

## Original Research Article

# Trends in the profile of non hodgkins lymphoma in North and South India: a study from two tertiary care hospitals in India

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## ABSTRACT

**Background:** A number of environmental and chemical factors have been thought to be implicated in the occurrence of Non-Hodgkin's Lymphomas (NHLs). To fill the knowledge gap in various aspects of the disease, this study was undertaken at this tertiary care centre in Delhi and Bangalore.

**Methods:** This was a prospective observational study conducted in two defense medical centres in India among patients of Non-Hodgkin's Lymphoma, registered at Command Hospital Airforce Bangalore and Army Hospital (Research and Referral), New Delhi, between March 2016 and March 2019.

**Results:** The disease showed a bimodal onset in both centres with 26 (26%) and 24 (24%) cases occurring in the age group of 31-40 years and 25 (25%) cases occurring in the age group of >60 years at CHAF (B) and AH (RR) respectively. B cell Lymphoma was the most common type of NHL seen in 85% and 89% patients, whereas T-cell lymphomas constituted 13% and 11% at CHAF (B) and AH (RR). 32 (32%) patients presented with an Ann Arbor Stage 1 or 2 disease whereas 68 (68%) patients were with Stage 3 or 4 disease at both the centres. IPI score was  $\geq 3$  in 45% and 43% patients.

**Conclusions:** NHL in India is a homogeneous and uniform disease. But there was increased detection of hepatosplenomegaly and associated hepatitis B/C in the southern part of India. Also, the occurrence of Cutaneous T cell lymphoma was only seen in the south India centre. The early stage NHLs have better survival and increase chance of complete response.

**Keywords:** B cell Lymphoma, Cutaneous T cell lymphoma, India, Non-Hodgkin's Lymphoma, T-cell lymphomas

## INTRODUCTION

Non-Hodgkin's Lymphomas (NHLs) are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment.<sup>1</sup> Since 1970s, the incidence rates of NHLs have risen dramatically, with incidence rates becoming almost double.<sup>2</sup> It is the most prevalent hematopoietic neoplasm, representing approximately 4% of all cancer diagnoses

and ranking seventh in frequency among all cancers. NHL is more than 5 times as common as Hodgkin disease.<sup>3</sup>

The incidence varies with race and geographical region.<sup>4</sup> In India, there are approximately 23,718 new NHL cases reported each year, though the age-standardized incidence rates are low (2.4 per 100,000) compared to the rates in other parts of the world.<sup>4</sup>

A number of environmental and chemical factors have been thought to be implicated in the occurrence of NHLs.<sup>5-8</sup> Also, better understanding of the pathogenesis of lymphomas has become possible with the help of IHC and its careful utilization aids identification and the characterization of immunophenotype in most of the lymphomas. There is wide variation in the incidence, type and presentation of NHL patients with in and different regions.

To fill this knowledge gap which exists regarding the geographical distribution, gender preponderance, risk factors, subtypes, clinical correlation its prevalence, prognostic factors and treatment outcome this study was undertaken at this tertiary care center in Delhi.

## METHODS

This was a study conducted in two defense medical centers in India. It was a prospective observational study conducted among patients of Non-Hodgkin's Lymphoma, registered at Command hospital Airforce Bangalore and Army Hospital (Research and Referral), New Delhi, between March 2016 and Mar 2019. The diagnosis of Non-Hodgkin's lymphoma was established by excisional biopsy from lymph nodes or involved tissues and subjecting them to immunohistochemistry. Patients who fulfilled the inclusion and exclusion criteria were enrolled in the study after obtaining written informed consent from them. The Inclusion criteria included patients with confirmed histopathological diagnosis of Non-Hodgkin's Lymphoma and those who were willing to participate in the study with required follow up visit while the exclusion criteria was any other malignancies other than Non-Hodgkin's Lymphoma and unwillingness to participate.

Ethics committee approval was taken before the start of study. All patients underwent hematological evaluation (including hemoglobin, total and differential leukocyte count, platelet count, peripheral smear study), biochemical (liver function tests, LDH, urea, creatinine, uric acid) and viral markers (HBsAg, Anti HCV and HIV) investigations. Confidentiality of the data was maintained throughout the study period and the data was accessible to principal investigator only. Data was presented as percentages for categorical variables and mean (SD) for normally distributed continuous variables and median (IQR) for skewed distributions.

## RESULTS

A total of two hundred (200) patients were diagnosed during the study period, there were 100 patients from Command Hospital Airforce Bangalore and 100 from Army hospital (R and R). The number of Males were 64 (64%) while females were 36 (36%) at command hospital Airforce Bangalore while in Army hospital (R and R) 62 (62%) were male and 38 (38%) were female with male female ratio of 1.77:1 and 1.63:1 respectively. The average age of patients was 45.5 and 45.36 years. The

disease showed a bimodal onset in both the centres with 26 (26%) and 24 (24%) cases occurring in the age group of 31-40 years and 24 (24%) and 25 (25%) cases occurring in the age group of >60 years at CHAF (B) and AH (RR) respectively. Most of the patients. 43 (43%) patients presented beyond 5th decade of life at both the centres in the North and South (Table 1). Nine patients at CHAF (B) had family history of cancer of whom 5 patients had history of NHL in first degree relatives while eight percent patients had positive family history for malignancy, of whom 4 patients have family history of Non-Hodgkin's lymphoma in first degree relatives at AH (RR). Fatigue, anorexia, fever and weight loss were common clinical presentation among enrolled patients in both the centres. B Symptoms (Type B symptoms: Fever, and/or night sweats, and/or weight loss of more than 10% of body weight) were seen in 50 (50%) at CHAF (B) and 45(45%) of patients at AH (RR) (Table 2). Raised serum LDH was the most common deranged parameter in 55% and 57% patients in both centres. Bone marrow involvement by the neoplastic process was detected in 25 (25%) of patients at both centres (Table 3).

**Table 1: Age and gender wise distribution of patients enrolled in study.**

Age (years)	No. of patients AH (RR)	No of patients CHAF(B)
<10	5	7
10-20	8	6
21-30	10	7
31-40	24	26
41-50	10	9
51-60	18	21
>60	25	24
Total	100	100

**Table 2: Clinical findings among patients.**

Symptomatology	No. of patients AH (RR)	No of patients CHAF (B)
Weight loss	30	31
Anorexia	59	58
Fatigue	58	57
Fever	34	21
Dyspnoea	13	18
Bleeding manifestations	6	11
B symptoms	45	50
Compressive symptoms	6	2
Neck swelling	35	29

B cell Lymphoma was the most common type of NHL seen in 85% and 89% patients, whereas T-cell lymphomas constituted 13% and 11% at CHAF (B) and AH (RR). Among B cell type, Diffuse Large B-cell Lymphoma (DLBL) was the most common subtype,

forming 56% of all NHLs at both the centres. It was followed by follicular lymphoma which was seen in 16% and 17% of all patients while the third commonest was marginal zone B- Cell lymphoma seen in 7% and 8% of cases at Bangalore and Delhi respectively.

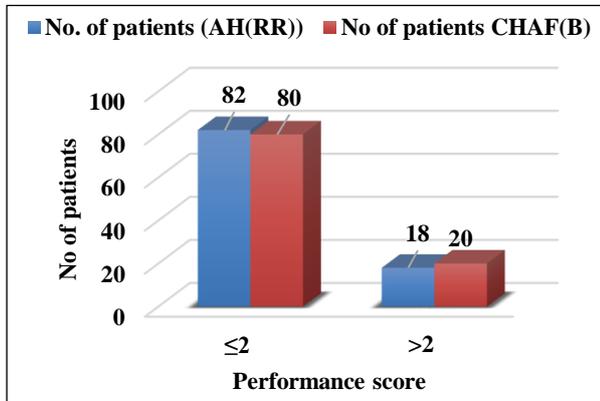


Figure 1: Performance score among study population.

Table 3: Laboratory parameter among study patients.

Laboratory parameter	No. of patients AH(RR)	No of patients CHAF(B)
Hemoglobin (<10 gm/dl in females/ <12 gm/dl in males)	18	11
Deranged LFT	17	15
Deranged RFT	8	4
Raised serum LDH	57	55
HbsAG positive	7	12
Anti HCV positive	4	5
HIV positive	3	6
Bone marrow involvement	25	25
Febrile neutropenia	46	32
Tumor lysis syndrome	6	9

Table 4: Histological type of non-Hodgkin's lymphoma.

Histological subtype	No. of patients AH(RR)	No of patients CHAF(B)
Diffuse large b-cell lymphoma	56	56
Follicular lymphoma	17	16
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma	1	3
Mantle cell lymphoma	4	3
Marginal zone b cell lymphoma	8	7
Burkitt lymphoma	2	1
Precursor t-acute lymphoblastic lymphoma/LBL	5	2
Anaplastic large cell lymphoma t cell type	6	8

Table 5: Stage and complete response among patients.

Stage	No. of patients AH(RR)			No of patients CHAF(B)		
	N=	CR n=	CR%	N=	CR n=	CR%
Stage I	12	11	92	14	13	92
Stage II	20	18	90	22	21	95
Stage III	26	20	77	24	18	75
Stage IV	42	28	66	40	26	65

Among T-Cell lymphoma, anaplastic large cell lymphoma (8%) and (6%) was the commonest (Table 4).

Performance status, Ann Arbor score and IPI score was also analysed in this study, which reported, 80 (80%) and 82 (82%) patients presented with Performance Score of 0-2, whereas 20 (20%) and 18(18%) patients presented with a poor Performance Score of 3-4 at CHAF(B) and AH(RR). 32(32%) patients presented with an Ann Arbor Stage 1 or 2 disease whereas 68(68%) patients were with Stage 3 or 4 disease at both the centres. IPI score was ≥3 in 45 % and 43 % patients (Figure 1, 2, 3). Stage wise assessment of all patients showed, 92% complete response rates in patients with stage I, while stage II patients showed 90% complete response rates at both the centres. However, the complete response rates declined to 75% and 65% at Bangalore and 77% and 66% with stage III and stage IV at Delhi respectively (Table 5).

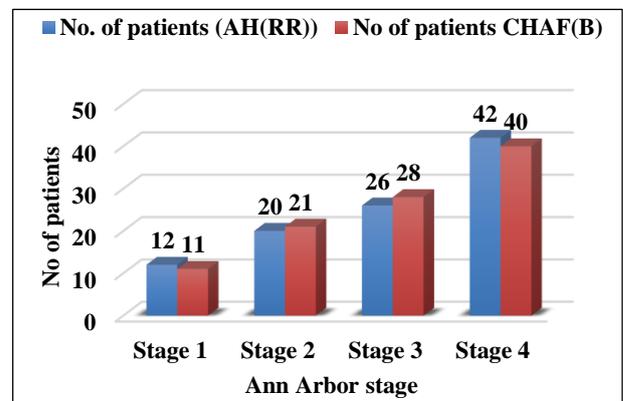


Figure 2: Ann Arbor stage among study patients.

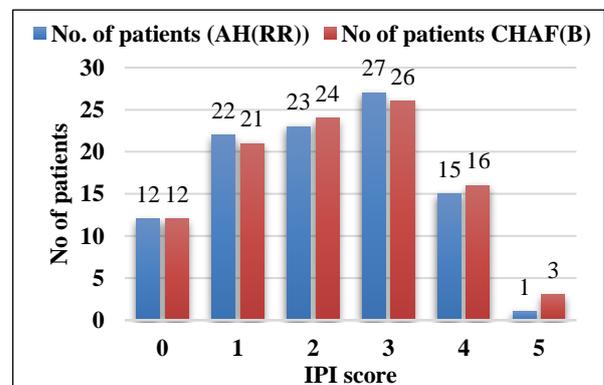


Figure 3: IPI score among study patients.

## DISCUSSION

Command Hospital Airforce Bangalore or CHAF (B) is the largest superseniority hospital of the defense forces in south India which caters to all the serving personals, their dependents and retired personals. Army Hospital (R and R) is the largest tertiary care centre of armed forces and is also the biggest Oncology centre for armed forces catering to patients from entire north and central India. In addition, these centres are also the Armed forces oncology referral centre for rest of the country. Therefore, these patients will provide an insight into the epidemiology, clinical - pathological profiles of Non-Hodgkin's lymphomas in these regions especially the Armed forces.

The study has signified male preponderance in all types of NHL. Overall ratio was 1.77:1 and 1.63:1 with no significant difference at both centres. These findings suggested a higher male to female ratio as compared to western literature (in the United kingdom it was 1.2:1), but it commensurate with the results obtained in Indian studies which showed a ratio of 1.6:1 to 3:1.<sup>9,10</sup> On the other hand, in north India the ratio was found to be 4.5:1 (Garg et al., 1985).<sup>11</sup> In Bangladesh it was 1.8:1 and in Pakistan it was observed to be 1.03:1.<sup>12,13</sup> Though the general trend of male preponderance has been clearly found in the study. Male predominance was observed in all histological subtypes in the study which was similar to that of Elias (1979).<sup>9</sup>

Average age of onset was around 45.5 and 45.36 years with median of 44 years in this study at both the northern and southern centers as compared to 55 years in studies conducted in Western countries.<sup>14,15</sup> Bimodal mode of onset was also observed with maximum incidence occurring in the age group of 31-40 years (entailing 26% and 24% cases) and >60 years age group (entailing 24% and 25% cases) with same trends in both the northern and southern parts of India. Though maximum incidence was seen around 5<sup>th</sup> decade of life. Studies have also showed that, majority of the of all B-cell lymphoma highest number of patients are in the 5<sup>th</sup> and 6<sup>th</sup> decade and of T-cell lymphoma in the 3<sup>rd</sup> decade.

Yu, Chen and O'Connel conducted study with an observation period of 1985 to 2004 reported highest incidence in the 7<sup>th</sup> decade, which was higher as compared to age of onset this study.<sup>16</sup> A similar study was done with an observation period of 1991 to 2000 in Austria by Mitterlechner, Fiegl and Muhlbock and concluded for both male and female, age of onset to be around 7<sup>th</sup> decade. Similar findings were reported from the UK based studies also.<sup>9,17</sup> The Indian population has a life expectancy much lower than the age of highest incidence observed by the various investigators i.e. around 7<sup>th</sup> decade and this has reflected as fewer number of patient in 7<sup>th</sup> and 8<sup>th</sup> decade in this study, that too supplemented by possibility of partial discordance attributable to the small number of patients enrolled in the limited institutional study.

In this study, patients with family history or risk factors like exposure to smoking, farming chemicals/pesticides etc. were 9% and 8% with an average of 8.5% from both the centres. A study of 622 white men with newly diagnosed non-Hodgkin's lymphoma and 1245 population-based controls in Iowa and Minnesota (Kenneth et al., 1992) (18) found men who ever farmed were at slightly elevated risk of non-Hodgkin's lymphoma (odds ratio=1.2) that was not linked to specific crops or particular animals. Increased risk amongst family members is thought to possibly be due to shared environmental risk factors between family members. Dubey et al, have also reported similar trends from Delhi as authors observation.<sup>19</sup>

In this study authors found that anorexia was the most common symptom reported by 60% of patients from both the centres, followed by fatigue (58% and 60 %), neck swelling (33% and 35%) and weight loss (28% and 30%) from CHAF(B) and AH(RR) respectively. Dyspnoea was reported by only 5% patients at CHAF (B) while 13% at AH (RR) of patient mainly due to compression by enlarged hilar and tracheal nodes. This difference could be explained also by the cold climate in the northern part of India in the winters leading to aggravation by bronchospasm and higher URTI. Bleeding manifestations were seen in 11% of cases at CHAF (B) 6% of cases at AH (RR) primarily due to thrombocytopenia due to bone marrow involvement.<sup>3</sup> Patients at CHAF (B) out of 11 were also suspected to have an acute viral hemorrhagic fever (KFD or dengue with positive serology). A study by Sudipta et al, on both Hodgkin's and Non-Hodgkin's Lymphomas in Rural India suggested neck swelling as the predominant symptom followed by weight loss, anorexia and fatigue however Dubey et al.<sup>17,19</sup> Authors found B Symptoms were present in 47.5% cases (50% and 45%) with more number of patients from south presenting with B- symptoms at onset. However, this did not translate into worse prognosis or response in these patients. Weight loss of more than 10% of body weight were seen in 30% of patients at both centres. Ours incidence of B symptoms was similar as compared to that of Garg et al, at 49.6% but lower than Ramani et al, who reported frequency of B symptoms at 65.2% respectively, which could be attributable to the limited size single institutional study.<sup>11,20</sup>

Lymphadenopathy was the most common sign present in 45% (46% and 44%) patients followed by pallor 23.5% (22% and 25%), hepatomegaly 20% (23% and 17%), splenomegaly 10% (11% and 9%), Ascites 5% (3% and 8%) and icterus (7% in both centres). A similar study by Sudipta et al, and Dubey et al, on Lymphoma in India also suggested corroborating findings.<sup>21,19</sup> In this study also peripheral lymphadenopathy was the commonest sign followed by pallor, splenomegaly and hepatomegaly. The occurrence of hepatosplenomegaly was higher in south India centre due to like occurrence of asymptomatic tropical malarial liver and spleen syndrome though the same could not be proved through investigation. Raised LDH was most common

laboratory finding detected in this study, detected in 56% cases (55% and 57%) followed by marrow involvement seen in 25% cases and anemia seen in 18% cases. These findings were in coherence with findings of Indian study done by Sudipta et al, and dubey et al.<sup>19,21</sup> Similarly serum LDH was significantly raised in non-Hodgkin's lymphoma cases in a study done by A. M. Ferraris et al.<sup>22</sup> Though bone marrow involvement was higher as compared to the study done by Sudipta et al, but comparable to the study by Moormeier et al, who concluded that bone marrow examination could detect disease in 20 to 40% of all NHL cases.<sup>21,23</sup>

A total of 68% patients were in advanced stage (Ann Arbor stage III/IV), whereas 32% patients were in limited stage disease (Ann Arbor I/II) in both centers portraying that there is no north south divide of the disease with effect to severity and that the Indian population presented in an advanced stage. Other Indian studies also showed similar results where the patients presented with advanced disease were about 71%.<sup>20,21</sup> Among the viral markers 02 and 03 patients tested positive for HIV, 10 and 07 for HBV whereas 07 and 04 patients tested positive for HCV. Suggesting a significant correlation between the viral infection and risk of developing NHL especially in CHAF (B) which had higher numbers of hepatitis positive cases and greater occurrence of hepatosplenomegaly Similar findings were reported by Dalmaso L et al.<sup>24</sup>

B- Cell lymphoma constituted an average 87% (85% and 89%) of total NHL cases whereas T- cell lymphoma contributed to 12% (13% and 11%) of total cases. We have found a higher proportion of B cell subtype as compared to study done by Naresh et al, and Skarin, Dorfman.<sup>25,26</sup> which revealed B cell lymphoma in 80% of the presenting cases. Though these findings are corroborating with the studies done in UK and USA.<sup>9</sup> Authors also found that Diffuse Large B-cell Lymphoma (DLBCL) was the most common subtype, forming 56% of all NHLs at both the tertiary care centres which is well in proportion as compared with other Indian studies where it's prevalence at presentation was noted to be 54.66 to 58% (24,25). It was followed by follicular lymphoma which was seen in 16-17% of all patients (17.66% as per Indian studies). Broadly the findings were similar to that of a study done by Naresh et al, hence elucidating DLBCL to be the largest subset of NHL.<sup>25</sup> There was a similar pattern of occurrence at AH (RR) and CHAF (B).

Among T-Cell lymphoma Anaplastic large cell lymphoma (8 and 6%) was the commonest which was significantly lower compared to that of Naresh et al, where it was reported to be 12%.<sup>24</sup> Authors found that T-cell acute lymphoblastic lymphoma formed 5% of total lymphoma cases which was similar to that of Naresh et al, where they reported T-cell lymphoblastic lymphoma in 6% cases.<sup>25</sup> Though these findings were higher in figures as compared to western studies, in which the incidence has been reported less than 3%.<sup>24</sup> Authors did find 2 case of peripheral T cell lymphoma in this study

both from Bangalore centre both of these patients were from Tamil Nadu and non at Delhi. This again could be attributable to the tropical climate and probably the hot humid climate causing severe pruritus may be a factor. This however requires investigation.

Authors also calculated IPI Score for all the patients, which suggested maximum number of patients with IPI Score 3 (43 and 45 % patients), followed by patients with IPI Score of 2 (23%). Only 15% patients were with IPI Score 4 and 01% in IPI Score 5. This suggests that a significant number of patients present with good prognostic scores, thus they have favorable treatment outcome and survivability with either of the institution of timely treatment. Complete remission rates with the treatment was about 95% for stage I and 90% for stage II at both the centres. Remission rates showed a steep decline with augmentation of stage with 76% (75 and 77%) complete remission in stage III and 66.5% (67% and 66%) in stage IV. These findings were corroborating with IPI wise complete remission rates of 82%, 38%, and 13% for low, intermediate and high IPI scores respectively.

Limitations of the study was small sample size, two hospital-based study and absence of control group.

## CONCLUSION

This study concluded that the NHL in India is a homogeneous and uniform disease which is not influenced by the geographical location and customs. However, there is an increased detection of hepatosplenomegaly and associated hepatitis B/C in the southern part of India. Also, the occurrence of Cutaneous T cell lymphoma was only seen in the south India centre. The occurrence of dyspnea was more in the North. B cell lymphoma to be the commonest type of NHLs with Diffuse Large B-cell Lymphoma (DLBCL) the most common subtype. The early stage NHLs has better survival and increase chance of complete response as compared to late stage disease.

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