) and an accident and emergency department.

It serves as the national referral hospital providing specialised medical and surgical care and is the teaching hospital for the University of Nairobi where undergraduate, postgraduate and fellowship programs are offered including a fellowship in nephrology.

The renal unit in KNH was founded in 1972. It currently has 35 HD machines and runs weekly renal and transplant clinics. In conjunction with the surgical department, the unit has been running a transplant program since 1979, with 1 – 2 patients undergoing transplants per month currently. It also currently serves as the primary location for on-site training of nephrologists and nephrology nurses and works closely with the East African Kidney Institute (EAKI) that handles nephrology training at the University of Nairobi.

3.2 Study Design

This was a single centre hospital-based cross-sectional analytic study.

3.3 Study Population

The study population was patients with ESRD on maintenance HD at the renal unit of KNH.

There are 110 patients who are on maintenance dialysis at the hospital. When running at maximal capacity 140 patients are served daily on four-hour dialysis sessions. Each patient's fluid status is assessed before dialysis by a nurse assigned to them for their session using a dialysis sheet that includes an assessment of the patients' weight, their vital signs before, during and after dialysis and any laboratory tests availed. Doctors routinely review patients as they do their daily ward rounds and can change the dialysis prescription based on their determination of the fluid status of the patient and targeted dry weight.

3.4 Patient Selection

3.4.1 Definition of Terms

Adherence – Participants who had not missed any session of HD in the past 2 weeks or missed any of their prescribed antihypertensive medication in the past week and they were compliant to the fluid and salt restricted diet as prescribed.

Hydration status by BIA – based on the work of *Wabel et al* (71), the hydration status was defined as:

Normohydration – a patient with extracellular fluid ranging between -1.1 to 1.1 litres of normal (corresponding to -7% to 7% relative OH)

Dehydration – a patient with less than 1.1 litres of extracellular fluid below normal (corresponding to less than -7% relative OH)

Fluid overload - a patient with greater than 1.1 litres of extracellular fluid above normal (greater than 7% OH)

Mild fluid overload – A patient with 1.1 to less than 2.5 litres of extracellular fluid above normal (corresponding to 7% to 15% relative OH)

Gross fluid overload – A patient with more than 2.5 litres of extracellular fluid above normal (corresponding to greater than 15% OH).

$$\text{Relative over-hydration} = \frac{\text{Excess extracellular volume}}{\text{Actual extracellular volume}}$$

Maintenance haemodialysis – Haemodialysis for more than 3 months

Residual renal function – The ability to produce urine

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive + False negative}}$$

$$\text{Specificity} = \frac{\text{False positive}}{\text{False positive + True negative}}$$

False positive rate (FPR) = 1 – specificity

3.4.2 Inclusion Criteria

i. Patient with chronic kidney disease on maintenance haemodialysis
ii. 18 years of age and above
iii. Informed written consent of the patient

3.4.3 Exclusion Criteria

i. Patient who has undergone bilateral limb amputation
ii. Patient with a metallic prosthesis
iii. Patient with a pacemaker or metallic intravascular device
iv. Pregnant patients

v. Very sick patients – Any patient who in the judgement of the principal investigator (PI) would not be able to give a history (to enable completion of the study questionnaire) or who would not be able to give informed written consent

3.5 Study Methods

3.5.1 Sample size calculation

The sample size was estimated using the sample size formula for comparing paired proportions (McNemar's Z test, 2 sided equality) as outlined below (72):

$$n_{per\ test} = \left(\frac{Z_{\propto/2}\sqrt{p_{disc}} + Z_{\beta}\sqrt{p_{disc} - p_{diff}^2}}{p_{diff}} \right)^2$$

$$p_{disc} = (1 - Se_1) + (1 - Se_2)$$

$$p_{diff} = (1 - Se_1) - (1 - Se_2)$$

Where: $n_{per\ test}$ – Desired sample size for each test

$Z_{\alpha/2}$ – Critical value specifying the two-tailed 95% confidence level (1.96)

Z_{β} – Critical value specifying the statistical power of 80% that is desired (-0.84)

Se_1 and Se_2 – estimates of prevalence of fluid overload from literature

Se_1 – Prevalence of fluid overload by bio-impedance as determined by *Bajaber et al* in Eldoret (22) – 69%

Se_2 – Prevalence of fluid overload from clinical assessment using a clinical score by *Wizemann et al* (28) – 35%

When the above values were used, the calculated sample size was 69 patients.

3.5.2 Sampling technique

Systematic random sampling was used until the target sample size of 69 patients was attained. Since the calculated sample size was 69 and there are 110 patients on haemodialysis at the renal unit in KNH, every second patient who came for dialysis on a particular day was sampled for possible recruitment into the study.

Patients who had been recruited into the study were not considered during sampling at subsequent visits to the dialysis unit.

3.5.3 Screening and Recruitment

The PI perused the medical records of all the patients due for haemodialysis at the renal unit on a particular day and determined if they met the inclusion criteria. Those who were eligible were sampled as described before in the ‘sampling technique’. Those who were selected for inclusion in the study were called into a consultation room where study procedures were explained to them in a language that they understood and voluntary signed informed consent was obtained prior to enrolment into the study.

Once enrolled into the study, patients were requested to have a chest radiograph taken and reported on the day of their next session of dialysis, before dialysis (the costs of which were fully catered for by the PI). A history, physical examination and BIA was done as per the study questionnaire, on the same day as the chest radiograph, while in the renal unit before their session of dialysis.

All patients who undertook the study procedures were then informed of the results of their fluid analysis and a printout of the bio-impedance results put in the patient file to notify the clinicians' attending to them of their current fluid status.

It was estimated that with a 20% loss to follow up rate, 86 participants would have to be recruited to obtain the desired sample size of 69. However, due to a lower drop-out rate than expected (actual dropout of 2.4%), recruitment was stopped at 82 participants when it was clear that the intended sample size had been reached.

3.6 Study period

The study was carried out between March and April 2019.

3.7 Study variables

The outcome variable was volume status as determined by either BIA or the CS. The predictor variables included BMI (in Kg/m^2), blood pressure, use of antihypertensive agents, fluid intake, salt intake, number of dialysis sessions, missed HD sessions, dialysis vintage and adherence. An adherent patient was one who had not missed any sessions of dialysis in the 2 weeks prior to evaluation or any doses of scheduled antihypertensive medication in the week prior to evaluation and had received education on fluid and salt restriction that he/she was following.

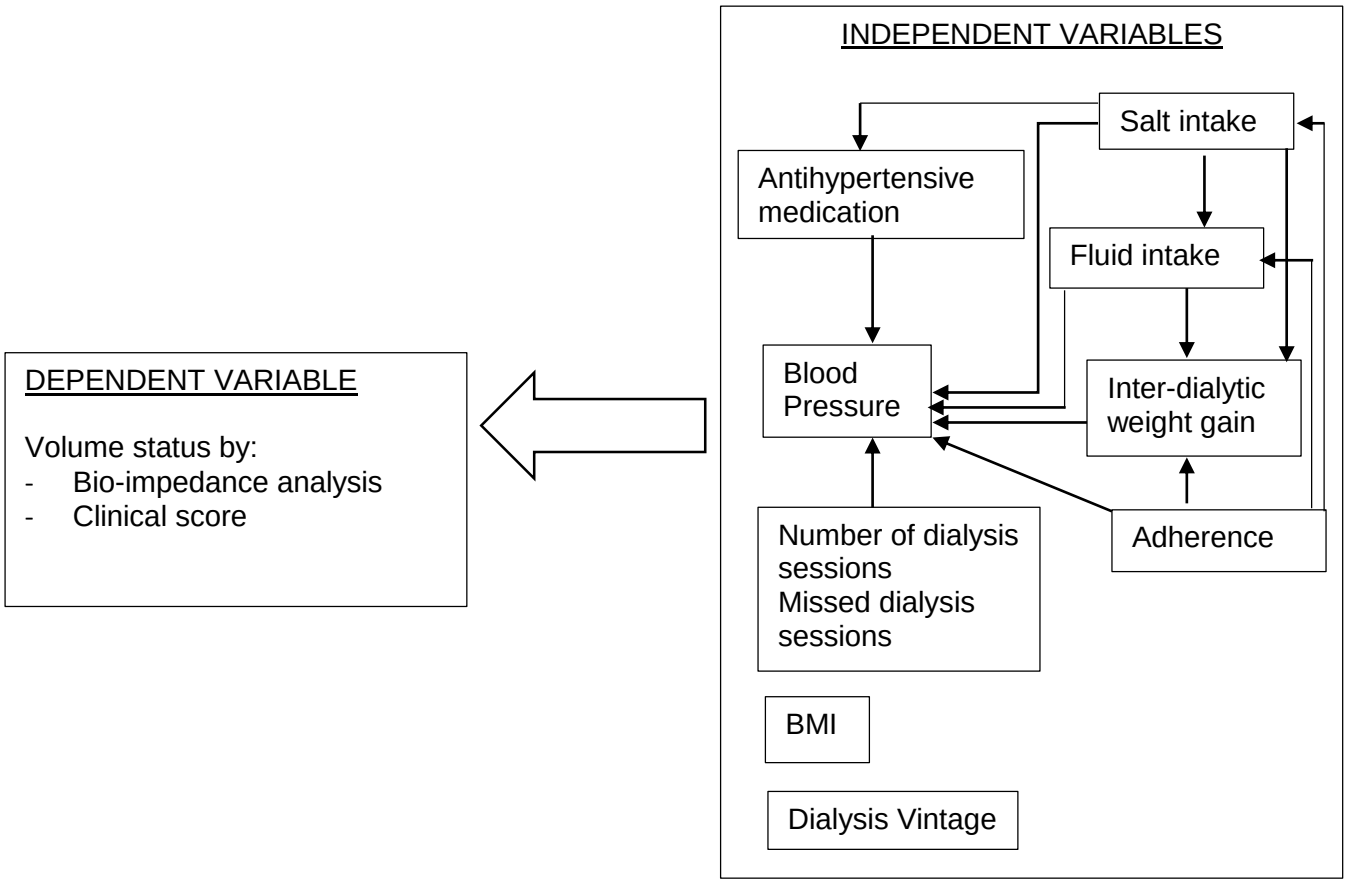

Figure 1: Conceptual framework

3.8 Data collection

3.8.1 Clinical methods

A predesigned questionnaire was used to obtain the patients demographics, history and thorough physical examination for the fluid status and to record the bio-impedance and chest radiograph data. All the assessment was before dialysis. The questionnaire was filled by the participant's assisted by the PI.

All the study data was obtained by the PI.

3.8.1.1 History and Examination

A detailed history was taken before the participant's session of dialysis including a history of symptomatic hypotension during the previous dialysis session and the level of exertional dyspnoea which was graded according to the New York Heart Association (NYHA) grading that classifies dyspnoea based on severity into grades 1 to 4 ranging from asymptomatic to dyspnoea at rest.

The participants were also asked about the duration since the diagnosis of CKD was made and the duration since start of dialysis. Their history of hypertension was obtained including the presence of hypertension and the number of antihypertensive or diuretic medication used. Furthermore, a history on prior education on salt and fluid use was obtained. Participants were also asked to estimate the amount of fluid consumed in day using the past 24 hours as a guide in the presence of the PI. The PI then estimated the amount of fluid consumed based description of the various cups used to drink them.

Oxygen saturation was obtained via a finger pulse oximeter. The patients were also assessed for the presence of ascites, pleural effusion and pulmonary oedema as per standard clinical practice.

The cardiovascular system was examined for the presence of a gallop rhythm and the level of oedema was graded depending on the severity from 1 to 4 as demonstrated in table 6 (73). The patient's grade was recorded as the highest whose signs the patient satisfied.

Table 6: A standardized method of assessing oedema

Sign / Grade	0	1	2	3	4
Visible	No	Yes	Yes	Yes	Yes
Pitting	No	Slight	More than slight	More than slight	“Can’t reach tibia”
Level	N/A	N/A	Below knee	Above knee	Above knee

Adapted from Nieman et al, 2013 (73)

3.8.1.2 Blood Pressure

Blood pressure was measured while seated in a quiet room using an appropriately sized cuff of a sphygmomanometer (74). Two readings were taken at least 5 minutes apart and an average determined.

Hypertension was defined as SBP greater than 140 mmHg or DBP greater than 90 mmHg, as per the 2012 KDIGO guidelines (75), while hypotension was defined as a SBP less than 90 mmHg or DBP less than 60 mmHg.

Intradialytic hypotension was defined as the presence of a decrease in systolic BP more than 20 mmHg or a decrease in mean arterial pressure by 10 mmHg that is associated with clinical events and need for nursing interventions (76).

3.8.1.3 Weight

Weight was measured using a digital scale placed on a firm flat surface with calibration done at the start and end of every measuring day. The participants were asked to remove heavy outer

garments and shoes and empty their pockets. They then stood in the middle of the platform and their weight determined and recorded in the study questionnaire to the nearest 0.5 Kilograms.

Furthermore, patients were asked about the weight after their last session of dialysis (to determine their IDWG) and their lowest ever weight to try to determine their dry weight.

3.8.1.4 Height

The height was measured with a standard stadiometer. The patients were asked to remove their shoes and any head dressing that may affect measurement. Two measures were taken and the average determined to the nearest centimetre.

3.8.1.5 Body Mass Index

The BMI was calculated based on the formula:

$$\text{BMI } (Kg/m^2) = \frac{\text{Weight (Kg)}}{\text{Height}^2\ (m^2)}$$

3.8.1.6 Radiographic assessment

A chest radiograph of the patient was obtained and assessed for markers of FO according to the stage.

Stage 1 – Dilated upper lobe veins, cardiomegaly

Stage 2 – Interstitial oedema (Kerley B lines)

Stage 3 – Alveolar oedema, pleural effusion

3.8.1.7 A clinical score of fluid status

A score of the fluid status of the patients was developed based on a score previously used by *Wizemann et al* (28). This score was modified by the PI in discussion with his supervisors to include other symptoms suggestive of dehydration during dialysis such as dizziness or fatigue not used by the previous investigators and simplifying the scoring of muscle cramps to a score of -1 instead of using grades of -1 to -4. In addition, the factors used to score FO were modified to include clinical and radiologic parameters such as presence of hypertension, pleural effusion or pulmonary oedema, ascites, gallop rhythm and oxygen saturation of less than 90% with chest radiograph features graded from 1 to 3 as shown in table 7. Furthermore, dyspnoea was graded using the NYHA classification. Individual participants were then scored as dehydrated, euvolemic or fluid overloaded where a negative score is considered to be dehydrated, a score of 0 normohydration and a positive score FO. The individual components used in the score were selected based on their utility as clinical signs and symptoms of the fluid status of HD patients.

The fluid status of the patients as determined by the CS was then correlated with the fluid status as determined by BIA and their level of agreement determined.

Table 7: A clinical score of fluid status

Symptoms		Score
Scored as dehydration	Intradialytic hypotension	-1
	Muscle cramps, dizziness or fatigue during current session of dialysis	-1
	Symptomatic dialysis hypotension treated by NaCl (0.9%) infusion	-1
Scored as normohydration	Absence of symptoms given in this table	0
Scored as fluid overload	Hypertension	+1
	SPO_2 less than 90%	+1
	Presence of ascites	+1
	Presence of pleural effusion or pulmonary oedema on clinical examination	+1
	Inter dialytic weight gain – per 1 kg gained	+1
	Presence of gallop rhythm	+2
	Dyspnoea based on NYHA class	0 to +3
	Chest radiography features based on stage	+1 to +3
	Oedema (ankles, tibial, graded)	0 to +4

3.8.1.8 Bio-Impedance Analysis

This was performed before dialysis after a history had been taken and the questionnaire filled. It was done by placing electrodes on one side of the body either left or right upper and lower limbs on the side without a fistula, if the patient had one, after lying supine for 10 minutes. A measurement of resistance and reactance was then determined based on the manufacturer's guidelines as outlined in Appendix 2. A second reading was obtained 5 minutes after the first and the two sets of values averaged. These values were then entered into a software and the fluid status determined based on the difference between the measured extracellular fluid and expected extracellular fluid. This was based on the fact that total body water accounts for 73% of body weight with intracellular fluid being 44% and extracellular fluid being 29% of body weight (77).

The machine used was the Quantum II bio-impedance analyser manufactured by RJL systems together with the BC 4 software from the same manufacturer. Using the values of resistance and reactance the software was able to compute total body water, intra- and extracellular volumes.

The BIA was done by the PI in accordance with the manufacturer's instructions on the use of the equipment. The procedure for using the machine is simple and has been outlined by the manufacturer as further described in Appendix 2. Furthermore, the PI had already been trained on how to use and calibrate the machine that was used in this study.

3.8.2 Quality control measures

All study procedures were only performed by the PI to reduce inter-observer bias.

The weighing scale was calibrated at the start and end of every research day.

The bio-impedance analyser was calibrated at the start and end of every research day. Calibration was carried out in accordance with the manufacturer's instructions as outlined in Appendix 2.

3.9 Data Management

The data collected was entered into a Microsoft Excel database and the hard copies of the forms stored in a locked cabinet to ensure privacy and security of the participant's information.

The data was coded, cleaned and transferred to STATA software for analysis.

Descriptive analysis of the patient characteristics and fluid status by CS and BIA was summarized in frequency tables. Mean, median, standard deviation and inter-quantile ranges were computed for continuous data while proportions were computed for categorical data.

Bio-impedance analysis was assumed to be the reference method to which the clinical score was to be compared. Data on the patients' clinical scores was summarized in a table comparing each individual score with the paired result on BIA (positive or negative for FO). Sensitivity and specificity of the clinical test was computed and summarized on the same table.

A Receiver Operating Characteristic (ROC) curve was plotted for scores obtained in order to establish the best cut-off point for determining FO using the CS (78).

Those above the best cut-off point on the clinical score were classified as positive for FO while those below the cut-off point were classified as negative. Data on patients' fluid status determined from the CS was summarized as proportions and percentages and presented in a table.

The proportion of patients classified as having FO by the clinical score and by BIA was summarized in a 2 by 2 contingency table and compared. To check for association between

assessment of fluid overload status by clinical score and BIA using these proportions, the McNemar's X^2 test of significance for paired data was computed.

If a non-significant McNemar's X^2 test was obtained, the level of agreement between the clinical score and BIA would be analyzed by computing the Cohen's kappa *(k*) statistic. Standard error, confidence interval and significance test for the *k* statistic were also to be calculated.

The association between each predictor variable collected and the outcome variable (fluid overload) assessed using BIA was analyzed by computing odds ratio (OR) and statistical tests of significance (chi-square, p-value and confidence intervals). The OR for the different predictor variables was compared. Data on possible confounders was analyzed using logistic regression with the outcome based on BIA.

Univariable and multivariable logistic regression was run to assess the factors associated with FO. A significance level of 0.20 was used in the univariable model and a significance level of 0.05 used in the multivariable model (79) (80). Hosmer-Lemeshow goodness of fit test was run to assess the logistic regression model (78).

3.10 Ethical Considerations

Permission to undertake this study was sought and obtained from the KNH/University of Nairobi Scientific and Ethical Review Committee under proposal number P822/012/2018.

Thereafter, authorization was obtained from KNH administration and a study registration certificate obtained for the same.

Patients were only enrolled into the study after the nature of the study including all tests to be undertaken has been fully explained to them in a language they understood and they agreed to participate in it.

Participation in the study was voluntary with no monetary gain for participants. Informed written consent was witnessed and signed by all who agreed to participate in the study.

No treatment was denied for those refusing to participate in the study, in addition their usual care was not be interrupted and where necessary was facilitated. Patients whose BP were noted to be high were encouraged to take their routine antihypertensive and referred to the renal unit staff for further management.

Confidentiality was adhered to by the PI. All identifiers were removed and patients given a study number.

All data collected was entered into a password-protected database under the custody of the PI.

The results of the study pertaining to the fluid status of participants were availed in the patients file for continued utilization in their care.

4 RESULTS

4.1 Demographic and clinical profile of study participants

A total of 100 patients were screened for inclusion into the study with 82 of them meeting the inclusion criteria. Of those recruited into the study, 2 participants' records were omitted from the final analysis due to incomplete data with both of them unable to get a chest radiograph on the day when clinical study procedures were to be carried out. This resulted in a final study population of 80 ESRD patients on maintenance HD for analysis.

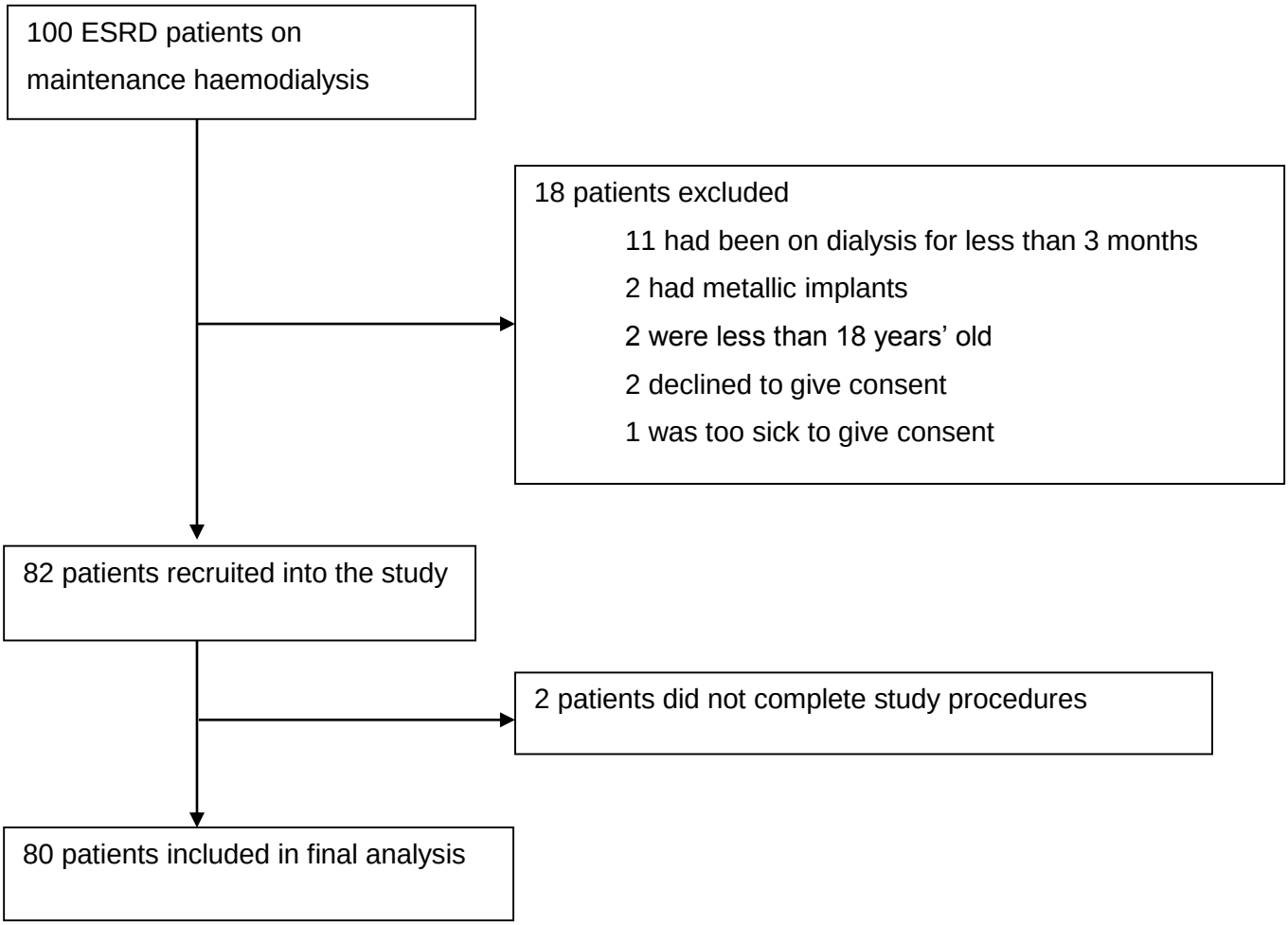

Figure 2: Study flow diagram for screening and recruitment

The study participants were aged 18 to 75 years with a mean age of 45.61 years. Male participants were 57.5% of the population with 63.75% having secondary level of education or higher. Those who were married were 71.25% and 93.75% had medical insurance cover that catered for the costs their dialysis sessions despite only 45% having employment at the time of the study. Most of the participants were residents of Nairobi (60%).

The mean SBP of the participants was 150 mmHg with 77.5% of the patients having systolic hypertension and 5% of the study population being hypotensive. On the other hand, mean DBP was 91 mmHg with 71.25% of participants having DBP more than 80 mmHg and 23.75% being normotensive.

The participants had a mean duration of CKD of 25.03 months with a range of 3 to 205 months, 32.5% of the patients had an arteriovenous fistula for dialysis. On average, the patients had 2 HD sessions a week with 95% of them having twice-weekly sessions. One study participant had 6 sessions during the week of review because he was scheduled for surgery as a renal transplant recipient during that period.

The study participants had a median dialysis duration of 9 months with an inter-quartile range (IQR) of 15 months (4 – 19). Those who had not missed any session of HD in the 2 weeks prior to participation in the study were 82.5% and 96% had residual renal function that was defined by the ability to produce urine. Median BMI was 21.94 with an IQR of 5.13 Kg/m^2 (19.5 – 25.63).

The mean actual fluid intake was 1010 ml with a range of 200 – 2800 ml, 90% of the patients had received education on fluid intake and 87.5% had received education on salt intake. The patients who were on 2 or 3 antihypertensive agents accounted for 55% with 76% of participants on a calcium channel blocker as part of their therapy.

Table 8: Demographic and clinical profile of study participants at the renal unit of KNH, 2019 (n=80)

VARIABLE	VALUES	MEDIAN	INTER-QUARTILE RANGE	MEAN	FREQUENCY n (%)
Age	18 – 75	45.0	20.5	45.61	-
Sex	Male	-		-	46 (57.5)
	Female	-		-	34 (42.5)
Level of education	None	-		-	1 (1.25)
	Primary	-		-	28 (35.00)
	Secondary	-		-	33 (41.25)
	Tertiary	-		-	18 (22.50)
Marital status	Single	-		-	11 (13.75)
	Married	-		-	57 (71.25)
	Divorced	-		-	8 (10.00)
	Widowed	-		-	4 (5.00)
Medical insurance	Yes	-		-	75 (93.75)
	No	-		-	5 (6.25)
Occupation	None	-		-	29 (36.25)
	Student	-		-	6 (7.50)
	Working	-		-	36 (45.00)
	Retired	-		-	9 (11.25)
Residence	Nairobi	-		-	48 (60.00)
	Kiambu	-		-	18 (22.50)

	Kajiado	-		-	3 (3.75)
	Muranga	-		-	2 (2.50)
	Nakuru	-		-	2 (2.50)
	Nyeri	-		-	2 (2.50)
	Other	-		-	5 (6.25)
AV fistula for dialysis	Yes	-		-	26 (32.50)
	No	-		-	54 (67.50)
SBP	81.5 – 239	149.00	34.25	150.31	-
DBP	46.5 – 154	90.75	25.25	91.39	-
Number of dialysis	1 – 6	2	0	2.01	-
sessions in a week	1	-		-	3 (3.75)
	2	-		-	76 (95)
	6	-		-	1 (1.25)
Residual renal	Yes	-		-	77 (96.25)
function	No	-		-	3 (3.75)

Sixty percent (60%) of patients were compliant as required to all facets of their management. This meant that they had not missed any session of HD in the past 2 weeks or missed any of their prescribed antihypertensive medication in the past week and they were compliant to the fluid and salt restricted diet as prescribed.

Table 9: Descriptive analysis of possible factors associated with fluid overload (n=80)

VARIABLE	VALUES	MEDIAN	IQR	MEAN	FREQUENCY n (%)
Duration of CKD (months)	3 – 205	12.5	24.5	25.03	-
Dialysis vintage (months)	3 – 76	9	15	14.78	-
Missed sessions of dialysis in the past 2 weeks	0	-		-	66 (82.50)
	1	-		-	10 (12.50)
	2	-		-	0
	3	-		-	2 (2.50)
	4	-		-	2 (2.50)
Education on fluid intake	Yes	-		-	72 (90.0)
	No	-		-	8 (10.0)
Actual fluid intake (ml)	200 – 2800	1000	450	1010.63	-
Education on salt intake	Yes	-		-	70 (87.50)
	No	-		-	10 (12.50)
Adding salt to food	Yes	-		-	6 (7.50)
	No	-		-	74 (92.50)
Antihypertensive agents used	0	-		-	11 (13.75)
	1	-		-	15 (15.00)
	2	-		-	26 (32.50)
	3	-		-	18 (22.50)
	4	-		-	7 (8.75)
	5	-		-	2 (2.50)
	6	-		-	1 (1.25)

Adherence	Yes	-	-	32 (40.0)
	No	-	-	48 (60.0)
BMI	Underweight	-	-	9 (11.25)
	Normal	-	-	52 (65.00)
	Overweight	-	-	18 (22.50)
	Obese	-	-	1 (1.25)

4.2 Volume status as determined by bio-impedance analysis

On average, the study participants had 3.02 L in excess of normal with a standard deviation of 1.79 L. The patients' volume status ranged from 0.53 L below to 8.23 L above normal with a median of 2.76 L. 88.75% of the participants were fluid overloaded with 57.5% of them having gross FO that is defined as having 2.5 L ECV above normal. Only 11.25% of the population was normovolemic with no patients being dehydrated when evaluated by BIA.

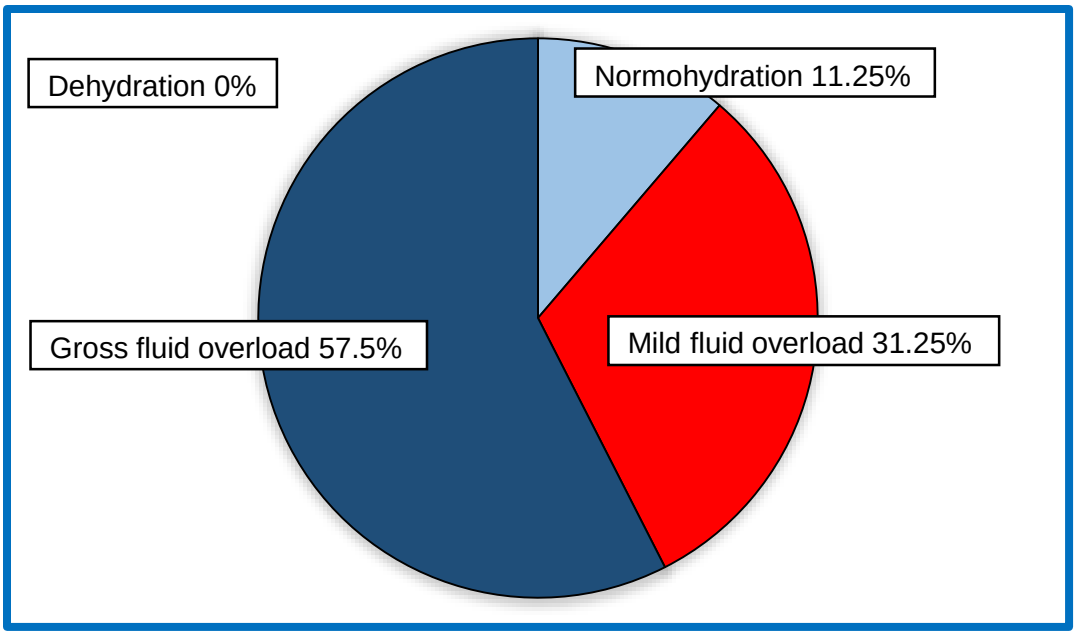

Figure 3: Volume status of study participants by BIA

4.3 Volume status by clinical score

The participants' clinical scores varied from -2 to 16 with a mean of 5.46 and a standard deviation of 3.68. All the possible values for the clinical score (-2 to 16) were used to generate sensitivity and FPR that were used to plot a ROC curve. From the ROC curve, the point closest to upper left corner was selected as the best cut-off point for the CS that was a cut-off of 4 as shown in figure 4.

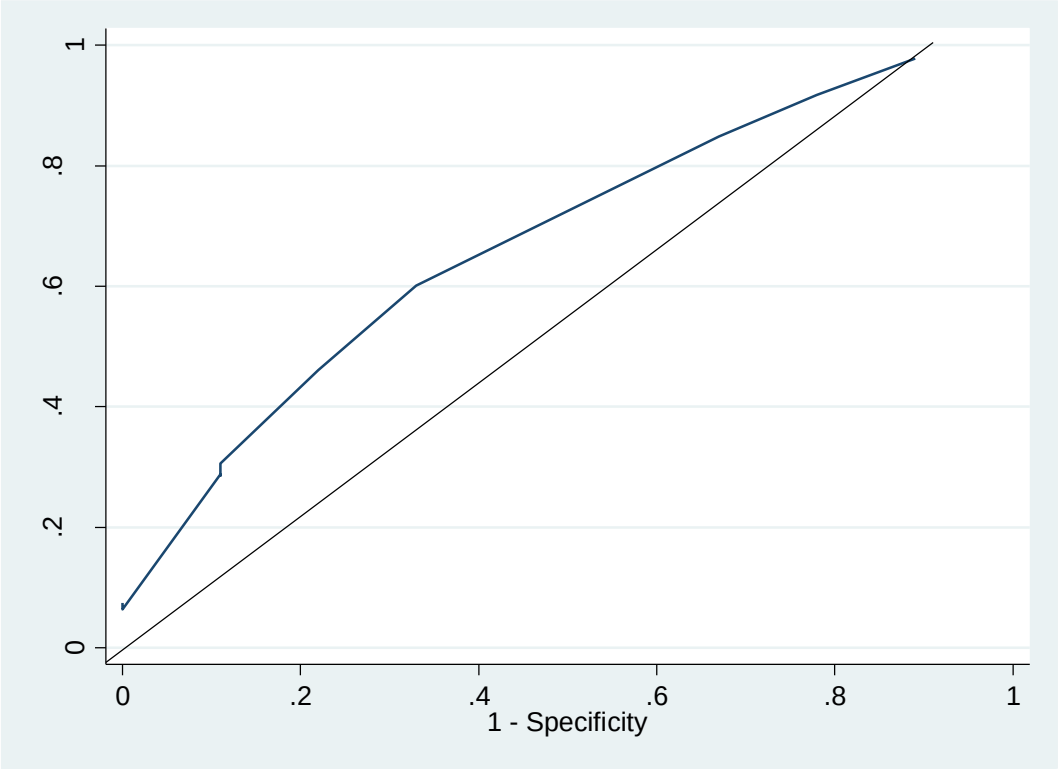

Figure 4: ROC curve for the clinical score

Table 100: 2 by 2 table of comparing patients with FO by BIA and CS at the best cut-off point

		Fluid status by BIA		
Fluid status by Clinical Score		Positive	Negative	Total
	Positive	45	2	47
	Negative	26	7	33
	Total	71	9	80

$$\text{Sensitivity} = \frac{45}{(45+26)} = 0.63$$

$$\text{Specificity} = \frac{7}{(7+2)} = 0.78$$

As shown in table 11, at the cut-off 4, the CS had a sensitivity of 63% and a specificity of 78%. Scores above 4 represented FO (58.75%) and scores of 4 and below represented those without FO (41.25%).

Table 111: Volume status of study participants by clinical score (n=80)

VARIABLE	VALUES	MEDIAN	IQR	MEAN	FREQUENCY n (%)
Volume status by clinical score	-2 – 16	5	4.25	5.46	-
	Fluid overload	-	-	-	47 (58.75)
	No fluid overload	-	-	-	33 (41.25)

4.4 Level of agreement between BIA and the clinical score

Fifty-two patients had the same result with BIA and CS, 45 with FO and 7 of them without. For 28 of the patients the 2 methods did not agree with 26 patients having FO by BIA but not by CS and 2 patients having FO by CS but not by BIA. A McNemar's chi square (X^2) was used to assess whether this observed difference was greater than what would be expected by chance.

The null hypothesis was that there was no difference in the proportion of patients diagnosed to have FO by BIA and CS. The calculated McNemar's X^2 was 20.57 with a p value <0.0001 (95% CI, 0.1758 – 0.4242). This leads us to reject the null hypothesis and provides strong evidence that BIA detects FO more than the CS. The true difference in proportion of patients diagnosed to have FO by the two methods lies between 17.58% and 42.42%.

Table 122: 2 by 2 table assessing association between BIA and the clinical score

BIO-IMPEDANCE ANALYSIS				
CLINICAL SCORE		**POSITIVE**	**NEGATIVE**	**TOTAL**
	POSITIVE	**45**	**2**	**47**
	NEGATIVE	**26**	**7**	**33**
	TOTAL	**71**	**9**	**80**
McNemar's Chi Square		**P value**	**95% Confidence Interval**	
20.57		<0.0001	0.1758 – 0.4242	

4.5 Factors associated with fluid overload

The mean dialysis duration of study participants was 14.78 months with a standard deviation of 16.08 months. Mean intake of fluid was 1010 ml daily with 10% of the patients not having received prior education on fluid intake and 12.5% having no prior education on salt intake. Eleven patients (13.75%) were not on any antihypertensive agents while 12.5% were on 4 or more agents.

Probable factors associated with FO were assessed using univariable and multivariable logistic regression. The factors that were assessed included duration of dialysis, whether a patient had been advised on fluid intake, a patient's actual fluid intake, whether they had been advised on salt intake, the number of antihypertensive agents they used if any and their BMI. Actual fluid intake, number of antihypertensive agents and BMI were analyzed as continuous variables.

From the univariable analysis, the duration a patient had been on dialysis, a patient's actual fluid intake and their BMI were the only factors found to be possible predictors of fluid overload diagnosed by BIA at 20% level of significance (P <0.20). These three factors were then added to the multivariable model.

Table 133: Univariable analysis of factors associated with fluid overload

VARIABLE	**VALUES**	**FO+ n=71**	**FO- n=9**	**OR**	**95% Confidence Interval**		**LRT P-value**
					Lower	Upper	
Duration of dialysis (months)[a]	3-76	71	9	1.05	0.967	1.147	0.13
Advised on Fluid Restriction	NO	6	2	Ref			
	YES	65	7	3.095	0.522	18.357	0.25
Actual Fluid In take (ml)[b]	200-2800	71	9	0.998	0.997	1.000	0.082

Advised on salt intake	NO	9	1	Ref			
	YES	62	8	0.8611	0.096	7.719	0.89
Number of antihypertensive agents used	0	11	0	Ref			
	1	13	2	0.903	0.537	1.517	0.70
	2	23	3				
	3	14	4				
	4	7	0				
	5	2	0				
	6	1	0				
Patient's BMI (kg/m^2)[c]	15.82-32.53	71	9	1.196	0.942	1.520	0.11

a, b, c: Variables eligible for inclusion in the multivariable model (P <0.20)

For the multivariable model, a stricter significance level of 0.05 was used. At this significance level, none of the factors assessed were found to be statistically significant. Therefore, none of these factors were found to be associated with fluid overload in the participants of this study.

Table 144: Multivariable analysis of factors associated with FO

VARIABLE	VALUES	OR	95% Confidence Interval		LRT P-value
			Lower	Upper	
Duration of dialysis (months)	3 – 76	1.054	0.962	1.154	0.258
Actual Fluid intake (ml)	200 – 2800	0.999	0.997	1.000	0.099
BMI (kg/m^2)	15.82 – 32.53	1.191	0.934	1.519	0.159

5 DISCUSSION

This study evaluated the fluid status of patients on maintenance HD at the renal unit in KNH using BIA. Of the 80 participants evaluated, 88.75% were fluid overloaded with 31.25% having mild fluid overload and 57.5% with gross fluid overload when assessed by BIA.

This proportion is higher than that reported during a study done at MTRH where 69% of the patients had fluid overload and 2% had ECV below normal (22). The investigators evaluated the prevalence of fluid overload of patients on HD for more than 3 months, by BIA assessment post dialysis, in patients who had achieved their dry weight in the opinion of attending healthcare workers. However, no clinical score was used to determine fluid status in their study. Several factors could explain the difference in proportion of patients with fluid overload in these two studies. One possible explanation is the exclusion of patients who had not attained their dry weight from their study making it is possible that they excluded patients who were more likely to be fluid overloaded. In addition, the BIA measurements were done post dialysis in the MTRH study compared to this study where it was done pre dialysis.

Passauer et al while assessing patients in 5 German dialysis centres reported 63% prevalence of fluid overload with 5% of patients dehydrated (20). In this study, they evaluated 370 patients before and after their midweek session of dialysis. However, they had a high proportion of diabetic patients (50%) compared to 17.5% in the current study. In addition, they used a body composition monitor (manufactured by Fresenius) that is a bio-impedance spectroscopy device that is different from the BIA machine used in this study. Furthermore, there may be differences in the populations with their study population having a mean age of 63 years (compared to 45 years in this study) and their study population being of European descent (compared to African descent in the current study). Dialysis was done thrice weekly compared to our study where it

was done twice weekly according to the dialysis unit's protocol. This reduced frequency of dialysis could account for the increased prevalence of FO relative to the other patient group.

Given that the hydration status of HD patients is an important predictor of mortality second only to the presence of diabetes with gross fluid overload being an additional independent predictor of mortality, it is worrying that most of the population of HD patients have fluid overload with almost 60% having gross fluid overload. Urgent steps need to be taken to rectify this for the benefit of the patients.

One of the main objectives of the study was to determine the level of agreement between BIA and the clinical score in maintenance HD patients at the KNH renal unit. There was a significant difference in the proportion of patients diagnosed to have fluid overload using BIA and the clinical score with a p-value of <0.0001. There was strong evidence that BIA detected fluid overload more than the clinical score. The best cut-off for the clinical score from the ROC curve was 4 with values above this signifying fluid overload.

This is similar to *Kalainy et al* (38) who reported that clinical parameters could not reliably predict the volume status of patient's pre-dialysis since they lacked the requisite sensitivity and specificity. In their study, they compared BIS to clinical parameters like BP, intradialytic hypotension, paradoxical hypertension during or after dialysis, pedal oedema and IDWG and biochemical parameters that included sodium, potassium, albumin, urea reduction ratio and cholesterol. They concluded that clinical assessment lacks precision to robustly assess fluid status. There are a few differences in the clinical evaluation done for the 2 studies, *Kalainy et al* evaluated dry weight, IDWG, pedal oedema and several measures of BP including pre and post dialysis BP, intradialytic hypotension and paradoxical hypertension. However, they did not evaluate oxygen saturation, presence of ascites, a gallop rhythm, pleural effusion or oedema or

any chest radiograph data. In addition, they did not weight or score the clinical or biochemical parameters in any way.

However, this differs from what *Wizemann and Schilling* reported when they compared fluid assessment by BIA, a clinical score and IVC diameter (28). In their study, 23 HD patients were followed up for mean period of 47± 4.9 weeks and the symptom score was recorded every 8 weeks by 2 nephrologists unaware of BIA results. They reported good agreement between BIA and the symptom score that was at 79% when clinical symptoms were shifting towards dehydration and 89% when towards fluid overload. The symptom score they used was similar to the one used in the current study in that it utilised symptomatic dialysis hypotension and the use of a saline infusion to manage that hypotension to score dehydration. They also used graded symptoms for dyspnoea and oedema to score fluid overload similar to our study. However, there are some differences in the scores in that *Wizemann et al* graded the severity of muscle cramps that was not done in our study. In addition, our study included hypertension, oxygen saturation by a finger pulse oximeter of less than 90%, presence of ascites, pleural effusion, pulmonary oedema or gallop rhythm and graded chest radiograph findings to score fluid overload that were not used by *Wizemann et al*. However, they performed BIA and IVC diameter after the session of dialysis when the clinical score had been carried out compared to the current study where both the BIA and clinical score were done pre dialysis.

Similarly, *Vasko et al* (27) evaluated clinical judgement guided by a systematic clinical approach that included a history, symptoms, laboratory parameters and routine diagnostic tests (echocardiography, ultrasonography and chest radiographs) compared to multi-frequency BIA in assessing pre-dialysis over hydration. They found that clinical judgement was the most important factor in over hydration assessment. Though they did not use a score, the data utilised is similar in many respects since both studies used patient history and examination and

chest radiograph data to inform clinical decision making compared to BIA. However, we did not use laboratory information as part of the clinical score in this study.

All the participants were evaluated at baseline without regard to prior symptoms or determining whether their dry weight had been achieved and this could probably affect the sensitivity and specificity of the clinical score. Including only asymptomatic patients and scoring the symptoms as they appear de novo would probably improve the sensitivity and specificity of the score as would only scoring symptoms that disappear on correction of volume status of the participant.

We also evaluated several factors for association with fluid overload including duration of dialysis, education about and practice of fluid restriction, education on salt restriction, BMI and number of antihypertensive agents used. In the univariable model, duration of dialysis, actual fluid intake and BMI showed a probability of association with fluid overload and were subsequently included in the multivariable model. When multivariable logistic regression was done, none of the factors was found to be statistically significant.

The fact that none of the factors were significant is similar to *Tapolyai et al* (55) who also found that BMI and duration of dialysis were not significantly associated with fluid overload. However, they found that number of antihypertensive agents used and the use of diuretic agents were associated with fluid overload in contrast to our study. In our study, 15.38%% of the patients were on diuretic agents. The use of different classes of agents to control the blood pressures in the two populations could probably account for the difference in significance. In addition, we cannot rule out there being differences on the populations with the population in comparison being from Hungary.

Previous studies have reported association between non adherence to fluid restriction being associated with fluid overload (63) (64). However, these studies both used the DDFQ which was not used in the current study with one of the populations being from Europe (63) and another

from India (64). The use of a standardised tool probably improved their sensitivity in detecting non-adherence and probably led to the difference in outcomes compared to the current study.

These results are also not in keeping with *Antlanger et al* who studied 244 patients in 3 centres in Vienna and reported that fluid overload had a significant negative correlation with BMI (57). This could probably be due to differences in the populations with the mean age being 58 years compared to 45 years in the current study and a lower mean BMI of 22.21 in this study (compare to 25.9 Kg/m^2).

5.1 Conclusion

The findings of this study show that a high proportion of patients on maintenance haemodialysis at the renal unit of Kenyatta National Hospital are fluid overloaded.

Furthermore, there was strong evidence that BIA detected fluid overload more than the clinical score at the best cut-off for the clinical score of 4.

None of the factors assessed in this study had a statistically significant association with fluid overload.

However, as these findings are from a small sample in a single centre, it is necessary to validate them using a larger multicentre study.

5.2 Strengths

1. This is the first study to evaluate the fluid status of patients on chronic HD at the renal unit in KNH using BIA.
2. This study evaluated the performance of a clinical score in fluid status assessment whose components are easily available and affordable even at grassroots level.

5.3 Limitations

1. The sample size of 80 patients is small and resulted in wide confidence intervals in the results decreasing the precision of the study.
2. This was a single centre study.
3. This study utilised a questionnaire to gather information and this may be subject to recall bias.
4. A single assessor evaluated all the study participants.

5.4 Recommendations

1. Use of bio-impedance analysis should be incorporated into the routine care of patients on maintenance haemodialysis in this population since it detects fluid overload more frequently than the clinical score.
2. More studies should be done to evaluate the performance of the clinical score in larger and more diverse populations.

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7 APPENDICES

7.1 APPENDIX 1: STUDY QUESTIONNAIRE

Study Identification Number ……

CAUTIONS/EXCLUSIONS

(Exclude if the answer to any of no. 1 – 6 is yes)

1. Do you have any metallic implants? Yes ☐ No ☐
2. Do you have a pacemaker? Yes ☐ No ☐
3. Are you pregnant? Yes ☐ No ☐

   If no to 3 above (female respondents):

4. LNMP? ……
5. Have you taken alcohol in the last 12 hours? Yes ☐ No ☐
6. Have you done extraneous exercise or been in a sauna in the last 8 hours?

   Yes ☐ No ☐
7. When was your last meal? <2 hrs ago ☐ 2-4 hrs ago ☐ >4 hrs ago ☐

   (Exclude if less than 2 hours, if between 2 and 4 hours wait for 4 hours to elapse since feeding, include if 4 hours after feeding)
8. Do you have an arteriovenous fistula? Yes ☐ No ☐

   If yes to 8 above,
9. On which side is the arteriovenous fistula? Right ☐ Left ☐

   (Perform BIA on the side without an AV fistula if present)

10. Temperature? ……
11. Date ……

BIODATA

12. Date of Birth ……

13. Age ……

SOCIO-DEMOGRAPHICS

14. Sex Male ☐ Female ☐

15. Education level: None ☐ Primary ☐ Secondary ☐ Tertiary ☐

16. Marital Status Single ☐ Married ☐ Divorced ☐ Widowed ☐

Separated ☐

17. Do you have medical insurance? Yes ☐ No ☐

18. Residence ……

19. Occupation ……

MEDICAL HISTORY

Chronic Kidney Disease

20. Time since diagnosis of Chronic Kidney Disease (Months) …….....

21. Did you have any of the following before the diagnosis of Chronic Kidney Disease?

Diabetes ☐ Hypertension ☐ Obstructive uropathy ☐

HIV ☐ Medication use ☐ Cancer ☐

Vascular Disease ☐ Glomerular disease ☐

Unrecovered Acute Kidney Injury ☐ Congenital defect ☐

Cystic Kidney Disease ☐ Heart disease ☐

Liver disease ☐

Other

……

……

22. Duration since start of dialysis? (Months) .....

23. How many times do you attend dialysis in a week?

1 ☐ 2 ☐ 3 ☐ >3 ☐

24. How many sessions of dialysis have you missed in the past 2 weeks? .....

25. Duration since last session of dialysis (days)? ……

26. Have you had any of the following complications during you last dialysis session:

Dizziness ☐ Muscle cramps ☐ Fatigue ☐

Low blood pressure ☐ Loss of consciousness ☐

Others

……

……

27. Do you produce urine? Yes ☐ No ☐

28. Have you been educated on daily fluid intake? Yes ☐ No ☐

29. What amount of fluid do you usually take in a day (ml)? ……

30. Have you been educated on salt intake? Yes ☐ No ☐

31. Do you add salt to your food? Yes ☐ No ☐

32. Are you on any anti-hypertensive medication? Yes ☐ No ☐

If yes list them

……

……

……

……

33. Do you miss any of your scheduled medication?

None ☐ 1 missed dose per week ☐ 2 missed doses per week (etc.) ☐

Fluid status

34. In the past week (or since you last session of dialysis) have you experienced any dyspnoea?

Dyspnoea: NYHA I ☐ NYHA II ☐ NYHA III ☐ NYHA IV ☐

PHYSICAL EXAMINATION

General examination

Seated blood Pressure (mmHg)	Systolic	Diastolic
1st Reading		
2nd Reading		
35. Average		

36. Pulse rate …….....

37. Respiratory rate ……

38. Oxygen saturation (SPO_2) ……...

39. Height (Meters) ……

40. Weight (Kilograms) ……

41. BMI ……

42. Lowest ever weight ……

43. Weight after last session of dialysis ……

44. Inter dialytic weight gain *(Current weight – Weight after last session of dialysis)*

……

45. Oedema: Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐

Systemic Examination

Respiratory System

46. Any evidence of a pleural effusion? Yes ☐ No ☐

47. Any evidence of pulmonary oedema? Yes ☐ No ☐

Cardiovascular System

48. Presence of gallop rhythm Yes ☐ No ☐

Abdomen

49. Any evidence of ascites? Yes ☐ No ☐

Chest radiography

50. Any evidence if fluid overload? Yes ☐ No ☐

If yes, what stage: Stage 1 ☐

Stage 2 ☐

Stage 3 ☐

CLINICAL SCORE OF FLUID STATUS

Symptoms		Possible Score	Actual Score
Scored as dehydration	1. Intradialytic hypotension	-1	
	2. Muscle cramps, dizziness or fatigue during current session of dialysis	-1	
	3. Symptomatic dialysis hypotension treated by NaCl (0.9%) infusion	-1	
Scored as normohydration	4. Absence of symptoms given in this table	0	
Scored as fluid overload	5. Hypertension	+1	
	6. SPO_2 less than 90%	+1	
	7. Presence of ascites	+1	
	8. Presence of pleural effusion or pulmonary oedema on clinical examination	+1	
	9. Inter dialytic weight gain – per 1 kg gained	+1	
	10. Presence of gallop rhythm	+2	
	11. Dyspnoea based on NYHA class	0 to +3	
	12. Chest radiography features based on stage	+1 to +3	
	13. Oedema (ankles, tibial, graded)	0 to +4	
14. Total			

BIO-IMPEDANCE

	Resistance	Reactance
1st reading		
2nd reading		
1. Average		

(Values below derived from BC4 software)

2. Total body water ..…….…….....
3. Intracellular fluid ……
4. Extracellular fluid ……
5. Expected extracellular fluid ……
6. Excess extracellular fluid ……
7. Relative over hydration ……

7.2 APPENDIX 2: MANUFACTURER'S INSTRUCTIONS

BIO-IMPEDANCE TESTING PROCEDURE

The exam area should be comfortable and free of drafts and portable electric heaters.

The exam table surface must be non-conductive and large enough for the subject to lie supine with the arms 30 degrees from the body and legs not in contact with each other.

The analyser battery should be a new 9-volt battery or recently charged.

The analyser calibration and patient cables should be checked regularly.

CALIBRATION

Frequent calibration does not cause any problem to the machine.

When to calibrate the machine

I. When the battery is replaced
II. When the BIA measurements appear unusual
III. When the subject cable may have incurred damage
IV. Prior to a large number of tests for a study

Procedure

i. Attach the 500-ohm resistor as shown in figure 3
ii. Turn the instrument on and note the resistance value displayed – it should be between 495 and 505 ohms
iii. Switch the instrument to reactance measurement and note the value displayed – it should be between -003 and 003.

iv. If the readings are between these values, it indicates the impedance circuits are in good working order

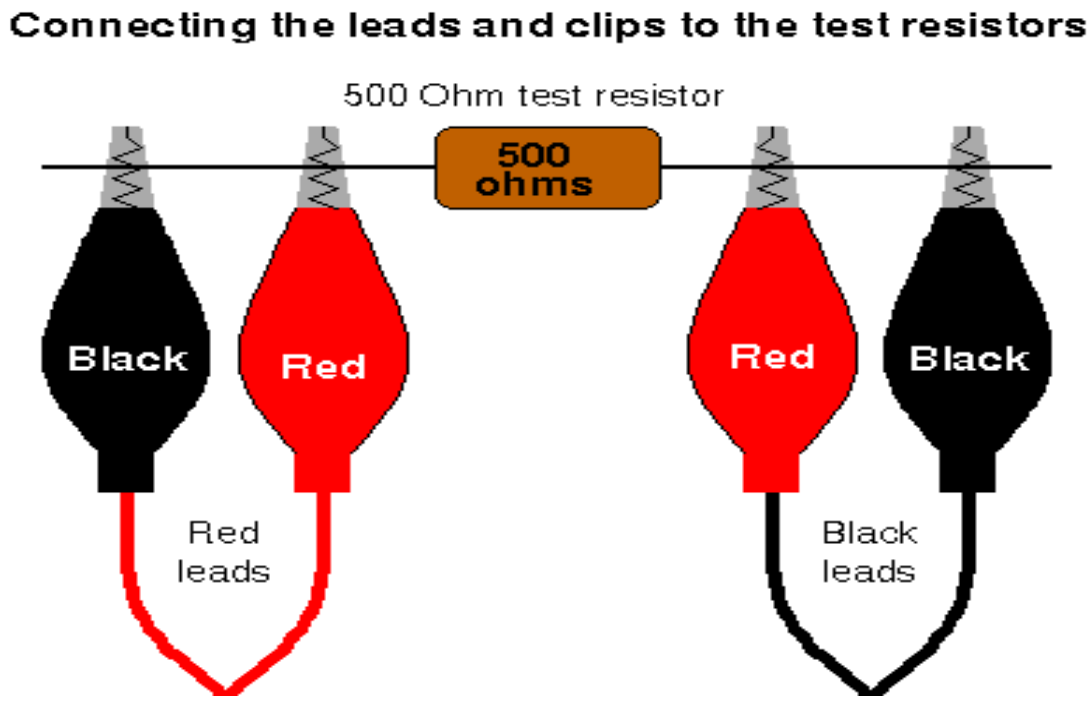


Figure 5: Calibration of bio-impedance analyser

SUBJECT PREPARATION

The subject should not have exercised or taken a sauna within 8 hours of the study.

The subject should refrain from alcohol intake for 12 hours prior to the study.

The subject's height and weight should be accurately measured and recorded.

The subject should lie quietly during the entire test.

The subject should not be wet from sweat after exercising.

The subject should not have a high temperature or be in shock.

TESTING PROCEDURE

The subject should remove the right shoe and sock (the study is generally completed on the right side of the body), whichever side is used should always be used subsequently.

The subject should lie supine with their arms 30 degrees from their body and legs not touching and remove jewellery on the electrode side.

The electrode sites may be cleaned with alcohol, particularly if the skin is dry or covered with lotion.

Attach the electrodes and patient cables as shown in the illustration.

Turn the analyser on and make sure the subject refrains from moving after the measurements have stabilized. Read the displayed Resistance (R) and Reactance (Xc) and record the subject's name, age, gender, height and weight.

Remove and dispose of the electrodes, be careful not injure the subject's skin or contaminate the operator.

The entire testing time is less than 5 minutes - the BIA analyser is on for less than one minute.

The results are available immediately from the software program.

The study may be repeated as often, as necessary.

Operator/examiners must demonstrate the following level of proficiency:

Two consecutive measurements made on a single, stable subject must result in values within one percent.

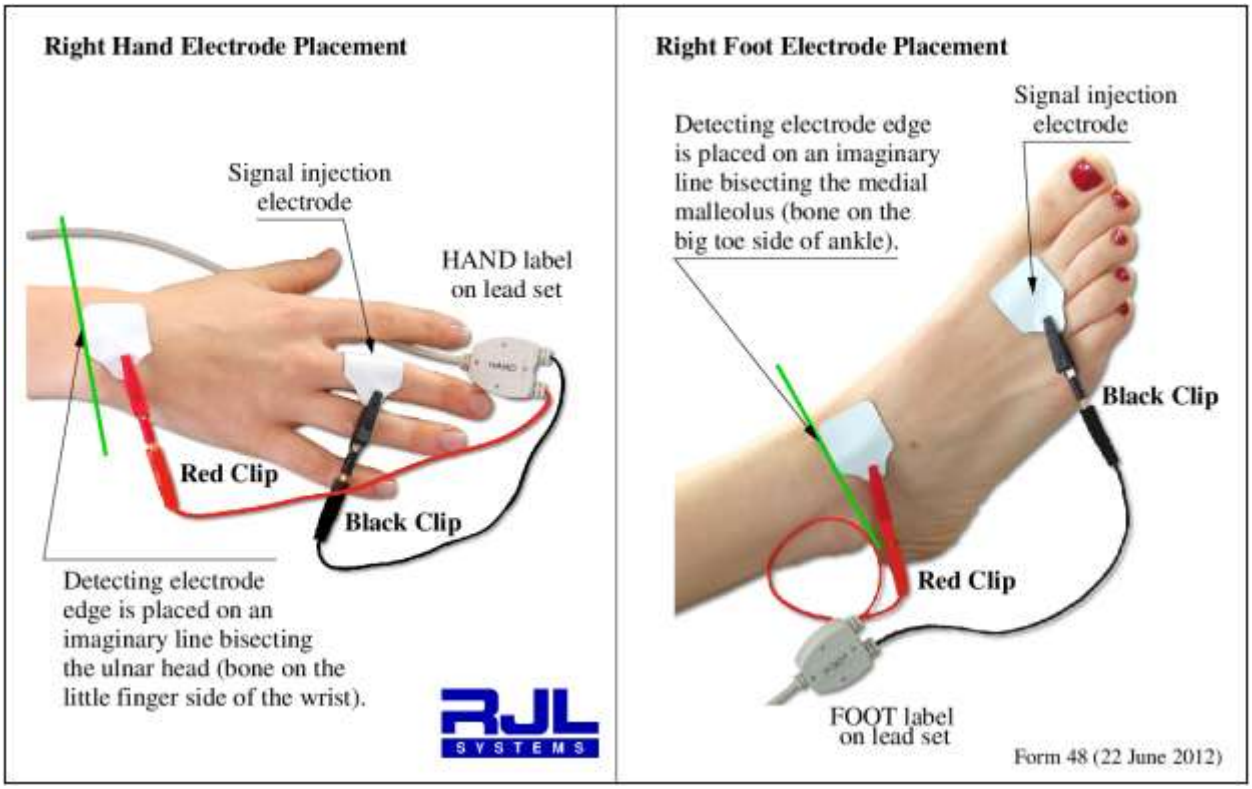


Figure 6: Electrode placement

7.3 APPENDIX 3: STATEMENT OF INFORMATION FORM

Study Title: DETERMINATION OF CONCORDANCE BETWEEN BIO-IMPEDANCE ANALYSIS AND A CLINICAL SCORE IN FLUID STATUS ASSESSMENT OF CHRONIC KIDNEY DISEASE PATIENTS ON MAINTENANCE HAEMODIALYSIS

Study Number: P822/12/2018

Investigator: Dr. Kamiti Muchiri (H58/87308/2016)

Resident in Internal Medicine, University of Nairobi

Phone: 0710287488, email: kamitimuchiri@yahoo.com

Supervisors: Prof. J.K. Kayima,

Department of Clinical Medicine and Therapeutics, University of Nairobi

Prof. E. N. Ogola

Department of Clinical Medicine and Therapeutics, University if Nairobi

Prof. S. O. McLigeyo,

Department of Clinical Medicine and Therapeutics, University of Nairobi

PURPOSE

I intend to carry out a study on patients on dialysis at Kenyatta National Hospital to identify those with too much fluid. I will check the amount of fluid in your body using two methods and compare them. The study will include patients who are 18 years and above who have been on dialysis for more than 3 months, who are not pregnant and do not have any metallic implants.

PROCEDURES

The study will be conducted through a set of questions from the investigator. Thereafter you will have a clinical examination done including measurement of your blood pressure, height and weight and then you will be connected to a machine that will measure the amount of fluid in your body. You will not feel any pain during this process but you may feel a small electrical current when the machine is switched on.

In addition, you will be sent for a chest x-ray for which you will not be charged any fee.

SAFEGUARDING PRIVACY

I pledge to keep your information secure. Your name will be removed from all the records of the study and a study number assigned to you instead.

Only people involved in the study will have access to our information.

I will not use your name when reporting the results of this study.

BENEFITS

By taking part in this study you will help us determine the amount of fluid in patients on dialysis and the best way of checking if you have excess fluid in your body.

If I find that you have too much or too little fluid in your body, the medical practitioners involved in your day-to-day care will be adequately informed and measures taken to correct this.

This will not only be of benefit to patients here in Kenyatta but also in the rest of the country.

RISKS

You will be exposed to a small amount of radiation while the chest x-ray is being done. However, this is a routine medical test and you do not have any greater risk compared to anyone else undergoing the same test.

You may feel a small electric current when the machine is switched on however this will cause no pain.

Should you have any complication that requires medical attention during the study, we undertake to provide the necessary care free of charge.

If you have any further question about this research you can call Dr. Kamiti Muchiri on 0710287488.

If you have any questions regarding your rights as a participant in this research you can contact Professor Chindia M. L., secretary KNH/UoN ERC by calling Tel 2726300 ext. 44102 Nairobi.

7.4 APPENDIX 4: TAARIFA YA HUDUMA

Kichwa cha Utafiti: DETERMINATION OF CONCORDANCE BETWEEN BIO-IMPEDANCE ANALYSIS AND A CLINICAL SCORE IN FLUID STATUS ASSESSMENT OF CHRONIC KIDNEY DISEASE PATIENTS ON MAINTENANCE HAEMODIALYSIS

Nambari ya Utafiti: P822/12/2018

Mchunguzi: Dr. Kamiti Muchiri (H58/87308/2016)

Mwanafunzi katika Idara ya Tiba ya Ndani, Chuo Kikuu cha Nairobi

Simu ya rununu: 0710287488, barua pepe: kamitimuchiri@yahoo.com

Wasimamizi: Prof. J.K. Kayima,

Idara ya Tiba ya Ndani, Chuo Kikuu cha Nairobi.

Prof. E. N. Ogola

Idara ya Tiba ya Ndani, Chuo Kikuu cha Nairobi.

Prof. S. O. McLigeyo,

Idara ya Tiba ya Ndani, Chuo Kikuu cha Nairobi.

UTANGULIZI

Mimi ni Dkt. Kamiti Muchiri, kutoka Chuo Kikuu cha Nairobi. Kwa sasa ninasomea uzamili katika Tiba ya Ndani. Sehemu moja ya masomo yangu ya uzanifu ni kwa kufanya utafiti. Ninafanya uchunguzi kuhusu kiwango cha maji yaliyo ndani ya mwili wa mgonjwa anayefanyiwa usafishaji wa damu.

LENGO

Lengo la utafiti huu ni kuamua kiwango cha maji yaliyo ndani ya mwili wa mgonjwa anayesafishwa damu na kutambua ni njia gani inayofaa kutumika kwa kupima wagonjwa wetu.

TARATIBU ZITAKAZO HUSISHWA

Ukikubali kushiriki katika utafiti huu utaulizwa maswali kulingana na fomu ya utafiti. Baada ya hapo utapimwa na daktari kwa kuchunguzwa mwili, kupimwa urefu na uzito na shinikizo la damu. Pia utawekwa kwenye mashine ya kuangalia kiwango cha maji mwilini. Ukimaliza hayo, utatumwa kupigwa picha ya kifua ambayo utarejeshea daktari ili aweze kuitafsiri bila kulipishwa chochote.

HAKI YAKO KAMA MSHIRIKI KATIKA UTAFITI HUU

Ushirika wako katika utatafti huu ni wa kujitolea.

Kuitikia kushiriki au kukataa kushiriki katika utafiti huu hautaathiri matibabu yako.

Unaweza kujiondoa kutoka utafiti huu wakati wowote.

Una uhuru wa kuuliza maswali kabla ya kutia sahihi yako katika fomu ya idhini na pia wakati wowote utafiti unapoendelea.

Maswala yote yatahifadhiwa kwa siri wakati wote.

MANUFAA YA USHIRIKI

Baada ya kufanya utafiti huu, tutaweza kujua kiwango cha maji yaliyo ndani ya miili ya wagonjwa wanaosafishwa damu hapa Hospitali ya Kenyatta.

Isitoshe tutakapojua hali ya maji yaliyo ndani ya mwili wako, tutawafahamisha madaktari wanaozingatia huduma yako ya kila siku ili wachukue hatua zinazofaa.

HASARA ZA USHIRIKI

Utakapo pigwa picha ya kifua, mwili wako utawekwa wazi kwa mionzi. Lakini hii ni picha inayofanywa kwa watu wengi bila madhara.

Ukipata shida yoyote kutokana na utafiti huu gharama ya matibabu yako itashughulikwa na mtafiti.

Ukiwa na swali lolote wakati wa utafiti unaweza kuwasiliana na wafuatao:

Dkt. Kamiti Muchiri, Chuo Kikuu cha Nairobi, Idhara ya mafundisho ya udaktari na matibabu ya mgonjwa, Simu ya mkono 0710287488 *AU*

Mwenyekiti, KNH/UoN Kamati inayoshughulikia Maadili, nambari ya simu 020-2726300/0722829500/0733606400/EXT 44102, sanduku la ofisi ya posta 20723, Nairobi.

7.5 APPENDIX 5: INFORMED CONSENT FORM

RESPONDENT AGREEMENT

The study has been explained to me. My questions have been answered. I have understood what it is about and I give consent to participate.

I understand that participation in the study is voluntary and there will be no penalty for declining to participate in the study.

I also understand that if I choose to stop participating at any point in the course of the study, I will still continue to receive the care and treatment that I am currently undergoing.

I have been informed that if I have questions about this study or my rights as a participant in the study, I may contact Dr. Kamiti Muchiri on 0710287488.

I have also been informed that the information I give to the investigator will be confidential.

Respondents signature ……

Phone number ……

Date ……

Interviewers signature ……

Date ……

Study Identification Number …..……....

CONTACTS OF THE INVESTIGATOR

Dr. Kamiti Muchiri

University of Nairobi,

P.O. BOX 30197-00100

Email: kamitimuchiri@yahoo.com

Phone: 0710287488

LEAD SUPERVISOR

Prof. J.K. Kayima

University of Nairobi,

P.O. BOX 30197-00100

Email:kaimajk@gmail.com

Phone: 0733730650

Kenyatta National Hospital/University of Nairobi Ethics and Review Committee Contacts

Prof L Chindia. Tel 2726300 Ext 44102

Email: uonknh_erc@uonbi.ac.ke

7.6 APPENDIX 6: FOMU YA RIDHAA YA TAARIFA

AHADI YA MHUSIKA

Muktadha wa utafiti huu umeelezwa na kufafanuliwa kwangu. Maswali niliyo nayo kuhusu muktadha huu yamejibiwa.

Nimeelewa chanzo cha utafiti huu na kukubali kuwa muhusika.

Zaidi, ninaelewa kwamba nimekubali kuhusika kwa utafiti huu bila kulazimishwa na nisipoitikia kuhusika na utafiti huu hakutakuwa na adhabu yoyote.

Ninaelewa kwamba nina hiari kujiondoa kwenye utafiti huu wakati wowote bila kuhatarisha matibabu yangu.

Isitoshe, ninafahamu kuwa iwapo nina maswali kuhusu utafiti huu, maswali hayo yataweza kujibiwa na mtafiti mkuu Dkt. Kamiti Muchiri kwenye nambari 0710287488.

Aidha, nimeelewa kwamba habari nitakayomwambia mchunguzi wangu itakuwa ya siri.

Sahihi ya mshirika ……

Nambari ya simu ……

Tarehe ……

Sahihi ya mchunguzi ……

Tarehe ……

Utangulizi wa utafiti ……

MKUU WA UCHUNGUZI

Dkt. Kamiti Muchiri

Chuo Kikuu cha Nairobi,

S.L.P. 30197-00100

Barua pepe: kamitimuchiri@yahoo.com

Rununu: 0710287488

MSIMAMIZI WA UCHUNGUZI

Prof. J.K Kayima

Chuo Kikuu cha Nairobi,

S.L.P. 30197-00100

Barua pepe:kaimajk@gmail.com

Rununu: 0733730650

KNH/UoN Kamati inayoshughulika na Maadili

Prof L Chinda. Simu 2726300 Ext 44102

Rununu: uonknh_erc@uonbi.ac.ke

7.7 APPENDIX 7: ETHICS COMMITTEE APPROVAL LETTER

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

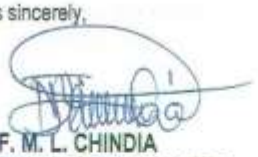
1. Name of the Principal Investigator/Researcher
   KAMITI MUCHIRI
2. Email address: kamitimuchiri@gmail.com Tel No. 0710287488
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
   DETERMINATION OF CONCORDANCE BETWEEN BIOIMPEDANCE ANALYSIS AND A CLINICAL SCORE IN FLUID STATUS ASSESSMENT OF CHRONIC KIDNEY DISEASE PATIENTS ON MAINTENANCE HEMODIALYSIS
6. Department where the study will be conducted RENAL UNIT
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the KNH Department where the study will be conducted.
   Name: Nancy Kigen Signature [signature] Date 16/4/19
8. Endorsed by KNH Head of Department where study will be conducted.
   Name: Dr Dawn Price Signature [signature] Date 16/4/19
9. KNH UoN Ethics Research Committee approved study number P822/012/2018
   (Please attach copy of ERC approval)
10. I KAMITI MUCHIRI commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
    Signature [signature] Date 08/04/19
11. Study Registration number (Dept/Number/Year) Renal /93 /2019
    (To be completed by Research and Programs Department)
12. Research and Program Stamp

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.

Version 2: August, 2014

For more details consult the KNH- UoN ERC website http://www.erc.uonbi.ac.ke

Yours sincerely,



PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UON
The Chair, Dept. of Clinical Medicine and Therapeutics, UON
Supervisors: Prof. J.K. Kayima, Prof. E.N. Ogola, Prof.S.O. McLigeyo

7.8 APPENDIX 8: STUDY REGISTRATION CERTIFICATE

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   KAMITI MUCHIRI
2. Email address: kamitimuchiri@gmail.com Tel No. 0710287488
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
   DETERMINATION OF CONCORDANCE BETWEEN BIOIMPEDANCE ANALYSIS AND A CLINICAL SCORE IN FLUID STATUS ASSESSMENT OF CHRONIC KIDNEY DISEASE PATIENTS ON MAINTENANCE HEMODIALYSIS
6. Department where the study will be conducted RENAL UNIT
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the KNH Department where the study will be conducted.
   Name: Nancy Kigera Signature [signature] Date 16/4/19
8. Endorsed by KNH Head of Department where study will be conducted.
   Name: Dr Dawn Price Signature [signature] Date 16/4/19
9. KNH UoN Ethics Research Committee approved study number P822/012/2018
   (Please attach copy of ERC approval)
10. I KAMITI MUCHIRI commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
    Signature [signature] Date 08/04/19
11. Study Registration number (Dept/Number/Year) Renal /93 /2019
    (To be completed by Research and Programs Department)
12. Research and Program Stamp

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.

Version 2: August, 2014

7.9 TURN-IT-IN ORIGINALITY REPORT

DETERMINATION OF CONCORDANCE BETWEEN BIO-IMPEDANCE ANALYSIS AND A CLINICAL SCORE IN FLUID STATUS ASSESSMENT OF PATIENTS ON MAINTENANCE HAEMODIALYSIS by Muchiri Kamiti

From Internal Medicine (Master of Medicine)

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