# Pattern of lymphoma subtypes in a cohort of Sri Lankan patients

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(Index words: Lymphoma, Non Hodgkin lymphoma, Hodgkin lymphoma, WHO lymphoma classification, Sri Lanka)

## Abstract

*Objectives* To investigate the pattern of World Health Organization (WHO) lymphoma sub types in a sample from Sri Lanka.

*Methods* Retrospective, descriptive study was carried out using biopsy specimens of patients diagnosed or suspected to have a lymphoma received by the Department of Pathology, University of Peradeniya for WHO sub typing. A sample of 227 cases diagnosed to have a lymphoma. All lymphomas were sub classified according to WHO 2007 revised classification of haematopoietic and lymphoid neoplasm using immunohistochemistry.

*Results* There were 35 (15.4%) Hodgkin Lymphoma (HL) and 192 (84.6%) non Hodgkin Lymphoma (NHL) specimens. Of the NHL the common sub types were diffuse large B cell lymphoma 87 (38.3%), follicular lymphoma 26 (11.5%) and peripheral T cell lymphoma 25 (11%). Of the HL the common sub types were mixed cellular 20 (8.8%) and nodular sclerosis 13 (5.7%). The mean age of the patients was 48.8±19.3 years and male to female ratio was 1.4:1. The observed patterns of both HL and NHL in the study population were similar to those of other South Asian countries such as India and Pakistan.

*Conclusions* In the Sri Lankan sample, common sub types of lymphoma were diffuse large B cell lymphoma and follicular lymphoma. The frequency of lymphoma subtypes in the Sri Lankan sample are in accordance with the globally observed variations and similar to those observed in other South Asian countries.

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## Introduction

Lymphoma is a diverse group of lymphoid neoplasms that comprise of Hodgkin Lymphoma (HL) and non Hodgkin Lymphoma (NHL). NHL group is particularly heterogeneous and has more than 40 different subtypes. Behaviour of these subtypes varies from low grade indolent to high grade aggressive and many of these have different treatment protocols. Therefore, sub classification of lymphoma is essential and the universally adopted classification system is the World Health Organization (WHO) Classification of Tumours of the Hematopoietic and Lymphoid Tissues [1].

The aetiology of lymphoma has not yet been fully understood and each subtype appears to have a different aetiology which may be influenced by genetic susceptibility, immune status, ethnicity, viruses, environmental factors, cultural factors and geographic factors [1,2]. Incidence of lymphoma subtypes is subjected to geographic and ethnic variations [2-6]. Investigation of incidence of lymphoma subtypes is important in assessing the disease burden. Observation of geographical and ethnic variations is helpful in attempts to identify the aetiology [2,3,6]. In South Asia, incidence of WHO subtypes of lymphoma are available only for India and Pakistan and no published reports are available for Sri Lanka. Therefore, we conducted the following study to investigate the pattern of WHO sub types of lymphoma in a sample of patients from Sri Lanka and compared them with global patterns.

## Methods

This is a retrospective descriptive study of 227 lymphomas diagnosed and sub typed at the Department of Pathology, Faculty of Medicine, University of Peradeniya over the period January 2010 to May 2014. The samples were from patients treated at the Teaching Hospital, Peradeniya and referrals from other regional hospitals. Cases suspected of mycosis fungoides were received from regional skin clinics. All lymphomas were sub classified according to WHO 2007 revised classification of hematopoietic and lymphoid neoplasms using haematoxylin and eosin stain and immunohisto-chemistry [1]. The immunostains used were Leucocyte common antigen (LCA), EMA, CD 20, CD 79a, CD 3, CD 5, CD 4, CD 8, CD45RO, CD 43, CD 23, Cyclin D1, CD 10, CD 30, CD 15, CD 138, CD 68, ALK, BCL 2, TdT, and Ki 67. Age, sex and clinical presentation were obtained from the pathology request forms accompanying the biopsies. Cases diagnosed as plasmacytoma/ multilple myeloma were not included in the analysis.

A literature review was conducted to identify the global variation of lymphoma subtypes according to

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WHO classification. For a detailed comparison, seven publications on lymphoma subtype patterns in several countries were selected, USA representing the West; India and Pakistan representing South Asia; Japan, Korea and China representing South East Asia [5, 7-12].

## Results

There were 227 cases; 35 (15.4%) were HL and 192 (84.6%) NHLs. Among those 131 (57.7%) were males and the male to female ratio was 1.4:1. The mean age of the sample was 48.8 ±19.3 years.

Of HLs, 20 (57.1%) had mixed cellular type, 13 (37.1%) had nodular sclerosis type and the rest (5.7%) had other types. None had nodular lymphocyte predominant HL or lymphocyte depleted classic HL sub types. The mean age of development of HL was 43.18 years ± 21.21 (Table 1).

Of the NHLs, 148 (77.1%) were B cell type and 44 (22.9%) were of T cell or null type. High grade diffuse large B cell lymphoma which accounted for 45.3% (87/192) was the commonest sub type. Low grade lymphoma sub types accounted for 28.1% (54/192). Of the T cell NHLs the commonest was Peripheral T cell lymphoma (n=25) 13%. The mean age of NHL was 49.83 years ± 18.81 years. Table 1 shows the pattern of lymphoma sub types and age and sex distribution of each subtype.

Nodal disease was the presentation in 187 (82.4%) and 40 (17.6%) presented with extra nodal disease. Of the nodal disease, cervical lymphadenopathy 89 (39.2%) was the commonest and generalized lymphadenopathy was present at the presentation in 19 (8.4%). The commonly affected extranodal sites were skin (n=16) and gastro-intestinal tract (n=5). Diffuse large B cedlym (Diffuse large B cell lymphoma) was the commonest type present in nodal (86.2%) and extra nodal disease (13.8%). Of the skin specimens 12 were mycosis fungoides and 4 were DLBL.

**Table 1. Lymphoma WHO subtypes**

| *Lymphoma sub type N=227* | *Frequency (%)* | *Mean age in years (SD)* | *Number of males (%)* | *Nodal n(%)* | *Extra nodal n(%)* |
|---|---|---|---|---|---|
| **Hodgkin lymphoma n=35** | | | | | |
| Nodular lymphocyte predominant | 0 | 0 | 0 | 0 | 0 |
| **Classic Hodgkin lymphoma** | | | | | |
| Mixed cellular | 20 (57.1) | 51.82 (20.9) | 15 (75) | 20 (100) | 0 (0) |
| Nodular sclerosis | 13 (37.1) | 33.8 (19.4) | 6 (46.1) | 13 (100) | 0 (0) |
| Lymphocyte rich | 1 (2.9) | 23 0 (0) | 1 (100) | 0 (0) | 0 (0) |
| Lymphocyte depleted | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Unclassifiable | 1 (2.9) | 27 | 0 (0) | 1 (100) | 0 (0) |
| **Non Hodgkin lymphoma B cell type N=148** | | | | | |
| Diffuse large B cell lymphoma | 87 (58.8) | 53.68 (16.91) | 52 (59.8) | 75 (86.2) | 12 (13.8) |
| SLL/CLL | 11 (7.4) | 49.08 (17.15) | 6 (54.5) | 10 (90.9) | 1 (9.1) |
| Follicular lymphoma | 26 (17.6) | 54.7 (13.09) | 11 (42.3) | 23 (88.5) | 3 (11.5 ) |
| Mantle cell lymphoma | 10 (6.8) | 52.56 (11.94) | 7 (70) | 9 (90) | 1 (10) |
| Marginal zone lymphoma | 6 (4) | 61.83 (13.03) | 3 (50) | 2 (33.3) | 4 (66.6) |
| Burkitt lymphoma | 1 (0.7) | | 1 (100) | 0 (0) | 1 (100) |
| Unclassifiable | 7 (4.7) | 55.40 (17.11) | 6 (85) | 7 (100) | 0 (0) |
| **Non Hodgkin lymphoma T cell /null type N=44** | | | | | |
| Anaplastic large cell lymphoma (T and Null type) | 6 (13.7) | 17.33 (9.89) | 5 (83) | 6 (100) | 0 (0) |
| Peripheral T cell lymphoma | 25 (56.8) | 47.2 (22.25) | 14 (56) | 19 (76) | 6 (24) |
| Mycosis fungoides | 12 (27.3) | 29.33 (13.4) | 4 (33.33) | 0 (0) | 12 (100) |
| Lymphoblastic lymphoma | 1 (2.3) | | 1 (100) | 1 (100) | 0 (0) |

A comparison of lymphoma WHO sub type pattern in Sri Lanka with those of the USA, India, Pakistan, China, South Korea and Japan is shown in Table 2.

**Table 2. Comparison of lymphoma WHO subtypes incidence patterns in the study sample (Sri Lanka), India, USA and South Korea**

| *Lymphoma WHO sub type* | *Sri Lanka* *n (%)* *n=227* | *India* [7,8] *n(%)* *n=3224* | *Pakistan* [9] *n(%)* *n=246* | *USA* [5] *n(%)* *n=114548* | *Japan* [10] *n(%)* *n=2260* | *Korea* [11] *n(%)* *n=5318* | *China* [12] *n(%)* *n=6382* |
|---|---|---|---|---|---|---|---|
| **Hodgkin lymphoma** | | | | | | | |
| NLPHL | 0 | 54 (1.7) | 0 | 308 (0.3) | 7 (0.3) | 8 (0.2) | 35 (0.5) |
| **Classic Hodgkin lymphoma** | 34 (15) | 397 (12.3) | 66 (26.7) | 9734 (8.5) | 158 (7.0) | 219 (4.1) | 798 (12.5) |
| Mixed cellular HL | 20 (8.8) | 142 (4.4) | 44 (17.9) | 1906 (1.6) | 52 (2.3) | 56 (1.1) | 606 (9.5) |
| Nodular sclerosis HL | 13 (5.7) | 116 (3.6) | 22 (8.9) | 6270 (5.5) | 70 (3.1) | 122 (2.3) | 145 (2.3) |
| Classic Hodgkin lymphoma - Other | 1 (0.4) | 25 (0.8) | 0 (0) | 1558 (1.4) | 27 (1.2) | 16 (0.3) | 47 (0.7) |
| Unclassified | 1 (0.4) | 114 (3.5) | 0 (0) | 0 (0) | 9 (0.4) | 17 (0.3) | 0 (0) |
| **Non Hodgkin lymphoma B cell type** | | | | | | | |
| Diffuse large B cell lymphoma | 87 (38.3) | 937 (29.1) | 119 (48.4) | 24246 (21.2) | 746 (33) | 1650 (31) | 2288 (35.9) |
| small lymphocytic lymphoma/chronic lymphocytic leukeamia | 11 (4.8) | 155 (4.8) | 4 (1.6) | 16984 (14.8) | 32 (1.4) | 97 (1.8) | 256 (4) |
| Follicular lymphoma | 26 (11.4) | 350 (10.9) | 9 (3.7) | 10705 (9.3) | 413 (18.3) | 91 (1.7) | 327 (5.1) |
| Mantle cell lymphoma | 10 (4.4) | 95 (2.9) | 4 (1.6) | 1691 (1.5) | 61 (2.7) | 98 (1.8) | 175 (2.7) |
| Marginal zone lymphoma | 6 (2.6) | 220 (6.8) | 4 (1.6) | 3247 (2.8) | 127 (5.6) | 720 (13.5) | 355 (5.6) |
| Nodal | 2 (0.8) | 52 (1.6) | 0 | | 32 (1.4) | 54 (1.0) | 5 (0.7) |
| Extra nodal | 4 (1.6) | 168 (5.2) | 4 (1.6) | | 95 (4.2) | 661 (12.4) | 350 (5.5) |
| Burkitt lymphoma | 1 (0.4) | 50 (1.6) | 7 (2.8) | 1102 (0.9) | 15 (0.7) | 111 (2.1) | 106 (1.7) |
| **Non Hodgkin lymphoma T cell type** | | | | | | | |
| Anaplastic large cell lymphoma | 6 (2.6) | 113 (3.5) | 4 (1.6) | 864 (0.8) | 45 (2) | 104 (1.4) | 196 (3.1) |
| Peripheral T cell lymphoma (not otherwise specified) | 25 (11) | 53 (1.6) | 10 (4.1) | 1031 (0.9) | 102 (4.5) | 211 (4) | 221 (3.5) |
| Mycosis fungoides | 12 (5.2) | 24 (0.7) | 5 (2.1) | 1773 (1.5) | 11 (0.5) | 21 (0.4) | 14 (0.2) |
| Adult T cell leukaemia/ lymphoma | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 226 (10) | 1 (0.01) | 0 (0) |
| E NK/T | 0 (0) | 19 (0.6) | 0 (0) | 1501 (1.3) | 36 (1.6) | 206 (3.8) | 949 (14.9) |
| Angioimmunoblastic T cell lymphoma | 0 (0) | 28 (0.9) | 0 (0) | 176 (0.2) | 115 (5.1) | 43 (0.8) | 185 (2.9) |
| Other types | 0 (0) | 0 (0) | 0 (0) | 1502 (1.1) | 0 | 230 (4.3) | 0 (0) |
| Lymphoblastic lymphoma | 1 (0.4) | 185 (5.7) | 11 (3.9) | 6127 (5.3)* | 21 (0.9) | 873 (16.2) | 301 (4.7) |

ENK/T - nasal extra nodal NK/T lymphoma - nasal type

## Discussion

Overall rates of lymphoma tend to be lower in Asia compared to North America, Europe and Australia [2,6] Age specific incidence rate (ASR) for USA during 2005-2009 was 19.6 compared to 2.4 in India, 2.1 in China and 5.1 in Japan [6]. In Sri Lanka, lymphoma ASR is 3.8 for males and 2.6 for females. Lymphoma is the 5th leading malignancy among males and 10th among females in Sri Lanka [13]. An ''epidemic proportion'' increase in NHL has been reported in the West since 1950s [2]. Although, HIV infection has been attributed to part of this increase, the reasons are unknown for most cases [2].

According to the present study, the most common sub type of lymphoma in the Sri Lankan sample was DLBCL in both nodal and extra nodal sites. Despite global variation in the patterns of lymphoma subtypes, DLBCL is the commonest lymphoma subtype. However, DLBCL is a heterogenous group in terms of clinical outcomes, morphology and cytogenetics [1]. Furthermore, it could arise de novo or progress from low grade B cell lymphomas such as follicular lymphoma and marginal zone lymphoma [1].

Of the low grade B cell lymphomas the commonest subtype in the Sri Lankan sample was follicular lymphoma. Patterns of low grade B cell lymphomas show significant geographical and ethnic variations. In the USA, SLL/CLL and follicular lymphoma are the two most common types of low grade lymphoma, whereas, in our sample, in India and in Pakistan the commonest type was follicular lymphoma and CLL/SLL was less common. Although follicular lymphoma is also common in the USA, molecular pathogenesis of follicular lymphoma in the US has been hypothesised to be distinct from those of Asian follicular lymphoma based on the differences in the frequencies of BCL 2 translocations in these geographic regions [14]. Incidence of CLL is four times higher in Caucasian Americans than in Asian Americans [2]. The prevalence of CLL/SLL remains low in all reviewed South Asian and East Asian countries further highlighting the genetic bias in white Caucasians. Mantle cell lymphoma, on the other hand, does not show a significant geographical variation in incidence, indicating that the pathogenesis of mantle cell lymphoma may be less affected by ethnicity associated genetic variations.

Among the East Asian countries, in South Korea, extranodal marginal zone lymphoma is the most common type of low grade lymphoma and the gastrointestinal tract is the most commonly affected site [11]. High prevalence of *Helicobacter pylori* gastritis in South Korea, which is a known aetiological agent for marginal zone lymphoma, has been indicated as the reason for this observation [11]. However, despite high prevalence of *H. pylori* infection, in Japan, the prevalence of follicular lymphoma is much higher than those of extranodal marginal zone lymphoma.

In our sample and in the reviewed countries there was very low frequuency of Burkitt lymphoma. Endemic Burkitt lymphoma is a classic, geographically exclusive B cell lymphoma which affects predominantly the equatorial African countries [1]. Burkitt lymphoma shows an aetiological association with Epstein - Barr virus and the geographical distribution pattern of Burkitts lymphoma overlaps with that of Plasmodium falciparum malaria, indicating a possible polymicrobial pathogenesis [1, 15, 16]. On the other hand, non AIDS associated, sporadic Burkitt lymphoma, which occur in the rest of the world is rarer.

Similar to our finding, worldwide too, incidence of T cell lymphomas are much lower than B cell types. However, the frequency of mycosis fungoides, a primary T cell lymphoma of skin, is higher in the Sri Lankan sample compared to other reviewed countries. This could be due to referral bias. The frequency of peripheral T cell lymphoma is also relatively higher in the Sri Lankan sample. The exact reason for this is not apparent. However, since peripheral T cell lymphoma is a diagnosis of exclusion of other specific T cell subtypes, non-availibility of immune markers for rarer sub types and molecular diagnosis in our institution could have contributed to this observation. In the countries we reviewed apart from Japan, Adult T cell leukaemia/lymphoma (ATLL) was rare. ATLL is confined to certain geographic regions such as South Western Japan, Caribean basin and parts of Central Africa [1]. This distribution pattern closely follows the prevalence pattern of HTLV -1 infection suggesting an aetiological link [1].

Compared to the reviewed countries relatively higher frequency of HL is observed in the Sri Lankan sample and Pakistan. Mixed cellular and nodular sclerosis types is the most common HL sub types in the reviewed countries. In the Sri Lankan sample, Pakistan and India the commonest HL sub type was mixed cellular, where as in the USA and Japan the commonest was nodular sclerosis type [5,8,9,10].

The study had several limitations. The results are from a single tertiary care centre and therefore, there can be referral bias. Referrals from several regional skin clinics may have increased the numbers of mycosis fungoides. Non availability of immunomarkers and genetic markers to diagnose rare lymphoma subtypes may have lead to underdiagnosis of such sub types and increase the ''not otherwise specified'' groups.

## Conclusions

In the Sri Lankan sample, 84.6% were NHLs and the rest were HLs. The most common sub types of NHL are diffuse large B cell lymphoma and follicular lymphoma. Of the HLs mixed cellular sub type was the commonest. The patterns of lymphoma subtypes in the Sri Lankan sample are comparable with the globally

observed variations and similar to those observed in other South Asian countries. This study further highlights the geographic and ethnic variation of certain lymphoma subtypes.

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## Declaration of Interest

There are no conflicts of interest.

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