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Non-Hodgkin Lymphoma in Nigeria: An Insight into the Clinical, Laboratory Features and Outcomes

Anazoeze Jude Madu[1*], Kaladada Korubo[2], Ifeoma Clare Ajuba[3], Ngozi Immaculata Ugwu[4], Augustine Ejike Okoye[4], Angela Ogechukwu Ugwu[1], Augustine Nwakuche Duru[1], Kenechi Anthony Madu[5], Ebele Muoghalu[6], Onyinye Eze[6], Nneka Amu[6], Chioma Ugwu[6], Gladys Ilechukwu[6], Chiemelie Obiatuegwu[6] and Frances Nwamaka Madu[7]

[1]Department of Haematology and Immunology, University of Nigeria Enugu Campus (UNEC), Enugu State, Nigeria.
[2]Department of Haematology, University of Port Harcourt, Rivers State, Nigeria.
[3]Department of Haematology, Nnamdi Azikiwe University. Anambra State, Nigeria.
[4]Department of Haematology, Alex Ekwueme Federal University Teaching Hospital Abalikili, Ebonyi State, Nigeria.
[5]National Orthpedic Hospital Enugu, Enugu State, Nigeria.
[6]Department of Haematology and Immunology, University of Nigeria Teaching Hospital, Enugu State, Nigeria.
[7]Department of Management, University of Nigeria Enugu Campus, Enugu State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Authors AJM, KK, ICA, NIU, AEO, AOU and AND designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AJM, KAM, EM, OE, NA, CU and FNM managed the analyses of the study while authors AJM, EM, GI, CO, FNM, KK, ICA, NIU, AEO, AOU and AND managed the literature searches. All authors read and approved the final manuscript.

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**Corresponding author: E-mail: Anazoeze@gmail.com, anazoeze@yahoo.com, anazoeze.madu@unn.edu.ng;*

ABSTRACT

Background: The prevalence of Non-Hodgkin lymphoma (NHL) has waxed and waned with the trends in HIV prevalence over the years. The clinical landscape as well as treatment experience in Africa has not earned the much needed attention.

Aim: This study aimed at giving insight to the clinical and laboratory variations as well as treatment outcomes in NHL in a group of Nigerian patients.

Methods: The clinical and laboratory details were obtained from all patients diagnosed with NHL from October 2015 to December 2018 in 3 tertiary health institutions in Nigeria. These were the patients seen or admitted to the Haemato-Oncology clinics and wards. They were followed-up till the time of this write-up, while those that were lost to follow-up were also noted.

Results: There were 77 patients in the study aged 16 to 81 years with a median age of 50 years. These include 45 males and 32 females. Majority (53.7%, n=36/67) of them had no palpable splenomegaly at diagnosis. Of 57 patients, 26.3% (n=15/57) had diffuse large B cell lymphoma, 15.8% (n=9/57) small lymphocytic lymphoma while 10.5% (n=6/57) each had intermediate and high grade lymphoma 14% (n=8/57). The other histological types seen were Follicular lymphoma 3.5%, Cutaneous T cell lymphoma 5.3%, maltoma 7% and bone marrow lymphoma 3.5%.

Patients with ≤ stage 2 Ann-Arbor were 16/66, while majority (40/66) were > stage 2 at diagnosis. The median haemoglobin concentration remained stable from 9.8g/dl at diagnosis to 12.3g/dl at 6 months, while the absolute neutrophil count dropped from 2.4 x 10^9/l to 1.2 x 10^9/l. The median leucocyte count at diagnosis was 6.8 x 10^9/l, while the platelet count was 185 x 10^9/l, both parameters were 5.3 and 187 x 10^9/L at six months post-diagnosis, respectively. Of the 64 patients who had their HIV status documented 7 were positive, giving prevalence rate of 12.6%.

Only 14 (18%) out of all the patients had immunophenotyping and only 8 of them were CD20 positive. Relapse rate among the cohort was 43.3% (26/60) while 34 (56.7%) were still on remission. 22 (30.6%) patients were lost to follow up, 18 (25%) had died while 32 (44.4%) were alive and had been seen in the clinic out of 72 patients recorded. The median follow-up time was 10 months and ranged from 0 to 45 months and the mean time of remission was 12 months (range 0-125.) Majority of the patients (55.5%, 35/63) received CHOP with or without Rituximab, 7.9% (5/63) received COAP as first line chemotherapy, while 13/63 (20.6%) had their regimen switched either due to relapse or sub-optimal response, while 10/63 (15.8%) received other combinations. Only 7 patients got Rituximab in combination with any regimen.

Conclusion: The management modalities and treatment outcomes for NHL in most resource-poor countries are sub-optimal and need to be adopted to suit the available resources in these areas and optimize survival /response. The use of treatment algorithms with expensive and unavailable chemotherapeutic agents may not suffice and cheaper available combinations maybe advocated for use in situations where the desirable is not available.

Keywords: Non-Hodgkin lymphoma; Rituximab; laboratory variations.

1. INTRODUCTION

Non-Hodgkin lymphoma (NHL) represents a progressive clonal expansion of B cells or T cells and/or NK cells arising from accumulation of lesions affecting proto-oncogenes or tumour suppressor genes, which results in cell immortalization. The occurrence of different histological and immunophenotypic subtypes has been shown to vary amongst people from different races and different geographical background and this may be explained by the genetic and environmental aetiologic factors [1]. Several cytogenetic lesions are associated with specific NHLs, reflecting the presence of specific markers of diagnostic importance in sub classifying various NHL types [2,3].

There has been an increase in incidence over the past several decades. It is known that the incidence of NHL in the equatorial belt of Africa has been observed to increase by 30,000 per year [4]. The most common NHL subtype is diffuse large B cell lymphoma (DLBCL) which represents about 30% of cases of NHL diagnosed in the United States. This is closely followed by Follicular lymphoma which makes about 20% of all NHLs, then MALT (mucosal associated lymphoid tumor) lymphoma (7.5%), SLL/CLL (7%) and Mantle cell lymphoma (6%) [1,5]. Burkitt's lymphoma accounts for 82% of all NHL among those 18 years and below. Among adults, DLBCL accounts for 55% of NHL. [1] It was found to have the highest incidence of all haematological cancers in a study done in

Maiduguri Nigeria which documented an incidence of 51.3% [6] . Also, in another work done in the Niger Delta, incidence of NHL was found to be 83% compared with 17% of Hodgkin's lymphoma [7].

NHL has varied clinical manifestations. These clinical features depend on factors such as site of tumour stage, grade, rate of growth and pressure effect of the tumour on adjacent organs. The most common presenting feature is progressive painless lymph node enlargement. About a third of patients present with extranodal involvement with the common sites being the gastrointestinal tract including Waldeyers ring, skin, bone marrow, sinuses and CNS. [8] B symptoms indicate poor prognosis and are usually seen late in the disease and not at presentation while bone marrow involvement presents as cytopaenias.

The aetiology of NHL remains largely unknown. Several reports suggest associations between NHLs and several infective agents as well as immunologic and environmental factors [9-11]. It may result from chromosomal translocations, environmental factors, immunodeficiency states such as HIV/AIDS, post solid organ transplant, and chronic inflammatory conditions such as celiac disease, rheumatoid arthritis and Sjogren disease [11,12]. Viral infections have been associated with certain subtypes of NHL such as EBV as seen in Burkitt's lymphoma; Human T – lymphotropic virus is associated with adult t-cell leukaemia/lymphoma, Herpes virus 8 is associated with primary effusion lymphomas [13,14].

Treatment of NHL varies widely and depends on tumour stage, histology (low, intermediate or high – grade), phenotype (B-cell T-cell or NK/null cell) and patient/host factors such as performance status, age [15,16] presence or absence of symptoms or co-morbidities and family history of lymphomas. [2] Treatment modalities include radiotherapy, chemotherapy and stem cell transplant, or a combination of these. [17]

There have been many studies on the heterogeneity within the NHLs according to histology but few descriptive studies have considered NHLs by clinical pattern laboratory features and outcome in Nigeria. Data on various aspects of NHL from developing countries including risk stratification, response to treatment and survival are scanty. [12] Our purpose is therefore to assess the clinical patterns, treatment, response and any notable increases in different histological subgroups of NHL and to establish baseline data for lymphoid neoplasms by subtypes in these centers.

2. PATIENT AND METHODS

Data was obtained retrospectively from the case notes of the patients both on admission and seen at the out-patient department of 3 tertiary health facilities- University of Nigeria Teaching Hospital, University of Port Harcourt Teaching hospital and Federal Teaching Hospital Abakaliki, all in Nigeria. This included individuals with a histological diagnosis of NHL over a 3 year period, from October 2015 to December 2018. Information obtained included their age, sex, HIV status, clinical stage, haemoglobin concentration, leucocyte and platelet count at diagnosis and at 3 monthly intervals. Other patient clinical information obtained included; spleen size, relapse status, number of cycles of chemotherapy received and presence of co-morbidities. Data on the type of chemotherapeutic regimen used and follow up complete blood counts were also recorded as well as duration of survival (mortality as at the time of data computation).

2.1 Data Analysis

This was done using SPSS 20.0 (Chicago, Illinois, USA) and data was expressed in tables. Correlation coefficient was analyzed using the Spearmann Rho and Kendaull tau_b correlation, 2-tailed test for discrete variables. The association between nominal and ordinal variables was assessed using the Monte-Carlos 2 –sided assessment of tolerance intervals for the Chi Square and Fischers exact test. Significance was assigned to values of p less than 0.05. The survival was plotted on Kaplan-Meier survival curve using several variables.

3. RESULTS

Out of 77 patients, 45 were males and 32 females, giving a male: female ratio of 1.5:1. Majority (53.7%, 36/67) of them had no palpable splenomegaly at diagnosis. The patients were aged 16-81 years with a median age of 50 years. The age distribution of the patients recorded in the study is shown on Fig. 1a. The figure shows the age frequency with each number of persons and the curve indicating the modal (peak) age incidence. The mean haemoglobin concentration at diagnosis was 9.9 g/dl. The mean 3, 6 and 9

months levels were 11.9 g/dL, 12.4 g/dL and 12.4 g/dL, respectively. The mean leucocyte count at diagnosis, 3rd, 6th and 9th month was 16.9, 16.8, 14.5 and 8.1 x 10^9/L, respectively. The mean platelet counts at diagnosis, 3rd, 6th and 9th month were, 206, 234, 194 and 244 x 10^9/L, respectively. While the mean absolute neutrophils count at diagnosis was 3.1 x 10^9/L, with a median value of 2.4 x 10^9/L. The values on the 3rd, 6th and 9th months post-diagnosis were 1.6, 1.9 and 1.3 x10^9/L, respectively. HIV screening test was found to be positive in 7/64 of the patients at diagnosis giving prevalence rate of 12.7%, while one patient each was found to be sero-positive for Hepatitis B and C. The median blood count values after 3 months of chemotherapy are shown on Fig. 1b. The spleen sizes ranged 0 to 26cm with a mean value of 5.6cm.

The majority of the patients 26.3% (15/57) had a histological diagnosis of diffuse large B cell lymphoma, 15.8% (9/57) small lymphocytic lymphoma while 10.5% (6/57) each were diagnosed with intermediate and high grade lymphoma 14% (8/57). The other histological types seen were Follicular lymphoma 3.5%, Cutaneous T cell lymphoma 5.3%, maltoma 7% and bone marrow lymphoma 3.5%. The histological types and the clinical findings on diagnosis across the various types are shown in Fig. 1b. The differences in the clinical and laboratory parameters at diagnosis in the different histological types are recorded in Table 1. Immunophenotyping (CD5, CD20, CD23, CD56, Cyclin D1, Tdt, Ki-67, BCL-2 and or MUM1) was done for 14 (18%) of the patients and CD20 positivity was noted in 8 of them. Of the patients that had their clinical stage documented at diagnosis, Stage 1 and 2 had 12.7% (8/55) each, 19 (34.5%) were stage 3 while 22 (40%) had stage 4 disease. Splenomegaly was observed in 31 (46.3%) out of 67 patients recorded. Splenomegaly was usually found in patients with Stage 4 disease (Table 2) and this also showed a direct positive relationship with disease stage (r=0.520, p=0.0001), see Table 2.

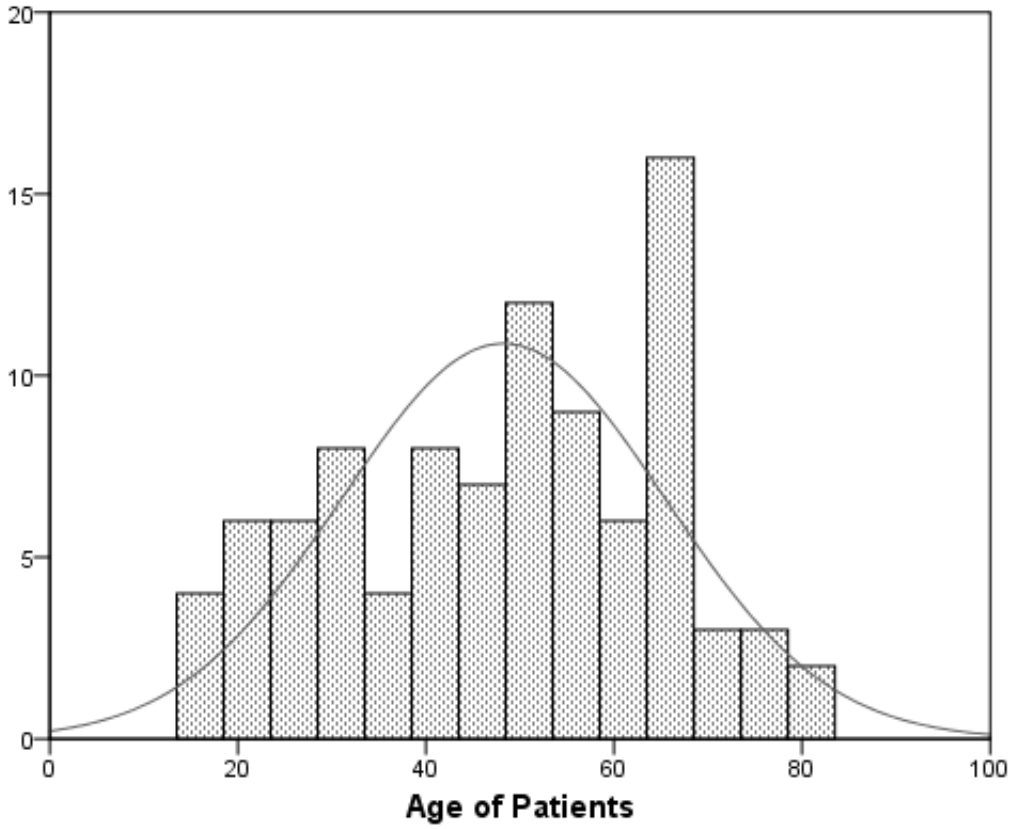

Fig. 1a. Age distribution of NHL patients

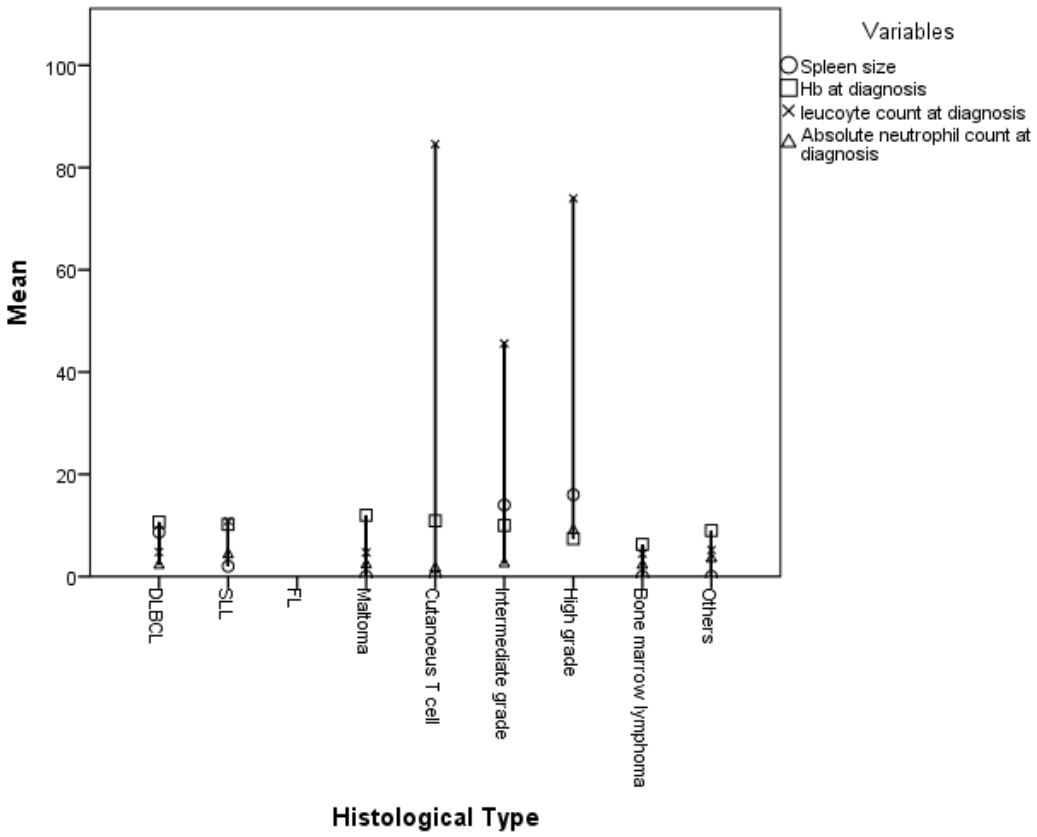

Fig. 1b. The distribution of some clinical and laboratory findings in NHL across the various histological subtypes

SLL= Small lymphocytic lymphoma, DLBC = Diffuse Large B cell lymphoma, FL = Follicular lymphoma

Table 1. Frequencies (median values) of some clinical parameters with histological type in Non-Hodgkin lymphoma

Histological type	Age (years)	Spleen size (cm)	Hb (g/dL)	White cell count (x 10^9/L)	Platelet count (x 10^9/L)	Duration of follow up/ survival (months)
DLBCL	44	0	11	5.2	191	12
SLL	62	0	8.7	7.1	166	9
Maltoma	43	0	9.7	8.4	239	2
High grade lymphoma	47.5	0	10	10.8	172	3.5
Intermediate grade lymphoma	50.5	14	10.6	10.8	202	0

SLL= Small lymphocytic lymphoma, DLBC= Diffuse Large B cell lymphoma

The spleen size was found to have an inverse relationship with the age and platelet count at diagnosis, (r=-0.190) p=0.023 and (r=-0.188) p=0.033, respectively. The Ann-Arbor clinical stage had an inverse relationship with the both the platelet count (r=-0.215, p= 0.035) and Hb at diagnosis (r=-0.253) p= 0.009). Patients who had a higher Hb at the 3rd month of therapy also had a longer remission (r=0.40; p=0.02). It showed no relationship with the duration of survival (r=0.099, p=0.513) p=0.739. See Table 2. There was no relationship between the Ann-Arbor stage and duration of remission or duration of survival (r=0.204, p=0.239 and r=0.099, p=0.513 respectively).

Table 2. Clinical parameters amongst the various Ann Arbor stages in Non-Hodgkin lymphoma (number= 64 patients)

Ann Arbor stage at diagnosis	Age (years)	Spleen size (cm)	Hb(g/dl)	White cell count (x 10^9/l)	Platelet count (x 10^9/l)	Duration of follow up/ survival (months)
Stage 1 (n=8)	63.5	NP	10.9	6	320	NA (7 alive/0 dead)
Stage 2 (n= 7)	50	NP	11.1	7.6	182	3.4 (4 alive/3LTFU)
Stage 3 (n=26)	52	NP	10.2	5.7	150	14.8 (14 alive/5 dead/ 7LTFU)
Stage 4 (n=23)	43	11	9.2	11.6	182	8.1 (8 alive/ 12 dead/ 3 LTFU)

Hb= Haemoglobin concentration, LTFU = Lost to follow up. NP = Not palpably enlarged

Majority of the patients (41.3%, 26/63) received CHOP (Cyclophosphomide, Doxorubicin, oncovin and prednisolone) regimen alone, 7.9% (5/63) received Rituximab with CHOP (R-CHOP) while a further 6.3% (4/63) received CHOP regimen in the first instance and later switched to other combinations. COAP (Cyclophosphomide, Oncovin, Cytosine Arabinoside and Prednisolone) regimen was received by 7.9% (5/63) of the patients while a similar number received it in the first instance and later switched to a different regimen. Fig. 1c shows some haematological parameters and mean duration of follow up in patients that received some chemotherapeutic combinations. Patients who received high number of cycles of chemotherapy had a longer duration of remission (r=0.537; p=0.0001). Only 15 of the patients had done immunophenotyping and 11 out of them were positive for CD20, while 4 of these received Rituximab. As at the time of this write-up of the 45 cases recorded, 21 (46.7%) had relapsed. Fig. 1d shows the Kaplan-Meier life curves of the patients placed on the various chemotherapeutic combinations.

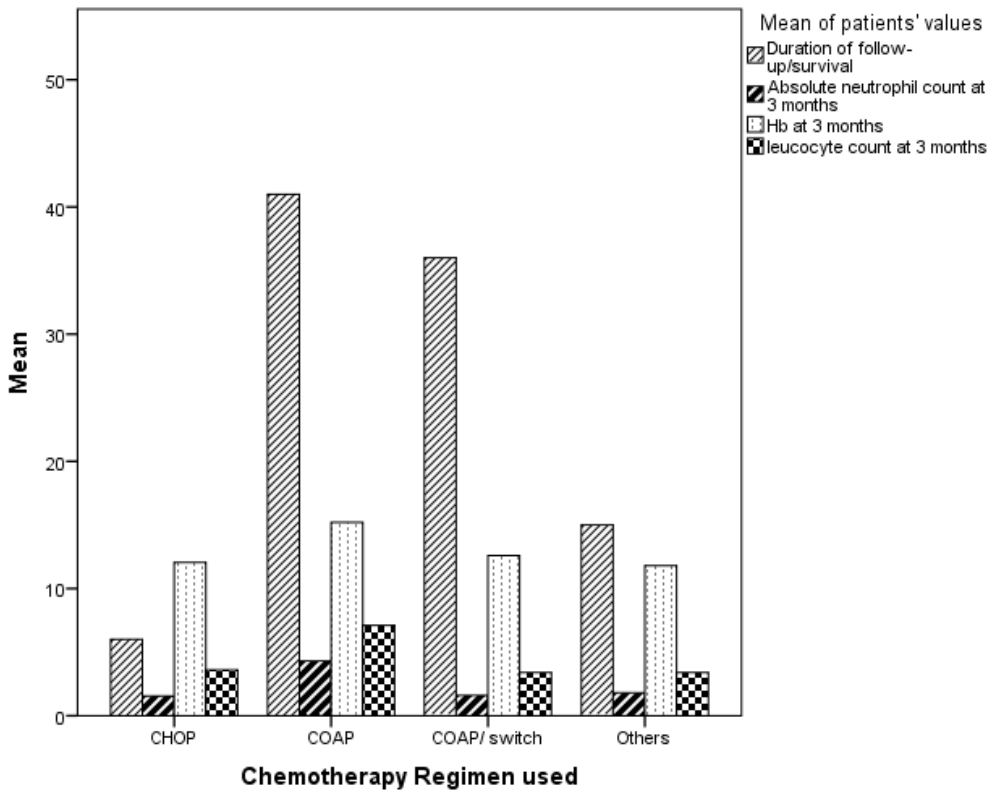

Fig. 1c. The distribution of some haematological parameters and mean duration of survival at the 3rd month of chemotherapy for NHL

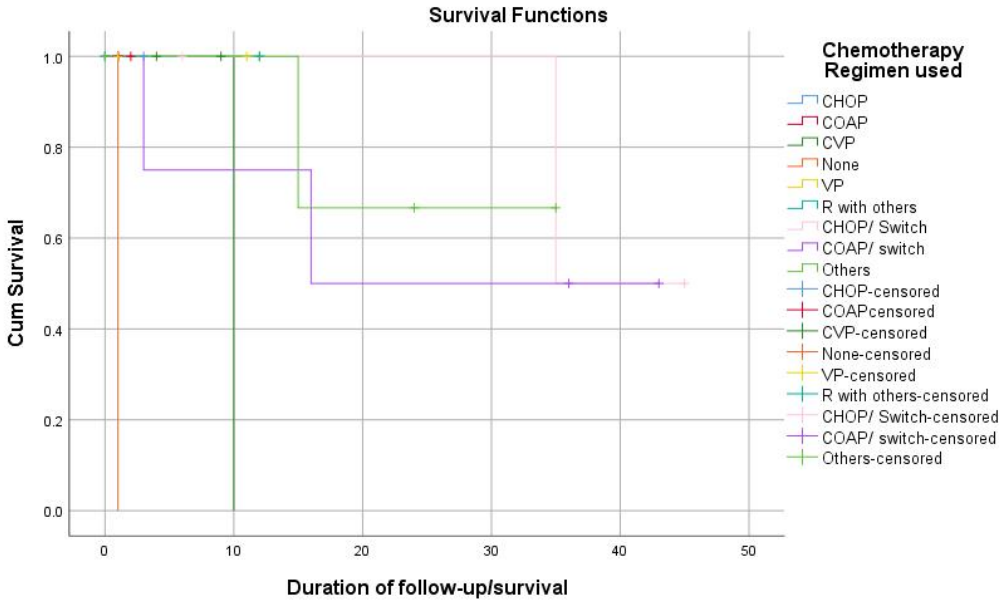

Fig. 1d. Kapplan-meier life curve of patients on the various chemotherapeutic combinations

While out of 72 patients whose records were available, 22 (30.6%) had been lost to follow up, 18 (25%) had died while 32 (44.4%) were alive and had been seen in the clinic. The mean survival/ duration of follow-up was 10 months with a range of 0 to 45 months. The duration of remission however ranged from 0 to 125 months with a mean value of 11 months. The number of cycles of chemotherapy received varied from 0 to 19 with a median value of 3.5. The number of cycles of chemotherapy showed a positive correlation with the duration of survival (p=0.051). The Pearson Chi Square test showed a significant value of 16.702 (p=0.008) and likelihood ratio of 19.902 (p=0.005) between the Ann-Arbor stage and the likelihood of death within 5 years. However the type of chemotherapy regimen used had no significant impact on whether the patients were dead or alive at the end of the study period (Pearson Chi square test p=0.337, likelihood ratio p=0.348).

4. DISCUSSION

The study assessed the clinical, laboratory and epidemiological features of patients being seen in tertiary health centers across Nigeria. The male: female ratio is similar to that observed in previous studies across the world [10,18]. The male predominance in the occurrence of NHL though had been noted in previous studies cannot be easily explained except by exposure to some occupational carcinogens peculiar to occupations predominated mainly by males. The median age incidence was found to be 50 years with the predominating subtype being diffuse large B cell lymphoma. However the age prevalence curve suggests there may be a bimodal age peak in the mid-twenties and later around 50 and 65years of age. A study done in Ibadan found a mean age of 29 years. [18] This portrays the underlying fact that Non-Hodgkin lymphomas are an amorphous group of lymphoid tumors which are most likely unrelated in either their aetio-pathogenesis or natural history.[19] This trend has been observed by Clark *et al*. [1]

The full blood counts of these patients showed anaemia and leucocytosis with mild neutropaenia at presentation. This trend was observed to be ameliorated by treatment across the various disease stages. This may imply that myelosuppression in this situation may be due to either tumor invasion or by cytokine secretion. However the extent to which either impacts on the marrow may require further research to elucidate. Approximately one-in-ten of the patients were also positive for HIV 1 and 2 screening tests. This HIV prevalence rate is higher than that of the general population and connotes the sustained predisposition to NHL by HIV. This also implies that NHL prevalence might be reduced by up to 10% if HIV prevalence is reduced to its barest minimum.

The Ann-Arbor stage was found to have a direct relationship with the haemoglobin concentration as well as the platelet count. This interesting observation may be worthwhile in validating the importance of low haematocrit readings in NHL patients and may also serve as a basis for future studies to determine if this is due to marrow invasion or other cytokine-related effects of lymphomas. Larger spleen sizes were associated with higher disease stages. This observation may be due to an expectedly higher tumor bulk and burden in patients with more advanced disease though this has not been documented as a measure of tumor bulk in NHL. Spleen size may therefore be a good guide to assess disease burden as well as an important tool in monitoring remission. Most of the patients (74.5%) had at least stage 3 disease. This may imply late presentation or prolonged time from first presentation to tissue diagnosis.

Majority of patients had diffuse large B cell lymphoma followed by small lymphocytic lymphoma, a low grade indolent tumor. This may also indicate that the prevalence of the various types of NHL may vary across different patient populations, an indication of a possible variability in the causative agents. In a Chinese study, (15) DLBCL was the most prevalent followed by endothelial NK/T cell lymphomas, while the study by Oluwasola et al. [18] showed the small non-cleaved subtype to be the most prevalent followed by the diffuse large cell type. However, this disparity must be viewed against the background knowledge had shown that 'wrong diagnosis' claimed a reasonable portion of patients who had no immunophenotyping.[20] Varying lymphoma subtypes may also be attributable to variations in the environmental carcinogens observed at varying levels in different geographical locations as well as protective impact of some genetic variants peculiar to some population clusters [21].

The treatment protocol used in these patients varied widely and majority of the patients received at least 4 cycles of chemotherapy. This did not impact on the outcome in terms of duration of survival. Previous survival studies in NHL in Uganda had also recorded sub-optimal survival which was attributed to lack of resources as well as HIV co-infection [22] This again showcases the heterogeneity of the disease spectrum of NHL as well as the fact that the cancer genomics of each peculiar tumor may play a major role in survival. This unfortunately was not within the scope of this work. The number of cycles of treatment received however was found to be related with the duration of survival. The gold standard in NHL treatment is R-CHOP and it is known that response rates dwindle significantly in the absence of Rituximab (ant-CD20) [23,24]. Majority of the patients in this group did not have immunohistochemistry done and therefore could not be placed on Rituximab. This may have adversely affected survival and underlies the need for some rebate as the cost of investigations and procuring on this drug is not affordable for the generality of the population [25].

This study had a maximum follow up of about 4 years and a quarter of the patients had died as at the time of this evaluation.

5. CONCLUSION

Non-Hodgkin lymphoma is predominant in males with a median age incidence of 50 years. Majority of the patients presented with at least Stage 3 disease and diffuse large B cell lymphoma subtype. Majority of the cases were still unconfirmed with immunohistochemistry and of those that were CD 20 positive only 5 of them could afford and received Rituximab. Treatment of NHL was mainly with CHOP chemotherapy and gave sub-optimal survival of 10 months in those recorded, with mortality in about a third of the patients.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical approval was obtained from the University of Nigeria Teaching Hospital health research and Ethics committee as well as the ethical review boards of the participating centers.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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