

## **PATTERN OF EXTRA NODAL INVOLVEMENT IN NON-HODGKIN'S LYMPHOMA**

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### ABSTRACT

**Objective:** Non-Hodgkin lymphoma (NHL) is a group of neoplastic lymphoproliferative disease originating mainly in the lymph nodes with numerous clinical manifestation and histological features. This study was intended to determine the pattern of extra nodal involvement in Non-Hodgkin's lymphoma (NHL) in a tertiary care hospital, Karachi.

**Methodology:** This was a cross-sectional study conducted at the Department of clinical oncology, Jinnah postgraduate medical Centre, Karachi by using non-probability consecutive sampling technique. The duration of the study was about 6 months from Nov 2020-May 2021. A total of 78 adult patients of age between 17 to 71 years of either gender with biopsy proven diagnosis of NHL were included in the study. Chi-square test was used to assess the significance between age, gender, stage of NHL, bone marrow and lymph node involvement with pattern of extra nodal involvement.

**Results:** The study results showed, out of 78, 53(67.9%) were males whereas 25(32.1%) were females with their mean age was  $46.71 \pm 14.36$  years. Frequency of Extra-nodal Sites of involvement showed that paravertebral fascia 8(10.3%) was the most frequent anatomical site of NHL, followed by thigh 7(9%), femur 5(6.4%), tonsils 4(5.1%). Histologically, Diffuse large B cell lymphoma (DLBCL) reported in about 52(66.7%) of all the cases, 14(17.9%) had B cell, 9(11.5%) had follicular lymphoma while only 3(3.8%) had Marginal zone lymphoma (MZL). Furthermore, there was a significant association observed between morphological types with gender ( $p=0.012$ ), with stage of disease ( $p=0.001$ ) and with lymph node involved ( $p=0.012$ ).

**Conclusion:** This study concluded that diffuse large B cell lymphoma was the most common morphological type observed. Paravertebral fascia and thigh were the most common anatomical sites for extranodal involvement in Non-Hodgkin lymphoma. Most of the cases were at stage IE with better prognosis and survival rate. Moreover, significant differences were found in the pattern of extra nodal Non-Hodgkin lymphoma.

**Keywords:** Extra nodal lymphoma, Morphological pattern, Non-Hodgkin's Lymphoma.

## INTRODUCTION

Lymphoma is characterized by the slow growing in addition to destructive human cancerous growth that arises from cells of the immune system at different phases of differentiation. They can be visible in a broad spectrum of immunologic, morphologic, and clinical manifestations. Lymphoid cells malignancies manifest as leukemia in which involvement of bone marrow and blood occurs, or as lymphoma wherein solid tumors of the immune system involved [1].

Lymphomas are generally categorized into two leading groups: Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL). NHL is frequently prevalent and represents approximately 85% of lymphomas.[2] It is predicted that NHL is most common cancer in US that is accounted for almost 4% of all the cancers. It is proposed by the “The American Cancer Society 2018” that around 41,370 men and 32,950 women together with both adults and children are diagnosed with NHL and nearly 11,510 men and 8,400 women are expired owing to NHL.[3] It is estimated that NHL is one of the common prevailing cancer in Pakistan[4]. According to annual cancer registry report by “Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC) presented in 2008 revealed that about 4.40% cases of NHL are observed [5]. Another research conducted in Pakistan indicated that of all types of lymphomas 73% cases represents NHL, wherein B-cell lymphomas were present in 86% cases. In Pakistan, it has been witnessed that diffuse large B- cell lymphoma (DLBCL) is more prevalent [6,7]. One of the research conducted by Bangash MH et al. presented DLBCL is accounted for 75% patients, 11.1% had marginal zone lymphoma (MZL), 6.6% had follicular lymphoma and anaplastic large cell lymphoma (ALCL) [8].

On the basis of histological features and phenotype of tumor cell, there are two types of HL: classical and non-classical types. The classical HL has four histological sub-types – the most common is nodular sclerosis, lymphocyte predominance, mixed cellularity, and lymphocyte depletion, whereas non-classical comprises the nodular lymphocyte that is most prevalent sub-type.[9] Generally, NHL can be categorized into two groups on the basis of prognosis: The aggressive and the indolent lymphomas, the indolent lymphomas exhibits a good prognosis with a survival rate of about 10 years. Follicular lymphoma (FL) is the most common type of indolent lymphoma which is accounted for 22% of NHL cases, subsequently 6% marginal zone lymphoma (MZL) and 8% representing small-cell lymphocytic lymphoma (SLL). On the other

hand, aggressive lymphomas comprised of diffuse large B-cell lymphoma (DLBCL) that is the most prevalent subtype, accounting for about 30% of cases after that 6% mantle cell lymphoma (MCL) and 8% adult T-cell leukemia/lymphoma represents NHL cases.[2]

The term extranodal can be defined as a rare form of lymphoid malignancy that is characterized by the neoplastic multiplication at sites excluding the probable localized lymph nodes or lymphoid tissues[10]. The most common extranodal sites of anaplastic large cell lymphoma (ALCL) included subcutaneous tissue, skin, bone, bone marrow, lung, and gastrointestinal tissues[11]. In addition to, distribution among the non-lymphoid tissues is non-uniform that included central nervous system (CNS), lung, gastrointestinal tract, bone, and skin [12]. Diagnosis can be made by the Positron emission tomography(PET) CT scan which is more valuable technique over contrast-enhanced computed tomography (CECT) for the assessment of extranodal involvement in non-Hodgkin and Hodgkin lymphoma patients [13]. FDG PET technique has been extensively used for disease staging, recognition of relapse, and observing of prognosis in Hodgkin and NHL patients [14]. Formerly, the imaging assessment and follow-up of lymphoma patients was based merely on outcomes at contrast-enhanced CT. Though, contrast-enhanced CT has restricted sensitivity in identifying lymphomatous involvement of normal-sized lymph nodes, spleen, bone marrow, and extranodal structures.[15]

In the past decades, the incidence of NHL and that of primary extranodal lymphoma has increased more rapidly than the nodal type. Studies have been published about various aspects of extra-nodal lymphoma; nevertheless there is a dearth of studies about morphological type and pattern of involvement. The aim of this study was to observe the pattern of extranodal NHL in terms of morphological type and site of extranodal involvement at tertiary care hospital, Karachi.

## METHODOLOGY

This was a cross-sectional study conducted at the Department of clinical oncology, Jinnah postgraduate medical Centre, Karachi by using non-probability consecutive sampling technique. The duration of the study was about 6 months from Nov 2020-May 2021. The ethical approval was taken from ethical review committee. A total of 78 adult patients of age between 17 to 71 years of either gender with biopsy proven diagnosis of NHL were included in the study whereas those patients who underwent chemotherapy were excluded from the study.

Informed written and verbal consent was obtained from all the patients. Basis Information regarding socio-demographic included age, gender, ethnicity & history of smoking and alcohol were recorded. Clinico-pathologic characteristics included duration of disease, presenting symptoms, Eastern Cooperative Oncology Group (ECOG) performance status, HBV and HCV status, laboratory findings included hemoglobin level, total leukocyte (white blood cells) count (TLC), platelet count (PLT), erythrocyte sedimentation rate (ESR) & serum lactate dehydrogenase (LDH) were also documented. Ann Arbor classification was used to classify patients according to the findings of bone marrow biopsy, computed tomography (CT) scans of abdomen & pelvis, MRI scan for spine, brain or soft tissue involvement and upper gastrointestinal (18) endoscopy in certain cases. The histological type, stage of disease and involvement of extra nodal lymphoma were also observed.

Data was analyzed using SPSS version 23. Mean and SD were calculated for quantitative variables. Frequency and percentage were calculated for qualitative variables. Chi-square test was used to assess the significance between age, gender, stage of NHL, bone marrow and lymph node involvement with pattern of extra nodal involvement. P-value  $\leq 0.05$  was taken as statistical significant.

## RESULTS

A total of 78 patients were included in the study. The mean age of the patients was  $46.71 \pm 14.36$  years. The mean Hb level, TLC, PLT, ESR, LDH were reported as  $11.09 \pm 2.44$  g/dl,  $9.06 \pm 3.56$  (/mm<sup>3</sup>),  $243.56 \pm 112.39$  ( $\times 10^9$ /L),  $39.35 \pm 25.38$  mm/hr &  $176.96 \pm 117.84$  (units/L). Out of 78, 53(67.9%) were males whereas 25(32.1%) were females. Ethnicity revealed 28(35.9%) were Sindhi, and 11(14.1%) was Punjabi. Out of 78 cases, 16(20.5%) were smokers, 7(9%) were alcohol consumers and 21(26.9%) were pan/gutka consumers. Most of the patients 63(80.8%) presented < 1 years duration of symptoms. In all, most of the cases presented with fever 68(87.2%), followed by weight loss 65(83.3%) and 57(73.1%) reported night sweat. About 12(15.4%) had bone marrow involvement. About 96.2% of the cases had ECOG status 0, 31(39.7%) had stage of tumor IE and 47(60.3%) had lymph node involvement, as shown in Table I.

Frequency of Extra-nodal Sites of involvement showed that the paravertebral fascia 8(10.3%) was the most frequent anatomical site of NHL, followed by thigh 7(9%), femur 5(6.4%), tonsils 4(5.1%) and other sites are depicted, as shown in Table II.

Stratification of morphological types with respect to age, gender, bone marrow involvement, stage of tumor & lymph node involvement revealed that 32 (61.5%) reported DLBCL had  $\leq 50$  years of age whereas 20(38.5%) reported DLBCL had  $> 50$  years of age. 5(55.6%) reported Follicular Lymphoma had  $\leq 50$  years of age whereas 4(44.4%) reported Follicular Lymphoma had  $> 50$  years of age. 6(42.8%) reported NHL B Cell had  $\leq 50$  years of age whereas 8(57.2%) reported NHL B Cell had  $> 50$  years of age. Only 3(100%) reported Marginal zone lymph had  $\leq 50$  years of age with an insignificant association between age and morphological types ( $p=0.287$ ). There was a significant association between gender and morphological types ( $p=0.012$ ). Furthermore, significant association observed between stage of disease and morphological types ( $p=0.001$ ) and lymph node involved and morphological types ( $p=0.012$ ), as shown in Table III.

Histologically, Diffuse large B cell lymphoma (DLBCL) reported in about 52(66.7%) of all the cases, 14(17.9%) had B cell, 9(11.5%) had follicular lymphoma while only 3(3.8%) had Marginal zone lymphoma (MZL), as shown in Fig I.

**Tab I: Demographic Characteristics of Study Participants. (n=78)**

<b>Variables</b>	<b>Descriptive</b>	<b>Variables</b>	<b>Descriptive</b>
<b>Age</b>	46.71±14.36	<b>Bone Marrow</b>	
<b>Hemoglobin level (g/dl)</b>	11.09±2.44	Yes	12(15.4%)
<b>TLC(/mm<sup>3</sup>)</b>	9.06±3.56	No	66(84.6%)
<b>PLT(*10<sup>9</sup>/L)</b>	243.56±112.39	<b>ECOG Status</b>	
<b>ESR (mm/hr)</b>	39.35±25.38	0	75(96.2%)
<b>LDH (units/L)</b>	176.96±117.84	2	3(3.8%)
<b>Gender</b>		<b>Fever</b>	
Male	53(67.9%)	Yes	68(87.2%)
Female	25(32.1%)	No	10(12.8%)
<b>Ethnicity</b>		<b>Weight Loss</b>	
Sindhi	28(35.9%)	Yes	65(83.3%)
Punjabi	11(14.1%)	No	13(16.7%)
Balochi	5(6.4%)	<b>Night Sweat</b>	
Pathan	13(16.7%)	Yes	57(73.1%)
Siraiki	1(1.3%)	No	21(26.9%)
Urdu	20(25.6%)	<b>Stage of tumor</b>	
<b>Smoker</b>		I	4(5.1%)
Yes	16(20.5%)	IE	31(39.7%)
No	62(79.5%)	IIE	8(10.3%)
<b>Alcohol Consumers</b>		III	1(1.3%)
Yes	7(9%)	IIIE	13(16.7%)
No	71(91%)	IV	9(11.5%)
<b>Pan/Gutka Chewer</b>		IVE	12(15.4%)
Yes	21(26.9%)	<b>Lymph node involved</b>	
No	57(73.1%)	Yes	47(60.3%)
<b>Duration of symptoms</b>		No	31(39.7%)
<1 year	63(80.8%)		
≥1 year	15(19.2%)		

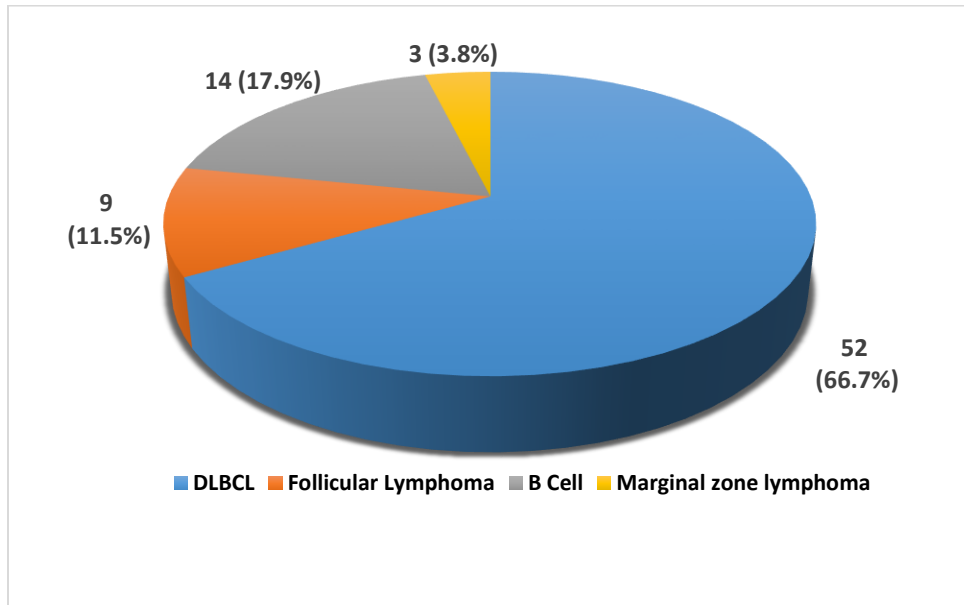
**Tab II: Frequency of Extra-nodal Sites of Involvement.**

Anatomical site	n (%)	Anatomical site	n (%)
Right arm	1(1.3)	Parotid gland	3 (3.8)
Submandibular	4 (5.1)	Nasal cavity	1(1.3)
Lower mandible	2 (2.6)	Brain	1(1.3)
Thyroid gland	3 (3.8)	Anterior chest wall	1(1.3)
Antrum	1 (1.3)	Nasopharynx	1(1.3)
Duodenal mass	1 (1.3)	Thigh	7 (9)
Femur	5 (6.4)	MALT (large intestine)	3 (3.8)
Lung	4 (5.1)	Tonsil	4(5.1)
Paravertebral fascia	8 (10.3)	Para spinal	2(2.6)
Hip joint	1 (1.3)	Pyriform Fossa	1(1.3)
Retroperitoneal	5 (6.4)	Transverse colon	1(1.3)
Mediastinum	1 (1.3)	Gastric lymphoma	2(2.6)
Spleen	3 (3.8)	Oropharynx	3 (3.8)
Right wrist	1(1.3)	Anterior chest wall	3 (3.8)
Liver	1(1.3)	Multiple site	3 (3.8)
Kidney	1(1.3)		

**Tab III: Stratification of patterns of extra nodal involvement with respect to age, gender, bone marrow, stages and lymph node involved.**

	MORPHOLOGICAL TYPES				
	DLBCL	Follicular Lymphoma	NHL B Cell	Marginal zone lymph	P-value
<b>Age Group</b>					
≤ 50 years	32 (61.5%)	5(55.6%)	6(42.8%)	3 (100%)	0.287
> 50 years	20(38.5%)	4(44.4%)	8(57.2%)	0	
<b>Gender</b>					
Male	37(71.2%)	2(22.2%)	11(78.6%)	3(100%)	0.012
Female	15(28.8%)	7(77.8%)	3(21.4%)	0	
<b>Bone Marrow</b>					
Yes	10(19.2%)	1(11.1%)	1(7.1%)	0	0.574
No	42(80.8%)	8(88.9%)	13(92.8%)	3(4.5%)	
<b>Stage of disease</b>					
I	1(1.9%)	1(11.1%)	2(14.2%)	0	0.001
IE	24(46.1%)	0	7(50%)	0	
IIIE	4(7.6%)	4(44.4%)	4(28.5%)	0	
III	1(1.9%)	0	0	0	
IIIE	6(11.5%)	0	4(28.5%)	3(100%)	
IV	5(9.6%)	3(33.3%)	1(7.1%)	0	
IVE	11(21.1%)	1(11.1%)	0	0	
<b>Lymph node involved</b>					
Yes	32(61.5%)	8(88.8%)	4(28.5%)	3(100%)	0.012
No	20(38.5%)	1(11.2%)	10(71.4%)	0	





**Fig I: frequency of histological types of NHL**

## DISCUSSION

Non-Hodgkin lymphoma (NHL) is a pattern of malignant lymph proliferative ailments originating primarily in the lymph nodes with several histological features and clinical manifestation. As a minimum 25% of NHL originates from tissues excluding lymph nodes and occasionally arises from sites other than lymphoid tissue. [16] Therefore, the present study demonstrated the pattern of extranodal involvement in NHL.

One study conducted among Pakistani population reported that the average age of patients with NHL was  $48.16 \pm 13.40$  years.[8] These findings were corroborated with another research in which affected age was observed 50 years (range: 15–78 years) (17). The present study was partially consistent with the above reported researches and revealed that the average age of the patients with NHL was  $46.71 \pm 14.36$  years.

As far as the gender is concerned, it was revealed by one of the previous study that most of the NHL patients were males with the ratio of M:F is 2.2:1[8]. Similarly, one retrospective analysis by Padhi S et al. conducted in India investigated 68 patients with primary extra nodal NHL wherein 45 were males and 23 were females.[18] The present study was in agreement with the above reported researches and showed the 67.9% male predilection over 32.1% females.

In another case control study conducted in India concluded that patients with history of cigarette smoking have 2 times more likelihoods of having NHL as compared to normal controls(19). As far as the present study is concerned, history of smoking showed in 16(20.5%) patients while 62(79.5%) were non-smokers patients thereby indicating that smoking was not a prognostic factor of NHL.

In Pakistan along with other Asian countries involved in the lymphoma belt, prevalence of DLBCL is strikingly raised as compared to the western countries[18,20]. These researches demonstrated that the DLBCL was the predominant phenotype with extranodal involvement [21,22]. The raised frequency also observed in accordance with another study [8]. Regardless of uncertain revelation, numerous factors are assumed to be the reason of this high incidence comprising consanguineous matrimonies, genetic and environmental influences[18]. The other commonly observed histological subtype was Marginal zone lymphoma(MZL) with gastric involvement. Further researches also demonstrated that MZL as the second most reportedly histological subtype subsequent to DLBCL reflecting as primary extranodal lymphoma[18,21]. Additionally, follicular lymphoma and ALCL are other phenotypes reflecting as primary extranodal involvement although these phenotypes were not exist markedly at extranodal site in further analysis of Asian countries[18,22]. The present study showed that most of the patients 52(66.7%) presented most common histological subtype DLBCL as primary extranodal lymphoma followed by 14(17.9%) had B cell, 9(11.5%) had follicular lymphoma while only 3(3.8%) had Marginal zone lymphoma (MZL).

Likewise, one research conducted in United States observed that Follicular lymphoma (FL) is the most frequently reported indolent B cell lymphoma and one fourth of patients showed stage I disease. Furthermore, 8% cases found integumentary system followed by 6.4% cases involved

GI tract and 5.6% observed head and neck as the most common extranodal primary sites. [23] The present study was inconsistent with the above cited research and indicated that most common extra-nodal sites of Involvement were the Paravertebral fascia 8 (10.3%), followed by the thigh 7(9%).

Another retrospective study investigated 36 patients who had lymphoid malignancy including the kidney, bladder, ureters, penile skin, or prostate, testis. Out of 36, 15(41.6%) had primary nodal involvement. Moreover, 7 cases had kidney involvement. One of the seven patients had primary renal lymphoma with DLBCL histologically. [24] The present study showed inconsistency with the above referred study and revealed that out of 78, only 1(1.3%) patient with NHL reported renal involvement while there was no history of involvement of other parts of genital system.

Similarly, another research by Naranget al also demonstrated most common extranodal site involvement in NHL. They evaluated 135 cases of non-Hodgkin lymphomas during the 3-year study period. Out of 135, 56(41.4%) cases observed with primary extranodal involvement. Involvement of gastrointestinal tract was reported in 18(32.1%) cases as common extranodal site. On the other hand, predominant subtype was B cell type in Non-Hodgkin lymphomas found in 48(85.7%) patients, whereas 8(14.2%) cases were of T cell type.[25]The present study was not supported the above research and showed that lymph node involved in 47(60.3%) cases. Furthermore, gastrointestinal tract was not the most common extranodal site involved in NHL. Whereas, only 3(3.8%) reported large intestine involvement. Concerning morphological subtypes, DLBCL was the predominant subtype constituting about 52(66.7%) cases.

Interestingly, one retrospective analysis demonstrated the stage of the disease with nodal and extranodal involvement in NHL. They studied 112 patients with Nodal-NHL and 267 with Extranodal-NHL. Approximately 3/4 of the N-NHL patients presented stage II, whereas 50% of the EN-NHL patients reported stage I ( $p < 0.01$ ). There was no statistically significant difference between EN-NHL and NHL with respect to 5-year overall survival (OS) ( $p = 0.25$ ).[26] As far as the present study is concerned, most of the patients 31(39.7%) had stage IE with EN-NHL indicating good prognosis. Most of the cases 52(66.7%) were diffuse large B cell lymphoma (DLBCL) histologically with the significant difference between all subtypes. ( $p = 0.001$ ).

There are scarce researches that emphasize the variances between EN-NHL and N-NHL in molecular level, its prognosis and overall survival rate. Presently, prospectively planned studies

are required for a comprehensive histopathological and molecular assessment of EN-NHL. These researches can lead to innovative perceptions for predictive valuations and divergent treatment strategies.

## CONCLUSION

This study concluded that diffuse large B cell lymphoma was the most common morphological type observed. Paravertebral fascia and thigh were the most common anatomical sites for extranodal involvement in Non-Hodgkin lymphoma. Most of the cases were at stage IE with better prognosis and survival rate. Moreover, significant differences were found in the pattern of extra nodal Non-Hodgkin lymphoma. Further studies are needed in terms of risk factors and treatment outcomes to better comprehend the genetic profile of this disease in our population.

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