PREVALENCE OF INDUCTION FAILURE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN KENYATTA NATIONAL HOSPITAL.

BY

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DECLARATION

I declare this writing as my original work, it has not been presented in any academic institution for evaluation, examination or award of a degree.

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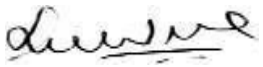

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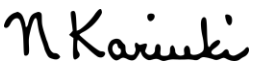

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LIST OF ABBREVIATIONS

ALL:	Acute Lymphoblastic Leukaemia
CD:	Cluster of Differentiation
CNS:	Central Nervous System
CR:	Complete remission
EFS:	Event-free survival
EOI:	End of induction
IF:	Induction failure
IT:	Intrathecal
IV:	Intravenous
KNH:	Kenyatta National Hospital
LIF:	Leukemic Induction Failure
MRD:	Minimal Residual Disease
MTX:	Methotrexate
NCI:	National Cancer Institute
OS:	Overall survival
PPR:	Poor prednisone response
SER:	Slow early response
TdT:	Terminal deoxynucleotidyl transferase
WBC:	White cell counts
WHO:	World Health Organization

OPERATIONAL DEFINITION OF TERMS.

Induction Failure: persistence of blasts cells of more than 5 per cent in the bone marrow at the end of induction (EOI)

Complete Remission: presence of less than 5 per cent malignant cells in a bone marrow at the end of induction and peripheral bold counts within normal limits.

National Cancer Institute (NCI) Risk: prognostic strata based on patients age and initial white cell count; thus, standard risk (WBC <50 x $10^{\wedge 9}$ /L and age >1<10 years) and high risk (WBC >50 x $10^{\wedge 9}$ /L or age <1>10 years)

CNS disease; presence of leukaemia cells in the cerebral spinal fluid with or without clinical manifestation.

ABSTRACT

Background: Acute lymphoblastic leukaemia (ALL) is the most prevalent malignancy of childhood worldwide accounting for 25-30 per cent of all cancers occurring in this age group. Induction is the first phase of treatment aimed at reducing the tumour burden to less than 5% blast cells in the bone marrow at the end of induction (EOI). Induction failure is the persistence of greater than 5% blast cells in the bone marrow at the end of induction and is an independent prognostic factor for overall survival that portends a poor outcome. The rate of induction failure is high in low- and middle- income countries (15-30%) compared to high-income countries (5-10%). The rate and factors contributing to induction failure among children with acute lymphoblastic leukemia in low-middle income countries like Kenya is poorly established. This study sought to establish the prevalence and factors associated with induction failure in childhood acute lymphoblastic leukemia in Kenyatta National Hospital and thereby provide valuable information for improvement of careof children with ALL for better outcomes.

Broad objective: The study objectives were to determine the prevalence and identify patient, disease and treatment factors associated with induction failure in children with acute lymphoblastic leukaemia treated in Kenyatta National Hospital (KNH).

Study design: A retrospective cross-sectional study that included all children aged 0-15 years diagnosed with acute lymphoblastic leukaemia and treated in Kenyatta National Hospital from January 2015 to December 2019. The study design was informed by a desired large sample size which could not have been achieved prospectively due to constraints of time.

Study site: The study was conducted in the Paediatric medical and oncology wards in KNH.

Material and Methods: Case records of 114 children aged 0-15 years with ALL treated in KNH between January 2015 and December 2019 were identified from the medical records department. All that met the inclusion criteria were abstracted to collect data regarding demographics, clinical presentation and examination findings, initial complete blood count (CBC) features, initial bone marrow aspirate features, treatment information and remission induction status at the end of induction as detailed in appendix 1. Data were entered using

IBM SPSS V.25. Descriptive statistics were generated for continuous and categorical variables as appropriate. Morphologic status and the independent variables were cross tabulated and Chi Square was used to assess for association between the dependent and independent variables and odds ratios calculated. P-values were obtained for levels of statistical significance at 95% confidence interval.

Results: Induction failure was seen in 33 of 102 children who completed induction (32.4%). Case fatality rate during induction was 10% (n=12). There was an association between central nervous system (CNS) disease and the dependent variable OR 3.43(1.33-8.86) (p=0.009). Central nervous system disease increased fourfold the risk of induction failure.

This study did not find any association between induction failure and demographic characteristics of patients such as gender OR 0.752 (1.75-3.23) (p=0.506), age OR 0.39 (0.14-1.06) (p=0.142) and BMI OR 1.10 (0.48-2.53) (P=0.247) at 95% CI.

Conclusion: The prevalence of induction failure was high in children diagnosed and treated for ALL in KNH. This is comparable to findings in other low-and middle-income countries. CNS disease was the only factor associated with induction failure.

CHAPTER ONE: BACKGROUND.

Acute lymphoblastic leukaemia (ALL) is the most frequently diagnosed malignancy of childhood worldwide. It accounts for about 25-30% of all cancers occurring in this age group (1, 2). Induction is the initial four-week phase of treatment of ALL aimed at achieving morphologic remission i.e., less than 5% blast cells in a bone marrow aspirate at the end of induction (3).

Induction failure is defined as the persistence of blast cells of greater than 5% in the bone marrow at the end of induction and is an independent prognostic factor for overall survival that portends a poor outcome (4, 5). The rate of induction failure is high in low- and middle- income countries (15-30%) compared to high-income countries (5-10%) (6, 7).

Some of the challenges to obtaining optimal induction outcomes in developing countries include; delayed diagnosis due to a low index of suspicion of ALL by both guardians and health care providers at the low level facilities, poor access to health care by the majority of people living in developing countries, abandonment of treatment and inadequacy of medical resources i.e. medical personnel, chemotherapeutic drugs, radiotherapy machines, diagnostic techniques and inadequate supportive care (8). Other well established poor prognostic factors are; male gender, age less than 1 year or older than ten years, high initial white blood cell count (>50 x $10^{\wedge 9}$ /L), immunophenotypes (T-cell ALL) and genetic abnormalities (BCR-ABL1 and hypodiploidy) (9). In order to achieve better outcomes of childhood ALL in low- and middle- income countries, the prevalence and drivers of induction failure must be established; and gaps in care highlighted to inform improvements in care for better outcomes. This study sought to establish the prevalence and factors associated with induction failure in childhood acute lymphoblastic leukemia in Kenyatta National Hospital and thereby provide valuable information for improvement of care of children with ALL for better outcomes.

CHAPTER TWO: LITERATURE REVIEW

2.0 Induction Failure.

Induction failure is defined as the persistence of blast cells of greater than 5 per cent in the bone marrow at the end of induction (9). An assessment of remission status at the end of the induction phase is the standard of care in the treatment of childhood ALL (9). Morphologic response status is categorized into: M1 (< 5% blasts/remission), M2 (5-25% blasts) or M3 (> 25% blasts). M2 and M3 are typically known as induction failure and portend a poor overall outcome (11). Children who fail to achieve complete remission after the initial phase of treatment have an increased risk of relapse and a low survival rate (10).

The prevalence of induction failure in developed countries is low at 5-10% (10-12). One study involving 44, 017 study participants with ALL treated by 14 co-operative study groups between 1985 and 2000 in Europe, America and Asia, found an induction failure (IF) rate of 2.4% (12). In the developing countries, IF is much higher at15-30% (13). This is due to, among other reasons, delays in diagnosis, inadequate medical resources and sub-optimal supportive care (14). One prospective study conducted in Moi Teaching and Referral Hospital in Kenya including 30 children aged 0-15 years diagnosed with acute lymphoblastic leukemia found an induction failure rate of 10%. Factors associated with induction failure were not established in this study (15). In a prospective study conducted in Karachi, Pakistan on clinical features and induction outcome of childhood acute lymphoblastic leukemia in a lower/middle income population involving 646 patients, induction failure rate was 30% (5).

Factor associated with induction failure are not widely studied in low/middle income countries. One study by *Oudot et al* looked at prognostic factors for leukemic induction failure in children

with acute lymphoblastic leukaemia and included 1395 participants. Some of the factors evaluated for association with induction failure were; age, gender, initial white blood cell (WBC) counts, central nervous system (CNS) disease, mediastinal mass, testicular involvement, immunophenotypes and French-American-British (FAB) classification. In the univariate analysis, factors associated with leukemic induction failure (LIF) included; WBC more than 100,000/L (P=0.001), mediastinal mass (P=0.017), T-Cell ALL (P=0.001), and t (9; 22) translocation (P=0.001). In that study, age, sex and CNS involvement were not predictive for LIF.

2.1 Definition.

Acute lymphoblastic leukaemia is a malignant transformation and proliferation of lymphoid progenitor cells diagnosed by the presence of over 20 per cent blast cells in the bone marrow at clinical presentation (16).

2.2 Epidemiology.

The number of new cases of childhood ALL in the US is 4.6 per 100,000 children aged 0-19 years (17). The incidence is higher in whites compared to black children at 5 and 2.8 per 100,000 children annually, respectively. The incidence in Sub- Saharan Africa is reportedly lower at 20 cases per million children (18). There is a slight male preponderance with a peak incidence age of between 1-4 years (18).

2.3 Pathophysiology.

The hallmark of acute lymphoblastic leukaemia is abnormal gene expression that is as a result of specific abnormalities of the chromosomes involved in differentiation and proliferation of lymphoid precursor cells (19).

The resultant aberrant lymphoblast is capable of uncontrollable self-renewal and undergoes developmental arrest at an early stage, causing accumulation of immature blast cells within the marrow and infiltration of the reticular-endothelial system and other extra-medullary sites (19).

As a result, the number of natural marrow elements that produce other blood cell lines including red blood cells, platelets and neutrophils is significantly reduced and consequently anaemia, thrombocytopenia and neutropenia occur (19).

2.4 Etiology.

The precise pathogenetic events leading to the development of acute lymphoblastic leukemia are unknown (3). Postulated theories suggest a multifactorial cause involving an interplay between environmental risk factors with a pre-existing genetic susceptibility (20). A two-step process of genetic mutation has been suggested. The first step occurs prenatally, generating a pre-leukemic clone. Postnatal, a second step involving the acquisition of secondary genetic changes leads to conversion into overt leukaemia. The postnatal step is thought to be triggered by a lack of exposure to common environmental organisms early in life (20).

2.5 Classification.

2.5.1 FAB Classification

The French- American and British (FAB) classification is based on the study of microscopic features and cytochemistry of blast cells with three morphological variants of ALL (21).

- L1 – small homogenous blast cells with a small nucleolus, regular nuclear membrane outline and high nuclear cytoplasmic ratio.
- L2 – heterogeneous blast cells with prominent nucleoli, irregular nuclear membrane outline and low nuclear cytoplasmic ratio.

- L3 – homogeneous cells with prominent nucleoli, basophilic cytoplasm and cytoplasmic vacuolation.

2.5.2 WHO classification

Table 1 lists the subtypes of acute lymphoblastic leukaemia according to updated (2016) WHO classification (22).

Table 1. WHO Classification of acute lymphoblastic leukemia 2016.

B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t (9;22) (q34.1; q11.2); *BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t (v;11q23.3); *KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t (12;21) (p13.2; q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyper diploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t (5;14) (q31.1; q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t (1;19) (q23; p13.3); *TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Note. NOS means not otherwise specified.

2.6 Clinical Presentation.

Clinical features are as a result of three main pathological processes; bone marrow failure, organ infiltration by blast cells and systemic effects of cytokines released by tumour cells (23). (Table 2)

CNS involvement can be the presenting feature in 5-8 per cent of children, and the most characteristic feature is usually seventh cranial nerve palsies (16).

Table 2. Presentation of ALL in children (pathological process, clinical signs and symptoms)

PATHOLOGICAL PROCESS	CLINICAL SIGN	CLINICAL SYMPTOM
1.Bone marrow failure	Anaemia	Pallor Shortness of breath Easy fatigability Palpitations Reduced level of activity
	Neutropenia	Recurrent infections
	Thrombocytopenia	Epistaxis Petechiae Bruising
2.Organ infiltration by blast cells Lymphoid organs (Liver, spleen, thymus)		Hepatosplenomegaly Lymphadenopathy Mediastinal mass
Extra medullary sites (CNS)		Convulsions Cranial nerve palsies
Extra medullary sites (Testis)		Testicular enlargement
3. Effects of cytokines (B symptoms)		Fever Night sweats Weight loss Malaise

2.7 Prognostic Factors.

Schultz KR et al in his review, highlights that current treatment of ALL aims to optimize the benefits of a more intense regimen for the high-risk patient while minimizing toxicity for the lower risk group by applying less intense regimens. This is otherwise known as Risk-adapted therapy (24). Better outcomes for those at highest risk of relapse and minimal treatment-related morbidity for the low-risk patients is, in fact, attributable to this novel approach to the management of ALL

(25). There are well established universally accepted prognostic factors, including; age at diagnosis, initial total white blood cell (WBC) counts, immune-phenotypic characteristics, genetic features and outcome of early therapy (19).

2.7.1 National Cancer Institute criteria.

Age and WBC counts are the two most important independent prognostic factors for B cell type leukaemia (26). The National Cancer Institute (NCI)/Rome criteria stratify patients using age and WBC count at presentation into prognostic strata with patients between the ages of 1 and 9.99 years and having a WBC count<50,000/mm^3 termed 'standard risk,' while the remainder are considered 'high risk' (26).

2.7.2 Disease characteristics.

Immuno-phenotypically, B cell ALL has a better prognosis compared to T cell ALL although the gap is rather narrow, especially in high-income countries where appropriate intensity chemotherapy and support is optimized. From the Malaysia-Singapore Acute Lymphoblastic Leukaemia 2003 study, T cell ALL notably had 6-year event free survival (EFS) and overall survival (OS) rates similar to those of patients with B-cell ALL (27).

Genetic factors are important determinants of prognosis for the B cell ALL. Certain genetic abnormalities confer better prognosis compared to others. Hyper ploidy (more than 50 chromosomes) and ETV6-RUNX1 (t (12; 21) (p13; q22)) patients have better outcomes compared to patients with BCR-ABL1 and hypodiploidy mutations who generally tend to have a dismal overall outcome (27).

2.7.3 Response to treatment

Early response to a steroid given over the initial seven days of treatment, as evidenced by presence of less than 1000 blast cells per cubic mm on a peripheral blood smear performed on the 7^{th} day post initiation of the steroid predicts a good outcome (28).

2.7.4 Minimal residual disease.

Minimal residual disease (MRD) is an important prognostic factor in childhood ALL. Molecular methods are employed to detect leukemic cells not otherwise detectable morphologically. It is used in patient risk stratification and to guide treatment therapies (29). This modality is unavailable in most developing countries.

2.8 Diagnosis.

Demonstration of ≥20% blast cells of the lymphoid lineage in a bone marrow aspirate constitutes the diagnosis of ALL (23). Identification of specific genetic abnormalities is critical for disease evaluation, optimal risk stratification, and treatment planning (23).

Work up.

Initial work up includes a thorough medical history and physical examination complimented by appropriate laboratory and imaging studies (23). Laboratory studies include; a complete blood count (CBC) with platelets and differentials, a blood chemistry profile, liver function tests, a coagulation panel and a complete screen for tumor lysis syndrome (23). Male patients should be evaluated for testicular involvement (23). A lumbar puncture and appropriate imaging should be carried out for evaluation of central nervous system (CNS) involvement. A chest x-ray is recommended for exclusion of mediastinal masses (23). Additionally, a cardiac evaluation is necessary due to use of anthracyclines, which are cardio toxic in most treatment protocols.

2.9 Treatment

2.9.1 Supportive care

Supportive care is paramount to good outcomes in the care of children with haematological malignancies. Aspects of supportive care include:

a) Blood products.

Bone marrow suppression with anaemia, thrombocytopenia and neutropenia is a typical finding in childhood ALL and is both disease-related and as a result of treatment (30). Red blood cells and platelets should be given to treat anaemia and thrombocytopenia as appropriate (30).

b) Anti-emetic therapy

Nausea and vomiting are common and bothersome treatment-related symptoms in children undergoing treatment for acute leukaemia (31). The 5-HT3 receptor antagonist, ondansetron, is the most frequently used agent to alleviate symptoms.

c) Tumour lysis syndrome

Tumour lysis syndrome is the most common life-threatening oncologic emergency encountered in treatment of childhood ALL (32). It occurs secondary to immense and rapid break down of tumour cells with resultant release of large amounts of nucleic acids and electrolytes such as potassium and phosphate into the circulation. Resultant biochemical abnormalities such as hyperkalemia, hyperphosphatemia, hyperuricemia, secondary hypocalcemia and acute uric acid nephropathy can occur (32). Prevention involves administration of prophylactic hypouricemic agents such as allopurinol, aggressive intravenous fluid hydration and correction of electrolyte imbalances.

d) Prophylaxis and treatment of infection.

Infection remains a significant cause of morbidity and mortality among patients with haematological malignancies (8). Immunosuppression results from the disease process itself or its treatment, thus predisposing these patients to infections including bacterial, viral and fungal.

The most frequent indication of the possibility of an infection is presence of a fever. A fever of more than 38 degrees Celsius should warrant septic screen, but antibiotics should be started empirically and adjusted later based on sensitivity studies (8).

e) Nutritional support.

The importance of nutrition in children with cancer cannot be overemphasized and malnutrition at any stage of disease should not be accepted as the norm (33). Nutritional strategies should be considered and integrated as a fundamental feature of pediatric oncology supportive care (33)**.**

f) Palliative care.

Palliative care refers to the care given to improve the quality of life of patients with life-threatening conditions. It entails the prevention and treatment of symptoms and side effects of the disease. Additionally, psychological, social and spiritual aspects are also addressed (34). The American Academy of Pediatrics advocates for an integrated, interdisciplinary approach to competent and compassionate care with components of palliative care offered at diagnosis and continued throughout the course of illness, whether the outcome ends in cure or death (34).

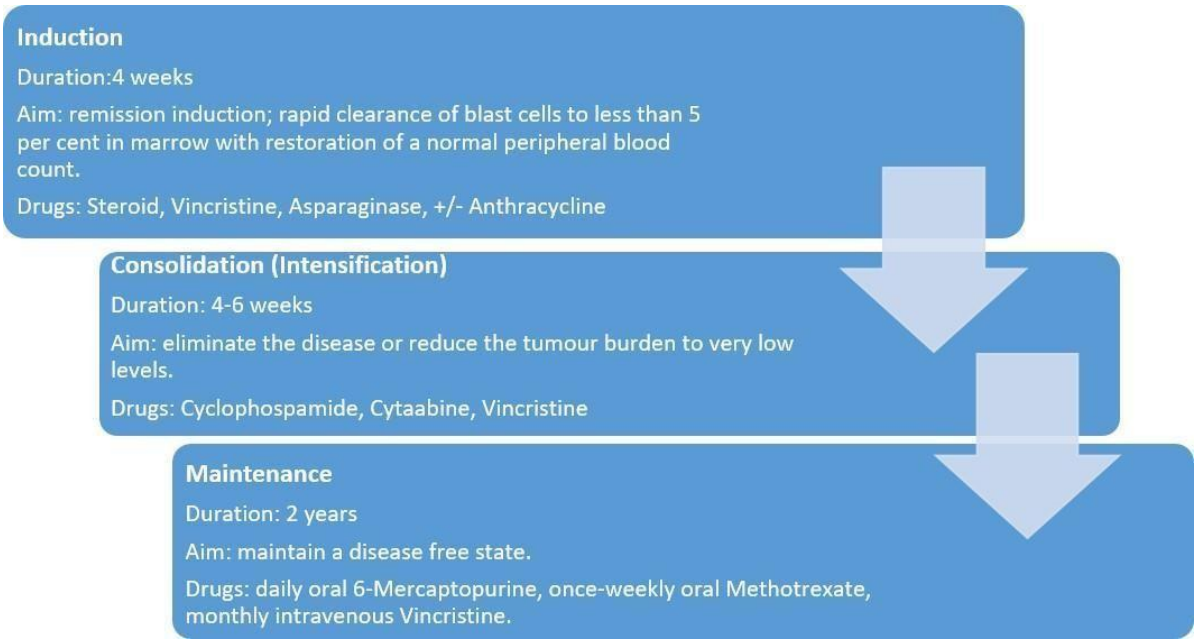
2.9.2 Definitive treatment.

A typical treatment schedule for ALL occurs in three phases; induction, consolidation and maintenance (23, 35). Figure 1 illustrates the three-phases, duration of each phase and drugs used.

Extra medullary site therapy.

CNS prophylaxis and/or treatment is aimed at preventing CNS disease by clearing cells that cannot otherwise be cleared with systemic chemotherapy because of the blood-brain-barrier (23). CNS treatment should be given to all patients during all three phases of treatment (23). Modes of CNS-directed therapy include intrathecal therapy (i.e., intrathecal methotrexate, cytarabine, and corticosteroid), cranial radiation, and/or use of systemic chemotherapy (i.e., Dexamethasone, high- dose methotrexate, intermediate-/high-dose cytarabine and L-asparaginase) (23). Patients with initial testicular involvement should receive testicular irradiation (23).

Figure 1. Phases of treatment, duration and drugs used.



CHAPTER THREE: STUDY JUSTIFICATION AND UTILITY, REASEARCH QUESTION AND OBJECTIVES.

3.1 Study Justification and Utility

Acute lymphoblastic leukaemia is the most frequently diagnosed malignancy of childhood worldwide. It is also the commonest occurring cancer among children treated in Kenyatta National Hospital. Induction is a fundamental phase of treatment aimed at initial tumor burden reduction and is an independent prognostic factor for overall survival and outcome of children with acute lymphoblastic leukemia. The rate of induction failure is high in low- and middle- income countries (15-30%) compared to high-income countries (5-10%). It is postulated that inadequate diagnostic capacity, lack of chemotherapeutic drugs, high rates of infection, inadequate supportive care and failure to complete treatment are partly the reasons contributing to poor outcomes. Other well established prognostic factors are; male gender, age less than 1 year or greater than 10 years, high initial white blood cell counts (>50 x $10^{\wedge 9}$ /L), immunophenotypes (T cell ALL), genetic abnormalities and outcomes of early therapy. In order to achieve better outcomes of childhood ALL in low- and middle- income countries, the prevalence and drivers of induction failure must be established; and gaps in care highlighted to serve as a basis for improvements in care for better outcomes. The study sought to establish the prevalence and factors associated with induction failure in childhood acute lymphoblastic leukemia in Kenyatta National Hospital and thereby provide valuable information for improvement of care of children with ALL in KNH.

3.2 Research Question.

What is the prevalence of induction failure in childhood acute lymphoblastic leukaemia in Kenyatta National Hospital?

3.3.1 Primary objective

To establish the prevalence of induction failure in childhood acute lymphoblastic leukaemia in Kenyatta National Hospital.

3.3.2 Secondary objective

To identify patient, disease and treatment factors associated with induction failure.

CHAPTER FOUR: METHODOLOGY.

4.1 Study design.

This was a retrospective cross-sectional study.

4.2 Study location.

The study was conducted in the Paediatric medical and oncology wards in KNH.

4.3 Study period.

March 2020-April 2021

4.4 Study population.

Paediatric patients aged 0 to 15 years with acute lymphoblastic leukaemia treated in KNH between January 2015 and December 2019.

4.4.1 Inclusion criteria

Study participants met the following criteria:

i. Aged between 0- 15 years.

ii. Confirmed diagnosis of ALL on marrow cytology.

iii. End of induction remission status as evidenced on a marrow cytology.

4.4.2 Exclusion criteria

- Incomplete medical records.
- Death prior to start of induction

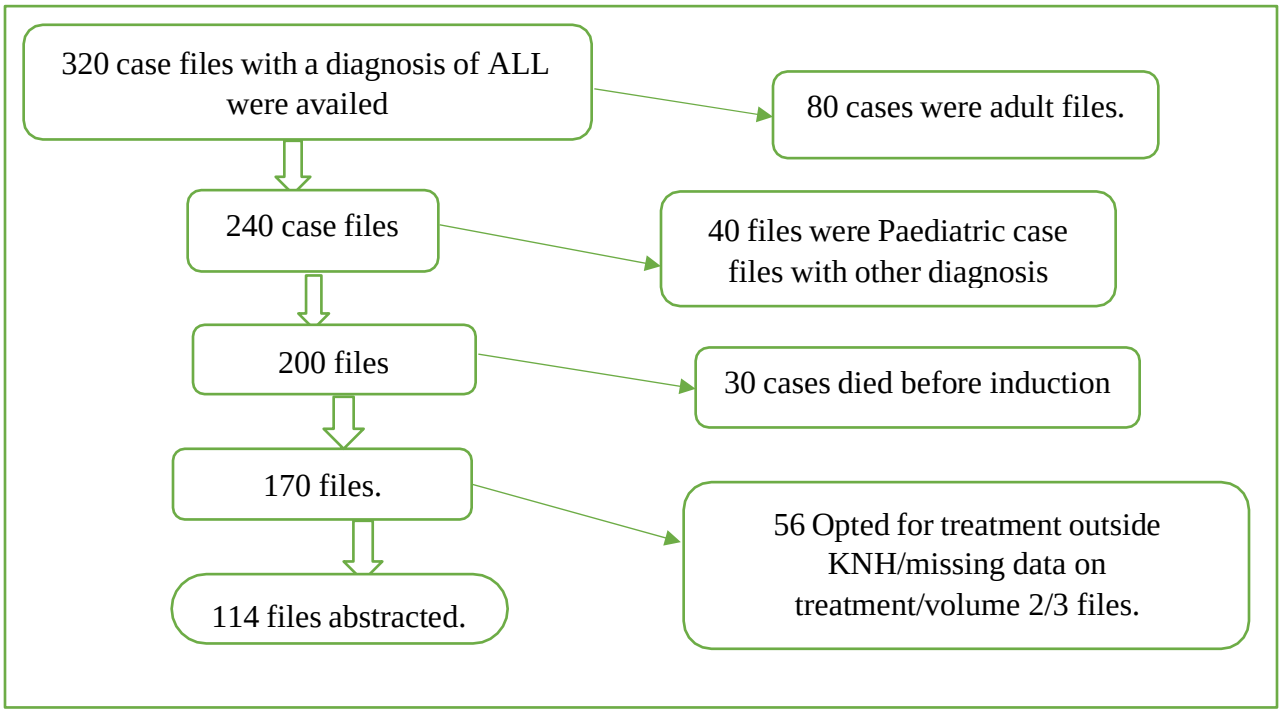
4.5 Sample size calculation.

This was a whole population study that reviewed all case records of all children aged 0-15 years with a diagnosis of ALL treated in KNH in January 2015 and December 2019 that met the inclusion criteria.

4.6 Sampling method.

A total of 320 case files with a diagnosis of ALL from January 2015 to December 2019 were reviewed. All that met the inclusion criteria were abstracted using the data collection form. The selection process is shown in the schematic diagram below.

Case records selection process.



4.7 Data collection Procedure

Case records were identified from KNH medical records department following approval by the Ethics and Research committee and those meeting the inclusion criteria were abstracted for data regarding demographics, clinical presentation and examination findings, initial complete blood

count (CBC) features, initial bone marrow aspirate features, treatment information and end of induction outcome as detailed in appendix 1. Demographic characteristics included were; age, gender and Body Mass Index. The Body Mass Index was determined using the weight and height taken and recorded for every child before initiation of induction and recorded on the chemotherapy treatment sheet. Presenting complaints at admission as documented by admitting clinician were grouped into eleven categories. Easy fatigability, dizziness, headaches and awareness of heart beat were grouped under the category of symptoms of anemia. Physical examination findings of interest were hepatosplenomegaly and/or lymphadenopathy as noted and documented by admitting clinician. Disease characteristics included were; NCI risk, CNS disease and baseline WBC counts. The diagnosis of ALL was ascertained by a bone marrow aspirate morphology consistent with ALL (presence of over 20 per cent blast) as reported by a pathologist which is the standard practice in KNH. Remission status was assessed based on the percentage of blast cells on an end of induction bone marrow aspirate and categorized into either induction failure (>5 blasts on a bone marrow aspirate morphology as reported by a pathologist) or complete remission (<5 blasts). It is the standard of care for all children to have remission status assessment at the end of induction within a week of completion of induction in KNH.

4.8 Data quality assurance procedure

All data abstraction tools (appendix 1) were inspected for completeness before proceeding to the next patient record to avoid any missed information. Data were transferred into a computer database on a daily basis to avoid backlog.

4.9 Ethical considerations

The research proposal was approved by the University of Nairobi Ethics and Research Committee. For confidentiality, the patients' files were analyzed within the records department of Kenyatta

National Hospital. The names of patients were not recorded and patient files were assigned unique numbers for identification. All data abstraction materials were stored safely under lock and key with access limited to the principal investigator.

4.10 Data management

4.10.1 Data entry

Data were entered into a password-protected database, verified and cleaned.

4.10.2 Data storage

Access to data collection material was limited to the principal researcher and the biostatistician. Once entered, database was pass-word protected.

4.10.3 Data analysis

Data were entered using IBM SPSS V.25. Descriptive statistics were generated for continuous and categorical variables as appropriate. Morphologic status and the independent variables were cross tabulated and Chi Square was used to assess for association between the dependent and independent variables and odds ratios calculated. P-values were obtained for levels of statistical significance at 95% confidence interval. Multivariate regression of the effects of patient, disease and treatment factors on morphologic remission were generated in individual models. A fourth model in which the dependent variable and all the independent variables were included in the same equation was generated. Adjusted Odds Ratios were calculated and P values at 95% CI.

4.11. Dissemination of study findings

The results were submitted to the department of Paediatrics and Child health. Soft copies of the results will also be submitted to the University of Nairobi repository for publication.

CHAPTER FIVE: RESULTS.

5.1 Demographic characteristics of the study population

One hundred and fourteen out of three hundred and twenty cases met the inclusion criteria and were reviewed. The percentage sex distribution in table 1 shows that 56% (n=64) were male while 44% (n=50) were female. As depicted in table 1, eighty per cent (n=92) of the study participants were aged between one and ten years. One participant (0.9%) was aged below 1 year. The mean age at diagnosis was 6.7 years. Forty-six per cent (n=53) of the total number of participants had a normal body mass index (BMI) of between the 3rd and 80th percentile while forty-seven per cent (n=54) were underweight and below the 3rd percentile.

Table 3: Demographic characteristics of the study population.

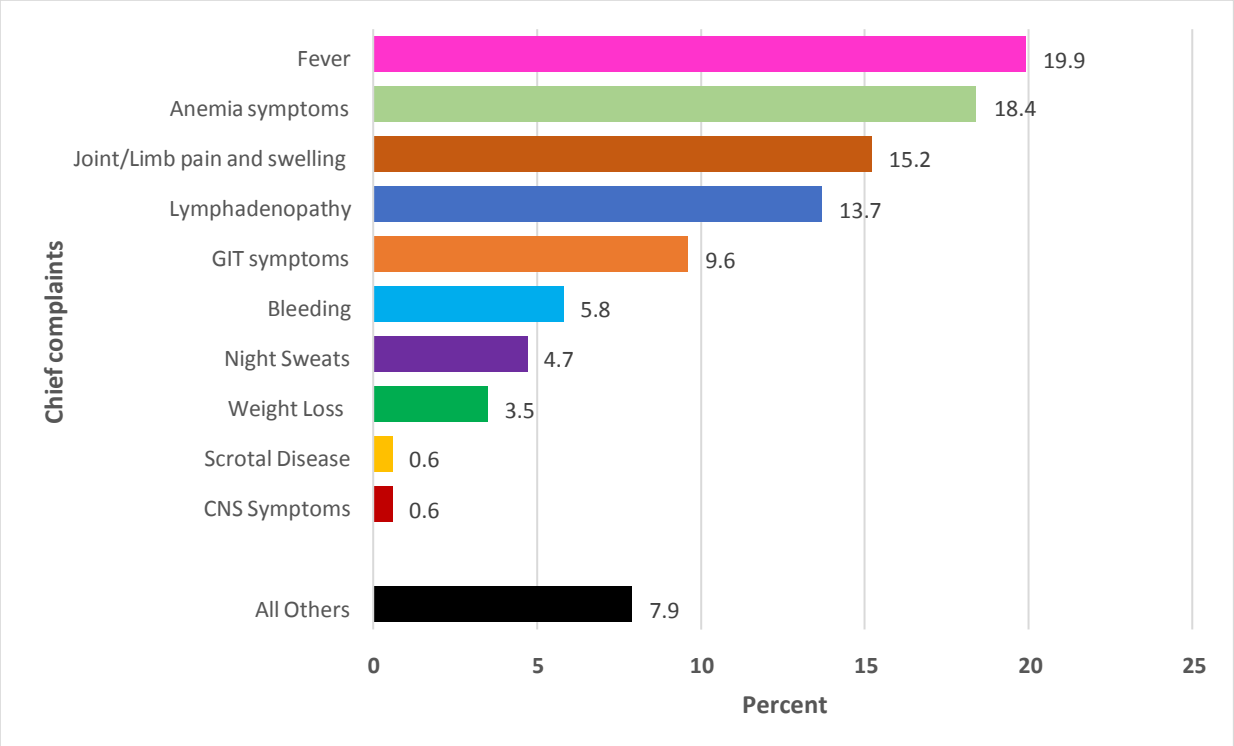
Sex	**Frequency**	**Percent**
Female	50	43.9
Male	64	56.1
Age		
< 1 Year	1	.9
1 to 10 Years	92	80.7
> 10 Years	21	18.4
BMI		
Underweight	54	47.4
Normal	53	46.5
Overweight	3	2.6
Obese	4	3.5

5.2 Clinical feature among children presenting with ALL at KNH

5.2.1 Presenting features.

Systematic review of all case files identified the commonest presenting complaints at admission of children with ALL in KNH as is outlined in percentage in figure 1. The commonest presenting features were fever 20% (n=68), anaemia symptoms (easy fatigability, dizziness, headache and awareness of heartbeat) 18.4% (n= 63), limb/joint pain and swelling 15.2% (n=52) and lymphadenopathy 14% (n=47). Six per cent (n=20) of the children had clinical features of thrombocytopenia such as bleeding from the nose and gums, bloody stools and frank blood in urine. Nine per cent (n=33) of the children had gastrointestinal related symptoms such as poor appetite and vomiting. One child (0.9%) presented with features suggestive of central nervous system disease at admission. One child (0.6%) had scrotal disease.

Figure 2. Presenting features of study participants at admission.



5.2.3 Examination and Laboratory findings.

Physical examination findings included in the study and aspects of the initial complete blood count are represented in percentages in table 2. Eighty-two (71.9%) of the children had lymphadenopathy while 74 (64.9%) were found to have hepatosplenomegaly. Laboratory evaluation revealed that over 70% of all children with ALL at KNH had bone marrow failure features at admission as depicted by findings of anaemia n=103 (90.4%), thrombocytopenia n=100 (87.7%) and neutropenia n=81 (71.1%).

Table 4. Clinical features among children with ALL at KNH

	Frequency (n=114)	Percent
Anaemia	103	90.4
Thrombocytopenia	100	87.7
Lymphadenopathy	82	71.9
Neutropenia	81	71.1
Hepatosplenomegaly	74	64.9

5.3 NCI Risk

Seventy-six (66.7%) of children treated in KNH with a diagnosis of acute lymphoblastic leukemia were categorized as standard risk patients (Total WBC < 50 x 10^9 /L and age >1/<10years) while 38 (33.3%) fell into the high-risk category (Total WBC >50 x 10^9 /L or age <1/>10years).

Table 4: National Cancer Institute Risk classification of study participants.

	Frequency (N=114)	Percent
Standard Risk	76	66.7
High Risk	38	33.3
Total	114	100

5.4 Central Nervous System Disease.

Cerebral spinal fluid analysis reports were reviewed for each patient and frequencies and percentages depicted in table 4 below. Eighty-seven (76%) of the children did not have CNS disease during the course of induction based on normal findings of at least three samples of cerebral spinal fluid analysis while the minority 27 (24%) had CNS involvement with disease.

Table 5.CNS involvement with disease of study participants.

CNS disease	Frequency (N=114)	Percent
Yes	27	24
No	87	76

5.5 Interval between admission and start of chemotherapy.

Figure 2 below shows that over 45 % (n=45) of all children admitted to KNH with clinical features suggestive of acute lymphoblastic leukaemia took more than two weeks for confirmation of diagnosis and initiation of induction chemotherapy. A small percentage, 10% (n=10) had a diagnosis confirmed and chemotherapy initiated within one week of admission.

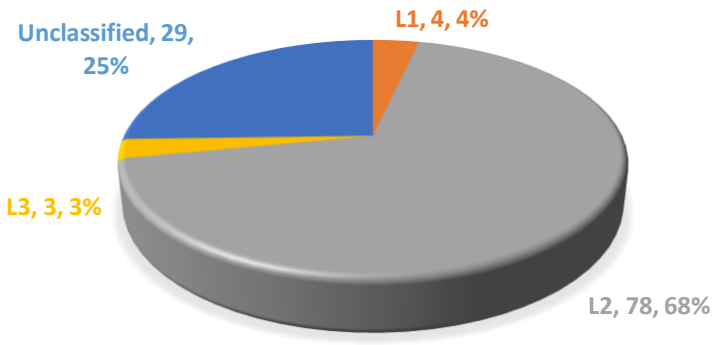
Table 6: Time interval in weeks between admission of study participants to KNH and start of treatment.

Duration in weeks	Frequency (n=114)	Percentage
<1 Week	10	9.8
1-2 Weeks	46	45
>3 Weeks	46	45

5.6 ALL Subtypes in children treated in KNH.

The prevalence of various ALL subtypes based on morphological classification in children with ALL seen at KNH is shown in figure 3. L2 subtype occurred most frequently in 78 (68%) of the participants. L1 and L3 subtypes were seen in less than 10 per cent of the cases cumulatively while 29(25%) of the cases were unclassified.

Figure 3: Baseline bone marrow FAB classification of study participants.



5.7 Outcomes of induction therapy in childhood ALL in KNH.

Three outcomes of induction chemotherapy were identified in the study participants as shown in table 3. Induction failure occurred in 33 (32.4%) while those who went into remission were 69

(67.6%). Mortality was the least occurring outcome with 12 deaths of the total participants occurring during induction giving a case fatality rate of 10%.

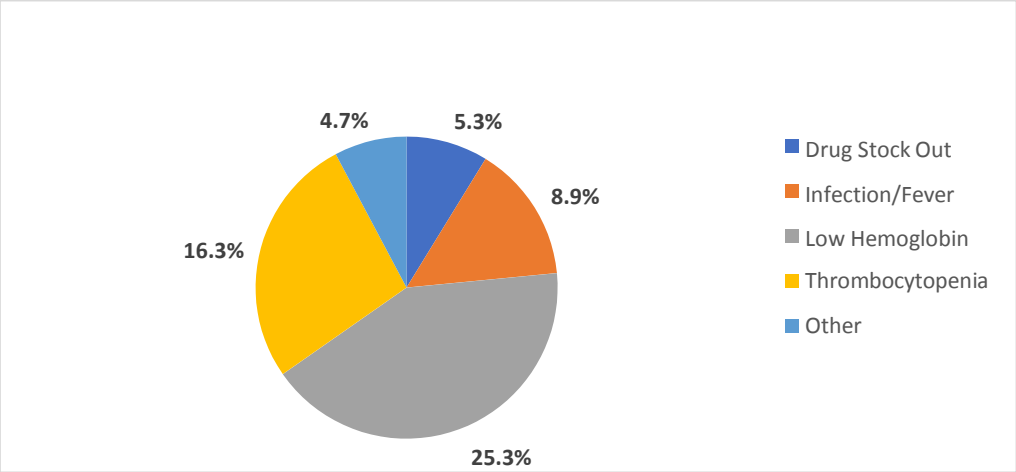
Table 7: Induction outcomes of study participants.

Outcome	Frequency (N=114)	Percent
Alive	102	89.5
Dead	12	10.5
Complete remission	69	67.6
Induction Failure	33	32.4

5.8 Interruption of treatment.

All cases of ALL treated in KNH completed induction chemotherapy, excluding all cases who died during induction. Reason identified that resulted in interruption of induction were as shown in figure 3 below. Low hemoglobin accounted for the majority of reasons for induction interruption at 25.3% followed by thrombocytopenia (16.3%) and presence of an infection (10%). Drug stock outs accounted for only 5.3%. Other reasons for induction interruption were absconders from hospital (1%).

Figure 4: Reasons for treatment interruption among study participants.



5.9 Factors associated with induction failure.

This study did not find any association between induction failure and demographic characteristics of patients including gender OR 1.75(1.73-3.23) (p=0.506), age OR 0.39(0.14-1.06) (p=0.142) and BMI OR 1.10(0.48-2.53) (P=0.247) at 95% CI as depicted in table 7. Disease characteristics such as FAB classification and the baseline total WBC counts had no association with the dependent variable OR 0.82(0.34-1.99) (p=0.106) and OR 0.63(0.22-1.84) (p=0.394) respectively at 95% CI. There was an association between CNS disease and the dependent variable OR 3.43(1.33-8.86) (p=0.009).

For NCI Risk, more data was collected from patients categorized as being of standard risk 66.7% (n=71) as compared to high risk 33.3% (n=31). From the cross-tabulation, a majority of patients classified as standard risk patients went into remission 73.2% (n=) 52 as compared to those who failed induction 26.8% (n=19). On the other hand, out of the data collected from the 31 high risk patients, there wasn't a large difference between high-risk patients going into remission 17 (54.8%) compared to the failed induction group 14 (45.2%). The results were however, not statistically significant OR 2.25(0.93-5.44) (P=.068).

Table 8: A bivariate table on patient, disease and treatment factors associated with induction failure or complete remission.

Variable	Induction Failure N=33		Complete Remission		Crude odd ratio 95 CI	P-value
	Frequency	Percent	Frequency	Percent		
Sex					1.75(1.73-3.23)	0.506
• Male	20	19.6	37	36.3		
• Female	13	12.7	32	31.4		
Age, years					0.39(0.14-1.06)	0.142
• <1	0	0.0	1	1.0		
• >1<10	23	22.5	58	56.9		
• >10	10	9.8	10	9.8		
BMI					1.10(0.48-2.53)	0.247
• Underweight	15	14.7	33	32.4		
• Normal weight	18	17.6	29	28.4		
• Overweight	0	0.0	3	2.9		
• Obese	0	0.0	4	3.9		
NCI Risk					2.25(0.93-5.44)	0.068
• Standard	19	18.6	52	51		
• High risk	14	13.7	17	16.7		
FAB Classification					0.82(0.34-1.99)	0.106
• L1	0	0.0	4	3.9		
• L2	22	21.6	45	44.		
• L3	2	2.0	0	10.0		
Baseline WBC Counts					0.63(0.22-1.84)	0.394
• >50*10 9	26	22.5	59	57.8		
• <50*10 9	7	6.9	10	9.8		
CNS Disease					3.43(1.33-8.86)	**0.009**
• Yes	13	12.7	11	10.8		
• No	20	19.6	58	56.9		
Interruption of treatment					0.54(0.23-1.26)	0.152
• Yes	18	17.8	47	46.5		
• No	15	14.9	21	20.8		
Interval between diagnosis and start of treatment.					1.22(0.53-2.81)	0.305
• < 1 week	5	4.9	5	4.9		
• 1 – 2 Weeks	12	11.8	34	33.3		
• > 2 Weeks No	16	15.7	30	29.4		
Duration to completion of treatment					1.27(0.54-2.98)	0.585
• 4-6 weeks	21	63.6	40	58.0		
• > 6 weeks	12	36.4	29	42.0		

5.10 Multivariate Analysis

Multivariate regression of the effects of patient, disease and treatment factors on morphologic remission were generated in individual models. A fourth model in which the dependent variable and all the independent variables were included in the same equation was generated. CNS disease was independently associated with induction failure. CNS disease had a fourfold increase in risk of induction failure compared to no CNS disease.

Table 9: Multivariate regression model of effects of Patient, Disease and Treatment Factors on dependent variable.

	Adjusted Odds Ratio	P-Value
Patient Factors		
Gender		
Female	0.758(.264-2.174)	0.607
Male [R]	1.00	
Age		
10 Years and below	0.608(.074-4.975)	0.643
Above 10 Years [R]	1.00	
BMI		
Under Weight or Overweight	0.651(.227-1.870)	0.426
Normal Weight [R]	1.00	
NCI Risk		
High Risk	1.535(.138-17.055)	0.727
Standard Risk [R]	1.00	
Disease Factors		
FAB Classification		
L1 and L2 combined	0.611(.216-1.730)	0.354
L3 and Not Determined [R]	1.00	
WBC (Baseline)		
Less than 50.00	0.571(.58-5.654)	0.632
50.00+ [R]	1.00	
CNS Disease		
Has CNS Disease	4.356(1.393-13.623)	**0.011**
Does not have CNS Disease	1.00	
Treatment Factors		
Interval between diagnosis and start of treatment		
More than 2 Weeks	1.826(.627-5.315)	0.269
Less than two weeks [R]	1.00	
Duration to completion of treatment		
4 – 6 Weeks	1.644(.502-5.383)	0.412
More than 6 weeks [R]	1.00	
Interruption of Treatment		
Treatment Interrupted	0.445(.127-1.562)	0.206
Treatment **Not** Interrupted [R]	1.00	
R= Standard Reference.		

CHAPTER SIX: DISCUSSION.

6.1 Demographic characteristics of the study population.

The sex distribution in this study shows that majority of the participants were male n=64 (56%) compared to females n=50 (44%). The findings of a male preponderance are in-keeping with the findings by *Stefan et al* in his study on cancer of childhood in sub-Saharan Africa. This is however contrary to a study conducted in Moi Teaching and Referral Hospital that found majority of the study participants to be female (67%). The reason for this could be because the study in Moi Teaching and Referral hospital had a very small sample size (n=30). There was a peak in age distribution at between 1-5 years n=44.7 (45%). These results are in keeping with the findings of the study on cancers of childhood in sub-Saharan Africa by *Stefan et al* that reporteda peak incidence of 13.4 per million in children aged 0-4 years with acute lymphoid leukaemia.

6.2 Clinical features of study participants.

The most commonly occurring presenting features at admission were fever n=68 (20%), symptoms of anaemia n=63 (18%), joint/limb pain and swelling n= 52 (15%) and generalized lymphadenopathy n=47 (14%). These results are similar to the findings reported by *Zehre et al* ina study conducted in Pakistan whereby, fever (88%), pallor (58.3%) and lymphadenopathy (25.3%) were the commonest presenting complaints. On physical examination, 72% (n=82) and 65% (n=74) of the study participants had lymphadenopathy and hepatomegaly respectively. Similar findings were reported by *Zehre et al.* Initial complete blood count evaluation revealed that study participants had bone marrow suppression features at admission. Ninety per cent (n=103) had low hemoglobin, eighty-eight per cent (n=100) had low platelets and seventy-one

per cent (n=81) had low neutrophil count. This is in keeping with findings of studies conducted in both low/middle and high-income countries.

6.3 NCI Risk and Central Nervous System disease.

Age and WBC counts are the two most important independent prognostic factors for B-cell type leukaemia. Immuno phenotyping is not routinely done in KNH, and although B-cell type leukaemia is the commonest reported immunophenotype, a small percentage of children have T-cell leukaemia. T-cell ALL tends to commonly occur in older males and is considered high risk. NCI Risk was done for all regardless of phenotypes in assumption that T-cell type would be fall into the high-risk category based on its occurrence in the older patient. In this study, sixty-six per cent (n=76) of the patients were standard risk while 33.3% (n=38) were high risk. Eighty-seven (76%) of the children did not have CNS disease during the course of induction based on normal findings of at least three samples of cerebral spinal fluid analysis while 24% (n=27) had CNS involvement with disease. This is significantly different from findings of many studies that report a 5-8% CNS involvement at admission in high-income countries. The difference can be attributed to early presentation, diagnosis and treatment of cases in high resource settings. Children in low-resource settings like Kenya present late due to; lack of awareness among caregivers, missed diagnosis at low level facilities and scarcity of specialized public hospitals where diagnosis can be made early and treatment initiated, among others.

6.4 Outcomes of Induction Chemotherapy in childhood ALL in KNH.

Induction failure occurred in 32.4% (n=33) of cases while those who went into remission accounted for 67.6% (n=69). The rate of induction failure established in this study is significantly higher than that seen in high-income countries such as Europe, America and Asia. This higher rate

of induction failure is expected in view of late presentation to hospitals, inadequate diagnostic and treatment capacity, interruptions of treatment and lack of sufficient supportive care in low-income countries like Kenya. Similar high induction failure rates have been reported in other low-to-middle-income countries such as the study by *Zehre et al* in Pakistan that reported an induction failure of 31.1%. Similarly, *Khan et al* in a study that included 98 participants in Lahore Pakistan reported an induction failure rate of 24 %. A total of 12 deaths occurred in the study participants during the course of induction giving a case fatality rate of 10%. *Ahoya et al* in her study on outcomes of induction in Moi Teaching and Referral Hospital found a lower Case fatality rate of 3.4%. This study however, had a much smaller sample size of only 30 participants. *Abdelmabood et al* reported a case fatality rate of 23% in his retrospective cohort study including 200 children aged less than 14 years. Case fatality rates are higher in low-income countries due to late presentation with advanced disease, delays in diagnosis and initiation of treatment, higher rates of infection and lack of adequate supportive care among cancer patients. The differences in case fatality rates among these three studies all conducted in low-to-middle-income countries are likely due to the significantly different sample sizes.

6.5 Factor associated with Induction Failure in childhood ALL in KNH.

In bivariate analysis, there was no significant association between induction failure and demographic characteristics of study participants such as gender OR 1.75(1.73-3.23) (p=0.506), age OR 0.39(0.14-1.06) (p=0.142) and BMI OR 1.10(0.48-2.53) (P=0.247) at 95% CI. This study results are similar to the French Acute Lymphoblastic Leukemia 93 Study in 1993 by *Oudot et al* that reported age and sex to be non-predictive of leukemic induction failure (LIF). Disease characteristics such as FAB classification and the baseline total WBC counts had no association with the dependent variable OR 0.82(0.34-1.99) (p=0.106) and OR 0.63(0.22-1.84) (p=0.394)

respectively at 95% CI. Eighty-three per cent (n=95) of the study participants had total WBC counts less than 50 x 10^9 /liter which is considered to confer low risk for induction failure. Similar to the study by *Oudot et al*, FAB classification was not predictive for LIF. On the contrary, initial WBC counts, unlike findings in this study, were predictive for LIF (P=0.001). NCI Risk was not predictive for induction failure in this study OR 2.25(0.93-5.44) (P=.068). Similarly, *Khan et al,* in his study in Lahore Pakistan, found Risk group to have no association with IF (p=0.349). CNS disease was the only factor predictive for induction failure in this study OR 3.43(1.33-8.86) (p=0.009). The study in Moi Teaching and Referral Hospital did evaluate factors predictive for induction failure while the study by *Oudot et al* did not find CNS disease to be predictive for LIF. It is postulated that CNS disease at diagnosis increases the risk of treatment failure both within the central nervous system and systemically. The study by *Oudot et al* was conducted in high-income countries where the occurrence of CNS disease is generally lower due to earlier presentation and diagnosis and early initiation of adequate treatment.

This study sought to establish treatment factors associated with induction failure. Interval between diagnosis and start of induction, reasons for interruption of induction and duration to completion of induction were analyzed for association with the dependent variable. This study did not find any of the factors to be predictive of induction failure OR 1.22(0.53-2.81) (p=0.152), OR 0.54(0.23-1.26) (p=0.305) and OR 1.27(0.54-2.98) (p=0.585) respectively at 95% CI. These findings were not comparable to any known study. The possible explanation for the lack of association between these treatment factors and the dependent variable could be due to the small sample size and confounding factors. At the multivariate level, CNS disease was independently associated with induction failure AOR 4.356(1.393-13.623) (P=0.011). Children with CNS disease

had a fourfold increase of falling into the induction failure group compared to children who did not have CNS disease.

6.6 Study limitations.

The study was retrospective in design and therefore key information on administration of chemotherapeutic drugs in sufficient doses could not be verified. The study had to rely on information provided on the treatment sheets of study participants.

This study was not able to explore all patient and disease factors that are associated with failure of induction such as genetic abnormalities and immunophenotypes which are expensive and not routinely done at Kenyatta National Hospital.

6.7 Strengths of the study.

The study was able to establish the prevalence of induction failure in childhood acute lymphoblastic leukaemia in Kenyatta National Hospital with minimal resources. These data provide valuable basis for larger prospective studies to further evaluate factors such as immuno phenotypes and genetic abnormalities that may be associated with induction failure which could not be established by this study.

CHAPTER SEVEN: CONCLUSION.

The prevalence of induction failure was high at 33% which is in keeping with findings in other low-and middle-income countries. Complete remission was achieved in 69% of cases. This study did not establish any association between patient factors (age, gender or body mass index) and induction failure.

Of the disease factors studied; National Cancer Institute (NCI) Risk, French-American-British (FAB) classification, initial white blood cell (WBC) counts and central nervous system (CNS) disease, CNS disease was the only factor associated with induction failure. Children with CNS disease had a fourfold increase in risk of failing induction compared to children without CNS disease.

RECOMMENDATIONS.

From the findings of this study, we recommend mandatory screening for CNS disease at admission with early initiation of treatment both centrally and systemically for those found to have CNS disease. Children with central nervous disease should be monitored more closely with serial cerebral spinal fluid analysis.

The high rate of induction failure reported by this study suggests the need for larger prospective studies to fully evaluate other patient and disease factors that may be associated with induction failure, such as genetic abnormalities and immunophenotypes which could not be established by this study as such tests are expensive and not routinely done in Kenyatta National Hospital.

There is need to lobby for an increase in allocation of funds towards the care of children with ALL. Such funds will enable genetic testing and immuno phenotyping of patients. This will further facilitate risk stratification of patients and thus practice of risk adaptive therapy to minimize toxicity in low-risk patients and intensify treatment in high-risk patients for eventual better outcomes.

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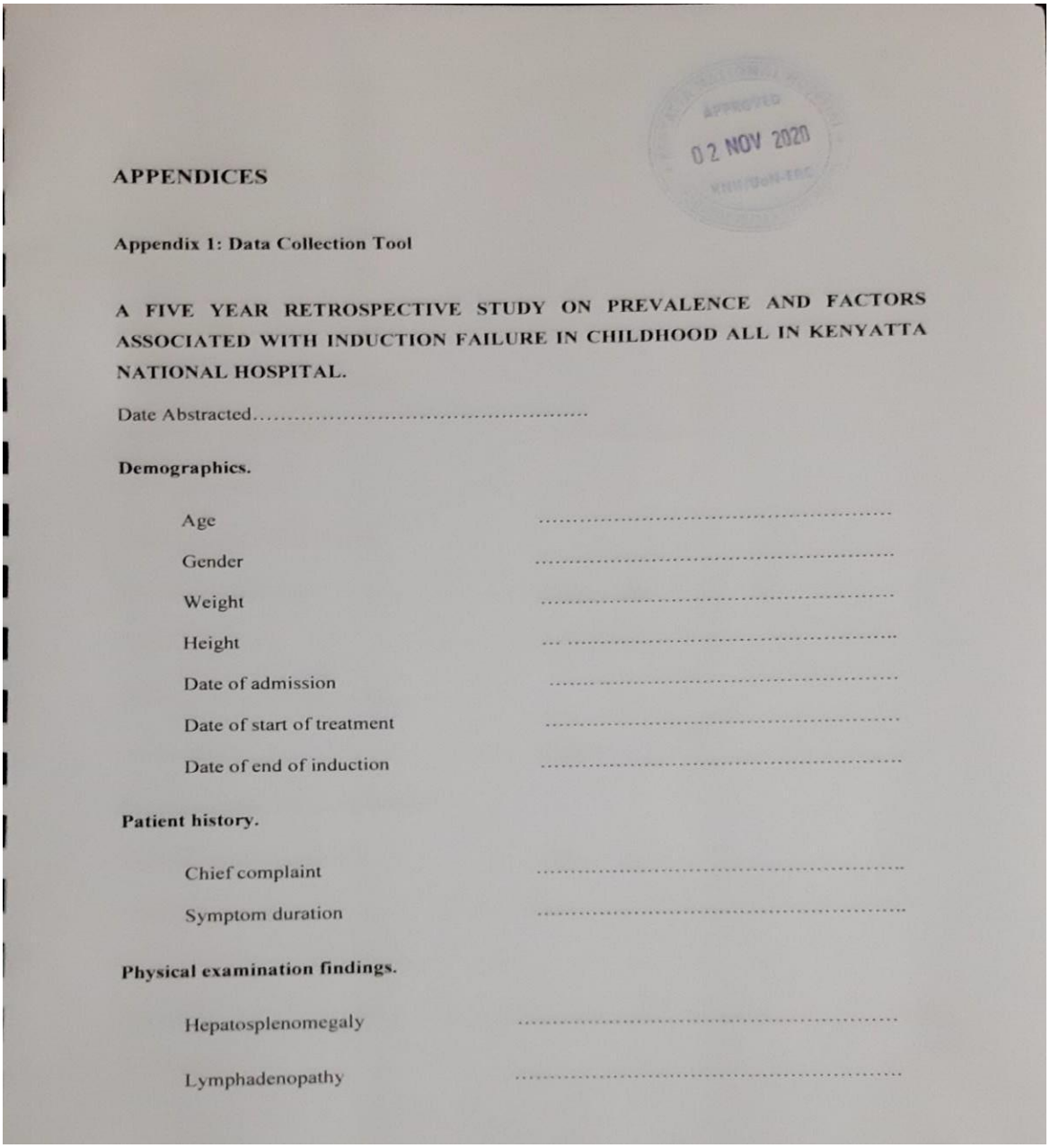
APPENDICES.

Appendix 1. Data collection tool.



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APPENDICES

Appendix 1: Data Collection Tool

A FIVE YEAR RETROSPECTIVE STUDY ON PREVALENCE AND FACTORS ASSOCIATED WITH INDUCTION FAILURE IN CHILDHOOD ALL IN KENYATTA NATIONAL HOSPITAL.

Date Abstracted.....

Demographics.

Age .....

Gender .....

Weight .....

Height .....

Date of admission .....

Date of start of treatment .....

Date of end of induction .....

Patient history.

Chief complaint .....

Symptom duration .....

Physical examination findings.

Hepatosplenomegaly .....

Lymphadenopathy .....

Laboratory findings.

Blood counts.

Baseline: Hb……Plts……Wbc……Neut……

EOI: Hb……Plts……Wbc……Neut……

Bone marrow aspirate findings.

Baseline: Percentage blasts……Fab classification……

EOI: Percentage blasts……Remission status……

Cerebral spinal fluid analysis.

Baseline: Normal cells…… Abnormal cells ……..

EOI: Normal cells……Abnormal cells……

National Cancer Institute risk:

Standard risk…… High risk……..

Treatment (induction) information

Regimen (kasili's protocol) [ ] other [ ]

Total no. of I.T doses……Steroid choice……

Interruption of treatment (induction) [Y] [N]

(Any of Vincristine, anthracycline, oral prednisolone, IT methotrexate not given once weekly for four weeks.)

Reason for treatment interruption (tick as appropriate)

a. Drug stock-outs
b. Infection/fever
c. Low haemoglobin
d. Neutropenia
e. Thrombocytopenia
f. Not determined

Treatment (induction) outcome

Death during induction [Y] [N]

Cause of death.....

Relapse [Y] [N]

If yes above, site of relapse

Appendix 2. KNH ALL treatment protocol
Acute Lymphoblastic Leukemia (ALL)

Option A

1. Induction (4 weeks)

Vincristine	1.5mg/m2 (max 2.0 mg), IV days 1, 8, 15, 22 (or weekly X 4)
Daunorubicin/Doxorubicin	25mg/m2, IV days 1, 8, 15, 22 (or weekly X 4)
Prednisone	40mg/m2/day for 28 days in 3 divided doses, then taper to zeroover 7 days
Methotrexate Intrathecal (MXT IT)	Once weekly for 5 doses age related doses (1-2 years 5.5mg; 3-5 years 7.5mg; 5-7 years 10mg; > 7 yrs 12.5mg)

Bone marrow aspirate day 30: for assessment of remission - if not in remission, reassess with a view to prognosticating case. In the meantime, start consolidation and for those not in remissions consider giving at least three consolidations.

2. Consolidation starts 10-14 days after completing induction

Cyclophosphamide	IV 1000 mg/m2 in saline over 8 hrs on day 1 and 8
Vincristine	1.5mg/m2 IV days 1 and 8, Give second course after 10-14 days as determined by level of blood counts.
Cytarabine	75mg/m2 SC days 1-4, 22-25, 29-32
Cranial Radiotherapy (DXT)	given to patients starting 7-14 days after completing consolidation

3. Maintenance (24 months) starts 4 weeks after completing consolidation and is still remission.

6-Mercaptopurine	75mg/m2/day, PO daily for 24 months.

Methotrexate	25mg/m2/week, PO weekly for 24 months. Rest period of two weeks in case of cytopenias for both 6MP and methotrexate
Vincristine	1.5mg/m2 IV day 1 monthly for 24 months
IT MTX	Every 8 weeks for 1st year for those without CNS disease
Adriamycin	25mg/m2 every three months for 24 months
Cyclophosphamide	300mg/m2 every three months for 24 months

In disease free events (continuing remission) this maintenance is continued for 24 months.

4. Reinduction - (4 weeks)

Vincristine	1.5mg/m2, IV days 1, 8, 15 and 22
Daunorubicin	25mg/m2, IV days 1, 8, 15 and 22 (Echo cardiogram done before each dose)
Dexamethasone	4 mg/m2/day, PO days 1-22, then taper to zero from day 22 to 29
IT MTX	day 1 (dose for age) every week for 4 weeks.

Reconsolidation

Cyclophosphamide	650 mg/m2 (maximum 1000mg) IV starting on day 28 then every two weeks times 3.
IT MTX	(dose for age) day 31, 38, 45 and 52 weekly for three weeks.
6-Mercaptopurine	60mg/m2/day, PO days 29-57 starting on day 28 for 28 days.
Cytarabine	75mg/m2, SC starting day 30 daily for four days and repeating every week for 3 weeks.

Rest 2 weeks then proceed to maintenance as in (option A)

Option B ideal situation

Induction: Phase 1

Prednisone	60mg/m2 orally on days 1 to 28
Vincristine	1.5mg/m2 (max. 2.0mg) IV on days 1,8,15 and 22.
Daunorubicin	25mg/m2 IV on days 1,8,15 and 22.
L-Asparaginase	5000 units/m2 IV on days 1 to 14. (Dose may be adjusted downward at 3,000unit/m2when given together with anthracycline).

Bone marrow on day 35 and if remission is achieved or not move to consolidation.

Consolidation: Phase II

Cyclophosphamide	650 mg/m2 (maximum 1000mg) IV starting on day 28 then every two weeks times 3.
IT MTX	(dose for age) day 31, 38, 45 and 52 weekly for three weeks.
6-Mercaptopurine	60mg/m2/day, PO days 29-57 starting on day 28 for 28 days.
Cytarabine	75mg/m2, SC starting day 30 daily for four days and repeating every week for 3 weeks.

If there is no remission or there is relapse consider reinduction as follows.

Reinduction: Phase I

Dexamethasone	10mg/m2 orally on days 1 to 28.
Vincristine	1.5mg/m2 (max. 2.0mg) IV on days 1,8,15 and 22.
Doxorubicin	25mg/m2 IV on days 1,8,15 and 22.

Cranial irradiation at 2,400 cGy is for 4 weeks instituted after remission is achieved.

Reconsolidation: Phase II

Cyclophosphamide	650 mg/m2 (maximum 1000mg) IV starting on day 28 then every two weeks times 3.
IT MTX	(dose for age) day 31, 38, 45 and 52 weekly for three weeks.
6-Mercaptopurine	60mg/m2/day, PO days 29-57 starting on day 28 for 28 days.
Cytarabine	75mg/m2, SC starting day 30 daily for four days and repeating every week for 3 weeks.

Maintenance

6-Mercaptopurine	60mg/m2 by mouth daily on weeks 10 to 18 and 29 to 130.
Methotrexate	20mg/m2 orally or IV weekly on weeks 10 to 18 and 29 to 130.

Appendix 3: Ethical Approval Letter.

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Ref: KNH-ERC/A/383

2nd November 2020

Dr. Betty Murugi Njoroge
Reg. No.H58/86926/2016
Dept. of Paediatrics and Child Health
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Njoroge

RESEARCH PROPOSAL – PREVALENCE OF INDUCTION FAILURE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA IN KENYATTA NATIONAL HOSPITAL (P219/03/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 2nd November 2020 – 1st November 2021.

This approval is subject to compliance with the following requirements:

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

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

Yours sincerely,

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

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The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
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PREVALENCE OF INDUCTION FAILURE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN KENYATTA NATIONAL HOSPITAL

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