

# Sub-types and treatment outcomes of adolescent and adult non-Hodgkin lymphomas in a resource poor setting

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## Abstract

**Background:** The diagnosis and treatment outcomes of Non- Hodgkin Lymphoma's (NHL) in resource poor countries in the absence of routine molecular studies and immunohistochemistry is challenging.

**Methods:** A retrospective review of case folders of NHL patients aged 13 years and above. Information obtained from the case folders included age, sex, histological subtype, subtypes using the Working Formulation and WHO classifications. Treatment given and follow up information were also evaluated.

**Results:** A total of 279 cases of NHL were identified within the study period. The mean age of the patients was  $48.8 \pm 17.0$  years. The male to female ratio was approximately 1.5:1. The majority of cases seen (53%) were diffuse large B- cell lymphoma. Chronic lymphocytic leukaemia/ small lymphocytic lymphoma (22.2%) was the next most common subtype. Other sub types seen, in order of frequency, included diffuse mixed cell lymphoma (6.4%), gastric lymphomas (3.9%), mediastinal B- cell lymphoma (2.9%), Burkitt's lymphoma (1.8%), splenic marginal zone B-cell lymphoma (1.1%), lymphoblastic lymphoma (1.1%), mucosa- associated lymphoid tissue (MALT) type B- cell lymphoma (0.7%) and follicular lymphoma (0.7%).

**Conclusion:** This study provides an overview of the distribution of NHL subtypes and their outcomes in a resource constrained setting. Immunohistochemistry, cytogenetics and specific molecular studies which are important in characterization of NHLs, should be made affordable and accessible in low income countries.

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**Citation:** Dei-Adomakoh YA, Asare EV, Amedonu ESA, Abrahams ED, Segbefia CI et al. (2017) Sub-Types and Treatment Outcomes of adolescent and Adult Non-Hodgkin Lymphomas in a Resource Poor Setting. Journal of Hematology and Oncology Research - 2(3):15-23. <https://doi.org/10.14302/issn.2372-6601.jhor-17-1423>

**Editor:** Krzysztof Roszkowski, Nicolaus Copernicus University, PL. Department of Oncology, Radiotherapy and Gynecologic Oncology

**Keywords:** Histological subtypes, Treatment, Non-Hodgkin lymphoma, working formulation, Ghana

**Received** Jan 05, 2017; **Accepted** Feb 02, 2017; **Published** Feb 09, 2017;

## Introduction

Non- Hodgkin lymphomas (NHL) are clonal malignant diseases that arise from the lymphoid system.<sup>1,2</sup> It accounts for 4% of all cancers and represents approximately 10% of all childhood cancers<sup>1</sup>. It accounts for 14–19 cases per 100,000 population in the West.<sup>1,2</sup> During the past few decades, incidence rates of NHL have risen<sup>3</sup> with an estimated rate of increase of 3-4% per annum In Europeans.<sup>4,5</sup> This has been attributed to an increase in mean age of the population, improvements in diagnosis, the HIV pandemic and immunosuppressive therapy.<sup>6</sup> NHL is found predominantly in males with a male to female ratio of 3:2.<sup>7,8</sup>

Especially in Sub-Saharan Africa, NHL classification, diagnosis and treatment present with a lot of challenges. Some of the classification schemes used include: the Rappaport, Lukes-Collins, Kiel, Working Formulation, REAL and World Health Organization (WHO). These classifications provide clinicians with diagnostic and prognostic information for the various subtypes of NHLs. For this study the working formulation and WHO classifications (few cases) were used.

Korle - BuTeaching Hospital (KBTH) where the study was conducted, is the largest hospital in Ghana with a bed capacity of 2000 and one of two major tertiary referral centers in the country. The Haematology department renders outpatient, inpatients and day care services to patients with a wide range of haematological disorders. On the average 50 patients are attended to on out patient basis weekly. The department has over 6000 patients in its database.

The stimulus for this study was the fact that Subtypes and treatment outcomes of adolescent and adult NHL in the foremost referral hospital in Accra, Ghana has not been done before.

## Materials and methods

A retrospective review of case folders of all patients aged 13 years and above, diagnosed with NHL between January 1, 2008 and October 31, 2013, at the haematology department of the KBTH, Accra, Ghana.

## Data collection

Detailed history and clinical information relating to age, sex, histological subtype, subtypes using the

working formulation, immunohistochemistry (where available), treatment given and outcomes were retrieved from case folders of eligible study participants.

## Data analysis

Data were captured using Microsoft Excel 2007 Database. Analysis was done with Statistical Package for the Social Sciences (SPSS) software version 20. Data were analyzed by simple descriptive statistics (i.e., proportions, ratios and percentages) and summarized in tables.

## Results

Out of a total of 279 adolescent and adult cases of NHL patients folders reviewed, the mean overall age was  $48.8 \pm 17.0$  years with minimum age of 13 years and maximum 87 years. There were 156 males (55.9 %) and 123 females (44.1 %) with a male to female ratio of approximately 1.5:1. The age and sex distribution of the adolescent and adult NHL is shown in figure 1 and this showed the most vulnerable age bracket of NHL in both sexes to be 50-69 years. The majority of cases seen (53%) were diffuse large B- cell lymphoma. Followed by chronic lymphocytic leukaemia / small lymphocytic lymphoma (22.2%). Diffuse mixed cell (6.4%) was the third most common and the least common NHL being mycosis fungoides (Table 1). Intermediate grade NHLs constituted the greatest proportion of all NHLs using the working formulation (Fig 2).

The age bracket shows 10 year-age intervals cross-tabulated against the frequency of new cases of Non- Hodgkin lymphoma per age group (Fig 1). Whereas significant cases (43 cases; 15.4%) were in the young population (below 30 years of age); the incidence increased gradually in the adult population with over half the cases (148 cases) falling between the ages of 30 and 69 years; after which there was a drastic decline in the elderly (69 years and above). There was a peak incidence at age interval of 50–69 years. Figure 3 shows an increasing trend in number of NHL cases diagnosed over 5 years.

Based on the Working Formulation classification with broad histologic categories of low-, intermediate-, and high-grade lymphomas, this study showed that out of the 279 patients, 83 (29.7%) had low grade NHL, 170 (60.7%) intermediate and 26(9.4%) had aggressive/high grade NHL (Fig 2).

Though, immunohistochemistry is not routinely done for patients due to the cost and lack of facilities,

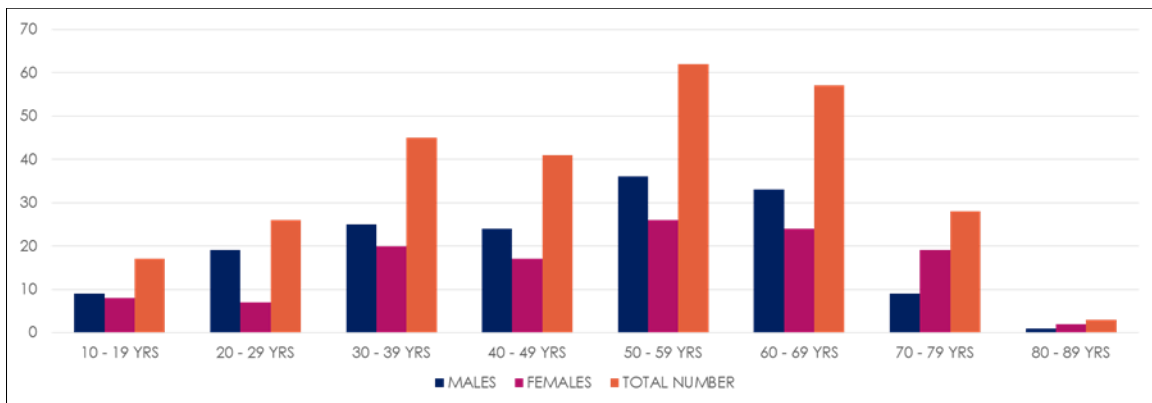
seventeen (6%) cases were done and report-based initial diagnosis and immunohistochemistry interpretations were correct for most cases (Table 2). However four required a change in diagnosis and treatment.

The study looked at first, second and third year outcomes for patients with NHL in a resource poor setting. Table 3 and 4 shows treatment outcomes in the first two years. In the first year two hundred and twenty 220 (78.9%) patients achieved clinical remission, forty eight 48 (17.2%) with poor response, two 2 (0.7%) patients did not respond to first line chemotherapy and were given second line. Figure 4 shows the three year

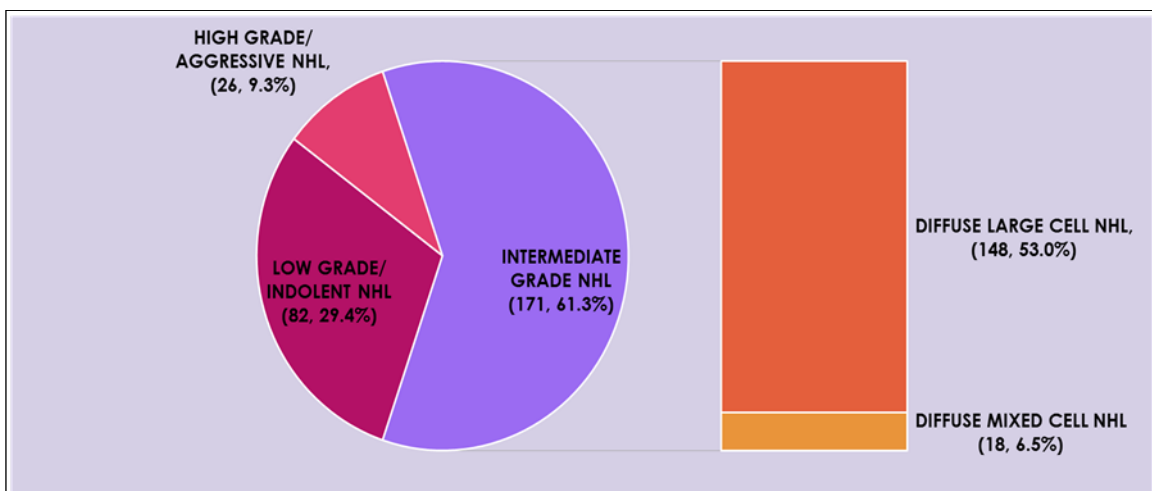
follow up of NHL cases post treatment. Survival rate of NHL in the first year was found to be high (98.6%). Subsequent years showed a decline in follow up cases and thus a decrease in survival rates.

**Discussion**

In Ghana, NHL has been reported to be quite common among children.<sup>9</sup> The incidence of NHL from previous studies in developed and middle income countries is higher compared to Hodgkin's lymphoma (HL).<sup>10-14</sup> The is variation in incidence according to age, sex, race, socioeconomic status and histologic subtypes.<sup>15</sup> The male preponderance in this study is not different from previous studies.<sup>16-18</sup> The sex of an individual is one of the greatest known risks for contracting lymphomas and leukaemias.<sup>19</sup> It has been reported that the preferential male involvement in lymphoid cancer is most marked in the youngest age group in NHL as well as HL.<sup>20</sup> In 1998, an international



**Figure 1:** Sex and age distribution of the NHL patients

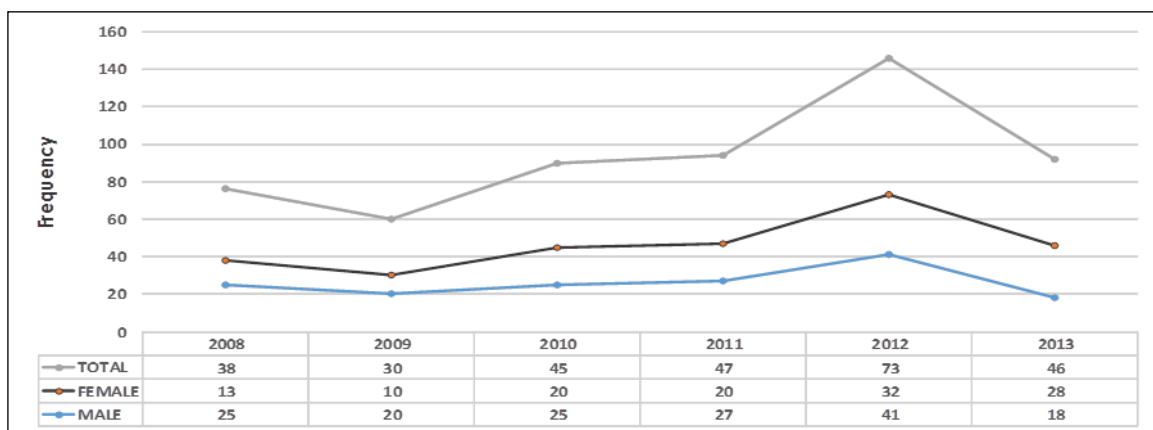


**Figure 2:** Distribution of the histologic category of NHL according to the Working Formulation

consortium reviewed pooled patient data and the male

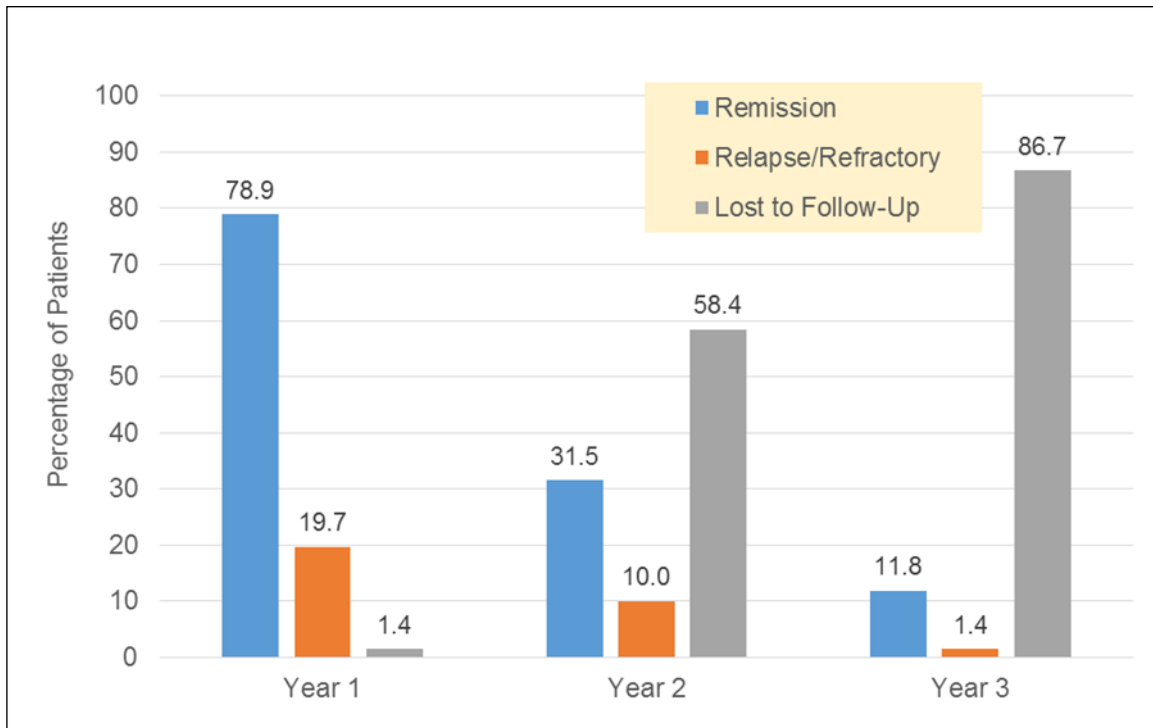
**Table 1:** Sex specific incidence of NHL subtypes

Subtypes of NHL	Sex		Total
	Male	Female	
Diffuse Large Cell NHL	85	64	148
Splenic Marginal Zone Lymphoma	2	1	3
Diffuse Mixed	9	9	18
Burkitts Lymphoma	2	3	5
Lymphoblastic Lymphoma	3	0	3
Diffuse Small Cell NHL	1	5	6
Mediastinal NHL	7	1	8
Chronic Lymphocytic Leukemia	20	22	42
Follicular Large Cell With Diffuse Areas	1	1	2
Gastric Lymphoma	5	6	11
Small Cell Lymphoma	15	5	20
Mycosis Fungoides	1	0	1
Others	5	4	9
Total	156	123	279



**Figure 3:** Year diagnosed and sex specific ratio of NHL patients

sex factor was identified as an adverse prognostic score decline in incidence above 69 years.



**Figure 4:** Post-treatment 3-Year Follow-Up of Patients with NHL

for advanced lymphomas.<sup>20</sup>

A significantly higher incidence has been

In this study, majority of the patients (60.0%) reported among adolescents and young adults in some

**Table 2:** Comparison of Histological diagnosis by working formulation to immunohistochemistry

NUMBER OF CASES	WORKING FORMULATION	IMMUNOHISTOCHEMISTRY RESULTS	DIAGNOSIS BY IMMUNOHISTOCHEMISTRY
7	DIFFUSE LARGE CELL	CD20 +	DIFFUSE LARGE B-CELL LYMPHOMA
1	DIFFUSE LARGE CELL	CD20+; BCL-2+; BCL-6+; CD23+	FOLLICULAR LYMPHOMA TRANSFORMING TO DIFFUSE LARGE B- CELL LYMPHOMA
1	DIFFUSE MIXED CELL	CD20+	DIFFUSE LARGE B- CELL LYMPHOMA
1	DIFFUSE SMALL CELL	CD20+	DIFFUSE LARGE B- CELL LYMPHOMA
1	DIFFUSE LARGE CELL	CD30+; LCA+; CD3-; CD20-; CD79a-	ANAPLASTIC LARGE CELL LYMPHOMA
1	SMALL CELL LYMPHOMA	CD3-; CD23-; CD20+; CYCLIN-D1-; CD5±	B- CELL SMALL LYMPHOCYTIC LYMPHOMA
1	MANTLE CELL LYMPHOMA	CD20+	MANTLE CELL LYMPHOMA
1	MEDIASTINAL NHL	CD3+; CD7+	T- LYMPHOBLASTIC LYMPHOMA
1	DIFFUSE LARGE CELL	CD20-; ALK-	PLASMABLASTIC LYMPHOMA
1	DIFFUSE LARGE CELL	CD20-; CD10-; BCL-2-; CD3+; Ki67+	AGGRESSIVE T- CELL LYMPHOMA
1	DIFFUSE LARGE CELL	CD3 (WEAKLY +); CD5+	PERIPHERAL T- CELL LYMPHOMA
TOTAL: 17			

were males. There was paucity of cases above the age of 69 years. This is however not surprising because the life expectancy in the general population in Ghana is averagely 65.75%.<sup>21</sup> This may be responsible for the

industrialized countries<sup>22,23</sup> whereas less developed countries still show high rates in childhood<sup>23</sup> and now adolescent and young adults. There were only five cases of Burkitts lymphoma during the study period probably

**Table 3:** FIRST YEAR OUTCOME FOR ALL NHL SUBTYPES

TYPE OF CHEMOTHERAPY GIVEN	CHOP	CVP	R-CHOP	CHLORAMBUCIL + PREDNISOLONE	CODOX-M/IVAC	TOTAL
<b>INDOLENT TYPE NHL</b>						
CR	37	34	2	2	0	75 (26.9%)
PR	3	1	0	0	0	4 (1.4%)
NR	1	0	0	0	0	1 (0.4%)
LTF	2	0	0	0	0	2 (0.7%)
TOTAL	43 (15.5%)	35 (12.5%)	2 (0.7%)	2 (0.7%)	0 (0.0%)	82(29.4%)
<b>INTERMEDIATE TYPE NHL</b>						
CR	120	3	9	0	0	132 (47.3%)
PR	32	4	0	0	0	36 (12.9%)
NR	1	0	0	0	0	1 (0.4%)
LTF	2	0	0	0	0	2 (0.7%)
TOTAL	155 (55.6%)	7 (2.5%)	9 (3.2%)	0 (0.0%)	0 (0.0%)	171 (61.3%)
<b>AGGRESSIVE TYPE NHL</b>						
CR	9	0	3	0	1	13 (4.65%)
PR	12	0	0	0	1	13 (4.65%)
NR	0	0	0	0	0	0 (0.0%)
LTF	0	0	0	0	0	0 (0.0%)
TOTAL	21 (7.5%)	0 (0.0%)	3 (1.1%)	0 (0.0%)	2 (0.7%)	26 (9.3%)
GRAND TOTAL	219 (78.5%)	42 (15.1%)	14 (5.0%)	2 (0.7%)	2 (0.7%)	279 (100%)

**Table 4: SECOND YEAR OUTCOME FOR ALL NHL SUBTYPES**

TYPE OF TREATMENT GIVEN	CHOP	CVP	R-CHOP	CHLORAMBUCIL + PREDNISOLONE	CODOX-M/IVAC	TOTAL
<b>INDOLENT TYPE NHL</b>						
CR	18	4	2	2	0	26 (9.3%)
PR	1	1	0	0	0	2 (0.7%)
NR	0	0	0	0	0	0 (0.0%)
RELAPSE	3	4	0	0	0	7 (2.5%)
LTF	21	26	0	0	0	47 (16.9%)
TOTAL	43 (15.4%)	35 (12.6%)	2 (0.7%)	2 (0.7%)	0 (0.0%)	82 (29.4%)
<b>INTERMEDIATE TYPE NHL</b>						
CR	47	1	7	0	0	55 (19.7%)
PR	2	0	0	0	0	2 (0.7%)
NR	0	0	0	0	0	0 (0.0%)
RELAPSE	12	0	2	0	0	14 (5.0%)
LTF	94	6	0	0	0	100 (35.9%)
TOTAL	155 (55.6%)	7 (2.5%)	9 (3.2%)	0 (0.0%)	0 (0.0%)	171 (61.3%)
<b>AGGRESSIVE TYPE NHL</b>						
CR	5	0	2	0	0	7 (2.5%)
PR	0	0	0	0	0	0 (0.0%)
NR	0	0	0	0	0	0 (0.0%)
RELAPSE	2	0	1	0	0	3 (1.1%)
LTF	14	0	0	0	2	16 (5.7%)
TOTAL	21 (7.5%)	0 (0.0%)	3 (1.1%)	0 (0.0%)	2 (0.7%)	26 (9.3%)
GRAND TOTAL	219 (78.5%)	42 (15.1%)	14 (5.0%)	2 (0.7%)	2 (0.7%)	279 (100.0%)

CR: CLINICAL REMISSION, PR: POOR RESPONSE, NR: NO RESPONSE, LTF: LOST TO FOLLOW-UP

because patients were adolescents and adults, whereas a study done by C. Segbefia et al<sup>24</sup> showed 30.7% of childhood malignant neoplasms being Burkitts lymphoma.

These observations emphasize the need to identify the risk factors for NHL in the young and follow them up into adulthood. In a study carried out in Ghana on malignant neoplasms with ethnicity and characteristics of NHL in children, it was observed that Non-Hodgkin's diffuse cell type formed the most common lymphoma (53.3%) and the most common pediatric malignancy (29.6%).<sup>9</sup> Even though the Working Formulation is now obsolete, the Intermediate grade of NHL was found to be the most common type of NHL; with the Diffuse Large Cell and Diffuse Mixed Cell types being the most common.

In terms of the epidemiologic risk factors such as comorbidities like HIV, though it was not routine to conduct this test because of the low prevalence in

Ghana, in the last five years it has gradually been incorporated into our diagnostic workup for NHL.

The Working Formulation may still be a good source of diagnostic and prognostic information and a tool for treatment planning in countries where immunohistochemistry is not available or unaffordable.

The major limitations were unavailability of immunohistochemistry and molecular studies to better characterize NHL, poor documentation, poor follow up data after the first year. Another limitation was the fact that the sample size was relatively small to be representative of Ghana plus the study was only done in one area in Ghana – the major referral and teaching hospital in Accra (KBTH) to arrive at a definitive conclusion.

In conclusion, this study provides an overview of the distribution of NHL subtypes and their outcomes in adolescent and adult patients in a resource constrained setting. Patient loss to follow up in the 2<sup>nd</sup> and 3<sup>rd</sup> year

post treatment was very high and the reasons for this should be explored in a future study. Immunohistochemistry, cytogenetics and specific molecular studies, which are important in characterization of NHL, should be made affordable and accessible in low-income countries.

**Authors Contributions:** YDA, EQ, EA, AA, CS and JKA, all contributed in data collection, analysis and manuscript write up

**Conflict of interest:**

The authors declare no competing financial interests.

**Acknowledgement:** We are grateful to the Department of Haematology and the patients for use of medical records.

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