IMMUNOHISTOLOGICAL TYPES OF HEAD AND NECK LYMPHOMAS AND THEIR CORRELATION TO HIV STATUS AMONG PATIENTS AT MUHIMBILI NATIONAL HOSPITAL.

Philemon Raphael, MD

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Muhimbili University of Health and Allied Sciences

College of Medicine

School of Clinical Medicine

Department of Otorhinolaryngology

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By

Philemon Raphael

This Dissertation is Submitted as a Partial Fulfillment Required for the Master of Medicine's Degree in Otorhinolaryngology at

Muhimbili University of Health and Allied Sciences

October, 2024.

CERTIFICATION

This signed document below certifies their recommendations hereby for acceptances of the dissertation titled "**Immunohistological types of head and neck lymphomas and their correlation to HIV status among patients at Muhimbili National Hospital** " as a requirement in partial fulfillment for the Master of Medicine's Degree in Otorhinolaryngology at Muhimbili University of Health and Allied Sciences.

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Dr. Daudi Ntunaguzi
(Supervisor)

Date_____

_____

Dr. Henry Swai
(Co-Supervisor)

Date: _____

DECLARATION AND COPYRIGHT

I, Philemon Raphael, declare that this dissertation is my original work and hereby acknowledge that it has not been / will not be presented elsewhere or at any other university) for a similar purpose.

Signature…… **Date**…….

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DEDICATION

This dissertation work is directly dedicated to my family, especially my lovely wife Lilian, our Son (Aldrich), and our parents from whom I deviated their valuable time to pursue this further study of Master of Medicine in Otorhinolaryngology at Muhimbili University of Health and Allied Sciences. I really appreciate their patience and encouragement throughout, may God bless them abundantly.

ABSTRACT

Background: Lymphoma is a heterogeneous and uncontrolled proliferation of lymphoid cells (i.e., B cells and T cells or natural killer cells). Recently, according to the literature, there has been a gradual but remarkable 3-4% annual increase in the occurrence of lymphocytic malignancy in the whole population. Although it has been revealed to be among the most common acquired immunodeficiency syndrome-defining malignancies, its trend in the head and neck was not reported in Tanzania.

Broad objective: This study was meant to determine the Immunohistological types of head and neck lymphomas and their correlation to Human immunodeficiency virus (HIV) status among patients diagnosed at Muhimbili National Hospital during the study period.

Methodology: This was a retrospective cross-sectional study (with data coverage between January 2021 to December 2023), and study duration was 6 months. The study involved 280 patient's medical records with diagnosis of head and neck lymphoma at Muhimbili National Hospital. Data including patient's age, sex, HIV status, histology and immunohistochemistry results were collected from the Hospital medical records (both from soft and hard files). Statistical Package for the Social Sciences (SPSS-25) and Microsoft Excel were used for analysis. Categorical variables were summarized through tables using frequencies and percentages, while the Pearson correlation coefficient was applied to determine the correlation relationship between HIV status and head and neck Lymphomas variables, Chi-square test was used to determine the association between variable findings, and their significance level was set at $p < 0.05$ with a confidence interval of 95%.

Results; The study involved 280 head and neck Lymphomas. Their ages ranged between 1 to 83 years, the common age group was 21- 40 years (29.3%) with mean age and standard deviation of 37.76 and 20.47 years respectively. There was slightly male predominance 155 (55.4%) with male to female ratio of 1.3:1.

Non-Hodgkin lymphomas **(**NHL) was the common type 210(75.0%) mostly involving age group 41- 60 years (32.4%) and males 122(58.1%) with male to female ratio of 1.4 :1. Hodgkin lymphomas (HL) was common in females 37(52.9%) and age group of 21-40 years (38.6%). These findings were statistically significant (P – value = 0.028)

For HL subtypes, the Classical variant was the most common (74.3%), more in males 27 (51.9%). It presented with bimodal peaks in age groups 1-20 and 21-40 years both rating 36.5%. In cases of NHL subtypes, diffuse large B cell lymphoma was the most common variant 108(51.4%) counting more in males 64(59.3%) and involved all age groups. These findings were not statistically significant (p – values > 0.005)

Of all 280 patent's medical records, HIV status documentations were only obtained in about 176(62.9%). Whereby regarding HL, 14(34.1) tested HIV positive. Among 135 patients with NHL, 41(30.4) were HIV positive. Pearson correlation coefficient for HL to HIV status was -0.070 and 0.116 for the NHL. All of these findings were not statistically significant with P-values of 0.667 and 0.181 respectively.

Conclusion: In this study, 75% of all participants had non-Hodgkin lymphomas. diffuse large B cell lymphoma comprised > 50% of all NHL subtypes and affected all age groups. Peripheral T-cell lymphomas became second instead of follicular cell lymphomas as reported by most studies from different parts of the world. The proportion of Nodular lymphocytes predominant HL was found to be relatively higher (25.7%), and in our setting classical HL had bimodal peaks in age groups 1-20 and 21-40 years. A weak positive correlation was found between types of NHL to HIV status.

Recommended are more emphasize on increasing diagnostic and treatment requirement supply for diffuse large B cell lymphoma, improvement in documentation of patient's medical records by clinicians, HIV screening in patients with non-Hodgkin Lymphomas.

TABLE OF CONTENTS

CERTIFICATION i
DECLARATION AND COPYRIGHT ii
ACKNOWLEDGEMENT iii
DEDICATION iv
ABSTRACT v
LIST OF TABLES x
LIST OF FIGURES x
ABBREVIATIONS LIST xi
DEFINITIONS OF TERMS xii
CHAPTER ONE 1
1.0 INTRODUCTION 1
1.1 Background 1
1.2 Problem statement 7
1.3 Conceptual framework 8
1.5 Main Research Question 9
1.6 Objectives 10
CHAPTER TWO 11
2.0 LITERATURE REVIEW 11
2.1 Types of head and neck lymphoma (Hodgkin and non-Hodgkin) and their distribution to age and sex. 12
2.2 The Immunohistological subtypes of head and neck lymphomas 13
2.3 HIV status among patients with head and neck lymphoma types. 13
2.4 The correlation of head and neck lymphoma types with the HIV status of the patients 14
CHAPTER THREE 16
3.0 METHODOLOGY. 16
3.1 Study design 16
3.2 Study duration 16

3.3 Study Area 16
3.4 Study population, ... 17
3.5 Sample size and selection 17
3.6 Sampling Strategy 18
3.7 Inclusion and Exclusion Criteria 18
3.8 Definition of Variables 18
3.9 Data collection methods and techniques 18
3.10 Investigation tools, validity, and reliability 19
3.11 Data analysis 19
3.12 Ethical issues 19
3.13 Study limitation and mitigation 19
3.14 Dissemination plan 20
CHAPTER FOUR 21
4.0 RESULT S 21
4.1 Age and sex distribution of the study participants at MNH 21
4.2 Types of head and neck lymphomas and their distribution to age and sex at MNH 22
4.3.0 Subtypes of Hodgkin and non–Hodgkin Lymphomas at MNH by sex 23
4.3.2 Subtypes of Hodgkin and non–Hodgkin Lymphomas at MNH by Age 24
4.4 To assess the HIV status among patients with head and neck Lymphomas 25
CHAPTER FIVE 27
5.0 DISCUSSION 27
CHAPTER SIX 30
6.0 CONCLUSION AND STUDY RECOMMENDATIONS. 30
6.1 Conclusion 30
6.2 Study Recommendations. 30
REFERENCES 31
APPENDICES 38
Appendix 1: Data Extraction Tool 38
Appendix 2: Ethical Clearances 40

Appendix 3: Introduction Letter 42
Appendix 4: Permission Letter 43
Appendix 5: Similarity Index.....44
Appendix 6: Waiver of Consent 45

LIST OF TABLES

Table 1: Age and sex distribution of study participants 21

Table 2: Types of Head and neck Lymphomas by age and sex 22

Table 3: Hodgkin and Non – Hodgkin Lymphomas subtypes by Sex 23

Table 4: Hodgkin and Non–Hodgkin Lymphomas subtypes by Age group 24

Table 5. Correlation of head and neck lymphomas to HIV status 26

LIST OF FIGURES

Figure 1: Conceptual framework 8

Figure 2: HIV status among patients with head and neck lymphomas 25

ABBREVIATIONS LIST

AIDS	–	Acquired Immuno-Deficiency Syndrome
CHL	-	Classical Hodgkin Lymphoma
EBV	-	Epstein-Barr virus
HBV	-	Hepatitis B virus
HIV	-	Human Immunodeficiency Virus
HL	-	Hodgkin Lymphoma
HTLV-1	-	Human T-cell lymphoma/leukemia
Ig	-	Immunoglobulins -A, G, M and D
IHC	-	Immunohistochemistry
MALT	-	Mucosa - associated lymphatic tissue
ML	-	Malignant Lymphoma
MNH	-	Muhimbili National Hospital
MUHAS	-	Muhimbili University of Health and allied Sciences
NHL	-	Non-Hodgkin Lymphomas
NK cells	-	Natural killer cells
SPSS	-	Statistical Package for the Social Sciences

DEFINITIONS OF TERMS

Lymphomas are the heterogenous and uncontrolled proliferation of lymphoid cells (i.e., B cells and T cells/NK cells.

Hodgkin Lymphoma is an uncommon monoclonal lymphoid tumor characterized by large mononuclear Hodgkin and multinucleated Reed-Sternberg cells background which frequently develops in cervical lymph nodes.

Non-Hodgkin Lymphoma is a lymphoid tissue neoplasm that develops from mature T cells, B cell precursors, and mature B cells.

Nodal lymphoma - Lymphoid tumor developing in the lymph nodes, spleen, thymus, and Waldeyer's ring. Except for non-Hodgkin Lymphomas whereby the spleen is regarded as extranodal

Extranodal lymphoma - lymphoid tumor developing in the sites other than lymph nodes, spleen, thymus, and the Waldeyer's ring. The extranodal sites are head and neck skin/soft tissues, central nervous system and gastrointestinal tract.

Waldeyer's ring is lymphoid tissues in the pharynx, formed by palatine, nasopharyngeal, tubal, and lingual tonsils.

Immunohistological types – These are Hodgkin and/ or Non-Hodgkin lymphomas and their subtypes.

Peripheral T cell lymphoma is a relatively rare, heterogenous neoplasm involving T Lymphocytes under NHL, with its subtypes Mycosis fungoides, primary cutaneous anaplastic large cell lymphoma, and Angioimmunoblastic T Cell Lymphomas.

Classical Hodgkin lymphomas – This is a subtype of Hodgkin Lymphomas comprising of Nodular sclerosis Hodgkin lymphomas, Mixed cellularity, lymphocytes rich and lymphocytes depleted Hodgkin lymphomas.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Lymphomas are a heterogenous clonal proliferation of undifferentiated lymphoid cells (i.e., B cells and T cells/NK cells). They are malignant tumors that originate from the lymphoreticular system and can grow from non–nodal structures (i.e., extranodal lymphoid tissues)(1,2)

The immune system consists mainly of T- and B-lymphoid cells, natural killer cells (NK- cells) are also available form of T cells. In immunological normal circumstances, these cells are within lymphoid organs (lymph nodes, spleen) and mucosa-associated lymphatic tissue (MALT). These structures are abundant within head-and-neck regions, mostly the Waldeyer's ring, oral cavity, thyroid and salivary glands (3). More than 200 lymph nodes are located around these anatomical sites of the body, which explains head and neck favorability for the development of lymphoid disease(4)

Malignant lymphomas are among the opportunistic tumors that occur commonly in Human Immunodeficiency virus infection (HIV) and acquired immunodeficiency syndrome (AIDS). This is due to low immunity and decreased immune surveillance(5–7). The contribution of genetic alteration to AIDS-related lymphomagenesis includes both multiple gene aberrations and mutation of c-myc. It is evidenced that there is chromosomal transportation between 8q24, the site of the cmyc proto-oncogene, immunoglobulin chromosomal locus, and inactivation of the tumor suppressor gene p53 (5). The surface of the cells that form the tumor, express surface immunoglobulin IgM, IgG, and IgA except for IgD (8).

HIV/ AIDS-related NHL occurs in various clinicohistopathological distinctions, developing as a result of malignant transformation of B cell replication components(5). Although the pathogenesis for AIDS-related non-Hodgkin lymphoma is not elucidated, immunosuppression has been considered whether it is from HIV/AIDS or therapy (9)

Several important factors are probably taken into account including the immune status of the host and the pathogenetic pathway since the tumor progenitors are influenced by distinct transforming events. The last factor is cell derivation whereby during different stages of cell differentiation, it gives rise to various tumors. This influences the biological features of the lymphomas and accounts for their pathogenetic(5)

Classification of Lymphomas

The World Health Organization recently classified them into two large groups, these are Hodgkin and non-Hodgkin Lymphomas(8,10).

Hodgkin Lymphomas are uncommon monoclonal lymphoid tumor characterized by large mononuclear Hodgkin and multinucleated Reed-Sternberg cells background which frequently develops in cervical lymph nodes. These cells are surrounded by non-neoplastic inflammatory cells, and the distinctive neoplastic cells are frequently encircled by T lymphocytes. Hodgkin Lymphoma are all B cells in origin and are further subclassified into classical and non-classical. The classical HL includes nodular sclerosis, Lymphocyte-rich, Mixed cellularity, and Lymphocyte-depleted classical Hodgkin lymphoma while the nodular lymphocyte-predominant Hodgkin lymphoma is the only form of non-classical HL. The later lacks Reed-Sternberg cells background but has features of lymphocyte-predominant cells referred to as popcorn cells (8,11–13)

Non-Hodgkin lymphomas are type of cancerous neoplasm developing in the lymphoid tissues, primarily the lymph nodes. Chromosomal translocation, different poisons, infections, and persistent inflammation may all contribute to the development of these malignancies. Clinically, NHL is termed as low or high-grade referring to indolent or aggressive neoplasm respectively(8,12).

They are further subclassified into precursor B-cell neoplasms, Mature (peripheral) B-cells, and T Cells together with Natural killer cell neoplasms(8). Precursor B-cells neoplasm **i**ncludes precursor B-lymphoblastic leukemia/lymphoma (i.e., precursor B-cell and acute lymphoblastic leukemia).

Mature (peripheral) B-cell lymphomas include diffuse large B-cell lymphoma (the far most common NHL subtype), Burkitt lymphoma, Burkitt cell leukemia, B-cell prolymphocytic leukemia, Hairy cell leukemia, Splenic marginal zone B-cell lymphoma, Plasmacytoma, Plasma cell myeloma, Follicular lymphoma, Mantle cell lymphoma, Nodal marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma of MALT type, Primary effusion lymphoma, Mediastinal large B-cell lymphoma, Lymphoplasmacytic lymphoma Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia and Lymphoplasmacytic lymphoma.

HIV-related NHL are mostly from B cells and are grouped into three distinct histologic categories, including anaplastic large-cell lymphoma, small-non-cleaved-cell lymphoma, and diffuse large-cell lymphoma (DLCL)**.** Others are unclassifiable with features intermediate between DLBCL and classical Hodgkin lymphoma, those are among the types to name a few(8,14–16).

Mature T and NK cell neoplasms

Are precursor T-lymphocytic leukemia, T-cell prolymphocytic and T-cell large granular, chronic lymphoproliferative disorder of NK cells, and aggressive NK-cell leukemia, adult human T-cell lymphoma/leukemia (HTLV1), extranodal NK/T-cell lymphoma (nasal type), peripheral T Cell Lymphomas (Mycosis fungoides/Sezary syndrome, anaplastic large cell lymphoma, primary cutaneous type) as well as systemic EBV+ T-cell lymphoma of childhood etc.(8,11)

The etiological risk factors of lymphoma

The predisposing factors of lymphoma are not clearly understood, only a few are known including immunodeficiency illnesses (e.g., diabetes mellitus and other chronic morbidities): autoimmune diseases, infections like bacteria and viruses (including HIV, HTLV-1, EBV, HCV, HBV, etc.). Others include environmental factors, occupational exposure to herbicides and pesticides, hair dyes, smoking, consuming foods with high animal fat, receiving blood transfusions, and genetic factors that have been identified as predisposing to lymphoma.(1,8,14)

Clinical presentation

Differential diagnosis of adenopathy involving thyroid and/or salivary gland, Waldeyer's ring (WR), nasal cavity, and the paranasal sinuses should include lymphomas (75% are nodal and 25% are extranodal)(14). Other presentations including fever, night sweats, weight losses known as B symptoms, and neck masses/lymphadenopathy in the cervical and/or supraclavicular regions. Some patients present with enlargement of other lymphatic organs like the spleen and tonsils. Symptoms due to infiltration of other organs particularly bone marrow (cytopenia) and Autoimmune diseases e.g., Sjogren's syndrome, rheumatoid arthritis, and Hashimoto's thyroiditis (17)(8,13,14)

Staging is according to Ann Arbor Staging System for Hodgkin Lymphoma (13,14) and its modification (i.e., Lugano classification for NHL) which includes the number and site of lymph nodes region involved (whether nodal or extranodal) concerning the side of the diaphragm as stipulated in the following table.

Ann Arbor Staging System for Lymphoma(14)

STAGE	INVOLVEMENT
I	Single extra lymphatic site or Single lymph node region or lymphatic structure
II	2 or more lymph node regions on the same side of the diaphragm, and it may or may not be accompanied by localized extra lymphatic site or organ
III	Both sides of the diaphragm's lymph nodes may be accompanied by the inclusion of the spleen or by localized extra lymphatic site or organ
IV	1 or more extra lymphatic organs or tissues which is Diffuse or disseminated with or without lymph node involvement.

Diagnosis of lymphomas is by histopathological examination on tissue biopsy. However, this method is not sufficient to diagnose the subtypes, at this point, Immunohistochemistry (IHC) has emerged to play a very crucial role in the identification of subtypes,(18,19) IHC allows a more precise diagnosis and characterization of the lymphoma.(20)

There are many recommended Immunostaining for Hodgkin Lymphoma. For instance, in Classical HL, CD3, CD15, CD20, CD30, CD45, CD79a, and PAX5. Those CHL cells expressing Reed-Sternberg background, are positive for CD30 in all patients and CD15 in most patients while CD20 may be positive in < 40% of patients but CD3 and CD45 are normally negative(13).

Recommended immunostains for NHL, particularly B-cell associated antigens are positive for CD 19, 20, 22, 79a) and negative for CD5 and CD 10. The later antigens characterize small lymphocytic lymphoma, mantle cell lymphoma, and follicular lymphoma. Among them CD23, CD43, and CD11c remain uncertain CD5, CD19, CD22, CD20, CD24, CD79a, and bcl-2 are expressed by cells of mantle lymphoma but they do not express CD10, CD23, or bcl-6 (8).

Other methods include flow cytometry, Molecular methods/testing like specific mutations of the tumor e.g., translocations(21,22)

Non – neoplastic proliferative reaction

Occasionally non – neoplastic proliferative reaction (e.g., Castleman disease) occurs in head and neck lymph nodes, adenoids, and tonsils and this is more common in the pediatric population. Most of these reactions do not usually require biopsy because the histopathological examination is not indicative, and they are non-specific, only a microscopic review can strongly suggest proper etiology(23). Immunohistochemistry, flow cytometry, cytogenetics, and molecular testing can be required to correctly characterize a reactive proliferation to discriminate it from neoplastic lymphomas(20,23)

Treatment of Hodgkin lymphoma

Combined chemoradiotherapy is the most standard mode of treatment, chemotherapy is usually with antibody-drug conjugates, Most HL are chemosensitive with a survival rate of 86%. (24,25). For NHL varies depending on the kind, stage, histology, and symptoms including stem cell transplant, immunotherapy, radiation, and chemotherapy, few situations require surgery. Radiotherapy is used to treat stage I and stage II while chemotherapy and immunotherapy (e.g., rituximab coupled with chemotherapy) are used to treat stage II with bulky disease, stage III, and stage IV (25–27)

1.2 Problem statement

The head and neck lymphoma remains the most common non-epithelial malignancy worldwide. Recently, its prevalence has been increasing gradually but noticeably among all demographic groups, however, the common lymphoma subtypes occurring in our local setting are unknown.

Malignant lymphomas are among the tumors that occur commonly with 20 folds increased risk in patients with Human Immunodeficiency virus infection (HIV) and acquired immunodeficiency syndrome (AIDS). Chronic illnesses such as HIV usually present with marked immunosuppression effects. This accounts for the number of opportunistic morbidities adding up the effect to lymphoma. All of these affect an individual's quality of life physically, and cosmetically, and even the treatment modality becomes challenging due to the immunosuppressive state.

However, very little was found to be known regarding the types and subtypes of lymphoma in the head and neck region. And they were all inadequately investigated in developing countries, for both the general population and people living with HIV/ AIDS.

This study gap led to limited information and awareness about the common head and neck lymphoma subtypes and their correlation to HIV. Most of which were only diagnosed in late stages and incidentally. To be specific, in Tanzania, there was no published research specifically on lymphoma in the head and neck region

1.3 Conceptual framework

The conceptual framework for this study is to describe the Immunohistological types of the head and neck Lymphoma and their correlation to HIV status among patients at MNH as a Retrospective Study.

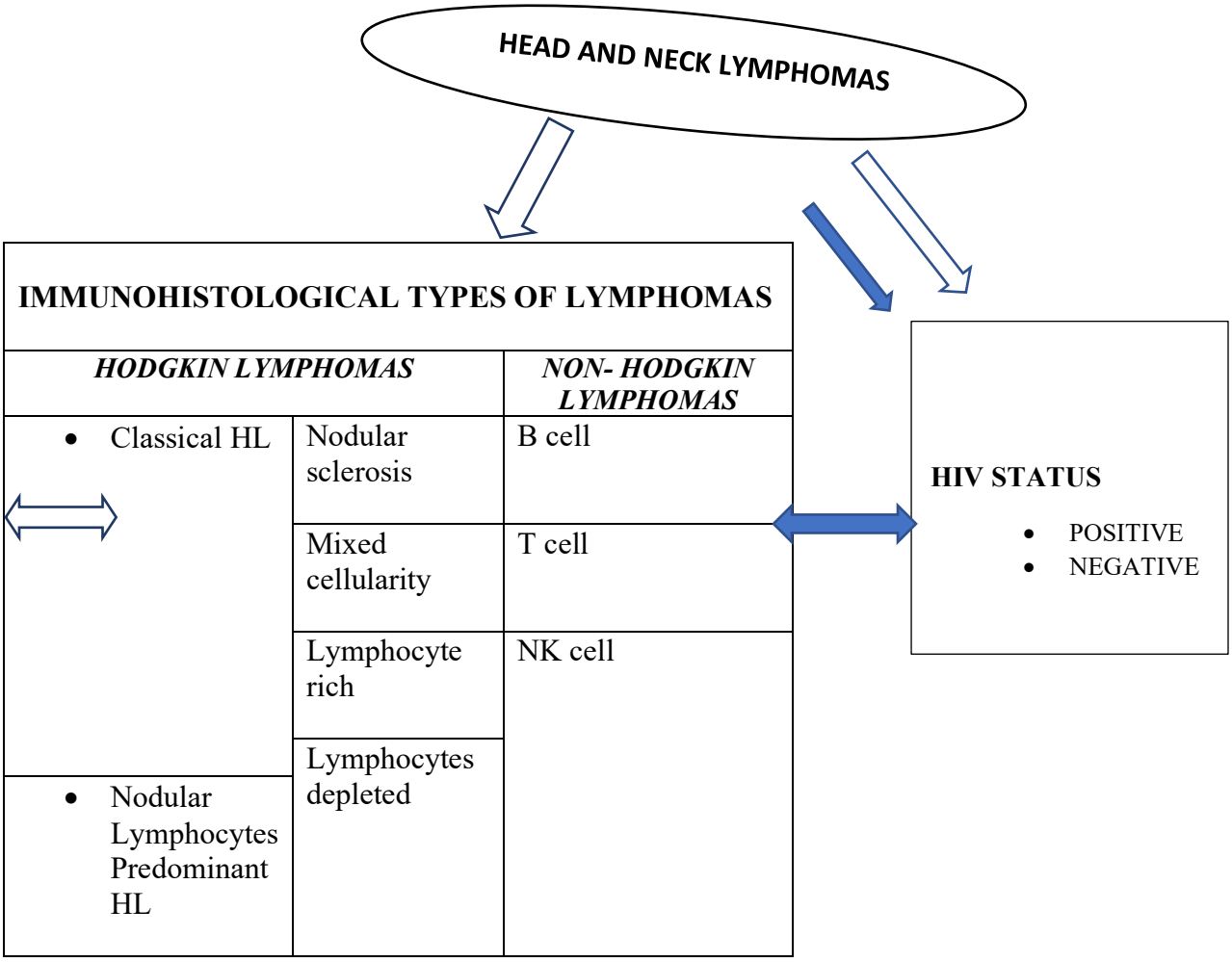


Figure 1: Conceptual framework

1.4 Rationale

This study will raise awareness about the common head and neck lymphoma types and subtypes (particularly in people with HIV and AIDS) among otorhinolaryngologists, oncologists, pathologists and other healthcare providers. This study's findings will provide the foundation for the Ministry of Health and other policy makers as well as stakeholders for further studies concerning lymphomas and allocation of required resources. This study is also a mandatory requirement in partial fulfillment for the award of a master of medicine degree in otorhinolaryngology at MUHAS.

1.5 Main Research Question

What are the Immunohistological types of head and neck lymphomas and their correlation to HIV status among patients at MNH between January 2021 to December 2023?

1.5.1 Specific Research Questions

1. What are the types of diagnosed head and neck lymphoma among patients who attended Muhimbili National Hospital between January 2021 to December 2023?
2. What are the subtypes of diagnosed head and neck Hodgkin and non-Hodgkin lymphomas among patients who attended Muhimbili National Hospital between January 2021 to December 2023?
3. What is the HIV status in patients diagnosed with head and neck lymphomas at Muhimbili National Hospital between January 2021 to December 2023?
4. What is the correlation between head and neck lymphoma and HIV status in patients at Muhimbili National Hospital between January 2021 to December 2023?

1.6 Objectives

1.6.1 Broad objective

To determine the Immunohistological types of head and neck lymphomas and their correlation to HIV status in patients at Muhimbili National Hospital.

1.6.2 Specific objectives

1. To determine the types of head and neck lymphomas at Muhimbili National Hospital.
2. To determine the subtypes of head and neck Hodgkin and non-Hodgkin lymphomas at Muhimbili National Hospital.
3. To assess the HIV status in patients with head and neck lymphoma at Muhimbili National Hospital.
4. To determine the correlation of head and neck lymphoma types to the HIV status of the study participants at Muhimbili National Hospital.

CHAPTER TWO

2.0 LITERATURE REVIEW

Otolaryngologist most frequently encounter patients who present with head and neck lymphoma(2). Lymphoma of the head and neck region is reported (between the years 2000 – 2007) to have a good response (i.e., good prognosis) with a 5years survival rate of 83% compared to (40-70%) of the past 25years(10,28). This necessitates the availability of information about this disease for early diagnosis and possible proper treatment.

Among malignancies of the head and neck region, lymphomas are the third most common after squamous cell cancers and thyroid cancers(2)**.** Data from the International Agency for Research on Cancer (IARC) revealed lymphoma incidence rate of 3.5% of all cancers (29). They are the most frequent malignant tumors in the head and neck region which do not originate from the epithelial lining (5%) and can arise as nodal, extranodal, or combined(30)**.**

Head and neck region is the second-most common locations after the gastrointestinal tract that is affected by extranodal non-Hodgkin lymphomas, accounting for about 5% of malignant neoplasms of the head and neck. (16). In Nigeria, the prevalence of lymphomas comprises 17.5% of all head and neck malignancies (19,30)

The Journal of Health Research published in 2015 in Tanzania reported that, of all head and neck malignancies in general, the least predominant cancer was lymphomas(31). But still, it was predominant among non-epithelial cancers. Recently there has been a gradual but remarkable (3-4% annual increment) in the occurrence of lymphocytic malignancy in the whole population(16).

2.1 Types of head and neck lymphoma (Hodgkin and non-Hodgkin) and their distribution to age and sex.

It has been reported that HL and NHL had 231,000 and 666,000 worldwide incidences respectively, and there were 24,000 and 78,000 deaths, respectively(32). This concurs with the incidence data obtained from studies done in Iran (64.5%), Iraq (76%), Southern India (78.7%), and Rwanda, all of them reported NHL predominance(33–35)

Also, the study done by Ezeldine et al in Sudan reported NHL (87.3% of cases) predominance over HL. There was a significant increase in NHL and a decrease in HL incidences significantly with age. On the same basis, males of all ages were reported to be more affected than females (36)

Globally, HL and NHL were the two major Lymphoma types (WHO). NHL is a major health concern originating from B (80-85%), T (15-20%), or natural killer NK (rare) lymphocytes(20). Even though an accurate estimate is difficult to ascertain, given the scarcity of information, it is approximated that 30,000 cases are more likely to be the annual incidence of NHL in Africa. And they are among the top ten leading causes of cancer in this region (41).

Another study done in West Africa reported that the Distribution between HL and NHL concerning age range is widely distinguished. While HL peaks twice at the age of 15 to 35 years and > 50 years old, NHL occurred at any age and its incidence was reported to increase with age, however, it predominated in adults (peaking in the seventh decade of life). Other studies done in the sub-Saharan region revealed that, both NHL and HL peak in the 20s(30,34)**.** Both Gender and age distribution concur with the findings from Poland, India(3,37), and Rwanda although HL lymphoma second peak is lacking in Rwanda (which might be explained by its population nature (few populations of individuals who are >65years old)(35)

In Tanzania, there is no study done only for head and neck lymphoma, but generally, it was revealed that most ML patients (65.3%), had localized tumors, although the spread of the disease considerably increased with aging. NHL involved individuals with ages ranging from 4 to 91 years. The effect of NHL was noticed more in males (64.08%) than females 35.92%, only the

distribution of NHL histological subtypes by sex was found to be statistically insignificant. For HL, its distribution with age follows a bimodal peak and the findings were similar to the findings observed in other studies(6,31,37)

2.2 The Immunohistological subtypes of head and neck lymphomas

Worldwide there is wide variation in the prevalence of different subtypes of non-Hodgkin's lymphoma. It is evidenced that different sub-types of NHL possess various epidemiological features(15)

The data obtained from the study done in Pakistan had findings similar to most of other studies from other regions, Burkitt's lymphoma (BL) was the most common in the B-cell of NHL while for the t-cell group, T-cell Lymphoblastic Lymphoma (TLL) was the most common subtype. Overall male gender predominance (3.3:1 ratio) was reported with BL being the most common in this gender and the median age was 8 years. (38,39)

Another study in Kuwait found large B-cell lymphoma as the most common NHL subtype and follicular lymphoma came second. Male gender was predominant, and in those patients who had diffuse large B-cell lymphoma, the median age during diagnosis was found to be 46 years old (15,36). This had corresponding findings to the study done in India (2019) whereby the Diffuse large B-cell lymphoma was the most common (> 30%) while follicular lymphoma was the second with approximately 20%, all other NHL subtypes had occurrences of < 10% (8)

In Turkey, both HL and NHL had a very distinct with slightly female gender predominance with mean age of 34 and 59 years respectively. The classical HL was predominated by mixed cellularity, followed by nodular sclerosing while lymphocyte-rich was the least subtype (2)

In Tanzania no documented findings that aim to study the head and neck lymphoma subtypes, this study has studied them and will build the foundation for future further researches.

2.3 HIV status among patients with head and neck lymphoma types.

Malignant lymphoma as one of the opportunistic tumors is frequently encountered among patients with HIV infections (including AIDS) due to low immunity and decreased immune

surveillance, After Kaposi's sarcoma, Malignant lymphoma is the second most common AIDS-defining malignancy (i.e., non-Hodgkin - including Burkitt's lymphoma (BL)] and Hodgkin's lymphoma (HL). (5–7,40)

In most countries of sub-Saharan Africa**,** HIV is a public health concern**,** and according to data, malignancies have become a morbidity burden and leading cause of death in HIV/ AIDS patients. Among others as mentioned above, non-Hodgkin's lymphoma (NHL) is one of the AIDS-defining malignancies due to its association with HIV infection(6,41). Since the error of AIDS epidemic, there has been a 2- to 3folds increase in the incidence of NHL in some countries, but to others, it has gone as much as 13fold (37).
In Rwanda, among those who were able to do serological HIV testing (< 45%), 25% tested positive of which the majority had nodal malignant lymphoma(35).

Another study done in northern Tanzania revealed an increased incidence of AIDS-related malignancies in individuals> 50 years old(41). A study done 15 years ago at Muhimbili National Hospital in Tanzania, revealed some individuals (21.6%) who were available for HIV testing of which Non-Hodgkin Lymphoma (NHL) predominated over Hodgkin Lymphoma (HL)(6). These findings necessitated the need for a recent study of this area.

2.4 The correlation of head and neck lymphoma types with the HIV status of the patients

In the USA, the occurrence of non-Hodgkin lymphoma in HIV infection is well established. The high-grade NHL lymphomas account for approximately 3% of the initial AIDS-defining malignancies of studied incidences in adolescents and adults. HIV/AIDS is reported to change the demographic of lymphoma and an increment is expected in the future(9).

Despite the absence of conclusive researches that regard the increased frequency of HL in HIV settings, one of the studies done in Italy revealed that HL in patients with HIV infection is correlated with a more advanced stage, poor histology, and prognosis, as well as increased occurrence of opportunistic infections. The distribution of HL in HIV was significant as compared to the general population.(42)

Some studies regard Hodgkin lymphoma as not HIV-related malignancy, however, it is reported that HIV-positive patients are multiple times more likely to develop HL than non- HIV individuals. (6,40) More implicated subtypes were mixed cellularity (MC) and lymphocyte depletion (LD) while non-Hodgkin's lymphomas, (NHL- HIV) are mostly from B cells and are grouped into three distinct histologic categories, i.e., anaplastic large-cell lymphoma, small-non-cleaved-cell lymphoma and diffuse large-cell lymphoma (DLCL)(42)

The study done in Brazil revealed the incidence of HL in HIV to be approximately 5-fold higher than those with HIV and HL contributed more to morbidity and mortality rates (32). This is contrary to findings reported in Sub-Saharan Africa whereby there was a 2- to 3folds increase in the incidence of NHL in some countries, but to others, it has gone as much as 13fold(38).

A study done in Tanzania reported the presentation of HIV related Hodgkin disease to be distinct from non-HIV related. Most NHL in HIV positive had a presentation of generalized lymphadenopathy, apparently implicating more aggressive lymphoma as compared to the HIV-negative related malignant lymphoma(6). Recent studies have also reported positive similar findings regarding the correlation between HIV and malignant lymphoma(43,44)

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CHAPTER THREE

3.0 METHODOLOGY.

3.1 Study design

This was a hospital-based retrospective cross sectional study design whereby patient records in the Department of Pathology at Muhimbili National Hospital were retrieved and analyzed.

3.2 Study duration

The study duration was 6 months from November 2023 to March 2024. This included 3 months for data collection and 3 months spent for analysis and writing the report. The study went 3 years retrospectively specifically for medical records of patients who were already diagnosed with head and neck Lymphomas between January 2021 to December 2023 (data coverage).

3.3 Study Area

This study was conducted at Muhimbili National Hospital (Upanga campus), particularly by retrieving data of ORL and oncology patients from the pathology department's archive. Being a tertiary and National Hospital in Tanzania, MNH serves also as a teaching hospital for the Muhimbili University of Health and Allied Sciences (MUHAS). It is located at Upanga in Ilala district (with 1500 bed capacity) serving more than 1000 outpatients and currently, it has another working base in Ubungo district known as Mloganzila Hospital (with a 600-bed capacity).

The department of ORL at MNH-Upanga has two firms contributed by five units including otology, head and neck surgery, rhinology, hyperbaric, allergology, audiology, speech and language therapy. Additionally, the department has 32 beds in each of its two inpatient wards (male and female patients), all mentioned departmental units have got outpatient clinic which is usually conducted throughout the week depending on the unit for follow-up patients.

3.4 Study population,

All patients who were diagnosed with Head and neck lymphoma at Muhimbili National Hospital. The study included those patients whose primary lymphoma was diagnosed based on histopathological examination of the fine needle aspiration cytology and/ or excised tumors/ incisional biopsy through their medical records.

3.5 Sample size and selection

The study involved all patient samples diagnosed with lymphomas for the past 3years. However, the minimum sample size was calculated using Slovin's Formula. This formula is usually recommended when there is no adequate data for the study and it assumes a small population variance(45,46).

Given as follows: $n = N/(1+Ne^2)$.

Whereas denoted;

"n" is the sample size

e = marginal error of 5% = 0.05 (decided by the researcher)

N = N is the population size (Estimated 12 months population of patients with head and neck lymphoma according to MNH records).

(Total patients with Head and neck lymphoma who attended MNH in March 2023 is approx. = 73, then for 12months, 73x12 = 876)

- $n = N/(1+Ne^2)$,
- $n = 876/ \{1 + (219 \times 0.0025)\}$
- $n = 274.60815$

- The minimum sample size was 275 patients with head and neck Lymphomas

3.6 Sampling Strategy

The sampling strategy was a convenience sampling method. The study was conducted as hospital-based by retrieving records of patients who attended the ORL department at MNH. In this strategy, each patient's records that met the study's inclusion criteria were included in this study as guided by the minimum sample size within 3 consecutive years from January 2021 to December 2023.

3.7 Inclusion and Exclusion Criteria

3.7.1 Inclusion Criteria

Medical records of patients of all ages who were already diagnosed with head and neck Lymphoma and whose records were available included in this study.

3.7.2 Exclusion Criteria

Completely missing medical records or inconclusive documented records of patients for instance missing Immunohistological results and slides and/or tissue were excluded.

3.8 Definition of Variables

3.8.1 Independent Variables

The independent variables in this study were demographic characteristics - age groups measured in years and sex as male or female) and head and neck lymphomas.

3.8.2 Dependent Variables

The dependent variable in this study were HIV status and Immunohistological types and subtypes.

3.9 Data collection methods and techniques

Patient's data including age, sex, HIV status, histology and immunohistochemistry results were collected directly by the principal researcher through retrieving the well-documented information (i.e., patients' medical records) from the health information system and hard copies (files and pathology archive) at MNH

3.10 Investigation tools, validity, and reliability

Data collection used a special study preformed form (Data extraction form) to obtain patient's information from the health information system and hard copies (files and pathology archive) at MNH. Recall bias was avoided since data collection did not involve questioning patients.

These data were transferred to the data compilation template in Microsoft Excel (data entry), followed by data arrangement, careful cleaning, and processing performance in a meaningful way thereafter transferred to the SPSS - data set.

3.11 Data analysis

The data obtained were managed (analyzed) by using both Statistical Package for Social Sciences (SPSS) version 25 and Microsoft Excel. Categorical variables were summarized using frequencies and percentages (Demographic distribution data, types and subtypes of Lymphoma as well as the HIV status.,

The Pearson correlation coefficient was used to assess the correlation between HIV status and head and neck Lymphoma. coefficient of 1 was regarded as a reference point from which the presence/ absence, strength, and direction of correlation were determined. The chi-square test was used to determine the association between variables, and their significance level was set at $p < 0.05$ with a confidence interval of 95%.

3.12 Ethical issues

Ethical clearance was obtained through waiver of consent from MUHAS Institutional Review Board. Permission to conduct the study was approved by the Institutional Review Board at MNH. and the findings obtained from the study have been reviewed again by supervisors from the Otorhinolaryngology department from both MUHAS and MNH before final submission.

3.13 Study limitation and mitigation

Missing clinical records particularly HIV status was expected study limitations, and it was resolved by analyzing the respective specific objective only among those who had complete data records.

3.14 Dissemination plan

The findings were presented before the panel in the Department of Otorhinolaryngology at MUHAS, then the approved dissertation has to be submitted to MUHAS, as a mandatory requirement for the Master of Medicine degree in Otorhinolaryngology program. Thereafter, a manuscript will be prepared hoping for future publishing of the study findings in appropriate national and/ or international journals.

CHAPTER FOUR

4.0 RESULT S

4.1 Age and sex distribution of the study participants at MNH

This study involved 280 patients aged 1- 83 years with head and neck Lymphomas at MNH. Among them, the most commonly involved age group was 21- 40 years 82 (29.3%). The mean age and standard deviation were 37.76 and 20.47 years respectively.

Among those 280 patient's medical records, there was slightly male predominance 155 (55.4%) with male to female ratio of 1.3:1 (Table 1).

Table 1: Age and sex distribution of study participants

Age group	Sex		Total
	Male (%)	Female (%)	
1 - 20	48 (64.9)	26 (35.1)	74 (26.4)
21- 40	48 (58.5)	34 (41.5)	82 (29.3)
41- 60	41 (51.9)	38 (48.1)	79 (28.2)
61- 80	15 (36.6)	26 (63.4)	41 (4.6)
> 80	3 (75.0)	1 (25.0)	4 (1.4)
Gland Total	155 (55.4)	125 (44.6)	280 (100.0)

4.2 Types of head and neck lymphomas and their distribution to age and sex at MNH

Among 280 study participants, majority of them, 210(75.0%) had non-Hodgkin lymphomas which were more common in males 122(58.1%) with male to female ratio of 1.4 :1

Hodgkin lymphomas counted only for a quarter fraction of total histopathological diagnoses 70(25%) and it was higher in females 37(52.9%) with male to female ratio of 1.1 :1. All these findings, were not statistically significant

The most common age group among patients with NHL was between 41- 60 years (32.4%). For those patients who had HL, the most common age group was 21-40 years (38.6%). All these findings, were statistically significant (P – value = 0.028) **as** illustrated in Table.2

Table 2: Types of Head and neck Lymphomas by age and sex

		Histopathology			
		Hodgkin Lymphomas (%)	**Non-Hodgkin Lymphomas (%)**	**Grand Total**	**P-value**
Sex	Male	33(47.1)	122(58.1)	155(55.4%)	
	Female	37(52.9)	88(41.9)	125(44.6%)	0.126
Total (%)		70(25.0%)	210(75. %)	280(100%)	
	1- 20	23(32.9)	51(24.3)	74(26.4%)	
Age	21- 40	27(38.6)	55(26.2)	82(29.3%)	
group	41- 60	11(15.7)	68(32.4)	79(28.2)	
	61- 80	9 (12.9)	32(15.2)	41(14.6)	0.028
	> 80	0	4(1.9)	4(1.4)	
Total (%)		70 (25.5)	210 (75.5)	280(100%)	

4.3.0 Subtypes of Hodgkin and non–Hodgkin Lymphomas at MNH by sex

Among observed HL subtypes, the Classical variant was the most common (74.3%) and this counted more in males 27 (51.9%).

In cases of NHL, diffuse large B-cell lymphomas (DLBCL) were by far the most common variant 108(51.4%) with male preponderancy 64(59.3%).

In the same regard of NHL, the least common subtypes were Marginal zone Lymphomas and primary CNS lymphomas (both counted to be 0.48% and only observed in females). In all aspects, the differences were not statistically significant (Table 3.)

Table 3: Subtypes of Hodgkin and Non – Hodgkin Lymphomas by Sex

Immunohistology	**SEX *(n=280)***			
	Female (%)	**Male (%)**	**Total (%)**	**Fisher's exact test**
Hodgkin Lymphomas subtype	37(52.9)	33(47.1)	70(25.0)	
Classical Hodgkins Lymphomas	25(48.1)	27(51.9)	52(74.3)	0.137
Nodular lymphocyte predominant HL	12(66.7)	6(33.3)	18(25.7)	
Non-Hodgkin Lymphoma subtype	88(41.9)	122(58.1)	210 (75.0)	
Adult T cell lymphomas /Leukemia	1(33.3)	2(66.7)	3 (1.4)	
B- cell Lymphoblastic Lymphomas	3(100)	0	3 (1.4)	
Burkitt Lymphomas	5(71.4)	2(28.6)	7 (3.3)	
Diffuse Large B Cell Lymphomas	44(40.7)	64(59.3)	108 (51.4)	
Extra-nodal NK/T -cell Lymphomas	0	2(100)	2 (0.95)	
Follicular cell Lymphomas	6(46.2)	7(53.8)	13 (6.2)	0.588
Lymphoplasmacytic Lymphomas	3(50.0)	3(50.0)	6 (2.9)	
Mantle Cell Lymphomas	1(33.3)	2(66.7)	3 (1.4)	
Marginal zone Lymphomas	1(100)	0	1 (0.48)	
Peripheral T- T-cell lymphomas	11(29.7)	26(70.3)	37 (17.6)	
Primary CNS Lymphomas	1(100)	0	1 (0.48)	
Small lymphocytic lymphomas	6(42.9)	8(57.1)	14 (6.7)	
T-Cell Lymphoblastic Lymphomas	6(6.8)	6(4.9)	12 (5.7)	
Grand Total	125(100)	155(100)	280(100.0)	

4.3.2 Subtypes of Hodgkin and non–Hodgkin Lymphomas at MNH by Age

Regarding Immunohistological subtypes, among 70 patients with HL, the Classical variant was the most common (74.3%), more in males 27 (51.9%). It presented with bimodal peaks in age groups 1-20 and 21-40 years both rating 36.5%, nodular lymphocyte predominant Hodgkin lymphoma was more common in the age group (21-40) years by 44.4%. None of them was found to affect age > 80 years.

For NHL subtypes, only DLBCL was found across all age groups and surprisingly it was the only variant whose patients aged >80 years. Three variants, extranodal NK/T cell lymphoma, Marginal zone, and Primary CNS, all were only found in one particular age group 41- 60, 21-40, and 1- 20 years respectively. All of these findings were not statistically significant with p-values of 0.350 and 0.214 respectively (Table 4.)

Table 4: Subtypes of Hodgkin and Non–Hodgkin Lymphomas by Age group

Immunohistology	**Age Groups *(n=280)***						
	1-20	**21-40**	**41-60**	**61-80**	**>80**	**Total**	**Fisher's exact test**
Hodgkin Lymphomas	23(32.9)	27(38.6)	11(15.7)	9(12.9)	0	70(25.0)	
Classical Hodgkins Lymphomas	19(36.5)	19(36.5)	8(15.4)	6(11.5)	0	52(74.3)	
Nodular lymphocyte predominant	4(22.2)	8(44.4)	3(16.7)	3(16.7)	0	18(25.7)	0.350
Non-Hodgkin Lymphomas	51(24.3)	55(26.2)	68(32.4)	32(15.2)	4(1.9)	210(75.0)	
Adult T cell lymphomas /Leukemia	1(33.3)	0	2(66.7)	0	0	3(1.4)	
B- cell Lymphoblastic Lymphomas	1(33.3)	0	2(66.7)	0	0	3 (1.4)	
Burkitt Lymphomas	5(71.4)	0	0	2(28.6)	0	7 (3.3)	
Diffuse Large B Cell Lymphomas	16(14.8)	36(33.3)	35(32.4)	17(15.7)	4(3.7)	108(51.4)	
Extra-nodal NK/T-cell Lymphomas	0	0	2(2.9)	0	0	2 (0.95)	
Follicular cell Lymphomas	4(30.8)	5(38.4)	4(30.8)	0	0	13(6.19)	
Lymphoplasmacytic Lymphomas	1(16.7)	1(16.7)	3(50.0)	1(16.7)	0	6(2.9)	
Mantle Cell Lymphomas	1(33.33)	0	1(33.33)	1(33.33)	0	3(1.4)	
Marginal zone Lymphomas	0	1(100)	0	0	0	1 (0.48)	
Peripheral T- T-cell lymphomas	12(32.4)	9(24.3)	13(35.1)	3(8.1)	0)	37(17.6)	0.214
Primary CNS Lymphomas	1(100.)	0	0	0	0	1 (0.48)	
Small lymphocytic lymphomas	4(28.6)	1(7.1)	4(28.6)	5(35.7)	0	14(6,7)	
T-Cell Lymphoblastic Lymphomas	5(41.7)	2(16.7)	2(16.7)	3(25.0)	0	12(5.7)	
Grand Total	74	82	79	41	4	280	

4.4 To assess the HIV status among patients with head and neck Lymphomas

Of all 280 study participants, only **176** (62.9%) patients' records had documentation of HIV status. Others 104(37.1%) were excluded from this specific objective because of incomplete/missing HIV data.

In this regard, 14(34.1) of 41 patients with HL tested HIV positive. Among 135 patients with NHL, 41(30.4) were HIV positive. (figure2)

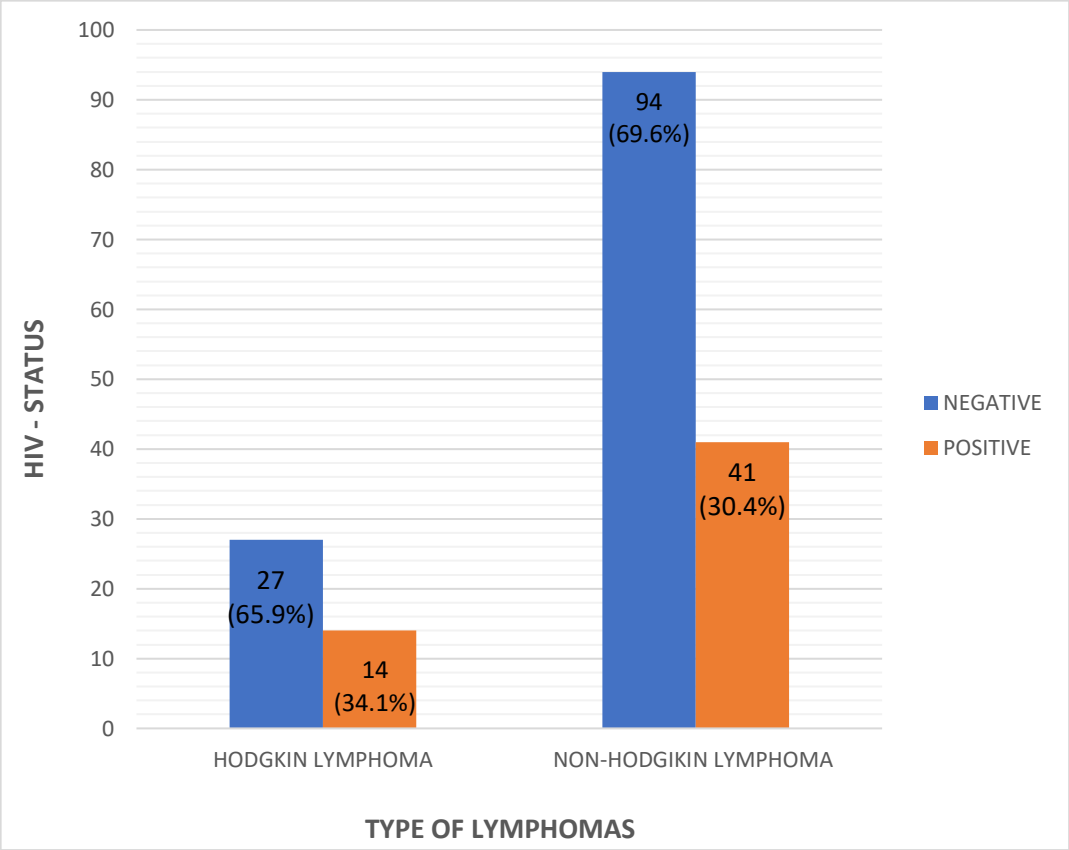


Figure 2 HIV status among patients with head and neck lymphomas

4.5 Correlation between head and neck lymphomas to HIV status

Pearson correlation coefficient for Hodgkin Lymphomas and NHL to HIV status was weak correlation with values - 0.070 and 0.116 respectively. All of these findings were not statistically significant with P- values of 0.667 and 0.181 respectively as illustrated on Table 5 below**.**

Table 5. Correlation of head and neck lymphomas to HIV status

Histology	**HIV Status *(n=176)***		**Total (%)**	**Correlation Coefficient**	**P- value**
	Negative (%)	**Positive (%)**			
Hodgkin Lymphomas	27(65.9%)	14(34.1%)	41(23.3%)	- 0.070	0.667
Non-Hodgkin lymphomas	94(69.6%))	41(30.4%)	135(76.7)	0.116	0.181
Grand Total	121	55	176		

CHAPTER FIVE

5.0 DISCUSSION

This was a retrospective study, aimed at documenting data on types and subtypes of head and neck Lymphomas among patients who were already diagnosed through Immunohistological workup. Another purpose was to determine the correlation of HIV to Lymphomas at MNH.

There were 280 Immunohistological confirmed cases of patients with head and neck lymphomas. Their age ranged from 1 to 83 years and most of their age were within the age group 21- 40 years 82 (29.3%) with mean age and standard deviation of 37.76 and 20.47 years respectively. There was slight male predominance 155 (55.4%) with male to female ratio of 1.3:1.

Similar characteristics of our study participants (gender, ratio, and mean age were all concordant with other studies done in New York, Ohio, Poland, India, Nigeria, and Tanzania(30,47,48) (3,37). On the other hand, over 50% of the study participants from a study done in Rwanda were young due to the nature of their population (few populations of individuals who are >65years old)(35).

Regarding types of head and neck lymphomas**,** among 280 study participants, the vast majority of them, 210(75.0%) had non-Hodgkin lymphomas. NHL was found to be more common in males 122(58.1%) with a male-to-female ratio of 1.4:1. NHL occurred across all age groups, but it was mostly found between 41- 60 years (32.4%) Similar to the study done in Kuwait and Rwanda to different ethnic groups(15,35).

Hodgkin lymphomas counted only for a quarter fraction of total histopathological diagnoses 70(25%) and it was higher in females 37(52.9%) with male to female ratio of 1:1.1 The most common age group among those patients who had HL, was 21-40 years (38.6%). Subjects in this category were significantly younger compared to those in the NHL as recorded similarly by Faruk et al and Fiacre et al (2,35). Almost similar findings were recorded in the study done by Dow University – Karachi and Munich-German(35,36).

On the contrary, some other studies (Storck K et al, Kamiński B et al, Ezeldine K. et al and Charalambos et al) reported a higher proportion of NHL. This might be due to differences between our sample size study design their prospective studies (3,18,36,49,50).

Another study done in West Africa, reported almost similar distribution of NHL in respect to age range but HL was reported peaking twice at the age of 15 to 35 years and > 50 years old. In our study, second peak is lacking similar to study findings in Rwanda (35). this might be explained by fewer study participants who had age > 61years (16%). Other studies done in the sub-Saharan region revealed that, both NHL and HL peak in the 20s(30,34).

In terms of Immunohistological subtypes, among observed HL subtypes the Classical Hodgkin Lymphomas variant was the most common (74.3%), and this counted slightly more in males 27 (51.9%) with male to female ratio of 1.1: 1. Also classical HL presented with bimodal peaks in two age groups 1-20 and 21-40 years both rating 36.5% at our setting. In comparison to the research done in Pakistan, Turkey and Sudan(2,18,36), our study recorded an increased proportion of Nodular lymphocyte predominancy HL and reduced occurrences of Classical HL cases. These discrepancies could be explained by differences in sample size and study design.

In cases of NHL, diffuse large B-cell lymphomas (DLBCL) were by far the most common variant 108(51.4%) with male preponderancy 64(59.3%). Similar to the study done by Marcelina et all in Poland and J.R. Anderson et al in USA (16,51), while it was different from the study done in Nigeria where Burkitt Lymphomas was observed in 25.5% of cases. as the most common NHL-variant(30). Surprisingly in this study, the second most common NHL-subtype was found to be Peripheral T-cell Lymphomas 37(17.6%) instead of follicular cell lymphoma as recorded by most of the studies for instance Ameen et al, Shahid et al, Aanaes et al(15,28,36). The most affected age group by DLBCL patients was 41- 60years, similar to the study done by Smm et al (52). The least common subtypes were Marginal zone Lymphomas and primary CNS lymphomas (both counted 0.48%) similar findings were obtained by Shamloo et al (53).

The slight alterations seen along both NHL and HL subtypes might be explained by the fact that, in our setting currently selective IHC is used rather than a full immunohistochemistry (IHC) panel increasing the chances of over/underdiagnosing these Lymphoma variants.

Also, our study assessed the HIV status among the head and neck Lymphoma patients. Of all 280 study participants, about 176(62.9%) patients' records had documentation of HIV status. Others 104(37.1%) were excluded from this specific objective because of incomplete/missing HIV data. Similar limitations were observed by Mwakigonja et al, Kaaya et al (21.6%), and Byiringiro et al (44.4%) (2,6,7,35). The reason for missing data in our setting might be explained by failure to counsel / denial of the patients for HIV testing and/or inadequate documentation.

In this regard, our study revealed a slightly increased number of patients who tested HIV positive among HL 14(34.1) and for those with NHL, 41(30.4) tested HIV positive. Other studies in Tanzania and Rwanda obtained a lower number of patients who had HIV positive(6,7,35).

A weak positive correlation (0.116) was found between NHL types to HIV status similar to the findings obtained by the study done by Mwakigonja et al (6), Kaaya et al (7) and Mremi et al (41). This can be explained scientifically by molecular alteration which takes place in HIV/AIDs individuals(54) exposing them to AIDs related malignancies like Lymphomas than in the general population(6,7,41). While for HL types, they were found negatively correlated to HIV status which was also not statistically significant.

CHAPTER SIX

6.0 CONCLUSION AND STUDY RECOMMENDATIONS.

6.1 Conclusion

In this study, 75% of all participants had non-Hodgkin lymphomas. Both NHL and HL occurred in young adult age groups but NHL was observed in older age groups. DLBCL comprised more than 50% of all NHL subtypes and affected all age groups. Peripheral T-cell lymphomas became second instead of follicular cell lymphomas as reported by most studies from different parts of the world. The proportion of Nodular lymphocytes predominant HL was found to be relatively higher (25.7%), and in our setting classical HL had bimodal peaks in age groups 1-20 and 21-40 years. A weak positive correlation was found between types of NHL to HIV status while for HL types were negatively related to HIV status.

6.2 Study Recommendations.

Regarding this study's findings in our setting as detailed above, then we kindly recommend the following;

1. More emphasize on increasing diagnostic and treatment requirement supply for diffuse large B cell lymphoma.
2. Improvement in documentation of patient’s medical records by clinicians for reference purpose whenever needed.
3. Sero-status testing for all patients diagnosed with head and neck Lymphomas and screening for lymphomas (especially NHL) in HIV -positive individuals at their respective clinics.
4. Prospective cohort study on a similar perspective, to study more detail on other related factors to head and neck Lymphomas.
5. Further advanced study regarding causal association to establish a detailed correlation between HIV and head and neck Lymphomas at the molecular level

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APPENDICES

Appendix 1: Data Extraction Tool

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

SCHOOL OF DIAGNOSTIC MEDICINE

DEPARTMENT OF OTORHINOLARYNGOLOGY

To be filled by the investigator

Part 1

Demographic characteristics - Data

1. Patient identification (MR number) ……
2. Identification to Pathology Archive (HP number) ……
3. Age of the patient ……

4. Sex of the patient
    a) Male
    b) Female

Part 2

(a) Histology -lab

1. Biopsy (Histology) results
    a) HL
    b) NHL

(b) (Immunohistology - Data)

2. Immunosubtyping results (subtype) ……

Part 3. HIV status

1. HIV- Status
    a) Positive
    b) Negative
    c) Unknown

PART 4:

Correlation of Head and Neck Lymphoma with HIV status of the patients.

Types of head and neck lymphoma	HIV status (positive/ negative/unknown)
HL	
NHL	

KEYS: HL: Hodgkin Lymphoma. NHL: Non-Hodgkin Lymphoma.

HIV: Human Immunodeficiency Syndrome

Appendix 2: Ethical Clearances

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION

Ref. No.DA.282/298/01.C/1949 Date: 23/10/2023

MUHAS-REC-10-2023-1949
PHILEMON RAPHAEL
COLLEGE OF MEDICINE
MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: IMMUNOHISTOLOGICAL TYPES AND THEIR CORRELATION TO HIV STATUS IN PATIENTS WITH HEAD AND NECK LYMPHOMA AT MUHIMBILI NATIONAL HOSPITAL

Reference is made to the above heading,

I am pleased to inform you that the Chairperson has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 23/10/2023
EXPIRATION DATE OF APPROVAL: 23/10/2024

STUDY DESCRIPTION:
Purpose:

The purpose of this retrospective cross-sectional study is to determine the Immunohistological types and their correlation to HIV status among patients diagnosed with head and neck lymphoma at Muhimbili National Hospital.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided:
https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2014801.pdf and in the MUHAS archives.

The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain data transfer agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain material transfer agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country,
8. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
9. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
10. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.

Dr. Kasusu Nyamuryekung'e

Ag. Chairperson, MUHAS Research and Ethics Committee



Appendix 3: Introduction Letter

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote;
Ref. No. HD/MUH/T.175/2021 06th November, 2023

The Executive Director,
Muhimbili National Hospital,
P.O. Box 65000,
DAR ES SALAAM

MUHIMBILI NATIONAL HOSPITAL
RECEIVED
06 NOV 2023
REGISTRY
File No:

Re: INTRODUCTION LETTER

We would like to inform you that the bearer of this letter is Phillemon Raphael with Reg. No. HD/MUH/T.175/2021 is a student at Muhimbili University of Health and Allied Sciences (MUHAS) "pursuing MMed. Otorhinolaryngology.

As part of his studies, he will be doing an elective research titled: **"Immunohistological Types and their Correlation to HIV Status in Patients with Head and Neck Lymphoma at Muhimbili National Hospital."** he is being supervised by Dr. Daudi Ntunaguzi from MUHAS and Dr. Henry Swai from MNH.

The research has been approved by the Chairman of University Senate.

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Msk Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

c.c Phillemon Raphael

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel. G/Line: +255-22-2150302/6; Ext. 1015; Direct Line:+255-22-2151378;Telefax:+255-22-2150465;E-mail:dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz

Appendix 4: Permission Letter

THE UNITED REPUBLIC OF TANZANI

MINISTRY OF HEALTH

MUHIMBILI NATIONAL HOSPITAL

In reply please quote;

Ref. No.: MNH/CRTCU/Perm/2023/552 Date: 07th November, 2023

Head of Department
- Central Pathology Laboratory
- Medical Records

Muhimbili National Hospital

RE: PERMISSION TO COLLECT DATA AT MNH

Name of Student	**Phillemon Raphael**
Title	**"Immunohistological Type and their Correlation to HIV Status in Patients with Head and Neck Lymphoma at MNH".**
Institution	Muhimbili University of Health and Allied Sciences
Supervisor	Dr. Daudi Ntunaguzi (MUHAS)
Co – Supervisor	Dr. Henry Swai (MNH)
Period	07th November, 2023 to 28th February, 2024

Approval has been granted to the above principal investigators to collect data at MNH. Dissemination of study findings at MNH shall be overseen by **Dr. Henry Swai** (MNH) supervisor.

Kindly ensure the named principal investigator abide to the ethical principles and other conditions of the research approval.

HEAD, TEACHING, RESEARCH & CONSULTANCY UNIT * MUHIMBILI NATIONAL HOSPITAL * P. O. Box 65000 DAR-ES-SALAAM

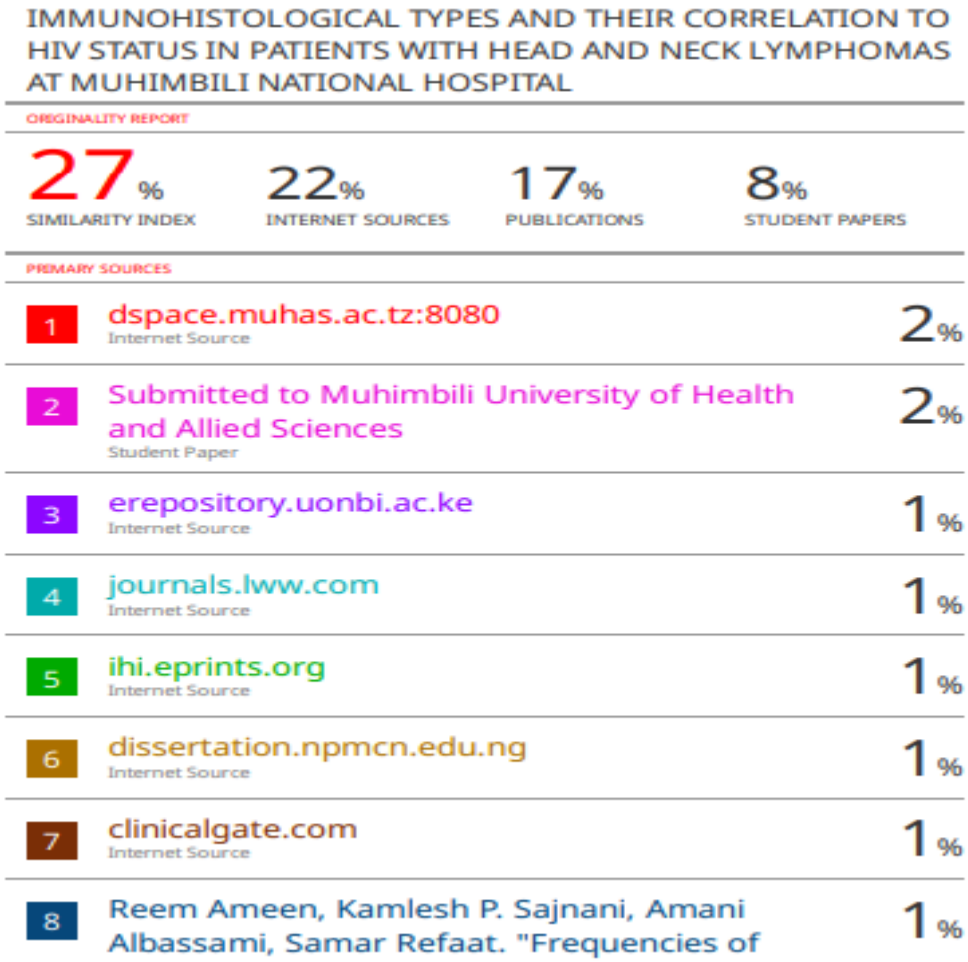
Sincerely,

Dr. Deus Buma
For: Head of Clinical Research, Training and Consultancy Unit

c.c DICT, DCSS
c.c **Dr. Henry Swai**
c.c **Phillemon Raphael**

Upanga West, Kalenga Street, Plot No. 10480/3, P.O. BOX 65000, Dar es Salaam, Tanzania.
Telephone: +255-22-2151367-9, Telephone: +255-22-2151351-2
Email: info@mnh.or.tz, Website: www.mnh.or.tz

Appendix 5: Similarity Index



IMMUNOHISTOLOGICAL TYPES AND THEIR CORRELATION TO HIV STATUS IN PATIENTS WITH HEAD AND NECK LYMPHOMAS AT MUHIMBILI NATIONAL HOSPITAL

ORIGINALITY REPORT

27%	22%	17%	8%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	dspace.muhas.ac.tz:8080 Internet Source	2%
2	Submitted to Muhimbili University of Health and Allied Sciences Student Paper	2%
3	erepository.uonbi.ac.ke Internet Source	1%
4	journals.lww.com Internet Source	1%
5	ihi.eprints.org Internet Source	1%
6	dissertation.npmcn.edu.ng Internet Source	1%
7	clinicalgate.com Internet Source	1%
8	Reem Ameen, Kamlesh P. Sajnani, Amani Albassami, Samar Refaat. "Frequencies of	1%

Appendix 6: Waiver of Consent

Waiver of consent were obtained from Institutional Review Boards of both Muhimbili National Hospital and Muhimbili University of Health and Allied Sciences.