PREVALANCE OF HYPONATREMIA AMONG ELDERLY PATIENTS AT THE MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA

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DECLARATION

Student's declaration:

This research thesis is my original work and has not been presented for a degree in any other university. No part of this research thesis may be reproduced without prior written permission of the author or Moi University.

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DEDICATION

I dedicate this work to my family: Melyne, Fatma and Faria for their prayers, support and inspiration. Special dedication to my dad and mum for their huge support through every mile of this journey.

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ABSTRACT

Introduction: Hyponatremia refers to a serum sodium level of less than 135mmol/L, and can be classified into various ways based on severity, tonicity, chronicity and volume status, with the most common and of clinical significance being hypotonic hyponatremia. It is the most common electrolyte abnormality in the elderly. Multiple factors are usually implicated in the development of hyponatremia in the elderly such as the low salt diet as recommended by clinicians, aging-related impaired water excretory capacity, and frequent comorbidities with exposure to medications. Considering all its etiologies, it is a factor of poor prognosis and is associated with increased hospital stay and institutionalization of the elderly. There is a growing size of elderly population in Kenya. However, the prevalence of hyponatremia in Kenya and sub-Saharan Africa is not well defined. Therefore, there is need for epidemiological data for evidence based early screening and diagnosis for successful management to prevent adverse outcomes.

Objective: To determine the prevalence, subtypes and factors associated with hyponatremia among the elderly patients.

Methods: This was a cross-sectional study conducted at the Moi Teaching and Referral Hospital (MTRH). The study population was all elderly patients aged ≥60 years in the emergency department. A total of 368 study participants were enrolled by systematic random sampling between April and June 2019. An interviewer administered structured questionnaire was used to collect socio-demographic and clinical data. Patients' medical records were also reviewed. Blood samples were collected for measurement of sodium, urea and glucose levels. Data was analysed for prevalence with statistical significance set at $p<0.05$.

Results: A total of 368 participants were included in the final analysis. Prevalence of hyponatremia was 70.38% (259/368). The most common subtypes were mild hyponatremia (n= 100; 27.2%) and hypotonic (true) hyponatremia (n=152; 41.3%). Other classes comprised of moderate hyponatremia (n=66; 17.9%), severe hyponatremia (n= 93; 25.3%), hypertonic hyponatremia (n= 60; 16.3%) and normotonic hyponatremia (n= 47; 12.8%). The most prevalent co-morbidity was hypertension (37.0%), followed by infections (24.7%), malignancies (19.6%), Diabetes Mellitus (11.1%) and stroke (9.8%). There was however no significant association between low salt diet and hyponatremia (OR=0.31; 95% CI 0.08 to 1.15; p=0.08). Use of thiazide diuretics (OR= 4.58; 95% CI 1.48 to 14.20; p=0.008) and age group 70-79 (OR=1.92; 95% CI 1.06 to 3.50; p=0.032) were identified as independent factors associated with hyponatremia among the elderly patients.

Conclusion: There is a relatively high prevalence of hyponatremia among the elderly patients at MTRH. Factors significantly associated with hyponatremia were age group 70-79, and the use of thiazide diuretics

Recommendations: Routine screening, monitoring and management of hyponatremia in the elderly due to its high prevalence and associated morbidity and cautious use of thiazides in the management of hypertension in the elderly due to the high risk of developing hyponatremia.

LIST OF ABBREVIATIONS

ACEs	Angiotensin Converting Enzyme Inhibitors
ADH	Anti-Diuretic Hormone
ARBs	Angiotensin Receptor Blockers
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CNS	Central Nervous System
CO	Calculated Osmolality
DALY	Disability Adjusted Life Years
DM	Diabetes Mellitus
EAH	Exercise Associated Hyponatremia
ECF	Extra Cellular Fluid
FES	Flame Emission Spectrophotometry
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
IES	Ion Selective Electrode potentiometry
IREC	Institutional Research and Ethics Committee
JEG	Joint European Guidelines
LOS	Length of hospital Stay
MELD	Model for End Stage Liver Disease
MO	Measured Osmolality

MTRH	Moi Teaching and Referral Hospital
[Na^+]	Sodium
ODS	Osmotic Demyelination Syndrome
OG	Osmolar Gap
OTC	Over the Counter drugs
RBS	Random Blood Sugar
RFT	Renal Function Test
SIADH	Syndrome of Inappropriate Anti Diuretic Hormone secretion
SSRIs	Selective Serotonin Reuptake Inhibitors
TBW	Total Body Water
UG	Uasin Gishu County
UN	United Nations
WHO	World Health Organisation

OPERATIONAL DEFINITIONS

Normal sodium values: This was defined as serum sodium values between 135-145 mMol/L

Hyponatremia: This was defined as serum sodium levels < 135 mMol/L

Mild hyponatremia: This was defined as serum sodium levels between 130-134mMol/L

Moderate hyponatremia: This was defined as serum sodium levels between 125-129 mMol/L

Severe hyponatremia: This was defined as serum sodium levels < 125mMol/L

Normal Plasma Osmolality: This was defined as values between 275-295 mOsm/L

Hypotonicity: This was defined as values < 275mOsm/L

Hypertonicity: This was defined as values > 295mOsm/L

Hypotonic (true) hyponatremia: This was defined as hyponatremia in the setting of hypotonicity

Normotonic hyponatremia: This was defined as hyponatremia in the setting of normal tonicity

Hypertonic hyponatremia: This was defined as hyponatremia in the setting of hypertonicity

Hyperglycaemia: This was defined as RBS of > 11.1 mMol/L

Calculated Osmolality: This was obtained by Smithline-Gardner formular 2[Na^+] (mMol/L) + Glucose (mMol/L) + Urea (mMol/L)

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CHAPTER ONE

1.0 INTRODUCTION

1.1 BACKGROUND

Hyponatremia refers to a serum sodium level of less than 135mEq/L.

The Joint European Guidelines (JEG) classifies hyponatremia in adults according to the serum sodium concentration as mild, moderate and severe.

Hyponatremia can also be classified according to fluid status, effective plasma osmolality; with hypotonic hyponatremia being the most common type of hyponatremia encountered in clinical practice. Onset and duration of hyponatremia as either acute or chronic is also an important consideration when deciding patient management plan. Classification by presence or absence of symptoms is also of utmost importance in guiding intervention.

Other forms of hyponatremia include redistributive hyponatremia and pseudohyponatremia with the error it poses, which has been discussed in details later on under chapter on literature review.

Hypo osmolality (serum osmolality < 275 mOsm/kg) always indicates excess total body water relative to body solutes or excess water relative to solute in the extracellular fluid (ECF), as water moves freely between the intracellular and the extracellular compartments. This imbalance can be due to solute depletion, solute dilution, or a combination of both (Eric E. et al. 2019).

Under normal conditions, renal handling of water is sufficient to excrete as much as 15-20 L of free water per day. Further, the body's response to a decreased osmolality is decreased thirst. Thus, hyponatremia commonly occurs when some condition impairs normal free water excretion. (Eric E. et al. 2019).

The high prevalence of hyponatremia among the elderly can be attributed to the aging impaired water-excretory capacity, and the frequent exposure to medications and disease conditions associated with hyponatremia in this population (Lindner G et al. 2014). This impaired water excretory capacity is mainly attributed to aging related reduction of glomerular filtration rate. Additionally, the decreased intrarenal generation of prostaglandins seen in advanced age may also be involved in the impaired ability of elderly individuals to excrete water (Clark B et al. 1994). Another contributing factor in elderly patients could be the age related reduction in the percentage of total body water content, leading to greater fluctuations in serum sodium concentration given that serum sodium levels = exchangeable total (sodium + potassium)/ total body water. Furthermore, a higher sensitivity to osmotic stimuli may be evident in geriatric population given that the relatively rare idiopathic syndrome of inappropriate antidiuretic hormone secretion (SIADH) is more frequently observed in elderly subjects (Helderman JH et al. 1978, Shapiro DS et al. 2010). Despite the above pathogenetic factors, the urinary diluting ability is preserved in most elderly persons, even with a low glomerular filtration rate (GFR), and hyponatremia develops only in the presence of increased water intake and additional precipitating or/and superimposed factors. In this context, elderly individuals frequently take drugs e.g. thiazide diuretics, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, non-steroidal anti-inflammatory drugs or and suffer from diseases e.g. DM, hypertension, infections, heart failure, liver diseases, malignancies, endocrinopathies that are well established causes of hyponatremia (Liamis G et al. 2008).

Moreover, many elderly patients with hypertension or heart failure follow a low salt diet that is associated with decrease serum sodium concentration. Additionally, in this

population, the frequent reduction in protein intake (habitual or due to superimposed illness) that impairs water excretion may also play a role in development of hyponatremia (Frenkel NJ et al. 2015, Liamis G et al. 2016).

Generally, hyponatremia is of clinical significance only when it reflects a drop in the serum osmolality (i.e., hypotonic hyponatremia), which is measured directly via osmometry or is calculated as 2 (Na^+) mEq/L + serum glucose (mg/dL)/18 + BUN (mg/dL)/2.8, (Eric E. et al. 2019).

The recommendations for treatment of hyponatremia rely on the current understanding of central nervous system (CNS) adaptation to an altered serum osmolality. In the setting of an acute drop in the serum osmolality, neuronal cell swelling occurs due to the water shift from the extracellular space to the intracellular space i.e., Starling forces. Therefore, correction of hyponatremia must take into account the chronicity of the condition. Acute hyponatremia (duration < 48 h) can be safely corrected quicker than chronic hyponatremia. Correction of serum sodium that is too rapid can precipitate severe neurologic complications. Most individuals who present for diagnosis, and individuals who develop it while in an inpatient setting, have had hyponatremia for some time, so the condition is chronic, and correction should proceed slowly. (Gross P, Reimann D, Henschkowski J, Damian M, 2001).

It is also important to note that there is Exercise-associated hyponatremia (EAH), which develops during or immediately after physical activity, that was first reported in athletes participating in long-duration, high-intensity exercise particularly in hot weather, but has since been described in otherwise healthy participants in a variety of sporting and recreational activities. EAH results from drinking hypotonic fluids (water or sports drinks)

beyond thirst and in excess of sweat, urine, and insensible water losses. (Hew-Butler T, Loi V, Pani A, Rosner MH, 2017)

For this research, emphasis shall be placed on the classification by tonicity. This is in a bid to differentiate the true hyponatremia, from the other forms of hyponatremia i.e. factitious hyponatremia/pseudohyponatremia, as this is based on the osmolality of blood. Generally, in true hyponatremia, the sodium levels are low, and the osmolality of blood is decreased while in factitious hyponatraemia, the sodium levels are low but the tonicity of blood is normal or high.

Hyponatremia is the most common electrolyte disorder in elderly patients and the incidence is about 7% in elderly healthy people but can exceed 40% in hospitalized patients. Considering all its etiologies, hyponatremia is associated with increased mortality and appears as a factor of poor prognosis. Alteration in the regulation of water homeostasis in the elderly result from multiple consequences of aging: change in body composition, alteration in renal function and hormonal changes (Hanotier P, 2015)

The high frequency of nutritional problems, particularly protein malnutrition, as well as the nil salt intake as is advised by ‘clinicians’ for elderly patients with hypertension may also serve to predispose the elderly to the development of hyponatremia.

Serum sodium falls by about 1 mmol/L with each decade increase in age and this may further serve to compound the hyponatremia problem (Nankabirwa H, et al., 2016).

Although diuretics especially thiazides are implicated as a frequent cause of hyponatremia on geriatric medicine, normovolemic hypotonic hyponatremia, and more particularly the syndrome of inappropriate antidiuresis is the most common cause. (Hanotier P, 2015)

Nevertheless, the cause of this syndrome can only be determined in approximately half of the cases and is usually a diagnosis of exclusion. Malignancies and medication chiefly psychotropic agents commonly prescribed in the elderly are the most frequent etiologies.

Hyponatremia could be a factor of frailty in geriatrics. Mild to moderate hyponatremia is generally considered asymptomatic but recent studies reported that asymptomatic hyponatremia contributes to neurological troubles like cognitive disorders, posture and gait impairments (Soiza R, et al, 2014).

In its other concerning effects on health, studies have also shown a strong association of hyponatremia as an independent risk factor for falls and could be associated with the development of osteoporosis (Ganguli A, at el., 2015).

While dissecting the problem of hyponatremia, data from some experiments has shown that low extra cellular [Na^+] directly affects cell homeostasis in neuronal cells as well as in osteoclast precursors, independently of reduced osmolality. (Benvenuti S, et.al. 2013). These data demonstrate the detrimental effects of hyponatremia extend beyond the "osmotic theory", in agreement with clinical observations. (Corona G, 2015).

Various studies have reported an association between hyponatremia, even when mild to moderate with mortality across many diverse conditions e.g. pneumonia, heart failure, acute myocardial infarction, cirrhosis and cancer. (Wald R, et al., 2010).

There are recent reports following extensive meta-analyses to assess the relationship between hyponatremia and mortality. Data from a meta-analysis study, involving 81 studies for a total of 147,948 hyponatremic subjects indicated that hyponatremia was associated with an increased risk of overall mortality (RR = 2.60[2.31–2.93]). Furthermore, hyponatremia appeared associated with an increased risk of death when patients were

analyzed separately based on specific diseases, such as myocardial infarction, heart failure, cirrhosis and pulmonary infections. Interestingly, a quite small difference in serum [Na^+] (mean 4.8 mmol/L) was detected in patients who died compared to survivors, albeit with the large numbers, small differences become significant (Corona G et. al. 2015).

Another meta- analyses performed in 2014 by Corona G et al, involving 13,816 hyponatremic patients, that sought to compare the mortality rate in human subjects with or without interval improvement of hyponatremia, with a mean follow –up of 33.6 months, found that an increase of serum sodium was obtained in about half of the patients, suggesting in principle that the management of patients with hyponatremia is far from being optimal

In the patients whom serum sodium [Na^+] was improved, the overall mortality rate was reduced up to 60% compared to patients with no improvement of their hyponatremia. While the data were obtained by considering any increase of serum sodium, the association between improvement of hyponatremia and reduced mortality was even stronger when the researchers performed a sensitivity analysis based on those studies in which a threshold for improvement of at least 130mmol/L was reported (up to 70% mortality rate reduction), thus increasing the strength of the relationship between significant increase in serum sodium and reduction of mortality rate. It was also observed that the reduced risk of mortality associated with hyponatremia improvement appeared to last during prolonged follow-up, with specifically reduced mortality persisting at 12 months of follow up, and a similar trend being observed at 36 months (Corona G et.al. 2015)

Another interesting finding from the meta-regression analysis was that the effect of the improvement of hyponatremia on the reduced risk of mortality increased as a function of

the prevalence of patients with a more advanced age. This observation is of particular importance to my study as hyponatremia occurs more commonly in elderly subjects.

This study thus, is of great importance in trying to establish the burden, sub-types and associations of hyponatremia among elderly patients who are being attended to at the MTRH emergency department and those that possibly need further admission for inpatient care.

The presence of this high prevalence of hyponatremia among this population from the previous studies, and the fact that hyponatremia by itself is an independent risk factor for mortality calls for the need to understand the level of morbidity and mortality contributed by this electrolyte abnormality especially among the elderly population who are at increased risk.

1.2 PROBLEM STATEMENT

There are an increasing number of reports of the rising prevalence of hyponatremia and especially among the elderly (Nair S et al. 2016, Lobo-Rodriguez C et al. 2016 & Gandhi S et al. 2016). This increase in prevalence of hyponatremia over time has a similar time course to the increase in adoption of low-salt diet (Drake-Holland AJ & Noble MI, 2016). Investigation into the Sodium electrolyte levels of individual subjects would be expected to reveal the suitability or otherwise of dietary salt intake. If this approach is adopted, it may be necessary to withdraw recommendation of low-salt diet to the entire population. (Drake-Holland AJ & Noble MI, 2016) found that low salt diet in the elderly and chronic sick resulted in increased severity of illness and demonstrated that low salt diet in the not obviously ill person could induce hyponatremic illness.

The increasing prevalence of hyponatremia, the high readmission and hospitalization rates associated with it, alongside its acute and chronic effects is a worrying development and an increasing burden for health services (Drake-Holland AJ, Noble MI, 2016). Most elderly patients in our setting have multiple comorbidities and are on different medication for the same, factors that have been shown to be associated with hyponatremia.

Treatment of hyponatremia depends on the severity and a clear understanding of the mechanisms of hyponatremia in each case. No treatment may be appropriate, but for those that require treatment, how do we proceed? What is the role of intravenous isotonic or hypertonic saline, fluid restriction and or diuretic therapy withdrawal? Various challenges are met when trying to solve these concerns. There is need to recognize true hyponatremia, determine its degree, recognize the severity of symptoms and assess need for hospitalization. This would potentially serve to minimize further declines in the serum sodium concentration thereby possibly decreasing intracranial pressure in patients at risk for developing brain herniation thus relieving symptoms of hyponatremia, and avoiding excessive correction of hyponatremia in patients at risk for osmotic demyelination syndrome (ODS).

There is need to have data on the prevalence, associated factors and different classes of this electrolyte abnormality in our institution, with the impact it has, so that prompt and appropriate steps and measures can be instituted, and the right timely interventions carried out to help the patients before adverse outcomes present.

1.3 STUDY JUSTIFICATION

There is paucity of data since prevalence of hyponatremia and more so among the elderly patients in Kenya and sub-Saharan African has not been well defined. Most data is from western countries.While hyponatremia is associated with a number of demographic markers, medications, and chronic disease states, knowing the relative magnitude of

predisposing factors and severity in our patients might aid in the prevention of severe hyponatremia. Possibly, medications like thiazides and antipsychotics could be avoided in patients at high risk. Alternatively, closer monitoring of electrolytes in hyponatremia prone patients could detect changes in serum sodium before they become dangerous.

According to a study published in the Journal of General Internal Medicine by Terzian C, Frye E, & Piotrowski Z in 1994, concerning admission hyponatremia among the elderly, 65 years and above, at a community teaching hospital, in America, they found that In-hospital mortality was 16% for patients with admission hyponatremia versus 8.0% for patients without admission hyponatremia. When they adjusted for patient and hospitalization characteristics with a logistic regression analysis, admission hyponatremia was a significant independent predictor of mortality (RR= 1.95).

Hyponatremia especially at admission is associated with poor prognosis in the elderly hospitalized population. (Terzian C, Frye E, & Piotrowski Z, 1994).

The purpose of this study is thus to evaluate and quantify the prevalence, types and associated factors of hyponatremia in the elderly patients at MTRH with their various clinical profiles and to establish the re admission rates of these patients, and to bring out the emphasis of the importance of being aware of and need for screening and a systematic management of hyponatremia particularly in the frail elderly people, even in the minor forms and those considered as asymptomatic for their better management.

1.4 RESEARCH QUESTION

1. What is the prevalence of hyponatremia among the elderly patients at Moi Teaching and Referral Hospital?
2. What are the various subtypes of hyponatremia among the elderly patients at Moi Teaching and referral Hospital?

3. What are the factors associated with hyponatremia among the elderly patients at Moi Teaching and Referral Hospital?

1.5 RESEARCH OBJECTIVES

1.5.1 Broad Objective

To assess the prevalence of hyponatremia among the elderly patients at Moi Teaching and Referral Hospital.

1.5.2 Specific Objectives

1. To determine the prevalence of hyponatremia among the elderly patients aged 60 years and above at Moi Teaching and Referral Hospital.
2. To describe the subtypes of hyponatremia among the elderly patients aged ≥ 60 years at Moi Teaching and Referral Hospital.
3. To describe the factors associated with hyponatremia among the elderly patients aged ≥ 60 years at Moi Teaching and Referral Hospital.

CHAPTER TWO

LITERATURE REVIEW

This first section begins by giving a detailed account of the general principles of regulation of sodium and water balance and factors at play under various scenarios, which is crucial in understanding why the elderly are predisposed to development of hyponatremia as will be highlighted subsequently in this chapter.

2.1 General principles of disorders of water balance and sodium balance

2.1.1 Introduction

Disorders of water balance and sodium balance are common, but the pathophysiology is frequently misunderstood. As an example, the plasma sodium concentration is regulated by changes in water intake and excretion, not by changes in sodium balance. As will be described, hyponatremia is primarily due to the intake of water that cannot be excreted, hypernatremia is primarily due to the loss of water that has not been replaced, hypovolemia represents the loss of sodium and water, and edema is primarily due to sodium and water retention. Understanding these basic principles is essential for appropriate diagnosis and treatment (Sterns RH, 2016)

2.1.2 Terminologies

The following terms are commonly used when discussing disorders of water and sodium balance, and an understanding of what these terms represent is essential for appropriate diagnosis and treatment.

Total body water: The total body water (TBW) as a percentage of lean body weight varies with age. Approximate normal values are 80 percent in premature infants, 70 to 75 percent

in term infants, 65 to 70 percent in toddlers, and 60 percent after puberty. These values vary with the amount of fat since fat has much lower water content than muscle. Thus, the TBW as a percentage of total body weight is lower in individuals with more fat. The TBW has two main compartments: the extracellular fluid and the intracellular fluid, which are separated by the cell membrane. The relative size of the two main compartments varies with age. The extracellular fluid component is increased in infants and young children compared with older patients, which also contributes to the younger patients' greater TBW percentage of lean body weight. The cell membranes are freely permeable to water but not electrolytes and therefore help to maintain the different solute composition of the two compartments: sodium salts in the extracellular fluid, with chloride and bicarbonate being the major anions; and potassium salts in the intracellular fluid, with large macromolecular organic phosphates being the main anions (Sterns RH, 2016).

Extracellular fluid volume: The extracellular fluid component varies with age and is increased in infants and young children. In normal adults, the extracellular fluid (ECF) volume constitutes approximately 33 to 40 percent of the TBW and is determined by the absolute amounts of sodium and water that are present in the ECF.

The ECF volume is regulated by alterations in urinary sodium excretion that are primarily mediated by variations in the activity of the renin-angiotensin-aldosterone and sympathetic nervous systems, which promote sodium retention, and the secretion of natriuretic peptides, which promote sodium excretion.

Effective arterial blood volume: The hormonal changes that regulate the ECF volume are mediated by sensors in the renal afferent glomerular arterioles (for renin), carotid sinus (for sympathetic activity), and atria and ventricles (for natriuretic peptides) that respond to

changes in pressure, not volume. In most settings, pressure and volume change in parallel with changes in sodium intake or with gastrointestinal or renal sodium losses due, for example, to diarrhea or diuretic therapy.

Loss of ECF volume can lead to a reduction in tissue perfusion. However, the ECF volume and tissue perfusion do not always change in the same direction. Two common examples are heart failure with edema and cirrhosis with ascites. In both disorders, the ECF volume is increased, but tissue perfusion is reduced due to a low cardiac output in most cases of heart failure and to vasodilation in cirrhosis (Sterns RH, 2016).

Reduced effective arterial blood volume or reduced effective circulating volume are terms that have been used to describe the discrepancy between hypoperfusion and the increase in extracellular volume in heart failure and cirrhosis. In both disorders, decreased tissue perfusion activates sodium-retaining hormones, which increase the extracellular volume but, due to the underlying disease, do not normalize tissue perfusion.

Intracellular fluid volume: In normal adults, the intracellular fluid volume constitutes approximately 60 to 67 percent of the TBW.

Plasma osmolality: The plasma osmolality (Posm) is determined by the ratio of plasma solutes and plasma water. Most of the plasma solutes are sodium salts with lesser contributions from other ions (e.g., potassium, calcium), glucose, and urea. The normal Posm is 275 to 295 mOsmol/kg.

The plasma osmolality can be estimated from the following equation:

Posm = 2 x [Na] + [glucose]/18 + blood urea nitrogen/2.8

The multiple of two accounts for the anions accompanying sodium, and the divisors of 18 and 2.8 for glucose and the blood urea nitrogen convert the values in mg/dL to mmol/L. If the glucose and urea concentrations are reported in mmol/L, the equation becomes:

Posm = 2 x [Na] + [glucose] + [urea]

The contributions of glucose and urea are small when their concentrations are within the normal range; they become significant when marked elevations develop as with uncontrolled diabetes mellitus or reduced renal function, respectively.

Of note, the plasma and ECF osmolality are the same as the intracellular osmolality since most cell membranes are freely permeable to water.

Plasma tonicity: Plasma tonicity, also called the effective plasma osmolality, is the parameter sensed by osmoreceptors and determines the transcellular distribution of water. Water can freely cross almost all cell membranes and moves from an area of lower tonicity (higher water content) to an area of higher tonicity (lower water content).

The main difference between plasma tonicity and plasma osmolality is that plasma tonicity reflects the concentration of solutes that do not easily cross cell membranes (mostly sodium salts) and therefore affect the distribution of water between the cells and the ECF. By contrast, the plasma osmolality also includes the osmotic contribution of urea, which is considered an "ineffective" osmole since it can equilibrate across the cell membrane and therefore has little effect on water movement across the cell membrane. Ethanol is another osmole that rapidly enters cells and therefore has no tonicity (Silver SM, 2016)

The formulas used to estimate plasma tonicity are similar to those for the plasma osmolality with the one exception that the contribution of urea is not included:

The following examples illustrate the clinical importance of plasma tonicity and the difference between tonicity and osmolality:

- Hyponatremia is, in most cases, accompanied by a fall in plasma tonicity, which results in osmotic water movement from the ECF into the cells, including brain cells, and can contribute to the neurologic symptoms of hyponatremia. In this setting, both the plasma tonicity and plasma osmolality are reduced.
- Hypernatremia is accompanied by an increase in plasma tonicity, which results in osmotic water movement out of the cells, including brain cells, and can contribute to the neurologic symptoms of hypernatremia. In this setting, both the plasma osmolality and plasma tonicity are increased
- By contrast, urea accumulation in renal failure is associated with urea equilibration across the cell membrane. The plasma osmolality is increased by the excess urea, but the plasma tonicity is unchanged because urea is an ineffective osmole. As a result, there is little transcellular water movement. If, however, a patient with renal failure develops hyponatremia or hypernatremia, the changes in plasma tonicity will result in movement into and out of cells, respectively, similar to that seen in patients without renal failure. The plasma osmolality may still be elevated in patients with hyponatremia, but the plasma tonicity will be reduced.

Urea equilibration across the blood-brain barrier occurs much more slowly than water equilibration. Thus, urea can transiently act as an effective osmole with respect to the brain when its plasma concentration changes rapidly (Bhave G, Neilson EG, 2011). The most common example of this phenomenon is the rapid fall in plasma urea concentration produced by hemodialysis in a uremic patient. In this setting, the removal of extracellular

urea occurs more quickly than urea can equilibrate across the cell membrane. Thus, the plasma osmolality falls much more rapidly than the intracellular osmolality, which promotes osmotic water movement into cells. In the brain, the water shift can result in cerebral edema and acute neurologic dysfunction, changes that partially explain the dialysis disequilibrium.

Dehydration: Dehydration is defined as a reduction in TBW below the normal level without a proportional reduction in sodium and potassium, resulting in a rise in the plasma sodium concentration. With primary loss of free water (as with unreplaced insensible losses or water loss in diabetes insipidus), the major biochemical manifestation is hypernatremia. Because water equilibrates across the cell membrane, approximately two-thirds of the water losses come from the cells and one-third from the ECF. Thus, 3 L of free water would have to be lost to produce the same reduction in ECF volume as the loss of 1 L of isotonic saline. Thus, signs of hypovolemia are not present unless there is a marked degree of free water loss. Hypernatremia does not usually occur in patients who have an intact thirst mechanism and access to water since stimulation of thirst can replace most of the water deficit. (Bhave G, Neilson EG, 2011)

2.1.3 Regulation of water and sodium balance

The kidney regulates water and sodium balance independently since water can be taken in without salt and salt can be taken in without water. Regulation of plasma tonicity and of the effective arterial blood volume involves different hormones, although there are some areas of overlap, such as the hypovolemic stimulus to the release of antidiuretic hormone (ADH).

Regulation of plasma tonicity: Changes in plasma tonicity are sensed by osmoreceptors in the hypothalamus. These receptors affect both water intake and water excretion by influencing thirst and the release of ADH, respectively. ADH is the primary physiologic determinant of the rate of free water excretion. Its major renal effect is to augment the water permeability of the luminal membranes of principal cells in the cortical and medullary collecting tubules, thereby promoting water reabsorption via osmotic equilibration with the hypertonic interstitium.

Signaling by ADH via the vasopressin 2 (V2) receptor initiates a sequence of intracellular events culminating in increased water permeability. Under the influence of ADH, preformed cytoplasmic vesicles that contain unique water channels (aquaporin-2) move to and fuse with the luminal membrane, thereby allowing water to be reabsorbed down the favorable osmotic gradient. Once the water channels span the luminal membrane and permit osmotic water movement into the cells, water is then rapidly returned to the systemic circulation across the basolateral membrane, which is both water permeable (even in the absence of ADH) and has a much greater surface area than the luminal membrane. When the ADH effect has worn off, the water channels aggregate within clathrin-coated pits, from which they are removed from the luminal membrane by endocytosis and returned to the cytoplasm. (Bhave G, Neilson EG, 2011)

Thus, regulation of plasma tonicity is achieved by alterations in water balance. Suppression of ADH release is the primary protective mechanism against water retention and the development of hyponatremia, while thirst is the primary protective mechanism against water loss and the development of hypernatremia. The osmoreceptors are extremely sensitive, responding to alterations in the plasma tonicity of as little as 1 percent. In

humans, the osmotic threshold for ADH release is approximately 275 to 295 mOsmol/kg. Below this level, there is little if any circulating ADH and the urine should be maximally dilute with an osmolality below 100 mOsmol/kg. Above the osmotic threshold, there is a progressive and relatively linear rise in ADH secretion. This system is so efficient that the plasma osmolality usually does not vary by more than 1 to 2 percent, despite wide fluctuations in water intake (Verbalis JG, 2003)

Persistent water retention resulting in hypoosmolality and hyponatremia occurs, with rare exceptions, only in patients with an impairment in renal water excretion due to an inability to suppress the release of ADH due to reduced effective arterial blood volume (as seen in true hypovolemia, heart failure, or cirrhosis), or the syndrome of inappropriate ADH secretion (SIADH) or advanced renal failure in which water retention is largely independent of ADH.

Water is continuously lost in sweat, and these water losses increase with higher environmental temperature. Avoidance of hyperosmolality and hypernatremia requires the intake and retention of exogenous water. This is achieved by increases in thirst and ADH release, which are induced by the elevation in plasma tonicity. Even though thirst is regulated centrally (including cortical areas that influence nonessential or social drinking), it is sensed peripherally as the sensation of a dry mouth. The cessation of thirst (satiety) is also mediated initially in the periphery by oropharyngeal mechanoreceptors that are stimulated by swallowing relatively large volumes of fluid

In contrast to the response to hypotonicity, in which renal water excretion is of primary importance, thirst is the major defense against hypertonicity and hypernatremia. Hypernatremia generally will not occur in a patient with a normal thirst mechanism and

access to water. It is primarily seen in patients with impaired mental status (older adult or critically ill) who do not experience thirst or in infants who can experience thirst but require others to provide fluid intake (Verbalis JG, 2003).

Regulation of effective arterial blood volume: Changes in body sodium content usually lead to changes in extracellular fluid (ECF) volume and effective arterial blood volume. Changes in effective arterial blood volume are sensed by three major pressure receptors that activate specific systems that regulate both systemic vascular resistance and sodium excretion:

- Receptors in specialized cells in the afferent glomerular arteriole (called juxtaglomerular cells) sense the perfusion pressure in the kidney and are an important determinant of the activity of the renin-angiotensin-aldosterone system, which increases with renal hypoperfusion,
- Receptors in the carotid sinus and aorta regulate the activity of the sympathetic nervous system. Increased sympathetic activity also increases renin release and,
- Cardiac receptors regulate the release of atrial natriuretic peptide (mostly from the atria) and brain natriuretic peptide (mostly from the ventricles).

Angiotensin II and norepinephrine are vasoconstrictors; aldosterone, angiotensin II, and norepinephrine also promote sodium reabsorption. The natriuretic peptides are vasodilators that increase sodium excretion.

In response to volume expansion due to a high salt intake, natriuretic peptide secretion is usually increased while the renin-angiotensin-aldosterone system is suppressed; changes that promote urinary excretion of the larger sodium load (Verbalis JG, 2003)

By contrast, volume contraction will have the opposite effect. In addition, a reduced effective arterial blood volume (even in an edematous patient) activates the renin-angiotensin-aldosterone and sympathetic nervous systems. These hormonal changes result in both sodium retention and vasoconstriction, thereby maintaining the ECF volume and systemic blood pressure. However, when the renin-angiotensin-aldosterone system is markedly activated in these conditions, vasodilatory and natriuretic peptides as well as other hormones (such as prostaglandins) are often also increased. These counter-regulatory factors act to moderate the degree of vasoconstriction and salt retention. The importance of these moderating factors is evident, for example, when prostaglandin inhibitors (such as nonsteroidal anti-inflammatory drugs) are given to a patient with cirrhosis or severe heart failure. The inhibition of vasodilatory prostaglandins leads to marked salt retention and acute kidney dysfunction. These adverse effects are due to the development of unopposed vasoconstriction and salt retention (Ghosh N, & Haddad H, 2011)

Role of ADH in volume regulation: A substantial reduction in the effective arterial blood volume can lead to the release of ADH mediated by volume-sensitive receptors rather than osmoreceptors (Dunn F, Brennan T, Nelson E & Robertson G, 1973). In humans, nonosmotic release of ADH only occurs acutely if the reduction in effective arterial blood volume is sufficiently large as to lower systemic blood pressure (Bie P, Secher N, Astrup A & Warberg J, 1986); small, acute reductions in plasma volume that are sufficient to increase the secretion of renin and norepinephrine have little effect on the release of ADH. Once hypotension occurs, there may be a marked rise in ADH secretion (in addition to renin and norepinephrine), resulting in circulating hormone levels that can substantially exceed that induced by hypertonicity (Bie P, Secher N, Astrup A & Warberg J, 1986).

In addition to increasing water reabsorption by the distal nephron (an effect mediated by V2 receptors), ADH acts to increase vascular resistance via the V1 receptors (hence the name "vasopressin"). These actions of ADH will partially restore the ECF volume and increase blood pressure; however, as noted above, most (approximately two-thirds) of the retained water will move osmotically into the cells. Water retention will also lower the plasma sodium concentration (Goldsmith S, 1987).

Combined regulation of plasma tonicity and effective arterial blood volume: The preceding discussion dealt with regulation of plasma tonicity (and osmolality) and the effective arterial blood volume as isolated events. However, changes often occur in both parameters. The hormonal response to intake that alters both tonicity and effective arterial blood volume results in the excretion of urine with a composition that is similar to what has been taken in.

As an example, the intravenous administration of one-half isotonic saline (sodium concentration of 77 mEq/L) will result in volume expansion and, because it is a solution that is dilute to plasma, will cause a reduction in the plasma sodium concentration. These changes in body composition and volume will lead to expansion of the extracellular volume induced by saline administration that will reduce the activity of the renin-angiotensin-aldosterone system and increase the secretion of natriuretic peptides, both of which will promote the appropriate excretion of the excess sodium; and reduction in plasma sodium concentration and plasma tonicity induced by the infusion of a dilute fluid will suppress the release of ADH, resulting in a reduction in urine osmolality and an appropriate increase in water excretion (Goldsmith S, 1987).

The changes are in the opposite direction with exercise on a hot day that leads to the loss of dilute sodium-containing fluid as sweat. The net effect is a rise in the plasma sodium concentration and a fall in the extracellular volume. This will lead to the increase in plasma sodium concentration and plasma tonicity that will stimulate ADH release, resulting in a rise in urine osmolality and a reduction in urinary water loss; the associated hypovolemia will activate the renin-angiotensin-aldosterone system and suppress the release of natriuretic peptides, resulting in a fall in urinary sodium excretion, with the net effect that the urine will be concentrated (to prevent further water loss) and contain relatively little sodium, an appropriate response to hypertonicity and volume depletion (Bhave G, Neilson EG, 2011)

The increase in plasma sodium concentration and plasma tonicity will also increase thirst and water intake. Retention of ingested water (due to reduced water excretion in the urine) will return the plasma sodium concentration toward normal. Retention of ingested salt (due to reduced sodium excretion in the urine) will return the extracellular volume toward normal.

A third example is the ingestion of salted potato crisps without intake of water. The occurring sequence would be that salt intake will transiently raise the plasma sodium concentration, plasma osmolality, and tonicity; thus stimulating ADH release thereby reducing water excretion to prevent a further rise in the plasma sodium concentration. The increase in plasma tonicity will also cause osmotic water movement from the cells into the ECF. The ensuing ECF volume expansion will increase the release of natriuretic peptides and suppress the renin-angiotensin-aldosterone system, resulting in increased sodium excretion, with the net effect being excretion of urine with a high sodium concentration

and low volume, similar to what was taken in. Retention of ingested water (due to reduced water excretion in the urine) will return the plasma sodium concentration toward normal and shift water back into cells. Excretion of ingested salt (due to increased sodium excretion in the urine) will return the extracellular volume toward normal (Bhave G, Neilson EG, 2011)

2.2 Definition and classification

Hyponatremia is an important and common electrolyte abnormality that can be seen in isolation or, as most often is the case, as a complication of other medical illnesses e.g., heart failure, liver failure, renal failure, pneumonia (Hoorn E, Zietse R, 2017). The normal serum sodium level is 135-145 mEq/L. Hyponatremia is defined as a serum sodium level of less than 135 mEq/L.

The Joint European Guidelines (JEG, 2016) classifies hyponatremia in adults according to the serum sodium concentration as follows:

Mild: 130-134 mmol/L

Moderate 125-129 mmol/L

Severe / Profound: <125mmol/L, though severe symptoms with central nervous system manifestation usually occur at levels below 110 -120mmol/L.

Hyponatremia can also be classified according to fluid status:

Hypovolemic hyponatremia-Total body water (TBW) decreases; total body sodium (Na^+) decreases to a greater extent. The extracellular fluid (ECF) volume is decreased.

Euvolemic hyponatremia-TBW increases while total sodium remains normal. The ECF volume is increased minimally to moderately but without the presence of edema.

Hypervolemic hyponatremia-Total body sodium increases and TBW increases to a greater extent. The ECF is increased markedly, with the presence of edema.

Redistributive hyponatremia-Water shifts from the intracellular to the extracellular compartment, with a resultant dilution of sodium. The TBW and total body sodium are unchanged. This condition occurs with hyperglycemia or administration of mannitol.

Pseudohyponatremia-The aqueous phase is diluted by excessive proteins or lipids. The TBW and total body sodium are unchanged. This condition is seen with hypertriglyceridemia and hyperproteinemic states like multiple myeloma or immunoglobulin infusion therapy as may occur with Intravenous immune globulin (IvIg) management.

Hyponatremia can be further sub classified according to effective plasma osmolality, as follows:

Hypertonic hyponatremia- Normal total body sodium and a dilutional drop in the measured serum sodium due to the presence of osmotically active molecules in the serum e.g. mannitol. Osmolality is increased.

Normotonic hyponatremia- Severe hyperlipidemia and paraproteinemia leading to low measured serum sodium concentrations with normal serum osmolality.

Hypotonic hyponatremia- Most common type of hyponatremia encountered in clinical practice. Also referred to as the “true hyponatremia” - Reflects the inability of the kidneys to handle the excretion of free water to match intake. Osmolality is decreased.

Hyponatremia can also be classified on basis of duration whether chronic; occurring over a long duration giving body time to adapt or acute; and of which determines the mode of correction.

It is worth noting that in translocational/redistributive hyponatremia-i.e. as seen in hyperglycemic states, and in Mannitol infusion therapy, there is increased tonicity of blood due to osmotically active substances in serum, which causes shift in intracellular fluid to extracellular compartment, diluting blood and causing dilusional hyponatremia. This type of hyponatremia is usually transient and rectifiable once the insulting process has been corrected.

Of note too, is that hyperglycemia has a direct impact on sodium levels. For every 100mg/dL (5.5 mmol/L) increase in serum glucose, sodium levels decreases by about 1.6mmol/L up to 400mg/dL (22.2mmol/L), thereafter above 400mg/dL, the decrease can be as great as up to 4mmol/L for every 100mg/dL (5.5mmol/L) rise thereof. This will be important in calculating the corrected sodium value in diabetic patients presenting with hyperglycemia and hyponatremia.

Urine studies involving checking the urine osmolality and urine sodium concentrations are most useful in differentiating the cause of hyponatremia, which was not the scope of this study.

Urine osmolality can be used to rule out conditions with impaired ability of body to handle free water from primary polydipsia whereby; Urine tonicity of more than 100mOsm/kg indicates kidneys impaired ability to dilute urine, while a tonicity of less than 100mOsm/kg indicates primary polydipsia

Consequently, urinary sodium levels are important in distinguishing Syndrome of Inappropriate Anti-Diuretic Hormone secretion (SIADH), from hypovolemia, whereby, in SIADH, sodium levels would be typically >20-40mEQ/L, while in hypovolemia the urinary sodium value would be low, typically <25mEq/L.

2.3. Pseudohyponatremia and "concerns" of pseudohyponatremia error

While considering the spectrum of hyponatremia, it is worth putting into consideration that "pseudohyponatremia is an artifact" that should not be treated. There are case studies demonstrating the potential dangers of failing to recognize pseudohyponatremia and treating it as if it were true hyponatremia (Yavuzer K, Muhammed H, Ziya S & Fuat G, 2016).

Historically, plasma sodium measurement has been made using one of two basic techniques:

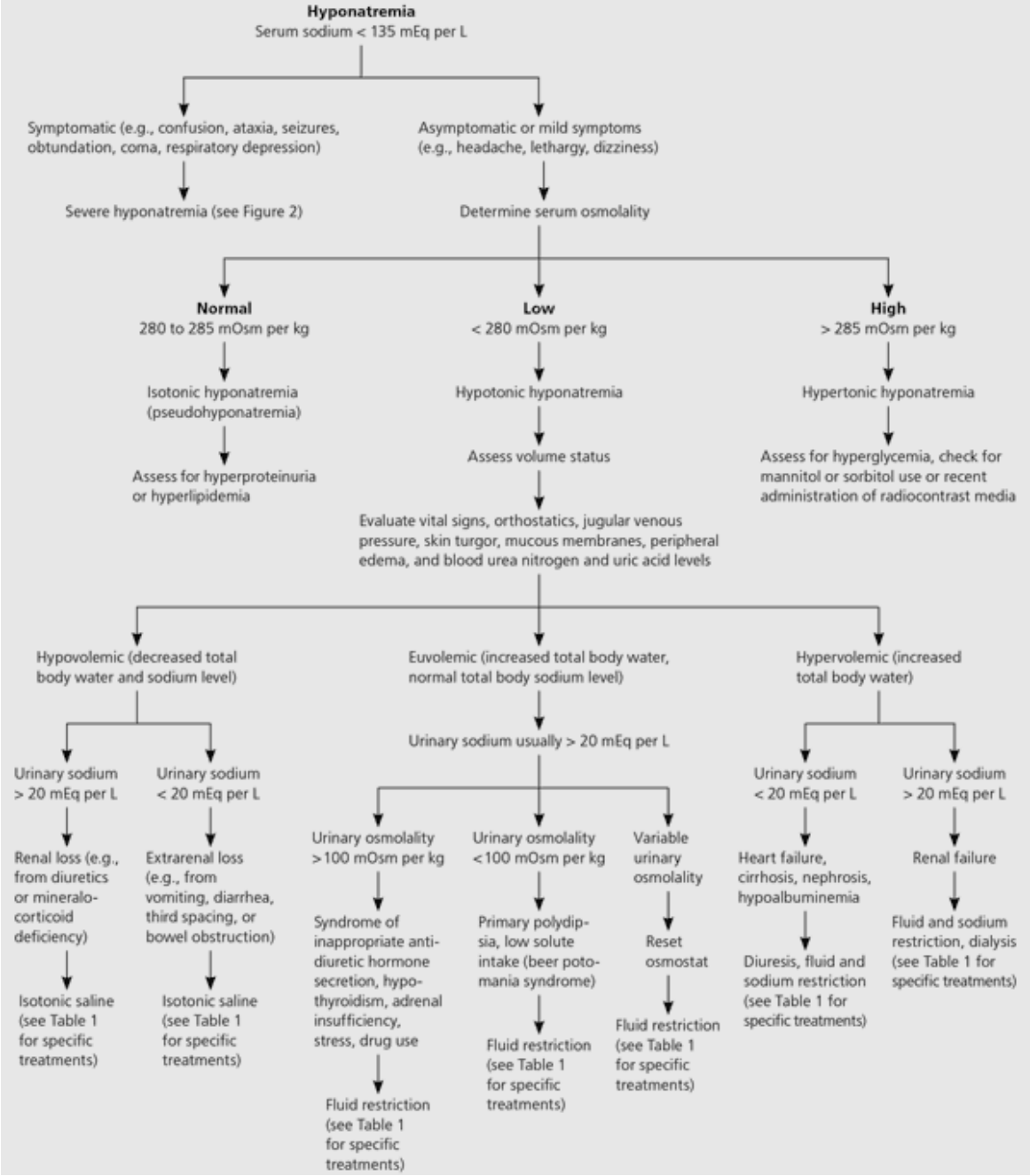
- **Flame emission spectrophotometry (FES),** the first and older technique that was used up to until 1980, that entails a step in serum dilution, and hence was prone to pseudohyponatremia misreading, though remains a reference method.
- **Ion-specific/selective electrode (ISE) potentiometry,** currently adopted by most labs, and has largely replaced FES, that is more convenient, of which the direct type measures undiluted plasma, is quite specific to pseudohyponatremic changes in blood, and almost exclusively excludes pseudohyponatremia, and is the technology utilized in blood gas analyzers.

Laboratories in Moi Teaching and Referral Hospital (MTRH) utilize this latest technology (ISE), using COBAS^{R} machine systems e.g. the Cobas Integra and Cobas C311 from Roche Diagnostics, and hence the concern or error of pseudohyponatremia shall have been addressed in the serum Sodium measurements. For the element of hyponatremia in known or newly diagnosed diabetics upon presentation, with the realization that elevated glucose levels may cause spurious fall in serum Sodium levels, necessary corrections shall be made during data analysis with appropriate formular put up to come up with corrected Sodium values.

2.4. Clinical significance, Aetiology, Diagnostics and Manifestation

A variety of the causes tend to overlap with the earlier on discussed classification of hyponatremia such as classification by tonicity and the causative mechanism like hyperglycemia in Diabetes Mellitus.

Causation too can be classified by various modalities such as by volume status and tonicity, which further helps in developing an algorithm of how to proceed in the evaluation of a patient with hyponatremia for treatment, with the initial step being categorizing the hyponatremia as to whether it is true hyponatremia (hypotonic) or factitious (hypertonic/normotonic/pseudo) hyponatremia, then volume status follows by conducting urine studies. The diagram below borrowed from an article in the American Journal of Family Physicians summarizes the idea:



Braun, M. M., Barstow, C. H., & Pyzocha, N. J. (2015). Diagnosis and management of sodium disorders: hyponatremia and hypernatremia. *American Family Physician*, *91*(5), 299–307.

Figure 1. Hyponatremia evaluation algorithm

The incidence of hyponatremia depends largely on the patient population and the criteria used to establish the diagnosis. Among hospitalized patients, 15-20% have a serum sodium level of less than 135 mEq/L, while only 1-4% have a serum sodium level of less than 130 mEq/L. The prevalence of hyponatremia is lower in the ambulatory setting. (Eric E & Simon M, 2018)

For example, in patients with acute ST-elevation myocardial infarction, the presence of hyponatremia on admission or early development of hyponatremia is an independent predictor of 30-day mortality, and the prognosis worsens with the severity of hyponatremia. (Goldberg A, Hammerman H & Petcherski et al 2004). Bae et al, 2016 reported that in hospitalized survivors of acute myocardial infarction, the presence of hyponatremia at discharge was an independent predictor of 12-month mortality. The study involved 1290 patients.

Similarly, cirrhotic patients with persistent ascites and a low serum sodium level awaiting transplant have a high mortality risk despite low severity (MELD) scores. The independent predictors—ascites and hyponatremia—are findings indicative of hemodynamic decompensation. (Heuman M,et al, 2004).

In patients with chronic kidney disease, hyponatremia is associated with an increased risk for all-cause mortality and for deaths unrelated to cardiovascular problems or malignancy. (Kim M, Baik S & Yea C, 2009).

Hyponatremia has also been found to be linked to an increased risk for cardiovascular- and malignancy-related mortality in these patients. The study included 45,333 patients with stage 3 or 4 chronic kidney disease, 9.2% of whom had dysnatremia (Huang H, Jolly S & Airy M, 2016).

It is worth noting that patients may present for medical attention with symptoms related to low serum sodium concentrations. However, many patients present due to manifestations of other medical comorbidities, with hyponatremia being recognized only secondarily. For many people, therefore, the recognition is entirely incidental. Patients may develop clinical symptoms due to the cause of hyponatremia or the hyponatremia itself.

Many medical illnesses, such as chronic heart failure, liver failure, renal failure, or pneumonia, may be associated with hyponatremia. These patients frequently present because of primary disease symptomatology e.g., dyspnea, jaundice, uremia, and cough (Bettari L et al. 2012)

Symptoms of hyponatremia range from nausea and malaise, with mild reduction in the serum sodium, to lethargy, decreased level of consciousness, headache, and (if severe) seizures and coma. Overt neurologic symptoms most often are due to very low serum sodium levels (usually < 115-120 mEq/L), resulting in intracerebral osmotic fluid shifts and brain edema. This neurologic symptom complex can lead to tentorial herniation with subsequent brain stem compression and respiratory arrest, resulting in death in the most severe cases.

The severity of neurologic symptoms correlates well with the rate and degree of the drop in serum sodium. A gradual drop in serum sodium, even to very low levels, may be tolerated well if it occurs over several days or weeks, because of neuronal adaptation. The presence of an underlying neurologic disease, like a seizure disorder, or nonneurologic metabolic abnormalities, like hypoxia, hypercapnia, or acidosis, also affects the severity of neurologic symptoms.

In interviewing the patient, obtaining a detailed medication history, including information on over-the-counter (OTC) drugs the patient has been using is important because many medications may precipitate hyponatremia (e.g., antipsychotic medications, antidepressants, antiepileptics and diuretics (Lu X, Wang X, 2017). A dietary history with reference to salt, protein, and water intake is useful as well. For patients who are hospitalized, reviewing the records of parenteral fluids administered is crucial. History of vomiting and diarrhea thus gastrointestinal losses may also be important in trying to elucidate the potential cause.

It is also worth taking a detailed history and documenting the various comorbidities present in the elderly while undertaking such a study. Comorbid conditions are commonly present with the geriatric population and associated with hyponatremia in elderly patients (Subhash C et al. 2019). In their study, they found out that 86.4% of patients in hyponatremic group had at least a comorbidity as compared to 69% in normonatremic group, which was statistically significant ($p<0.001$). Moreover, they observed the presence of multiple comorbid conditions as a significant risk factor for development of hyponatremia in elderly (OR= 2.113; 95% CI 1.608 to 2.775; $p< 0.001$). Hence, the various underlying conditions, medication history and prevailing signs and symptoms commonly associated with hyponatremia will form part of the variables under consideration.

2.5. Burden and spectrum of Hyponatremia

Hyponatremia is the most common electrolyte disorder in elderly patients. The incidence is about 7% in elderly healthy people but can exceed 40% in hospitalized patients. Considering all its etiologies hyponatremia is associated with increased mortality and appears as a factor of poor prognosis. Alteration in the regulation of water homeostasis in

the elderly result from multiple consequence of aging including but not limited to change in body composition, alteration in renal function and hormonal changes (Hanotier P, 2015). In a systematic review and meta-analysis conducted by Corona G et al (2016), to elucidate and compare the economic burden of patients with hyponatremia, involving 46 studies encompassing a total of 3,940,042 patients; among these, 757,763 (19.2%) were hyponatremic. Across all studies, hyponatremia was associated with a significantly longer duration of hospitalization (3.30 [2.90-3.71; 95% CIs] mean days; P < .000). Similar results were obtained when patients with associated morbidities were analysed separately. Furthermore, hyponatremic patients had a higher risk of readmission after the first hospitalization (odds ratio 1.32 [1.18-1.48; 95% CIs]; P < .000). A meta-regression analysis showed that the hyponatremia-related length of hospital stay was higher in the elderly patients (Slope = 0.002 [0.001-0.003; 95% CIs]; P < .000 and Intercept = 0.89 [0.83-0.97; 95% CIs]; P < .001). A negative association between serum [Na (+)] cut-off and duration of hospitalization was detected. A $3,000 (app Kshs. 300,000) higher hospital costs per patient was realised and associated with the hyponatremic patients when compared with the cost of normonatremic subjects.

In a related study by (Boscoe A, Paramore C. & Verbalis J.G., 2006), appearing in the BioMed Central (BMC Journal), the largest open access peer reviewed public health journal in the world, a medical journal addressing research questions in clinical medicine, public health and epidemiology, they tried to establish cost of illness of hyponatremia;

Utilizing a prevalence-based cost of illness framework that incorporated data from publicly available databases, published literature and a consensus panel of expert physicians, the panel members provided information on: classification of hyponatremia patients, treatment

settings for hyponatremia (i.e., hospital, emergency room, doctor's office), and health care resource use associated with the diagnosis and treatment of hyponatremia. Low and high prevalence scenarios were estimated and utilized in a spread sheet-based cost of illness model. Costs were assigned to units of resources and summarized across treatment settings. They found that the prevalence estimate for hyponatremia ranged from 3.2 million to 6.1 million persons in the U.S. on an annual basis. Approximately 1% of patients were classified as having acute and symptomatic hyponatremia, 4% acute and asymptomatic, 15%–20% chronic and symptomatic, and 75–80% chronic and asymptomatic. Of patients treated for hyponatremia, 55%–63% are initially treated as inpatients, 25% are initially treated in the emergency room, and 13%–20% are treated solely in the office setting. The direct costs of treating hyponatremia in the U.S. on an annual basis were estimated to range between $1.6 billion and $3.6 billion (1.6 trillion and 3.6 trillion Kshs)! The researchers concluded that treatment of hyponatremia represented a significant healthcare burden in the U.S. and that newer therapies and appropriate strategies that may help mitigate hyponatremia could minimize the costs associated with this condition.

Hyponatremia could be an independent risk factor of falls and could be associated with the development of osteoporosis. (Soiza R et al. 2014).

This concurs to a meta-analysis that was done by Will Boggs MD in 2018 whereby he reviewed various articles and found that mild hyponatremia was common in older adults and though once thought to be asymptomatic, recent studies have linked it to attention deficits, gait disturbances, fracture risk, cardiovascular events, and mortality.

This review of the literature emphasizes the importance of screening and a systematic management of hyponatremia in the elderly people, even in the minor forms and those considered as asymptomatic.

In a study whose findings were published in February 2018, in the Clinical Journal of the American Society of Nephrology, Dr. Kristen L. Nowak from University of Colorado did a study involving 5,435 men (mean age, 74) who participated in the MrOS study to investigate possible associations between hyponatremia and cognitive impairment and decline; Clinical hyponatremia (serum sodium <135 mmol/L) was associated with 2.35-fold increased odds of cognitive impairment at baseline. Clinical hyponatremia was significantly associated with cognitive decline as well.

As has been seen that hyponatremia is strongly associated with falls in the elderly, it is worth shedding some light on the burden of falls as a health concern. According to the WHO Global Burden of Disease database (2017), globally, falls are a major public health problem. An estimated 424, 000 fatal falls occur each year, making it the second leading cause of unintentional injury death, after road traffic injuries. Over 80% of fall-related fatalities occur in low- and middle-income countries, with regions of the Western Pacific and South East Asia accounting for more than two thirds of these deaths. In all regions of the world, death rates are highest among the elderly population who sustain falls. A fall was defined as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level. (WHO, 2017)

Though not fatal, approximately 37.3 million falls are severe enough to require medical attention occurring each year. Such falls are responsible for over 17 million DALYs

(disability-adjusted life years) lost. The largest morbidity occurs in the elderly; young adults aged 15–29 years and children aged 15 years or younger (WHO, 2017).

While nearly 40% of the total DALYs lost due to falls worldwide occurs in children, this measurement may not accurately reflect the impact of fall-related disabilities for older individuals who have fewer life years to lose. In addition, those individuals who fall and suffer a disability, particularly older people, are at a major risk for subsequent long-term care and institutionalization (WHO data book, 2017)

The financial costs from fall-related injuries are substantial. For people aged 65 years or older, the average health system cost per fall injury in the Republic of Finland and Australia are US$ 3,611 (app. Kshs. 361,100) and US$ 1,049 (app. Kshs. 104,900) respectively. Evidence from Canada suggests the implementation of effective prevention strategies with a subsequent 20% reduction in the incidence of falls could create a net savings of over US$ 120 million (app. Kshs 12 Billion) each year (WHO data book, 2017).

WHO further continues to note that age is one of the key risk factors for falls. Older people have the highest risk of death or serious injury arising from a fall and the risk increases with age. For example, in the United States of America, 20–30% of older people who fall suffer moderate to severe injuries such as bruises, hip fractures, or head traumas. This risk level may be in part due to physical, sensory, and cognitive changes associated with ageing, hyponatremia, in combination with environments that are not adapted for an aging population.

Nevertheless, as mentioned earlier, there is some evidence that correction of hyponatremia can improve cognitive performance and postural balance, potentially minimizing the risk of falls and fractures. Oral vasopressin receptor antagonists (vaptans.) are a promising

innovation, but evidence of their safety and effect on important clinical outcomes in frail elderly individuals is limited. (Soiza R et al, 2014)

Approach to hyponatremia in particularly the elderly individuals is particularly challenging as the underlying cause is often multi-factorial, a clear history may be difficult to obtain and clinical examination may be unreliable. Established treatment modalities are often ineffective and carry considerable risks, especially if the diagnosis of underlying causes is incorrect (Soiza R et al, 2014)

The clinician needs to have a clear understanding of the mechanisms of hyponatremia in each case with its degree/classification, whether treating would be appropriate, and how to proceed, as well as the role of intravenous isotonic or hypertonic saline, fluid restriction and or diuretic therapy withdrawal.

Concerning hyponatremia in patients who are also being admitted for inpatient care, a study by (Terzian, Frye, & Piotrowski, 1994) involving elderly patients, 65years and above at a community teaching hospital in the US, they found that in hospital mortality was 16% in these patients versus 8.0% for patients without hyponatremia at the time of admission - that is double the proportion and this is alarming rate!

When the researchers adjusted for patient and hospitalization characteristics, with a logistic regression analysis, they found that hyponatremia in patients at the time of admission was a significant independent predictor of mortality (RR=1.95). It was also associated with poor prognosis in the elderly hospitalized population.

As has been seen, hyponatremia contributes to frailty in the elderly, results in institutionalization of patients and increases hospital stay alongside posing poor prognosis to patients, and thus there is need to correctly and timely intervene as appropriate.

It is important to appreciate that hyponatremia is associated with a number of demographic markers, medication and chronic disease states, and knowing the relative magnitude and predisposing factors might aid in the prevention of severe hyponatremia. Medications like thiazides and antipsychotics could possibly be avoided in patients at high risk. On the other hand, closer monitoring of electrolytes especially in the elderly could detect changes in serum sodium before they become dangerous. Further research is however needed to establish effective strategies for prevention of severe hyponatremia (Buran G, 2009).

2.6. Mechanism of diuretic induced hyponatremia

Diuretics have been linked to causation of hyponatremia from numerous previous studies conducted. Nevertheless, virtually all severe cases of severe diuretic- induced hyponatremia have been due to thiazide type diuretics (Sonnenblick M et al. 1993, Friedman et al. 1989, Ashraf N et al. 1981, Fichman MP et al. 1971, Chow KM et al. 2003, Mozes B et al. 1986). Being core medication used in management of hypertension, with hypertension being a major comorbidity in the elderly, it is critical to elucidate the mechanisms at play that lead to this phenomenon when dealing with hyponatremia especially in the elderly.

Loop diuretics inhibit sodium chloride reabsorption in the thick ascending limb of the loop of Henle. The reabsorption of NaCl without water in the medullary aspect of this segment is normally the first step in the generation of the hyperosmotic gradient in the medullary interstitium, in the presecnce of ADH, the highly concentrated interstitium allows water to be reabsorbed in the medullary collecting tubule down the favourable osmotic gradient between the tubular lumen and the interstitium, resulting in the excretion of a concentrated urine (Richard H, 2018). Administration of a loop diuretic interferes with this process by

impairing the accumulation of NaCl in the medulla. Thus, although the loop diuretic can increase ADH levels by inducing volume depletion, responsiveness to ADH is reduced because of the impairment in the medullary gradient (Szatalowics VL et al. 1982). As a result, water retention and the development of hyponatremia will be limited unless distal delivery is very low or water intake is very high (Richard H, 2018).

The thiazides, in comparison, act in the cortex in the distal tubule; as a result, they do not interfere with medullary function or with ADH-induced water retention. Additionally, thiazides increase water permeability and water reabsorption in the inner medullary collecting duct, an effect that is independent of ADH (Cesar K.R, Magadi AJ, 1999). In addition to water retention, the combination of increased sodium and potassium excretion (due to the diuretic) and enhanced water reabsorption (due to ADH) can result in excretion of urine with a sodium and potassium concentration higher than that of plasma (Ashraf N et al. 1981). Therefore, loss of fluid can directly promote the development of hyponatremia independent of the degree of water intake hence a greater predilection to causing hyponatremia.

CHAPTER THREE

METHODOLOGY

3.1 STUDY DESIGN

This was a cross sectional study design. The design was chosen because it is best suited for determination of prevalence and description of associated factors, without necessarily showing causal effects.

3.2 STUDY SETTING

The study was conducted at the emergency department of Moi Teaching and Referral Hospital. MTRH is the second largest public national referral hospital in Kenya. It is located in Eldoret, Kenya. It is an 800- bed capacity; Moi University affiliated hospital, serving a broad mix of rural, urban poor and urban middle class population in western Kenya. It serves a population of 16 million people (40% of Kenya's population) in western Kenya and is the primary care centre for the 300,000 urban population of Eldoret town

3.3 STUDY POPULATION

3.3.1 Target population

The target population was elderly patients being attended to at the emergency department of Moi Teaching and Referral Hospital. Monthly number of elderly patients seen at the emergency department who are either admitted or discharged after management, and are aged 60 years and above on average varies from about 450 to 600 patients according to data from the Hospital records department.

3.4 SAMPLE SIZE

In sample size calculation, based on the objectives to be achieved, two formulae were employed separately then the one resulting in the largest sample size was adopted.

For objective one, involving prevalence studies, Fisher's formular was utilized thus:

$$\mathbf{n = \frac{Z^2 P (1\text{-}P)}{e^2}}$$

Whereby:

n= sample size

Z= confidence level at **95%** (standard value **of 1.96**)

P= estimated prevalence or proportion of elderly patients with admission hyponatremia; from other studies **40%. (Hanotier P, 2015)**

e= range of confidence interval placed at **0.05**

Substituting for n above**: -** $\mathbf{\frac{(1.96*1.96)\ (0.40)\ (1\text{-}0.40)}{(0.05)^2}}$

$$\mathbf{= (3.8416*0.40*0.60) / 0.0025}$$

Sample size n = 368

For the second objective involving factors associated, a formular by (Peduzzi et al. 1996) was employed thus:

$$\mathbf{n = \frac{10k}{p}}$$

Whereby:

n= sample size

k= number of associated factors (predictors), placed at **14** in this study

p= proportion of successes (prevalence) placed at **40%. (Hanotier P, 2015)**

Substituting for n above**: -** $\frac{\mathbf{10*14}}{\mathbf{0.4}}$

$$= 1400 / 4$$

Sample size n = 350

As seen from above, Fisher's formulae of determination of sample size of prevalence studies yielded the larger sample size for more precision of 368 hence was adopted.

3.5 SAMPLING TECHNIQUE

Probabilistic Systematic random sampling technique was used to select the participants for the study. A sampling interval of five was used as described below:

The 3 monthly average number of elderly patients seen at the emergency department needing admission or who get discharged after management, and are aged 60 years and above on average ranges between 450 to 600 patients according to data from the Hospital records department for month of April to June 2017 and 2018 (MTRH records department, 2018).

For the 3 months the study is expected to run (April-June 2019), the expected total number of patients to be seen will range from 1,350 (450*3) to 1,800 (600*3).

Calculated sample size = 368 from the formula earlier above.

Sampling interval = **N/n** = Expected target population size of the period **/** Sample size calculated

=1800 (upper limit considered) / 368 = 4.89 approx. **= 5**

Hence, every 5^{th} elderly patient was approached and recruited into the study. When the desired number was achieved, recruitment was halted.

The starting point was the first elderly patient registered for medical attention on the first day the study commenced.

3.6 ELIGIBILITY CRITERIA

3.6.1 Inclusion criteria

- Elderly patients, aged 60years and above, seeking medical care presenting at the emergency department of MTRH.

3.6.2 Exclusion criteria

- Those patients who had intravenous fluid administration/ blood infusion or medication such as sodium bicarbonate therapy done before blood samples were withdrawn as this would interfere with the results.

3.7 STUDY PROCEDURE

3.7.1 Recruitment of subjects

Chronological and continuous review of the patients' admission details at the records area of the emergency department was made to identify every fifth elderly patient by systemic random sampling attended to or at the waiting bay then subsequently approached. If the participant did not fulfill the eligibility criteria, the next 5^{th} patient was chosen to maintain at most randomness in sampling as possible. This occurred between April and June 2019. The participants who met the criteria were approached and requested to participate in the study. Figure 2 below shows a summary of the study flow algorithm.

The purpose of the study and the potential harms and benefits were explained to the participants individually in a language they understood and all their questions were answered. Those who met the inclusion criteria and consented to participate in the study were enrolled after signing informed consent forms (Appendix II and III).

The age was self-reported and confirmed from the documents (clinical data and/or national identity card). Recruitment was done until the desired sample size was achieved.

For the identified patients who were missed in the initial recruitment area at the emergency department, due to lateness in time of arrival or any other reason, prompt steps (within 24hrs) were taken to quickly follow the patients to the wards and their initial profiles taken, keenly noting any interventions made which would affect the accuracy of the results. This occurred in 12 of the patients who had undergone significant intravenous fluid administration and/or blood transfusion before samples were taken either at the Emergency department or as in patients. The subjects were subsequently excluded from the recruitment process. See recruitment schema figure 3 below.

3.7.2 Study Procedures

After recruitment, the participants' socio-demographic characteristics and clinical data were collected by the study questionnaire (Appendix I).

Renal function test (RFT) values were determined via withdrawing blood sample from the patient after consent was sought, and placing the specimen in the required vaccutainer, then taking to the biochemistry lab for analysis, results of which would be obtained after several hours. Sequentially, using a glucometer with strips, a quick finger prick was performed to determine the Random Blood Sugar (RBS), results of which were instantaneously obtained. This was mostly done by me, with the aid of my research assistant in situations whereby I was not available due to one reason or the other, and of whom I had satisfactorily trained well concerning the study procedures. In situations where none of us was available, which accounted for least number of times, the patients were promptly followed within 24 hours

of admission to their respective admission destinations and various parameters of interest taken keenly noting any interventions done as has been earlier on mentioned.

For those with dysglycaemia and/or markedly deranged RFTs, the same information was communicated to the attending clinicians for appropriate action as they deemed fit in their clinical acumen. The algorithm for the study procedure is summarized in Figure 2 below.

Serum osmolality was then determined through calculation to separate true hyponatremia from factitious hyponatremia, given by the formula:

Calculated osmolality = $2[Na]^+$ + Glucose + Urea. This formula gave the least variation between measured and calculated plasma osmolality in a study done involving 100 normal controls, 100 general ward inpatients and 100 ICU patients hence was applied, according to a study by (Worthley LI, et al., 1987)

In another study as reported verbatim, "When the mean calculated osmolality- (CO) was compared to the mean measured osmolality- (MO), the Smithline-Gardner formula above gave an Osmolar Gap- (OG) close to zero. Other formulae gave an OG of 1 – 3 mOsm/kg." (Soiza et al., 2014)

The MTRH laboratory used has international standardization with accreditation and regularly validates test results as recommended by oversight bodies. The glucometer used is also one that is certified. This ensured internal validity of the study results.

3.7.3 Laboratory procedures

Blood sample (about 3ml) was drawn from the venepuncture for the renal function tests - Urea, Electrolytes and Creatinine (UECr) (Appendix IV), and drop of blood obtained by finger prick test for Random Blood Sugar screening (RBS) (Appendix V) from each participant. The full panel of renal functioning was conducted as the participants were

assured of being told their kidney functioning status as part of the benefits of the study. The blood samples were then taken to the laboratory after labelling. The results would come within two to four hours. The principal researcher and/or assistant researcher would then inform the subjects who had participated in the study their clinical results by making a phone call or following up in person. As had been alluded to earlier on, the relevant clinicians were promptly notified accordingly, for the patients who had deranged results for appropriate action. The algorithm for the study procedure is summarized in Figure 2 below.

3.8 DATA VARIABLES

3.8.1 Primary outcome/ dependent variables

1. Serum sodium levels. Hyponatremia was defined as a serum Sodium level of < 135mMol/L, according to the Joint European Guidelines (2016) (Appendix I).
2. Other important parameters such as serum Urea and Serum RBS levels (Appendix I) not acting as the main outcome of interest, but were important in calculating the plasma osmolality in order to arrive at the classification of hyponatremia by tonicity, a major objective of the study, hence differentiate true hyponatremia from other forms of hyponatremia:

- RBS of > 11.1 mMol/L was regarded as hyperglycemia while that of <= 3.3mMol/L was regarded as hypoglycemia.
- For patients with elevated serum glucose levels above 11.1mMol/L, Sodium correction was done as had been earlier on highlighted as this can give spurious hyponatremia due to dilution effect and the corrected Sodium values was used to calculate the osmolality. For every 5.5Mmol/L increase of glucose above 11.1 mMol/L, a correction

of 1.6Mmol/L was added to the measured Sodium up to a value of 22.2Mmol/L of glucose, thereafter, for every 5.5Mmol/L increase; a correction factor of 2.4Mmol of Sodium was added. Relevant formulae were enacted on the data analysis software.

- The normal plasma osmolality range was considered to be 275-295mOsm/L. values below 275mOsm/L was considered hypotonic while values above 295mOsm/L was considered hypertonic. Again, appropriate formulae were put up on the data analysis software.

3.8.2 Secondary data and independent variables

1. Age. That was later stratified into four categories viz a viz 60-69, 70-79, 80-89, 90 >
2. Gender. Male vs. female
3. Residence. Either coming from within Uasin Gishu County where MTRH is located or from without. To help describe the distribution of patients by locality seeking health services at the facility.
4. Transport costs to and from MTRH to serve as a surrogate marker of distance patients have to travel to access the facility.
5. Salt consumption - Inclusion in food-at cooking or on table) – Yes or; Not consuming salt at all.
6. Nutritional History: - Feeding Habits - General Food intake: Subjective by patient or as observed by relatives as to whether Poor or Good.
7. History of falls and or fractures within elderly period. Many studies have shown great association between hyponatremia in the elderly and falls.
8. Diabetes mellitus, Hypertension, Malignancies, Infections and Stroke – Category one grouping of conditions/comorbidities; as obtained from other studies

9. Other systemic conditions/ comorbidities - Category two grouping of conditions; involving the various bodily systems in particular e.g. cardiovascular, renal, nervous etc.
10. Presenting/ prevailing history and examination of signs and symptoms such as diarrhoea, vomiting, convulsions, altered mental status- targeted association to severe hyponatremia manifestation
11. Medication history and use - several studies have demonstrated associations of certain medication e.g. Thiazide diuretics, ACEs/ARBSs, psychotropics e.g. SSRI and hyponatremia.
12. Number of previous admissions within the preceding year; to bring out burden in terms of rehospitalisation rates, institutionalisation and possible association with hyponatremia
13. Duration since last admission; to equally bring out management of hyponatremia and comorbidities among the elderly as most literature has suggested.
14. Admitting destination; whether medical, surgical etc. to bring out where the different patients were admitted with the conditions contributing to majority of admissions and hence any associations with hyponatremia.

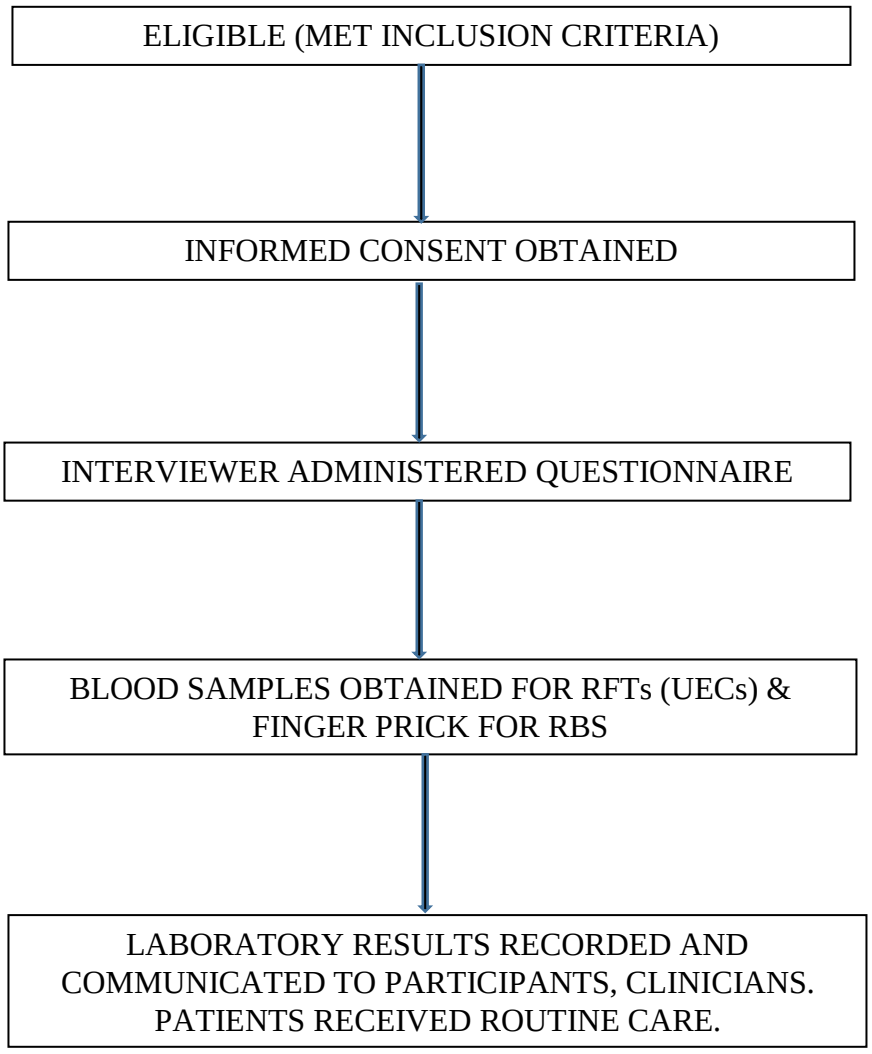


Figure 2: Algorithm of study procedure

3.9 DATA MANAGEMENT

3.9.1 Materials and data collection

A structured interviewer administered questionnaire was used to collect data from the subjects' demographic and clinical information including the history of presenting illness. The only unique identifier the questionnaire contained was the subject's birth dates and the study number. A master list was maintained which linked the study number to subject's

identifiers in order to provide primary care providers with the results of laboratory studies. The master list was maintained in the study computer.

3.9.2 Data cleaning

Data was cleaned during collection, data entry and analysis. Data collection sheets and questionnaires were checked for completeness and errors at the end of each day during data collection. Missing data and non-responders was excluded from the analysis. There was no need to collect more data since as the data was being cleaned, any anomalies were promptly being noted and addressed accordingly by instantaneous replacement of the study participants until the desired number of study participants was obtained, to ensure full data capture that was accurate. This however occurred only twice.

3.9.3 Data entry

Double entry was done to minimize error. Data entry and cleaning were done using computer Excel database. Data was entered into computer Microsoft Excel before exporting to R STATA software version 15.

3.9.4 Data protection and security:

Paper records were kept by lock and key not accessible to anyone. Computer was password protected. The database so developed was encrypted and the password made available to the principal investigator alone. This ensured that confidentiality of the patient data was maintained. An up to date Kaspersky antivirus with internet firewall was also utilized. Data backup was done using external drives and memory sticks and kept in separate locations to cushion against data loss.

3.9.5 Sharing

Data was encrypted when sharing through internet. The identifiable descriptions like date of birth were stripped off.

3.9.6 Dissemination of Results

The results of the study will be disseminated through a written thesis and an oral defense in a forum that shall be convened by the School of Medicine, Moi University. The results will also be published in a peer-reviewed journal.

3.9.7 Statistical Data Analysis

Descriptive statistics such as median and the corresponding interquartile range were used to summarize continuous variables (e.g. age, transport cost expenses) that assumed the Gaussian distribution, while the continuous variables that violated the Gaussian assumptions such as number of admissions within the past year were summarised using frequencies and corresponding percentages. Gaussian assumptions were assessed using Shapiro and Wilk test. Categorical variables such as gender, residence either within or without Uasin Gishu County, salt intake, history of falls and fractures within elderly period and nutritional history based on food intake as reported subjectively by patient or accompanying relatives as to whether poor or good among others were summarized too using frequencies and the corresponding percentages. Category one and two conditions/comorbidities, as depicted above on the variables section as well as the presenting/ prevailing symptoms and signs were summarised using frequencies and corresponding percentages then presented using bar graphs.

Association between hyponatremia and categorical independent variables were assessed using Pearson's Chi Square Test and Fisher's Exact Test.

Pearson's Chi Square test was used to assess the association between hyponatremia status and independent categorical variables.

Fisher's exact test was used whenever the Chi Square assumptions were violated.

The prevalence of hyponatremia was reported alongside the corresponding 95% confidence intervals (95% CI).

Data analysis was done using STATA version 15 SE.

3.10 ETHICAL CONSIDERATIONS

Prior to initiating research study, the research proposal was vetted and approved in the department of internal medicine Moi University before seeking ethical approval by the Institutional Research and Ethics Committee (IREC) that was granted.

Patients who were recruited to the study were informed that participation is voluntary and they could withdraw from the study at any point. The purpose of the study was explained at an appropriate educational level. To ensure understanding, all participants were required to sign a consent form. Participants were informed that the project did not carry monetary benefits and all tests performed for the study purposes were incurred.

Patient data were de-identified and entered into a research database. Data was stored into one master database matched by the participant's unique identification number and void of personal identifiers. All subsequent data analyses used this dataset to protect the confidentiality of participants. The principal investigator and research assistant upheld the highest level of confidentiality and privacy for all participants. Despite no monetary benefits accorded to the subjects, they however gained by knowing their renal function status, serum sodium levels, random blood sugar - a good screen for diabetes mellitus, and any abnormalities noted were appropriately communicated to the attending clinician for judicious action.

CHAPTER FOUR

RESULTS

4.1 SCREENING AND RECRUITMENT OF PARTICIPANTS

A total of 403 participants were screened for the study between April and June of 2019. Of these, 368 fulfilled the inclusion criteria, and were recruited.

Figure 3 shows the recruitment schema for the study.

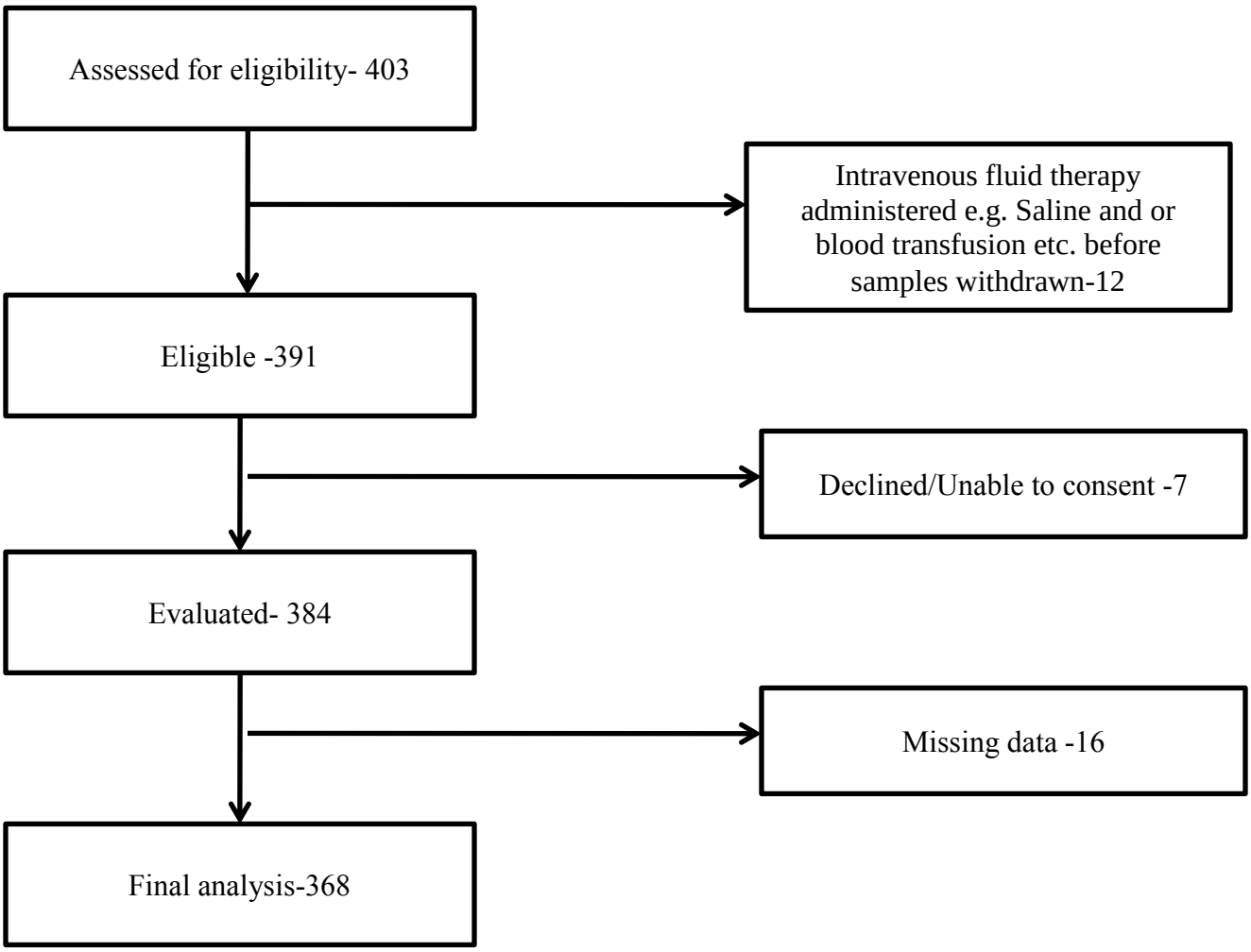


Figure 3: Recruitment Schema

4.2 SOCIODEMOGRAPHIC CHARACTERISTICS

Table 1: Socio-Demographic characteristics

The median age was 71 years (IQR: 65-79).

Variable	Freq / Median	%/ IQR
Sex		
Female	179	48.6
Male	189	51.4
Age in years		
60-69	167	45.38
70-79	114	30.98
80-89	71	19.29
>=90	16	4.35
Residence UG county		
No	228	62
Yes	140	38
Transport	600	300, 1200
Salt consumption		
No	40	10.9
Yes	328	89.1
Nutritional History		
Good	209	56.8
Poor	159	43.2
Hx of Falls/Fractures within elderly period		
No	217	59
Yes	151	41

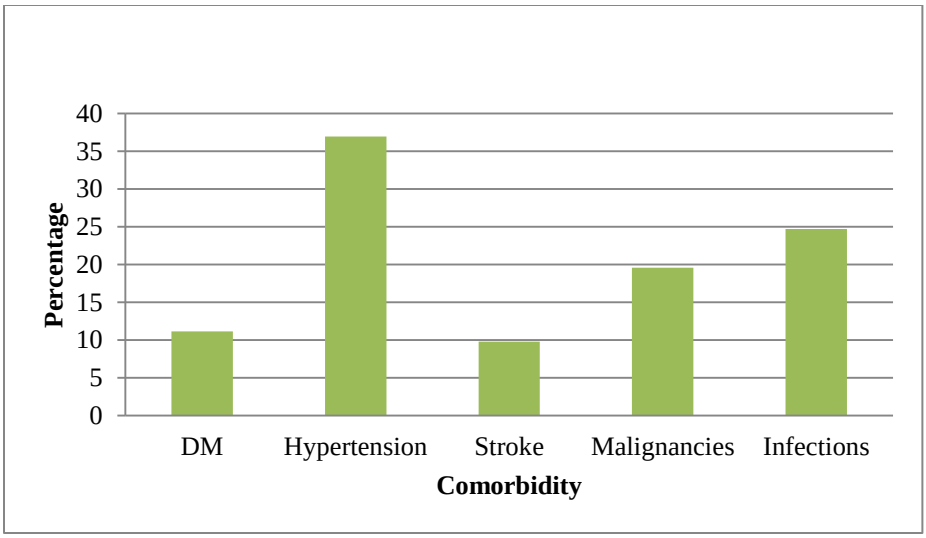
A total of 368 elderly participants were enrolled in the study. Table 1 represents the demographic characteristics by the shown parameters. Slightly more elderly males participated in the study vs. elderly females, 189 (51.4%) vs. 179 (48.6%). As regards to the classification by the various age groups, the highest proportion of the participants were in the age bracket of 60-69 years representing 45.38%, followed by 70-79 years accounting for 30.98%, 80-89 years accounting for 19.29% and the least age category being 90 years and above which accounted for a proportion of only 4.35%. The proportion of participants

who came from outside Uasin Gishu county was higher than the participants from within the county, 228 (62%) vs. 140 (38%). The median transport cost was 600 Kshs, (IQR: 300-1200). The proportion of participants consuming salt included in cooked food or added table salt or both was about nine times the proportion of those who totally excluded salt in their diet, 89.1% vs. 10.9%. When asked about their nutritional history based on the general food intake as reported by the participants, or observation by the accompanying relatives/caretakers, more participants in the study admitted to be eating well with good nutritional habits as opposed to those answering otherwise, 209 (56.8%) vs. 159 (43.2%). More participants admitted to have had a history of falls and or fractures within the elderly period, 217 (59%) vs. 151 (41%).

4.3 CLINICAL CHARACTERISTICS

Table 2a: Underlying comorbidities (Category 1 conditions) (n=368)

Comorbidity	Frequency	%
DM	41	11%
Hypertension	136	37%
Stroke	36	10%
Malignancies	72	20%
Infections	91	25%



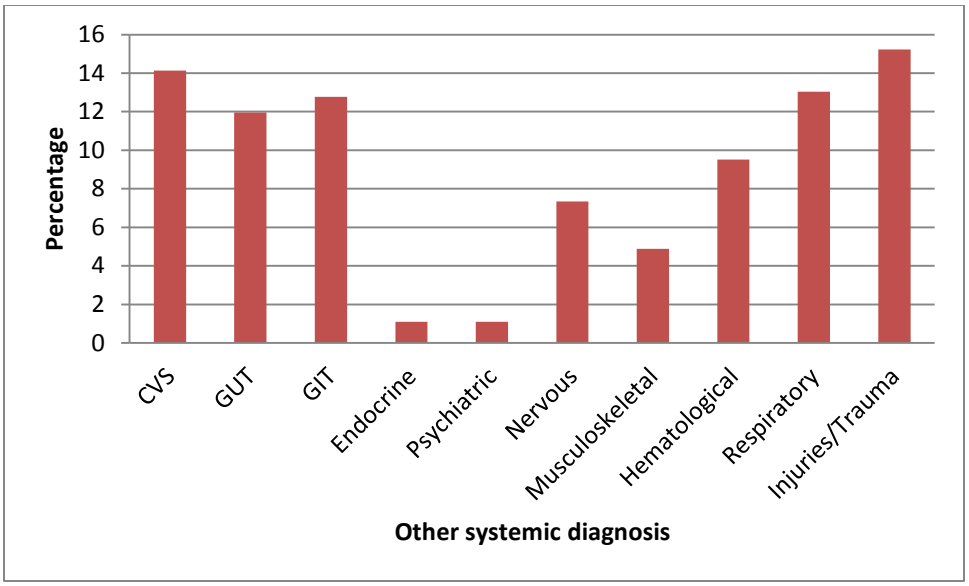
DM-Diabetes Mellitus

Figure 4a: Bar graph showing underlying Comorbidities (category one conditions)

Table 2 and Figure 4 above depict the various underlying comorbidities by frequency also labelled as category one conditions in the study. Hypertension was the most prevalent underlying category one condition affecting 136 (37%) of the subjects, followed by infections 91 (25%), various malignancies 72 (20%), Diabetes Mellitus 41 (11%), with the least comorbid condition being stroke representing 36 (10%) of the participants.

Table 2b: Other comorbidities by system diagnosis (Category 2 conditions) (n=368)

Other Systemic Diagnosis	Frequency	%
CVS	52	14.13
GUT	44	11.96
GIT	47	12.77
Endocrine (Thyroid)	4	1.09
Psychiatric	4	1.09
Nervous	27	7.34
Musculoskeletal	18	4.89
Haematological (Anaemia)	35	9.51
Respiratory	48	13.04
Injuries/Trauma	56	15.22



CVS-Cardiovascular System; GUT-Genitourinary System; GIT-Gastrointestinal System

Figure 4b: Bar graph showing other comorbidities by system involvement (Category 2 Conditions)

Table 2b and Figure 4b above depict the frequencies of other system specific comorbidities involvement, also labelled as category two conditions among the various participants in the study. The most prevalent category two systemic condition was injuries/ trauma presenting as road traffic accidents, falls/fractures and assaults accounting for 56 (15.22%) of the subjects. This was closely followed by cardiovascular system, gastrointestinal and genitourinary system, with endocrine and psychiatric conditions contributing the least proportion each with 4 (1.09%) participants as shown above.

Table 2c: Presenting signs and symptoms commonly associated with hyponatremia (n=368)

Signs and Symptoms	Frequency	%
Diarrhea	29	7.88
Vomiting	98	26.63
Convulsions	16	4.35
Altered mental state e.g. coma/confusion/disorientation	78	21.2

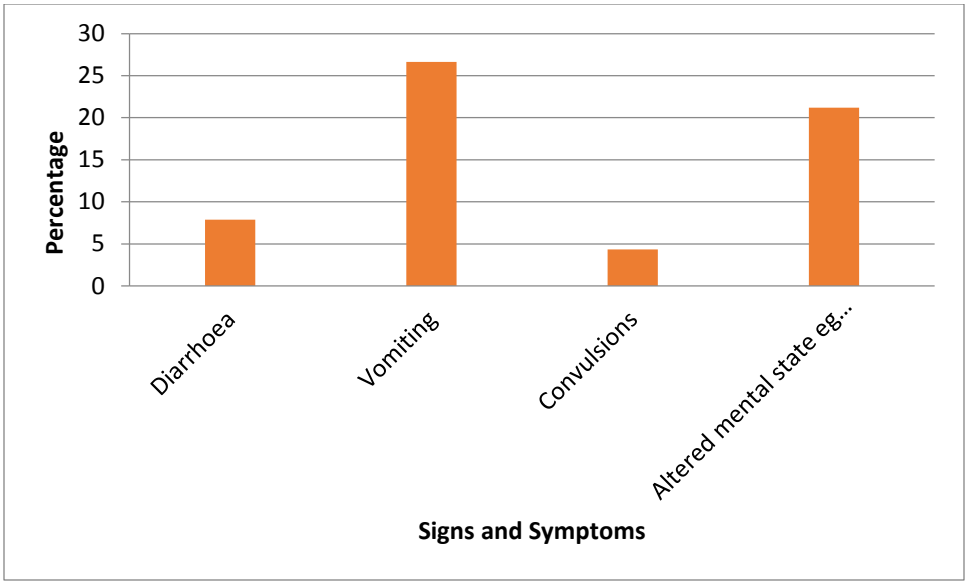
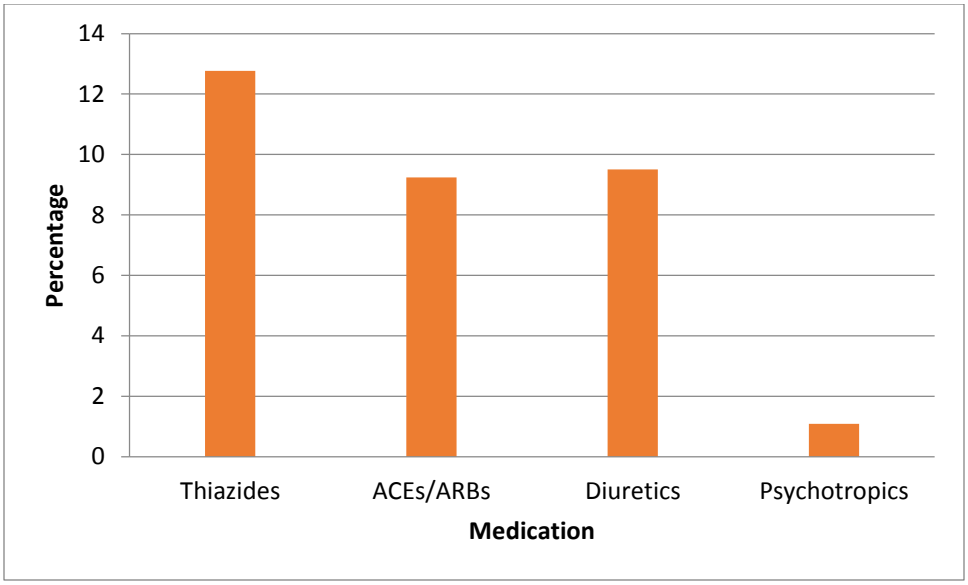


Figure 4c: Bar graph showing prevailing signs and symptoms commonly associated with hyponatremia.

Table 2c and figure 4c above show frequency of the signs and symptoms, commonly associated with hyponatremia that the participants exhibited during recruitment stage, either occurring at home prior to presentation at the emergency area or prevailing during the interviewing process. The highest proportion of subjects had a history of vomiting 98 (26.63%), followed by altered mental status 78 (21.2%), diarrhoea 29 (7.88%) and convulsions 16 (4.35%).

Table 2d: Medication history and use (n=368)

Medication	Frequency	Percentage
Thiazides	47	12.77
ACEs/ARBs	34	9.24
Other diuretics	35	9.51
Psychotropics	4	1.09



ACEs-Angiotensin Converting Enzyme inhibitors; ARBs-Angiotensin Receptor Blockers

Figure 4d: Bar graph showing medication history and use

Table 2d and figure 4d above depict the frequency of medication history and use, with emphasis to those that have been implicated to have a tendency in causing hyponatremia, which the participants were on, at the time of study. The most common type was thiazide diuretics; especially Hydrochlothiazide 47 (12.77%), which was followed by other diuretics; loop and potassium sparing 35 (9.51%), ACE/ARBs; Enalapril, Captopril, Losartan and Telmisartan 34 (9.24%) and the least proportion of patients were on psychotropics 4 (1.09%); including antidepressants like tricyclic antidepressants, (TCAs), selective serotonin reuptake inhibitors (SSRIs), anticonvulsants and antipsychotics.

Table 3a: Number of admissions within the preceding year (n=368)

Variable	Frequency	%
Number of previous admissions within past year		
1	82	22.28
2	33	8.97
3	20	5.43
>3	15	4.11
N/A(INDEX)	218	59.21

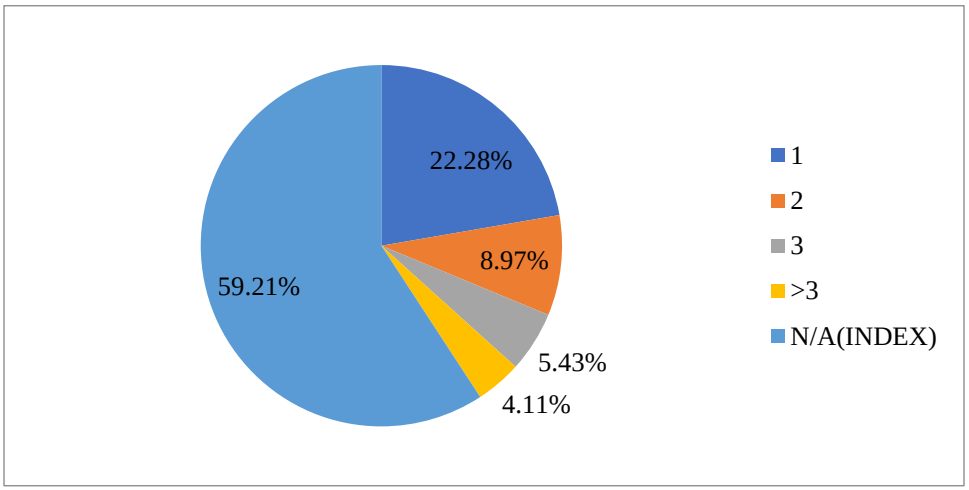
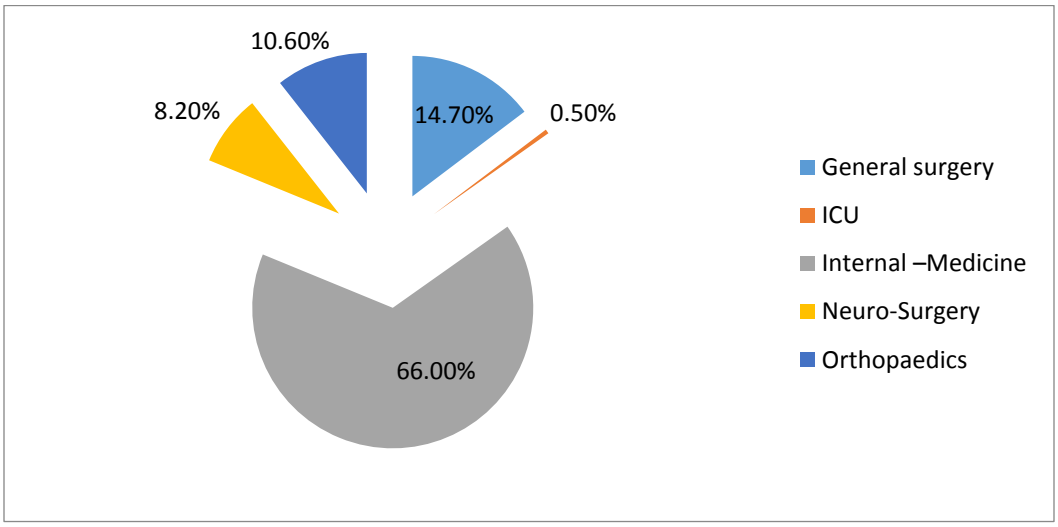


Figure 5a: Pie chart showing the frequency of admissions within the preceding year

Table 3 and figure 5 above represents the frequency of admissions within the previous year. Majority of the elderly patients, more than half, were undergoing their index admission 218 (59.21%), with one previous admission accounting for 82 (22.28%), two prior admissions 33 (8.97%), three previous admissions 20 (5.43%) while the least proportion was represented by those having been admitted more than three times in the preceding year 15 (4.11%).

Table 3b: Inpatient admitting destination (n=368)

Variable	Freq.	%
Admitting destination		
General surgery	54	14.70
ICU	2	0.50
Internal –Medicine	243	66.00
Neuro-Surgery	30	8.20
Orthopaedics	39	10.60



ICU- Intensive Care Unit

Figure 5b: Exploded pie chart showing the frequencies of various inpatient admitting destinations

Table 3b and figure 5b above represent the various admitting destination points. Out of the 368 subjects admitted for inpatient care, the highest proportion of the participants were admitted in the medical wards; 243 (66%), accounting for more than half of the admissions. General surgery department; had the second most frequent admissions 54 (14.70), orthopaedics; coming third with 39 (10.60), neurosurgery; following with 30 (8.20%), while the least destination was Intensive Care Unit; with only 2 (0.50%) of the subjects.

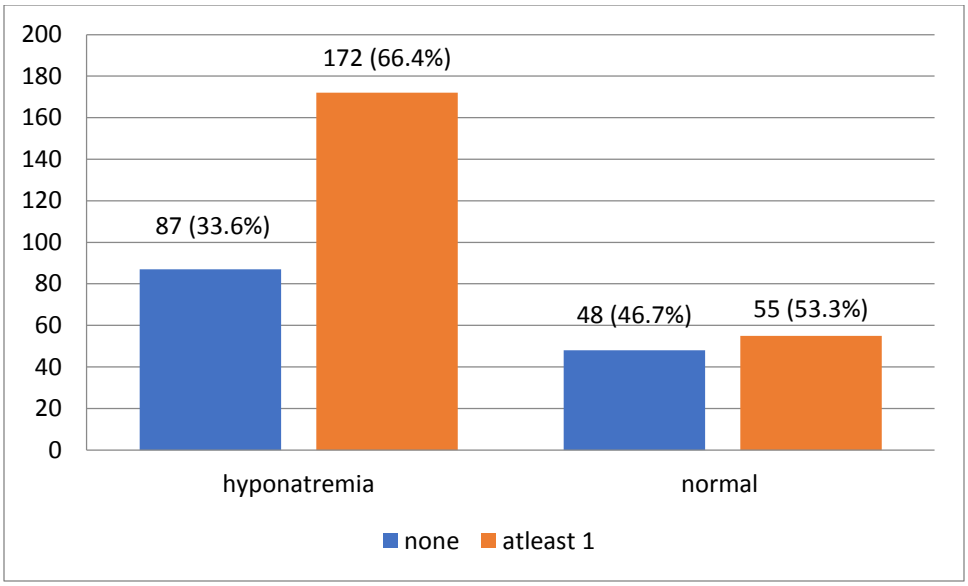


Figure 5c: Comparative bar graph showing the number of comorbidities between the hyponatremic patients vs. those with normal serum sodium.

Figure 5c above depicts the proportion of patients with no comorbidity i.e. a single diagnosis vs. those subjects with at least one other comorbidity between the two groups; with hyponatremia vs. those with normal serum sodium levels. As noted, about two thirds of the patients with hyponatremia were having comorbidities, as opposed to about half of the patients with normal serum sodium levels (66.4% vs. 53.3%).

4.4 PREVALENCE OF HYPONATREMIA AMONG THE ELDERLY PATIENTS

Table 4: Serum Sodium Profiles and prevalence determination (n=368)

Class	Frequency	%
Normal	103	28.0
Hyponatremia	259	**70.38**
Hypernatremia	6	1.62

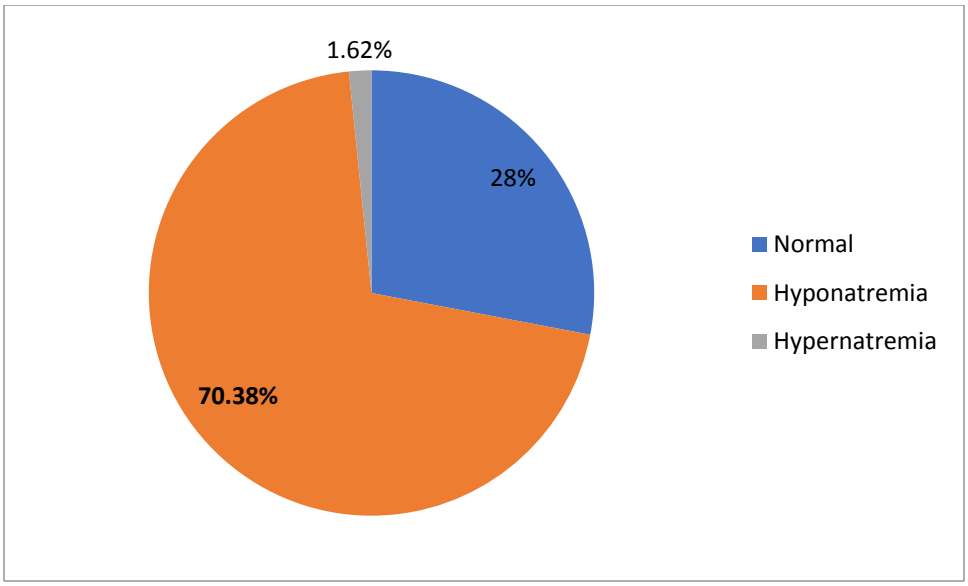


Figure 6: Pie chart showing serum sodium profiles with hyponatremia prevalence determination.

Table 4 and figure 6 above depict the serum sodium profiles of the subjects. The overall prevalence of hyponatremia was highest at 70.38% (95% CI: 65.43, 75.00). Participants with normal sodium levels contributed 28% while the least proportion was of individuals with hypernatremia who accounted for 1.62% of the total study population.

4.5 SUBTYPES OF HYPONATREMIA

Table 5a: Classification by tonicity (n= 259)

Subtypes	Frequency	%
Hypotonic (True)	152	58.67
Hypertonic	60	23.12
Normotonic	47	18.21

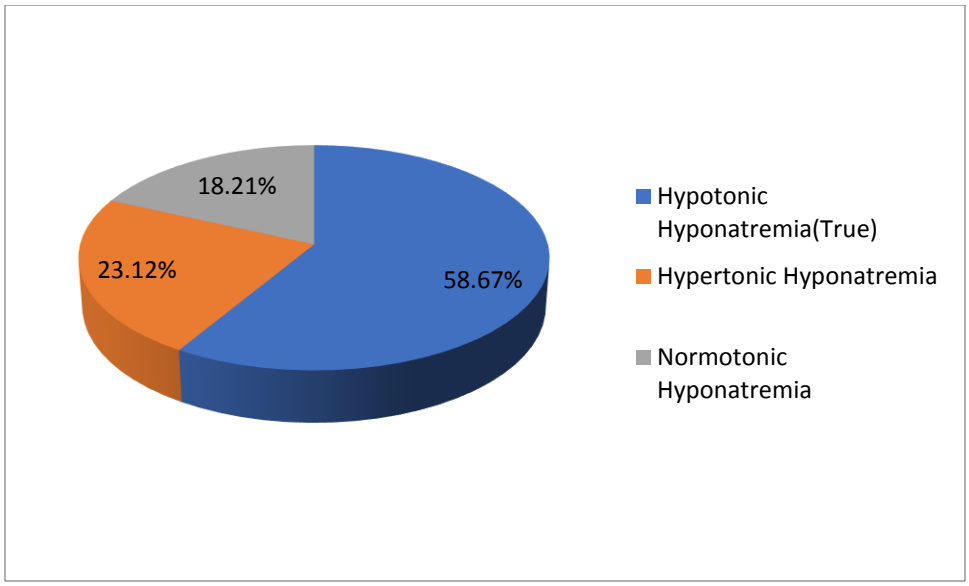


Figure 7a: Pie chart showing classification of hyponatremia by tonicity.

Table 5a and figure 7a above represents the classification of hyponatremia by serum osmolality. Of the 259 patients with hyponatremia, the highest proportion of participants had hypotonic hyponatremia otherwise referred to as true hyponatremia accounting for 58.67%. This was followed by hypertonic hyponatremia, at 23.12% with the least proportion being normotonic hyponatremia at 18.21%.

Table 5b: Classification by severity (n= 259)

Severity	Freq	%
Mild hyponatremia	100	38.61
Moderate hyponatremia	66	25.48
Severe hyponatremia	93	35.91

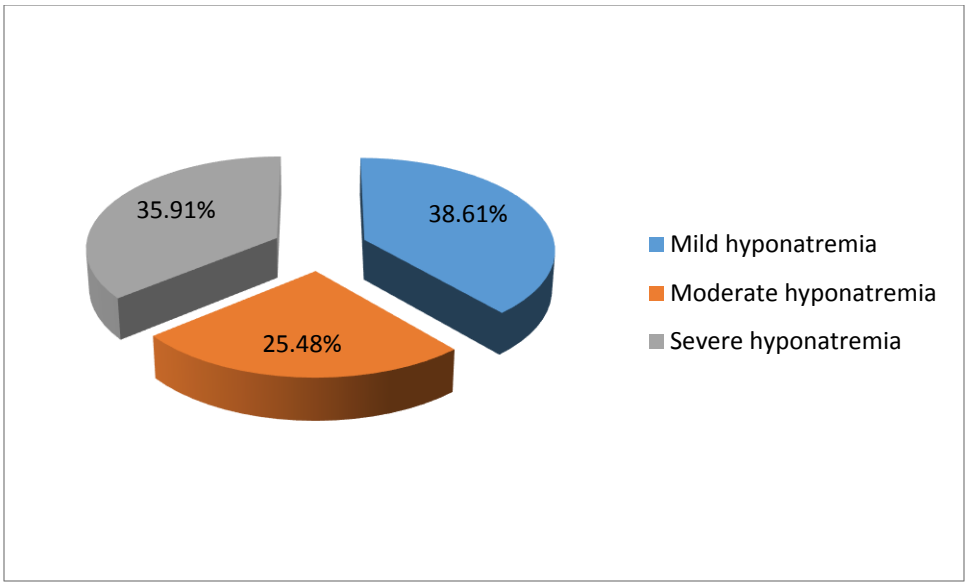


Figure 7b: Exploded pie chart showing classification of hyponatremia by severity.

Table 5b and figure 7b above describes the classification of hyponatremia by severity as determined through serum sodium levels measurement and not symptoms. Of the 259 patients with hyponatremia; out of the 368 participants in the study, the highest proportion of patients had mild hyponatremia accounting for 38.61%, which was closely followed by severe hyponatremia, at 35.91%. The lowest proportion was those with moderate hyponatremia contributing to 25.48% of the subjects.

4.6 FACTORS ASSOCIATED WITH HYPONATREMIA

Table 6a: Socio demographic factors associated with Hyponatremia-Univariate Analysis

Variable	Hyponatremia		P-value
	No (n=109)	Yes (n=259)	
	Freq (Row) or %	Freq (Row) or %	
Age in years			**0.036[f]**
60-69	61 (36.5)	106 (63.5)	
70-79	26 (22.8)	88 (77.2)	
80-89	16 (22.5)	55 (77.5)	
Above 90	6 (37.5)	10 (62.5)	
Sex			**0.039[c]**
Female	44 (24.6)	135 (75.4)	
Male	65 (34.4)	124 (65.6)	
Residence UG County			0.912[c]
NO	68 (29.8)	160 (70.2)	
YES	41 (29.3)	99 (70.7)	
Salt consumption			**0.012[f]**
NO	5 (12.5)	35 (87.5)	
YES	104 (31.7)	224 (68.3)	
Diet			0.568[c]
POOR	30 (27.5)	79 (72.5)	
GOOD	79 (30.5)	180 (69.5)	
History of Falls/Fractures			0.145[c]
NO	58 (26.7)	159 (73.3)	
YES	51 (33.8)	100 (66.2)	
Number of previous admissions in the preceding year			**0.017[f]**
Index *	75 (35.2)	138 (64.8)	
1	18 (22)	64 (78)	
2	10 (30.3)	23 (69.7)	
3	1 (5)	19 (95)	
>3	5 (25)	15 (75)	

UG - Uasin Gishu County;

***** – index admission, no prior admission within preceding year

[c] Chi square test, [f] Fishers' Exact test

Table 6a above represents the socio-demographic characteristics in relation to hyponatremia for univariate analysis.

Older age (p=0.036), female gender (p=0.039), salt consumption (p=0.012) and increasing number of admissions (p=0.017) were significantly associated with hyponatremia in the univariate analysis.

Table 6b: Category one and two conditions associated with hyponatremia – Univariate

Variable	Hyponatremia		P-value
	No (n=109)	Yes (n=259)	
	Freq (Row) or %	Freq (Row) or %	
Diabetes			**0.003[f]**
NO	105 (32.1)	222 (67.9)	
YES	4 (9.8)	37 (90.2)	
Hypertension			**<0.001[c]**
NO	84 (36.2)	148 (63.8)	
YES	25 (18.4)	111 (81.6)	
Stroke			0.607[c]
NO	97 (29.2)	235 (70.8)	
YES	12 (33.3)	24 (66.7)	
Malignancies			0.179[c]
NO	83 (28)	213 (72)	
YES	26 (36.1)	46 (63.9)	
Infections			0.434[c]

NO	85 (30.7)	192 (69.3)	
YES	24 (26.4)	67 (73.6)	
CVS			0.265[c]
NO	97 (30.7)	219 (69.3)	
YES	12 (23.1)	40 (76.9)	
GUT			0.286[c]
NO	99 (30.6)	225 (69.4)	
YES	10 (22.7)	34 (77.3)	
GIT			0.18[c]
NO	99 (30.8)	222 (69.2)	
YES	10 (21.3)	37 (78.7)	
Endocrine			**0.046[f]**
NO	106 (29.1)	258 (70.9)	
YES	3 (75)	1 (25)	
Psychiatric			0.839[f]
NO	108 (29.7)	256 (70.3)	
YES	1 (25)	3 (75)	
Nervous			0.999[c]
NO	101 (29.6)	240 (70.4)	
YES	8 (29.6)	19 (70.4)	
Musculoskeletal			0.158[c]
NO	101 (28.9)	249 (71.1)	
YES	8 (44.4)	10 (55.6)	
Hematological (anemia)			0.071[c]
NO	94 (28.2)	239 (71.8)	
YES	15 (42.9)	20 (57.1)	
Respiratory			0.452[c]
NO	97 (30.3)	223 (69.7)	
YES	12 (25)	36 (75)	
Injuries/Trauma			0.852[c]
NO	93 (29.8)	219 (70.2)	
YES	16 (28.6)	40 (71.4)	

CVS - Cardiovascular System; GUT – Genitourinary system; GIT – Gastrointestinal system

[c] Chi square test [f] Fisher's Exact test

Table 6b above represents univariate logistic regression among the comorbidities associated with hyponatremia.

In the univariate analysis, Diabetes mellitus (p=0.003), hypertension (p<0.001) and endocrine disorders (p=0.017) that comprised of the thyroid gland; predominantly hypothyroidism, with three patients on follow up for hypothyroidism, and one patient being newly diagnosed with myxedema, were significantly associated with hyponatremia among the participants.

Table 6c: Symptoms, signs and medication associated with hyponatremia -Univariate

Variable	Hyponatremia		P-value
	No (n=109)	Yes (n=259)	
	Freq (Row)or %	Freq (Row)or %	
Diarrhoea			0.128[f]
NO	104 (30.7)	235 (69.3)	
YES	5 (17.2)	24 (82.8)	
Vomiting			0.07[c]
NO	87 (32.2)	183 (67.8)	
YES	22 (22.4)	76 (77.6)	
Convulsion			0.33[f]
NO	106 (30.1)	246 (69.9)	
YES	3 (18.8)	13 (81.3)	
Altered mental state			0.557[c]
NO	88 (30.3)	202 (69.7)	
YES	21 (26.9)	57 (73.1)	
Thiazide			**0.001[f]**
NO	105 (32.7)	216 (67.3)	
YES	4 (8.5)	43 (91.5)	
ACEs			**0.017[f]**

NO	105 (31.4)	229 (68.6)	
YES	4 (11.8)	30 (88.2)	
Diuretics*			0.357[c]
NO	101 (30.3)	232 (69.7)	
YES	8 (22.9)	27 (77.1)	
Psychotropics			0.839[f]
NO	108 (29.7)	256 (70.3)	
YES	1 (25)	3 (75)	

ACEs – Angiotensin Converting Enzyme Inhibitors
* - Loop diuretics and Potassium sparing diuretics
[c] Chi square test [f] Fisher's Exact test

Table 6c above depicts the univariate logistic regression among the symptoms, signs and medication associated with hyponatremia.

Among the prevailing signs and symptoms as well as medications used by the subjects, use of thiazide diuretics (p=0.001) and ACEs (p=0.017) were significantly associated with hyponatremia.

Table 7a: Factors associated with hyponatremia (Unadjusted Odds ratio)

Variable	**Unadjusted Odds Ratio**	**[95% Conf. Interval]**	
Age in years			
60-69	1		
70-79	1.948	1.136	3.339
80-89	1.978	1.043	3.75
Above 90	0.959	0.332	2.768
Male vs Female	1.608	1.022	2.532
Exclusive salt (Yes vs No)	0.308	0.117	0.808
Fall (Yes vs No)	0.715	0.455	1.124
Number of previous admissions			
None	1		
One	1.932	1.067	3.499

Two or more	2.075	1.009	4.267
DM (Yes vs No)	4.375	1.52	12.595
Malignancy (Yes vs No)	0.689	0.4	1.187
Diarrhea (Yes vs No)	2.124	0.789	5.721
Vomiting (Yes vs No)	1.642	0.958	2.815
Thiazide (Yes vs No)	5.226	1.827	14.944
ACE (Yes vs No)	3.439	1.181	10.011
GIT (Yes vs No)	1.650	0.789	3.45
Muscular (Yes vs No)	0.507	0.195	1.322
Hematological (Yes vs No)	0.524	0.258	1.067

Table 7b: Factors associated with hyponatremia (Adjusted Odds ratio)

Variable	**Adjusted Odds Ratio**	**P-value**	**[95% Conf. Interval]**	
Age in years				
70-79	1.92	**0.032**	1.06	3.50
80-89	2.05	0.051	1.00	4.22
Above 90	1.13	0.847	0.32	4.06
Male vs. Female	1.49	0.121	0.90	2.48
Salt consumption (Yes vs. No)	0.31	0.080	0.08	1.15
Fall (Yes vs. No)	0.79	0.356	0.47	1.31
Number of previous admissions				
None	1			
One	1.77	0.095	0.91	3.44
Two or more	1.34	0.480	0.59	3.04
DM (Yes vs. No)	2.41	0.130	0.77	7.51
Malignancy (Yes vs. No)	0.74	0.360	0.39	1.41
Diarrhoea (Yes vs. No)	2.11	0.189	0.69	6.42
Vomiting (Yes vs. No)	1.42	0.289	0.74	2.74
Thiazide (Yes vs. No)	4.58	**0.008**	1.48	14.20
ACE (Yes vs. No)	1.65	0.398	0.52	5.23
GIT (Yes vs. No)	1.63	0.277	0.68	3.93
Muscular (Yes vs. No)	0.33	0.064	0.10	1.07
Haematological (Yes vs. No)	0.45	0.051	0.20	1.00

DM – Diabetes Mellitus; ACE – Angiotensin Converting Enzyme Inhibitors; GIT – Gastrointestinal system

Table(s) 7 above portray multiple logistic regression analysis for the factors associated with hyponatremia both for the unadjusted and adjusted Odds ratio.

In this model, variables significant in the univariate level at 0.20 level of significance were included. Prior to fitting the model collinear variables were excluded in this case hypertension was associated with thiazides, ACE and number of previous admissions hence hypertension was excluded. Endocrine system was also excluded because there were very few patients (n=4), and hence was not fitting in the model. When selecting variables for inclusion in the multiple logistic regression, the threshold is normally relaxed since a variable might be non-significant at univariate and become significant at multiple hence recommended using of the 0.2 threshold. (Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *American Journal of Epidemiology*. 1993; 138(11):923-936. doi: 10.1093/oxfordjournals.aje.a116813).

The statistically significant factors associated with hyponatremia on univariate analysis were age (p=0.036), sex (p=0.039), salt consumption (p=0.012), number of previous admissions (p=0.017), Diabetes Mellitus (p=0.003), Hypertension (p<0.001), endocrine disorders (p=0.046), use of thiazide diuretics (p=0.001) and medication with ACEs (p=0.017) as shown in tables 6a, 6b and 6c above.

In the multivariate analysis, only patients who were taking thiazide diuretics (OR= 4.58; 95% CI 1.48 to 14.20; P=0.008) and age group 70-79 (OR=1.92; 95% CI 1.06 to 3.50; P=0.032) were found to be statistically significantly associated with hyponatremia (see tables 7a & 7b).

CHAPTER FIVE

DISCUSSION

5.1 PREVALENCE OF HYPONATREMIA

This cross sectional study has found a high prevalence of hyponatremia (70.38%) among the elderly patients, with hypotonic hyponatremia (true hyponatremia) being the most prevalent subtype of hyponatremia. Use of thiazides and older age remained significant as independent factors associated with hyponatremia in the multivariate analysis. Thiazide diuretics use was the factor most strongly associated with hyponatremia, consistent with other previous studies (Liamis G et al. 2008, Lindner G et al. 2014).

The median (IQR) age of the participants was 71 (65-79). This was comparable to the study by Nankabirwa H et al. who found the median age of the subjects to be 70 (IQR: 65-77). As the age of the patients increased with the age groups, the proportion of patients with hyponatremia increased and this association was found to be statistically significant ($p=0.036$). This finding was comparable to those of a study done in India at a General Medicine and Allied specialities Medical College and Hospital over a period of one year between January 2016 to December 2017) concerning hyponatremia among the elderly by Shanmugasundaram R et al. who found older age group to be strongly and independently associated with hyponatremia ($p<0.001$). Hyponatremia was more common in elderly females compared to males consistent with the findings of Miller M et al. and Nidhi K et al. As described earlier, this could be due to the body fat content differences between males vs females hence varying total body water and consequently sodium levels.

Prevalence of hyponatremia is known to increase in frail patient groups particularly elderly patients where hyponatremia is observed in almost half of acute geriatric admissions

(Mannesse CK et al. 2013, Hoyle GE et al. 2006). Of note, an increasingly higher proportion of patients who presented with hyponatremia had higher number of readmissions within the preceding year, a finding that was statistically significant ($p=0.017$). However, whether this could be attributed to hyponatremia or the comorbidities prevalent in the elderly may need further studies to elucidate. A study done by Chua M et al. found that participants who had hyponatremia on admission had strong association with increased institutionalisation rates and significant loss of independence ($p<0.001$) as compared to their counterparts after adjusting for other factors.

Nankabirwa H, et al. in 2016 in Uganda at Mulago National Referral Hospital, evaluated hyponatremia prevalence among elderly patients 60 years and above but admitted with heart failure. Two hundred and eleven patients were involved in the study and 24.2% of them had hyponatremia. The relatively low prevalence obtained in a similar setting to this study could be attributed to the low sample size of 211 vs. 368, and given that only a subset of the elderly patients having a particular comorbidity was chosen, thereby excluding significant others who may have been inadvertently omitted.

Audra B, et al. who while trying to determine the economic burden of hyponatremia, did a study in the United States in 2006, and used publicly available hospital discharge data from 1000 hospitals in 33 states of how many elderly patients were admitted and those with documented hyponatremia in the initial evaluation. Records from more than seven hundred thousand patients were evaluated in totality over a one-year period and out of this, 75% of the patients were found to have hyponatremia, which was in fact chronic and asymptomatic, the highest in the group.

A similar study was done in China in 1991 by Natkunam A, et al. Eighteen thousand patients were evaluated over six-month duration. Hyponatremia was reported in 76% of the patients.

This study was comparable to a study done by Subhash C, et al. in 2019 at a teaching hospital in India involving a prospective observational study whereby 950 elderly patients 60 years and above were evaluated over a 12-month period. About half of the patients, 47.9% were noted to have hyponatremia. The low prevalence could be explained by the fact that they excluded patients who had factitious hyponatremia.

Most previous studies conducted endeavoured to classify hyponatremia based on volume status such as that done by Subhash et al. 2019 & Nidhi et al. 2017. This study classified hyponatremia based on the serum tonicity, being also the initial step in evaluating patients with hyponatremia. Hypotonic hyponatremia also referred to as true hyponatremia accounts for the most common occurring subtype of hyponatremia, and is of utmost clinical significance, and of which correction may be necessary depending on the onset and severity of the symptoms, and depends on classification by determination of serum osmolality. The findings in this study was in accordance to this premise given that more than half of the patients with hyponatremia had the hypotonic subtype (n=152; 58.67%).

Factitious hyponatremia comprising of normotonic and hypertonic hyponatremia accounted for 41.33% of the patients with hyponatremia. This is a significant proportion, and further exemplifies the fact that there is need for systematic screening and classification of hyponatremia based on tonicity to determine which patients would benefit from intervention since not all forms of hyponatremia warrant correction. There are cases whereby clinicians failed to recognise true hyponatremia leading to overt correction upon

resolution of the triggering factor with an often poorer course. Classification by severity based on the serum sodium cut offs was similar across board in all the previous studies. Mild hyponatremia was the most common subtype among the 259 patients with hyponatremia (n= 100, 38.61%), findings similar to the large study by Audra et al. who found 75% of the patients with mild but chronic asymptomatic hyponatremia.

This study is comparable to the study by Nankabirwa et al. who found the prevalence of mild hyponatremia accounted for the highest proportion (52%) of the patients. These findings are comparable with the study by Sophie B. et al done in 2019 who while evaluating the association between falls and hyponatremia in the elderly found the prevalence of mild hyponatremia to be 75.0%; CI 13.2 to 18.6 among the patients. Mild hyponatremia thus appears to be a significant finding in the elderly patients, which was previously regarded to be asymptomatic and not worth addressing, but recent studies have demonstrated increased links with cognitive deficits, falls and fractures in the elderly and documented benefits with intervention. This fact may be supported by findings of a meta-analysis done by Giovanni C et al. in 2015 involving a total of 13, 816 patients. Across all fifteen studies looked at, any improvement of hyponatremia was associated with a reduced risk of overall mortality (OR= 0.51; 95% CI 0.31 to 0.86), with the reduced mortality persisting at follow-up (OR= 0.55; 95% CI 0.36 to 0.84) for 12 months. Meta regression analyses showed that the reduced mortality associated with hyponatremia improvement was more evident in older subjects and in those with lower serum Na+ at enrolment.

Diarrhoea (7.8%) and vomiting (26.6 %) were the most common presenting symptoms with more than three quarters of the patients with these symptoms presenting with hyponatremia. These findings are comparable to the studies by Nankabirwa et al. and

Subhash et al. who found vomiting to account for 28.9%. Notably, more patients presented with vomiting in all the studies. This study was however different from that by Nankabirwa et al. who found vomiting being independently associated with hyponatremia (OR=2.94; 95% CI 1.29 to 6.70, p=0.010). The findings could be attributed to gastrointestinal losses, with vomiting accounting for one of the leading factors associated with development of severe hyponatremia especially if protracted and occurring acutely.

Severe hyponatremia is usually associated with neurological manifestations including confusion, disorientation, drowsiness, neuromuscular hyperexitability, hyper-reflexia, stupor, convulsions and coma in the worst form. Even though classification of severe hyponatremia based on serum sodium is by values less than 125 mMol/L, the central nervous system effects are frequently observed when the value falls below 120mMol/L (Joint European Guidelines, 2014). Proportion of patients with severe hyponatremia in this study was (n= 93; 25.2 %), while those with neurological manifestations were (n=94; 25.5%).

Convulsions comprising (4.3%) and altered mental status comprising (21.2%) were the most prevalent neurological manifestations, with 8.7% of the patients with severe hyponatremia by serum sodium values exhibiting severe CNS manifestations. These findings were comparable to previous studies done by several researchers albeit different categorisation methods such as Subhash et al. who found; confusion (19.7%), drowsiness and impaired consciousness (14.1%), seizures and coma (3%); Nidhi et al. who found lethargy (22.5%), severe neurological features (10.4%) while Nankabirwa et al. found altered mentation (12.3%) as the most predominant sign. Despite contrasting findings where various clinical presentations were similar across all classes of hyponatremia in

Nankabirwa H et al study, a study by Thompson C 2010 depicted those with mild hyponatremia to be asymptomatic, those with moderate hyponatremia tended to have anorexia, nausea and headache while those with severe hyponatremia had confusion, coma seizures and death.

As Drake-Holland AJ and Noble MI in a study done in 2016 note, there is increasing prevalence of hyponatremia. This increase in prevalence of hyponatremia over time has a similar time course to the increase in adoption of low-salt diet. In this study, nearly all patients (89.1%) include salt in their diet cooked either in food or addition on the table. These findings were similar to that by Nankabirwa H et al. who found 91.0 % of the patients added salt. In this study, salt intake was associated with hyponatremia in the univariate analysis but the association was lost on multivariate analysis after controlling for other confounders. Nankabirwa H et al. however found no statistically significant association. This study thus implies that people can still suffer from hyponatremia despite salt intake, possibly due to low salt intake as may be prescribed by clinicians to hypertensive patients or other prevailing factors e.g. underlying comorbidities and certain medication.

Investigation into the Sodium electrolyte levels of individual subjects would be expected to reveal the suitability or otherwise of dietary salt intake. If this approach is adopted, it may be necessary to withdraw recommendation of low-salt diet to the entire population. Drake-Holland AJ & Noble MI, 2016 found that low salt diet in the elderly and chronic sick resulted in increased severity of illness and demonstrated that low salt diet in the not obviously ill person could induce hyponatremic illness.

Hyponatremia has been proposed as a contributor to falls and hence fractures in the elderly, and has become a major global issue with the aging of the population (Spencer C et al. 2017). This could be due to the mild cognitive impairment, resulting in unsteady gait and falls probably due to the loss of glutamate (a neurotransmitter involved in gait function) as an osmolyte during brain adaptation to chronic hyponatremia, and secondly by contributing directly to osteoporosis and increased bone fragility by inducing increased bone resorption to mobilize sodium stores in bone (Negri AL, Ayus JC, 2017). In this study, more than two thirds of the elderly patients (66.2%) with a history of falls/ fractures within the elderly period had hyponatremia. These findings are similar to the study by Spencer C et al. who found that significantly more elderly patients with hyponatremia presented to the emergency department due to falls compared to elderly patients without hyponatremia (73.7% vs. 52.6%; OR 2.5, 95% CI: 2.10 to 3.02; $p< 0.001$) and also had worse outcomes measured by significantly higher odds of intubation, longer hospital length of stay, higher proportion of intensive care unit (ICU) admission and higher mortality rate, regardless of adjustment by injury severity score.

Comorbid conditions are commonly present with the geriatric population subsequently predisposing them to hyponatremia as earlier on highlighted (Shapiro DS et al. 2010, Hoyle GE et al. 2014, Clayton JA et al. 2006). This study found a significantly higher proportion of patients with hyponatremia to be having at least one other comorbidity (66.4%), as opposed to subjects with normal serum sodium levels (53%) who had no comorbidity; findings that were in conformity to previous studies which have suggested association between hyponatremia in the elderly and multiple comorbidities. Mohan et al. in their study found up to 73% of hyponatremic patients had comorbidities, while Subhash et al. in their

study found 86.4% of the patients being hyponatremic, and elicited an even stronger association between the patients who had two or more pre-existing condition and hyponatremia.

Among the category one conditions, hypertension was the most prevalent disease (n= 136; 37%), out of which more than three quarters (81.6%) had hyponatremia perhaps related to thiazide use a finding that was statistically significant ($p<0.001$). These findings were similar to the study by Subhash et al. who found that hypertension was the most common comorbid condition (63.2%), while Nidhi K et al in their study demonstrated 27.9% of the patients had hypertension and had a strong association with hyponatremia. Hypertension being the most frequent comorbid condition associated with the elderly, widespread prescription of thiazides, which was used by one third of hypertensive patients in this study, makes the thiazide-induced hyponatremia to be described as a 'silent epidemic' (Mann SJ et al. 2006).

The proportion of patients with Diabetes Mellitus was (n=41; 11%) with four patients having markedly elevated levels of serum glucose (above 33mmol/L), similar to the study by Nankabirwa H et al. of whom participants with diabetes comprised 9.5% of subjects who participated in the study. While only 2 % of the diabetic patients in Nankabirwa's study had hyponatremia, this current study had nearly all patients (90%) having hyponatremia a finding that was statistically significant ($p= 0.003$). This was after correcting for hyponatremia among the patients who had hyperglycaemia given that for every 100mg/dl rise in serum glucose, sodium levels reduce by about 1.6mmol/L owing to the dilutional aspect of serum, as glucose is osmotically active and hence drawing water from the intracellular to extracellular compartment. This spuriously low sodium levels

should never be corrected by supplementation because upon resolution of the aggravating factor and normalisation of the glucose levels, the sodium value often corrects. “Pseudohyponatremia is an artifact” that should not be treated. There are case studies demonstrating the potential dangers of failing to recognize pseudohyponatremia and treating it as if it were true hyponatremia (Yavuzer K, Muhammed H, Ziya S & Fuat G, 2016). These findings could be explained by the fact that a high proportion of the subjects constituting half of the patients with DM had elevated serum glucose levels, with up to 80% of them having hypertonic hyponatremia resulting in a dilutional effect, despite adjusting for the effects of hyperglycaemia. Furthermore, Liamis et al noted that in patients with uncontrolled DM, serum concentration of [Na^+] is variable, reflecting the balance between the hyperglycaemia-induced water movement out of the cells that lowers [Na^+], and the glucosuria-induced osmotic diuresis, which tends to raise [Na^+].

Endocrine disorders entailing hypothyroidism alongside psychiatric conditions were the least prevalent in this study each representing (n= 4; 1.09% of the patients. Subhash et al. in their study similarly found the least proportion of patients having endocrine disorders (3.6%). There was nevertheless a weak association (p=0.046) in the univariate analysis between endocrine disorders and hyponatremia, possibly because few patients had conditions related to this system, with three of them being patients on follow up for hypothyroidism with normal thyroid function tests, and had normal serum sodium levels, while one patient was newly diagnosed at the emergency department with myxedema coma after presenting with typical features. These findings are similar to a study done by Takanobu N et al. in 2018 in Japan whereby they found that the prevalence of hyponatremia was significantly higher in patients with overt hypothyroidism even after adjusting for

potential confounders like age, sex, kidney function and serum albumin levels, and increased with increasing severity of hypothyroidism (OR=1.43; 95% CI 1.15 to 1.78; p= 0.001).

Hyponatremia is sometimes associated with hypothyroidism, particularly in patients with severe primary hypothyroidism and myxedema (Schrier RW 2006, Derubertis FR et al. 1971, Hanna FW et al. 1997, Skowsky WR et al. 1978). Thus, thyroid function should be evaluated in any patient with otherwise unexplained hypotonic hyponatremia. However, because hypothyroidism and hyponatremia are each relatively common disorders in hospitalised patients, their coexistence may not be necessarily causal. Other explanations for hyponatremia should be sought unless hypothyroidism is severe. In patients with severe myxedema like the patient who was newly diagnosed, low sodium levels could be due to decreased cardiac output leading to the release of Anti Diuretic Hormone (ADH) via the carotid sinus baroreceptors, and decreased glomerular filtration rate (GFR) may also be a contributing factor (Derubertis FR et al. 1971, Hanna FW et al 1997, Kreisman SH, et al. 1999)

Among the medication, thiazides were independently associated with hyponatremia (OR= 4.58; 95% CI 1.48 to 14.20; p= 0.008), with patients four times likely to have hyponatremia. These findings were comparable to the study by Subhash et al. and Liamis G et al. who both depicted thiazides as one of the commonest cause of hyponatremia, with hypertension the commonest comorbid condition. Other large studies too in most developed countries have found that thiazides are the diuretics most strongly associated with hyponatremia (Sonnenblick M et al 1993, Romanovsky A et al 2011). These findings

were however different from the study by Nankabirwa et al., who found that use of loop diuretics was the factor most strongly associated with hyponatremia (OR=2.51; 95% CI 1.20 to 5.26; p=0.01) perhaps because the study involved patients with heart failure, loop diuretics being the cornerstone of management with possible use of significantly higher doses.

Virtually all severe cases of severe diuretic- induced hyponatremia have been due to thiazide type diuretics (Sonnenblick M et al. 1993, Friedman et al. 1989, Ashraf N et al. 1981, Fichman MP et al. 1971, Chow KM et al. 2003, Mozes B et al. 1986).

This study reported the prevalence of hyponatremia to be 70.38% among the elderly participants. This finding is consistent with studies by Audra B et al. 2006, Jorge J et al. 2016, Natkunam A et al. 1991, Subhash C et al. 2019 and Nankabirwa H et al. 2015, which have shown that hyponatremia prevalence in the elderly, can range from 24% to as high as 75% irrespective of the region.

5.2 STUDY STRENGTHS AND LIMITATIONS

Strengths: The classification of hyponatremia by tonicity, contrary to other studies, by determination of serum osmolality, improved our understanding of prevalence of true hyponatremia.

Limitation: This study was cross-sectional and so causal relationships between hyponatremia and the various factors described cannot be established.

- A more objective determination of the nutritional status was not undertaken but was mitigated by taking a detailed nutritional history. This was due to the debilitated nature of some of the patients that could not allow for taking anthropometric measures like

subjecting them to a weighing scale; and estimation was not a good idea, as this would introduce inaccuracies in the data set.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

This study shows that the prevalence of hyponatremia among the elderly patients in MTRH is high at about 70.38%. Hypotonic hyponatremia (true hyponatremia) is the most common subtype with most patients presenting with mild hyponatremia. Comorbidities were often present in the elderly patients with hypertension being the most common condition in this population. Factors significantly associated with hyponatremia were age group 70-79 and use of thiazide diuretics.

6.2 RECOMMENDATION

1. Routine screening, monitoring and management of hyponatremia in the elderly due to its high prevalence and associated morbidity.
2. Cautious use of thiazides in the management of hypertension in the elderly due to the high risk of developing hyponatremia (4x increased risk).
3. There is need to carry out a prospective study to establish the outcomes of elderly patients with hyponatremia in our setting.

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APPENDIX I: QUESTIONNAIRE AND DATA COLLECTION FORM

Patient study no: _____ Date of birth: _____ / Age: _____ (yrs.) Gender: _____ (M/F) County of Origin: _____ (Within UG / Outside)

Serum sodium (Na^+): _____ (mMol/L) Serum Urea: _____ (mMol/L) RBS: _____ (mMol/L)

Salt intake – (Inclusion at cooking/addition on table (Y) / or not at all (N)) :_____(Y/N)

Nutrition history: - General food intake – (subjective - from patient / objective - from relatives): _____ (GOOD/POOR)

History of falls / fractures in elderly period: _____(Y/N)

Comorbidities - Category 1: (Infections/DM/HTN/Stroke/Malignancies):

_____

_____

_____

Comorbidities – Category 2: (Other Systemic e.g. Renal/Cardiovascular/GIT/Nervous/MSS etc.):

_____

_____

_____

Presenting / Prevailing signs and symptom / brief HPI:

(diarrhea/vomiting/confusion/coma etc.):

_____

_____

_____

Medication history, types and use:

_____

_____

_____

Current presenting / working diagnosis / or reason for admission -:

_____

____

Admitting destination (for those undergoing admission): _____ (e.g. medical ward/general surgical ward/ orthopedic/ hospice referral /ICU etc.)

Number of previous/prior admissions within the past year: _____

Transport cost and expenses from home to MTRH to & fro: _____ (Kshs)

APPENDIX II: CONSENT FORM- ENGLISH

REVALENCE OF HYPONATREMIA AMONG ELDERLY PATIENTS AT MTRH

MOI UNIVERSITY COLLEGE OF HEALTH SCIENCES / MOI TEACHING AND REFERRAL HOSPITAL

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

INFORMED CONSENT FORM

Lead Researcher:

Winston Ongalo, MBChB, Moi University, School of Medicine

Contact Person: Dr. Winston Ongalo at 0710-950-839

Researchers' statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you would need to help you decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything less about the research or the form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. We will give you a copy of this form for your records.

PURPOSE OF THE STUDY

The purpose of this study is to learn about the prevalence and associated factors of hyponatremia and its subtypes among elderly patients.

STUDY PROCEDURES

After you have read, agreed and signed this consent form, you will have more information collected today during the clinic visit. If you meet the requirements to join the study, the evaluation will take about 15 minutes to complete.

If you decide not to take part in this study or if you do not meet the eligibility requirements, we may still use some of your information.

Evaluations:

As part of the study, you will have the following evaluations:

1. About 3ml of blood will be taken from your arm for standard lab tests.

2. A drop of blood from your finger prick shall be taken for performing a random blood glucose test.

RISKS, STRESS, OR DISCOMFORT

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, light-headedness, and in rare cases, fainting or infection.

Interviews will contain some questions of a sensitive nature. This information will be confidential but should you choose not to answer, it will in no way affect your treatment or relations with the hospital. There are no costs to you for participating in the study. In the event of study-related injury, illness, or distress, contact: Dr. Winston Ongalo at 0710-950-839.

BENEFITS OF THE STUDY

If you participate in this study, there may be direct benefit to you. You will learn about your health status as regards your renal function status that will include your serum Sodium levels and your random blood sugar that is a good screen for Diabetes mellitus disease. If any of these is found to be abnormal, it shall be communicated to you and your primary physician to facilitate further management.

SOURCE OF FUNDING

The principal researcher will personally fund the study.

CONFIDENTIALITY OF RESEARCH INFORMATION

The information you provide, and blood test results will be shared with the research team in this study. However, it will not be possible to identify you individually from this information. The study team will provide you with an identification number. The identification number (not your name or other information that could be used to identify you) will be used during analysis of the study. Data linking your unique ID number and name will be encrypted and stored electronically. Only the study staff investigators will have access to this information. All other data will be collected and stored encrypted electronically. Sharing this information will also not identify you. Government or university staff sometimes reviews studies such as this one to make

sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviews will protect your privacy. The study records will not be used to put you at legal risk of harm.

There are some limitations to this protection. We will voluntarily provide the information to the institutional Review and Ethics Committee (IREC) of Moi University.

National privacy regulations may not apply to these groups; however, they have their own policies and guidelines to assure that all reasonable efforts will be made to keep your personal information private and confidential.

OTHER INFORMATION

Taking part in this research study is voluntary. You may choose not to take part in the study. You could still receive other treatments. Saying no will not affect your rights to health care services. You are also free to withdraw from this study at any time. If after data collection you choose to quit, you can request that the information provided by you be destroyed under supervision and thus not used in the research study. You will be notified if new information becomes available about the risks or benefits of this research, then you can decide if you want to stay in the study.

COMPENSATION

You will receive no financial payments because of participating in this study.

RESEARCH-RELATED INJURY

If you think you have a medical problem or illness related to this research, contact Dr. Winston Ongalo at 0710-950-839 right away. He will refer you for treatment.

Printed name of study staff obtaining consent Signature Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researchers listed

on the first page of this consent form. If I have questions about my rights as a research subject, I can contact Moi University Institutional Review Ethics Committee (IREC) via telephone number 053- 2033471/2/3

Printed name of subject	Signature	Date
(Must be dated by the participant if literate)		

Printed name of witness	Signature	Date
(If participant is illiterate)		(Must be dated by witness)

APPENDIX III: CONSENT FORM- KISWAHILI

PREVALENCE AND ASSOCIATED FACTORS OF HYPONATREMIA AND ITS SUBTYPES AMONG ELDERLY PATIENTS

MOI UNIVERSITY COLLEGE OF HEALTH SCIENCES/MOI TEACHING AND REFERRAL HOSPITAL

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC) – (BODI YA UTAFITI NA KAMATI YA MAADILI)

FOMU YA KIBALI CHA KUSHIRIKI KWENYE UTAFITI

Jina la mtafiti mkuu:

Winston Ongalo, MBChB, MMed, Moi University School of Medicine

Jina la mtu wakuwasilisha kuhusu utafiti: Dr. Winston Ongalo 0710-950-839

Taarifa kutoka kwa utafiti

Unaombwa kushiriki katika utafiti huu. Dhumuni ya hii fomu ya idhini ni kukupa habari Zaidi kuhusu utafiti huu ili iweze kukusaidia kuamua kama ungependa kushiriki katika utafiti huu au hapana. Tunaomba uisome hii fomu kwa makini. Watafiti wataongea na wewe kuhusu utafiti huu na uko huru kuuliza maswali wakati wowote kuhusiana na chochote tutakachokifanya katika utafiti huu, hatari na manufaa ya kushiriki katika utafiti huu na pia haki zako kama mshiriki wa utafiti huu. Tukishakujibu maswali yako yote, utachagua kushiriki kwenye huu utafiti au kukataa. Kama utakubali kushiriki katika utafiti huu, utaombwa kuweka sahihi katika hii fomu ya idhini. Utapewa nyaraka kuweka kwa ukumbusho wako.

LENGO LA UTAFITI

Madhumuni ya utafiti huu ni kuelewa wingi wa ugonjwa wa upungufu wa chumbi katika damu kati ya wagonjwa ambao ni wazee na kuweza kubaini mambo yanayohusiana na shida hii.

UTARATIBU WA UTAFITI

Baada ya kusoma, kukubali na kuweka sahihi kwa fomu ya idhini utaulizwa maswali kuhakikisha kuwa unayo mahitaji yote ya kushiriki katika utafiti huu. Ukikubali kushiriki, itakuchukua muda wa dakika kumi na tanoa kukamilisha utafiti huu. Ukiamua kutoshiriki kwenye utafiti huu, ama kama hautatimiza matakwa yote ya utafiti huu, huenda tukatumia majibu yako kama vile miaka na jinsia yako.

Tathmini

Mambo haya yatafanyika kwenye utafiti huu:

1. Damu kiwango cha mililita tatu kitatolewa kutoka kwa mshipa wa mkono ili kufanyiwa vipimo kwenye maabara.
2. Vilevile, tone la damu litachukuliwa kwa kidole chako cha mkono kwa kudunga ili kuweza kutathmini kiwango cha sukari kwenye damu.

ARI ZINAZOAMBATANA NA KUSHIRIKI KATIKA UTAFITI

Kutoa damu inaweza kukukosesha starehe, kuvunja damu, ama kuvimba mahali shindano imedunga, kichwa nyepesi na kwa visa vichache kuzirahi ama kuambukizwa magonjwa.

Pia maswali utakayo ulizwa leo yanaweza kuwa maswali nyeti kwako. Mazungumzo au taarifa yeyote tutakayopata toka kwako itatunzwa kwa siri kubwa na kutoka jibu ni hiari yako. Kama utakataa kushiriki kwa huu utafiti, bado utaendele kupokea matibabu unayohitaji, na haita athiri uhusiano wako na hospitali. Hautalipishwa ada kushiriki katika utafiti huu. Kama unatatizo lolote linalohusiana na utafiti unaweza kuwasiliana na Dr. Winston Ongalo **0710-950-839** aweze kukusaidia.

MANUFAA YA KUSHIRIKI KATIKA UTAFITI

Kuna manufaa kwako unapo shiriki katika utafiti huu. Utaweza kujua hali ya jinsi figo yako inafanya kazi, kiwango cha chumvi katika damu na kiwango chako cha sukari kwenye damu ambayo inaweza kubainisha iwapo kuna uwezekano wa kuwa na ugonjwa wa kisukari na ikiwa inaanza jinsi ya kujilinda. Hii itasaidia madaktari wanaokushughulikia kujua jinsi gani watakusaidia iwapo itajulikana una matatizo hayo.

WADHAMINI WA UTAFITI HUU

Jina: Dkt. Winston Ongalo

USIRI WA TAARIFA ZA UTAFITI

Matokeo ya utafiti huu itapewa daktari wako na mashirika yanayoshirikiana katika utafiti huu. Walakini, haitawezekana kukutambua wewe kibinafsi kutoka kwa hii habari. Kikundi cha utafiti kitakupatia namba ya utambulisho. Namba ya utamubulisho (code) sio jina lako ama habari yoyote ambayo inaweza tumika kukutambulisha ndiyo itatumika. Rekodi wa utafiti ndiyo pekee yao watakuwa na funguo. Kuchapishwa kokote matokeo ya huu utafiti hautatumia jina lako

kukutambulisha wewe binafsi. Rekodi zako zinaweza pitiwa na Bodi ya Utafiti na Kamati ya Maadili ya chuo kikuu cha Moi.

Tafadhali kumbuka ya kwamba ni chaguo lako kushiriki ama kutoshiriki katika huu utafiti. Una huru wa kuacha kushiriki katika huu utafiti wakati wowote. Bado utaendelea kupata matibabu yako ya kiafya kikamilifu kama hautashiriki katika huu utafiti.

MALIPO

Hautalipwa ridhaa kwa muda wako uliotumia katika kumaliza uchunguzi unaohusiana na huu utafiti.

MAJERUHI YATOKANAYO NA UTAFITI HUU

Kama umejeruhiwa kwa sababu ulishiriki katika utafiti, mpigie Dr. Winston Ongalo namabari ya simu **0710-950-839** haraka iwezekanavyo ili aweze kukupatia matibabu au kukutafutia njia ya kupata matibabu.

Jina la mwenye kukuchukua kibali cha kushiriki utafiti Sahihi Tarehe

Kwa kuzingatia yote hapa juu, ninakubali kushiriki katika huu utafiti. Nimesoma hii fomu ya kukubali (ama imesomwa na nikaelezewa wazi), maswali yangu yote yamejibika na ninakubali kushiriki katika huu utafiti. Na ninakubali kupokea nakala ya fomu ya kukubali. Kama nina maswali zaidi kuhusu utafiti ama majeraha yanayohusiana na utafiti, nitawasiliana na mtafiti Daktari Winston Ongalo kwa namba ya simu: 0710-950-839. Na maswali kuhusu haki zangu kama mshiriki katika utafiti ama malalamiko kuhusu utafiti, wasiliana na msimamizi wa IREC kwa namba ya simu: 053-2033471/2/3

SAHIHI AMA ALAMA YA MSHIRIKI: **Tarehe:**
(Lazima tarehe iwekwe na mshiriki kama amesoma)
SAHIHI YA MSHAHIDI: **Tarehe:**
(Kama hana elimu ya kumwezesha kusoma lazima tarehe iandikwe na mshahidi)

APPENDIX IV: PROCEDURE FOR DRAWING VENOUS BLOOD

Venous blood was drawn for renal function test. The procedure was explained to the participant and verbal consent obtained. Universal safety procedures were observed. Venous blood draw was from the median cubital vein (in the antecubital fossa) of the less dominant upper limb.

Below is an overview of the steps that were followed:

1. Arm was selected and a tourniquet placed on the arm above the draw site. The median cubital vein was selected.
2. Site was cleansed with a sterile alcohol/methylated spirit preparation pad.
3. A needle was inserted into the vein and the collection tube was engaged.
4. Three millilitres of blood was collected into a red-topped vacutainer blood collection bottle.
5. Tourniquet was removed once the quantity of blood desired had been obtained.
6. A small gauze pad and Band-Aid was placed on the venous blood drawn site.
7. The blood collection tube was labelled with the patient's information and a corresponding laboratory request form dully filled.
8. Blood collection tubes were batched until five samples were obtained before being taken to the laboratory for analysis.

APPENDIX V: PROCEDURE FOR RENAL FUNCTION TEST (RFT)

Blood samples for determination of RFT were collected at a central laboratory at the time of recruitment by the principal investigator, or research assistant, or the attending clinicians or laboratory technicians as per the person who was available. Care was taken to ensure that no intravenous fluid administration was administered before taking the blood specimen as all the clinicians had been informed of the study protocols. In the few situations where this occurred, the various interventions done prior to blood sample collection was keenly noted. Serum Sodium levels were determined through Direct - Ion Specific Electrode Potentiometry using the Cobas Integra® 400 plus analyzer from Roche Diagnostics. See appendix IV for procedure

The Roche Cobas Integra 400 plus chemistry analyser is used for diagnostic clinical chemistry testing. Classic chemistry, electrolytes, specific proteins, therapeutic drug monitoring, drugs of abuse, and thyroid hormone testing are consolidated into one system with one reagent cassette design. The instrument carries out all test orders automatically and is equipped with measuring modules:

- FP photometer for Fluorescence polarimetry
- Absorbance photometer for Absorbance photometry
- ISE (Ion-Selective Electrode) for module Ion selective potentiometry

Samples are automatically transferred from a sample tube or cup to the module where the measurements are made. All optical measurements use the same transparent plastic containers, called cuvettes. The graphical user interface -running under Windows NT -provides quick and easy access to sample, control, and calibration data, while continuously monitoring all system functions. Color-coded icons alert one to changes in the system status. Connection to a host system allows for automatic transfer of results to and from the COBAS INTEGRA 400 plus

RFT assay –Sodium determination

RFT Analyser used: Cobas Integra® 400

CHEMICAL PRINCIPLES OF PROCEDURE:

An Ion-Selective Electrode (ISE) makes use of the unique properties of certain membrane materials to develop an electrical potential (electromotive force, EMF) for the measurements of ions in solution. The electrode has a selective membrane in contact with both the test solution and an internal filling solution. The internal filling solution contains the test ion at a fixed concentration. Because of the particular nature of the membrane, the test ions will closely associate with the membrane on each side. The membrane EMF is determined by the difference in concentration of the test ion in the test solution and the internal filling solution. The complete measurement system for a particular ion includes the ISE, a reference electrode and electronic circuits to measure and process the EMF to give the test ion concentration. The sodium and potassium electrodes are based on neutral carriers and the chloride electrode is based on an ion exchanger. The Cobas Integra® 400 plus analyser performed all measurements and calculations automatically, and the screen displayed the Sodium, Potassium and Chloride values at the end of assay.

Calibration

The instrument: Cobas Integra® 400 plus analyzer was calibrated by the manufacturer. Thereafter, the instrument automatically self-adjusted during first-time power up and during each assay. In the event of the system being unable to make appropriate internal adjustments, an error message was displayed. Calibrators included ISE Standard Low and ISE Standard High. According to the manufacturer's instructions, after opening, a calibrator vial was used for only one calibration. After calibration, the sodium slope had to be 55-63 and the EMF readings had to be as close to zero as possible, thus indicating that there were no large changes in the slope.

Reagents/Materials:

Sodium Electrode, Potassium Electrode, Chloride Electrode, Reference Electrode, ISE DiluentGen.2, ISE Internal StandardGen.2, ISE Reference Electrolyte, ISE Cleaning Solution. **Quality Control:**

To assure quality of both testing and patient results, two levels of quality control were performed at the minimum:

1. Once every twenty-four hours.
2. If a new pack of reagent was put into use or

3. If a calibration was performed.

Storage:

Reference Electrolyte, Internal Standard, and Diluent were stored at 15-25°C. ISE Cleaning Solution was stored at at 2-8°C while electrodes stored at 7-40°C. Labels were routinely scanned for expiration dates.

On-board stability:

ISE Reference Electrolyte at 4 weeks, ISE Diluent at 2 weeks while ISE Internal Standard at 2 weeks

Specimen:

Serum or heparinized plasma collected using standard sampling tubes or tubes containing separating gel were used. Samples were separated from the clot or cells promptly after collection.

Stability: 8 hours at 2-8°C in primary tube, 3 days at 2-8°Cif removed from gel tube.

Analytical Measurement Range (AMR):

Sodium: 80 -180 mmol/L

Potassium: 1.5 -10 mmol/L

Chloride: 60 -140 mmol/L

Expected Values:

Sodium 135 -145 mmol/L

Potassium (plasma) Adult: 3.4 -5.0 mmol/L, Infant (Day 0 -30): 3.7 -5.9 mmol/L, Child (1mo. -2 yrs.): 4.1 -5.3 mmol/L, Plasma potassium levels are reported to be approximately 0.3 mmol/L lower than serum levels.

Chloride 96 -108 mmol/L

RFT ASSAY- UREA DETERMINATION:

CHEMICAL PRINCIPLES OF PROCEDURE:

The Cobas Integra® 400 plus analyzer Urea/BUN (UREAL) bottle contains an in vitro diagnostic reagent system intended for use on Cobas systems for the quantitative determination of the urea/BUN (blood urea nitrogen) concentration in serum and plasma.

Urea is hydrolysed by urease to form ammonium and carbonate. In the second reaction, 2-oxoglutarate reacts with ammonium in the presence of glutamate dehydrogenase (GLDH) and the coenzyme NADH to produce L-glutamate. In this reaction, two moles of NADH are oxidized to NAD for each mole of urea hydrolysed.

Urea + 2H2O--- Urease---> 2 NH_4^+ + CO_3^{2-}

NH_4+ + 2-oxoglutarate + NADH ---GLDH---> L-glutamate + NAD^+ + H2O

The rate of decrease in the NADH concentrations is directly proportional to the urea concentration in the specimen. It is determined by measuring the absorbance at 340nm.

Specimen:

Serum or Plasma. For plasma samples, the only acceptable anticoagulant by manufacturer is Lithium heparin (Li-heparin) and not ammonium heparin. This is because bacterial growth in the specimen and high atmospheric ammonia concentrations as well as contamination by ammonium ions may cause erroneously elevated results.

Stability in serum/plasma: 7 days at 20-25^{0}C, 7 days at 2-8^{o}C, 1 year -20^{o}C.

Reagents/Materials:

Integra UREA/BUN 500 tests

Cassette UREAL

R1: NaCl 9%

R2 TRIS buffer: 220 mmol/L, pH 8.6; 2-oxyglutarate: 73 mmol/L; NADH: 2.5 mmol/L; ADP: 6.5 mmol/L; urease (jack bean) : >300 ukat/L; GLDH (bovine liver) : >80 ukat/L; preservative; nonreactive stabilizers.pH 8.6

Storage and Stability: The on board reagents for use were stored at 10-15^{o}C with a shelf life of 8 weeks

Calibration: Calibrator: Calibrator f.a.s. uses deionized water as zero calibrator. Calibrator mode: Linear regression. Calibrator replicate: Duplicate recommended. Calibration Frequency: The instrument was calibrated after instrument service or repair, or whenever it was dictated by quality control results, and after every 4 weeks.

Quality control: Quality Control frequency: Two levels of quality control were performed at the minimum whereby once every twenty-four hours and whenever a new cassette or reagent was put in use or if a calibration was performed.

Analytical Measurement Range (AMR): For Serum/Plasma: 0.3-40MMol/L, with values greater than AMR of >40MMol/L reported as high. The expected range was 0.3-8.3MMol/L of urea in serum/plasma. **Calculations:** N/A **Interpretation:** N/A

APPENDIX VI: PROCEDURE FOR MEASURING RANDOM BLOOD SUGAR (RBS)

After consenting, the subject's capillary blood was obtained by using a sterile needle/ lancet to perform a prick on the fingertip. RBS level was determined by the On-Call® Plus Blood Glucose Monitoring System. It is an electrochemical enzymatic assay for the quantitative detection of glucose in capillary whole blood from the fingertip, forearm, and/or palm by people with or without diabetes at home and by healthcare professionals as an aid in the monitoring the effectiveness of diabetes control programs. It has a control solution for use with the On-Call® Plus Blood Glucose meter and strips as a quality control check to verify the accuracy of blood glucose test results.

Comparison with predicate: The On-Call® Plus Blood Glucose Monitoring System was compared to a standard predicate – The One Touch Ultra Blood Glucose Monitoring System and a negligible variance of 2% was obtained which was inconsequential.

Principle:

The glucose meter, determines the concentration of glucose in the solution based on electrochemical technology, which uses electrochemical test strips to perform the measurement. A drop of blood is applied to the end tip of the disposable test strip after connecting it to the glucometer. The blood is then automatically absorbed into the reaction cell where the reaction takes place. In each test strip, there is an enzyme called glucose oxidase. This enzyme reacts with the glucose, in the blood sample and creates an acid called gluconic acid. The gluconic acid then reacts, with another chemical in the testing strip called ferricyanide. The ferricyanide and the gluconic acid, then combine to create ferrocyanide. Once ferrocyanide has been created, the device runs an electronic current

through the blood sample on the strip. This current is then able to read the ferrocyanide and determine how much glucose is in the sample of blood, on the testing strip. That number is then displayed on the screen of the glucose-testing meter.

However, it is important to note that there are two most common methods used in electrochemical measurement of glucose which are Colorimetric method and Amperometric method. The On-Call® Plus Blood Glucose Monitoring System uses the amperometric method described above. In the colorimetric method, the typical sensors such as Light Emitting Diodes (LEDs) or photo sensors form the analog interface. These sensors are followed by a Trans-Impedance Amplifier (TIA) for the glucose concentration measurement in the solution. The Color Reflectance principle is used in this method to sense the color intensity in the reaction layer of the test strip by the photometry. The glucose meter generates a numerical value that is a measurement of the glucose concentration present in the solution.

Reagent preparation: No reagents are needed to perform the test once control solution has been run on the calibrator chip.

Testing Procedure:

1. Procedure was explained to the subject/caregiver and consent obtained
2. The subject's finger was cleaned with methylated spirit swabs and allowed a few seconds to dry.
3. The finger was then pricked using a lancet and gently squeezed.
4. A drop of blood was placed at the end of a glass capillary allowing the glass capillary to fill.
5. The end of blood filled capillary tube was then placed onto the end of glucose test strip sample placement area already preloaded on to the glucometer machine till a beep indicating sufficient sample was heard then withdrawn.
6. Test result was automatically displayed in 5seconds.

Control solution stability/ traceability: An open and closed stability study of the control solution that has been done to mimic the actual use condition by the manufacturer documented a 3-month use life of the control solution.

Precision/Reproducibility: This was evaluated by the manufacturer according to EN ISO 15197:2003. Repeatability evaluation, with three test strip lots using blood samples at five glucose concentrations measured 10 times on 10 glucose meters each revealed consistent findings with a cumulative variance of 3.07% which was insignificant and acceptable. These findings are important as I used 8 lots of glucose test strips.

Linearity/ Assay reportable range and detection limit:

The minimum threshold for glucose detection was 1.11Mmol/L. The test was linear up to a glucose concentration of 33.3Mmol/L. Values outside these ranges were reported as either lower or higher than reference range.

APPENDIX VII: IREC /MTRH APPOVAL LETTERS

MU/MTRH-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2019/05
Approval Number: 0003260

14th March, 2019

Dr. Ongalo Winston Jenneby,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
14 MAR 2019
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Ongalo,

RE: FORMAL APPROVAL

The MU/MTRH- Institutional Research and Ethics Committee has reviewed your research proposal titled: -

"Prevalence of Hyponatremia among Elderly Patients at Moi Teaching and Referral Hospital, Eldoret".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 3260*** on 14th March, 2019. You are therefore permitted to begin your investigations.

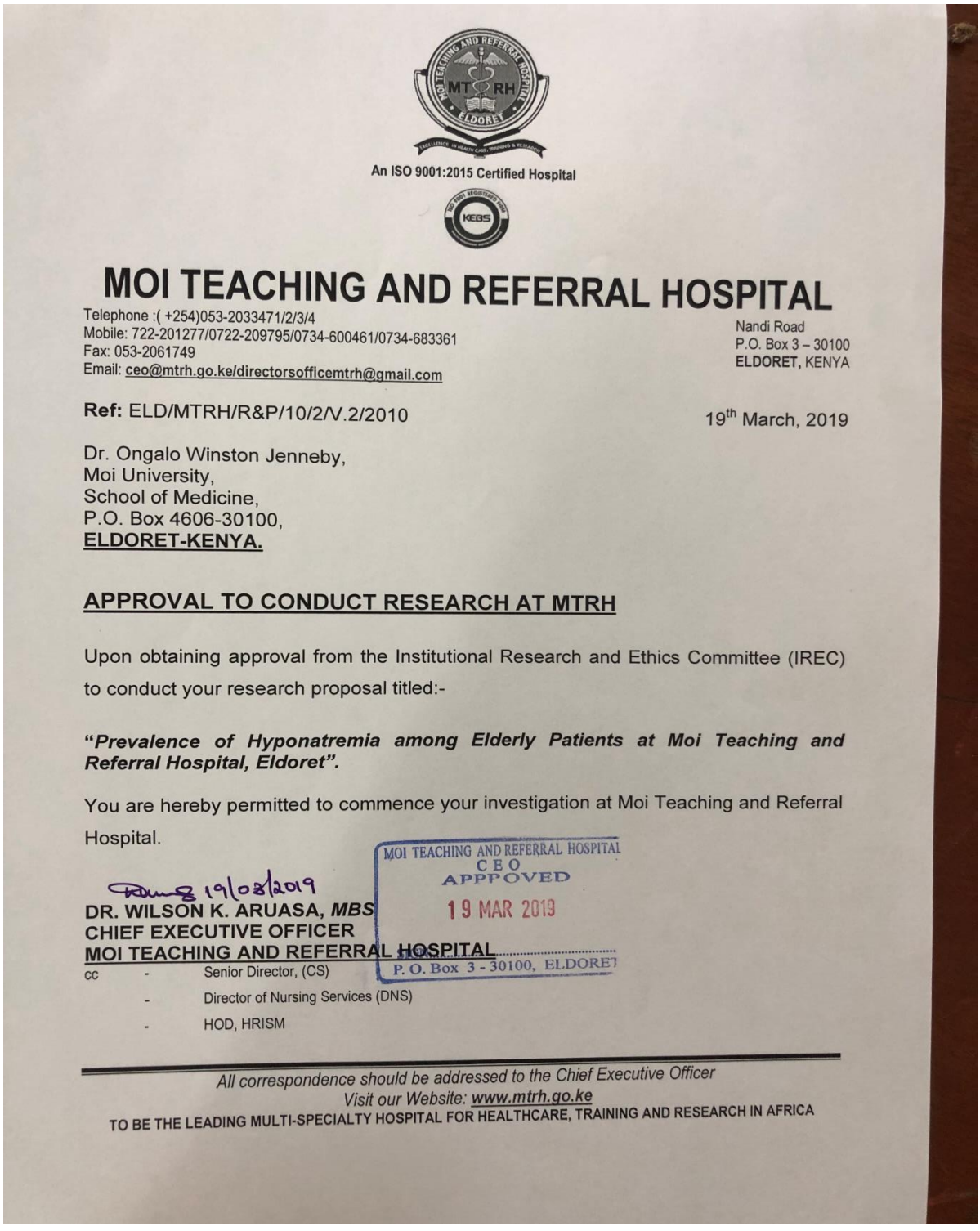
Note that this approval is for 1 year; hence will expire on 13th March, 2020. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date. You will be required to submit progress report(s) on application for continuation, at the end of the study and any other times as may be recommended by the Committee.

Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. You will also be required to seek further clearance from any other regulatory body/authority that may be appropriate and applicable to the conduct of this study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD



An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

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Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

19th March, 2019

Dr. Ongalo Winston Jenneby,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Prevalence of Hyponatremia among Elderly Patients at Moi Teaching and Referral Hospital, Eldoret".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

MOI TEACHING AND REFERRAL HOSPITAL
CEO
APPROVED
19 MAR 2019
P. O. Box 3 - 30100, ELDORET

19/03/2019

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM