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CLINICAL SPECTRUM AND SUBTYPE DISTRIBUTION OF NON-HODGKIN'S LYMPHOMA BASED ON THE WORLD HEALTH ORGANIZATION CLASSIFICATION OF TUMORS OF LYMPHOID TISSUES (2017): AN ANALYSIS FROM A TERTIARY CARE CENTER IN WESTERN INDIA

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Abstract – *Objective:* *The subtype distribution and clinical profile of Non-Hodgkin's Lymphoma (NHL) show a wide variation in the different geographical locations. There is paucity of data regarding this from Western India. This study was aimed to evaluate the clinical spectrum and distribution of NHL subtypes at a tertiary care hos-pital of Western India.*

Patients and Methods: *This prospective observational study was conducted over a period of 2 years among 178 NHL patients of all ages. Clinical evaluation and investigations including histopathological examination and immunohisto-chemistry of involved tissue, bone marrow examination, and other relevant tests were performed. Cases were categorized according to World Health Organization classification of tumours of lymphoid tissues (2017).*

Results: *There was a male preponderance (66.3%), and the commonest age group affected was 41-50 years (24.1%). The predominant symptom was neck swelling (51.1%), and the commonest sign was lymphad-enopathy (70.2%), cervical lymph nodes being the most commonly involved (51.1%). Extra-nodal in-volvement was seen in 37.6% patients, the head-and-neck being the most commonly involved site (16.3%). Majority of the NHLs were B-cell lymphomas (75.3%). Diffuse large B-cell lymphoma was the commonest subtype (36.5%) followed by peripheral T-cell lymphoma, not otherwise specified (10.7%). Pediatric NHL comprised of 11.2% of NHL, T-cell lymphoblastic lymphoma (T-LBL) being the com-monest subtype (25%).*

Conclusions: *Our analysis confirmed findings of various previous studies from India with few key differences. Mantle cell lymphoma had marginally higher frequency than follicular lymphoma, and was the second common-est B-cell NHL. Burkitt's lymphoma had lower frequency than T-LBL in children, and was the second commonest childhood NHL.*

KEYWORDS: *Clinical spectrum, Distribution pattern, Non-Hodgkin's lymphoma, Western India, World Health Organi-zation classification.*

INTRODUCTION

Non-Hodgkin's Lymphoma (NHL) represents a group of malignant lymphoproliferative disorders originating from either B- or T-lymphocytes by clonal expansion. The incidence of NHL is increasing worldwide including India over the past few decades. It is the 13th most common malignancy and accounts for 2.8% of all malignancies across the globe. It represents the ninth most fre-

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quent (2.7%) cancer in India with 35,828 new cases and 20,390 deaths in 2020[1]. The incidence of NHL is higher in urban areas compared to rural areas. Delhi has the highest age-adjusted incidence rates, followed by Mumbai[2].

NHL is heterogeneous both biologically as well as clinically. It includes different histological subtypes each with distinct clinical characteristics, prognosis and responses to therapy[3]. Pattern of clinical presentation as well as patient population of NHL varies with geographical regions, age, race and ethnicity. Compared to developed nations, the key differences in the clinical presentation in India include: median age of 54 years (almost a decade less), higher male-to-female ratio, higher proportion of patients with B-symptoms (40-60% *vs.* 20-30%), and poor Eastern Cooperative Oncology Group (ECOG) performance status (≥ 2) at diagnosis (50% *vs.* 20-30%)[2].

There is well documented variation in the distribution of various subtypes of NHL in different geographical regions globally. Worldwide, diffuse large B-cell lymphoma (DLBCL) continues to be the dominant histologic subtype comprising 30-35% of all NHL cases and this proportion has been stable over the years[4]. Various studies have shown considerable differences in the distribution of NHL subtypes between Asian and Western countries. A higher proportion of B-cell NHL such as DLBCL and follicular lymphoma (FL) is seen in United States of America (USA) compared to a higher prevalence of T-cell NHL in Asian countries[5]. Moreover, studies have shown higher rates of gastric lymphoma in Northern Italy, endemic form of Burkitt's lymphoma (BL) in children in equatorial Africa, nasal T-cell lymphomas in China, certain small intestinal lymphomas in the Middle East, and adult T-cell leukemia/lymphoma in Southern Japan and the Caribbean[2]. The distribution of various subtypes of NHL in India shows important differences from the rest of the world, with a higher frequency of DLBCL (60-70% *vs.* <40%) and T-cell NHL (10-20% *vs.* <10%), and a lower frequency of FL (<20% *vs.* 30-40%)[2]. The various subtypes of NHL in India also differ among different regions of the country. DLBCL was the most common NHL subtype reported in various single center studies and a multicenter registry-based study from India with a frequency ranging from 34 to 55%[6-9].

As treatment and prognosis of NHL vary greatly, depending on the histopathological subtype and clinical presentation, identifying these characteristics is necessary for its optimum management and better therapeutic outcome. Although adequate comparative data regarding the clinical patterns and distribution of histopathological subtypes of NHL from various parts of India are available in the literature, there is lack of such data from Western India. We, therefore, carried out this analysis to evaluate the clinical spectrum and subtype distribution pattern of NHL among patients presenting to a large tertiary care center from Western India. To the best of our knowledge, this is the first study in this region of country.

PATIENTS AND METHODS

Study design and study population

This prospective observational study was conducted in a large tertiary care hospital from Jodhpur, Rajasthan, India over a period of 2 years from April 2019 to March 2021. A total of 178 patients of either sex and all ages with newly diagnosed NHL attending the inpatient or outpatient department were included in this study. Previously diagnosed cases of NHL, plasma cell myeloma, plasmacytoma, cases with leukemic presentation, and cases in which either B- or T-cell immunophenotype could not be ascertained were excluded from the study.

Study procedure

Ethical approval (SNMC/IEC/IIP/2019/029) for this study was obtained from the Institutional Ethics Committee. A written informed consent was taken from all patients prior to their enrolment in the study. A detailed medical history was obtained from each participant and meticulous clinical examination was carried out. ECOG performance status was determined for each patient. All patients were subjected to relevant blood investigations including complete blood count, peripheral smear examination and serum lactate dehydrogenase (LDH). The diagnosis of NHL was established by histopathological examination followed by immunohistochemistry (IHC) using a standard panel of antibodies on lymph nodes or other involved tissues. All cases were classified into subtypes in accordance with the criteria of World Health Organization classification of tumors of lymphoid tissue (2017). Molecular diagnostic techniques were also performed in selected cases wherever indicated. Bone marrow (BM) examination including BM aspiration and trephine biopsy was performed in each case by standard method. Cerebrospinal fluid analysis was also performed whenever relevant. Imaging studies by chest X-rays, abdominal and pelvic sonography, computed tomogram scan of brain, head-and-neck, chest, abdomen and pelvis, positron emission test with computed tomogram, or combination of these were done wherever in-

dicated and for staging evaluation. The staging of NHL was performed by Lugano classification. In this study, the primary involvement of the lymph nodes was defined as nodal lymphoma, whereas the primary involvement of Waldeyer's ring and other organs was defined as extranodal lymphoma. Patients with DLBCL were assigned to one of the four prognostic scores according to the international prognostic index (IPI).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 21.0 for Windows (Version 21.0 for Windows; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (±SD) while categorical variables were indicated as frequency (n) and percentage (%). The significance of difference was analyzed using Student's t-test for continuous variables and Fisher's exact test for categorical values. A two-tailed *p*-value <0.05 was considered as statistically significant.

RESULTS

Age and gender distribution of patients with NHL

The mean age (± SD) of patients with NHL at diagnosis was 46.4 ± 18.1 years, with a range of 3 to 90 years. The most common age group affected (24.1%) was 41-50 years, with maximum number of cases of both B-cell NHL (24.6%) as well as T-cell NHL (22.7%) found in this age group. The overall male-to-female ratio was 1.97:1 with male preponderance in all age groups (Table 1).

Clinical characteristics of patients with NHL

Neck swelling was the most common presenting complaint (51.1%), followed by generalized weakness and fatigue (46.1%), weight loss (38.8%), fever (34.8%), anorexia (29.2%), and abdominal pain (25.8%). The most common sign was peripheral lymphadenopathy being observed in 57.9% cases. Pallor was present in 32% cases. Hepatomegaly and splenomegaly were detected in 25.3% and 29.8% cases, respectively. Pedal edema was found in 15.7%, ascites in 7.8%, and pleural effusion in 5.6% cases. B-symptoms (fever >38°C, and/or night sweats, and/or weight loss of more than 10% of body weight in the last 6 months) were noted in 46.1% cases. Bulky disease was found in 23.0% and BM involvement in 20.8% patients. Anemia was found in 44.4% and elevated LDH level in 59.6% of patients. Overall, 14.6% patients were presented with poor ECOG performance status (3-4). Majority of the patients (57.9%) were presented with advanced stage disease (stage III and IV). Presence of B-symptoms, bulky disease, anemia and raised LDH showed significant difference between B-cell NHL and T-cell NHL (p <0.001, 0.007, 0.035 and 0.008, respectively). Among patients with DLBCL (n=65), 30.8% had low IPI, 41.5% had intermediate IPI and 27.7% had high IPI (Table 2).

The nodal NHL were observed in 62.4% and extra-nodal NHL in 37.6% cases. Cervical lymph

TABLE 1. Age and gender distribution of patients with NHL (n=178).

Age groups (years)	B-cell NHL (n=134)			T-cell NHL (n=44)			All cases (n=178)		
	Male (n=88) n (%)	Female (n=46) n (%)	Total (n=134) n (%)	Male (n=30) n (%)	Female (n=14) n (%)	Total (n=44) n (%)	Male (n=118) n (%)	Female (n=60) n (%)	Total (n=178) n (%)
0-10	2 (2.3)	1 (2.2)	3 (2.2)	2 (6.7)	1 (7.1)	3 (6.8)	4 (3.4)	2	6 (3.4)
11-20	5 (5.7)	3 (6.5)	8 (6)	4 (13.3)	2 (14.3)	6 (13.6)	9 (7.6)	5 (8.3)	14 (7.9)
21-30	4 (4.5)	4 (8.7)	8 (6)	3 (10)	1 (7.1)	4 (9.1)	7 (5.9)	5 (8.3)	12 (6.7)
31-40	7 (8)	5 (10.7)	12 (9)	5 (16.7)	2 (14.3)	7 (15.9)	12 (10.2)	7 (11.7)	19 (10.7)
41-50	19 (21.6)	14 (30.4)	33 (24.6)	7 (23.3)	3 (21.4)	10 (22.7)	26 (22)	17 (28.3)	43 (24.1)
51-60	22 (25)	8 (17.4)	30 (22.4)	3 (10)	2 (14.3)	5 (11.4)	25 (21.2)	10 (16.7)	35 (19.7)
61-70	17 (19.3)	8 (17.4)	25 (18.6)	5 (16.7)	1 (7.1)	6 (13.6)	22 (18.6)	9 (15)	31 (17.4)
71-80	9 (10.2)	2 (4.3)	11 (8.2)	1 (3.3)	2 (14.3)	3 (6.8)	10 (8.5)	4 (6.7)	14 (7.9)
81-90	3 (3.4)	1 (2.2)	4 (3)	0 (0)	0 (0)	0 (0)	3 (2.5)	1 (1.7)	4 (2.2)
91-100	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	88 (100)	46 (100)	134 (100)	30 (100)	14 (100)	44 (100)	118 (100)	60 (100)	178 (100)

Abbreviations - NHL, non-Hodgkin's lymphoma.

TABLE 2. Clinical characteristics of patients with NHL.

Patient profile	*All cases (n=178)*	*B-cell NHL (n=134)*	*T-cell NHL (n=44)*	*p-value*
Age (years), Mean ± SD	46.4 ± 18.1	47.8 ± 10.6	43.6 ± 22.7	0.098
Age >60 years, n (%)	49 (27.5)	40 (29.5)	9 (20.5)	0.250
Males, n (%)	118 (66.3)	88 (65.7)	30 (68.2)	0.856
Duration of symptoms (months), Mean ± SD	3.9 ± 2.8	4.0 ± 3.4	3.6 ± 2.6	0.476
B-symptoms†, n (%)	82 (46.1)	51 (38.1)	31 (70.5)	<0.001
Lymph node enlargement, n (%)	125 (70.2)	94 (70.1)	31 (70.5)	1.000
Hepatomegaly, n (%)	45 (25.3)	32 (23.0)	13 (29.5)	0.549
Splenomegaly, n (%)	53 (29.8)	42 (31.3)	11 (25)	0.455
Bone marrow involvement, n (%)	37 (20.8)	24 (17.9)	13 (29.5)	0.133
Bulky disease, n (%)	41 (23)	24 (17.9)	17 (12.7)	0.007
Primary nodal involvement, n (%)	111 (62.4)	85 (63.4)	26 (59.1)	0.720
Primary extranodal involvement, n (%)	67 (37.6)	49 (36.6)	18 (40.8)	0.720
Haemoglobin (g/dL), Mean ± SD	11.1 ± 2.95	11.2 ± 2.18	10.1 ± 3.38	0.013
Anemia‡, n (%)	79 (44.4)	53 (39.6)	26 (59.1)	0.035
Serum LDH (U/L), Mean ± SD	775.67 ± 36.16	638.57 ± 73.54	782.41 ± 115.56	<0.001
Raised serum LDH (>ULN), n (%)	106 (59.6)	72 (53.7)	34 (77.3)	0.008
Poor ECOG PS (>2), n (%)	26 (14.6)	17 (12.7)	9 (20.5)	0.223
Advanced stage disease (III-IV), n (%)	103 (57.9)	76 (56.7)	27 (61.4)	0.603
IPI group (for DLBCL, n=65)				
Low (IPI score 0-1), n (%)	-	20 (30.8)	-	-
Intermediate (IPI score 2-3), n (%)	-	27 (41.5)	-	-
High (IPI score 4-5), n (%)	-	18 (27.7)	-	-

†Fever >38°C, and/or night sweats, and/or weight loss of more than 10% of body weight in the last 6 months.
‡Haemoglobin <12 g/dL in females and <13 g/dL in males.
Abbreviations - NHL, non-Hodgkin's lymphoma; SD, standard deviation; LDH, Lactate dehydrogenase; ULN, Upper limit of normal; ECOG, Eastern cooperative oncology group; PS, Performance status; IPI, International prognostic index; DLBCL, Diffuse large B-cell lymphoma.

node was the most common nodal site of involvement (51.1%), followed by the abdominal nodes (28%), inguinal nodes (20.2%), axillary nodes (18.0%), supraclavicular (15.2%), mediastinal nodes (6.7%), and others. The most frequent extranodal site was head-and-neck (16.3%) including Waldeyer's ring (8.4%), followed by gastrointestinal tract (GIT) (11.8%), skin (3.9%), liver (2.8%), bone (3.9%), and others (Table 3).

Distribution of different subtypes of NHL

Majority of the NHL were B-cell type (75.3%) while T-cell type was seen in 44 (24.7%) cases. Overall, DLBCL was the most common subtype of NHL (36.5%) followed by peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) in 10.7% cases. Among the B-cell NHL, majority of the cases were DLBCL (48.5%), followed by mantle cell lymphoma (MCL) in 11.2%, FL (9%), BL (5.2%), and others. Majority of T-cell NHL were PTCL, NOS (43.2%), followed by anaplastic large cell lymphoma (ALCL) in 18.2%, and T-cell lymphoblastic lymphoma (T-LBL) in 15.9% cases (Table 4).

Majority of the NHL (88.8%) were found in adults (≥18 years). Childhood lymphoma (<18 years of age) constituted only 11.2% of cases. B-cell NHL was dominant among both adult (77.8%) as well as pediatric age group (55%). Among adults, the commonest type of NHL was DLBCL (38.6%), whereas T-LBL (25%) was the most common NHL in children. Among B-cell NHL, pediatric-type follicular lymphoma (PTFL) and B-cell lymphoblastic lymphoma (B-LBL) were exclusively noted in children, and BL was more common in children than adults, whereas other subtypes were commoner in adults. Among T-cell NHL, T-LBL was more common in children, whereas other subtypes were either more common or exclusively present in adults (Table 4).

The nodal NHL was more common than extranodal NHL among both B-cell NHL (63.4%) as well as T-cell NHL (59.1%). B-cell NHL was accounted for 73.1% cases of extranodal NHL while remaining 26.9% were T-cell NHL. DLBCL and PTCL, NOS were the most common subtypes among nodal (39.6% and 11.7%, respectively) as well as extranodal (31.3% and 8.9%, respectively) NHL (Table 4).

TABLE 3. Distribution of nodal and extranodal sites of involvement in patients with NHL on initial presentation.

Nodal sites (n=111)	*n (%)*	*Extranodal sites (n=67)*	*n (%)*
Cervical nodes	91 (51.1)	GIT	21 (11.8)
Supraclavicular nodes	27 (15.2)	Intestine (small and large)	14 (7.9)
Axillary nodes	32 (18)	Small intestine	6 (3.4)
Mediastinal nodes	12 (6.7)	Large intestine	12 (6.7)
Abdominal nodes	28 (25.2)	Stomach	7 (3.9)
Para aortic nodes	12 (6.7)	Liver	5 (2.8)
Mesenteric nodes	11 (6.2)	Head and neck	29 (16.3)
Retroperitoneal nodes	11 (6.2)	CNS	4 (2.2)
Periportal nodes	11 (6.2)	Orbit	2 (1.1)
Other abdominal nodes	12 (6.7)	Waldeyer's ring	15 (8.4)
Inguinal nodes	36 (20.2)	Tonsil	11 (6.2)
		Base of tongue	2 (1.1)
		Alveolus and hard palate/palate	2 (1.1)
		Parotid	3 (1.7)
		PNS, nasopharynx and nasal cavity	5 (2.8)
		Lung	2 (1.1)
		Retroperitoneum	2 (1.1)
		Renal	2 (1.1)
		Adrenal	1 (0.6)
		Testes	4 (2.2)
		Skin	7 (3.9)
		Bone	7 (3.9)

Abbreviations - NHL, Non-Hodgkin lymphoma; GIT, Gastrointestinal tract; CNS, Central nervous system; PNS, Paranasal sinus.

DISCUSSION

In the present study, the mean age (± SD) of patients was 46.4 ± 18.1 years, closer to that reported in a study from India (39.9 years)[10]. On the other hand, the mean age in most Western and Asian countries was reported to be between 50 and 60 years[11,12]. The younger age of our patients was consistent with the pattern seen in most other malignancies in India, might be due to the effect of a younger population pyramid in this country. A male preponderance was observed in our study (66.3%), with a male-to-female ratio of 1.97:1, consistent with other studies from India[10,13]. However, it differed from other studies carried out in Asia, North America and Europe with ratio of 1.6, 1.2 and 1.1, respectively[2]. The possible justification might be that male individuals in India are comparatively more exposed to the occupational and environmental carcinogenic agents and are at higher risk to the occurrence of all kinds of malignancies including NHL.

The predominant symptom in our study was neck swelling (51.1%), and the most common presenting sign was peripheral lymphadenopathy (57.9%), similar to findings reported in other studies from India[10,14-16]. The most commonly involved lymph node group was cervical (51.1%), concurrent with findings reported in other studies from India[10,15]. B-symptoms were present in 46.1% of patients in our study, similar to frequency in studies by Garg et al[6] (49.6%) and Sud et[14] al (47.5%). A comparatively lower frequency was reported in a study from South India (23.9%)[17], whereas a higher frequency was observed in a study from Eastern India (63.16%)[10]. The variability in results could be attributable to the limited sample size and single institutional nature of these studies.

BM involvement at diagnosis was noted in 20.8% of cases in this study, similar to that in a study by Sud et al[14] (25%). A higher frequency of BM involvement (30.3%) was observed in a study by Mondal et al[18]. Various studies from other countries also reported a higher frequency of BM involvement in NHL, ranging from 20 to 40%[19,20]. Our study results showed anemia in 44.4% of patients. Anemia was seen in 18% cases in a study by Sud et al[14]. The marked results in our study could be attributed to the late presentation as the degree of anemia is directly proportional to the burden of disease. We found elevated LDH in 59.6% of cases, similar to other Indian studies[14,16]. Majority of the patients (57.9%) were presented with advanced stage disease (stage III and IV) in our study, similar to other Indian studies[10,14]. These results have shown that the majority of Indian population is presented late in an advanced stage.

TABLE 4. Distribution of different WHO classification (2017) based subtypes of NHL according to age group, gender and primary site of involvement.

WHO subtypes	All cases (n=178) n (%)	Gender		Age group		Primary site	
		Males (n=118) n (%)	Females (n=60) n (%)	<18 years (n=20) n (%)	≥18 years (n=158) n (%)	Nodal (n=111) n (%)	Extranodal (n=67) n (%)
B cell NHL	**134 (75.3)**	**88 (74.6)**	**46 (76.7)**	**11 (55)**	**123 (77.8)**	**85 (76.6)**	**49 (73.1)**
DLBCL	65 (36.5)	45 (38.1)	20 (33.3)	4 (20)	61 (38.6)	44 (39.6)	21 (31.3)
MCL	15 (8.4)	9 (7.6)	6 (10)	0 (0)	15 (9.5)	11 (9.9)	4 (6)
FL	12 (6.7)	9 (7.6)	3 (5)	0 (0)	12 (7.6)	11 (9.9)	1 (1.5)
BL	7 (3.9)	6 (5.1)	1 (1.7)	4 (20)	3 (1.9)	3 (2.7)	4 (6)
HGBCL	4 (2.2)	3 (2.5)	1 (1.7)	0 (0)	4 (2.5)	2 (1.8)	2 (3)
MALT lymphoma	4 (2.2)	2 (1.7)	2 (3.3)	0 (0)	4 (2.5)	0 (0)	4 (6)
SLL	4 (2.2)	2 (1.7)	2 (3.3)	0 (0)	4 (2.5)	4 (3.6)	0 (0)
LPL	4 (2.2)	2 (1.7)	2 (3.3)	0 (0)	4 (2.5)	3 (2.7)	1 (1.5)
PCNSL	3 (1.7)	2 (1.7)	1 (1.7)	0 (0)	3 (1.9)	0 (0)	3 (4.5)
SMZL	2 (1.1)	0 (0)	2 (3.3)	0 (0)	2 (1.3)	0 (0)	2 (3)
TCRBCL	2 (1.1)	1 (0.8)	1 (1.7)	0 (0)	2 (1.3)	1 (0.9)	1 (1.5)
B-LBL	2 (1.1)	1 (0.8)	1 (1.7)	2 10)	0 (0)	1 (0.9)	1 (1.5)
PMBCL	2 (1.1)	1 (0.8)	1 (1.7)	0 (0)	2 (1.3)	0 (0)	2 (3)
PBL	2 (1.1)	0 (0)	2 (3.3)	0 (0)	2 (1.3)	0 (0)	2 (3)
PTFL	1 (0.6)	1 (0.8)	0 (0)	1 (5)	0 (0)	1 (0.9)	0 (0)
PEL	1 (0.5)	1 (0.8)	0 (0)	0 (0)	1 (0.6)	0 (0)	1 (1.5)
Unclassified	4 (2.2)	3 (2.5)	1 (1.7)	0 (0)	4 (2.5)	4 (3.6)	0 (0)
T cell NHL	**44 (24.7)**	**30 (25.4)**	**14 (23.3)**	**9 (45)**	**35 (22.2)**	**26 (23.4)**	**18 (26.9)**
PTCL, NOS	19 (10.7)	13 (11)	6 (10)	1 (5)	18 (11.4)	13 (11.7)	6 (8.9)
ALCL	8 (4.5)	6 (5.1)	2 (3.3)	3 (15)	5 (3.2)	6 (5.4)	2 (3)
T-LBL	7 (3.9)	4 (3.4)	3 (5)	5 (25)	2 (1.3)	3 (2.7)	4 (6)
AITL	2 (1.1)	2 (1.7)	0 (0)	0 (0)	2 (1.3)	2 (1.8)	0 (0)
HSTCL	2 (1.1)	1 (0.8)	1 (1.7)	0 (0)	2 (1.3)	0 (0)	2 (3)
ENKTCL, nasal type	2 (1.1)	2 (1.7)	0 (0)	0 (0)	2 (1.3)	0 (0)	2 (3)
MF/SS	2 (1.1)	1 (0.8)	1 (1.7)	0 (0)	2 (1.3)	0 (0)	2 (3)
Unclassified	2 (1.1)	1 (0.8)	1 (1.7)	0 (0)	2 (1.3)	2 (1.8)	0 (0)

Abbreviations - WHO, World Health Organization; NHL, Non-Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; MCL, Mantle cell lymphoma; FL, Follicular lymphoma; BL: Burkitt's lymphoma; HGBCL, High-grade B-cell lymphoma; MALT lymphoma, Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; SLL, Small lymphocytic lymphoma; LPL, Lymphoplasmacytic lymphoma; PCNSL, Primary CNS lymphoma; SMZL, Splenic marzinal zone lymphoma; TCRBCL, T-cell/histiocyte-rich large B-cell lymphoma; B-LBL, B-cell lymphoblastic lymphoma; PMBCL, Primary mediastinal (thymic) large B-cell lymphoma; PBL, Plasmablastic lymphoma; PTFL, Pediatric-type follicular lymphoma; PEL, Primary effusion lymphoma; PTCL, NOS, Peripheral T-cell lymphoma, not otherwise specified; ALCL, Anaplastic large cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma; AITL, Angioimmunoblastic T-cell lymphoma; HSTCL, Hepatosplenic T-cell lymphoma; ENKTCL, Extranodal NK/T-cell lymphoma; MF/SS: Mycosis fungoides/Sézary syndrome.

In our study, 37.6% patients presented with primary extranodal disease. A lower prevalence of extranodal NHL was seen in various other Indian studies with frequency varying from 20.5 to 27.7%[18,21-23]. Our result was close to the incidence of extranodal NHL in studies from Western countries, varying from 24 to 48%[24]. Asian countries like China and Japan have even higher incidence of extranodal NHL, ranging from 44 to 60%[25,26]. This may be attributable to a higher prevalence of extranodal NK/T-cell lymphoma (ENKTCL) in these countries compared with India. The most common extranodal site involved in our study was head-and-neck (16.3%), followed by GIT (11.8%). A study from South India also reported similar findings[23]. Another study from South India reported the central nervous system as the most common extranodal site, followed by GIT[22]. Among GIT lymphomas, stomach was the most common site in a study from South India[23], whereas small bowel lymphomas (6.7%) were predominant in our study. The heterogeneity of the clinical presentation of NHL in various studies can be explained by the fact that different

TABLE 5. Distribution of most common subtypes of NHL in India and other countries.

Study	Country	Year	No. of NHL Cases	Subtypes of NHL (% of all NHL cases)			
				B-NHL		T-NHL	
				Common est	2nd most common	Common est	2nd most common
Naresh et al[7]	India	2000	2773	DLBCL (34)	FL (12.6)	T-LBL (6)	ALCL (4.3)
Sahni and Desai[8]	India	2007	935	DLBCL (50.2)	FL (13.1)	ALCL (4.8)	PTCL (4.6)
Nimmagadda et al[9]	India	2013	1433	DLBCL (55)	FL (11)	ALCL (3)	PTCL (2.7)
Sud et al[14]	India	2020	200	DLBCL (56)	FL (16.5)	ALCL (7)	T-LBL (3.5)
Devi et al[15]	India	2017	100	DLBCL (45)	BL (6)	ALCL (15)	AITL (5)
Mondal et al[19]	India	2014	347	DLBCL (35.2%)	FL (19.3)	ALCL (12.1)	T-LBL (8.6)
Sharma et al[21]	India	2019	130	DLBCL (60.8)	FL (4.8)	PTCL (15.2)	ALCL & T-LBL (4)
Morton et al[24]	USA	2006	114548	DLBCL (28)	SLL (20)	T-LBL (5)	PTCL (5)
Yang et al[25]	China	2011	5549	DLBCL (41.2)	MALT lymphoma (6.3)	ENKTCL (17.1)	PTCL (4)
Arora et al[29]	India	2013	4026	DLBCL (46.9)	FL (10.5)	PTCL (5.9)	ALCL (5)
Gogia et al[30]	India	2018	390	DLBCL (68.5)	FL (9)	PTCL (3.9)	ALCL (2.3)
Akter et al[31]	Bangladesh	2019	160	DLBCL (48.4)	FL (11.2)	PTCL (12.8)	T-LBL (9.6)
Mushtaq et al[32]	Pakistan	2008	169	DLBCL (70.4)	FL (5.3)	PTCL (5.9)	CTCT (3)
Present study	India	2022	178	DLBCL (36.5)	MCL (8.4)	PTCL (10.7)	ALCL (4.5)

Abbreviations - NHL, Non-Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; T-LBL, T-cell lymphoblastic lymphoma; ALCL, Anaplastic large cell lymphoma; PTCL, NOS, Peripheral T-cell lymphoma, not otherwise specified; BL, Burkitt's lymphoma; AITL, Angioimmunoblastic T-cell lymphoma; SLL, Small lymphocytic lymphoma; MALT lymphoma, Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; ENKTCL, Extranodal NK/T-cell lymphoma, nasal type; CTCL, Cutaneous T-cell lymphoma; MCL: Mantle cell lymphoma.

histologic subtypes clinically present in different manner. The clinical presentation of NHL also depends on geographic, demographic, etiologic, ethnic and environmental factors.

In our study, B-cell NHL comprised 75.3% of cases, and remaining 24.7% were T-cell NHL. This was consistent with the findings reported in other studies from India[7,8,17,21]. In contrast, a higher proportion of B-cell lymphoma was reported in another study from India (87%)[14]. A large study in China reported a higher frequency of T-cell lymphoma[26]. The incidence of T-cell NHL appears to increase worldwide as we move from West to East. Researchers has suggested that environmental factors including Epstein-Barr virus infection as well as exposure to pesticides and chemical solvents are strongly associated with the higher frequency of T-cell NHL in China considering the agricultural area[5,27].

Table 5 lists the frequency of most common subtypes of NHL in India and other countries. In the current study, DLBCL was the most common subtype of NHL (36.5%). Our finding was consistent with studies by Naresh et al[7] (35.2%) and Mondal et al[19] (34%). Our result was also comparable to the studies from USA (28%)[24], Europe (25-30%)[28], and China (41.2%)[25]. On the contrary, a higher proportion of DLBCL was noted in other studies from India (45-68.5%)[8,9,14,15,21,29,30], Bangladesh (48.4%)[31], and Pakistan (70.4%)[32]. The possible reasons for this variation might be the variations in sample size, study population, geographical location, and socio-demographic pattern.

Second most common subtype of NHL in this study was PTCL, NOS (10.7%), similar to finding of a study from India (15.2%)[21]. In contrast, another study from India showed ALCL as the second most common subtype (15%) of NHL[15], whereas FL was the second most common subtype of NHL in various other Indian studies with frequency ranging from 9 to 19.3%[7-9,14,18,29,30]. Compared to other Indian studies, our study had low frequency of FL (6.7%), and MCL (8.4%) was more common than FL. This may be attributed to the fact that many of aforementioned studies from India were carried out in South India that is socioeconomically more developed compared with this region of country. FL is known to occur more commonly in countries with higher socioeconomic status, and

TABLE 6. Various studies comparing distribution of common subtypes of NHL in different regions of India.

Study	Naresh et al[7]	Sahni and Desai[8]	Devi et al[15]	Mondal et al[19]	Sharma et al[21]	Arora et al[29]	Gogia et al[30]	Present study
Region of India	Southwestern	Southwestern	Northeast	Eastern	Northeast	South	North	Western
City	Mumbai	Mumbai	Imphal,	Kolkata	Guwahati	Vellore	New Delhi	Jodhpur
State	Maharashtra	Maharashtra	Manipur	West Bengal	Assam	Tamil Nadu	New Delhi	Rajasthan
Year	2000	2007	2017	2014	2019	2013	2018	2022
No. of NHL Cases	2773	935	100	347	130	4026	390	178
Subtypes of NHL	% of all NHL cases							
B-NHL	**79.1**	**79.3**	**66**	**74.1**	**74**	**78.6**	**89**	**75.3**
DLBCL	34	50.2	45	35.2	60.8	46.9	68.5	36.5
FL	12.6	13.1	5	19.3	4.8	10.5	9	6.7
BL	1.8	3	6	5.8	0.8	3.4	1.3	3.9
MCL	3.4	2.1	5	2.6	3.2	1.6	5	8.4
SLL	5.7	5.4	-	5.5	3.2	4	1.3	2.2
MZL/SMZL	2.1	0.5	1	-	0.8	0.3	2.3	1.1
MALT lymphoma	6.1	2.7	1	2	-	2.17	-	2.2
T-NHL	**16.2**	**18.8**	**23**	**25.9**	**24**	**20.2**	**11**	**24.7**
T-LBL	6	6.9	-	8.6	4	0.4	1.8	3.9
ALCL	4.3	4.8	15	12.1	4	5	2.3	4.5
PTCL	2.9	4.6	-	1.7	15.2	5.9	3.9	10.7
AITL	1	0.4	5	1.4	-	1.4	0.8	1.1

Abbreviations - NHL, Non-Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; BL, Burkitt's lymphoma; MCL: Mantle cell lymphoma; SLL, Small lymphocytic lymphoma; MZL, Marzinal zone lymphoma; SMZL, Splenic marzinal zone lymphoma; MALT lymphoma, Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; T-LBL, T-cell lymphoblastic lymphoma; ALCL, Anaplastic large cell lymphoma; PTCL, Peripheral T-cell lymphoma; AITL, Angioimmunoblastic T-cell lymphoma.

a higher proportion of FL was noted in Western studies (28-32%)[18]. Naresh et al[7] opined that the low rates of FL in developing countries might be due to the fact that many cases of DLBCL might be progressed from previously undiagnosed FL and that unique environmental or genetic factors might have contributed to such progression.

In our study, the most common T-cell subtype was PTCL, NOS (43.2%), followed by ALCL (18.2%) and T-LBL (15.9%). These results were in line with the findings of many studies from India[21,29,30]. On the other hand, the most common subtype among T-NHL was T-LBL (6%) in study by Naresh et al[7] and ALCL (7%) in study by Sud et al[14]. The higher frequency of PTCL, NOS in our study could be attributable to the hot and tropical climate causing severe pruritus which might probably be a contributing factor. This, however, requires further investigation. The higher frequency of T-LBL in a study by Naresh et al[7] may be explained by the fact that they might have included the cases with leukemic presentation in their study giving a higher prevalence. In our study, we included the cases with isolated lymphomatous presentation, similar to Arora et al[29]. Table 6 lists the various studies comparing distribution of common subtypes of NHL in different regions of India.

Limitations of the study

An important limitation of the present study is that this was a small-scale study conducted at a single center with limited sample size that might have not represented the data of whole region of this part of the country. Another limitation was the absence of a control group. Thus, further large and multicenter studies from this region of the country are required. However, this analysis is a valuable contribution to the NHL literature from this country.

CONCLUSIONS

Our study showed that the maximum number of NHL patients were in the age group of 41-50 years with overall male preponderance. Neck swelling was the predominant symptom and lymphadenopathy was the most common presenting sign, cervical lymph nodes being most commonly involved. The most frequently involved extranodal site was the head-and-neck, followed by GIT. Majority of patients presented with advanced stage disease. Majority of the NHLs were B-cell lymphomas. DLBCL was the most common subtype of NHL followed by

PTCL, NOS. A lower frequency of FL than MCL was seen in contrast to other Indian studies, and MCL was the second most common B-cell NHL. T-LBL was the most common subtype of NHL in children unlike BL in other studies. Large and multicenter studies from this region of the country are required to confirm these findings.

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The present study was approved by the Institutional Ethics Committee (SNMC/IEC/IIP/2019/029). The participants were informed about the study design and objectives. All participants provided informed con-sent for inclusion in the study prior to their enrolment.

Consent for publication:

All participants provided informed consent for anonymous data publication before they participated in the study.

Availability of data and materials:

All relevant data of this study are available from the corresponding authors upon reasonable request. The data are not publicly available.

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Govind R. Patel and Gopal R. Prajapati substantially contributed to research design; Govind R. Patel per-formed the study acquisition; Govind R. Patel performed data analysis and wrote the manuscript; Gopal R. Prajapati revised it critically, and approved the final manuscript.

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