CLINICAL AND PATHOLOGIC FEATURES OF NON-HODGKIN'S LYMPHOMA AMONG PATIENTS SEEN AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other University

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DEDICATION

-Njoki Bae

For your advice, your patience and your faith, more so because you always understood, my one and only companion through many a long night of writing, without whom this book may have never been completed, I dedicate this book to my one and only true love and wife.

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To all my colleagues and friends.

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LIST OF ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
AR-NHL	AIDS-Related Non-Hodgkinôs Lymphoma
BL	Burkittôs Lymphoma
BMI	Body Mass Index
BSA	Body Surface Area
CNS	Central Nervous System
cART	Combination Antiretroviral therapy
CHOP	Cyclophosphamide, Doxorubicin, Vincristine and prednisone
DLBCL	Diffuse Large B cell Lymphoma
EBV	Ebstein Barr Virus
ECOG	Eastern Cooperative Oncology Group
GI	Gastro-Intestinal
HAART	Highly Active Antiretroviral Therapy
HCT	Haematopetic cell Transplant
HIV	Human Immunodeficiency Virus
IPI	International Prognostic Index score
KNH	Kenyatta National Hospital
LDH	Lactate dehydrogenase
NHL	Non-Hodgkinôs Lymphoma
NK	Natural Killer
PTLPD	Post transplantation lymphoproliferative disorders
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and prednisone
R-IPI	Revised International Prognostic Index score
SCID	Severe combined immunodeficiency disease

TBSA	Total body surface area
UON	University of Nairobi
USA	United States of America
WHO	World Health Organisation

ABSTRACT

Background: The incidence of Non-Hodgkinôs Lymphomas (NHL) varies among different geographical regions in the world. NHL are the fifth most common cancer in the US and 12th most common cancer in Europe andfor the latter increasing dramatically in last decade.While many reports exist in the worldwide literature, published studies specific on NHL in Africa, Kenya in particular are scarce. In addition, most of these studies provide scanty information on the heterogeneity of these neoplasms and this directly influences the management and outcome.

Aim: The purpose of this study was to describe the clinical and pathologic features, related to Non-Hodgkinôs Lymphoma among patients aged 13 years and above, attending Kenyatta National Hospital between January 2006 and December 2015.

Method: This was a hospital based retrospective study. This study involved obtaining case records of patients aged 13 years and above, with a diagnosis of Non-Hodgkinôs Lymphoma made between January 2006 and December 2015. The Kenyatta National Hospital records department served as the study site. Retrieval of the clinical and pathological data from the patient files was analyzed using SPSS 21.2 for windows data analysis software

Results: A total of 209 patient files were reviewed. There was a male preponderance with 59.8% being male, and the M/F ratio of 1.5:1. The median age of patients was 43 years. High grade type accounted for 49% and there was a predominance of B cell over T cell NHL noted; DLBCL 38.3%, Burkittôs Lymphoma 3.8% and B cell (not otherwise specified) 5.3%. Almost half of cases at the point of diagnosis, presented at stage III with both nodal and extra nodal site involvement accounting for 52.7%. Aggressive grades of NHL were seen more in the HIV positive cases. Out of 207 patients, 67.9% received chemotherapy, 21.5% received both chemotherapy & radiotherapy and 3.6% were treated with radiotherapy upfront. The difference in remission status at four and six courses was significant ($P<0.001$).Those with ECOG stage 0 did well as opposed to those with a poorer performance status at 6 cycles and above. Longer duration of follow-up was associated with early stage of disease and this was seen to be significant *P=0.011*.

Conclusions: NHL locally is well distributed among age groups and has a male preponderance. Majority of cases reviewed were in stage III at the time of diagnosis and had both nodal and extra-nodal site involvement. A good number of cases were at performance status 0 at time of diagnosis with the commonest type of tumour being Diffuse Large B Cell lymphoma. HIV positive cases accounted for 19.1% of cases and there was a trend of HIV being associated with aggressive phenotypes but this was however not seen to be of statistical significance. Complete remission was achieved in 47.7% of cases that received 6 courses of CHOP. Early disease patients were more likely to be followed up for longer durations and on the whole, the outlook for NHLs treated at KNH in the late 2000s appears to have improved tremendously since the 1990s.

1.0 CHAPTER ONE: INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is one of the malignant lymphomas that has been widely studied across the globe (1). In the West and Asia, a lot of literature has been published on clinicopathology (2-15) and prognosis (16-19) including the US, Europe and India. Despite availability of this literature, little remains known about Non-Hodgkinôs lymphomas in Africa, Kenya included. Limited retrospective studies are available in Kenya concerning the clinicopathology and prognosis of NHL hence this poses a temporal gap in the knowledge of NHL. The aim of this study was to fill in the existing knowledge and temporal gap on NHLôs clinicopathologic features and outcome.

Globally in 2008, the incidence of NHL was 356,000 cases and mortality from NHL at 192,000 cases(1). It is increasingly appreciated that NHL is the eighth most commonly diagnosed cancer in men and the eleventh in women(1). This disease entity accounts for 5.1% of all cancer cases and 2.7% of all cancer deaths worldwide. North America, Europe, Oceania, as well as several African countries reported to have the highest incidence of NHL. The occurrence of NHL is higher in men than women (1).

Recent data from the USA demonstrated a high incidence of 125,850 cases of NHL in 2016. This disease entity is much more common in adults than in children, rates increase dramatically by age 50 years. Although Burkitt lymphoma is relatively rare in the United States, it is one of the most common types of childhood lymphoma, particularly among boys. It has a bimodal age distribution with a second peak in older adulthood. Incidence rates for NHL were higher in males than in females.(2)

There exists a paucity of data from the region on NHL in the African continent. A Study done in Rwanda demonstrated predominance of B-cell lymphomas. The disease seemed to affect adolescents and young adults more than 80% aged 15-40 years(3). A study done in Nigeria among the Haemato-oncology admissions revealed a progressive increase in lymphoid malignant cases over a15-yearperiod 1996-2010. The incidence of NHL was 61.1% with most frequent age group between 46-59 years with predominance seen in males(4).

In Kenya, studies from early 1980ôs demonstrated no significant differences in the sex distribution in NHL and the average age of occurrence of NHL was 41years. It was also noted that NHL had a high mortality rate in early years before 1990(5). A later study published in 2004 demonstrated that NHL affected more males than females in a ratio of 2.5:1, with a bimodal peak in occurrence of less than 40 years and 60years. Unlike western data where follicular lymphoma is common among the Caucasian populations (6) not much data is

available for the predominant subtypes among the Kenyan population. In Kenya, studies related to NHL provide the clinical picture of the years between 1990 and early 2004; these could possibly be outdated with regard to the changes in the clinicopathology and prognosis of NHL. Therefore, this study aimed to update the existing knowledge of NHL.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology

There has been a double increase in the incidence of non-Hodgkinôs lymphoma (NHL) over the last two decades in the US and other developed countries in the west. The improved cancer reporting, changes in lymphoma classification, and increases in AIDS-associated NHL contributed to the increase in cancer reporting.These factors are estimated to account for only about 50% of the increase in observed incidence(7). There is a higher proportion of follicular and diffuse lymphoma in North America and Europe, and a higher proportion of T-cell lymphoma in Asia(1). This in part may be due to a greater variability in the incidence of B-cell NHL compared with T-cell NHL, which is consistent with the results of a study reporting that increase in NHL rates from 1973 to 1988 in the USA was accounted for by B-cell NHL(1).

A Study done in 2012 in India, estimated NHL to have an incidence rate of 2.2/100,000 persons and a mortality rate of 1.5/100,000 persons. NHL was commoner in men with a male to female ratio of1.6:1 in Asia compared to 1.2 and 1.1 in North America and Europe, respectively. The median age of patients with NHL in India is lower by almost 10 years compared to that of Western countries(8). The median age of 54 years at occurrence of NHL is similar to other Asian countries. The younger age at presentation in India is possibly due to the large proportion of young Indians where 65% of the population in India is under 35 years of age and this was responsible for the young age at presentation of NHL. The lower proportion of indolent lymphoma (predominantly seen in the elderly population) in India is probably the result of the same bias. Age-specific incidence rates of NHL peaks at 75 years in Indian males and 70 years in Indian females.(8)

A study done in Nigeria demonstrated a male preponderance (Male: Female ratio 1.6:1) in occurrence of NHL. An increase in the lymphoid malignant cases was 84.0% over a period of 15 years withNHLaccounting for 61.1%of these cases.The mean age of NHL patients was 52.5 years for males and 49.5 years for females respectively(4).

In a study done in Sudan, B cell NHLs represented 87.1% while T cell NHLs were 12.9%. There were few similarities with the Nigerian study, such as a male predominance (Male: Female ratio 1.6:1) and age at occurrence of NHLswhich was (47-67) years(9).

A Ugandan study demonstrated Burkittôs lymphoma (BL) (mainly EBV positive) and Diffuse Large B cell Lymphoma accounting for 71% of the NHL. There was a male predominance (75% in BL, DLBCL 70%). The Mean age for BL was 31.3 years, while other subtypes were at 45.3 years respectively (10). This data was similar to the Sudan and Nigerian studies.

Furthermore, a weak association between HIV and NHL was probably due to the reduced survival of immunosuppressed HIV individuals with NHL(10).

In Kenya, a study published in 2004 demonstrated a bimodal age distribution in occurrence of NHL, were 52% of cases had ages less than 40 years and 18.4% age greater than 60 years. There was a male preponderance (Male: Female ratio of 2.5:1). Follicular lymphoma and small lymphocyte lymphomas were common in the elderly and middle-aged groups whereas BL, Precursor B/T cell lymphoblastic lymphoma/leukemia were in the younger aged group(6). The HIV seroprevalence rate in this study was 32.5% of those patients tested. HIV sero status was not correlated with disease outcomes. A recent study in 2009 demonstrated the risk of developing aggressive phenotype non-Hodgkinôs lymphomas was high among HIV infected individuals and was associated with worse prognosis than among non-HIV infected ones(11).

2.2 Development of Non-Hodgkin Lymphoma

The mechanisms responsible for the initiation and propagation of tumor growth remain elusive. There are no clear-cut mechanisms responsible for the development of NHL. There are list of various mechanisms proposed for development of NHL. The role of chronic antigenic stimulation is to increase B-cell proliferation, which in turn increases the probability of random genetic errors. In cases in which a virus acts as the foreign stimulant, the virus itself may infect a normal cell and integrate viral DNA into the host genome, thereby transforming the cell into a malignant cell capable of self-replication.

There is the role of chronic antigenic stimulation leading to a compensatory downregulation of the T-cell response i.e. immunosuppressive state. Other factors that independently precipitate an immunosuppressive state may act as co-factors in lymphomagenesis by further inhibiting the recognition and protective eradication of a malignant cell. Environmental carcinogens and their interaction with lymphoid cells cause a lymphoid cell to undergo mutation and its growth progresses uninterrupted due to some immune dysfunction(7).

2.3 Risk factors of Non-Hodgkin's Lymphoma

Three common mechanisms provide a framework for the emergence and perpetuation of NHL. This include, an episodic or persistent immunosuppressive state, which may be the result of primary (e.g.SCID) or acquired immunodeficiency (e.g. HIV/AIDS) or exposure to an immunosuppressive agent such as UVR or blood transfusion, chronic antigenic stimulation due to an autoimmune condition (e.g. Rheumatoid Arthritis), viral infection (e.g. EBV), or allergic/ inflammatory agent (e.g. Crohnôs Disease). The disruption of normal cell proliferation i.e. each

neoplasm emanates from a genetic mutation, which is either a random error or a mutation instigated by an oncogenic agent. Consequently, the growth of the malignant cell into a tumor is promoted by one or more co-factors that interfere with the usual regulatory mechanisms(7).

2.4 Clinicopathology of Non-Hodgkin's Lymphoma

The clinical presentation of NHL is diverse depending upon the type of lymphoma and the areas involved. NHLs may exhibit an indolent course characterized by lymphadenopathy waxing and waning over years. Of the highly aggressive types, death occurs within weeks if left untreated.

Aggressive lymphomas can be acute or subacute, both are characterized by a rapidly growing mass, systemic B symptoms (i.e., fever, night sweats, weight loss), and/or elevated levels of serum lactate dehydrogenase and uric acid. Examples of such lymphomas with this aggressive or highly aggressive presentation include diffuse large B cell lymphoma, Burkitt lymphoma, adult T cell leukemia-lymphoma, and precursor B and T lymphoblastic leukemia/lymphoma(12).

Indolent lymphomas present insidiously at times, with slow growing lymphadenopathy, hepatomegaly, splenomegaly, or cytopenias. Such lymphomas with this indolent presentation include follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and splenic marginal zone lymphoma(12).

There is a significant patient-to-patient variability in the natural history of these tumors. Less common presentations, most frequently seen with T cell lymphomas, include skin rash, pruritus, generalized fatigue and malaise, fever of unknown origin, ascites, and effusions. Approximately 50 percent of these patients will develop extranodal disease (secondary extranodal disease) while between 10 and 35 percent of patients will have primary extranodal lymphoma at initial diagnosis. The initial presentation may reflect involvement of extranodal tissues(13).

Patients with primary gastrointestinal (GI) tract lymphoma may present with anorexia, weight loss, nausea and vomiting, chronic pain, abdominal fullness, early satiety, symptoms associated with visceral obstruction, or even acute perforation and GI hemorrhage. Malabsorption syndrome can occur occasionally with these patients(14).

Patients with primary CNS lymphoma may present with headache, lethargy, focal neurologic symptoms, seizures, paralysis, spinal cord compression (0.1 to 6.5%), or lymphomatous meningitis(15).In patients with chronic lymphocytic leukemia and indolent B cell NHLs, exaggerated (hypersensitivity) reactions to insect stings or bites, especially mosquito bites, may

be noted. Presence of this phenomenon may precede the diagnosis of NHL and/or may suggest the presence of a previously undiagnosed lymphoma(16,17).

2.5 Non-Hodgkin's Lymphoma Staging

Ann Abor classification was the first system widely utilized for staging non-Hodgkin Lymphomas. Its development was for staging of Hodgkin disease(18) and referred to as the Ann Arbor Staging System. Although primarily an anatomic staging system, the Ann Arbor stages are a modification based on the presence or absence of systemic symptoms. Adjustments over the years for the use in staging of Hodgkin disease has been done, but still it represents a backbone of the staging system recommended today for non-Hodgkin Lymphomas(19).

2.6 Histological Classification of Non-Hodgkin's lymphoma

The last 8 years have seen major advances in the knowledge of the lymphoid neoplasms and their treatment. There exist new insights into the biology and management of both clonal proliferations with limited malignant potential, as well as the aggressive lymphoid neoplasms where more targeted and effective therapies were established.

The morphology and cell lineage forms the basis of the 2016 WHO classification of NHL(20). Various subdivisions are recognized and include Mature B-cell neoplasms, T-cell and NK neoplasms, Hodgkinôs Lymphoma, Post-transplant lymphoproliferative disorders and Histiocytic and dendritic cell neoplasms(20)(21).

2.7 Prognosis of Non-Hodgkin's Lymphoma

2.7.1 International Prognostic Index (IPI)

The International Prognostic Index (IPI) is a system developed for classifying patients with aggressive non-Hodgkin's lymphoma according to universally recognized clinical features. The model applicable to all these patients (the international index) incorporates various clinical features that reflected the growth and invasive potential of the tumor (i.e. tumor stage, serum LDH level, and number of extranodal disease sites), the patient's ability to tolerate intensive therapy (i.e. age and performance status) and the patient's response to the tumor (performance status)(22).

A simplified model for use in younger patients (the age-adjusted international index) utilizes a subgroup of these clinical features (performance status, LDH level and tumor stage). Both of these models identified four risk groups of patients based on the rate of complete response and the rate of relapse from complete response(22).

A study done on patients with aggressive non-Hodgkin lymphoma (DLBCL) wasan evaluation for pretreatment features that were predictive of survival following treatment with doxorubicin

-containing chemotherapy regimens. The following factors did correlate significantly with shorter overall or relapse-free survival:

- Age >60
- LDH concentration Ónormal
- ECOG performance status Ó2
- Ann Arbor clinical stage III or IV
- Number of involved extranodal disease sites >1

In this system, point scoring for each of the above characteristics present in the patient, for a total score ranging from zero to five, representing increasing degrees of risk

- Low risk ð IPI score of 0 or 1
- Low intermediateð IPI score of 2
- High intermediateð IPI score of 3
- Highð IPI score of 4 or 5

This applied to the initial group of 2031 patients with aggressive NHL treated with anthracycline-based regimens that excluded rituximab. It was noted the five-year overall survival rates for patients with scores of zero to one, two, three, and four to five were 73%, 51%, 43%, and 26 %, respectively(23ï 25).

Use of IPI for patients receiving rituximab: The addition of rituximab for CD-20 positive tumors to standard chemotherapy has resulted in significant improvements in the overall survival rates. The combination of rituximab plus CHOP specifically or CHOP-like regimens is the most commonly employed treatment for DLBCL. The original IPI scoring system valid for use in this patient group was revised to form the Revised International Prognostic Index score (R-IPI)(26).

Data published in 2004 from Kenya 5.3% of patients evaluated achieved complete remission following four courses of chemotherapy, the number increased exponentially to 55.6% in those who received six courses of chemotherapy(6). This was a major improvement in the prognosis from earlier years 1990ôs(6,27).

A later study in 2009 demonstrated complete remission rates among HIV-negative patients that were similar to those reported from well-established centers, the rate among HIV-positive patients was however lower than those in well-established centers(11).

2.7.2 Eastern Cooperative Oncology Group (ECOG) performance scale

ECOG describes a patientôs level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.). See Appendix E for further description.

2.7.3 Clinical Presentation of AIDS-Related Non-Hodgkin's Lymphoma.

The clinical course of AR-NHL during the pre-antiretroviral (pre-cART) era run a much more aggressive course compared to the patients without HIV infection. Generally, AR-NHL is characterized by higher grade (40ï 60%), advanced clinical stage (60ï 70%) often characterized by B symptoms, extranodal disease (80%) and shortened survival (median 7-8 months) in comparison to lymphomas in HIV-seronegative or indeterminate patients. The median CD4+ lymphocyte count was 100/µL prior to the cART era. The median CD4+ lymphocyte counts increased to between 150ï 200/µL and higher in the cART era since patients had less immunosuppression (28).

In sub-Saharan Africa, it was recognized that patients with AIDS-related malignancies did not present with as profound immunosuppression as was observed earlier in the epidemic in the US (28).This observation was likely attributed to the altered natural history of HIV infection in the cART era and less predominance of high-grade histologies(28).

A recent case-control study of NHL in the backdrop of HIV infection in Uganda demonstrated Burkittôs lymphoma and large B-cell lymphomas represented 71% of adult cases. EBV was present in 35% of the cases and HIV infection documented in 34% of adult cases versus 20% of controls.

In addition, a recent large retrospective study of NHL in Uganda revealed the documented HIV-seropositive patients was 32%. From this series, a third of cases were females of which only 60% of cases had documented clinical staging and the majority (90%) presented with stage III or IV disease. It was recognized that at time of receiving chemotherapy for lymphoma, the outcomes between the HIV seropositive patients although dismal was approaching those of HIV-seronegative or indeterminate cases. This underscores the impact of administration of cART at the time of initiation of chemotherapy (29).

The trends in the HIV prevalence rates in Kenya over last 30years has declined, initially ranging between 16% in the 1990s and about 6% in 2010. A Study in Kenya on treatment outcomes of AR-NHL demonstrated, Diffuse large B-cell lymphoma comprised 32% of the total NHL cases, 67% of the cases were classified as HIV-positive and 37% classified HIV-negative cases. This was explained in part by the high HIV prevalence in Kenya (11).

Interestingly unlike the case in Uganda, Burkittôs lymphoma was not frequent as expected from other reports that have placed it second to diffuse large B-cell lymphoma in frequency among HIV- positive cases. HIV-positive lymphoma cases in this series tended to have lower CD4 lymphocyte counts, arguably being out of the BL range. (HIV-BL tends to occur among patients with preserved immune function, with CD4 lymphocyte counts above 200 cells/ml.)
Majority (70%) of these cases had diagnosis of lymphoma in stage III and IV(18) with significant extralymphatic presentation (11)and high score of close to 75%.
Survival for HIV-negative cases in this series was superior to those of HIV-positive cases irrespective of time of initiation of cART. These findings were contrary to those in Uganda and western countries and attributed to factors such as failure to complete treatment, opportunistic illness related deaths, and treatment related deaths and losses to follow-up making a significant contribution to these findings(11).

2.8 Treatment of Non-Hodgkin's Lymphoma

The general treatment principles for advanced stage DLBCL apply to most disease presentations and patient populations. The advent of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens, has resulted in disease-free survival rates of 35% to 45% at four years (24). Survival has further improved with the addition of rituximab to standard CHOP-based therapy (R-CHOP) in an approximately 10% to 15% overall increase in survival beginning at one year from initiation of therapy in patients of all ages with almost no increase in toxicity (30)(31). It is clear that rituximab -containing CHOP or CHOP-like regimens provide superior survival to the same regimen without rituximab, regardless of the patient's age.
In practice, the number of chemotherapy cycles given varies based upon the clinicianôs choice between a defined number of cycles independent of response (e.g. administer six to eight cycles) or a response-based evaluation to determine the number of cycles (e.g., administer two cycles after the attainment of a complete response). Clinical trials have demonstrated survival at three years was the same for those administered six cycles (78% overall survival) versus eight cycles of R-CHOP-14 (73% overall survival). There was clearly no benefit of eight cycles over six cycles (32).
As regards to the role of autologous hematopoietic cell transplantation (HCT) in the overall outcomes, treatment-related mortality, event-free survival, and overall survival was better among patients who received treatment with conventional chemotherapy or high-dose chemotherapy followed by autologous HCT(33).

2.9 Justification of the Study

Currently, NHL is a common cause of morbidity and mortality and therefore warrants investigation. NHL has a high mortality rate if left untreated and high percentage are curable if treated appropriately. Thereôs need to study the treatment outcome of NHL. The last studies done previously were over a decade ago and the findings are likely to be outdated. There were initial studies done in the pre-HAART era and early times of the HAART era, we now wanted to investigate the relationship between NHL and HIV in the post HAART era. There are limited studies with sufficient details to provide a window into the natural history and clinical management of the disease.

The above-mentioned scarcities and challenges of treatment in the Kenyan setting provide a backdrop to review the status and realities of the therapeutic approaches to NHL in sub-Saharan Africa. Therefore, this study aimed at filling the existing knowledge and temporal gap in research on NHL in general, HIV-related NHL, its clinical and pathological features and outcome.

2.10 Research Question

What are the clinical and pathological features of Non-Hodgkinôs Lymphoma?

2.11 General Objective

To describe the clinical and pathological features of Non-Hodgkinôs Lymphoma among patients aged above 13 years seen at Kenyatta National Hospital between January 2006 and December 2015.

2.12 Primary Objectives

1. Describe the clinical features of patients with NHL.
2. Describe the pathological features of patients with NHL.

2.13 Secondary Objectives

1. Determine the outcome of NHL (i.e. complete remission, relapse free survival and overall survival.)
2. Determine the level of immunodeficiency (i.e. CD4 count or viral load) at the occurrence of NHL in AIDS related NHL.

3.0 CHAPTER THREE: METHODOLOGY

3.1 Study Design

This was a hospital-based retrospective study which accessed Non-Hodgkinôs Lymphoma patient records between January 2006 and December 2015. This study accessed all the readily available and existing case records of patients above 13 years, who had a diagnosis of Non-Hodgkinôs Lymphoma at the time.

3.2 Study Setting

The study was conducted at Kenyatta National Hospital (KNH) Nairobi. KNH is a 1800 bed capacity tertiary level hospital, located in Nairobi County, Kenya. The catchment is largely from the surrounding metropolis with many referrals also from almost all parts of the country and East and central Africa. The Hematoncology clinic serves nearly 100 patients per clinical session.

3.2 Study Population

Data retrieval was from case records of patients with Non-Hodgkinôs Lymphoma aged 13 years and above, who received treatment at Kenyatta National Hospital between January 2006 and December 2015. Patient records from both the Cancer treatment center and Haemato-oncology clinics were studied.

3.3 Inclusion Criteria

- Patient age of 13 years and above with a tissue diagnosis of NHL.
- Patient must have attended KNH between January 2006 and December 2015.

3.4 Exclusion Criteria

- Patients with other malignancies and medical conditions compounding the diagnosis of NHL

3.5 Patient Variables

Information that was obtained include patientsô demographics data such as age at diagnosis, sex, marital status, clinical and pathologic diagnosis details such as histology, date of diagnosis, disease stage at diagnosis, number of sites involved, HIV status, NHL subtypes, and patients performance status at diagnosis.

Further information included the hematological parameters at time of diagnosis and in course of treatment, treatment given upfront and the chemotherapy protocol and number of courses, date of last treatment, date of disease relapse or progression.

3.6 Sample Size Determination

Sample size was calculated using the (Daniel, 1999) formula(34);

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

Where,

n = Desired sample size

z = value from standard normal distribution corresponding to the desired confidence level (Z=1.96 for 95% CI)

p = expected true proportion (estimated at 13.0%, from a retrospective study conducted by Abinya N. A. et al (2004) over a period of ten years i.e. January 1990 to January 2000 inclusive at the Kenyatta National Hospital; looking at non-Hodgkinôs lymphoma, found 13.0% of them were Burkittôs lymphoma.)

d = desired precision (0.05)

$$n_n = \frac{1.96^2 0.13(1 - 0.13)}{0.05^2} = 174$$

A Sample size of 174 patients was required for the study.

3.7 Data Collection Procedure and Permission

Permission to conduct the research was obtained from the KNH/UON Ethics Research Committee. Following the permission to do the study, patient records were accessed at KNH records office based on the existing and available records. The investigator applied the inclusion criteria to obtain the case records. Having selected patient record files that fit the inclusion criteria, the investigator then documented in the sociodemographic questionnaire some of the variables reflected in the patient record files. These include age, sex, marital status, clinical and pathologic diagnosis details such as histology, date of diagnosis, number of sites involved, HIV status and NHL subtypes.

3.8 Data Collection Instruments

Staging of the NHL was assessed using the Ann Abor Classification.

The histological classification was derived from histological reports as described by the pathologist and adapted as closely as possible to the 2016 WHO classification.

Prognosiswas derived from the International Prognostic index (IPI) score and functional status from the Eastern Cooperative Oncology Group (ECOG) performance scale (See appendix B, C, D)

3.9 Data Analysis

The Data collected by the investigatorswas stored into a password protected Microsoft Access database managed by the statistician. After completion of the data entry exercise, a comparison between the data from the Microsoft Access database to the hard copies was done to ensure accuracy. Inconsistency wastested by running simple frequencies & correlations, and there were no inconsistencies identified. Data analysis was performed using Statistical Package for Social science (SPSS) software version 21.2 for windows.

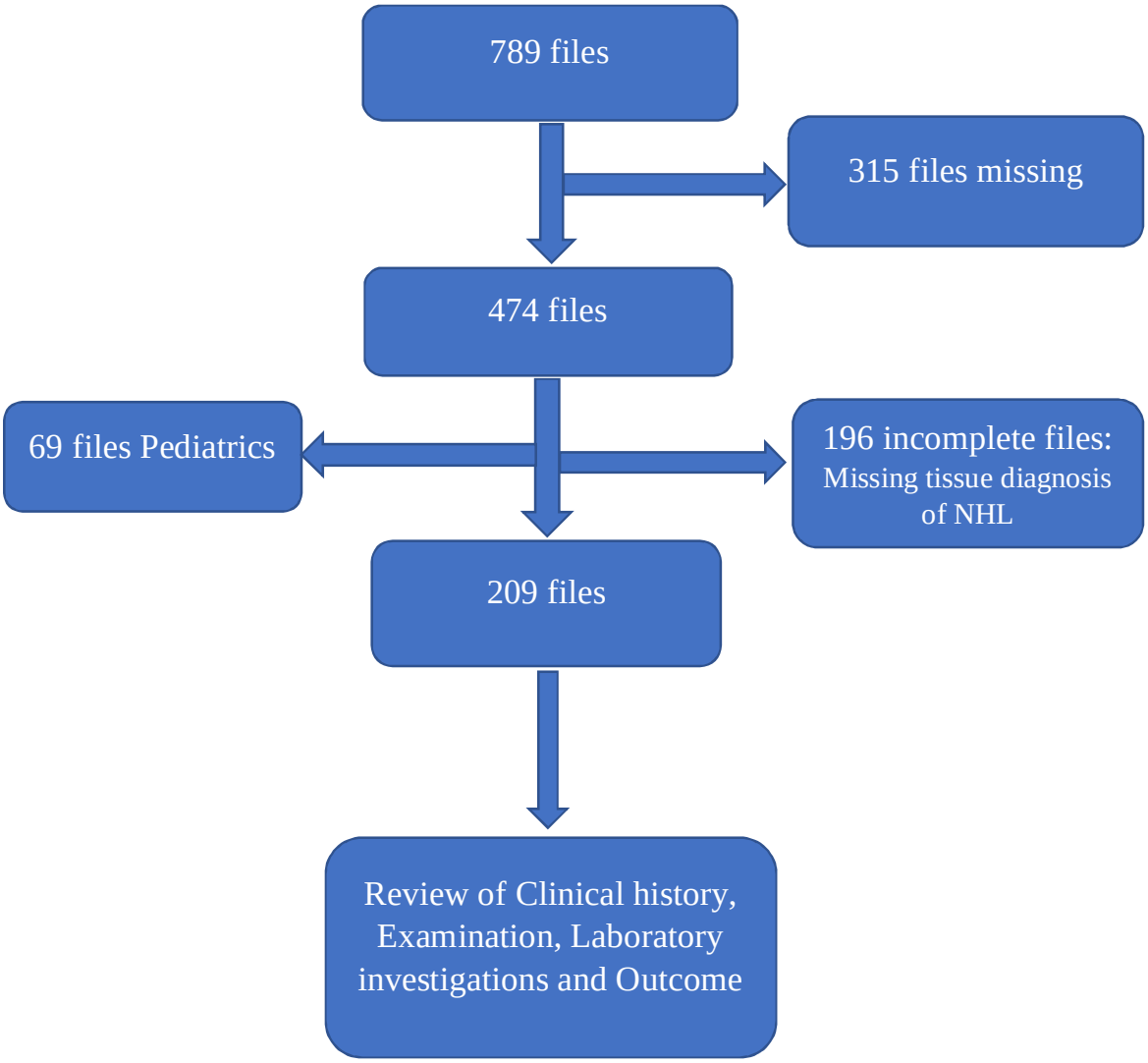
Patient characteristics were summarized into means/medians for continuous data while categorical variables as percentages. The level of significance wasconsidered as P value of Ò 0.001.

3.10 Ethical Considerations

The researcher requested for permission for data collection from the KNH/UON Ethical Review Committee. This was a retrospective study where all information was obtained from patientsômedical records; therefore no patients were interviewed as only the clinically relevant data from the records was retrieved. Confidentiality was kept by excluding patient names, IP number and any other identifying information when capturing the clinically relevant information from the patient files to the data entry sheets. Data obtained from this study was not used for any other purpose other than meeting the objectives of this proposal. Following data analysis, the findings are to be shared with relevant stakeholders such as the University of Nairobi, Kenyatta National Hospital and the publications and research bodies only.

4.0 CHAPTER FOUR: RESULTS

Total of 789 patients with Non-Hodgkinôs Lymphoma were admitted during the study period of January 2006 to December 2015. Of these 474 files were retrieved, 209 met the inclusion criteria as shown in the flow chart below.



4.1 The Demographic Profile

Records were available for a total of 209 patients, of whom 125 were males (59.8%) and 84 (40.2%) females. The Male: Female ratio was 1.5:1. Eighty three out of 209 (39.7%) were aged less than 40 years, 83 (39.7%) were aged 40-59.9 years and 43 (20.6%) were aged 60 years and above. The median Age was 43 years with an interquartile range of 26 years. (Table 1)

Table 1:Demographic details of patients with Non-Hodgkin's Lymphoma's

Characteristics	**No.**	**%**
Sex (n = 209)		
Male	125	59.8
Female	84	40.2
Age at diagnosis (n = 209)		
<40	83	39.7
40 ï 59.9	83	39.7
Ó60	43	20.6

4.2 Clinical parameters at diagnosis of NHL:

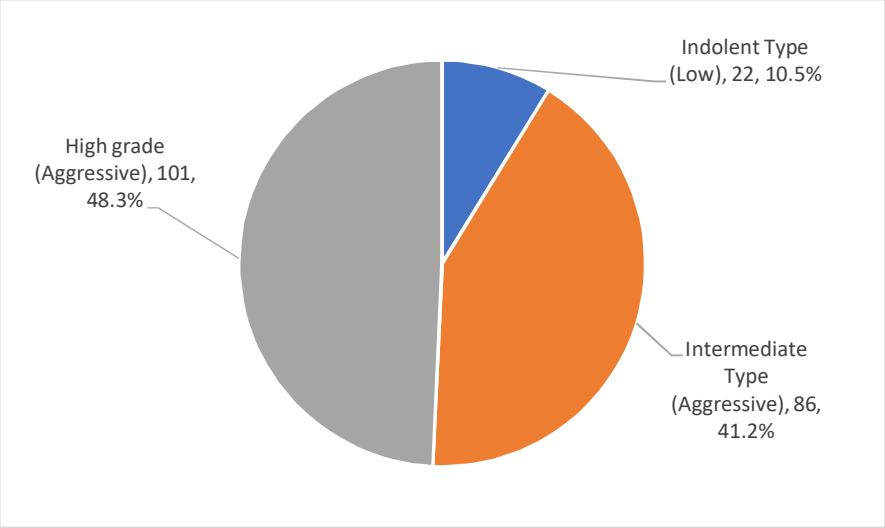
Less than half of the patients presented with localised disease (Ann Abor stage I (9.6%) and II (31.1%) respectively) whereas those with Ann Abor stage III & IV accounted for 49.3% & 10% respectively. (Table 2)

Table 2 : Disease stage at diagnosis of patients with Non-Hodgkin's Lymphoma

Disease stage at diagnosis (n = 209)	Frequency	%
Stage I	20	9.6
Stage IIA, IIB	65	31.1
Stage III	103	49.3
Stage IV	21	10.0

Out of the 209 cases; High grade (highly-aggressive) type accounted for 101 (48.3%), intermediate Type (aggressive) 86 (41.2%) and indolent type 22 (10.5%).(Figure 1)

Figure 1: Histological grade of NHL



Out of 209 cases evaluable for site, 59(28.8%) had disease limited to lymph nodes, 38(18.5%) had disease in extra-nodal sites and 108 (52.7%) had disease involving both nodal and extra-nodal sites. 4 cases did not have documentation of which nodal site was involved. The specific extra nodal sites of involvement amongst 38 patients were GIT 16 (42.1%), bone marrow 12 (28.9%); ear, nose, throat 6(15.7%); testes/ovaries 4(10.5%), others. (Table 3)

Table 3 :Site of involvement at diagnosis of patients with Non-Hodgkin's Lymphoma

Sites of involvement (n = 205)	***Frequency***	***%***
Nodal	59	28.8
Extra-nodal	38	18.5
Nodal + extra-nodal	108	52.7

Of patients aged <40 years, 32.9% had nodal disease, 20.7% had extra-nodal disease, and 46.3% had nodal and extra-nodal disease. Of patients aged > 60 years, 25.5% had nodal disease, 6.9% had extra-nodal disease and 67.4% had nodal and extra-nodal disease. These differences were however not statistically significant (P=0.123). 4 cases did not have documentation of which nodal site was involved. There was no association between age groups and nodal sites (Table 4)

Table 4: Association of Sites involvement according to age group (n = 205) P=0.123 (NS)

Age Group	**Nodal**		**Extra Nodal**		**Nodal + Extra Nodal**	
	No.	**%**	**No.**	**%**	**No.**	**%**
<40 (n =82)	27	32.9	17	20.7	38	46.3
40 ï 59.9 (n =80)	21	26.2	18	22.5	41	51.2
Ó60 (n =43)	11	25.5	3	6.9	29	67.4

The indolent type of NHL had a better performance status at diagnosis in comparison to the high grade NHL, which was associated with poorer performance status. 4 cases died within a short period of first contact and were in performance status 5. There was a significant association between histologic grade and performance status at diagnosis were P<0.010 (Table 5)

Table 5: Relationship between performance status and histology (n = 205) P<0.010 (S)

Histology	**0**		**1**		**2**		**3**		**4**	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Indolent type ï low ***(n=18)***	12	66.6	2	11.1	3	16.6	1	5.5	0	0.0
Intermediate type - aggressive ***(n=86)***	31	36	13	15.1	16	18.6	13	15.1	12	13.9
High grade ï highly aggressive ***(n=101)***	20	19.8	13	12.8	21	20.7	30	29.7	14	13.8

Of the 205 cases evaluated for ECOG performance status at diagnosis, 63 (30.7%) were in performance status 0 which were the majority of cases, whereas 26 (12.6%) were in performance class 4 that had the least number of cases. 4 cases died within a short period of first contact and were in performance status 5. (Table 6)

Table 6: Performance status at diagnosis of with NHL

Performance status ECOG (n =205)	***Frequency***	***%***
0	63	30.7
1	29	14.1
2	40	19.5
3	47	22.9
4	26	12.6

Tests for HIV infection were carried out in 179 out of 209 cases evaluable. For the rest no information was available. Of the 179 tested, 40 (19.1%) were positive and 139 (66.5%) negative. (Table 7)

Table 7: HIV Status of patients with Non-Hodgkin's lymphoma

HIV status checked (n= 209)	***Frequency***	***%***
Positive	40	19.1
Negative	139	66.5
Not documented	30	14.4

Of the 40 cases who were positive for HIV infection, 3 (17.5%) cases were of the indolent phenotype, 15 (37.5%) were of intermediate (aggressive) phenotypes and 22 (55%) high

grade (highly-aggressive) phenotypes. There was a trend of HIV being associated with aggressive phenotypes and this was however not seen to be of statistical significance (P=0.565) (Table 8)

Table 8: Grade of NHL and HIV Status

	HIV Status			
	Positive		Negative	
	No.	%	No.	%
Indolent type ï low	3	7.5	14	10.3
Intermediate type - aggressive	15	37.5	60	44.1
High grade ï highly aggressive	22	55.0	62	45.6

Disease stage was available for 209 cases, 22 cases had indolent type (Low), intermediate (aggressive) type 86 cases and High grade (highly-aggressive) 101 cases. Indolent phenotypes were common in Ann Abor stage I & II 10 (45.5%) where as highly aggressive phenotypes were common in Ann Abor stage IV 20 (19.8%). There was a significant association between disease stage and histology P<0.001 (Table 9).

Table 9: Association of histological grade with disease Stage (n = 209)* (P<0.001)

Histology Grade	I, IB		II, IIB, III, IIIB		IV, IVB	
	No.	%	No.	%	No.	%
Indolent type ï low ***(n=22)***	10	45.5	12	54.5	0	0.0
Intermediate type - aggressive ***(n=86)***	11	12.7	73	84.8	2	2.32
High grade ï highly aggressive ***(n=101)***	4	3.96	77	76.2	20	19.8

Histological characteristics of 209 cases were evaluated. Diffuse large B cell lymphoma accounted for majority of cases 80 (38.3%) and was the commonest B cell neoplasm reported, small lymphocytic lymphoma/chronic lymphocytic leukemia 16 (7.7%) cases and was the commonest T cell neoplasm recorded. Other descriptions not well categorized were, non-Hodgkin's lymphoma not otherwise specified 39 (18.6%), B-Cell lymphoma Unclassified type with features intermediate between DLBCL and Burkittôs 3 (1.4%), B-Cell lymphoma (Not otherwise specified) 18 (8.6%), T-Cell lymphoma (Not otherwise specified) 9 (4.3%). (Table 10)

Table 10:Pathologic details of patients with Non-Hodgkin's lymphoma

Characteristics	No.	%
Histology (n = 209)		
Non-Hodgkin's lymphoma unclassified type	39	18.6
Small lymphocytic lymphoma/chronic lymphocytic leukemia	16	7.7
Anaplastic large B-cell lymphoma	6	2.9
Diffuse large cell B-cell lymphoma	80	38.3
Angioimmunoblastic T cell lymphoma	1	0.5
Lymphoplasmacytic lymphoma	1	0.5
Burkittôs lymphoma	8	3.8
Ritcher's transformation	4	1.9
Cutaneous T cell lymphoma	8	3.8
Follicular lymphoma	4	1.9
B-Cell Lymphoma unclassified type with features intermediate between DLBCL and Burkitts	3	1.4
B-Cell lymphoma (not otherwise specified)	18	8.6
T-Cell lymphoma (not otherwise specified)	9	4.3
Lymphoplasmacytic lymphoma	2	1.0
MALT	7	3.3
Mantle cell lymphoma	3	1.4

4.3 Treatment

Of the 194 cases evaluable, 142 (67.9%) cases received chemotherapy, 45 (21.5%) received both chemotherapy & radiotherapy and 7 (3.6%) were treated with radiotherapy upfront. 15 cases were lost to follow up. Out of 194 cases evaluable for chemotherapy, only 65 (33.5%) received six courses and above. The rest did not get adequate treatment. Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy was given to 155 out of 194 cases evaluable (82.9%), and cyclophosphamide, vincristine and prednisone (COP) to 8 (4.3%) of the cases evaluable. Less than 50% of the cases received at least six courses of chemotherapy (Table 11).

Table 11:Treatment Details of Patients with Non-Hodgkin's Lymphoma

Characteristics	No.	%
Treatment upfront (n=194)		
Radiotherapy	7	3.6
Chemotherapy	142	67.9
Chemo-radiotherapy	45	21.5
Type of Chemotherapy (n=187)		
CHOP	155	82.9
R-CHOP	15	8.0
MACOP-B	1	0.5
COP	8	4.3
ICE	2	1.1
DHAP	1	0.5
ABVP	4	2.1
Chlorambrucil	1	0.5

After four courses of chemotherapy 27 out of 142 cases evaluable, 3 (11.1%) achieved complete remission, 12 (44.4%) partial remission, 8 (29.6%) stable disease and 4 (14.8%) progressive disease. After six courses 65 out of 142 cases evaluable, 31 (47.7%) achieved complete remission, 2 (3.1%) partial remission, 7 (10.8%) stable disease and 6 (9.2%) progressive disease. The rest (50 cases) did not get adequate treatment i.e. they received less than four courses of chemotherapy. The difference in remission status at four and six courses was significant (P<0.001).

Table 12: Association between treatment outcome and number of courses of chemotherapy (P<0.001).

	CR		PR		SD		PD		RL		D	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
After 4 courses ***(n=27)***	3	11.1	12	44.4	8	29.6	4	14.8				
After 6 courses ***(n=65)***	31	47.7	2	3.1	7	10.8	6	9.2	17	26.2	2	3.1

209 cases were analysed for duration of follow-up in weeks against sex. Of the male cases 32 (26.2%) followed up for less than 12 weeks, 15 (12%) between 12-18 weeks and 67 (54.9%) more than 25 weeks. Of the female cases 17 (20.2%) followed up for less than 12 weeks, 11 (13.1%) between 12-18 weeks and 44 (52.4%) more than 25 weeks. These differences were not statistically significant P = 0.472. (Table 13)

Table 13:Relationship between duration of follow-up in weeks and gender (P=0.472).

	<12		12-18		19-24		>25	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Male ***(n=125)***	32	26.2	15	12	11	9.0	67	54.9
Female ***(n=84)***	17	20.2	11	13.1	12	14.3	44	52.4

209 cases were evaluable for follow-up against stage of disease. Patients diagnosed with early stage disease were followed up for longer duration than those diagnosed with advanced disease. There was an association between early stage disease and duration of follow-up and this was seen to be significant P=0.011. (Table 14)

Table 14:Association between disease stage at diagnosis and duration of follow-up in weeks (P=0.011)

	<12		12-18		19-24		>25	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Stage I (n=20)	11	55.0	2	10.0	3	15.0	4	20.0
Stage IIA, IIB (n=64)	14	21.9	10	15.6	4	6.3	36	56.3
Stage III (n=103)	22	21.8	11	10.6	11	10.9	59	58.4
Stage IV (n=21)	2	9.5	2	9.5	5	23.8	12	57.1

5.0 CHAPTER FIVE: DISCUSSION

Non-Hodgkin's lymphomas represent a diverse group of neoplasms hurdled together under one entity. Non-Hodgkin's lymphoma (NHL) is one of the malignant lymphomas that has been widely studied across the globe. Broadly speaking NHL has a male preponderance, affecting more males than females and the ratio described in this study of 1.5:1 which tallies with what has been described in other studies done elsewhere(1). It is increasingly appreciated that NHL is the eighth most commonly diagnosed cancer in men and the eleventh in women worldwide (1) and in the US, incidence rates for NHL were higher in males than in females(2). In an earlier study by Abinya and colleagues in 2004, there was a male preponderance reported, with a male: female ratio of 2.5:1. Data from the Nairobi cancer registry (2004-2008) reported the incidence rate of NHL was 3.7%, with 5.3% being males and 2.8% females (35).

From Western literature, it is reported that the median age at diagnosis is the sixth decade of life although Burkittôs lymphoma tends to occur more commonly in the younger age groups. The median age of patients with NHL in India is lower by almost 10 years compared to that of Western countries(8). The younger age at presentation in India was possibly due to the large proportion of young Indians under 35 years of age, making up 65% of the population. This was responsible for the young age at presentation of NHL. The lower proportion of indolent lymphoma (predominantly seen in the elderly population) in India was probably the result of the same bias. The median age of 54 years at occurrence of NHL is similar to other Asian countries. The mean age of NHL patients was 52.5 years for males and 49.5 years for females respectively(4). This data was similar to the Sudan and Nigerian studies. Taking this into the Kenyan context, this study found the median age was to be 43 years. This may be largely because Kenya has a youth population, with the countryôs median age being 19.2 years (36).

There exists certain racial variations among NHL patients reported around the globe, were European and North-American Caucasians reporting follicular lymphoma being more common among their population and the Asian population reporting more of the T-cell types tend to feature more prominently. One such attempt at documenting the distribution of NHL amongst the African populations noted the occurrence of endemic Burkitt's lymphoma along the lymphoma belt. Abinya and colleagues in 2004, described the occurrence of follicular lymphoma and small lymphocyte lymphomas occurring commonly in the elderly and middle-aged groups whereas BL, Precursor B/T cell lymphoblastic lymphoma/leukemia were in the younger aged group(6). In a study done in Uganda the Mean age for BL was 31.3 years, while other subtypes were at 45.3 years respectively. In this study indolent phenotypes of NHL had

the lowest peak in those < 40years, whereas the younger patients presented with more aggressive phenotypes.

In this study, out of the 209 cases 124 (59.3%) had stage III & IV disease. Clinical staging data from Uganda noted (90%) of participants presented in stage III or IV disease. Similarly, in a study done in India, 85% of the participants were at stage III or IV. The large number of patients presenting in advanced stages at diagnosis could be explained by delay in the referral systems and late presentation to hospital (37).

About 30.7% of the patients analyzed had ECOG PS 0, reflecting the reasonably good general condition of patients with NHLs at diagnosis. However, one should not forget that patients with PS >3 are unlikely to have been successfully referred to KNH.

From an earlier study done in Kenya in late 1990ôs the distribution of nodal and extra-nodal disease was fairly similar, and this was found interesting. Nodal disease occurred more frequently than extra-nodal disease, but since aggressive lymphoma types which were predominant in this series tend to be extra-nodal, this finding is not surprising. According to a Zambian study, approximately 50 percent of NHL patients will develop extranodal disease (secondary extranodal disease) while between 10 and 35 percent of patients will have primary extranodal lymphoma at initial diagnosis. The initial presentation may reflect involvement of extranodal tissues(13). In this study, a total of 52.7% had nodal and extra nodal disease whereas 18.5% had primary extranodal lymphoma at diagnosis. These results significantly match the Zambian results above and the earlier finding in Kenya and the trend doesnôt seem to have changed. The presence of extra-nodal disease pushes disease stage higher for the different histologic subtypes.

An attempt was made retrospectively to apply the WHO 2016 Classification of Lymphomas which was fairly simple to apply however this still left out 18.6% of the cases not histologically characterized. Unfortunately, the need for application of Immunohistochemistry has made it difficult to apply the newer lymphoma classification. This could be explained partly by the fact that not all immunohistochemistry panels were run at the time of diagnosis and limitations that exist with the quality of histology reporting in our setting.

In a study done by Shen and colleagues (38), the researchers found 53.7% of the 79 patients who participated in the study to have Diffuse large B-cell Lymphoma (DLCB). This percentage made DLCB to stand as the most predominant NHL in the Chinese patient population enrolled for the study. Similar to this study, DLCB was found to be the most predominant NHL with 38.3% incidence rate. In another study done across North Africa and Middle East, 86.9% of

the participants were found to have DLCB, with Algeria and Egypt having 52.8% and 41.5% incidence rate respectively.

A study done in Uganda stated that there was a male predominance (75% in BL, DLBCL 70%). In this study, commonest subtype of NHL was Diffuse Large B Cell lymphoma (38.3%).

A recent study in Kenya done in 2009 demonstrated the risk of developing aggressive phenotype non-Hodgkinôs lymphomas was high among HIV infected individuals and was associated with worse prognosis than among non-HIV infected ones(11). This difference was highly significant ($P < 0.0001$). 15.6% of HIV-positive patients died during first-line treatment compared with none of the HIV-negative counterparts. This was a highly significant difference ($P < 0.0001$). Abinya and colleagues in 2004, noted the prevalence (HIV) among NHL cases was 32.5% of those tested. The HIV seroprevalence rate for Kenya was about 7.1% at the time. The prevalence of positive serology for (HIV) infection was 19.1% of those tested in this study and the HIV seroprevalence rate for Kenya is about 5.6% (39). The widespread availability and uptake of HAART has significantly reduced the risk of HIV transmission and therefore lowering the prevalence rates. Furthermore, it can be argued that there was bias towards testing those who were suspected to be infected. However it is our policy that all NHL cases are tested for HIV infection upfront, although this policy was not been adhered to strictly during the course of this study.

It is instructive to note that very few (3 cases) of the indolent lymphoma types tested positive while the aggressive & highly aggressive types had high frequencies of HIV seroprevalence. One case was BL whereas 26 cases were diffuse large B cell lymphomas. Subgroup analysis was not carried out to correlate HIV infection with nodal or extra-nodal disease because of small numbers. The observed changes in frequency of specific subtypes following the use of HAART can be explained by the dramatic decrease in the proportion of HIV-infected patients with profound immunosuppression. Even though these studies are correct when looking at the HIV positive population, it is of interest to note that in this study, HIV negative participants also displayed high percentages of aggressive-NHL prevalence (both intermediate and high grade) adding up to: 92.5% prevalence (HIV positive) versus 89.7% prevalence (HIV negative).

In some studies, it was also noted that NHL had a high mortality rate in early years before 1990(5). A Study done in 2012 in India, estimated NHL to have an incidence rate of 2.2/100,000 persons and a mortality rate of 1.5/100,000 persons. In this study 63.6% of the participants were likely to die in less than 12 weeks following NHL diagnosis. However, mortality rate was at 3.1% of the 65 participants who were undergoing 6 courses of

chemotherapy. This could be explained by the fact that a good percentage (11.1%) of the participants in this study were more likely to be reach complete remission after 4 courses of chemotherapy or attain complete remission (47.7%) after 6 courses of chemotherapy.

In the Ugandan study, there was a weak association observed between HIV and NHL and this was reported to probably be due to the reduced survival of immunosuppressed HIV individuals with NHL (10). There was a trend of HIV being associated with aggressive phenotypes and this was however not seen to be of statistical significance (P=0.565) in this study. The reason for this weak association could possibly be explained by the numbers being too small to allow for further subgroup analysis. Also the documentation of data on CD4 count and viral load was inadequate to be analyzed and statistically representative of the HIV positive sample in this study.

A case-control study of NHL in the backdrop of HIV infection in Uganda demonstrated Burkittôs lymphoma and large B-cell lymphomas represented 71% of adult cases. Unlike in Uganda, in a study done in Kenya in 2004, Burkittôs lymphoma was not frequent as the Kenyan study placed it second to diffuse large B-cell lymphoma in frequency among HIV- positive cases (21.9%) of HIV positive patients achieved complete remission compared with (75%) of HIV negative ones. Similar to the 2004 Kenyan study, in this study, among HIV positive patients, DLBCL stood at (40%), seconded by Burkittôs Lymphoma (37.5%). In this study the trends havenôt changed much from the initial findings in 2004, among the HIV positive patients DLBCL stands at (38.2%).

The median CD4+ lymphocyte count was 100/µL prior to the cART era. The median CD4+ lymphocyte counts increased to between 150ï 200/µL and higher in the cART era since patients had less immunosuppression (28). In this study due to lack of data from files, the CD4 count and viral load of the participants was sporadically available, making the little available data to be statistically weak for a valid and representative analysis.

In the first IPI pilot study, the initial group of 2031 patients with aggressive NHL treated with anthracycline-based regimens that excluded rituximab, were followed up over five years, it was noted the five-year overall survival rates for patients with scores of zero to one, two, three, and four to five were 73%, 51%, 43%, and 26 %, respectively(23ï 25). In this study LDH levels were sporadically recorded in the files or missing data in the files, this made it difficult to compute the IPI score and therefore make a conclusion on the outcome of patients in relation to their IPI.

The combination of rituximab plus CHOP specifically or CHOP-like regimens is the most commonly employed treatment for DLBCL (26). Similarly in this study the most commonly

used treatment was CHOP, with 82.9% of the participants receiving that treatment. CHOP is the most commonly used treatment regimen for most aggressive lymphomas.

In 2004 from Kenya 5.3% of patients evaluated achieved complete remission following four courses of chemotherapy, the number increased exponentially to 55.6% in those who received six courses of chemotherapy(6). In this study, 11.1% of the participants achieved complete remission following 4 courses of chemotherapy and 47.7% achieved complete remission after six courses for those who had adequate treatment. CHOP was used in 82.9% of the cases evaluable. The standard dosing per course was considered adequate in virtually all patients but the relative dose intensity was not calculated. Unfortunately, the treatment was not sustained and 40.9% of the cases received six courses and above. The recommended number of courses is six to eight, depending on the stage at which complete remission is achieved after which a further two consolidating courses are given. Achievement of complete remission with front-line chemotherapy is the first step towards cure of any chemocurable neoplasm and adequacy of treatment determines this. After four courses, only 11.1% of the patients evaluable achieved complete remission and the number shot up to 47.7% after six courses for those who had adequate treatment. These differences were highly significant. It is instructive to note that compared with historical controls, the outcome for these patients in this institution appears to have improved. The problem was that less than 50% of the patients could afford to go through the intended course of chemotherapy, mainly because of cost.

Of the patients that had complete remission at end of 6 cycles of CHOP 22 (33.8%) relapsed; 13.6 % were HIV positive, 54.5% HIV negative and 31.8% had the HIV status not documented. This could be explained by the mere fact that HIV positive patients tend to have more frequent reviews in the CCC clinics and therefore were easier to follow-up as compared to the other groups.

There was an overall improvement in the response to treatment noted in this study. This may be because slight improvement in the follow-up of patients, histology reporting with the adoption of routine immunohistochemistry that was previously rare, this allowed adequate classification of our NHL.

6.0 CHAPTER SIX: CONCLUSION

6.1 Conclusion

From this series NHL is well distributed among age groups and has a male preponderance. Majority of cases reviewed were in stage III at the time of diagnosis and had both nodal and extra-nodal site involvement. A good number of cases were at performance status 0 at time of diagnosis with the commonest type of tumor being Diffuse Large B Cell lymphoma (38.3%). HIV positive cases accounted for 19.1% of cases and there was a trend of HIV being associated with aggressive phenotypes but this was however not seen to be of statistical significance. A good percentage of the highly aggressive phenotypes were likely to test positive for HIV infection. Complete remission was achieved in 47.7% of cases that received 6 courses of CHOP, standard treatment was offered to the majority of the patients but a good number could not afford to complete the treatment because of the cost of drugs and radiology investigations. Those who completed treatment had a 47.7% chance of achieving complete remission which compares well with results from middle income countries. Losses to follow-up after 6 cycles of chemotherapy were high, further making it difficult to test various prognostic variables. Early disease patients were more likely to be followed up for longer durations and on the whole, the outlook for NHLs treated at KNH in the 2006 onwards appears to have improved tremendously, but cost is still a major impediment for adequate delivery of treatment. Our hope is with the advent of NHIF oncology services package, we believe treatment outcomes are likely to improve.

6.2 Recommendations

Digital records system should be established in records department and in clinical areas. This will ensure that proper documentation is done. This further enable one track the patients file seeing that a single patient may have more than one file between two or three clinics and therefore vital data is lost and subsequently loss of continuity of care. HIV testing should be offered upfront and clearly documented at time of diagnosis. A lymphoma assessment tool should be developed and pinned to each patient file so that assessment of response to treatment can be made during the course of the patientsô follow-up i.e. at mid-cycle and nd of 6 cycles.

Prospective studies should be done to investigate the relationship between NHL and HIV, outcome, toxicity profiles to enable us better understand NHL.

6.3 Study Limitations

The potential lack of complete information recorded in the patient files presented as a limitation. This limited the researcherôs ability to obtain information such as type of salvage treatment, date of salvage treatment, courses of salvage treatment, outcome of salvage treatment, last date of follow up, date of death if recorded, cause of death if known survival duration, follow up duration.

The manual filing system also presented a challenge during the process of identification of cases of interest.

The lack of a tool to access and track the progress of disease presented challenges in the identification of those with refractory disease, relapse or progressive disease and the outcome of patient at the end of treatment was also a limitation in this study.

6.4 Financial Disclosure

This research was financially facilitated by the Kenyatta National Hospital Research Programs department and the PIôs personal savings. However, the content herein does not represent the views and opinions of the concerned funders.

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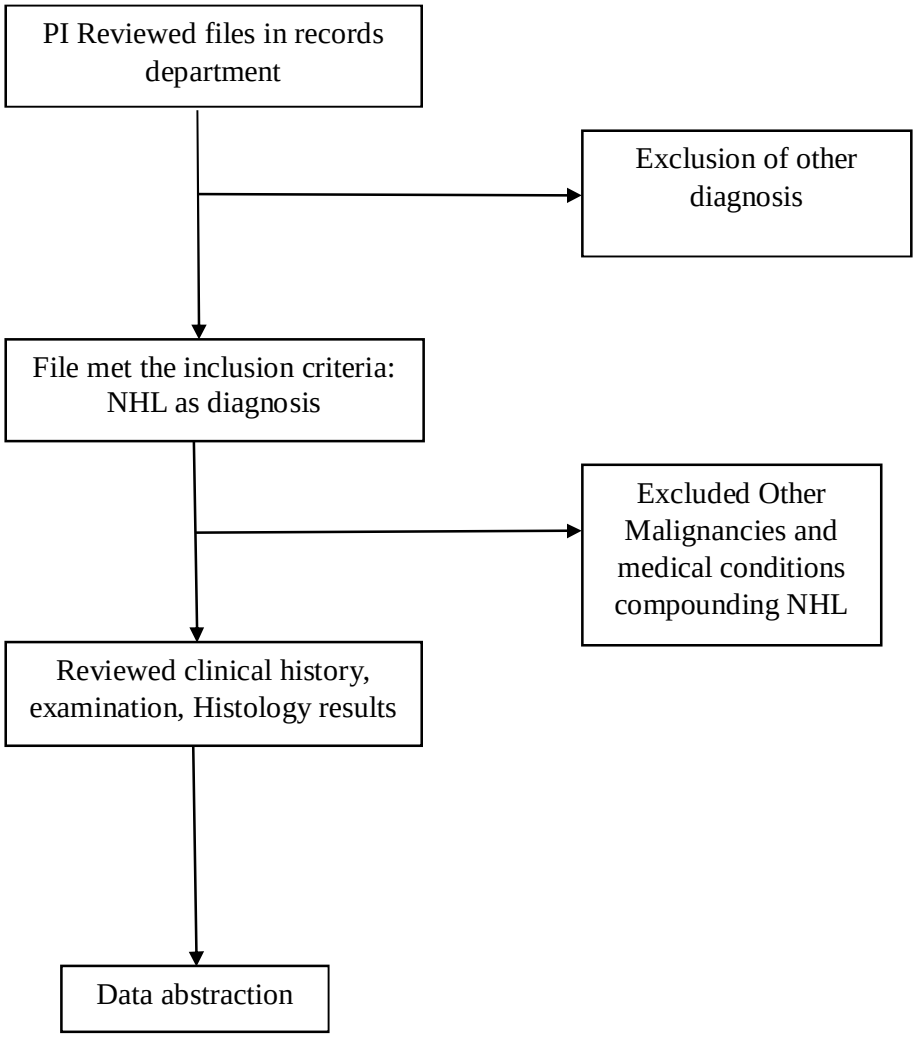
APPENDICES

Appendix A: Flow Chart



Appendix B: Research Work Plan

ACTIVITY	TIME
Development of proposal and defense presentation	June-September 2017
Proposal submission for ethical approval	October 2017
Data collection	February 2018
Data analysis	May 2018
Report writing	June 2018
Results presentation	July 2018
Submission of report	July 2018

Appendix C: Study Budget

KNH Research and Programs

Awards are limited to a maximum of Kshs. 400,000.00

Name: Dr. DOMINIC MUNENE MUTURA

Study Title: CLINICAL AND PATHOLOGIC FEATURES OF NON-HODGKIN'S LYMPHOMA AMONG PATIENTS SEEN AT KENYATTA NATIONAL HOSPITAL.

Study Budget

Components	**Unit of Measure**	**Duration/ Number**	**Unit Cost (Kshs)**	**Total Cost (Kshs)**
Personnel				
Research Assistant	1 person	98 Days	1500.00	147000.00
Statistician				30000.00
Participants				
Transcribing Fee				
Printing				
Consent Form				
Assent Form				
Questionnaires	1 copy	4 pages	10.00	40.00
Final Report-Coloured	6 copies	1 page	20.00	120.00
Final Report-Black & White	1 copy	79 pages	10.00	790.00
Photocopying				
Consent Form				
Assent Form				

Questionnaires	800 copies	4 pages	3.00	9,600.00
Final Report-Black & White	5 copies	79 pages	3.00	1185.00
Final Report Binding	6 copies	1 page	500.00	3000.00
Diagnostic Services				
Other costs				
ERC Fees				2000.00
Records Access Fee				1500.00
Poster Printing	1	1	2,500.00	2,500.00
Total				**197735.00**

Budget items Justification:

1st Justification: Looking at 789 files, working with 1 research assistant who is able to review 8 files in a day, each file requires 1 hour and research assistant is working 8 hours in a day in order to achieve the required sample size in 98 days.

2nd Justification: The statistician will be remunerated with a one off payment for data analysis.

3rd Justification: Printing of 1 copy of the study tools and the rest of the tools where photocopied, the extra copies where to take care of the spoilt copies.

4th Justification: This being a retrospective study, there was a requirement for payment to KNH records department in order to be allowed access to the files.

The final results will be presented in a poster.

Appendix D: Ann Abor classification

Stage	Definition
I	Involvement of a single lymph node (LN) region (I) or of a single extranodal organ or site (IE)
II	Involvement of two or more LN regions, on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more LN region on the same side of the diaphragm (IIE)
III	Involvement of LN regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (III S) or by localized involvement of an extralymphatic organ (III E) or both (IIISE)
IV	Noncontiguous involvement of one or more extralymphatic site with or without LN involvement
Annotation	**Definition**
A	No B symptoms
B	At least one of the following within the last 6 months:
	a. Weight loss >10%
	b. Unexplained persistent or recurrent fever
	c. Drenching night sweats
X	Bulky disease ($\geq$ 6 cm in diameter or mass > 1/3 of mediastinal) diameter
E	Extension to a single extralymphatic organ adjacent to a known involved site

Appendix E: 2016 WHO classification of Lymphoma

MATURE B-CELL NEOPLASMS

- Chronic lymphocytic leukemia /small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis*
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic B-cell lymphoma/leukemia, unclassifiable
- Splenic diffuse red pulp small B-cell lymphoma
- Hairy cell leukemia-variant
- Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- Mu heavy chain disease
- Gamma heavy chain disease
- Alpha heavy chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases*
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT
- lymphoma)
- Nodal marginal zone lymphoma
- Pediatric nodal marginal zone lymphoma
- Follicular lymphoma
- In situ follicular neoplasia*
- Duodenal-type follicular lymphoma*
- Pediatric-type follicular lymphoma*
- Large B-cell lymphoma with IRF4 rearrangement*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- In situ mantle cell neoplasia*
- Diffuse large B-cell lymphoma (DLBCL), NOS
- Germinal center B-cell type*
- Activated B-cell type*
- T cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL, NOS*
- EBV+ Mucocutaneous ulcer*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8 positive DLBCL, NOS*
- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberration*
- High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
- High grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical
- Hodgkin lymphoma

MATURE T-AND NK-NEOPLASMS

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK cell leukemia
- Systemic EBV+ T-cell Lymphoma of childhood*
- Hydroa vacciniforme-like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*

- Indolent T-cell lymphoproliferative disorder of the GI tract *
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis- like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative
- disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD8 positive aggressive epidermotropic
- cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma*
- Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma*
- Nodal peripheral T-cell lymphoma with TFH phenotype*
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma, ALK negative *
- Breast implant-associated anaplastic large cell lymphoma

HODGKIN LYMPHOMA

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis PTLD
- Florid follicular hyperplasia PTLD*
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)
- Classical Hodgkin lymphoma PTLD

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumour
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumour
- Disseminated juvenile xanthogranuloma
- Erdheim/Chester disease

Appendix F: International Prognostic Index (IPI)

Risk factors for the Definition of the International Prognostic Index (IPI)

General Index	Parameter
1	Age >60years
1	LDH higher than normal
1	ECOG performance status >2
1	Ann Abor stage III or IV
1	More than 1 extranodal site
5	Max score 3

Risk groups of the IPI index

No. of Risk factors	No. of Risk factors	IPI Group
0-1	0	Low
2	1	Low Intermediate
3	2	High Intermediate
4-5	3	High

Appendix G: Eastern Cooperative Oncology Group (ECOG) performance scale.

Researchers and doctors utilize this scale to assess how a patientôs disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis use these criteria and scales. The Principal Investigator in this study used the scale for the same above mentioned use.

ECOG PERFOMANCE STATUS

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix H: Socio demographic Questionnaire

Title: **Clinical and Pathologic features of Non-Hodgkin's Lymphoma among Patients seen at Kenyatta National Hospital**

Get information from the patient record file.

(Only if all items are ticked proceed to the questions below)

SECTION 1.

Criteria for inclusion (Tick where applicable).

Has Non-Hodgkinôs Lymphoma	
Is 13 years and above	
Attended KNH between the January 2006 and December 2015 time period	

Study Codeé é é é é é .. Dateé é é é é é

Age (years)é ... Gender (Male/Female)é Residenceé ...

Status (Married/single/separated/widowed)é Age (years) at diagnosisé

Weight (Kgs.)é . Height (cm)é . BMIé . TBSA (M^2)é

Date of 1st Treatment (dd/mm/yr.)é é .. Date at Last treatment (dd/mm/yr.)é é ..

SECTION 2.

1) What was the Grade of NHL?
   i) Indolent Type (Low)
   ii) Intermediate Type (Aggressive)
   iii) High grade (Aggressive)
   iv) Not documented

2) Regarding the Ann Abor staging,
   i) What was the clinical stage (Ann Abor)?
      (a) I
      (b) II
      (c) III
      (d) IV

   ii) What was the Ann Abor Stage modifier?
      (a) A-Asymptomatic
      (b) B-Presence of B symptoms
      (c) E-Single extra nodal site
      (d) S- Splenic involvement

   Indicate the final Ann Abor stageé é é é

3) What was the type of NHL? (E.g. Follicular, Small cell cleaved etc.)

    i) Specifyé .....

4) Which disease sites were involved?
    i) Nodal
    ii) Extranodal
    iii) Both (i) and (ii)
    iv) Not indicated
5) How many nodes where involved?
    i) Specifyé é é é é
6) Which of the following symptoms were active during the course of the illness
    i) Fever (Temperature> 38^0)
    ii) Night sweats
    iii) Weight loss
    iv) Persistent lymphadenopathy
    v) All the above
7) Which of the following significant illnesses were found during the time of diagnosis of NHL?
    i) Rheumatoid Arthritis
    ii) Systemic Lupus Erythematosus (SLE)
    iii) Chronic Kidney Disease
    iv) Post organ transplantation state
    v) Post chemotherapy for other malignancy not Lymphoma
8) What was the patientôs HIV status?
    i) Positive
    ii) Negative (Proceed to Question 12)
    iii) Not documented

9) Was the HIV positive patient on HAART?
    i) Yes
    ii) No
    iii) Not documented
10) What was the documented viral load?
    i) é é é ..
11) What was the documented CD4+ Count?
    i) é é é ..

12) Fill in the Complete blood count parameters at specific times shown below:
    i) At diagnosis: WBC COUNTé ...HBé é é é .
    ii) After 4th Cycle: WBC COUNTé ....HBé é é é .
    iii) After last Cycle: WBC COUNTé ...HBé é é é .
13) What was the documented LDH level in the following timelines?
    i) At diagnosis?
        (a) é é é é é é é .(Indicate value)
    ii) After four chemotherapy cycles?
        (a) é é é é é é é . (Indicate value)

iii) After the last cycle of Chemotherapy?

(a) é é é é é é é . (Indicate Value)

14) What is the calculated IPI score for the patient?

i) 0 (Low risk)
ii) 1 (Low Intermediate risk)
iii) 2 (Intermediate risk)
iv) 3 (High risk)
v) 4 (High risk)
vi) 5 (High risk)

SECTION THREE.

1) What was the patients ECOG status?
   i) 0-Fully active
   ii) 1-Ambulant but restricted strenuous activity
   iii) 2-Ambulant (up and about) > 50% of waking hours but unable to do light chores
   iv) 3-Confined to a chair/bed >50% of waking hours
   v) 4- Completely disabled, canôt self-care
   vi) 5- Dead

2) Which of the following treatments did the patient receive upfront?
   i) Chemotherapy alone
   ii) Radiotherapy alone
   iii) Both (a) and (b)
3) Which chemotherapy regimen was given?
   i) CHOP
   ii) CHOP + Rituximab
   iii) MACOP-B
   iv) COP
   v) Others (specify)é é é é .
4) How many cycles of chemotherapy were administered?
   i) 4
   ii) 6
   iii) 8
   iv) Other (specify)é .
5) What was the dosage of Gray (Gy) administered to the patient?
   i) é é é é é . (Specify)
6) Did the patient receive any alternative therapy?
   i) Palliative care
   ii) Surgery
   iii) Palliative surgery
7) What was the documented health status at point of completion of therapy?
   i) Specifyé é é é é é é é é é é é é ..

8) Did the patient relapse in the course of treatment?
    i) Yes
    ii) No
9) If answer is yes above, indicate the 2nd line course of chemotherapy
    i) Specifyé é é é é é é é é é é é ..

Appendix I: KNH-UON ERC Research Permit approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KENYATTA NATIONAL HOSPITAL APPROVED 21 MAR 2018 KNH/UoN-ERC P.O. Box 20723-00202 NRB.

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/110

21st March, 2018

Dr. Dominic Munene Mutura
Reg. No.H58/80997/2015
Dept.of Clinical Medicine & Therapeutics
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Mutura

RESEARCH PROPOSAL - CLINICAL AND PATHOLOGIC FEATURES OF NON-HODGKIN'S LYMPHOMA AMONG PATIENTS SEEN AT KENYATTA NATIONAL HOSPITAL (P723/12/2017)

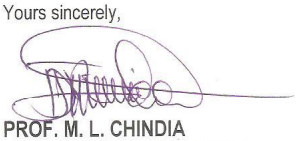
This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 21st March 2018 – 20th March 2019.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) 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

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chairperson, KNH-UON ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Clinical Medicine & Therapeutics, UoN
Supervisors: Prof. N.A. Othieno-Abinya, Dr. Joseph M.D. Maina, Dr.Marybeth C. Maritim,
Dr. Andrew Gachii, Dr. Catherine N. Nyongesa

Appendix J: KNH Research Permit approval

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

Tel: 2726300/2726450/2726550
Fax: 2725272
Email: knhadmin@knh.or.ke

Ref: KNH/AD-MED/42B/VOL.I/

Date: 27th March 2018

Dr. Dominic Munene Mutura
Department of Clinical Medicine & Therapeutics
School of Medicine
College of Health Sciences
University of Nairobi

RE:APPROVAL TO CONDUCT A STUDY IN MEDICINE DEPARTMENT

Following approval of your study by the KNH/UoN ERC and completion of the KNH study registration certificate, permission is hereby granted for you to collect data from Medicine Department to enable you complete your study on ***"Clinical and pathologic features of non-Hodgkin's lymphoma among patients" at*** Kenyatta *National Hospital, Nairobi County, Kenya.*

Kindly liaise with the Senior Assistant Chief Nurse Medicine Department for facilitation.

DR. P.ETAU
HOD - MEDICINE

Copy to: Senior Assistant Chief Nurse - Medicine

Appendix K: Study Registration Certificate

KNH/R&P/FORM/01

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

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

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   DR DOMINIC MUNENE MUTURA.
2. Email address: munenedominic@gmail.com Tel No. 0721359620
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
   CLINICAL AND PATHOLOGICAL FEATURES OF NON-HODGKINS LYMPHOMA AMONG PATIENTS SEEN AT KENYATTA NATIONAL HOSPITAL
6. Department where the study will be conducted ..... INTERNAL MEDICINE
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the Department where the study will be conducted.
   Name: ..... Signature ..... Date .....
8. Endorsed by KNH Head of Department where study will be conducted.
   Name: ..... Signature ..... Date 29/3/18
9. KNH UoN Ethics Research Committee approved study number P723/12/2017
   (Please attach copy of ERC approval)
10. I DR DOMINIC MUNENE MUTURA. commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
    Signature..... Date 26.03.2018
11. Study Registration number (Dept/Number/Year) Medicine /135/_____
    (To be completed by Research and Programs Department)
12. Research and Program Stamp _____

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

KENYATTA NATIONAL HOSPITAL
29 MAR 2018
P.O. Box 20723 - 00202 NAIROBI
Research Resource Centre

Version 2: August, 2014