MALNUTRITION INFLAMMATION COMPLEX SYNDROME AMONG AMBULANT END STAGE RENAL DISEASE PATIENTS ON MAINTENANCE HAEMODIALYSIS AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

This dissertation is my original work and has not been presented for the award of a degree in any other university.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACE-i	-Angiotensin Converting Enzyme inhibitor
AIDS	-Acquired Immunodeficiency Syndrome
AUC	-Area Under Curve
AVF	-Arterio-Venous-Fistula
AVG	-Arterio-Venous Graft
BIA	-Bioelectrical Impedance Analysis
BMI	-Body Mass Index
CCF	-Congestive Cardiac Failure
CKD	-Chronic Kidney Disease
CRP	-C-Reactive Protein
CVC	-Central Venous Catheter
CVD	-Cardiovascular Disease
DEXA	-Dual Energy Xray Absorptiometry
DM	-Diabetes Mellitus
DOPPS	-Dialysis Outcomes and Practice Patterns Study
EPO	-Erythropoietin
ESRD	-End Stage Renal Disease
HD	-Haemodialysis
HEMO	-Haemodialysis
HIV	-Human Immunodeficiency Virus
HR	-Hazards Ratio
IGF	-Insulin Like Growth Factor
IL	-Interleukin
ISRNM	-International Society of Renal Nutrition and Metabolism
KNH	-Kenyatta National Hospital

LDL	-Low Density Lipoprotein
MHD	-Maintenance Haemodialysis
MIA	- Malnutrition Inflammation Artherosclerosis
MICS	-Malnutrition Inflammation Complex Syndrome
MIS	-Malnutrition Inflammation Score
Mmed	-Master of medicine
MqSGA	-Modified quantitative Subjective Global Assessment
NKF K/DOQI	-National Kidney Foundation Kidney Disease Outcomes Quality Initiative
PEW	-Protein Energy Wasting
PI	-Primary Investigator
RCO	-Registered Clinical Officer
Rpm	-Rotations per minute
S/P	-Status Post
SGA	-Subjective Global Assessment
SPSS	-Statistical Package for Social Sciences
TIBC	-Total Iron Binding Capacity
TNF a	-Tumor Necrosis Factor alpha
UoN	-University of Nairobi
USA	-United States of America
USRDS	-United States Renal Data System
WHO	-World Health Organisation

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ABSTRACT

Background: Malnutrition and inflammation are highly prevalent conditions among maintenance haemodialysis (MHD) patients and are often co-existent, consequently being referred to as Malnutrition Inflammation Complex Syndrome (MICS). MICS, or its individual components, negatively impact morbidity and mortality outcomes in MHD patients. There is a knowledge gap on the burden of MICS and its determinants among MHD patients at Kenyatta National Hospital (KNH) and this study sought to fill part of the gap.

Objectives: The objective of this study was to determine the burden and correlates of malnutrition and inflammation among ambulant haemodialysis patients at KNH.

Design: This was a cross-sectional descriptive study.

Setting and Population: The study was done at the KNH renal unit among one hundred and thirty four patients on MHD.

Methods: Relevant clinical, socio-demographic and nutritional history were obtained from the patient and file. A general and focused physical examination was done to get information on height, weight, sub cutaneous fat and muscle loss and these were entered into the Malnutrition Inflammation Score sheet and patient proforma. Blood samples were taken for C-Reactive protein (CRP), Albumin and Total Iron Binding Capacity (TIBC). The prevalence and severity of MICS was determined using the Malnutrition Inflammation Score (MIS) at a score of 6 and above. Data analysis was done using the statistical package for social sciences (SPSS) version 21.0.

Results: A total of 134 patients were recruited into the study between December 2015 and January 2016. The mean (SD) age was 44.2 (15.8) years. Male to female ratio was 1.6:1. The commonest aetiology of ESRD was hypertension at 45.5%. The prevalence of MICS was 61.2% with 100% of the study patients having above normal CRP levels (5mg/ml). Of the 82 patients with MICS, 22% had moderate to severe MICS. MICS was only found to be significantly associated with female gender (p=0.013). The correlation between MICS and CRP was insignificant with a pearson's correlation co-efficient, r, of 0.015 (p = 0.865).

Conclusion: This study demonstrated a high prevalence of MICS at the KNH renal unit with a significant number of patients having moderate to severe MICS.

1.0 INTRODUCTION

The number of patients on maintenance haemodialysis has been on the increase globally due to an increase in the number of patients with Chronic kidney disease (CKD) (1, 2).

Despite technological advances and expertise in haemodialysis, the mortality rate remains high at about twenty percent annually (2, 3). Approximately half of these deaths are due to cardiovascular diseases (4-6). Correcting the traditional cardiovascular risk factors such as hypertension and dyslipidaemia and improving dialysis techniques has not led to a significant drop in the high rate of mortality (7). This has necessitated a search for other factors contributing to the high morbidity and mortality among maintenance haemodialysis (MHD) patients.

Evidence from studies show that malnutrition and inflammation, as seen in the malnutrition inflammation complex syndrome (MICS) are among the factors causing the high morbidity and mortality mainly through acceleration of cardiovascular events (8-10). MICS and its constituents such as low serum albumin and body mass index (BMI) are stronger predictors of survival outcomes compared to high serum cholesterol or cysteine in MHD patients (11, 12). Interventions based on nutritional supplementation (13), looking for causes of inflammation and managing them (14), have resulted in improved clinical outcomes. This has led to increased research in the area of malnutrition and inflammation in the recent past (10). Consequently, there are guidelines such as that given by the National kidney foundation and dialysis outcome quality initiative (NKF K/DOQI) on regular screening, caloric requirements and supplementations (15).

Among the many ways to assess MICS, Malnutrition Inflammation score (MIS) has been shown to be a comprehensive tool that has been validated among MHD patients with good outcome predictability. KNH lacked data even on the burden of MICS and its associated risk factors among haemodialysis patients. This study set out to find out the burden, severity and factors that may be associated with MICS among MHD patients at KNH.

2.0 LITERATURE REVIEW

2.1 Epidemiology of CKD and ESRD

The burden of CKD has been on the increase globally making it a public health priority. In a recent study on global burden of diseases 2010 (16), CKD was ranked as the 18th cause of mortality globally. This is in contrast to a period 20 years earlier when it ranked the 27th cause of mortality globally. The increase in CKD burden also resulted in a 82% increase in CKD related mortality between 1990 and 2010, making it the third highest increase after HIV/AIDS and diabetes (16). In tandem with this global increase, more patients are diagnosed with CKD in the Sub Saharan region and this is attributed to an increase in the incidence of non communicable diseases such as diabetes and hypertension (1). At KNH in Kenya, a cross section study done in 2014 by Nyamai showed that 54.5% of ambulatory type 2 diabetes mellitus patients had evidence of CKD (17).

End stage renal disease (ESRD) is the severest stage of CKD and has been defined by a creatinine clearance of less than 15ml/minute/1.73m^2 in a patient with established CKD (15). The global estimate of CKD patients with ESRD in 2010 was reported to be approximately 2.7 million by Sichart et al (18). Over 75% of these patients were on haemodialysis as the mode of renal replacement therapy.

There has been significant technological improvement in haemodialysis. Despite this, the mortality rate remains high. According to the United states Renal Data system(USRDS) reports, two thirds of haemodialysis patients will have died at 5 years, with an annual mortality rate reported as 20% (2, 19). Half of these deaths have been attributed to cardiovascular disease(4, 6). Available evidence shows that malnutrition and inflammation, mainly through acceleration of cardiovascular events, puts patients on MHD at an increased risk of morbidity and mortality (8, 20).

2.2 Malnutrition Inflammation Complex Syndrome (MICS)

Malnutrition and inflammation often co exist among MHD patients. The two conditions have common aetiologies, causal dependence and evaluation methods. In addition, intervention measures aimed at either of them have often led to improvement in the other. This interdependence of malnutrition and inflammation resulted in the constitution of the Malnutrition Inflammation Complex syndrome (21-23). In this study, Malnutrition inflammation complex syndrome was defined as the presence of malnutrition and inflammation as determined by a malnutrition inflammation score of at least six.

There has been a growing interest in studying various aspects of MICS among MHD patients. Carrero in 2010 in a review of lessons learnt about inflammation in ESRD in the preceding 10 years noted that there were more than 3500 studies about MICS or its constituent elements (10). The basis for this growing interest is the fact that MICS is highly prevalent among MHD patients and that it increases both morbidity and mortality. In one study in the USA, a unit increase in the Malnutrition Inflammation score (MIS), used for assessing MICS, was associated with a 1.5 fold increase in mortality risk (24). The prevalence of malnutrition varies from one region to another depending on the assessment methodology used and population characteristics.

2.3 Evaluation of malnutrition and inflammation

Body composition in ESRD patients on MHD is under constant dynamism. These changes are mainly due to the changes in fluid compartments. There are many ways to assess malnutrition and inflammation in these patients but each, as an individual component has its own merits and demerits. A desirable assessment tool should have prognostic correlations with the condition it's assessing.

Two composite tools, namely the subjective global assessment (SGA) and the MIS are widely available for assessing the status of MICS.

In chronic kidney disease patients, SGA is incorporated into the complete nutritional assessment and has been recommended for that use by the NKF K/DOQI (15). Validation of SGA in haemodialysis patients has been done (25). Two past studies by Oduor and Shosi have used SGA at the KNH renal unit and found it to be a sensitive, easy and valid tool for evaluation of malnutrition (26, 27). These findings by Shosi and Oduor on the use of SGA are important because MIS, intended for use in this study, is a modification of SGA and all the first seven subjective components are drawn from the SGA.

2.4 Malnutrition Inflammation Score (MIS)

Malnutrition inflammation score was initially developed and validated by Kalantar et al in 2001 (11). It has ten components, divided into three distinct sections of medical history, physical exam, and laboratory measures (Appendix 5). In the history section, change in end dialysis dry weight over the preceding 3 to 6 months, dietary intake, gastro intestinal symptoms such as loss of appetite and vomiting for the preceding 2 to 4 weeks, functional capacity and co-morbid conditions is obtained. A physical examination is done to determine subcutaneous fat loss, muscle wasting and BMI. Serum albumin and total iron binding

capacity (TIBC) are the two laboratory parameters. Each MIS component has four levels of severity from 0 (normal) to 3 (very severe). The sum of all 10 MIS components ranges from 0 to 30, with 0 being normal and 30 the severest degree of MICS. A cut off of an aggregate of 6 points is used to identify those with MICS. Severity is graded as mild for aggregate scores of between six and ten and moderate to severe for aggregate scores above ten. In the study by Kalantar (11), MIS was compared with conventional SGA, anthropometry, near-infrared measured body fat percentage, serum C-reactive protein, and 12-month prospective hospitalization and mortality rates. MIS had significant correlations with hospitalization and mortality as well as measures of nutrition, inflammation and anaemia in dialysis patients. The correlations were higher for MIS than either the conventional SGA or individual laboratory values as a predictor of outcome. In a multicenter study, mortality and hospitalization predictability of MIS was assessed among 378 haemodialysis patients and MIS was found to be comparable with serum CRP and serum interleukin-6 (28). The correlation with CRP and IL-6 was also reported by Rambod indicating that MIS has a strong correlation with the inflammatory status in MHD patients (29). In this study by Rambod, 809 stable haemodialysis patients were followed up for 5 years and MIS was demonstrated as a stronger predictor of Quality of life, depression, hospitalisation and mortality compared to its individual constituents including albumin, BMI and CRP. In addition, each increase in 2 units of MIS was associated with doubling of the risk of mortality.

Beberashvili (24) in a follow up of 73 HD patients in Israel, comparing different tools for serial nutritional assessment for a period of 18 months found that MIS was a valid tool for follow up. In this study, MIS demonstrated a high inter observer agreement which was eighty-four, lending it credibility for use amongst different assessors. One unit increase in MIS was associated with a fifteen percent increased risk for mortality and this is comparable to other studies (29). MIS has also been validated by different investigators and more importantly in different population groups and countries. Roxana et al evaluated the usefulness of MIS in 200 haemodialysis patients in Brazil and found that it was a simple tool that could be used by various cadres of staff and it correlated well with reduced survival for scores above 8 compared to less than 8 (52% compared to 93%) (30). Ho et al in a 12 month follow up study of 257 MHD patients while studying the utility and cut offs of MIS, demonstrated that patients with scores of over 8 had 100% mortality (31).

The reliability and consistency of MIS has also been studied. Ailema et al (32) in a study to assess the reliability and consistency of MIS among 45 Brazilian adult dialysis patients

found that the intra-class correlation coefficient was high and that the agreement between MIS observations was adequate. As'habi et al in a cross sectional study of 291 MHD patients in Tehran compared Dialysis Malnutrition Score (DMS) and MIS and using SGA as the comparator, MIS had a high specificity at 96% at a cut off of 7 (33). The sensitivity, positive and negative predictive values were 87 %, 97% and 83% respectively. The reproducibility of MIS was highest compared to SGA and DMS. Pisetkul et al did another study showing a high sensitivity for MIS and more so in predicting one-year mortality among MHD patients (34). They found MIS to have a sensitivity of 75% and specificity of 88%. In addition, MIS has the advantage of assessing the history of dietary intake, the functional status, physical well being as well as providing a window through the laboratory investigations into the internal nutritional and inflammation state (29).

MIS correlates well with both the malnutrition and inflammation status and is hence appropriate for screening for MICS. The strength of a screening tool is its ability not only to identify the population with a condition, but also have prognostic implications (11, 28, 29, 35). A cut off of 6 has been found to be significantly associated with morbidity and mortality risk as shown by both Rambod, Yamada and Ho (29, 31, 36). Moreover, MIS has a good prognostic value for quality of life, cardiovascular death, erythropoietin responsiveness, mental state and all cause mortality among patients on maintenance haemodialysis (31).

Other measures of malnutrition and Inflammation.

Albumin is a good indicator for both nutritional status and inflammation and has been shown to correlate well with morbidity and mortality outcomes despite the many factors that affect its serum concentration (4, 37). Lowrie, in a study on the death risk among 12,000 haemodialysis patients found out that a serum albumin of less than 40mg/dl was strongly associated with mortality risk (38). Other studies in different set ups have come up with similar findings (39, 40). Other than the nutritional status, there are other factors that may influence serum albumin concentration such as body fluid status, inflammation, Diabetes mellitus, race and gender (41-44). Albumin as a single entity would therefore require correcting for many other confounders.

Body mass index (BMI) is used to assess nutritional status. According to the WHO classification using BMI derived from the Quetelet index, a BMI of less than 18.5kg/m^2 is considered underweight and points towards malnutrition. BMI however does not have the discriminatory ability to differentiate between various body compositions, more so in patients

with oedema. Further to that, it has a low sensitivity and some studies have not shown any correlation between BMI and morbidity and mortality outcomes among MHD patients (45).

C-reactive protein (CRP) is a marker of inflammation used in clinical settings. Among haemodialysis patients, a single or repeated high CRP has been shown to have a positive correlation with mortality and morbidity and more so in patients with cardio metabolic diseases (5, 28, 46). Kalantar et al demonstrated that every 10µg/ml increase in CRP was associated with a 39% increased risk of death (47). Iseki et al in a study of 163 dialysis patients noted that the risk of death among HD patients with a CRP of greater than 10 mg/l was significantly higher at 5 years compared to those in whom it was less than 10 mg/l (48). In MHD patients, CRP has a positive correlation with nutritional indices, including MIS, and its increase may potentially point towards malnutrition (11, 23).

Other single indices that measure body composition such as Dual energy X-ray absorptiometry, bioelectrical impedance analysis, near infrared interactance have been used in the past but do not seem to be reliable especially in outcome predictability (11, 28).

2.5 Epidemiology of MICS

The prevalence of malnutrition and inflammation among ESRD patients on MHD is high. Depending on the study method and setting, the prevalence of malnutrition and inflammation, often occurring together as a malnutrition inflammation complex syndrome (MICS), has been reported in the upward of 90 %.

In a five year prospective study of 809 maintenance haemodialysis patients in the USA, Rambod and colleagues found a baseline prevalence of malnutrition/inflammation of 46% using the malnutrition inflammation score (MIS). In this study, 30% of the patients were blacks, 54% were Hispanics and the rest were non Hispanic whites (29). Diabetes mellitus was identified as a factor that is associated with severe MICS, constituting 60 % of the co-morbid conditions with severe MICS. Diabetes exerts its effect and lead to increased MIS scores because of its chronic inflammatory state and poor nutrient intake and assimilation (49). Other factors identified to be associated with increasing severity of MICS were a single marital state and a dialysis vintage of more than 60 months.

In a study of 109 dialysis patients in the USA, Stevinkel and colleagues found out that 44% of these patients had malnutrition according to the Subjective Global Assessment tool (SGA). Inflammation, assessed using C-reactive Protein (CRP) occurred in 32%. Of note in this

study was the overlap between malnutrition and inflammation. Seventy three percent of the patients who had inflammation had malnutrition while 53% of those who had malnutrition had features of inflammation. This demonstrates the common co existence of the two conditions (21).

Malnutrition is a global problem affecting MHD patients both in developed and low resource countries. Combe et al in an analysis of the DOPPS study data, across Europe and USA, using the modified quantitative Subjective Global Assessment (mqSGA) found that 18%-22% were moderately and severely malnourished (50). In a study done in Karachi among 62 MHD patients, over 90% of the patients were identified as having malnutrition and inflammation by the MIS (51). Forty seven percent of the patients in this study had moderate to severe malnutrition, a finding that is similar to what Chen found in china among 75 MHD with a prevalence of 48%, using MIS. Two studies done in Africa among MHD patients also demonstrated a high prevalence of Malnutrition. Aatif et al from Morocco, in a prevalence cross sectional study of 40 dialysis patients found the prevalence of malnutrition ranging from 12.5% to 65% as assessed by a body mass index (BMI) of less than 18.5 kg/m^2 and serum albumin of less than 35 mg/dl respectively (52). In Kenya, Oduor found out that 48.1 % of MHD patients had malnutrition (26). Data from these studies, from four different continents show that malnutrition and inflammation are highly prevalent among MHD patients. The prevalence is higher among the low resource countries compared to developed countries.

Studies from other parts of the world also indicate that malnutrition and inflammation are highly prevalent in spite of the assessment method used. In Stockholm Sweden, Qureshi and his colleagues did a cross sectional study looking at factors affecting malnutrition among 128 MHD patients. He used the Subjective Global Nutritional Assessment. Forty-six patients (36%) had a normal nutritional status, 65 patients (51%) were mildly malnourished and 17 patients (13%) were moderately or severely malnourished (53). In another study in Sweden, Carrero and colleagues, using muscle atrophy to assess the nutritional status of 229 dialysis patients found out that 39% had malnutrition (9). In these two studies, although the methods of assessment used were different, malnutrition was still demonstrated to be highly prevalent. Gracia et al used the International Society of Renal Metabolism and Nutrition (ISRMN) criteria to assess for protein energy wasting (PEW) among 122 patients undergoing MHD at a single centre in Spain. They found out that 37% had PEW. Of interest in this study, 49.6% of

the patients had serum albumin of less than 3.8 g/l, which is indicative of malnutrition and inflammation (54).

In Brazil, Oliveira et al (55) in a cross sectional study using various nutritional assessment tools including SGA and BMI to assess malnutrition among 58 maintenance dialysis patients had a prevalence ranging from 12.1-94.8%. BMI had the lowest sensitivity identifying those with malnutrition at 12.1%. Freitas in a cross sectional study in Brazil using SGA in 344 MHD, found mild to moderate nutrition in 22.4%. Factors associated with severity of malnutrition included dialysis vintage of over 5 years, a low serum creatinine, young age below 18 years, low BMI and male gender (56). BMI has often been shown to have a low sensitivity compared to the other tools such as MIS and SGA, (47, 52, 55).

2.6 Pathophysiology

The factors underlying the prevalent malnutrition and inflammation among haemodialysis patients are diverse but seem intertwined.

Known causes of malnutrition among haemodialysis patients include reduced dietary intake due to uremic anorexia (57) and dietary restrictions (58). The milieu of various inflammatory cytokines such as tumour necrosis factor a, Interleukin 6 and others may contribute to anorexia and hence malnutrition.

Factors related to CKD/ESRD including increased resting metabolic rate, persistent inflammation, metabolic acidosis, intestinal dysfunction, multiple endocrine disorders, co morbid conditions and the dialysis process have been identified as contributors to protein energy malnutrition (59). Ballmer et al found a strong association of a negative nitrogen balance and reduced albumin synthesis in relation to chronic metabolic acidosis, an effect that is partly mediated by attenuated effects of insulin like growth factor 1 and thyroid hormones (42). Correction of this acidosis has resulted in improvement (60). Impairment of intestinal protein assimilation among patients with ESRD has been long documented (61).

Dialysis related causes of malnutrition and inflammation are mediated through nutrients extraction into the dialysate, induced inflammation as a result of membrane contact and the resultant hyper catabolic state (62-64). In their study to establish the effect of haemodialysis on protein synthesis, Lofberg et al demonstrated that the rate and capacity for protein synthesis during a haemodialysis session were reduced by 13 % and 22% respectively (63).

The resting energy expenditure has been shown to increase between twelve to twenty percent during a haemodialysis procedure (65).

Other aetio-pathogenic mechanisms include decreased clearance of pro inflammatory cytokines and decreased levels of anti oxidants (66). Co morbid conditions such as diabetes (67), HIV and CCF, are in themselves pro inflammatory states. Others include dialysis related inflammation resulting from exposure to dialysis tubing, incompatible dialysis membranes (68, 69), failed arterio-venous grafts, impurities in the dialysate, dialysis water back diffusion and dialysis catheters. Infections too play a great role in the propagation and sustenance of inflammation and malnutrition (53).

2.7 Patient Factors associated with MICS

Several risk factors correlate with the severity of MICS, or its constituent elements.

Type of vascular access determines the severity and prevalence of malnutrition and inflammation. Central venous catheters (CVC) tend to increase markers of inflammation more compared to use of arterio-venous fistulae and graft (70). Allon et al in an analysis of 1846 patients from the HEMO study identified that the adjusted relative risk for mortality when using a catheter compared to an AV access was 1.59 (71). The mechanism of this increased mortality is due to increased infections, inflammation and cardiovascular related deaths (71). Further affirming this is a finding that change of venous access to CVC leads to increased CRP levels (72).

Duration of dialysis correlates with the severity of MICS. Dialysis duration of more than 60 months has been shown to proffer severe MICS scores and poor outcomes (56, 73, 74). The mechanism through which this occurs is loss of nutrients to the dialysate, a relatively high basal catabolic rate and increased inflammation generally (75).

Co-morbid conditions especially Cardiovascular disease (CVD) (5), and Diabetes mellitus (5, 29, 49, 73) are associated with severe MICS and poor survival of MHD patients. Both are pro inflammatory states and this leads to a vicious cycle.

Female gender has been found to confer better scores of inflammation and thus survival advantage among MHD patients (76, 77). Whereas it is not clear what may be causing this difference, some studies seem to suggest that female hormones may be responsible and progesterone especially has been cited (73). Rambod however found females to have worse outcomes compared to males and the reasons for this were not clear (29).

Other patient characteristics that may be related to worse MICS scores include young age (56), low BMI (29, 56), and a single marital status (29). In the previously mentioned study done by Freitas et al, those who were within the age bracket of 19-30 years had more markers of malnutrition such as low BMI, and albumin. Some of the factors that may have contributed to this are insufficient food intake, a higher energy requirement during growth as well as a high activity index (56). A reverse epidemiology of BMI as a cardiovascular risk factor may explain the bad outcomes in MHD patients with a low BMI (40, 78).

2.8 Consequences of MICS on morbidity and mortality

The interaction between inflammation and malnutrition among MHD patients results in increased morbidity and mortality compared to other CKD patients. Some of the consequences of MICS include refractory anaemia and hypo responsiveness to erythropoietin, increased cardiovascular disease and reverse epidemiology of cardiovascular risk factors. Others are poor quality of life, increased frequency of hospitalisation and depression.

Refractory anaemia in MICS is thought to be due to a blunted response to erythropoietin stimulating agents as well as bone marrow suppression by cytokines (79). Blood loss and inadequate nutritional intake and utilisation are also responsible for anaemia (20, 80).

Patients with CKD are at an increased risk for cardiovascular disease (6, 81). Both inflammation and wasting have been linked to poor cardiovascular outcomes in MHD patients (23). Continued inflammation of the vascular bed and consequently atherosclerosis leads to coronary artery disease for instance (53, 77, 82).

CKD patients are often hospitalised due to a variety of reasons. Studies have shown that patients with MICS in CKD, whether undergoing dialysis or not have more frequent admissions, have a poor quality of life and generally an increased mortality (24, 29, 47). The frequent hospitalisations in part explain the reduced quality of life (47), which may also be related to the high prevalence of depressive symptoms (83). Two studies at Kenyatta National hospital among MHD patients showed a reduced health related quality of life (84, 85).

MICS is an independent predictor of mortality among MHD patients. An increase in the severity of MICS by one point of MIS has been associated with a 50-100% increased risk of death (24, 29).

2.9 Management

The National Kidney Foundation and Kidney Dialysis Outcome Quality Initiative (NKF K/DOQI), the American Dietetic Association and their European counterparts recommend for adequate and timely screening for malnutrition and institution of relevant medical nutrition therapy.

Screening is recommended before initiation of dialysis and every four to six months thereafter (15, 86). Also advocated in the guidelines is adequate oral nutritional supplementation and intra-dialysis parenteral supplementation in a select group of patients including those with severe malnutrition and a high negative nitrogen balance (15, 86, 87). Specific recommendations for acidosis correction including increasing the weekly dialysis dose, carbohydrates as well as daily protein intake have been put forward with emphasis to individualisation of therapy. The targeted protein intake recommended is 1.2 g/kg/day and a caloric intake of 35 kcal/kg/day, to maintain a positive energy and nitrogen balance. Studies have shown improvement in clinical and laboratory parameters namely BMI, dry weight serum albumin and TIBC, when oral (88) and intra-dialysis parenteral nutrition (89) supplementation is done.

In systematic reviews and meta analyses by Bossola et al (13) and Rebecca et al (90), that included both randomised and non-randomised trials, there is a large body of evidence that both enteral and parenteral interventions with micro as well as macro nutrients lead to improvement of various parameters. These include as appetite, weight gain, increase in serum pre-albumin and albumin as well as activity level and quality of life. Use of statins (14) have been shown to lower the levels of CRP by up to 50% in some studies (91) and improve on morbidity. Identification of prevalent MICS through MIS at regular screening schedules helps interrogate the cause and institute interventions such as change of central venous catheters to fistulae and this has been shown to halt both malnutrition and inflammation. Other novel therapies being tried include use of ACE inhibitors, IGF 1, anabolic steroids, anti-oxidants. Most of these studies are small and of short durations and large randomised clinical trials are still needed to show how these interventions affect inflammation, morbidity and mortality in the end.

3.1 STUDY JUSTIFICATION

ESRD patient numbers are on the increase in Kenya (17). MHD is the main modality of renal replacement therapy. Despite technological advances and addressing known traditional risk factors such as dyslipidemia, hypertension and proteinuria, morbidity and mortality are still high among MHD patients (2). Malnutrition and inflammation (MICS) are highly prevalent among ESRD patients on MHD (29). In addition, MICS as assessed by MIS and other markers of inflammation such as CRP have been shown to independently increase the risk of morbidity and mortality in MHD patients (29). This has led to increased research in the subject of malnutrition and inflammation among MHD patients the world over (10). There is documented evidence that clinical and laboratory parameters improve when patients with MICS are identified early and management such as increased dialysis dose, intradialytic nutritional supplementation and addressing individual causes of malnutrition and inflammation are instituted (90).

KNH, and Kenya at large, lack data on the prevalence of MICS and its associated factors. It was hoped that this data on the prevalence of malnutrition and inflammation would inform policy formulation as regards screening, intervention and consequently improved morbidity among MHD patients. Furthermore, data from this study would perhaps form a basis for other studies in this subject.

3.2 STUDY QUESTION

- What is the burden of malnutrition inflammation complex syndrome among ambulant end stage renal disease patients on maintenance haemodialysis at KNH?

3.3 BROAD OBJECTIVE

- To determine the burden of malnutrition inflammation complex syndrome and some of its determinants among ambulant end stage renal disease patients on maintenance haemodialysis at KNH.

3.4 SPECIFIC OBJECTIVES

3.4.1 The primary objectives of this study were:

1. To determine the prevalence of Malnutrition Inflammation Complex Syndrome among ambulant end stage renal disease patients on maintenance haemodialysis at KNH using the malnutrition inflammation score.
2. To determine the severity of Malnutrition Inflammation Complex Syndrome among ambulant end stage renal disease patients on maintenance haemodialysis at KNH using MIS.

3.4.2 The secondary objectives of this study were:

1. To determine the correlation between malnutrition inflammation score and C-reactive protein among ambulant end stage renal disease patients on maintenance haemodialysis at KNH.
2. To determine the correlation between malnutrition inflammation score and select determinant factors namely age, gender, dialysis vintage, type of vascular access and number of dialysis hours per week.

4.0 RESEARCH METHODOLOGY

4.1 Study design

This was a descriptive cross sectional study.

4.2 Study location

This study was conducted at the renal dialysis unit at the Kenyatta National Hospital, Nairobi, Kenya. Kenyatta National hospital is a tertiary referral hospital and receives patients from within Kenya and in the region of central and East Africa. It is the teaching hospital for the University Of Nairobi medical school. There are about 260 patients currently undergoing maintenance haemodialysis at the facility, with about 189 having been on dialysis for more than three months, making it the largest, single dialysis centre in the country. It has twenty dialysis machines, catering for about fifty-two out patients per day. There are 6 nephrologists and over 50 renal nurses, in addition to nutritionists and other support staff. The unit also has a laboratory for routine tests with eight qualified laboratory technologists.

4.3 Study Population

The study population were patients on maintenance haemodialysis for at least three months.

4.4 Case definition

Malnutrition inflammation complex syndrome was considered present in those who had a composite malnutrition inflammation score of six and above.

A score of between 6 and 10 denoted mild MICS, whereas a score of between 11 and 30 denoted moderate to severe MICS.

4.5 Inclusion and exclusion criteria

Assenting/consenting patients who were aged 13 years and above, the age at which they are admitted to the KNH adult renal physician follow up clinic and had been on MHD for at least 3 months.

Patients getting albumin infusion or had albumin infusion in the preceding twenty one days were excluded.

4.6 Sample size

Sample size estimation was done using the formula for a finite population (92).

$$n = \frac{NZ^2P(1-P)}{d^2(N-1) + Z^2\ P(1-P)}$$

Where n is the sample size

Z is the constant for a desired confidence interval of 95% which is 1.96

P is the proportion, =0.386 (from the study by Yamada et al, the prevalence of MICS was 38.6%, giving the proportion P, of 0.386 i.e 38.6/100 multiplied by one (36).

d is the margin of error and is 0.05

N=is the total number of patients available which is 200

Substituting actual numbers in the formula,

$n = \frac{200x(1.96^2)0.386(1-0.386)}{0.05^2(200-1)+1.96^2\ \ 0.386(1-0.386)}$=129.3280=130 Patients.

4.7 Screening, recruitment and consenting

Retrieved records of patients who presented for dialysis were reviewed to establish their suitability. For those identified, the purpose of the study was explained. Those who accepted to join the study gave informed written consent or assent. The investigators then administered the study proforma. Colour coded identifiers were then attached to the files to avoid repeat recruitments. Consecutive sampling and recruitment was done for 134 patients.

4.8 Data collection

4.8.1 Patient history as per MIS

The first seven components of MIS from history were assessed and categorised. The total score was then gotten from the addition of scores in each of the 10 items. Each component had a score of between 0 (normal) and 3 (severe). A total score of between 0 and 30 was expected. Patients with a score of 6 and above were considered to have MICS, with those with scores of between 6 and 10 having mild MICS whereas a score of more than 10 denoted moderate to severe MICS.

1. The overall change in the end dialysis dry weight in the past 3 to 6 months was assessed. The current weight was taken between 15 to 30 minutes post dialysis. The weight in the previous 3 to 6 months was obtained from the dialysis charts. The weights that were closest to 6 months were used. The change in weight was then categorised as 0 if there was no loss or a loss of less than 0.5 kg. A score of 1, 2, 3 was given for weight losses of between 0.5 kg and less than1kg, more than 1 kg but less than 5% and more than 5% respectively.
2. Dietary intake for the preceding 2 weeks was assessed. A score of 0 was given if the appetite was good with no deterioration of dietary intake. A score of 1 was given if the intake was sub-optimal for solid diet, denoted by an increased liquid diet, but less than the solid diet in proportion. A score of 2 was given for a moderate overall decrease to a full liquid diet. A score of 3 was given to those on starvation or only managing hypo-caloric liquid like water.
3. Gastro intestinal (GI) symptoms for the preceding 2 weeks were assessed and categorised. A score of 0 was given if the appetite was good with no GI symptoms. A score of 1 was given for occasional poor appetite and nausea. A score of 2 for occasional vomiting or diarrhoea or frequent anorexia but not more than half the time. A score of 3 was given for frequent (Occurring more common than not for the 2 weeks period) vomiting or diarrhoea or severe anorexia.
4. Functional capacity was assessed and categorised as 0 if it was normal, with the patient feeling fine. A score of 1 was given if the patient had difficulty with baseline ambulation and felt tired frequently. A score of 2 and 3 was given if the patient had difficulty with otherwise independent activities e.g going to the bathroom, and bed/chair ridden or little to no physical activity respectively.
5. Co-morbidity including number of years on dialysis. The categorisation used was mainly based on the number of years on dialysis patients with severe co-morbid conditions in grade 3 or 4 were on in-patient management and these were excluded. A score of 0 was given if the duration of dialysis was less than 1 year and the patient was healthy. A score of 1 was given for a dialysis duration of 1 to 4 years and didn't have a major co-morbid condition (MCC). A score of 2 was given if the patient had had dialysis for more than 4 years or one MCC and a score of 3 for multiple co-morbidity or any severe co-morbidity.

4.8.2 Physical examination

4.8.2.1 Subcutaneous fat

The investigators examined for subcutaneous fat loss below the eyes, at the triceps and biceps muscles. The examination was done post dialysis. The region that gave the highest score was used for scoring. At the peri- orbital region, subcutaneous fat loss was graded depending on the hollowness. A slightly bulged fat pad around the eyes was considered normal and scored as zero, mild hollowness was scored as 1, with the extreme scoring of 3 being a hollow look, depression, dark circles and loose skin around the eyes. At the triceps and biceps muscles, with the elbow flexed, the skin was lightly pinched using the index finger and thumb and the skin fold assessed to determine the amount of subcutaneous fat. Subcutaneous tissue loss was graded as severe (A score of 3) when there was very little space between the folds, and the fingers felt touching. The score was normal (a score of 0) if there was ample fat tissue between the fingers, and mild to moderate (score 1 and 2) if the pinch had significant depth, near ample, and inadequate pinch but fingers not touching respectively. This was then entered into the MIS score sheet as item 6 (under physical examination).

4.8.2.2 Muscle wasting

Signs of muscle wasting were examined for at the temple, shoulder and chest. The score was from 0 to 3. This was done post dialysis. At the temporalis muscle, a score of 0, denoting normal was given if there was a visible bulge of the muscle. A score of 1 was given if there was a depression of the muscle only appreciated on palpation, 2 if the depression was slight but visible on inspection and the underlying bone was not palpable easily and 3, if there was hollowing, scooping or depression on inspection and the underlying bone felt easily on palpation. At the chest, a score of 3 was given if the ribs in the lower chest were obviously ridged, with the space between the ribs hollow on inspection. Two if easily felt on palpation with significant depression between the ribs, accommodating a finger easily, 1 if there was significant muscle tissue between the ribs, not accommodating a finger easily. A score of 0 was given if the ribs were not easily palpable and were not visible on inspection. At the shoulder, with the shoulder joint at adduction, a well-rounded, full shoulder was given a score of 0. A score of 3 was given to a shoulder that looked square, with obvious bony prominences at the shoulder joint on inspection. A score of 1 was given if there was moderate rounding of the shoulder, with slight depressions along the bony prominences and 2 if it the depressions were obviously seen on inspection with mild squaring of the shoulder. The highest score from the examined regions was then entered in the MIS under item 7, under physical examination.

4.8.2.3 BMI

For calculation of BMI, patients' post dialysis weight and height was obtained by the investigators. BMI was then calculated using the formula:

BMI= Wt/Ht^2 (kg/m^2).

Height

The post dialysis height was measured to the nearest 0.5 cm with the patient standing barefoot, feet together, the back square against the wall tape, eyes looking straight ahead, with a setsquare resting on the scalp and against the wall tape from which the reading was done.

Weight

The post dialysis weight was measured to the nearest 0.1 kilogram using a lever balance scale with the patient barefoot and in light clothing. Past 3 months' post dialysis weight was obtained from the file/ weights chart. The BMI was then calculated using the Quetelet index expressed as weight in kilograms divided by height in squared meters. (Appendix 2)

4.9 LABORATORY METHODS

4.9.1 Sample collection

Subsequent to obtaining consent, a pre dialysis 4 mls of blood sample was taken for assay of serum albumin and TIBC, which are part of the MIS score, as well as for the assay of CRP for determination of inflammation.

The investigators drew the samples aseptically and all attempts were made to ensure that the samples were obtained at a time when the other routine samples for blood counts and blood urea nitrogen and creatinine are drawn. The drawn samples were then placed in a plain bottle for albumin, TIBC and CRP measurement.

4.9.2 Sample handling and processing

The collected samples were taken to the biochemistry laboratory at KNH for immediate processing but for samples that were not processed immediately, they were separated into serum and cellular components and frozen at -20 degrees Celsius for subsequent day processing (Appendix 3).

The measurement of serum C-RP, albumin and TIBC were done using a fully automated clinical chemistry analyser, Cobas 410, using photometric assay techniques.

Albumin concentration was determined in g/l using the photometric colorimetric test using Bromocresol green method (Appendix 3). The obtained values for each patient were then categorised and assigned a score of between 0 and 3. A score of 0 was given for serum albumin levels of 4.0 g/dl and above, a score of 1 for serum albumin levels of between 3.5 to 3.9 g/dl. Serum albumin levels of between 3.0-3.4 g/dl were given a score of 2 and those less than 3.0 g/dl were given a score of 3. This was done under item 9 of the MIS.

TIBC was determined from a directly assayed iron concentration in a centrifuged supernatant multiplied by a diluent factor of 3. The results were expressed in micrograms per decilitre (Appendix 3). The categorisation was then done according to the MIS, item 10. The scores were 0 for TIBC of 250 mg/dl or more, 1 for TIBC between 200 to 249 mg/dl, 2 for 150 to 199 mg/dl and 3 for TIBC less than 150 mg/dl.

C-RP was determined by photometric turbidimetric assay and the cut off used for the upper limit of normal is 5 mg/l (Appendix 3). CRP levels were then dichotomised as either high or normal, using a cut off of 5 mg/L. A CRP of 6 mg/L and above thus indicated significant inflammation. No follow up CRP was done in this cross sectional study.

The utilised samples were kept at -20 degrees Celsius until the study is complete and results presented/validated after which they will be discarded as per standard bio safety procedures.

4.9.3 Quality control and assurance

All blood samples were collected pre dialysis as per the MIS protocol. Attention was paid to requisite quantities, accurate labelling and timely delivery and assay of samples to minimise on pre analytical errors.

Daily Calibration using controls and/standards was done as per the manufacturers' specifications and only those sample assays that pass the laboratory's internal quality control were accepted for analysis.

Qualified laboratory personnel did all sample assays. For external quality control, every 30^{th} sample was taken to Lancet laboratories for assay.

4.10 DATA MANAGEMENT AND ANALYSIS

4.10.1 Study variables

4.10.1.1 Independent variables

1. Demographic factors such as age and sex and these were as reported by the patient and corroborated from the files.
2. Underlying co-morbid conditions as reported by the patient and were corroborated by a previously documented diagnosis in the file. These included a diagnosis of diabetes mellitus, being on treatment for the same, diagnosis of hypertension, being on treatment for the same and other co-morbid conditions.
3. Dialysis vintage. This was documented as the total number of months the patient had been on dialysis.
4. Type of vascular access. This was determined by a physical exam and categorised as a central venous catheter, arterio-venous fistula and arterio-venous graft.
5. Number of haemodialysis hours per week, which was the sum of hours on dialysis for the number of dialysis sessions in the preceding one week as documented in the file.

4.10.1.2 Dependent variables

1. Malnutrition inflammation scores as was obtained by summation of the 10 components of the MIS, as described under the history section of the methodology. An aggregate score of more than 5 was used to identify the presence of MICS.
2. C-Reactive Protein level as was determined in the laboratory by immunoturbidimetry techniques. Any value of more than 5mg/l was considered to denote significant inflammation. CRP being a marker of inflammation was then used to explore how it correlated with MICS in our set up.

4.11 DATA HANDLING

4.11.1 Entry and validation

The raw data was entered into MS excel sheets, cleaned and verified and archived in both hard and soft copies. Backup copies were also stored in an external hard disc.

4.11.2 Analysis and presentation

Processing and analysis of the data was done using a computer program, the Statistical Package for Social Sciences (SPSS) version 21.0 with the help of a qualified statistician. All data was kept in a security code protected computer.

For continuous data e.g. age, measures of central tendency such as mean and median was calculated while proportions were obtained for categorical data such as sex and vascular access type.

Prevalence of Malnutrition inflammation complex syndrome was determined using proportions of those with a malnutrition inflammation score of more than five among the study participants and expressed as a percentage, whereas severity was categorised into normal, mild and moderate to severe for those with MIS scores of less than six, six to ten and more than ten respectively.

Prevalence of inflammation by CRP was determined as a proportion/percentage of those with a CRP score of more than 5 mg/l among the study participants. No further categorisations of CRP were done for this study because any single value higher than 5 mg/ml was significant.
Univariate analyses were done for associations between dependent and independent variables and that between CRP and MIS using Pearson correlation co-efficient (r). Comparisons between groups were done using the Student t test.

Statistical tests were done at 5% level of significance (95% confidence interval).
Presentation of results was done in flow charts, tables, and pie charts.

5.0 ETHICAL CONSIDERATIONS

Approval

The study was commenced after approvals from the faculty in the department of Internal Medicine and Therapeutics and the Kenyatta National Hospital and University of Nairobi Ethics and Research committee and only consenting/assenting patients were included in the study. Those who declined participation were not victimised in any way.

Privacy and confidentiality

Coding of patients' identification information was done for privacy. Information gathered was held in confidence by the investigator, and has only been used for the study and for improved management of the patient where it is was deemed necessary by the primary investigator. Raw data was kept under lock and key for the entire study period and will subsequently be destroyed once results have been presented and accepted at final submission.

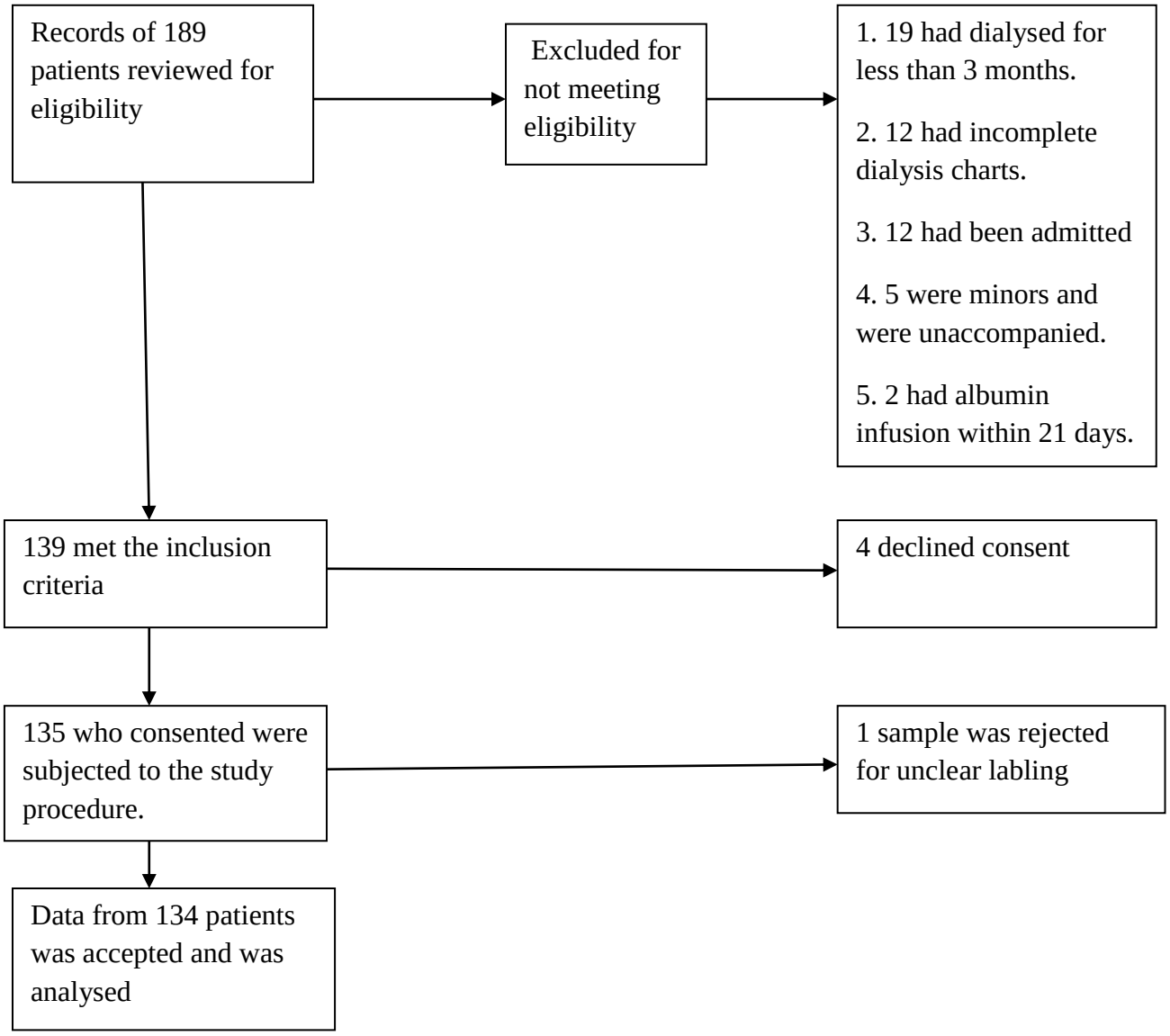
Study administration

The research investigators ensured that data was collected efficiently, on time and that it was recorded accurately. The supervisors offered guidance to the PI throughout the process. The statistician offered guidance during proposal development, data entry, and analysis of the data. All the data was kept in a secure lockable cabinet and the computer used had a security code.

6.0 RESULTS

Between December 2015 and January 2016,189 patients were screened at the renal unit of KNH. One hundred and thirty nine met the inclusion criteria but only 134 were finally analysed, four declined consent and one sample rejected at the laboratory.

Figure 1. Patient flow and recruitment



Diagrammatic representation of the recruitment of patients.

6.1 SOCIO-DEMOGRAPHIC CHARACTERISTICS

Most patients were males comprising 61.9%. The male to female ratio was 1.6:1. The mean (SD) age was 44.2 (15.8) years with a range of 15 to 75 years. Those in age category 13 to 30 years comprised the highest percentage at 23.9%. More than half of the patients were married at a frequency of 68.7%. Sixty-one patients came from within Nairobi comprising 46.3%, followed by those who came from the former central region at 33.6% with only 20.1% being from the rest of Kenya. (Table 1)

Table 1. Socio-demographic characteristics of patients

Variable	**Frequency (%) n=134**
Mean (SD),years	44.2 (15.8)
Range in years	15-75 years
Age	
13-30	32 (23.9)
31-40	31 (23.1)
41-50	18 (13.4)
51-60	26 (19.4)
>60	27 (20.1)
Gender	
Male	83 (61.9)
Female	51 (38.1)
Marital status	
Single	37 (27.6)
Married	92 (68.7)
Separated	5 (3.7)
Residence	
Nairobi	62 (46.3)
Central	45 (33.6)
Eastern and Kajiado	14 (10.4)
Other	13 (9.7)

6.2 CLINICAL VARIABLES

The aetiology of Kidney disease as documented in the file was predominantly hypertension at a frequency of 45.5%, affecting 61 patients. Glomerulopathy, diabetes and obstructive uropathy comprised 20.1%, 19.4% and 9% respectively. The remaining 6% was due to other causes such as HIV, drug toxicities and connective tissue disorders. (Table 2)

Majority of the patients (70.9%) had twice a week dialysis for a total duration of 8 hours. The rest dialysed only once a week. No patient dialysed at the recommended 12 hours per week. (Table 2)

Ninety- four (70.1%) patients had a central venous catheter as the vascular access, with only one patient having a graft and the remainder, 39 (29.1%) patients had arterio-venous fistula. (Table 2)

Most patients (46.3%) had dialysed for between 12 and 48 months followed by those who had dialysed for less than 12 months at 33.6% with only 20.1% having dialysed for more than 48 months. (Table 2)

Table 2. Clinical variables of patients

Variable	Frequency (%), n=134
Aetiology of kidney disease	
Hypertension	61 (45.5)
Diabetes	26 (19.4)
Glomerulopathy	27 (20.1)
Obstructive uropathy	12 (9.0)
Other	8 (6.0)
Dialysis hours per week	
≤4	39 (29.1)
5-8	95 (70.9)
Type of vascular access	
Central venous catheter	94 (70.1)
Arteriovenous fistula	39 (29.1)
Arteriovenous graft	1 (0.8)
Vintage (Number of months on dialysis)	
Median (IQR)	18 (9-42.8)
Mean (SD)	28 (28.8)
Category (Months)	
<12	45 (33.6)
12-48	62 (46.3)
>48	27 (20.1)

6.3 HISTORY AND PHYSICAL EXAMINATION ATTRIBUTES OF MIS

Majority (69.4%) of the patients had insignificant weight loss of less than 0.5 kg in the preceding 3 to 6 months. Less than half the patients had sub-optimal dietary intake (42.5%) and manifestations of gastrointestinal symptoms (44.8%). Functional capacity was impaired in the majority (70.1%) of patients with most (61.2%) experiencing mild incapacity such as difficulty with baseline ambulation. More than three quarters of the patients had signs of decreased subcutaneous fat and muscle wasting. Among these, five (3.7%) patients had severe subcutaneous fat loss and seven (5.2%) had severe signs of muscle wasting (Table 3).

Table 3. History and physical examination attributes of MIS

Variable	Frequency (%), n=134
Change in end dialysis dry weight	
<0.5 kg	93 (69.4)
>0.5 kg but <1 kg	21 (15.7)
>1 kg but <5 %	16 (11.9)
>5 %	4 (3.0)
Dietary intake	
Good appetite	77 (57.5)
Somewhat sub-optimal solid diet intake	56 (41.8)
Moderate overall decrease to full liquid diet	1 (0.7)
Gastrointestinal (GI) symptoms	
No symptoms	74 (55.2)
Mild symptoms, poor appetite or nauseated occasionally	43 (32.1)
Occasional vomiting	15 (11.2)
Frequent diarrhoea	2 (1.5)
Functional capacity	
Normal	40 (29.9)
Occasional difficult with baseline ambulation	82 (61.2)
Difficult with otherwise independent activities	12 (8.9)
Decreased fat stores	
Normal	25 (18.7)
Mild	71 (53.0)
Moderate	33 (24.6)
Severe	5 (3.7)
Signs of muscle wasting	
Normal	25 (18.7)
Mild	72 (53.7)
Moderate	30 (22.4)
Severe	7 (5.2)

6.4 BMI AND LABORATORY PARAMETERS

The mean (SD) BMI as determined by the Quetelet index was 21.2 (3.4) kg/m^2 . The range of the BMI was 14.2 to 31.8 kg/m^2. Eighty-eight patients, (65.7%) had a BMI of 20 kg/m2 or more with 20.9% having a BMI of less than 18.5 kg/m^2.

Mean (SD) serum albumin was 3.6 (0.6) g/dl. The range of the serum albumin was 1.3 to 4.6 g/dl. Majority of patients (75.4%) had serum albumin of 3.5 g/dl or more. Most of them were in the category of 3.5 g/dl to 3.9 g/dl. Overall, more than a quarter of the patients had serum albumin of 4 g/dl or more which is the cut off for normal according to MIS.

The mean (SD) TIBC was 252.9 (53.1) mg/dl. More than a third of the patients had a serum TIBC of 250 mg/dl or more. The range of the TIBC was 117 to 652.9 mg/dl.

All the study patients had high CRP with a mean (SD) of 37 (11.1) mg/l. The range was 24.5 to 101.6 mg/l. This was high compared to the upper limit of normal, 5 mg/l, used in this study to denote significant inflammation. Only a single CRP measurement was done for exploring a correlation with MICS.

Table 4. BMI and Laboratory parameters

Variable	Frequency, n (%). N=134
BMI (kg/m^2)	
Mean (SD), range	21.2 (3.4), 14.2-31.8
MIS Category	
≥20	88 (65.7)
18-19.99	25 (18.7)
16-17.99	15 (11.2)
<16	6 (4.5)
WHO Category	
<18.5	28 (20.9)
≥18.5	106 (79.1)
Serum albumin g/dl	
Mean (SD), range	3.6 (0.6), 1.3-4.6
MIS Category	
≥4.0	38 (28.4)
3.5-3.9	63 (47.0)
3.0-3.4	20 (14.9)
<3.0	13 (9.7)
WHO category	
≥ 3.5	101 (75.4)
<3.5	33 (24.6)
Serum TIBC (mg/dl)	
Mean (SD), range	252.9 (53.1), 117-652
Category	
≥250	51 (38.1)
200-249	75 (56.0)
150-199	6 (4.5)
<150	2 (1.5)
CRP, Mean (SD) mg/l, range	37.0 (11.1), 24.5-101.6

6.5 PREVALENCE AND SEVERITY OF MICS

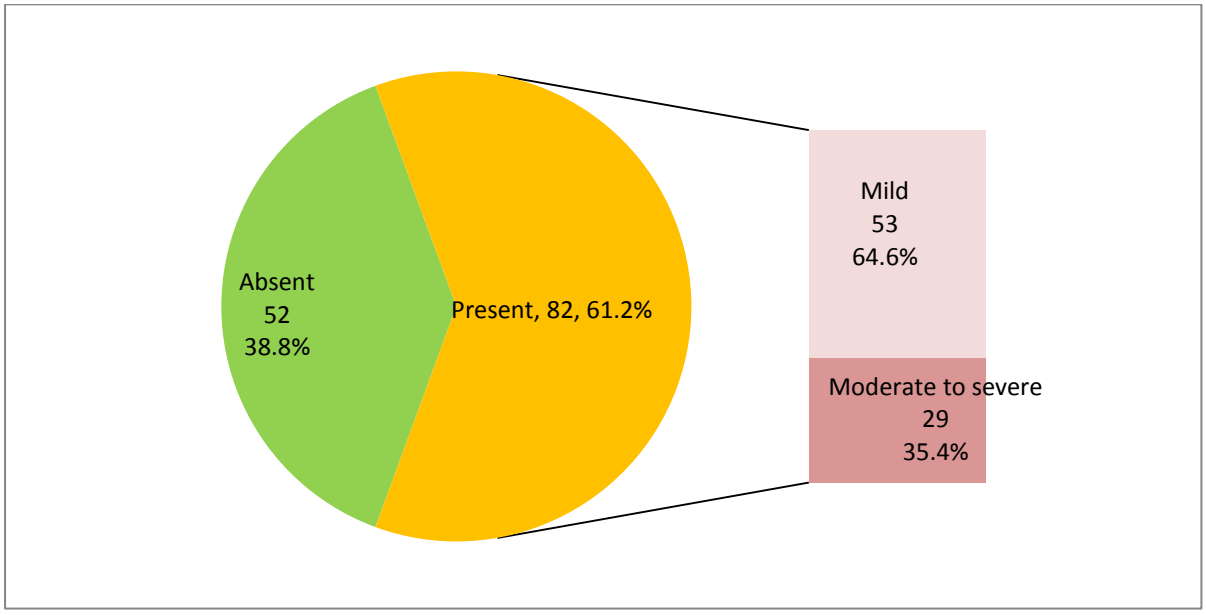
Malnutrition Inflammation Complex syndrome was considered to be present for any patient who had a score of 6 and above, as determined by the malnutrition inflammation score. The prevalence of MICS was high at 61.2% (95% CI, 53-69.4) affecting 82 patients. Among those who had MICS, 53 (64.6%. CI, 53.6-74.7) had a MIS score of between 6 and 10 placing them under mild severity while the rest had moderate to severe MICS. The MIS range was 1 to 18. (Table 5)

Table 5. Prevalence and severity of MICS in patients undergoing MHD

Variable	Frequency (%), n=134	95% CI
MICS		
Present	82 (61.2)	53.0-69.4
Absent	52 (38.8)	30.6-47.0
MICS severity (n=82)		
Mild (6-10)	53 (64.6)	53.6-74.7
Moderate to severe (11-30)	29 (35.4)	25.3-46.4

The prevalence of MICS was high at 61.2% with 35.4 % having moderate to severe MICS

Figure 2. Prevalence and severity of MICS in patients undergoing MHD



6.6 FACTORS ASSOCIATED WITH MICS

MICS was more likely to affect females, with an odds ratio of 2.6 and this was the only factor that reached statistical significance, (p value of 0.013). Patients who had a high CRP were more likely to have MICS but this fell short of statistical significance. The values of CRP were dichotomised into normal or high with the cut off 6 mg/ml and above being high. The mean (SD) CRP for those who had MICS was 38.4 (13.0) mg/l compared to 34.7 (6.7) mg/l, p value 0.056. There was no statistically significant association between prevalence of MICS and marital status, age, dialysis vintage, type of vascular access and dialysis hours per week. There was no correlation between MIS and CRP.

Table 6. Factors associated with MICS

Variable	MICS		OR (95% Cl)	P value
	Present	Absent		
Gender				
Male	44 (53.0)	39 (47.0)	1.0	
Female	38 (74.5)	13 (25.5)	2.6 (1.2-5.6)	0.013
Age in years				
13-30	20 (62.5)	12 (37.5)	1.3 (0.5-3.8)	0.589
31-40	17 (54.8)	14 (45.2)	1.0 (0.3-2.7)	0.956
41-50	12 (66.7)	6 (33.3)	1.6 (0.5-5.5)	0.457
51-60	18 (69.2)	8 (30.8)	1.8 (0.6-5.6)	0.307
>60	15 (55.6)	12 (44.4)	1.0	
Marital status				
Single	23 (62.2)	14 (37.8)	1.1 (0.5-2.4)	0.803
Separated/divorced	4 (80.0)	1 (20.0)	2.7 (0.3-25.0)	0.384
Married	55 (59.8)	37 (40.2)	1.0	
Type of vascular access				
Central venous catheter	58 (61.7)	36 (38.3)	1.0	
Arteriovenous fistula	24 (61.5)	15 (38.5)	1.0 (0.5-2.1)	0.986
Arteriovenous graft	0	1 (100.0)	-	1.000
Dialysis hours per week				
Up to 4 hours	22 (56.4)	17 (43.6)	0.8 (0.3-1.6)	0.467
5-8 hours	60 (63.2)	35 (36.8)	1.0	
Mean CRP (SD) mg/l	38.4 (13.0)	34.7 (6.7)	-	0.056

7.0 DISCUSSION

The burden of malnutrition inflammation complex syndrome among patients undergoing maintenance haemodialysis at KNH prior to this study was unknown. This was the first study that set out to determine the burden and some correlates of MICS. This study reports the findings of the prevalence and severity of MICS as determined by the MIS as well as the exploratory findings of some of the correlates.

The prevalence of MICS in this study as measured by the 10 point malnutrition inflammation score (MIS) was 61.2% (95% CI, 53-69.4), affecting 82 of the 134 patients studied. Of these 82 patients, 53 (64.6%) had mild MICS and 29 (35.4%) had moderate to severe MICS. Overall, these constituted 40% and 21.1% of the patients under study, respectively. All patients (100%) had ongoing inflammation according to CRP and the mean CRP was more than 6 times the upper limit of CRP used in this study.

7.1 PREVALENCE AND SEVERITY OF MICS

The prevalence of malnutrition and inflammation among MHD patients either as separate entities or as constituents of MICS has been found to be ranging from below 20% to as high as 97%. The main drivers of the differences are patient characteristics, region where the study was done and most important, the methods used to determine the presence of MICS or its constituents. The prevalence we report in this study is higher than that reported in most developed countries.

A prevalence of 61.2% found in our study was high. A number of factors may explain this. The tool used, MIS, has a high sensitivity to identify malnutrition and inflammation among MHD patients compared to other parameters such as serum albumin, BMI and SGA (11). Consequently, the use of MIS may have led to more patients with malnutrition and inflammation being identified compared to the lower prevalence (26, 27) seen previously when the latter methods were used at the same setting.

Slightly over forty percent of the patients had experienced reduced dietary intake and symptoms of reduced appetite, nausea, vomiting and/or diarrhoea. This may have in effect led to the signs of wasting and loss of functional capacity, which were present in over 80% and 70.2% respectively. Both reduced dietary intake and presence of GI symptoms, in the end, affect the other components of MIS and hence MICS (93). The implication of our finding of a high prevalence of both reduced dietary intake and gastro intestinal symptoms, as components of MICS, is that they could be targeted as modifiable factors to reduce the

overall prevalence and severity of MICS. There are recommendations from studies to use appetite stimulants, increasing the number of dialysis hours and intra dialysis nutritional supplementations, with favourable outcomes on MICS (13).

In a study done by Yamada et al in Japan among 422 MHD patients to validate other nutritional tools using MIS, he found the prevalence of MICS to be 38.6% (36). Only 2.6% of the patients were in the category of moderate to severe MICS compared to 22 % in our study. This is much lower than what we found but key differences may have caused this. All patients in their study had dialysis for 12 hours per week divided into four hourly sessions as opposed to most of our patients (70.9%), who dialysed for only 8 hours a week and the rest dialysing for four hours. The proportion of patients who had diabetes in our study was more than in their study population, (19.4% compared to 16.3%). Diabetes has been associated with increased severity of MICS in some studies (5).

Yamada et al also excluded patients with severe co-morbidities including severe cardiovascular disease, severe GI symptoms and progressive malnutrition. Severe cardiovascular disease has been shown to increase markers of inflammation, increase basal metabolic rate and lead to reduced nutrient intake and assimilation (53). Our study did not exclude these categories of patients and this may explain the prevalence difference. In deed, over 15% of our patients had severe GI symptoms and 45.5% had hypertension.

Twelve hours of dialysis per week has been shown to result in better scores in markers of malnutrition and inflammation as well as general morbidity and mortality (15). None of the patients in our study dialysed for 12 hours when compared to areas where the prevalence of MICS has been found to be low and patients are on a 12 hours a week dialysis regime (36, 53). Inference can be made that our patient population dialysed sub-optimally and this may have contributed to the high prevalence of MICS and hence there is perhaps a need to increase the weekly dialysis hours to 12.

In a cross sectional study done in Karachi by Zehra et al among 62 MHD patients, looking at the frequency of MICS using MIS in patients on MHD for more than 3 months, he found a prevalence of more than 90% (51). This is higher than a prevalence of 61.2 % that we documented. Most of their patient characteristics were similar to our study population. Karachi is in Pakistan, which is a developing country like Kenya. Their patients had dialysis for 8 hours or less a week, with a mean (SD) age of 46 (12.59) years. The mean serum albumin was 3.64 (0.55) g/dl, mean BMI was 22.3 (3.69) kg/m^2. Moderate to severe MICS

was documented in 48% of their patients, which is higher than what we found at 22%. Like in their study, the mean BMI and albumin we found was above the cut offs of 18.5 kg/m^2 and 3.5 g/dl used to evaluate for malnutrition in some centres including KNH.

Two factors may explain the difference between the prevalence in our study and the one by Zehra et al. First, whereas we used a cut off of six for MIS to identify those with MICS, they used a lower cut off of 1. They did not provide a reason for using this low cut off. A cut off of 6 is what is recommended and has been shown to be sensitive and specific not only for identifying those with MICS, but also in predicting long term morbidity and mortality (11, 24). Secondly, the proportion of females in their study was higher (55%) than it was in our study (38.1%). Female gender has been documented to have a significant association with the prevalence and severity of MICS (29). Indeed, our study findings found a similar association (p=0.013).

Rambod et al (29), in a study of 809 MHD patients in the USA, found the prevalence of MICS to be about 46%. Like in our study, he used MIS for evaluation of MICS. The prevalence in our study was higher than they documented. Most of the patient characteristics in their study, e.g. a mean age above 60 years, a higher prevalence of diabetes at slightly above 50% and many years on dialysis would have favoured a higher prevalence compared to what we found. The key difference was that more than 50% of their patients were on insurance and could access all the requirements of dialysis, including more dialysis sessions per week. Lack of resources has been cited as a cause of sub optimal number of dialysis sessions among patients undergoing MHD at KNH (27). Studies in other resource poor countries have equally demonstrated a high prevalence of MICS (52). A universal health access program could perhaps help improve the level of access to dialysis.

Chen et al, (94), in a study of 75 patients in China found a higher prevalence (48%) of MHD patients who had a MIS score of greater than 10 (moderate to severe) compared to what we found at 21.6%. The mean (SD) duration of dialysis was more than that in our findings, 39.48 (12.96) months compared to 28 (28.8) months. They studied an aging population with a mean age (SD) of 63 (11.9) years compared to ours at 44.2 (15.8). Both an advanced age and longer duration on MHD in months have been associated with increased prevalence and severity of MICS (56), and this may explain the prevalence differences. Possible explanations for the young average age in our study are attrition to death, transition to renal transplant and default from dialysis due to various reasons, including the high cost of dialysis.

In 2001 at the KNH renal unit, Oduor et al did a study on the frequency of protein energy malnutrition (PEM) among patients with ESRD on MHD (26). This is the only study ever done in the past at the unit looking at the components of malnutrition and inflammation using SGA and CRP. For a period of 6 months, they recruited and studied 54 patients. The prevalence of PEM was high at 48.1%. Similar to the findings in our study, the pre dialysis mean (SD) serum albumin was 3.6 (7.1) g/dl, and the use of central venous catheters was almost 70% like in our study. The prevalence in our study may have been higher due to the use of MIS instead of SGA. MIS has all the seven components of SGA and the addition of the 3 components of BMI, serum albumin and TIBC added to its increased sensitivity and specificity (11, 29). The mean (SD) BMI in the Oduor study was 22 (3.9) kg/m^2 which is also similar to our study, 21.2 (3.4) kg/m^2. It is likely that the findings would be similar if there were no methodological differences.

It therefore seems that the burden of some constituents of MICS have not improved since the year 2001 among MHD at the KNH renal unit. Part of the explanation would be that the proportion of patients on CVC access has remained the same, which was 67% as compared to 70.1% in our study. Moreover, just as it was 15 years ago, patients have remained on eight or less hours of dialysis per week. The significance of 12 hours of dialysis per week has been highlighted earlier on. CVCs have been associated with increased markers of inflammation such as CRP and a change to AVF as the dialysis access has actually been shown to lead to a reduction of these markers (71).

A single measurement of CRP was done in this study to explore for its correlation with MIS. All patients had a high CRP, with a mean (SD) of 37 (11.1) mg/l against an upper limit of 5 mg/l for normal. The range for the CRP values was 24.5 to 101.6 mg/l. The high CRP may also explain the high prevalence of MICS as CRP has been shown to positively correlate with MICS (94).

Factors that were common in our study patients and have been shown to increase markers of inflammation were hypertension, diabetes (47, 95), (both of which constituted 64.9%) as well as kidney disease itself. These were however, co variates (as co-morbid conditions) in the MIS and as such, the study was not powered to analyse their individual effect on MIS and CRP. The effects of factors such as infections, impurities in dialysis water and membrane incompatibility were not studied and may have led to inflammation hence a high CRP. Their

inclusion is not likely to have influenced the outcome of exploring the correlation between CRP and MIS, as both were done under the same conditions.

Fifteen years ago, Oduor et al found a CRP of greater than 5 mg/l in only 30% of the patients they studied at the KNH renal unit (26). They used a less sensitive method of latex agglutination but they too, like in our study, did not exclude patients with co-morbid conditions that would lead to high CRP values. A high single CRP value correlates with mortality among MHD and this correlation has been shown even at 5 years from the baseline measurement (50). In a study of 169 patients that were followed up for 5 years, Iseki (48), demonstrated that patients who had a single measure of CRP of more than 10 mg/l had an increased mortality at 5 years as opposed to those with CRP less than 10 mg/l. Further to this, a CRP increase of more than 10 µg/ml has been shown to increase mortality by 39% (47). The effect of individual factors leading to the high CRP in all patients was not studied as the design of our study inherently lacked the power to do so. Establishing such factors may then form points of intervention.

The findings of a high prevalence of MICS and its constituents portend a big health problem among dialysis patients. It has been demonstrated in studies that a decline in serum albumin, high MIS scores and a low BMI confer a greater risk for morbidity and mortality among MHD patients. For instance, Rambod et al demonstrated that a 2-point increase in MIS was associated with doubling of the risk of mortality (29). The risk of this mortality is especially high for patients with MIS scores above eight (30).

The study did not exclude other co-morbid conditions, and some were part of the MIS assessment tool. This may have led to an overstated prevalence necessitating cautionary interpretation.

Interventional measures such as regular screening for MICS, at the beginning of MHD and every 6 months have been recommended (15). Similarly, nutritional supplementation both oral and parenteral, and in both the intra-dialysis and off dialysis period are part of the recommendations to correct components of MICS and retard its progression (15, 86, 96). In places where these measures have been implemented the prevalence and severity of MICS have been found to be low (36). We therefore recommend active periodic surveillance and interventions aimed at nutritional supplementation and amelioration of factors that may be contributing to inflammation. This should be followed by studies to evaluate the impact of these interventions on the prevalence and severity of MICS.

7.2 FACTORS ASSOCIATED WITH MICS

There was a statistically significant association between MICS and female gender, with MICS occurring in 74.5% of females as compared to 53.0% of males (p=0.013). Previous studies have shown conflicting results in the association of gender and MICS. For instance, Rambod et al found that female gender was associated with a higher prevalence of MICS with worse outcomes (29). In contrast, Dzekova showed males to be affected more than females (76). The reasons for these differences remain largely unknown and need more studies.

The results did not show significant statistical difference for the association of MICS and dialysis hours per week, type of vascular access and dialysis vintage. The study was not powered to get these exploratory associations. Inadequate dialysis may have also contributed to the lack of association. Oduor et al demonstrated that about 80% of patients undergoing MHD at the renal unit were inadequately dialysed (26). Studies that have shown the association of MICS and the above factors had a greater proportion of their patients being adequately dialysed with 12 hours of dialysis per week (9, 55, 70). This contrasts the findings in our study where all patients had eight or less hours of dialysis per week.

All patients had elevated serum CRP and the mean (SD) was 37.0 (11.1) mg/l. There was no correlation between CRP and MIS perhaps due to the skewed distribution of CRP values. (Pearson's correlation co-efficient (r) = 0.015, p=0.865).

8.0 CONCLUSION

This study has added to our knowledge on the current burden of MICS at the KNH renal unit. The prevalence is high (61.2%) and more than one third (35.3%) of these patients have moderate to severe MICS, with all patients having ongoing inflammation. The only significant association found with MICS was female gender, therefore particular attention needs to be paid to this group of patients, and more so, studies to identify the reasons for this predisposition are suggested. About 30% and 70% of patients dialyse for 4 hours and 8 hours per week respectively. Optimal dialysis is achieved with 12 hours of dialysis per week and therefore this is a gap identified through this study and needs to be addressed. Similarly, a great proportion (70.1%) of the patients on MHD uses CVCs as the vascular access as opposed to AVFs and AVGs. The barriers to AVF and AVG creation need to be identified and addressed. Finally, the study has revealed that the prevalence of malnutrition and

inflammation is higher than that documented 15 years ago among ambulant MHD patients at KNH. It may be worthwhile to evaluate the cause for this.

9.0 RECOMMENDATIONS

1. There needs to be regular screening for MICS and its individual constituents as our study has revealed that a great proportion of patients on MHD are affected. Such an active program is not in place at the moment.
2. Further studies to determine the contributors to the high prevalence of MICS are recommended.

10.0 STUDY LIMITATIONS

1. The subjective nature of the questions on dietary intake and GI symptoms in the MIS may have introduced recall bias.
2. The study findings may only be unique to KNH and thus not be generalised.
3. Co-morbid conditions that were not clinically overt were not excluded and may have influenced the high prevalence.

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Appendix 1. STUDY INFORMATION AND CONSENT FORM

Study title: Malnutrition Inflammation Complex Syndrome among ambulant End Stage Renal Disease patients on maintenance haemodialysis at Kenyatta National Hospital (KNH).

My name is Dr Matiko. I am a postgraduate student in Internal Medicine at the University of Nairobi. I am undertaking a study in the renal unit at KNH among 130 maintenance haemodialysis patients to determine the prevalence and severity of malnutrition and inflammation by use of the malnutrition inflammation score. I will also be determining how some patient characteristics such as age, duration of time on dialysis and other diseases suffered by the patient affect the nutritional status. Malnutrition and inflammation affect outcomes in patients on dialysis and knowing whether one has them will help in instituting timely interventions.

Procedures

You are being asked to participate in a study that will take between 25 to 30 minutes. If you agree to participate, we expect you to sign a consent form indicating that you are voluntarily participating in the study and that you have been explained to and understood the objectives, benefits and risks of the study. We will also ask you some questions from the study proforma and write your responses. You will also undergo a general physical examination, an examination to determine your fat and muscle bulk, as well as weight and height. We will also withdraw 4 mls (Slightly less than a tea spoonful) of blood from your cubital region(on the arm) which will be used to measure serum albumin, total iron binding capacity and C-reactive protein.

Risks

At the site of skin puncture.

a) Swelling or bruising at the site By participating in the study you are exposed to the following risks.

b) Pain at the cubital region at the site of veni puncture, which may last for up to 10 minutes

c) Minimal bleeding of skin puncture due to accumulation of blood under the skin.

All efforts shall however be made to avoid any of these risks occurring to you, and should they occur to you, feel free to inform Dr Matiko or contact him on 0721931271.

Benefits

By participating in this study you will benefit by

a) Having all the above examinations and tests done free of charge.

b) A copy of the results will be availed in your file and the doctor informed of the same and a copy given to you upon request during the next clinic visit.

c) You will receive interventional advice and appropriate management based on the results by your attending physician and nutritionist.

Right to Refuse or Withdraw.

Your participation in this research is voluntary. If you do choose to participate, but prefer not to answer certain questions, you are free to do so. You are also free to terminate the interview and withdraw from the study at any time without losing any benefits or quality of management. You are free to ask questions before signing the consent form. If you agree to participate in the study, please sign on the consent form.

Reimbursement

We shall do this study within your normal scheduled visit time and all blood samples will be obtained alongside those for other routine tests and the results availed to you during your next scheduled visit thus eliminating the need for unscheduled visits that would necessitate reimbursement.

UTAMBULISHO NA MAELEZO YA UTAFITI KUHUSU LISHE NA UVIMBE MUWAKO MIONGONI MWA WAGONJWA WA FIGO WALIO KWENYE "DIALYSIS" KATIKA KITENGO CHA MAGONJWA YA FIGO KATIKA HOSPITALI YA KITAIFA YA KENYATTA.

Naitwa daktari Matiko. Mimi ni mwanafunzi wa stashahada katika chuo kikuu cha Nairobi. Ninafanya utafiti kwenye kitengo cha magonjwa ya figo hapa kwenye hospitali ya rufaa ya taifa, Kenyatta miongoni mwa wagonjwa wenye mchangamano wa matatizo ya lishe na uvimbe muwako. Pia nitabaini ambavyo baadhi ya hali sifa za wagonjwa zinavyoathiri hali ya wagonjwa. Lishe na uvimbe muwako zinaathiri kufaulu kwa "dialysis" na kujua hali ya wagonjwa kutasaidia kuwapa tiba kinga kwa muda muafaka.Utafiti huu unatarajiwa kufanywa kwa muda wa miezi miwili na tunatarajia kupata washiriki takribani mia moja na thelathini.

Vitendo fanyika

Unaombwa kushiriki kwenye utafiti utakaochukua kati ya dakika 25 hadi 30. Ukikubali kushiriki, unatarajiwa kutoa idhini yenye sahihi ili kuhakiki ridhaa yako kama mshiriki;na kwamba umeelezwa kuhusu malengo, manufaa na madhara yanayohusiana na utafiti huu. Pia tutakuuliza maswali machache na kukufanyia uchunguzi ili kubaini miongoni mwa mengine, uzito, urefu, na hali yako ya lishe.

Utatolewa damu kiasi cha mililita nne (Sawa na kijiko kidogo cha chai) ili kufanya vipimo vya maabara vitakavyohitajika.

Madhara

Unaposhiriki katika utafiti huu,kuna uwezekano wa kupatwa na madhara yafuatayo

a) Maumivu ya sehemu ya ngozi itakayodungwa sindano kutoa damu
b) Kutokwa na kiasi kidogo cha damu
c) Uvimbe mdogo kwenye ngozi mahali patakapotolewa damu

Tutajaribu kadri ya uwezo wetu kuhakikisha madhara haya hayakupati ila endapo kutakuwa na dhara lolote, wasiliana na mimi daktari Matiko mara moja ama kupitia kwa namba ya simu 0721931271.

Manufaa ya kushiriki

Mshiriki kwenye utafiti huu atanufaika kwa njia zifuatazo

a) Huduma zote zinazohusiana na utafiti zitafanywa bila gharama yoyote
b) Nakala ya matokeo ya vipimo vilivyofanywa itapelekwa kwa daktari wako pindi tu majibu yatakapotoka, na wewe pia utapewa nakala yako pale utakapo ihitaji kufikia kiliniki inayofuatia
c) Kwa wale watakao gunduliwa kuwa na tatizo kwenye vipimo vyao ndani ya utafiti huu, huduma za ushauri na tiba zitatolewa baada ya mapendekezo kwa wahudumu wako wa afya hapa kwenye kitengo cha wagonjwa wa figo.

Haki ya kutokushiriki

Kushiriki kwako kwenye utafiti huu ni kwa ridhaa yako binafsi na endapo hutakuwa huru kujibu swali lolote hilo linakubalika.Kutoshiriki kwenye utafiti huu hakutakuzuia kupata huduma zako za kawaida. Pia unaruhusiwa kuuliza swali ili kufafanuliwa zaidi kuhusu vipengele visivyoeleweka kabla ya kutoa idhini. Endapo unakubali kushiriki kwenye utafiti huu,tafadhali tia sahihi kwenye idhini.

Tunakuhakikishia kuwa taarifa zote zinazohusiana na wewe ,zikiwemo takwimu, zitahifadhiwa kwa umakini na zitatumiwa na mtafiti mkuu kwa ajili ya huu utafiti peke yake.

Fidia

Utafiti huu utafanyika ndani ya muda wa kawaida utakao kuwa umekuja kiliniki na matokea ya uchunguzi wa maabara yatakuwa tayari mara tu utakaporudi kwenye tiba kwa muda utakaokuwa umeratibiwa. Kwa sababu hiyo, hutarajiwi kuja kwa muda mwingine wa ziada na hivyo basi hakutakuwepo na kurejeshewa gharama za usafiri.

Consent form

I, ----------, consent to participate in the study on "Malnutrition inflammation complex syndrome among ambulant end stage renal disease patients on maintenance haemodialysis at the Kenyatta national hospital". I do this with full understanding of the purposes of the study and the procedures involved which include answering to some questions and having laboratory tests, all of which have been explained to me by Dr. Matiko

Signature of patient---------- Signature of witness----------
Thumb print…….. Date----------

Consent administered by (PI/Assistant)…….. … Signature……

If you have questions during the course of the study, you may contact the following:

Dr. Matiko Giabe Mobile phone: 0721 931 271 or Professor Kayima 0733 730650

OR

The Chairman of Ethical and Review Committee Kenyatta National Hospital Tel:254 020 2726300 ext 44355, 726300-9

Idhini

Nambari ya ushiriki…… Umri……

Mimi……
….. Natoa idhini mwenyewe bila aina yoyote ya kushurutishwa au kulazimishwa kushiriki katika utafiti uliotajwa hapa kuhusu utafiti wa viwango vya utapia mlo na uvimbe muwako miongoni mwa wagonjwa wanaosafishwa damu kwa "dialysis" katika hospitali ya kitaifa ya Kenyatta. Nimeelezewa kikamilifu kuhusu madhumuni na hali yake na naelewa kuwa nitaulizwa maswali kadhaa na nipimwe damu. Pia naelewa kuwa naweza kujiondoa wakati wowote iwapo nitabadilisha mawazo. Haya yote yameelezwa kwangu na Dkt Matiko.

Sahihi ya mshiriki…… Sahihi ya shahidi……
Alama ya kidole …… Tarehe……

Jina la aliyechukua idhini…… Sahihi……

Ukiwa na maswali au jambo lolote unalohitaji kuelezewa zaidi tafadhali wasiliana na Dkt. Matiko Giabe kwa nambari ya simu ifuatayo: 0721 931 271 ama Professor Kayima 0733730650

Parent/Guardian consent for a minor to participate

I, ……., the parent/guardian of…….. give consent for his/her participation in the study on "Malnutrition inflammation complex syndrome among ambulant end stage renal disease patients on maintenance haemodialysis at the Kenyatta National Hospital". I do this with the full understanding of the purpose of the study and the procedures my child will undergo, including answering to some questions and having blood samples drawn for some tests, all of which have been explained to me by Dr Matiko/his research assistant. It has also been made clear to me that participation is voluntary and my child can withdraw or decline taking part in the study without any prejudice to his/her medical care.

Signature/thumbprint of parent/Guardian……. Date……...

Permission obtained by…….. Signature…….

Assent form for participants below 18 Years of age.

I……., assent to participate in the study on "Malnutrition inflammation complex syndrome among ambulant end stage renal disease patients on maintenance haemodialysis at the Kenyatta National Hospital". I do this with full understanding of the purpose of the study and involved procedures such as answering to some questions, a physical exam and having blood samples drawn from me as has been explained to me by Dr Matiko/his research assistant. It has also been made clear to me that my participation is voluntary and I can withdraw or decline participation in the study without my medical care being compromised.

Signature/thumbprint……Witness Guardian/Parent……

Assent administered by……. Signature…….

Date…….

Ruhusu ya mzazi/mwangalizi wa mshiriki mwenye umri chini ya miaka kumi na nane.

Mimi……, mzazi/mwangalizi wa……
Naidhinisha kushiriki kwake kwenye utafiti juu ya viwango vya utapia mlo na uvimbe muwako miongoni mwa wagonjwa wanaosafishwa damu kwa “dialysis” katika hospitali ya kitaifa ya Kenyatta. Nimeelezwa kikamilifu kuhusu madhumuni ya utafiti huu na kwamba mwanangu anatarajiwa kujibu maswali kadhaa, kupimwa na kutolewa damu kwa ajili ya vipimo vya maabara. Pia nimeelezwa kuwa kushiriki kwake ni kwa hiari na anaweza kujiondoa kwenye utafiti huu wakati wowote na bado ataendelea kupata huduma ya afya kikamilifu. Haya yote yameelezwa kwangu na Dkt Matiko/Msaidizi wake.

Sahihi/Alama ya kidole ya mzazi/Mwangalizi……Tarehe……

Jina la mtafiti/Msaidizi wake…….. Sahihi……

Ridhaa ya kushiriki kwa wenye umri chini ya miaka kumi na nane.

Mimi…….natoa ridhaa ya kushiriki kwenye utafiti juu ya viwango vya utapia mlo na uvimbe muwako miongoni mwa wagonjwa wanaosafishwa damu kwa “dialysis” katika Hospitali ya Kitaifa ya Kenyatta.Nimeelezewa kikamilifu kuhusu utafiti huu na ninaelewa kwamba nitaulizwa maswali kadhaa, kupimwa na kutolewa damu kwa ajili ya vipimo vya maabara. Pia nimeelezwa kuwa kushiriki kwangu ni kwa hiari na ninaweza kutoshiriki au kujiondoa kwenye utafiti huu na nikaendelea kupata huduma za afya kikamilifu. Haya yote yameelezwa kwangu na Dkt Matiko/msaidizi wake.

Sahihi/Alama ya kidole…….. Shahidi ……

Jina la mtafiti/msaidizi wake……..Sahihi……..

Tarehe……

Appendix 2: PHYSICAL EXAMINATION PROCEDURE

1. **Subcutaneous fat**

It was assessed by examining the fat pad directly below the eye and by gently pinching the skin above the triceps and biceps. The fat pads should appear as a slight bulge in a normally nourished person but are hollow in a malnourished person. When the skin above the triceps and biceps is gently pinched, the thickness of the fold between the examiners fingers is indicative of the nutritional status. The examiner then scores the observations on a four point scale as per the MIS sheet.

2. **Muscle wasting**

Muscle mass and wasting was assessed by examining the temporalis muscle, the prominence of the clavicle, the contour of the shoulders (rounded indicates well nourished, square indicates malnutrition), visibility of the scapula, the visibility of the ribs and the interosseous muscle mass between the thumb and forefinger, and the quadriceps mass. These are scored on a four point scale from zero to three, denoting increasing severity as is on the MIS sheet.

3**. Body Mass Index**

BMI was calculated by dividing weight (kg) by height squared (m)

i.e. $BMI=Wt/Ht^2(Kg/m^2)$

Standing height was measured once to the nearest 0.5 cm, without shoes, the back square against the wall tape, eyes looking straight ahead, with a set square resting on the scalp and against the wall. Weight was measured once with a lever balance to the nearest 100 grams with the patient in light garment and without shoes.

BMI was entered and scored according to the MIS.

Appendix 3: LABORATORY METHODS

Methods for measuring serum Albumin

Serum albumin was determined using the Cobas 410 machine at the KNH biochemistry laboratory.

The Bromocresol green (BCG) method was used, which is a photometric colorimetric assay.

The principle behind the assay is the formation of a coloured complex of albumin and BCG in a citrate buffer. The absorbance of this coloured complex is proportional to the albumin concentration in the sample.

The assay was done at a wavelength of 580-630 nm and a temperature of 37◦C.

Procedure

2µl of the sample was mixed with 300µl of the reagent

The absorbance was measured against the blank at 300 seconds to determine the concentration

Normal range according to this method is 3.7-5.3 g/dl or 37-53 g/l, but the categorisation used was as per the MIS as indicated in the methodology section in the text.

TIBC

The iron binding protein transferrin in serum is saturated upon treatment with excess iron III ions. Unbound (excess) iron is adsorbed onto aluminium oxide and precipitated. The transferrin bound iron (TIBC) in the supernatant is then determined.

Procedure

1.0 ml iron III chloride and 0.5 ml of the sample is pipetted into the reaction tube then mixed well.

After 3-5 minutes 0.25-0.35 g of aluminium oxide was added and then capped and placed on a rotator or roller mixer for 10 minutes. The tubes were then removed and centrifuged at 5,000 rpm.

Iron concentration was then determined from the supernatant and TIBC obtained by multiplying the iron concentration by three. A TIBC value of 250-450 µg/dl is normal in adults. The categorisation was done as per the MIS score as illustrated in the text under laboratory methodology.

CRP

CRP was determined using photometric-turbidimetric techniques.

Human CRP in patient specimen, standard or control reacts with anti-human CRP antibodies in the presence of an enhancer / accelerator buffer. The resulting immune complexes generate a turbidity of the reaction mixture which is proportional to the CRP concentration and can be measured by turbidimetry.

Two microlitres (2l) of the sample, 80 µl of anti-human C-reactive protein antibody was mixed gently with 320 µl of the buffer, incubated for one minute at room temperature and the absorbance read against the blank.

The sample absorbance was then obtained after incubation for 5 minutes.

The CRP concentration was obtained by multiplying the standard concentration by the absorbance of the sample divided by the absorbance of the standard and results expressed in mg/dl or mg/l. The upper limit of CRP concentration in adults is 0.5 mg/dl or 5 mg/l and readings above this were regarded as significant for inflammation.

Appendix 4: PATIENT DATA COLLECTION PROFORMA

Study Code No:_____ Date:_____

Section I: Demographic data

O/P number……

1. Age.....years. ☐

(1) 13-30 (2) 31-40 (3) 41-50 (4) 51-60 (5) >60.

2. Sex…… ☐ male=1 female=2

3. Marital status..... ☐

1=Single 2=Married 3=Separated 4=Other, specify……..

Physical Address (County, sub county, location)……..

Phone number…….

Section B: History

1. Aetiology of kidney disease ☐

1=Hypertension 2=Diabetes 3=Glomerulopathy 4=Obstructive uropathy 5=Other, specify…….

3. Sessions of dialysis per week……

4. Number of hours per dialysis session……

A. i) session 1..... ii) session 2..... iii) session 3.....

B. Dialysis hours per week……..

C.i) ≤4hrs ii) 5≤8hrs iii) 9≤12hrs iv) >12hrs ☐

5. Type of vascular access ☐

1=Central venous catheter 2=Arteriovenous fistula 3=Arteriovenous graft 4= Other, specify…….

6. Dietary intake over the past 1 month ☐

0=Normal 1= Less than normal but able to take solid foods 2=Reduced to a full liquid diet/supplements 3=Non caloric liquid/Starvation

7. Gastrointestinal symptoms over the last 2-4 weeks ☐

0=No symptoms with good appetite 1=Poor appetite with occasional nausea 2=Occasional vomiting/diarrhoea 3=Frequent diarrhoea, vomiting, anorexia

8 . Functional capacity? ☐

0=Normal/feeling fine 1=Occasional difficulty with baseline ambulation or feeling tired frequently 2=Difficulty with otherwise independent activities eg going to the bathroom 3=Bed/chair ridden with little to no activities.

9 .a) Co morbid conditions.....(Evaluate severity)

b) Duration on dialysis in months…….. ☐

0=Less than 12 months. 1=Between 12 months to 48 months 2=Over 48 months

Physical exam

10. a) Current body weight……(kg) Current height……(m)

Wt 3-6 months ago (From file) …… Percentage change in weight……

0=No decrease in dry weight or weight loss less than 0.5kg 1=Weight loss ≥0.5kg but <1 kg 2=>1kg but <5% 3=Weight loss >5% ☐

b)BMI (Kg/m^2) ---------- ☐

0=≥20 1=18-19.9 2=16-17.99 3=<16

11. Signs of decreased fat stores below the eyes, triceps, biceps, chest ☐

0=No change 1=Mild loss 2=Moderate loss 3=Severe loss

12. Signs of muscle wasting at the temple, clavicle, scapula, ribs, interosseous ☐

0=Normal/No change 1=Mild wasting 2=Moderate wasting 3=Severe wasting

STUDY CODE……. **DATE OF LAB ANALYSIS…….**

Laboratory parameters

13. Serum albumin g/dl..... ☐

0=≥4.0 1=3.5-3.9 2=3.0-3.4 3=<3.0

14. Serum TIBC mg/dl..... ☐

0=≥250 1=200-249 2=150-199 3=<150

15. Serum CRP _____ mg/dl

16. MIS _____ ☐

1=<6 2=6-10 3=>10

Study administered by……. Signature……..

Appendix 5: Malnutrition Inflammation Score (MIS)

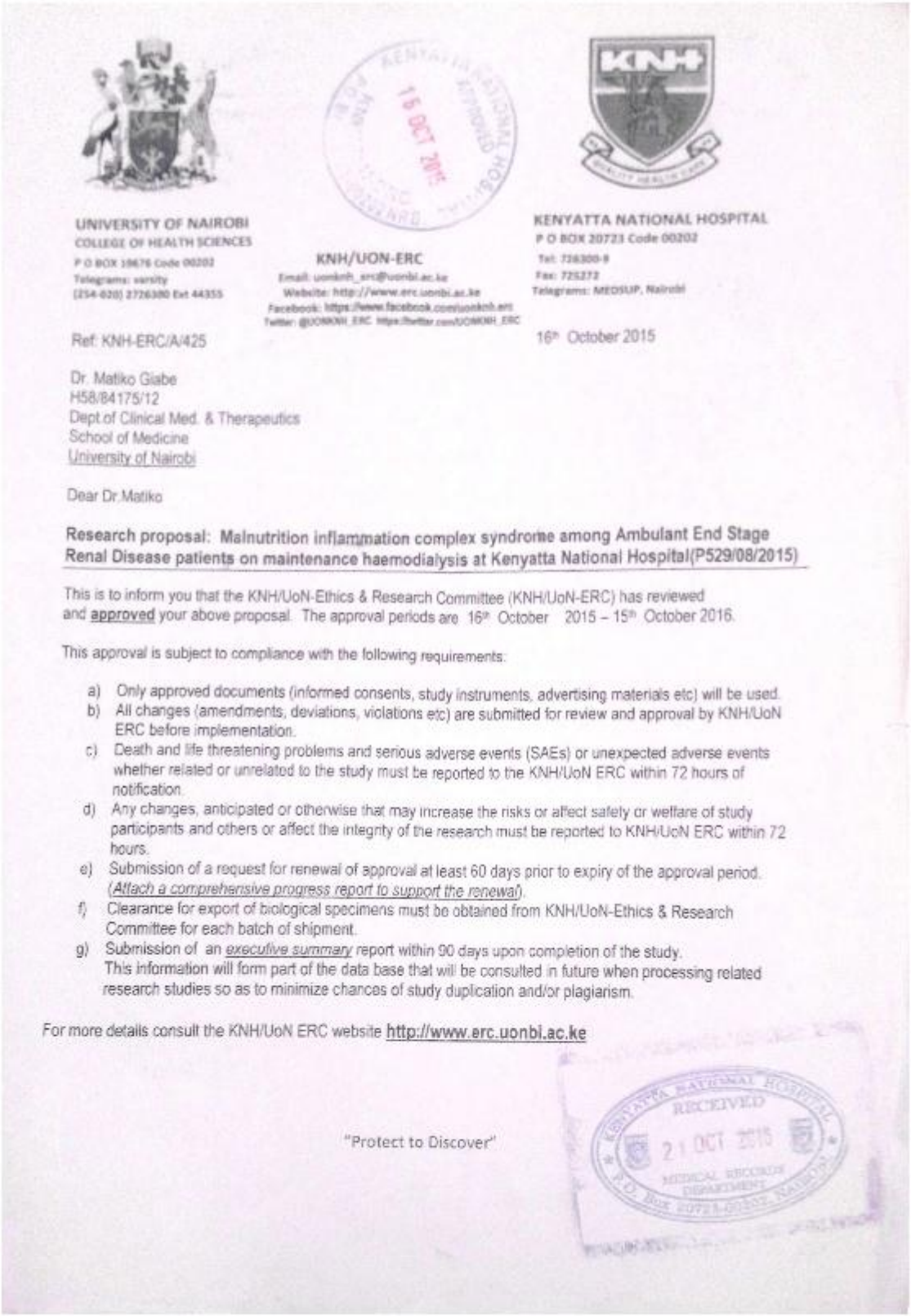
(A) Patients' related medical history:			
1- Change in end dialysis dry weight (overall change in past 3-6 months):			
0	1	2	3
No decrease in dry weight or weight loss <0.5 kg	Minor weight loss (≥0.5 kg but <1 kg)	Weight loss more than one kg but <5%	Weight loss >5%
2- Dietary intake:			
0	1	2	3
Good appetite and no deterioration of the dietary intake pattern	Somewhat sub-optimal solid diet intake	Moderate overall decrease to full liquid diet	Hypo-caloric liquid to starvation
3- Gastrointestinal (GI) symptoms:			
0	1	2	3
No symptoms with good appetite	Mild symptoms, poor appetite or nauseated occasionally	Occasional vomiting or moderate GI symptoms	Frequent diarrhea or vomiting or severe anorexia
4- Functional capacity (nutritionally related functional impairment):			
0	1	2	3
Normal to improved functional capacity, feeling fine	Occasional difficulty with baseline ambulation, or feeling tired frequently	Difficulty with otherwise independent activities (e.g. going to bathroom)	Bed/chair-ridden, or little to no physical activity
5- Co-morbidity including number of years on Dialysis:			
0	1	2	3
On dialysis less than one year and healthy otherwise	Dialyzed for 1-4 years, or mild co-morbidity (excluding MCC*)	Dialyzed >4 years, or moderate co-morbidity (including one MCC*)	Any severe, multiple co-morbidity (2 or more MCC*)
(B) Physical Exam (according to SGA criteria):			
6- Decreased fat stores or loss of subcutaneous fat (below eyes, triceps, biceps, chest):			
0	1	2	3
Normal (no change)	mild	moderate	Severe
7- Signs of muscle wasting (temple, clavicle, scapula, ribs, quadriceps, knee, interosseous):			
0	1	2	3
Normal (no change)	mild	moderate	Severe
(C) Body mass index:			
8- Body mass index: BMI = Wt(kg) / Ht^2(m)			
0	1	2	3
BMI≥20 kg/m^2	BMI: 18-19.99 kg/m^2	BMI: 16-17.99 kg/m^2	BMI<16 kg/m^2
(D) Laboratory Parameters:			
9- Serum albumin:			
0	1	2	3
Albumin≥ 4.0 g/dL	Albumin: 3.5-3.9 g/dL	Albumin: 3.0-3.4 g/dL	Albumin: <3.0 g/dL
10- Serum TIBC (total Iron Binding Capacity): ♣			
0	1	2	3
TIBC≥ 250 mg/dL	TIBC: 200-249 mg/dL	TIBC: 150-199 mg/dL	TIBC: <150 mg/dL
Total Score = sum of above 10 components (0-30):			

MIS. *Major comorbid conditions include congestive heart failure class III or IV, full-blown AIDS, severe coronary artery disease, moderate to severe chronic obstructive pulmonary disease, major neurologic sequelae, and metastatic malignancies or s/p recent chemotherapy. Suggested equivalent increments for serum transferrin are 200 (0), 170 to 200 (1), 140 to 170 (2), and 140 mg/dL.

A score of less than 6 is considered normal. A score of 6 to 10 is considered as mild.

A score of 11 and above is considered as moderate to severe (11).

Appendix 6: Ethical Approval Letter



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Ref: KNH-ERC/A/425

16th October 2015

Dr. Matiko Glabe
H58/84175/12
Dept of Clinical Med. & Therapeutics
School of Medicine
University of Nairobi

Dear Dr.Matiko

Research proposal: Malnutrition inflammation complex syndrome among Ambulant End Stage Renal Disease patients on maintenance haemodialysis at Kenyatta National Hospital(P529/08/2015)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 16th October 2015 – 15th October 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

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

"Protect to Discover"

KENYATTA NATIONAL HOSPITAL RECEIVED 21 OCT 2015 MEDICAL RECORDS DEPARTMENT P.O. BOX 20723-00202 NAIROBI

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chairperson, KNH/UoN-ERC
The Dean, School of Medicine,UoN
The Chair, Dept.of Clinical Med. & Therapeutics,UoN
The Assistant Director, Health Information Dept. KNH
Supervisors: Prof. J.K. Kayima, Dr. A.J. Were, Prof.C.S.Kigondu