ORIGINAL ARTICLE

FREQUENCY, DISTRIBUTION OF SUBTYPES AND IMMUNOHISTOCHEMICAL PROFILE OF NON-HODGKIN LYMPHOMA IN PAEDIATRIC AND ADOLESCENT PATIENTS

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Background: Non-Hodgkin lymphoma is a common malignant disorder in paediatric and adolescent age group. There is a need of large-scale studies to understand the disease pattern in Pakistan as no official registry exist in most of the developing countries. This study comprised a large cohort of 223 patients, spanned over a decade from January 2008-December 2019 and aimed to report the prevalence of subtypes, demographics and immunohistochemical profile from this region. **Methods:** Retrospective study, conducted at Indus hospital and health network and Ziauddin university hospital, Karachi, Pakistan. Sequential data analysis was carried out on all consecutive samples including both needle and excisional biopsies of patients below 18 years of age. Morphological examination of H&E stained sections along with immunohistochemistry is performed in order to identify subtypes and immunophenotypic patterns using an extensive panel of markers. **Results:** Our results demonstrate 66% B-cell lymphomas while 34% T-cell lymphomas. Overall male to female ratio was 3.3:1 with median age 8 years (1.1–17 years). Among B-cell lymphoma, Burkitt lymphoma is most common while in T-cell, T-lymphoblastic lymphoma is the most common subtype. In anaplastic large cell lymphoma category, null cell phenotype was predominant, i.e., 65%. T-NHL frequency is found to be higher in our population. However, results of immunohistochemistry are similar to published literature. **Conclusion:** The study will help to identify disease patterns in terms of subtypes of NHL and its immunohistochemical profile that plays a vital role in diagnostic, prognostic and therapeutic implications.

Keywords: Non Hodgkin Lymphoma, Paediatric, Immunohistochemistry, Lymphoblastic Lymphoma

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INTRODUCTION

Malignant lymphomas including Hodgkins Lymphoma (HL) and Non-Hodgkins Lymphoma (NHL) rank as the third most common malignant disorders in the paediatric population and are preceded by leukaemia and central nervous system (CNS) tumours only.[1] The proportion of NHL in the paediatric group has been reported to be 5–7%.[2] The overall prevalence of NHL is more in the developed countries with highest rates in Australia and North America followed by intermediate rates in Europe and Pacific Islands and lowest frequency in Asia and Western Europe.[3]

In Pakistan, NHL is the fourth most common malignancy with a male predominance in all age groups.[4] These lymphomas are comprised of a number of clinic-pathologic subtypes having heterogeneous features. The prevalence of NHL in the paediatric and adolescent population are graded as high grade tumours with an aggressive clinical behaviour in comparison to NHL in adults which are usually graded as low to intermediate in nature. NHL can occur at any site including nodal and extranodal locations and spread in an unpredictable manner. It is broadly classified as B-cell and T-cell types. The most widely used classification system is WHO Classification of Tumours of Haematopoietc and Lymphoid Tissues. NHLs are mainly sub classified on basis of morphology and immunophenotypic profile. Diffuse Large B-Cell Lymphoma (DLBCL) is most frequent subtype of NHL[5] followed by Burkitt Lymphoma (BL), Anaplastic Large Cell Lymphoma (ALCL) and Lymphoblastic Lymphomas which comprise 90% of NHL cases observed in children.[6]

Non-Hodgkins Lymphoma is a very heterogeneous group of malignancies that exhibit a wide spectrum of histologic and immunophenotypic features. This study comprised of a large cohort, spanned over a decade, and aimed at reporting the prevalence of various subtypes, demographics of NHL, and their immunohistochemical profile in the paediatric and adolescent patients. Immunophenotypic subtyping carries diagnostic as well as prognostic significance in these cases in terms of grading and response to specific chemotherapeutic regimens. Therefore, sequential data analysis was carried out on all consecutive samples in order to identify immunophenotypic patterns in our paediatric population.

MATERIAL AND METHODS

This retrospective study is conducted at the department of histopathology of Indus hospital and health network and

Ziauddin University hospital, Karachi. A total of 223 cases were retrieved from the electronic data for over a period of 11 years spanning from 01st January 2008 to 31st December 2019. The clinical data constituted of hospital record number, age, gender, anatomical sites involved at the time of diagnosis and results of immunohistochemistry (IHC). The samples included both needle and excision biopsies. The inclusion criteria for the study were patients who were treatment naïve, below the age of 18 years and belonged to either gender. Patients who had received chemotherapeutic regimen for any malignant disorder or had the relapse of any type of lymphoma were excluded from the study. Following the morphological examination of Haematoxylin and Eosin (H&E) stained slides, a panel of immunohistochemical stains were applied on formalin fixed paraffin embedded tissue. The panel of lymphoid antibodies that were used in this study for the diagnosis of NHL included: TdT, CD34, CD117, CD99, CD1a, CD45, CD79a, CD19, CD20, CD10, BCL-2, BCL-6, MUM-1, CD3, CD4, CD5, CD8, CD30, EMA, ALK-1, and Ki-67. Appropriate controls were placed on the same slide as the patient's samples and the results were reported only after the assurance that the controls had worked properly. The cases were diagnosed and classified according to WHO classification.[7]

Statistical analysis was performed using SPSS version 24.0. The frequency of discrete variables mentioned as numbers with percentages while mean and standard deviation was used for the continuous variables. The association of age groups, i.e., 0–5 years, 6–10 years, 11–15 years and 16–17 years with variables such as gender, subtypes of lymphomas and site of involvement at the time of presentation were assessed using Pearson Chi-Square or Fisher Exact test as per the requirement. The statistical significance was observed at *p*-value less than 0.05.

RESULTS

A total of 223 cases of NHL were included in the study. Basic characteristics of patients are mentioned in Table-1.

Non-Hodgkins Lymphoma is divided into subtypes according to WHO classification and age categories (Table-2). In the NHL group, patients were subdivided into B-Cell (n=145) and T-Cell (n=78). In the B-Cell NHL, the most frequent subtype was Burkitt Lymphoma, i.e., 48 (33.1%) while in the T-Cell NHL, the most common subtype was T-cell Lymphoblastic Lymphoma (TLL), i.e., 46 (58.9%). In ALCL, T-Cell subtype was 34.6% as against the predominantly Null cell type which accounted for 65.4%.

The gender distribution in various subtypes of NHL on the basis of gender is illustrated in Figure-1. Overall male to female ratio in NHL was 3.3:1 with male predominance, i.e., 76.7% was observed in the study cohort. In B-NHL group, highest male preponderance was observed in Burkitt Lymphoma while in T-NHL group, it was found in T-cell Lymphoblastic Lymphoma (Figure-1). The median age in NHL was 8 years (1.1–17years) (Table-1). In terms of age stratification (Figure-2 and Table 2), the stratum of ages 6–10 years had the highest overall number of patients, i.e., 80 (36.2%). On the basis of subtypes in the B-NHL group, the highest number of patients was the 0–5years stratum with Burkitt Lymphoma, i.e., 22 (45.8%) being the most common subtype (Table-2).

In T-NHL group, the highest number of patients was the 11–15 year stratum with T-cell Lymphoblastic Lymphoma, i.e., 24 (54.5%) being the most common subtype (Table-2). In terms of nodal involvement at the time of presentation, abdominal lymph node was observed as the most common site in this cohort (19.5%) (Table-1). The most frequent extranodal site observed was gastrointestinal tract (13%). Detailed results of immunohistochemistry for antigenic expression are given in Table-3.

Table-1: Characteristics of study participants

Variables	Values N (%)
Total No. of patients	223
B-NHL	145 (65.0)
T-NHL	78 (34.9)
AGE, years	
Mean ± SD	8.6 ± 4.0
Median (Range)	8 (1.1 – 17.0)
GENDER	
Male	171 (76.7)
Female	52 (23.3)
DISTRIBUTION (According to age categories)	
1-5 years	61 (27.3)
6-10 years	81 (36.3)
11-15 years	72 (32.2)
16-17 years	9 (4.0)
SITE	
Abdomen lymph nodes	43 (19.5)
Cervical lymph node	42 (19)
Gastrointestinal tract	29 (13.1)
Pleural fluid	13 (5.9)
Bone	12 (5.4)
Lymph Node (Unspecified)	11 (5.0)
Respiratory tract	11 (5.0)
Face	10 (4.6)
Mediastinum	10 (4.5)
Site not specified	6 (2.7)
Mesenteric	5 (2.3)
Oral cavity	4 (1.8)
Inguinal	4 (1.8)
Pelvic	3 (1.4)
Retroperitoneum	3 (1.4)
Submandibular	3 (1.4)
Renal	3 (1.4)
Axillary	2 (0.9)
Ascitic fluid	2 (0.9)
Brain	2 (0.9)
Eye	2 (0.9)
Skin	1 (0.5)

Table-2: Distribution of subtypes of Non-Hodgkin Lymphoma (n=223)

Subtypes	Total no. of patients	1–5 years (n=61)	6–10 years (n=81)	11–15 years (n=72)	16–17 years (n=9)	*p*-value
B-Cell Non-Hodgkin Lymphoma	145	48/145 (33.1)	54/145 (37.2)	38/145 (26.2)	5/145 (3.5)	0.625
Burkitt Lymphoma, (%)	48	22 (45.8)	17 (35.4)	9 (18.8)	0	
DLBCL, (%)	42	9 (21.4)	14 (33.3)	17(40.5)	2 (4.8)	
B-Lymphoblastic Lymphoma, (%)	28	7 (25.0)	10 (35.7)	8 (28.6)	3(10.7)	
High Grade B-Cell Lymphoma, (%)	27	10 (37.0)	13 (48.2)	4 (14.8)	0	
T-Cell Non-Hodgkin Lymphoma	78	13/78 (16.7)	27/78 (34.6)	34/78 (43.6)	4/78 (5.1)	
T-cell Lymphoblastic Lymphoma, (%)	46	5 (11.4)	12 (26.1)	25 (54.3)	4 (9.1)	
Anaplastic Large Cell Lymphoma (ALK +), %)	21	6 (28.6)	11 (52.4)	4 (19.0)	0	
Peripheral T Cell Lymphoma, (%)	6	1 (16.7)	1 (16.7)	4 (66.6)	0	
Anaplastic Large Cell Lymphoma (ALK -), (%)	5	1 (20.0)	3 (60.0)	1 (20.0)	0	

Table-3: Antigen expression in subtypes of Non- Hodgkin Lymphoma n (%)†

Antigens	B-Cell						T-Cell	
	DLBCL	BL	High Grade B-Cell Lymphoma	BLL	ALCL (ALK +)	ALCL (ALK-)	PTCL	TLL
CD45 (n=35)	4/5† (80)	2/2 (100)	1/1 (100)	3/4 (75)	16/17 (94.1)	3/5 (60)	4/4 (100)	2/2 (100)
TdT (n=56)	0/34 (0)	0/39 (0)	0/23 (4.3)	21/27 (77.8)	0/6 (0)	0/2 (0)	0/5 (0)	35/42 (83.3)
CD34 (n=28)	0/29 (0)	0/27 (0)	0/19 (0)	13/26 (50)	0/5 (0)	0/2 (0)	0/5 (0)	15/43 (34.9)
CD99 (n=15)	0/5 (0)	1/3 (33.3)	0/6 (0)	2/3 (66.7)	1/2 (50)	NT	NT	11/12 (91.7)
CD117 (n=1)	NT	NT	NT	0/1 (0)	0/3 (33.3)	0/3 (33.3)	0/1 (0)	1/3 (33.3)
CD79a (n=107)	28/29 (96.6)	23/24 (95.8)	12/12 (100)	25/26 (96.2)	0/5 (20)	0/3 (0)	0/1 (0)	20/46 (43.5)
CD20 (n=110)	32/32 (100)	40/40 (100)	21/21 (100)	17/22 (77.3)	0/17 (0)	0/2 (50.0)	0/6 (0)	0/26 (7.7)
CD19 (n=5)	1/1 (100)	NT	NT	4/5 (80)	NT	NT	NT	0/7 (0)
CD10 (n=113)	28/38 (73.7)	45/46 (97.8)	19/21 (90.5)	19/22 (86.4)	1/1 (100)	NT	0/2 (0)	1/5 (20)
BCL6 (n=31)	17/21 (80.9)	6/6 (100)	5/5 (100)	2/2 (100)	NT	NT	NT	1/1 (100)
BCL2 (n=28)	13/24 (54.2)	0/41 (0)	9/18 (50)	4/7 (57.1)	NT	NT	NT	1/1 (100)
MUM1 (n=17)	15/23 (65.2)	1/4 (25)	0/3 (0)	1/1 (100)	NT	NT	NT	NT
CD3 (n=60)	0/42 (0)	0/47 (0)	0/27(0)	0/28 (0)	7/21 (33.3)	2/5 (40)	6/6 (100)	44/44 (100)
CD5 (n=7)	0/1 (0)	0/3 (0)	0/2 (0)	0/2 (0)	0/5 (0)	0/2 (0)	2/3 (66.67)	5/6 (83.3)
CD4 (n=6)	NT	NT	NT	NT	3/5 (60)	0/2 (0)	1/3 (33.3)	2/4 (50)
CD8 (n=6)	NT	NT	NT	NT	NT	1/2 (50)	3/8 (37.5)	2/2(100)
CD1a (n=5)	NT	NT	0/1 (0)	NT	0/3 (0)	0/1 (0)	0/2 (0)	5/20 (25)
CD30 (n=26)	2/5 (40)	NT	NT	0/2 (0)	20/20 (100)	4/4 (100)	2/6 (33.3)	0/3 (0)
ALK1 (n=19)	NT	NT	NT	NT	19/19 (100)	0/5 (0)	0/2 (0)	0/2 (0)
EMA (n=17)	NT	NT	NT	0/2 (0)	14/16 (87.5)	3/3 (100)	0/1 (0)	NT
Ki67 (n=135)	30/30 (100)	48/48 (100)	24/24 (100)	17/17 (100)	4/4 (100)	1/1 (100)	4/4 (100)	7/7 (100)

DLBCL- Diffuse Large B-Cell Lymphoma; BL- Burkitt's Lymphoma; BLL- B-Lymphoblastic Lymphoma; ALCL-Anaplastic Large Cell Lymphoma; PTCL-Peripheral T Cell Lymphoma; TLL-T-Lymphoblastic Lymphoma

† - n=Positive antigen/N=Total number of cases in which antigen tested; NT- NOT TESTED

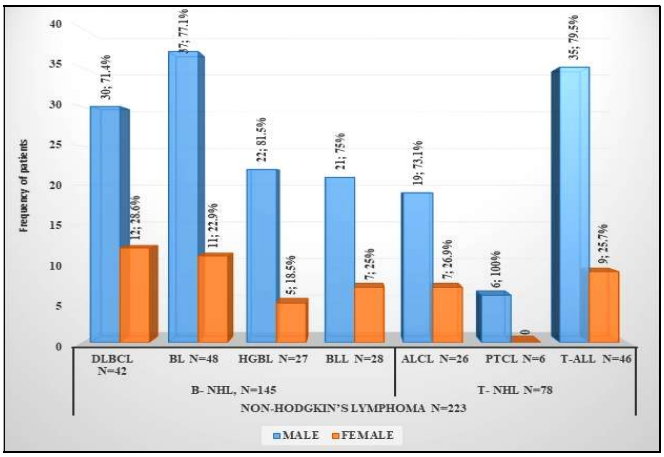

Figure-1: Distribution of subtypes of Non-Hodgkin Lymphoma according to gender

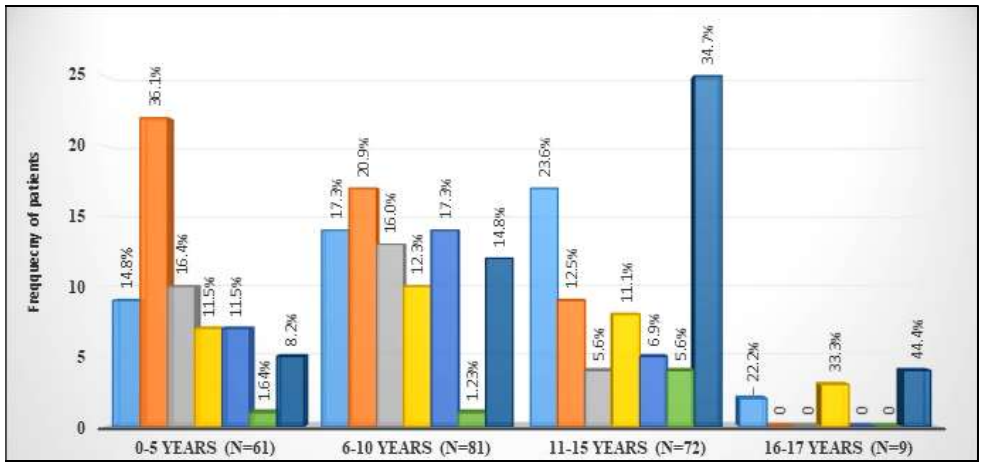

Figure-2: Distribution of subtypes of Non-Hodgkin Lymphoma according to age categories

DISCUSSION

Due to the lack of any national cancer registry in Pakistan, the precise incidence of childhood cancers is unknown. Incidence of lymphoma is highest in countries which are part of an extensive area named as "lymphoma belt" spans from Southwest Asia, Middle East to Northern Africa.[8] Non-Hodgkins Lymphoma is a very heterogenous malignancy with variable frequencies according to age of patient, gender, ethnicity as well as the histological subtype. Childhood NHL is known to carry distinct epidemiological, histopathological and clinical features over a large geographical area and with a wide variation between the developing and the developed world.

The distribution of lymphomas has a contrasting pattern when studies are compared from the resource-constrained countries and the developed world. The western literature reports a ratio of 1.5:1 for NHL: HL prevalence. However, a number of studies from Southeast Asian countries, i.e., Pakistan[9], Bangladesh[10] and India[11] as well as Asian countries like China[12] have reported findings which were in concordance with the literature from the West with a higher percentage of NHL cases in comparison to HL. In Africa despite being a developing country, the higher number of NHL cases can be attributed to the higher incidence of Burkitt Lymphoma.[13]

The male to female ratio in the paediatric NHL cases in the present study was observed to be 3.3:1. This finding was similar to the gender distribution in cases of paediatric as well adolescent NHL which reported a male preponderance both from the West as well as the developing world, i.e., Southeast Asia,[14] Middle East[15] and Africa[16]. The male preponderance observed in the present study are in concordance with the published literature. Overall results of this study showed 66% B-NHL and 34% T-NHL, however reported literature shows a relatively lower frequency of T-NHL, i.e., 12–15%. The most common subtype of NHL in this study was Burkitt Lymphoma with a frequency of 21.7%. This finding was concordant with other local study by Faizan *et al*. 43.8% (32/71).[17] In the present study T-Cell Lymphoblastic Lymphoma had the highest occurrence, i.e., 57.8% in T-Cell NHL. The finding of T-Cell Lymphoblastic Lymphoma being the most common T-Cell NHL subtype was also reported from India by Manipadam *et al*. (32.1%).[18]

The present study reported the median age in NHL cases to be 8 years with range being 1.1–17 years. Studies from other developing countries has also reported that the baseline age in majority of the NHL cases was between 5–10 years.[18] On the basis of subtypes, Burkitt Lymphoma was the most common in the <10 years group while T-Cell Lymphoblastic Lymphoma was the most frequent subtype in the >10 years group in the present study. An Indian study by Manipadam *et al*. also reported Burkitt Lymphoma as the most common subtype in the <10 years group however, DLBCL was observed as the most common NHL subtype in the >10 years group in their study.[18] In terms of age groups, the present study reported the highest number of patients, i.e., 36.2% (80/221) of NHL cases belonged to the age stratum of 6–10 years. In terms of age groups in the present study, the most common subtypes in NHL were Burkitt Lymphoma in the 0–5 years and 6–10 years and T-Cell Acute Lymphoblastic Lymphoma in the 11–15 and 16–17years groups. A study by Wright *et al*. reported Lymphoblastic Lymphomas as the most common subtype in the 0–5 years group, Burkitt Lymphoma in the 5–10 years and ALCL in the >10 years group.

In paediatric NHL, sites of involvement have a prognostic significance and generally considered for intensive therapy like bone marrow, mediastinum and central nervous system involvement. The nodal presentation in the NHL cases was observed mainly in the cervical area, i.e., 17.6% which was similar to a

study by Laurent *et al*[19] who reported a cervical involvement in 13.9%. In terms of extranodal presentation, abdomen was the most frequent site in the present study, i.e., 19.5% while Laurent *et al*. reported a frequency of 20% at the site below the diaphragm.[19] Studies have also reported a similar finding of a higher frequency of extranodal presentation in the paediatric population as compared to the adults who have more nodal presentation.

The present study is a single centered study and the biases that are a part of this type of sampling have been taken into consideration. However, due to the absence of any national cancer registry and studies comprising of large cohorts, these single centered studies can contribute greatly towards the proper documentation as well as the understanding of the disease and treatment dynamics in our part of the world.

Immunohistochemistry with appropriate antibody panels identify the specific lineage and developmental stage of the lymphoma. The panel of markers, selected according to differential diagnosis on the basis of provided clinical history and morphological examination. The present study observed certain findings in terms of immunohistochemical profile.

There were a large proportion of immature B-cell lymphomas, i.e., 74 (33%). All markers of immaturity and multiple lineage specific markers were used to classify the subtypes. Amongst B-LL, only 9 (4.0%) cases showed negativity for both Tdt and CD34 expression. After the revision of WHO classification for haematolymphoid tumours, these types of cases are now categorized as high-grade B-cell lymphomas.[7] This is the limitation of our study that molecular testing was not done to confirm the diagnosis of high-grade B-cell lymphomas. Diagnosis was made on the basis of morphology and immunohistochemistry (IHC) although it is not surrogate of molecular testing.

In TLL, dual negativity of Tdt and CD34 was observed in 10.9% of the cases. Another finding was the absence of TdT in 15.2% (7/46) of the TLL cases which was similar to foreign literature related to expression of TdT in TLL patients. These small number of cases are less likely to express aberrant B-Cell markers, CD10, CD34 and myeloid antigens but retain expression of cytoCD3, CD5, and CD7 with either CD4 and/or CD8.[20] In this cohort, 43.5% cases of T-LL showed aberrant expression of CD79a that is significantly higher than reported literature. Also observed in TLL, was the CD99 positivity in 4.3% patients in the absence of TdT, CD34 and CD117 and helps in the determination of the precursor nature of the disease.[21] CD99 in TLL has been reported as high as 55%.[22]

Burkitt lymphoma is a B-Cell neoplasm that express a variety of B-lineage markers but absence of immature markers. A high frequency of CD10 expression has been reported in paediatric cases of Burkitt lymphoma[23] which is also observed in 97.8% of cases in the present cohort. According to published reports, paediatric NHL cases are mostly of high-grade type, it is also evident in this cohort by 100% positivity of Ki-67. All cases of Burkitt lymphoma were confirmed by fluorescence in situ hybridization (FISH) for t(8;14) MYC/IGH.

DLBCL, a mature B-Cell neoplasm which is characterized by the expression of B-cell markers and mainly categorized into germinal center (GCB) and activated B-cell (ABC) subtypes. GCB DLBCL has been consistently associated with better outcomes and its incidence is higher in younger patients.[23] In 42 cases of DLBCL, Germinal cell subtype [(CD10+) or (CD10-/BCL6+/MUM1-)] was present in 76.2% while non-Germinal cell subtype/activated B-cell type [(CD10-/BCL6+/MUM1+) or (CD10-/BCL6-/MUM1+/-)] was observed in 11.4% cases. The higher percentage of GCB subtype in comparison to non-GCB was similar to the findings reported by Girgis *et al*.[24] Additionally, the expression of BCL2 in DLBCL is associated with inferior outcomes[23] and it was found to be expressed in 30.9% cases in this cohort.

All anaplastic large cell lymphoma cases are CD30-positive. The lineage specified for anaplastic large cell lymphoma is mature T-cell, however null-cell disease (i.e., no T-cell, B-cell, or natural killer-cell surface antigen expression) does occur. In ALCL, the T-Cell versus Null cell subtype, negative for pan T cell markers was found to be 34.6% versus 65.4%. This finding was similar to international literature which reports that >75% of the ALCL cases are CD3 negative.[25] More than 90% of paediatric ALCL cases have a chromosomal rearrangement involving the *ALK* gene and its absence is associated with an inferior outcome in adult patients but no impact in the paediatric population.[23] Anti-ALK immunohistochemical staining pattern is quite specific for the type of *ALK* translocation. Mature T-cell lymphoma has a post-thymic phenotype and it is very rare in children excluding ALCL.[23] The most common subtype in children is the peripheral T-cell lymphoma not otherwise specified which was observed in 2.7% of the cases in the present study.

CONCLUSION

Our cohort of paediatric patients with lymphoma shows characteristics that seem to be similar to the published literature. Higher frequency is observed in males however, no significant association between age and subtypes is found in our study. Identification of subtypes of NHL plays a vital role in diagnostic, prognostic and therapeutic implications.

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AUTHORS' CONTRIBUTION

SJ: Conceived, designed and critically reviewed the manuscript. FL, NY: Interpretation of all cases. NM, BK and FL: Data collection. NM, SJ and BK: Writing of manuscript FL and BK: Editing and statistical analysis. SJ, NY and NM: Review and final approval of manuscript. All authors read and approved the final manuscript.

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