CLINICO-PATHOLOGIC PROFILE AND TREATMENT OUTCOME OF CHILDREN WITH NON-HODGKIN'S LYMPHOMA SEEN AT HEMATO-ONCOLOGIC UNIT, TIKURANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

A RESEARCH THESIS TO BE SUBMITTED TO ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES; PEDIATRICS AND CHILD HEALTH DEPARTMENT IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE SPECIALTY CERTIFICATE PROGRAM IN PEDIATRICS AND CHILD HEALTH

BY: DURETI JEMAL (PEDIATRICS YEAR III RESIDENT)
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ADDIS ABABA, ETHIOPIA

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Contents

Acronym

MD ……..…….....Medical Doctor

U.S. ……..……...United States

NHL……..…...Non-Hodgkin Lymphoma

M……..…….....male

F…….....…….female

EBV……...…..Epstein-Barr virus

RVI……....retro viral infection

H&N……..Head and Neck

CBC……..……..……...complete blood count

Hgb……..……..…...hemoglobin

ESR……..……erythrocyte sedimentation rate

CMT……..……..……....combined modality treatment

LDH……..…….....lactate dehydrogenase

OS……..…...overall survival

PFS……..…….progression free survival

EFS……..……..…….....event free survival

DFS……..……disease free survival

SSA……..sub-Saharan Africa

IFRT……involved field radiotherapy

DPCH……...Department of Pediatrics and Child Health

SPSS…….....….Statistical Package for Social Sciences

PI……..…principal investigator

Yr……..…….year

SFOP……. Studies of the French Society of Pediatric Oncology

List of Tables

List of figures

Acknowledgment

I would like to express my deepest gratitude to Addis Ababa University College of Health Sciences, Department of Pediatrics and Child Health for allocating the budget and giving me the chance. I would like to express my respect to my advisors Dr. Solomon Tessema Memirie and Dr. Abdurkadir Gidey for their invaluable comments throughout the development of this proposal and their interest and readiness to help me until the end of the study.

Abstract

Background: Lymphoma is general term for cancers that develop in the lymphatic system and is the third most common childhood malignancy. It is classified into two broad categories, different manifestations and treatment approach: Hodgkin and non-Hodgkin lymphoma. Non- Hodgkin lymphoma accounts for approximately 60% of all lymphomas in children and adolescents with a higher incidence in sub-Saharan African (SSA) countries. With the current modality of treatment, localized NHL (stage I to II) has an approximate 95% to 100% 5-year event-free survival (EFS) and more than 80% for children with advanced-stage disease (stage III to IV). Despite the increasing burden, infrastructure for diagnosis and treatment of hematolymphoid malignancies remains inadequate in SSA. To our knowledge there is no study done in Ethiopia on NHL survival.

Objective: To assess the clinico-pathologic profile and treatment outcome of children with Non-Hodgkin's Lymphoma who sought care at pediatric oncology unit in Tikur Anbessa Specialized Hospital (TASH).

Method: We conducted a hospital-based retrospective cross sectional study at the pediatric oncology unit at TASH. The study period was from July 1st to August 31st, 2021. Data of 149 children who meet the inclusion criteria were analyzed using Statistical Package for Social Sciences (SPSS) version 25. We conducted both descriptive and analytical statistics. We run Chi square test, Log Rank test and Cox regression to assess association among the variables of interest. Kaplan Meier estimates were used for five-year overall survival analysis. P-values of <0.05 were considered statistically significant differences or association.

Result: Most (44.3%) childhood cases of NHL occurred between five to ten years of age, more commonly affecting males than females (2.38:1 ratio). More than half of the patients presented with advanced stage and commonest presentation is abdominal swelling. Burkitts lymphoma is the commonest histologic type. Advanced disease stage is significantly associated with low hemoglobin level, high LDH and older age.. In this study we did not find significant differences in the EFS rate by different prognostically relevant variables. The five year OS was 66.5% and EFS was 63.1%.

Conclusion Five year over all and event free survival for childhood NHL at TASH is lower than what has been reported elsewhere including the average in developing countries.

1. Introduction

1.1 Background of the study

Lymphoma is a type of cancer affecting cells of the lymph system. The lymph system is part of the immune system that consists of a network of lymph nodes, lymph vessels, and organs, including the thymus, spleen, and bone marrow.(1) Lymphoma can arise from any of these tissues. Lymphomas constitute 10 -15% of all childhood cancers in the more developed countries; they are third in relative frequency after acute leukemia and brain tumors.(2)The 2 broad categories of lymphoma, Hodgkin lymphoma and non-Hodgkin lymphoma, have different clinical manifestations and treatments(1).

Non-Hodgkin lymphoma (NHL) is the third most common malignant tumor in children representing approximately 8–10% of all childhood cancers in patients between 5 and 19 years. It also accounts for approximately 60% of all lymphomas in children and adolescents and predominantly affects males (male to female ratio 2.5:1) [3].

Although most children and adolescents with NHL present with de novo disease, a small number of patients have NHL secondary to specific etiologies, including inherited or acquired immune deficiencies (e.g., severe combined immunodeficiency syndrome, Wiskott-Aldrich syndrome), virus-associated malignancy (e.g., HIV, EBV), and as part of genetic syndromes (e.g., ataxia telangiectasia, Bloom syndrome) [1]. In sub-Saharan African (SSA) countries the increased incidence of NHL, compared with the rest of the world, is related to endemic malaria in many parts of this region. The development of Burkitt's lymphoma, a subtype of NHL, is associated with Epstein Barr virus and chronic malaria infection. (3) However, most children in North America and Europe in whom NHL develops have no obvious genetic or environmental etiology [1].

Pediatric NHL is mostly (more than 95%) high-grade and includes four major subtypes: Burkitt's Lymphoma (BL), Lymphoblastic Lymphoma (LBL), Diffuse Large B-cell Lymphoma (DLBCL) and Anaplastic Large Cell Lymphoma (ALCL)(4) The incidence of NHL subtypes differs among age groups. In the age group 0-14 years BL accounts 38% followed by LBL 29% and in the age group 15-19 years, DLBC accounts for 37% followed by BL 21% (1).

Among pediatric patients, endemic Burkitt's lymphoma (eBL) predominates in much of SSA, representing more than 80% of all hematologic malignancies and more than 90% of NHLs (5). Endemic Burkitt's lymphoma is almost invariably associated with Epstein-Barr virus (EBV) and follows a distribution that mirrors the malaria belt through central Africa (6),(7).

Children can experience a very wide range of symptoms when affected by NHL, depending on where in the body the lymphoma cells are present. Some common symptoms include: Enlarged lymph nodes in the neck, underarm, or groin (usually painless and firm); enlarged spleen or liver, feeling full and fatigue, difficulty breathing or cough, unexplained fevers, unintentional weight loss, or sweating profusely at night, vomiting or abdominal paincaused by obstruction from enlarged lymph nodes in intestines (2). Primary sites in childhood NHL are Abdomen (35%), mediastinum (26%) and head and neck (13%). Approximately 70% of children present with advanced–stage disease including extra nodal disease with gastrointestinal, bone marrow and central nervous system (CNS) Involvement (4).

Excisional biopsy is preferred for histopathological diagnosis and once the diagnosis of NHL is established, extent of disease (stage) should be determined by CT scan or MRI or PET scan to allow selection of appropriate therapy. Bone marrow, cerebrospinal fluid, pleurocentesis /paracentesis should be tested for cytology or by flow cytometry for immunophenotypic origin (T, B, or null) and cytogenetics (karyotype), though most are not performed in our set up due to availability and financial constraint(8). Laboratory studies known to have prognostic significance include erythrocyte sedimentation rate (ESR), initial WBC and Hgb but serum electrolyte, organ function studies and LDH should be determined as a base line before treatment initiation (9).

A number of factors have been shown to impact survival among patients with NHL. In resource-rich settings, these have included the tumor stage, bulk and histopathologic type, age, serum lactate dehydrogenase (LDH) level, performance status, and the number of nodal and extra nodal sites involved(9),(8). Receipt of both chemotherapy and supportive therapy (e.g., Granulocyte colony-stimulating factor, G-CSF) has also influenced treatment outcomes(10). In resource-poor settings, factors predictive of worse survival include older age, higher tumor stage, high LDH levels, and low hemoglobin concentration(9). Additionally, HIV infection has been found to impact both the incidence and survival rates of patients with NHL(11).

Revised staging classification of childhood and adolescent NHL final version was approved at the Fourth International Childhood, Adolescent and Young Adult NHL Symposium in New York, in 2012.(12) According to this staging classification, patients are grouped into four categories (stage I-IV) based on the site of nodal involvement and extra nodal sites.

The primary modality of treatment for childhood and adolescent NHL is multi agent systemic chemotherapy and/or immunotherapy with intrathecal chemotherapy.(1) Surgery is used mainly for diagnosis. Radiation therapy is used only in special circumstances, such as CNS involvement in LBL or the presence of acute superior mediastinal syndrome or paraplegias. Newly diagnosed patients, especially those with BL or LBL, are at high risk for TLS, these patients require vigorous treatment. (1)

Dramatic improvements have occurred over the past 35 years in childhood and adolescent NHL prognosis. (12,13) Currently, localized or limited stage NHL (stage I to II) has an approximate 95% to 100% 5-year event-free survival (EFS) rate while the 5-year EFS has doubled from approximately 40% (30 years ago) to more than 80% for children with advanced-stage disease (stage III to IV) (12)(13). Despite the increasing burden, infrastructure for diagnosis and treatment of hematolymphoid malignancies remains inadequate in sub-Saharan Africa (SSA).(14), there has been no study done in Ethiopia on NHL survival.

1.2 Statement of the Problem

Cancer has become the second leading cause of death, behind cardiovascular disease, with more than 8.7 million attributable deaths worldwide in 2015(15). Low-income countries contribute up to 60% of this death(15). In the sub-Saharan region of Africa, the incidence of hematolymphoid malignancies is escalating in large part because of the human immunodeficiency virus (HIV) epidemic as well as population growth and aging(14). NHL is the second commonest pediatric cancer only next to acute leukemia in Ethiopia(16). Despite the increasing burden, infrastructure for diagnosis and treatment of hematolymphoid malignancies remains inadequate in SSA(15).

Although 70% of pediatric tumors are sensitive to treatment and survival rates approach 80% in developed countries, greater than 80% of affected children in Africa die from their disease(17),(18). Mortality rates for most pediatric cancers are close to 100% in developing countries, including Ethiopia(19).

The outcome differs significantly between developed and developing countries for various reasons including shortage of qualified human power and setups for proper diagnosis and management, delayed presentation, unavailability of chemotherapeutic agent and poor supportive care (14).

Tikur Anbessa Specialized Hospital (TASH), which is the biggest hospital in the country and serving as the only pediatric oncology unit, manages most patients who access health care and are diagnosed with NHL in Ethiopia.

1.3 Significance of the study

There are no published data regarding childhood NHL profile and treatment outcome in our country and hence this study will give us the clinical and histopathological profile and the outcome as compared to the outcome in developed and in other developing countries. It will also determine the factors that affect the outcome in our setup so that it will add an input to the existing knowledge and may help as a baseline for further prospective studies.

1.4 Operational definitions

Treatment response

1. Complete response is defined as the complete resolution of disease on clinical examination and imaging studies, or at least 70-80% reduction in size

2. Partial response is defined as a decrease by more than 50% in the sum of the product of the perpendicular diameters of representative nodes or extra nodal lesions with clinical improvement.

3. Stable disease is the ones which doesn't fit to either of definitions listed on number 2 or 4

4. Progressive disease is defined as a 25% or more increase in the size of at least one measurable lesion, or the appearance of a new lesion, or recurrence of "B" symptoms which cannot be explained otherwise.(4)

5. Overall 5 year survival in the study group who are alive five years after they were diagnosed with or started treatment they may or may not have come back

6. Event free survival is the length of time after primary treatment in which the patient remains free of certain complications or events, these events may include return of cancer on the primary or other sites, Patients who do not experience a complete disappearance or remission after complete course of chemotherapy treatment..

Bulk NHL

Mediastinal mass in which the greatest diameter measures more than one third the diameter of the chest measured at the level of the apex of the diaphragms chest X-ray or A lymph node mass that measures >6 cm in the transverse (axial) diameter on CT scan.

Neutropenic Fever

Neutropenia defined as neutrophil count < 1000cells/microliter

Fever in Neutropenic Patients is defined as :

- A Single oral temperature of > 38.3 or
- A Temperature of 38.0 ^{o}c Sustained over 1hr.

2. Literature Review

The Berlin-Frankfurt-Münster (BFM)-group clinical studies done from 1975 to 2001 in children and adolescents with non-Hodgkin's lymphoma, 6 consecutive cooperative multicenter studies were conducted into which a total of 2 190 protocol patients were enrolled. The probability of event-free survival (pEFS) at 5 years was 60% in the first study and increased to 84% in study NHL-BFM 95 while the overall survival probability increased from 65 to 89%. Landmarks in the development were the recognitions that childhood NHL is a heterogeneous disease and different biological subtypes require specifically adapted treatment strategies, that within subtypes the required treatment intensity varies significantly and that the appropriate prognostic parameters for stratification of treatment intensity differ between different NHL sub entities (20).

Studies of the French Society of Pediatric Oncology analysis on children/adolescents with H&N B-NHL prospectively enrolled in the SFOP LMB-89 trial (July 1989-June 1996). One hundred and twelve of 561 patients (20%) had H&N involvement. The mean age of the patients was 8.4 years. Ninety-seven percent of H&N patients achieved CR and event-free and overall survival at 4 years was 95.5% (5 deaths in patients with CNS disease). On multivariate analysis, EFS was significantly better in H&N patients than in non-H&N patients but not OS.(21)

A study done in USA using cancer registry data from 13 states from 1992 through 2001 among 2442 persons younger than 30 years diagnosed with NHL, 40% were children aged 0 to 19 years and 60% were young adults (aged 20-29 years). A higher proportion of young adults were diagnosed at stage I (35%) and a lower percentage were diagnosed at stage IV (34%) compared with childhood NHl cases (30% and 38%, respectively). 28% of children diagnosed with diffuse large B-cell lymphoma, the other common subtypes were lymphoblastic (24%) and Burkitt (22%) lymphomas. The 5-year survival rates were 85% for children and 75% for young adults (22).

The Mexican Association of Pediatric Oncology and Hematology conducted a retrospective study to analyze the clinical characteristics and outcomes of children with diagnosis of B-NHL in Mexico, From January 2000 to December 2016, 166 pediatric patients were diagnosed with B-cell NHL at the participant institutions. Median age at diagnosis was 8 years Male to female ratio was1.3:1. The most frequent primary site of involvement was abdomen (48%). Among all B-NHL patients, 82% had the advanced-stage disease [86 (52%) patients had stage III and 49 (30%) patients had stage IV], 50% had elevated LDH, 39% had B symptoms, 24% had bone marrow (BM) involvement and 10% had CNS involvement. BL was diagnosed in 126 patients (76%) (Including 26 BLL), and DLBCL in 39 patients (23%). The five-year EFS for all patients was 66.6%, 5-year PFS was 82.7%, and 5-year OS 76.3%. According to histology outcome, the

5-year EFS were 63% for BL/BLL, and 80% DLBCL; the 5-year PFS were 81% for BL/BLL, and 91% for DLBCL, and the 5-year OS were 71% for BL/ BLL, and 83% for DLBCL (23).

The clinical features and relative frequencies of NHL subtypes in five developing regions of the world were compared to the findings in the developed world. Five expert hematopathologists classified 4848 consecutive cases of lymphoma from 26 centers in 24 countries using the World Health Organization classification, and 93.6% were confirmed to be NHL, with a significantly greater number of males than females in the developing regions compared to the developed world ($P<0.05$). The median age at diagnosis was significantly lower for both low- and high-grade B-cell lymphoma in the developing regions. Among the B-cell lymphomas, diffuse large B-cell lymphoma was the most common subtype (42.5%) in the developing regions. Burkitt lymphoma (2.2%), precursor B- and T-lymphoblastic leukemia/lymphoma (1.1% and 2.9%, respectively) the developing regions had significantly more cases of high-grade B-cell lymphoma (59.6%) and fewer cases of low-grade B-cell lymphoma (22.7%) compared to the developed world (39.2% and 32.7%, respectively) (24).

Cancers occurring in children in Africa are often under diagnosed or at best diagnosed late. As a result, survival is poor, even for cancers considered 'curable'. A study based on cancer registries in three Eastern African countries (Kenya, Uganda and Zimbabwe) assessed the 5-year survival estimates for the most common types of cancers affecting children aged 0-14 years such as Kaposi sarcoma, Wilms tumor, NHL including Burkitt's lymphoma, retinoblastoma, and acute lymphocytic leukemia diagnosed over the period 1998-2009 and followed up till the end of 2011. In Harare and Kampala, the 5-year relative survival was <46% for all cancer types. Survival from childhood cancers in Africa is still poor, even for cancers with good prognosis and potential for cure [31].

A retrospective cohort study was carried out in Tertiary Center in Cape Town, South Africa using clinical and laboratory records of children newly diagnosed with B-cell NHL from January 2005 to December 2014. Seventy-five children ≤15 years of age were included. The majority had Burkitt's lymphoma (n=61). Overall, (n=19) were HIV positive and 16% had concurrent active tuberculosis. Bulky disease was present in 65.7% and 30.1% were classified as Lymphoma Malins B risk group C. The 5-year survival estimates for HIV-negative and HIV-positive children were similar, 81% versus 79% for event-free survival and 85% versus 83.9% for overall survival(25).

A Retrospective review of patient's charts diagnosed and treated as LBL during the period between July 2007 and end of December 2012 was done at the children cancer hospital Egypt – A single center experience. This study included 77 patients. The median age at diagnosis was 9 years. The 4 years overall survival (OS) and event free survival were 86.5% and 82.2%, respectively(26).

All Malawian children admitted to Queen Elizabeth Central Hospital, from August 2000 to March 2002 with confirmed BL were studied, Median age was 9.2 years (IQR 7.7–11.8), 48 (66%) were male and two were HIV-infected. Twelve (16%) presented with stage I/II disease, 36 (49%) stage III, and 25 (34%) stage IV. Thirty-four (47%) children had abdominal disease and 60 (82%) the projected EFS at 12 months is 50% in stage I, 50% in stage II, 24% in stage III, 25% in stage IV, and 33% for all patients(27).

Outcomes of children with NHL in Kenya, a sub-Saharan low-income country, and the association between health insurance status at diagnosis and treatment outcomes were studied. All children diagnosed with NHL in 2010-2012 were included. Most patients presented late: stage I (7%), stage II (11%), stage III (66%), stage IV (16%). Of all 63 patients with NHL, 35% abandoned treatment, 22% had progressive or relapsed disease, 14% died and 29% had event-free survival. Most patients (73%) had no health insurance at diagnosis. Treatment outcomes in children with or without health insurance at diagnosis differed significantly (p=0.005). The most likely treatment outcome in children with health insurance at diagnosis was event-free survival (53%), whereas in children without health insurance at diagnosis it was abandonment of treatment (44%). (28)

3. Objectives

General objectives

- To assess the clinico–pathologic profile and outcome of children with Non-Hodgkin's lymphoma at Tikur Anbessa Specialized Hospital Pediatric hemato-oncology unit.

Specific objectives

- To Describe demographic profile of children with NHL
- To assess clinico-phathologic pattern of children with NHL
- To assess treatment outcome of children with NHL.
- To identify factors that affect treatment outcome of NHL.

4. Methods and Materials

4.1 Study setting

The study was conducted in Tikur Anbessa Specialized Hospital hemato-oncology unit, Addis Ababa, Ethiopia. Tikur Anbesa Specialized Hospital, established in 1974, is the largest tertiary hospital in the country. The hospital is administered by Addis Ababa University and is the largest and oldest teaching hospital in Ethiopia providing teaching for about 300 medical students and 350 Residents every year. Black Lion hospital offers diagnosis and treatment for approximately 400,000 patients a year.

It was used as the only hemto-oncology treatment unit in the county until recently. A separate unit for children with cancer begun in March 2013 with initiatives taken by the international network for cancer treatment and research, USA (INCTR-USA) in collaboration with George town university hospital-. Pediatric hemato-oncology ward has 26 Beds and the cancer center has 16 beds dedicated to pediatric patients. Currently there are 3 pediatric hemato-oncologists working in the pediatric unit. The unit renders both inpatient and outpatient services for more than 600 patients every month.

4.2 Study design

The study was conducted using a hospital-based retrospective cross--sectional study design.

4.3 Study period

We included children diagnosed and managed as having NHL in the pediatric hemato-oncology unit for the period January 2014 to January 2020, as full documentation of patient charts where started since. Data was collected from May 2021 to June 2021.

4.4 Study population

All children age less than 15 years who were diagnosed with Non-Hodgkin's lymphoma during the study period were included in the study.

4.5 Sample size

With the general assumption that this study will be presented with a level of confidence of 95% and 5% precision, I used single population proportion formula to calculate the minimum sample size for this study. The expected proportion of NHL patients was taken from Estimates of Cancer Incidence in Ethiopia in 2015 Using Population-Based Registry Data which shows about 14% of all childhood malignancies were NHL. (16)

Sample size: $n=\frac{Z^2P(1-P)}{d^2}=\frac{1.96^2*0.14*(1-0.14)}{0.05^2}=185$

where : n= the minimum sample size

p=the expected prevalence of NHL

d= the level of precision (margin of error)

z= the value at 95% confidence level

Adding 10% of the calculated value for missing and incomplete data makes the final sample size required 203. To obtain the required sample size needed for this study all consecutive cases during the study period were included.

4.6 Inclusion and exclusion criteria

Inclusion criteria

- All histo-pathologically confirmed NHL cases with patient age less than 15 years during the study period.

Exclusion criteria

- Those on NHL treatment but who doesn't have histopathologic confirmation.

4.7 Data collection and measurements

Pediatric NHL case records were collected by chart retrievers from pediatric hemato-oncology clinic, the primary investigator revised the charts and collected data using a structured questionnaire. The questionnaire was piloted and revision was made accordingly. The questionnaire consists of socio-demographic information, clinical profile and treatment outcome of pediatric NHL patients.

4.8 Data handling

The collected data was checked by the investigator for cleanliness and its completeness. Patient records with incomplete data were excluded. After quality check, data were entered into SPSS statistical software.

4.9 Study variables

Independent variables

- Sociodemographic data: age, sex, address, residence, religion, birth order
- Histologic type, major presenting symptom, tumor bulk, HIV status, chemotherapy type, cycle of chemotherapy, ESR, LDH, Stage, Hgb

Dependent variables

- Response to treatment
- Death
- Event free survival
- Overall survival

4.10 Data Quality Assurance

Primary investigator collected data and its completeness checked and coded. The converted soft copy was again cross checked with the hard copy for neatness, completeness and its consistency before any statistical analysis performed.

4.11 Data analysis

After thorough cleaning and checking for its completeness data entered into Statistical Package for Social Sciences ver. 25 (SPSS) for subsequent descriptive analysis in terms of mean, frequencies and percentage when appropriate. Chi square test used to assess association among the variables. Multivariate cox proportional regression model used to determine individual predictors effect on EFS. Five-year overall and event free survival estimated using Kaplan–Meier statistics. Statistically significance taken for p values of <0.05 for all statistical tests.

5. Ethical considerations

Ethical clearance to conduct this study was obtained from the Pediatrics and Child Health Department's Research and Publications Committee of the School of Medicine, College of Health Sciences, and Addis Ababa University. Confidentiality fully maintained during data collection and analysis. Participants will be anonymous during dissemination of results.

6. Dissemination of findings

The finding of the study will be presented on the research defense day and a formal report will be submitted to the DPCH with both soft and hard copy. The result could also be published on local or international scientific journals.

7. Result

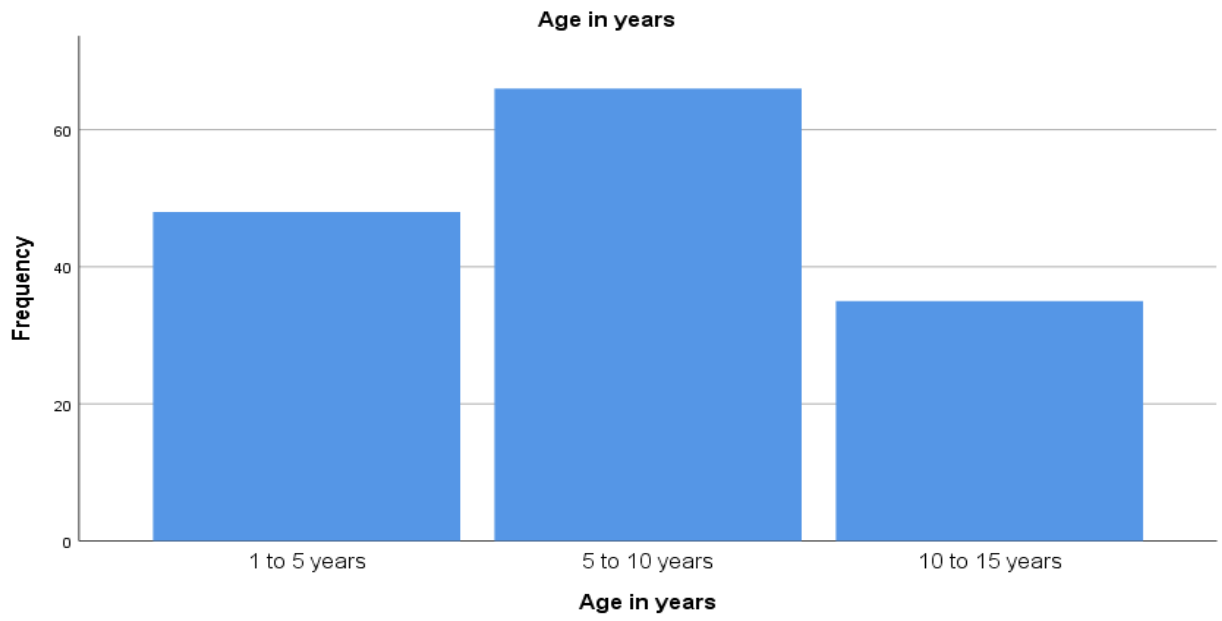
During the study period, from July 1st to August 31st, 2021, 128 patient charts were retrieved and an additional. 21 patients were identified from the cancer register. The later cases were communicated via phone and available clinic pathological profiles were extracted from the cancer registry excel data. All the 149 cases had both clinical and pathological diagnosis of NHL and were included in the analysis.

The distribution of patients according to their age is displayed below (fig.1).

The largest share (44.3%) of the cases were between five and ten years of age and the rest 32.2% and 23.5% of the cases were in those between 1 to 5 years and 10 to 15 years, respectively.

The duration of illness before diagnosis ranges from 2 weeks to 74 weeks with a median of 12 weeks and IQR of 12. In 21 cases the duration of illness is not known. The distribution of cases based on the duration of illness depicted below showed skewness to the right (fig. 2).

Figure 1: Distribution of patients in different age categories



Of the total 149 cases, males were 105 (70.5%) and 44 (29.5%) were females with male to female ratio of 2.4:1. In the specific age groups, the male to female ratio varies. In the age group 1 to 5 years the male to female ratio is 1.3:1 , the male to female ratio is 4.6:1 and 1.8:1 in age groups 5 to 10 years and 10 to 15 years, respectively (Table 1)

Table 1 . Distribution of sex among Age groups.

Age in years		Sex of patient			
		Male		Female	
		Count	Column N %	Count	Column N %
Age in years	1 to 5 years	24	22.9%	19	43.2%
	5 to 10 years	60	57.1%	13	29.5%
	10 to 15 years	21	20.0%	12	27.3%

Figure 2. Distribution of cases based on the duration of illness

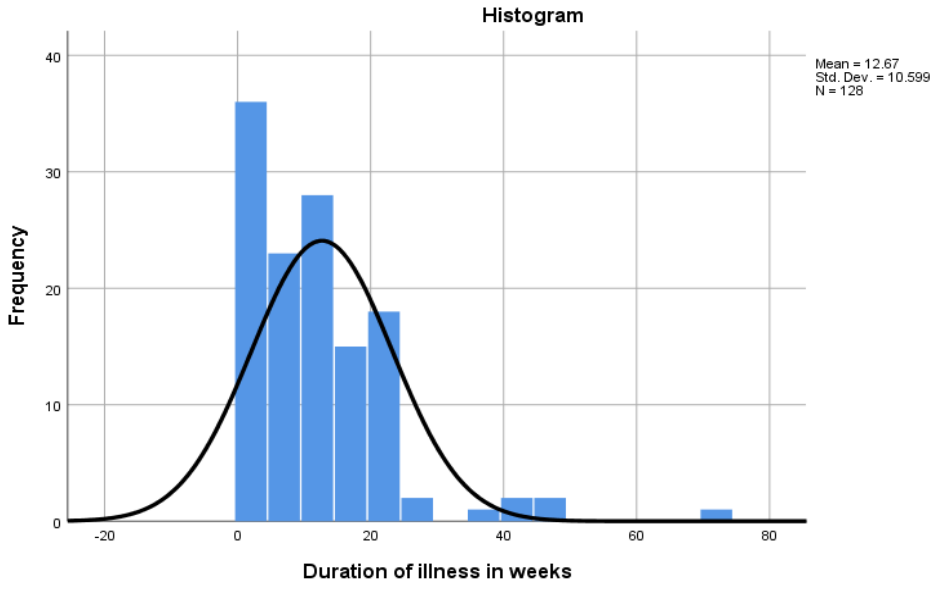
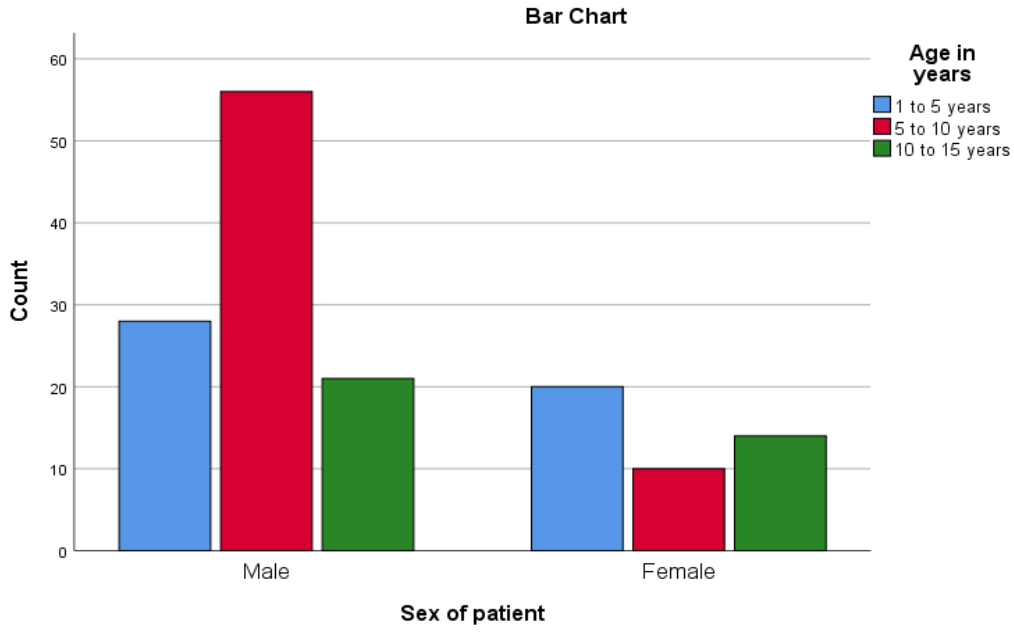


Figure 3. Distribution of cases in age group and sex



The majority of cases were from the Oromia region which is 57(38.3%) of 149 patients followed by Addis Ababa with 38 (25.5%) patients, and 24(16.1) and 11(7.4%) of the patients were from SNNPR and the Amhara regions, respectively (see fig. 4 and table 1). 51% of them reside in urban areas while 49% are from rural areas.

Figure 4: Geographic distribution of cases

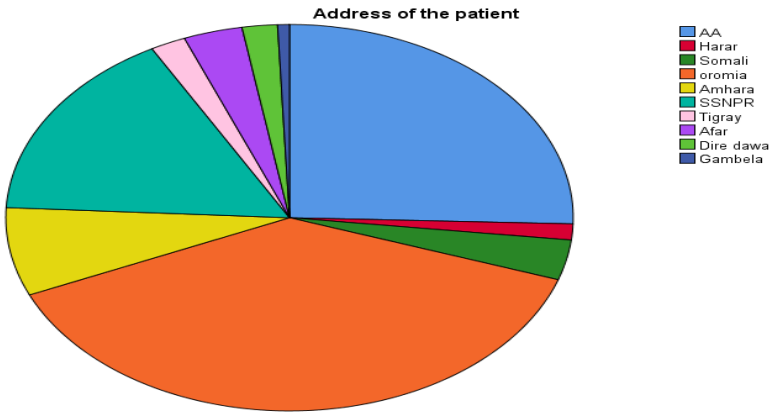
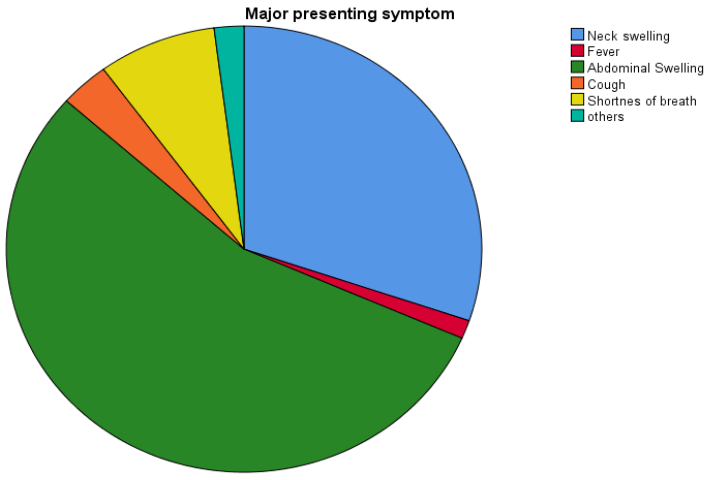


Table 2 Address Of the patient

Address	Frequency	Percent	Cumulative Percent
AA	38	25.5	25.5
Harar	2	1.3	26.8
Somali	5	3.4	30.2
oromia	57	38.3	68.5
Amhara	11	7.4	75.8
SSNPR	24	16.1	91.9
Tigray	3	2.0	94.0
Afar	5	3.4	97.3
Dire dawa	3	2.0	99.3
Gambela	1	.7	100.0
Total	149	100.0	

Majority of the patients 82 (55%) presented with the complaint of abdominal swelling and 45(30.2%) of the patients presented with complaint of neck swelling. (See figure 5). On the initial CBC 48.3% of the patients had hemoglobin of 11g/dl or above. The WBC count was less than 15000 in 73.8% of the patients, regarding the lactate dehydrogenase (LDH) 56.4% of the patients had LDH greater than 500 IU/dl.

Figure 5: Major initial presenting symptoms



In our study, 80 of the patients (53.7%) had Burkitt's histology, 17 (11.4%) was DLBL type, 8(5.4%) had Lymphoblastic lymphoma. 0f the 149 cases 44 (29.5%) the histology type was not known.

Most of our patients presented with advanced stage i.e. III/IV disease (47.7% stage III and 18.8% stage IV). Stage II and I diseases constituted 17.4% and 6% of the cases, respectively. In 10.1% of the cases the stage of the disease at presentation was not known.

Of the total 149 patients PIHCT was done for 84 of them only, 4 patients were found to be reactive. For 65 patients their RVI status was not determined. 11(7.4%) patients had history of tuberculosis treatment on presentation.

Initial treatment in most of the cases was Chemotherapy only 140 (94%), 7(4.7%) had both surgery and chemotherapy while only 2 patients took Radiotherapy. 141 patients completed ALCL protocol while 8 patients took HR ALL protocol chemotherapy.

Table 3 : Patient sociodemographic and clinical characteristics

Patient characteristics		Number	Percent %
Sex of patient	Male	105	70.5
	Female	44	29.5
Address of the patient	AA	38	25.5
	Oromia	57	38.3
	Amhara	11	7.4
	SSNPR	24	16.1
	Tigray	3	2.0
	Afar	5	3.4
	Benishangul Gumuz	0	0.0
	Dire dawa	3	2.0
	Gambela	1	0.7
	Harar	2	1.3
	Somali	5	3.4
Major presenting symptom	Neck swelling	45	30.2
	Fever	2	1.3
	Bleeding	0	0.0
	Abdominal Swelling	82	55.0
	Cough	5	3.4
	Shortness of breath	12	8.1
	Others	3	2.0
Stage of the disease at presentation	Stage I	17	11.2
	Stage II	30	20.1
	Stage III	75	50.3
	Stage IV	27	18.4
Histology type	Burkitts Lymphoma	80	53.7
	Lymphoblastic Lymphoma	8	5.4
	Diffuse large B cell lymphoma(DLBCL)	17	11.4
	Anaplastic large cell lymphoma(ALCL)	0	0.0
	Unknown	44	29.5
LDH level at presentation	Unknown	21	14
	less than 500	44	29.5
	greater than 500	84	56.4
Hgb level at presentation	Unknown	21	14
	Hgb less than 11	56	37.6
	Hgb greater than 11	72	48.3
WBC count at presentation	Unknown	21	14
	less than 15,000	110	73.8
	greater than 15,000	18	12.1

Chi square test performed to assess association disease stage and histology with sex, age group, major presenting symptom, range of hemoglobin ,WBC, and LDH levels. Significant association found with stage of the disease and age group, LDH and WBC count ($p<0.05$) as described in (Table 4 below). With regard to the association of histopathologic type to other variables like LDH, WBC, major presenting symptom and stage no statistically significant association was found.

Table 4 Association of stage of disease with other clinical variables

		Stage I/II	stage III/IV	P value
Sex of patient	Male	60	44	0.266
	Female	21	23	
Age in years	1 to 5 years	16	27	0.020
	5 to 10 years	46	26	
	10 to 15 years	19	14	
Major presenting symptom	Neck swelling	24	20	0.504
	Fever	0	2	
	Bleeding	0	0	
	Abdominal Swelling	45	37	
	Cough	4	1	
	Shortnes of breath	7	5	
	others	1	2	
Histology type	Burkitts Lymphoma	43	36	0.301
	Lymphoblastic Lymphoma	2	6	
	Diffuse large B cell lymphoma(DLBCL)	9	8	
	Anaplastic large cell lymphoma(ALCL)	0	0	
	Unknown	27	17	
WBC count at presentation	Unknown	11	9	0.000
	less than 15,000	45	20	
	greater than 15,000	16	47	
LDH level at presentation	Unknown	11	9	0.000
	less than 500	43	24	
	greater than 500	24	36	
Hgb level at presentation	Unknown	11	9	0.844
	Hgb less than 11	29	27	
	Hgb greater than 11	41	31	

Table 5 Association of type of chemotherapy with post chemo complication

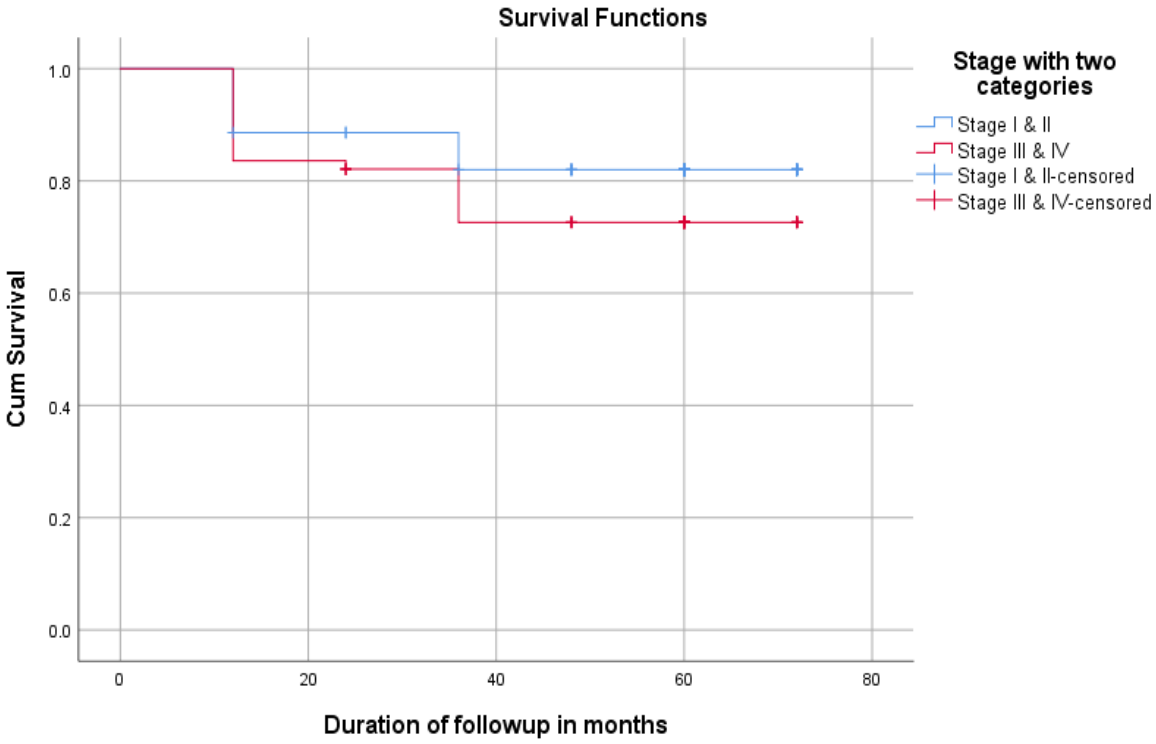
		ALCL protocol	P VALUE
Post chemo neutropenia	Yes	49	0.112
	No	92	
Post chemo Anemia	Yes	14	0.000
	No	127	
Post chemo Thrombocytopenia	Yes	5	0.000
	No	136	
Post chemo Mucositis	yes	29	0.764
	no	112	
post chemo typhilitis	yes	23	0.365
	no	118	
Neutropinic fever during treatment	Yes	56	0.546
	No	31	
None	No	125	0.313
	Yes	16	

Three years and Five years over all and event free survival estimated for cases who completed their treatment using Kaplan Meier survival estimate. From the total 149 of the patients, 144 cases completed their treatment & included for the three year OS and EFS. Five patients who completed treatment were lost from their subsequent follow-up and six patients relapsed. 32 deaths were documented 19 of them were in the first year. The 3 year OS was 77.8% and EFS

was 73.6%. The five year OS was 66.5% and EFS was 63.1%. A total of 18 patients were lost from follow up.

Overall survival was calculated as the time to death or the last recent follow up since initiation of treatment. Event free survival was determined as the time to event analysis to relapse, death or progressive disease since initiation of treatment.

Figure 6 Five-year OS survival with stage of the disease



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.808	1	.179

Cox regression model used to assess the pretreatment variables prognostic effect on EFS (table 6). In this study, none of the variables found to have prognostic significance on EFS.

Table 6: Pretreatment prognostic factors on Event-free survival using cox regression proportional model

	Sig.	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
Grouped New LDH count	0.918	1.019	0.709	1.465
Grouped new Hgb count	0.817	1.047	0.71	1.543
Grouped New stage	0.634	1.11	0.723	1.703
Age in years	0.979	1.004	0.742	1.358
Sex of patient	0.745	0.929	0.595	1.45
Major presenting symptom	0.891	1.009	0.883	1.154

8. Discussion

The clinical, histopathological and treatment outcomes of children with NHL was studied in developed as well as developing countries but there was no published data found in Ethiopia.

In this retrospective study, 149 children with diagnosis of NHL were studied. Large number of the cases (44.3%) occurred in age ranges between five and ten years and males were more affected than females.. When we compare to other studies done in Egypt, South Africa, Mexico, French and USA, the age distribution of cases was similar and males were found to be affected in higher proportion than females. Early age of the disease and significant male predominance is commonly reported in developing countries. (26, 25, 23, 21, 22, 24).

Majority of the patients 82 (55%) presented with the complaint of abdominal swelling and 45(30.2%) of the patients presented with complaint of neck swelling. The duration of illness before diagnosis ranges from 2 weeks to 74 weeks with a median of 12 weeks and IQR of 12. Similar finding reported in a research done in Malawi with 47% presenting with abdominal disease. Another research done in Mexico showed abdominal involvement as the commonest presentation (48%) (23, 27).

Most of our patients presented with advanced stage i.e. III/IV disease (47.7% stage III and 18.8% stage IV). These findings were comparable with the research done in Kenya, Mexico, USA and it was also demonstrated in a study done in 5 developing regions of the world, most pediatric NHL cases present with advanced stage. (28, 23, 22, 24)

In our study, 80 of the patients (53.7%) had Burkitt's histology, 17 (11.4%) was DLBL type, 8(5.4%) had Lymphoblastic lymphoma. 0f the 149 cases 44 (29.5%) the histology type was not known. Among pediatric patients, endemic Burkitt lymphoma (eBL) predominates in much of SSA, more than 90% of NHLs in some published cohorts. Almost invariably associated with Epstein-Barr virus (EBV) and malaria. This study was also comparable to a study done in Mexico where 76% present with BL. (6,7,23)
But a study done in 5 developing regions of the world which included 24 countries compared with developed world in NHL subtypes distribution DLBCL was the most common subtype (42.5%), this was also seen in study done in USA where (28%) of children DLBCL vs Burkitt (22%) of lymphomas. This can be partly explained by the fact that there is high malaria and EBV infection in our country as well but conclusion cannot be made as a significant number of patients in our study do not have specific histology type done (29.5%) (24,22,6)

Initial treatment in most of the cases was Chemotherapy only 140(94%), 7(4.7%) had both surgery and chemotherapy while only 2 patients took Radiotherapy. 141 patients completed ALCL protocol while 8 patients took HR ALL protocol chemotherapy.

Analytical study using Chi square Significant association was found with stage of the disease and age group, LDH and WBC count ($p<0.05$) statistically significant association between sex of patients and age group was also found.

From the total 149 of the patients, 144 cases completed their treatment & included for the three year OS and EFS. Five patients who completed treatment lost from their subsequent follow up. six patients relapsed. 32 deaths documented 19 of them were in the first year. The 3 year OS was 77.8% and EFS was 73.6%. The five year OS was 66.5% and EFS was 63.1%. A total of 18 patients lost from follow up, and there was no death documented on the 5^{th} year and above.

which is lower compared to both developing and developed countries and the global data at large.A report from Egypt showed OS and EFS of 86.5% & 82.2%, a report from Mexico The five-year PFS was 82.7%, and 5-year OS 76.3%.. The 5-year survival rates were 85% for children in USA , a report from South Africa The 5-year survival estimates 81% for event-free survival and 85% for overall survival.(26,23,22,25).

9. Limitation of the study

This was a retrospective study, and data was collected through chart reviewing which may affect its quality. The sample size could not be attained from the available patient charts, as a result incomplete data charts were included in the study accordingly and analyzed separately.

10. Conclusion

In this retrospective study, most cases of NHL occurred in those between five to ten years of age. Males are affected in a higher proportion than females. More than half of the patients presented with advanced stage and commonest presentation is Abdominal swelling. Burkitts lymphoma is the commonest histologic type. Disease stage had statistically significant association with hemoglobin, LDH, Age. Five year over all and event free survival is lower than other developed, developing countries and the global data.

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