PREVALENCE AND FACTORS ASSOCIATED WITH HYPONATREMIA AMONG PAEDIATRIC ONCOLOGY PATIENTS AT KENYATTA NATIONAL HOSPITAL- A HOSPITAL-BASED CROSS-SECTIONAL STUDY

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DECLARATION

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

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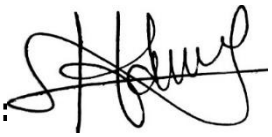
Signed:  **Date:** 23/06/2023

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DEDICATION

I would like to dedicate this work to the following people:

- All children suffering from paediatric malignancies.
- My family for their encouragement and support.

COLLABORATING INSTITUTIONS

1. Kenyatta National Hospital
2. University of Nairobi

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LIST OF ABBREVIATIONS

W.H.O	:	World Health Organization
K.N.H	:	Kenyatta National Hospital
UON	:	University of Nairobi.
ERC	:	Ethics and Research Committee
BMI	:	Body Mass Index
LMICs	:	Low and Middle-Income Countries
TPN	:	Total Parenteral Nutrition
NSAIDs	**:**	Non-Steroidal Anti-Inflammatory Drugs
SIADH	:	Syndrome of Inappropriate Anti-Diuretic Hormone Secretion
HER -2	:	Human Epidermal growth factor Receptor 2
ALK	:	Anaplastic Lymphoma Kinase
MEK	:	Mitogen-activated protein kinase kinase
ADH	**:**	Anti-Diuretic Hormone
COR	:	Crude Odds Ratio
AOR	:	Adjusted Odds Ratio
CI	:	Confidence Interval
CNS	:	Central Nervous System
AQP2	:	Aquaporin-2
Hyper-CVAD	:	Hyperfractionated Cyclophosphamide,Vincristine, Adriamycin, Dexamethasone, Methotrexate, Cytarabine.
CODOX-M/IVAC	:	Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate,Ifosfamide,Etoposide and Cytarabine

ABSTRACT

Introduction: Hyponatremia is an independent predictive factor of survival in cancer patients; and its prompt correction is imperative. Data on the prevalence and factors associated with hyponatremia among paediatric oncology patients in Africa are scarce.

Objective: To determine the prevalence and factors associated with hyponatremia and the proportion of promptly corrected hyponatremia among paediatric oncology patients at Kenyatta National Hospital.

Methodology: A hospital-based cross-sectional study. The proportion of children with hyponatremia was estimated and a 95% confidence interval provided. Multivariable logistic regression analysis was used to determine factors associated with hyponatremia.

Results: The overall prevalence of hyponatremia was 43.3% (95% CI 38.55%- 55.78%). Of these, approximately 23% had mild hyponatremia, 18% had moderate hyponatremia and 2.7% had severe hyponatremia. Only 29% of those patients having moderate and severe hyponatremia received prompt correction. Age, BMI for age, current chemotherapeutic medications, chemotherapy cycle and TPN were not statistically significant in this study.

Conclusions: There is a high prevalence of hyponatremia among paediatric cancer patients receiving care at KNH and approximately two thirds of the paediatric cancer patients with moderate and severe hyponatremia seeking care at KNH do not receive prompt correction for their hyponatremia.

Recommendations: Paediatric cancer patients should be given more attention and routinely be screened for hyponatremia and other electrolyte disorders. Timely intervention should be instituted for hyponatremia if present in these paediatric cancer patients. Larger studies assessing factors associated with hyponatremia and outcome of paediatric oncology patients with hyponatremia are needed in our set-up.

CHAPTER ONE

INTRODUCTION

1.1 Background

Cancer is a major cause of death among children and adolescents in Africa and globally(1). Globally, over 400,000 children have been diagnosed with cancer annually(1). Nevertheless, 44% of them die before diagnosis(2).

The impact of childhood cancer in Africa is soaring and despite its relatively low incidence, the mortality rate is disproportionately high(3).

The probability of surviving a diagnosis of childhood cancer ranges from 80% in high-income countries to 15-45% in low and middle-income countries(1).

The poor survival of childhood cancers in LMICs can be attributed to delayed diagnosis and advanced disease, inability to get the right diagnosis, lack of relevant therapy, neglect of treatment, toxicity-related deaths (including electrolyte abnormalities) and preventable relapse(1).

In addition to the childhood cancer burden itself, electrolyte abnormalities are very vital independent prognostic factors for paediatric cancer patients(3)

The common electrolyte disorders seen in paediatric cancer patients involve sodium, potassium, calcium, and magnesium(4). Of these, hyponatremia is the most frequent and has the highest impact independent of its cause(4,5).

Hyponatremia is an independent prognostic factor and marker of mortality in paediatric oncology patients(6). It has been implicated greatly with higher mortality, longer hospital stay, high risk of re-admission, and is an important determinant of hospitalization cost among paediatric cancer ptients(4,7,8).

However, effectual and apt normalization of hyponatremia has a positive impact on prognosis and the hospital stay span with subsequent economic and life savings(4,8). The financial cost related to hyponatremia is immensely high with higher incidences of re-admission. For example, in the United States, it was estimated to cost an additional $3000 per patient when juxtaposed with the cost of normonatremic patients(3).

Several studies have shown that comorbid conditions, age, nutritional status, TPN, BMI, chemotherapy cycle, and current medications predispose paediatric cancer patients to hyponatremia(3,9).

While it is a common concept that management of other complications is necessary for paediatric patients with cancer, little emphasis is given to hyponatremia and other electrolyte disorders(3).

There is limited data on the same in our context and the paediatric oncology population worldwide, therefore this study assessed the extent of hyponatremia in paediatric oncology patients in our setup and established associated factors.

CHAPTER TWO

LITERATURE REVIEW

2.1 Epidemiology and Burden of childhood cancers

Cancer is one of the main causes of death among children and adolescents(1). Although genetic factors and specific prenatal and postnatal exposures increase the likelihood of having various childhood cancers, the cause remains unknown in most cases(10).

Worldwide, deaths associated with cancer are estimated at 13% every year with 70% of the reported cases being in LMIC(11).

Globally, over 400,000 children and adolescents are diagnosed with cancer annually(1) and 44% of them die before diagnosis(2). Worldwide, every three minutes a child is diagnosed with cancer(2).

Although the real incidence or prevalence of childhood cancers in Africa is unknown, childhood cancer is disproportionately widespread in Sub-Saharan Africa than in developed nations (4.6% of cancers versus 0.5%)(2).

The estimated frequency of childhood cancers at KNH is around 125 cases annually(12). In 1996, Macharia did a review of childhood cancers at KNH and found a hospital-based prevalence of 1.27 %(12).

In 2019, Mutua and Mwika did a study to assess childhood cancers at KNH and the prevalence of the common childhood cancers was reported as shown below:

- Leukaemia -30.6%,
- Retinoblastoma -23.3%,
- Wilms tumour- 16.9%,
- Lymphoma -16%,
- Malignant neoplasm of connective and soft tissue -9.1%
- Neuroblastoma - 4.1%.(13)

The same study showed these cancers were seen more frequently amongst ages 0 - 4 years at 64% and females were less affected than Males. In terms of mortality trends, the same study showed Retinoblastoma reporting a lowly rate of mortality at 6.9% whilst leukemia and Neuroblastoma reported the highest rate of mortality at 47.1%.(13)

The probability of surviving a diagnosis of childhood cancer ranges from 80% in high-income countries to 15-45% in low and middle-income countries(1). The reason for lower rates of survival in LMICs includes delayed diagnosis and highly advanced disease, failure to get the correct diagnosis, lack of relevant therapy, desertion of treatment, toxicity-related death (including electrolyte abnormalities) and preventable relapse(1).

2.2 Electrolyte abnormalities in cancer patients

In patients with cancer, electrolyte disorders are among the most frequent complications(4). A study done by Alem et al in Ethiopia showed an overall

prevalence of 60.7 %(3). The most common electrolyte abnormalities reported in these patients involve alterations in sodium, potassium, calcium, and magnesium levels(4).

Of these, hyponatremia is the most common electrolyte disorder and has been shown to have the highest impact in these patients(4).

2.3 Hyponatremia in cancer patients

Hyponatremia is a serum/plasma sodium concentration lower than 135 mmol/L(4). It can either be acute (occurring within 48hrs) or chronic (occurring slowly)(4).

The severity of hyponatremia can be graded based on the serum levels as follows:

- mild (130-134 mmol/L),
- moderate (125-129 mmol/L) and
- severe (< 125 mmol/L) (4)

2.4 Incidence and prevalence of hyponatremia in cancer patients

In patients with cancer, hyponatremia is the most frequent electrolyte disorder(4,14)

It has a variable incidence and prevalence dependent on the cancer type, clinical setting, and serum sodium cut-off levels(4,14,15). Several studies have shown a variable incidence of 4-44 % (4)and a high prevalence ranging from 47.6 % (3)to as high as 72%(9).

Of the few studies on the same in the paediatric cancer population, the study by kishimoto et al in 2016 on paediatric cancer patients below 18 years of age, showed the prevalence of hyponatremia to be 72%(9).

2.5 Pathophysiology and factors associated with hyponatremia in cancer patients

Most individuals with hyponatremia are mostly asymptomatic(15). However, when symptoms occur, they are often non-specific and confounded by other comorbidities(16). Symptoms are usually diverse spanning from mild cognitive disturbances to severe neurologic symptoms such as headaches, lethargy, poor level of concentration, vomiting, confusion, hallucinations, and coma(15).

In cancer patients, the pathophysiological mechanisms leading to hyponatremia are multifactorial(4). Although the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) is the leading cause of hyponatremia in cancer patients(15), other causes inducing hyponatremia in these patients include:

1) Cancer-related causes like paraneoplastic syndromes such as SIADH, metastasis to the brain, adrenals, and kidneys(4).
2) Treatment of cancer: They cause hyponatremia directly due to their mechanism of action (e.g vinca alkaloids might induce SIADH; platinum derivates are often related to hyponatremia; and target therapies and certain anti-angiogenetic agents, stimulate hyponatremia, despite the

underlying mechanism being unknown) or due to the side effects like gastrointestinal and kidney losses, and heart failure caused by cardiotoxic drugs such as anthracyclines and target therapies including anti-HER-2, anti-ALK, and anti-MEK. Immunotherapeutic agents can also cause direct damage to the adrenals or pituitary gland, favoring hyponatremia development(4).

3) Concomitant drugs such as diuretics, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, and neuroleptics used in these patients can cause hyponatremia(4).
4) Comorbid conditions like kidney failure, heart failure, liver cirrhosis, thyroiditis, and hypercortisolism can also lead to hyponatremia(4).

Studies have shown that several factors are associated with the existence of electrolyte abnormalities and hyponatremia in patients with cancer.

The study by Alem et al in Ethiopia showed that comorbidities, body mass index (BMI), age, the status of nutrition, and medications were linked to electrolyte disorders(3). The same study showed that underweight patients had higher odds of electrolyte disturbances while younger patients reported considerably lesser odds for sodium alteration. Increasing age was a strong independent risk factor for hyponatremia(3).

A study by Kishimoto et al in 2016 in Kobe Rosai Hospital, Tokyo assessing Risk Factors for Hyponatremia in paediatric oncology patients on chemotherapy, showed age 10 to 18 years, TPN, first or second

chemotherapy cycle as independent risk factors with great impact on the development of hyponatremia(9).

2.6 Burden and impact of hyponatremia in cancer patients

Various studies assessing the burden and impact of hyponatremia in patients with cancer showed that, regardless of cause, it correlates negatively with the outcome of patients(5).

Current evidence has shown a vital negative prognostic role of hyponatremia for patients who receive cancer medications(4), whilst a timely treatment of this electrolyte disorder taking into consideration the right timing to avert neurological damage, improves patients' outcomes(4).

Hyponatremia is an independent prognostic factor and marker of survival in this subset of patients(6)

It has been implicated greatly with higher mortality, longer hospital stay, worsening outcome, conditioning survival, influencing the quality of life, and the possibility to receive anti-cancer medications(4,7,8).

Besides the burden of cancer itself, hyponatremia also has a high economic burden and is linked to an extended hospital length of stay and higher risk of readmission and may constitute an important determinant of hospitalization costs(17)

2.7 Correction of hyponatremia in cancer patients

Early signs and symptoms of hyponatremia can be difficult to notice and are mostly understated hence timely assessment and treatment are vital in preventing neurocognitive damage and other complications(16). Therefore clinicians need to monitor serum/plasma sodium levels in all patients with cancer(4).

The approach to the management of hyponatremia mainly depends on its aetiology, symptomatology, and hyponatremia severity(4).

Independent of the cause, effective and prompt correction of hyponatremia has been associated with improvement in the outcome of cancer patients(4).

Prompt treatment and correction of this electrolyte disorder need to consider the right timing to avert neurological damage which is a serious complication in these patients(4).

Treatment modalities available for hyponatremia include diuretics, saline solution administration, fluid restriction, and selective vasopressin receptor antagonists(4).

Studies have shown that prompt correction with effectual and apt normalization of hyponatremia records encouraging results on prognosis and the duration of stay in the hospital with a potential impact for both economic and life savings(4,8)

The degree of hyponatremia and its normalization has also been shown to modify median survival in these patients(6)

For instance, a higher hyponatremia rate has a noteworthy and independent relationship with a longer stay in the hospital and a higher rate of mortality. Patients with cancer who have had their hyponatremia corrected in the hospital recorded an overall lower mortality risk(7).

The latest literature also supports the correction of hyponatremia has more positive impacts such as levels of sodium in the blood, duration of hospital stay, hyponatremia symptoms, and hospital complications(18).

Although studies have not specified a time frame for the prompt correction of hyponatremia in these patients, most management protocols that exist recommend correction of hyponatremia for these patients over 24-48hrs(14,16).

Therefore, to be pragmatic enough and take into consideration the challenges in our setup, we evaluated the promptness of hyponatremia correction over a time frame of 48hrs in this study.

Table 1: Table detailing previous studies on the prevalence of hyponatremia and associated factors among oncology patients.

Title/Author/Year	Setting	Type of study and Sample population	Key Findings
Analysis of Risk Factors for Hyponatremia During or Following Chemotherapy in Children with Cancer: kishimoto et al (2016)	Kobe Rosai Hospital, Tokyo	A Hospital-based, Retrospective Cohort Study 111 paediatric cancer patient	Prevalence of hyponatremia was 72%. The study identified age 10 to 18 years, TPN, first or second chemotherapy cycle as independent risk factors for hyponatremia. Clinical conditions of patients and chemotherapeutic agents may have a profound impact on the development of hyponatremia
Factors influencing the occurrence of electrolyte disorders in cancer patients, Alem et al (2021)	Jimma Medical Centre, southwest Ethiopia	Facility based cross-sectional study. 84 cancer patients aged 18 years and above	The overall prevalence of electrolyte disorders was 60.7%. Prevalence of hyponatremia was 47.6%. The presence or absence of comorbid diseases, age, body mass index (BMI), nutritional status, and current prescribed medication use were associated with electrolyte disorders
Electrolyte disorders in cancer patients: a systematic review, Berardi et al (2019).	systematic review, journal of cancer metastasis and treatment.	systematic review	Electrolyte disorders are very common complications in cancer patients. variable incidence of hyponatremia (4-44%). They might be associated to a worsening outcome, influencing quality of life, possibility to receive anticancer drugs, and conditioning survival. Prompt correction seems to have a positive impact.
Incidence and Impact of Baseline Electrolyte Abnormalities in Patients Admitted with Chemotherapy Induced Febrile Neutropenia, Shaikh et al (2011).	Aga Khan University Hospital, Karachi, Pakistan.	prospective, observational study, 215 cancer patients with febrile neutropenia	Decline in electrolyte levels is frequently observed in patients presenting with FN. Hyponatremia seen in 67.9% of these patients. These abnormalities can have independent negative impact on the outcome for such patients.
Hyponatremia in Hospitalized Cancer Patients and Its Impact on Clinical Outcomes, Doshi et al (2012).	University of Texas M.D. Anderson Cancer Center	Retrospective analysis of 3,357 cancer patients	Hyponatremia in patients with cancer is associated with longer hospital stay and higher mortality
Is hyponatremia a prognostic marker of survival for lung cancer? petereit et al (2011)	ELK Berlin/Tumor-Centre, Buch, Germany	hospital based retrospective study, 2048 adult lung cancer patient	Hyponatremia can influence survival of patients with lung cancer. The degree of hyponatremia and its normalization can modify median survival. Plasma sodium could be a relevant prognostic marker of survival for lung cancer.

2.8 Problem statement and Justification

Hyponatremia represents the most common malignancy-related electrolyte disorder and has been shown to worsen prognosis and affect the outcome.
However, Prompt correction of hyponatremia has been shown to have a positive impact.

Despite hyponatremia having these important prognostic implications in cancer patients, little emphasis is given to it compared to other complications.
It is often under-recognized in clinical practice, leading to worsening outcomes.

A study done by kishimito et al in 2016 analysing the risk factors for hyponatremia in paediatric cancer patients on chemotherapy showed a high prevalence of 72%, yet there is paucity of data on the same in paediatric oncology patients in Africa and specifically in Kenya. No study has been done in our setup on the same.

No policies or guidelines exist on its magnitude, recognition, and management.
This poses great implications in terms of patient outcomes and economic savings.

2.9 Study utility

Understanding the prevalence of hyponatremia and associated factors will highlight the magnitude of this disorder and improve knowledge of this important and underscored complication in this subset of patients.

Consequently, this will influence changes in the management protocol of these patients and strengthen its anticipation, prompt recognition, and timely and effective treatment.

The overall result will be improved outcomes in these patients in terms of quality of life, reduced morbidity and mortality, shortened duration of hospital stay, and reduced re-admissions.

2.10 Research Question and Study Objectives

2.10.1 Research Question

What is the prevalence and factors associated with hyponatremia among paediatric oncology patients at KNH and what proportion are promptly corrected?

2.10.2 Primary Objectives

1. To determine the prevalence of hyponatremia among paediatric oncology patients at KNH.

2.10.3 Secondary Objectives

1. To determine the proportion of paediatric oncology patients at KNH with hyponatremia who are promptly corrected.
2. To determine the factors associated with hyponatremia among paediatric oncology patients at KNH.

CHAPTER THREE

METHODOLOGY

3.1 Study design

A hospital-based cross-sectional study was utilized.

3.2 Study setting

This study was carried out at the KNH Paediatric Oncology wards (Ward1E and 3D) and ophthalmology Wards (1C).

KNH is the largest tertiary referral facility in Kenya and therefore most children with cancer are treated at this facility.

KNH has approximately one hundred paediatric oncology in-patients per month receiving different modalities of treatment.

3.3 Study population

The study population comprised of Paediatric oncology patients already admitted in wards 3D, 1E, and 1C and those discharged from the same wards.

3.3.1 Inclusion criteria

1. Child aged 0-18 yrs.
2. Confirmed diagnosis of a malignancy.
3. KNH admission sodium level results.

3.3.2 Exclusion criteria

1. A child with missing data on the following important independent variables:

a) Age

b) Confirmed diagnosis of malignancy

c) KNH admission sodium level results.

3.4 Case Definitions

1. Paediatric oncology patient- patients aged 0-18 years with a confirmed diagnosis of a malignancy
2. Hyponatremia- serum/plasma sodium level below 135 mmol/L
3. Degrees/ Grades of hyponatremia:
    a) Mild hyponatremia: sodium level of 130-134 mmol/L.
    b) Moderate hyponatremia: sodium level of 125-129 mmol/L.
    c) Severe hyponatremia: sodium level of < 125 mmol/L.
4. Associated factors- factors influencing the existence of hyponatremia in these patients. Factors of interest are:
    - Age
    - BMI for Age
    - Type of malignancy
    - Current chemotherapy medications
    - Chemotherapy cycle and
    - Total parenteral nutrition.
5. Prompt correction- completion of correction for moderate and severe hyponatremia within 48hrs of diagnosis.
6. TPN- Total parenteral nutrition is the intravenous infusion of nutrients, bypassing the usual process of eating and digestion.

3.5 Sample size calculation

- **For the prevalence of hyponatremia**, we utilized Fischer's sample size formula which is:

$$n=\frac{z^2\, p\,(1-p)}{d^2}$$

n = Sample Size

z = standard normal deviation of the preferred level of confidence (95% CI set at 1.96).

p = probable prevalence of outcome of interest within the study population. The prevalence of hyponatremia in paediatric cancer patients was estimated at 72% in a study done in Tokyo japan and this was used for the primary objective in this study.

d = desired study precision set at 7.5%.

The sample size was thus calculated:

$$n=\frac{1.96^2 \times 0.72(1-0.72)}{0.075^2}$$

$$n=137.68$$

The minimum sample size was 138

3.6 Sampling methods

The study utilized a consecutive sampling technique. Every subject meeting the inclusion criteria was selected until the required sample size was achieved.

3.7 Study tools

A case record form was used to capture details of interest from the patients' files.

Relevant information captured include:

1. Demographics,
2. BMI for age,
3. Type of malignancy,
4. Current chemotherapy medications,
5. Chemotherapy cycle,
6. Whether or not the patient is on total parenteral nutrition,
7. Presence or absence of hyponatremia,
8. Degree of hyponatremia,
9. Whether or not a prompt treatment for hyponatremia was done.

3.8 Study procedures

The data collection process begun after approval from KNH-UON ERC.

Waiver of consent was sought from the KNH-UON ERC and granted as the data was extracted from patients' files.

The Principal Investigator recruited research assistants to collect data and trained them on the study procedure.

The principal investigator and the research assistants were responsible for collecting data.

3.8.1 Screening and enrollment procedure.

Files of potential study participants were identified by visits to the paediatric oncology inpatient wards, ophthalmology wards and records department. The files of admitted patients were retrieved from the wards while those of the

discharged patients from the records department using the ward admission book.

Files were screened for eligibility using a study eligibility checklist.

A list of every patient who met the inclusion criteria was made and every consecutive file from the list selected until the required sample size was reached.

3.8.2 Data collection procedure

Each study participant was assigned a unique identifier and a case record form attached to each file and this was used to capture data of interest to the study.

Key variables of interest were obtained from patients' files as follows:

- Patients' demographic data, anthropometry, type of malignancy, chemotherapy medications and cycle, and whether the patient is on TPN were captured from the files at first contact.
- Evaluation of hyponatremia and degree of hyponatremia were done by assessing if the patient has had hyponatremia in the last admission by checking sodium levels done at KNH laboratory. We used only sodium levels from KNH laboratory for quality control purposes. Quality control at the KNH laboratory is assured by the presence of experienced personnel and adherence to laboratory protocols as concerns sample handling and processing. The laboratory is also accredited by the Kenya Medical Laboratory Technicians and Technologists' board and other external institutions.

- Prompt correction of hyponatremia was evaluated by assessing if correction for moderate and severe hyponatremia was completed within 48hrs of hyponatremia diagnosis. All participants with moderate and severe hyponatremia were evaluated for this.

3.9 Data Management and Analysis

Data from the case record forms were coded, entered, and cleaned in Microsoft Excel.

SPSS Version 25.0 statistical software was used for data analysis.

Categorical data was summarized as frequencies and percentages and represented in graphs and charts.

Continuous data was summarized as mean (SD) if normally distributed and median (IQR) if skewed.

The proportion of children with hyponatremia was estimated and a 95% confidence interval provided.

The prevalence of hyponatremia was estimated from the number with hyponatremia/total study population, then converted into a percentage.

The proportion of promptly corrected hyponatremia was estimated from the number promptly corrected/ total with moderate and severe hyponatremia, then converted into a percentage.

Multivariable logistic regression analysis was used to evaluate the relationship of age, BMI for age, type of malignancy, current chemotherapy medications, chemotherapy cycle and total parenteral nutrition with hyponatremia.

The level of the relationship was evaluated using an Odds ratio with a 95% confidence interval and $P \leqslant 0.05$ was considered as statistically significant.

3.10 Ethical Considerations

The researcher sought approval from the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee to carry out the study. Approval for data collection was also sought from the KNH Paediatrics and Ophthalmology departments after Ethics approval.

Waiver of consent was sought from the ethics committee since data was extracted from the patients' files.

Strict confidentiality, anonymity, and privacy was fully guaranteed throughout the entire study. No information concerning the individual study findings was shared with any unauthorized third party devoid of the written consent of the Ethics and Research Committee.

The findings of the study will be availed to the health facility to improve the care of paediatric oncology patients. They will also be presented to the Department of Paediatrics and Child Health academic staff and students of the University of Nairobi in partial fulfillment of the requirements of the Master of Medicine program.

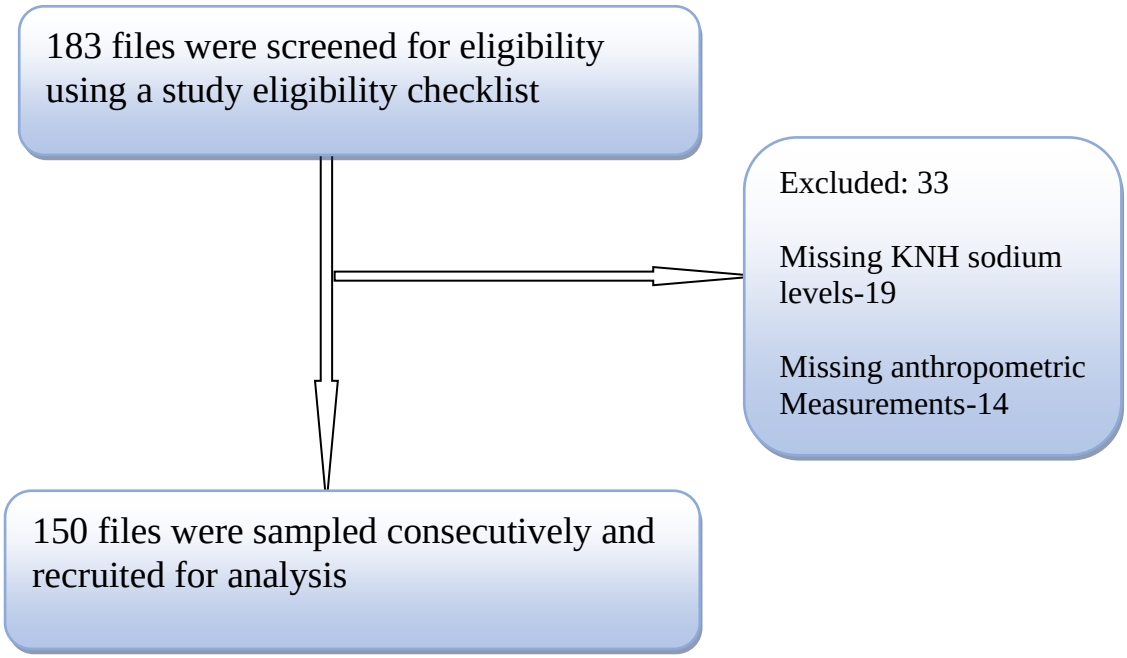
CHAPTER FOUR

RESULTS

4.1 Study Procedure

Figure 1: Figure showing study procedure

Files were screened for eligibility using a study eligibility checklist.



4.2 Descriptive characteristics of study population

150 patient files were analysed in this study. The data was assessed for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests as well as inspection of the histogram and this revealed that the body mass index was distributed normally about the mean. However, age, weight and height were not distributed normally about the mean.

Majority of the patients, 91 (60.7%) were male. Majority (56%) were aged between 6- 14 years with median age of 10 years (IQR 8.125-1.875 years). Majority of the patients were underweight (46.7%).

The commonest malignancies were the haematological malignancies (53.3%) and majority of the patients were on Vinca alkaloid based chemotherapeutic drugs (44%). Majority of them were on more than the second chemotherapy cycle (57.3%) and majority were not on TPN (96%).

The summary of the descriptive statistics are shown in the table below:

Table 2: Table showing Descriptive Statistics of Study Population

Variable	Categorization(where applicable)	Frequency (n)	Frequency (%)	Median (IQR)
Gender	Male	91	60.7	
	Female	59	39.3	
Age	0-5 years	66	44	3 (2.0-4.0)
	6-14 years	84	56	10(8.125-11.875)
Weight				19.70Kgs(IQR14.28-27.65)
Height				1.16 Ms (IQR 0.968-1.373)
BMI for Age	<-1 SD (underweight)	70	46.7	13.6 (IQR 12.6 -14.2)
	-1 to 1 SD (normal)	56	37.3	16.1 (IQR15.3-16.98)
	>1 SD (overweight)	24	16	18.3 (IQR 17.4-20.4)
Type of malignancy	Haematological	80	53.3	
	Solid	70	46.7	
Current chemotherapeutic medications	Vinca alkaloid drugs	66	44	
	Alkylating agents	25	16.7	
	Mixed (vinca and alkylating)	28	18.7	
	Others	31	20.6	
Chemotherapy cycle	First cycle	36	24	
	Second cycle	28	18.7	
	Other cycles	86	57.3	
TPN	present	6	4	
	Absent	144	96	

4.3 Primary Objective

4.3.1 Prevalence of Hyponatremia

Hyponatremia (serum sodium <135 mEq/L) was recorded as present in 65 patients: 43.3% (95% CI 38.55%-55.78%). We also analysed the degree of hyponatremia in these patients. Of the 65 patients with hyponatremia, 34 (22.67%) had mild hyponatremia, 27(18.00%) had moderate hyponatremia and 4 (2.67%) had severe hyponatremia. This is illustrated in the figure below:

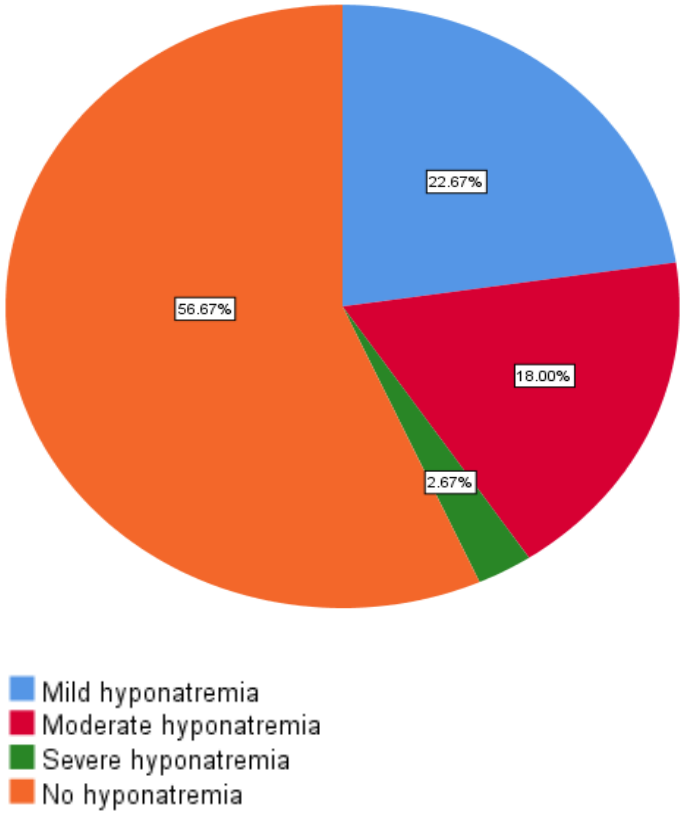


Figure 2: pie chart showing prevalence and degree of hyponatremia

4.4 Secondary Objectives

4.4.1 Promptness of Hyponatremia Correction

Only 09 patients (29.03%) of those who had moderate & severe hyponatremia (n=31) received prompt correction while the rest did not.

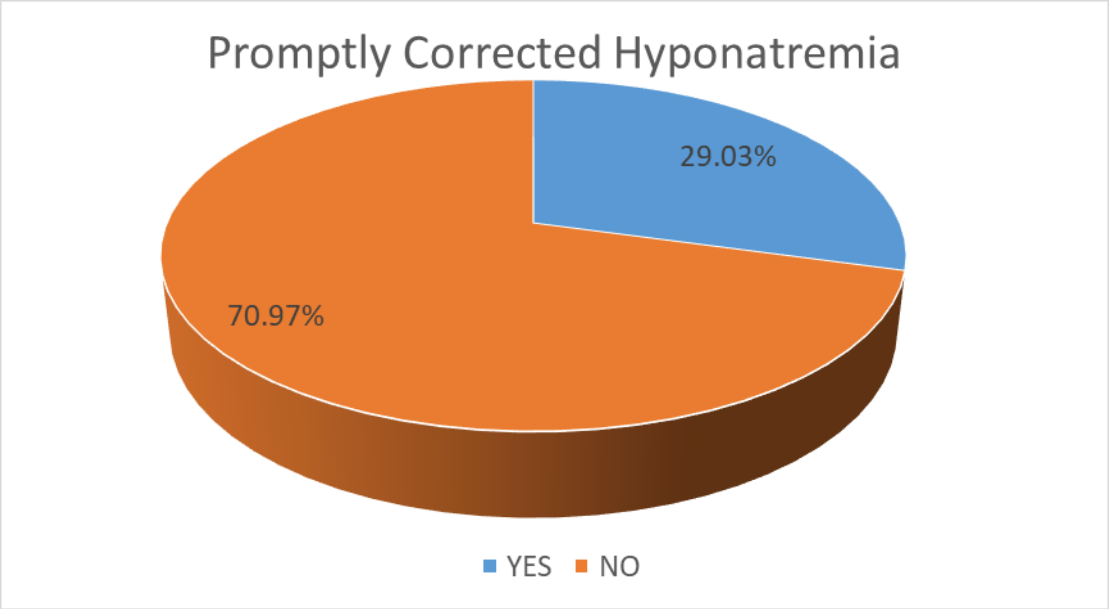


Figure 3: pie chart showing promptness of hyponatremia correction

4.4.2 Factors associated with hyponatremia

To assess the association of each independent variable with the occurrence of hyponatremia, multivariable regression analysis was performed. Degree of association was assessed using an Odds ratio with 95% confidence interval and $P \leqslant 0.05$ was considered as statistically significant.

Age, BMI for age, type of malignancy, current chemotherapy medications, chemotherapy cycle and total parenteral nutrition were the candidate variables for multivariable logistic regression analysis. Their presence or absence were found to have influence on the occurrence of hyponatremia

though this influence was statistically not significant in this study. This may be explained by the sample size used in this study.

Age was one of the independent variables for multivariable logistic regression analysis. There was a significant difference in the odds of developing hyponatremia between the different age groups. Children aged 0-5 years had significantly higher odds of developing hyponatremia (AOR= 1.43 (95% CI: 0.70-2.94), P value=0.370) while the odds were lower for those aged 6-14 years (AOR=0.713 (95% CI:0.34-1.49), P value=0.382). Generally, a decreasing age had a strong positive correlation with developing hyponatremia. However, this was not statistically significant.

BMI for age was among the factors associated with hyponatremia. After performing multivariable regression analysis, underweight patients had significantly lower odds of developing hyponatremia (AOR= 0.66 (95% CI:0.24-1.81), P value=0.421). overweight patients and those having normal BMI had higher odds of developing hyponatremia though there was no significant difference in the odds of developing hyponatremia among those having normal BMI (AOR=0.969 (95% CI:0.37-2.55), P value= 0.95) and overweight patients (AOR= 1.048(95% CI:0.92-1.19), P value=0.559). However, this was not statistically significant.

The type of malignancy is also a factor associated with occurrence of hyponatremia. After multivariable regression analysis, patients with

haematological malignancies had slightly higher odds of developing hyponatremia (AOR=1.020(95% CI:0.46-2.25), P value=0.961) compared to patients with solid malignancies (AOR=0.98 (95% CI:0.45-2.16), P value=0.958). However, this was not statistically significant.

The type of chemotherapeutic drugs and the number of chemotherapy cycles are other important factors associated with hyponatremia.

Patients on vinca alkaloid chemotherapy drugs had strong odds of developing hyponatremia (AOR=2.333(95% CI:0.68-8.03), P value=0.178). There was no significant difference in the odds of developing hyponatremia among patients on alkylating agents (AOR=1.768(95% CI:0.57-5.50), P value=0.325) and patients on mixed alkylating and vinca alkaloid regimen (AOR=1.73(95% CI:0.66-4.51), P value=0.26). The odds of developing hyponatremia were significantly lower by almost 2.5 times in the patients on other chemotherapy regimens (AOR=0.874(95% CI:0.42-1.81), P value=0.573) when compared to vinca alkaloids. However, this was not statistically significant.

Patients on one chemotherapy cycle were almost 5 times less likely to develop hyponatremia (AOR= 0.351(95% CI:0.22-1.51), P value=0.062) compared to patients in their second cycle (AOR=1.550(95% CI:0.66-3.64), P value=0.314) and more than two cycles (AOR=1.584(95% CI:0.54-4.61), P value=0.399). There was no significant difference in the risk of developing hyponatremia among patients on their second cycle and those on more than two cycles. However, this was not statistically significant.

We also assessed the influence of total parenteral nutrition (TPN) on hyponatremia. After multivariable regression analysis, the presence of TPN had inverse correlation with hyponatremia. Patients on TPN had lower odds of developing hyponatremia (AOR=2.706(95% CI:0.48-15.34), P value=0.267) compared to those who were not on TPN (AOR=2.959(95% CI:0.50-17.60), P value=0.233) However, this was not statistically significant.

Factors associated with hyponatremia are summarized in the table below:

Table 3: Table showing multivariable analysis of factors associated with hyponatremia

Variable	Categorization (where applicable)	Frequency (%)	COR (95% CI)	P value	AOR (95% CI)	P value
Age	0-5 years	44	1.333 (0.69 – 2.56)	0.389	1.403 (0.70-2.94)	0.370
	6-14 years	56	0.65 (0.39 – 1.44)	0.087	0.713 (0.34 -1.49)	0.382
BMI for Age	<-1 SD (underweight)	46.7	0.673 (0.33 – 1.38)	0.287	0.661 (0.24 – 1.81)	0.421
	-1 to 1 SD (normal)	37.3	0.949 (0.37 – 2.41)	0.912	0.969 (0.37 – 2.55)	0.95
	>1 SD (overweight)	16.0	1.054 (0.42 – 2.67)	0.892	1.048 (0.92-1.19)	0.559
Type of malignancy	Haematological	53.3	1.199 (0.63– 2.29)	0.474	1.020 (0.46-2.25)	0.961
	Solid	46.7	0.702(0.44-1.59)	0.582	0.98 (0.45 – 2.16)	0.958
Current chemotherapeutic medications	Vinca alkaloid drugs	44.0	1.646 (0.67-4.03)	0.326	2.333 (0.68-8.03)	0.179
	Alkylating agents	16.7	1.624 (0.64-4.11)	0.306	1.768 (0.57 -5.50)	0.325
	Mixed (vinca and alkylating)	18.7	0.957 (0.39-2.34)	0.923	1.73 (0.66 – 4.51)	0.263
	Others	20.6	0.608 (0.25-1.49)	0.306	0.874 (0.42-1.81)	0.573
Chemotherapy cycle	First cycle	24.0	1.327(0.48-3.65)	0.584	0.351(0.22-1.51)	0.062
	Second cycle	18.7	1.159(0.49-2.74)	0.736	1.550(0.66-3.64)	0.314
	Other cycles	57.3	1.538(0.69-3.43)	0.292	1.584(0.54-4.61)	0.399
TPN	Present	4.0	0.348 (0.06 – 1.96)	0.35	2.706 (0.48 – 15.34)	0.267
	Absent	96	2.877 (0.51 – 16.24)	0.231	2.959 (0.50-17.59)	0.233

COR: Crude odds ratio; AOR: Adjusted odds ratio

CHAPTER FIVE

DISCUSSION

5.1 Prevalence of Hyponatremia

The prevalence of hyponatremia in this study was 43.3% (95% CI 38.55%-55.78%). Of these 22.67% had mild hyponatremia, 18.00% had moderate hyponatremia and 2.67% had severe hyponatremia.

These findings are similar to those reported by Doshi et al. in 2012 where hyponatremia was noted in 47% of admissions, and was mild in 36%, moderate in 10% and severe in 1% (7). Similarly, a study by Peri in 2019, reported a prevalence of 38.7% of hyponatremia where low serum sodium concentration was associated with symptom severity(19). Also, Bartalis et al. (2021) reported the prevalence of hyponatremia in patients with lung cancer of between 3 and 94.8% with an average of 25%(20). In contrast, a whopping percentage of hyponatremia of 76% was reported by Castillo et al. in 2016 in a study on patients diagnosed with lymphoma, breast, colorectal, small cell lung, or non-small cell lung cancers (21).

The prevalence and degree of hyponatremia is of great importance as it can be used as a prognostic and predictive factor with the degree of hyponatremia being shown to modify median survival in these patients. Not only is severe and acute hyponatremia associated with an increased risk of mortality, there is evidence that also moderate and mild chronic hyponatremia increases the risk of death. Hyponatremia has been associated with an

increased risk of death in elderly patients, those with heart failure, pneumonia, cirrhosis and renal failure(6–8).

5.2 Promptness of hyponatremia correction

In this study, only 29.03% of those who had moderate & severe hyponatremia received prompt correction while the rest did not.

Although studies have not specified a time frame for the prompt correction of hyponatremia in paediatric cancer patients, most management protocols that exist recommend correction of hyponatremia over 24-48 hrs(14,16). To take in to consideration the challenges in our set-up, we evaluated promptness of hyponatremia correction over a time frame of 48hrs. However, the influence (outcome) of this on the paediatric cancer patients was not evaluated as this was not part of the study.

Treatment of hyponatremia depends on the presence, severity and onset of symptoms and the extracellular volume. Symptomatic patients require immediate intervention to avoid serious complications including neurological damage hence the need for timely assessment and treatment(6–8). However, if serum sodium is adjusted too quickly, the adaptive mechanisms that limit brain swelling during the development of chronic hyponatremia also make the brain prone to osmotic demyelination. Therefore, the serum sodium level should be raised in a controlled manner. Referencing a study by Castillo et al. in 2012, the rate of correction should be kept <12 mEq/L in 24 hours and <18 mEq/L in 48 hours (22). Asymptomatic patients with euvolemic or

hypervolemic hyponatremia are usually managed initially by fluid restriction, with the goal of achieving a negative water balance(22).

Effective and prompt correction of hyponatremia has been associated with improved outcomes in cancer patients and this needs to be timely to avert possible serious complications (4,22).

Studies have also shown that prompt treatment with effective normalization of hyponatremia has encouraging results both on prognosis and duration of stay in the hospital with potential impact for both economic and life savings(4,8). The degree of hyponatremia and its timely normalization has also been shown to modify median survival in these patients whereby cancer patients who had their hyponatremia corrected in the hospital had an overall lower mortality risk(6,7)

5.3 Factors associated with Hyponatremia

Previous studies have found that Age, BMI for age, type of malignancy, current chemotherapy medications, chemotherapy cycle and total parenteral nutrition to be significantly associated with the occurrence of hyponatremia in paediatric oncology patients.

However, these factors were not statistically significant in our study. This may be due to the small sample size and the fact that this study was not powered for this type of analysis.

5.4 Generalisability of study Findings

This is the first study to look at hyponatremia in paediatric oncology patients in our set up.

The prevalence of hyponatremia reported by this study is consistent with findings in other studies and significantly affirms the importance of hyponatremia in the outcome of these patients.

The statistical non-significance of factors influencing hyponatremia in this study may be attributable to the small sample size and therefore a larger study may be needed to determine this.

Generally, the findings of the study are a representation of the situation at Kenyatta National Hospital and our region by large.

Therefore, these findings should be addressed to improve care and outcome of paediatric oncology patients in our set up.

5.5 Study Strengths and Limitations

5.5.1 Strengths

- This is the first study to look at hyponatremia in paediatric cancer patients in our set-up hence has high utility.
- It is also the first study to look at promptness of hyponatremia correction among paediatric oncology patients in our set-up.

5.5.2 Limitations

- This is a cross-sectional study and will not be able to adequately describe hyponatremia changes as they occur with time.
- Outcomes such as length of stay and mortality were not explored in this study.

- Previous studies done for promptness of correction were mainly focusing on outcome hence no study to compare timeliness of correction was available.

5.6 Conclusions

1. The prevalence of hyponatremia (43.3%) among paediatric cancer patients receiving care at KNH is high.
2. Two out of three paediatric cancer patients with moderate and severe hyponatremia seeking care at KNH do not receive prompt correction for their hyponatremia.
3. Several factors such as age, BMI, type of malignancy, chemotherapy drugs and cycle influence the presence of hyponatremia among paediatric oncology patients at KNH. However, these were not statistically significant in this study.

5.7 Recommendations

- Paediatric cancer patients should be given more attention and routinely be screened for hyponatremia and other electrolyte disorders.
- Timely intervention should be instituted for hyponatremia if present in the paediatric cancer patients.
- Larger studies should be done to look at factors influencing hyponatremia and outcome of paediatric oncology patients with hyponatremia in our set-up.

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APPENDICES

Appendix 1: Study Eligibility Checklist

Fill in the spaces and tick in the boxes appropriately

Date (D/M/Y):……

Data collector's initials:……

Patient serial number:……

Inclusion criteria (if any criteria is marked "NO", the patient is not eligible for enrolment).

1. Child aged 0-18 yrs. YES[ ] NO[ ]
2. Confirmed diagnosis of malignancy YES[ ] NO[ ]
3. KNH admission sodium level results YES[ ] NO[ ]

Exclusion criteria (if any criteria is marked "YES", the patient is not eligible for enrolment).

1. Missing data on :
    a) Age YES[ ] NO[ ]
    b) Confirmed diagnosis of malignancy YES[ ] NO[ ]
    c) KNH admission sodium level results YES[ ] NO[ ]

Appendix 2: Case Record Form

Fill in the spaces and tick in the boxes appropriately.

IP NO:……

SERIAL NUMBER:……

AGE:……Years……Months

SEX: MALE [ ] FEMALE [ ]

ANTHROPOMETRY: WEIGHT (kgs)……HEIGHT (Ms)……BMI……

TYPE OF MALIGNANCY:……

CURRENT CHEMOTHERAPY MEDICATIONS: ……

CHEMOTHERAPY CYCLE :……(indicate first, second, third, etc)

TOTAL PARENTERAL NUTRITION: YES [ ] NO [ ]

HYPONATREMIA: YES [ ] NO [ ]

DEGREE OF HYPONATREMIA: MILD (130-134 mmol/l)…… [ ]

: MODERATE (125-129 mmol/l)……. [ ]

: SEVERE (<125 mmol/l)…… [ ]

PROMPT TREATMENT OF HYPONATREMIA: YES [ ] NO [ ]

Appendix 3: Study Budget

ITEM	QUANTITY	UNIT PRICE	TOTAL
STATIONERY/PRINTING			
Case record forms	200	15	3,000
Study eligibility checklist	200	15	3,000
Notebook	2	50	100
Pens	10	10	100
Box file	1	250	250
Final manuscripts	4	500	2,000
Poster presentation	1	2,000	2,000
COMMUNICATION	3	1000	3,000
RESEARCH ASSISTANT	1	10,000	10,000
DATA ANALYSIS	1	30,000	30,000
ETHICS FEE	1	2,000	2,000
TOTAL			**55,450**

Appendix 4: Study Timelines

Event	Dec 2021	Jan 2022	Feb2022	March2022-August2022	Sept2022-Nov 2022	Jan2023-Feb2023	March 2023	April 2023	May 2023
Research question									
Research proposal									
Faculty approval									
Ethical approval									
Data collection									
Data analysis									
Thesis writing									
Poster presentation									
Thesis submission									

Appendix 5: UON/KNH Ethics and Research Committee Approval Letter

UNIVERSITY OF NAIROBI
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KENYATTA NATIONAL HOSPITAL
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Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/272

15th July, 2022

KENYATTA NATIONAL HOSPITAL APPROVED 15 JUL 2022 P. O. Box 20723 - 00202, NAIROBI

Dr. Ahmed Kashif Maalim
Reg. No. H58/37582/2020
Dept. of Paediatrics and Child Health
Faculty of Health Sciences
University of Nairobi

Dear Dr. Maalim,

RESEARCH PROPOSAL: PREVALENCE AND FACTORS ASSOCIATED WITH HYPONATREMIA AMONG PAEDIATRIC ONCOLOGY PATIENTS AT KENYATTA NATIONAL HOSPITAL (P143/02/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P143/02/2022.** The approval period is 15th July 2022 – 14th July 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept., KNH
The Chair, Dept. of Paediatrics and Child Health, UoN
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Appendix 6: Turnitin Similarity and Plagiarism Report.

PREVALENCE AND FACTORS ASSOCIATED WITH HYPONATREMIA AMONG PAEDIATRIC ONCOLOGY PATIENTS AT KENYATTA NATIONAL HOSPITAL- A HOSPITAL-BASED CROSS-SECTIONAL STUDY

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