

## RESEARCH COMMUNICATION

# Hodgkin's Lymphoma in Pakistan: A Clinico-epidemiological Study of 658 cases at a Cancer Center in Lahore

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## Abstract

**Objectives:** To study the clinico-epidemiological profile of Hodgkin's lymphoma (HL) in Pakistan. **Patients and Methods:** We retrospectively studied all histopathologically proven cases of HL, who presented between Dec 1995 to June 2003 at Shaukat Khanum Memorial Cancer Hospital and Research Hospital (SKMCH & RC). All the relevant information was obtained through the hospital based cancer registry and medical records of the selected patients. **Results:** Six hundred and fifty eight histopathologically confirmed cases of HL were identified. There were 505 males and 153 females, with a male to female ratio of 3.3: 1. Patients ranged in age from 1 year - 84 years. The mean age at presentation was 23.8 years. Three hundred and twenty cases (48.6%) belonged to age group  $\leq 18$  years and 338 cases (51.4%) were  $> 18$  years of age. Histopathologically, mixed cellularity (MC) constituted 63.8% of cases, followed by nodular sclerosis (NS) 19.9%, lymphocyte predominant (LP) 7.3% and lymphocyte depleted (LD) 1.2%. Early stage (stage I and II) disease was present in 43.9% of patients at presentation, while 56.1% patients presented with advanced stage (stage III and IV). The majority of patients (81.2%) presented with cervical lymphadenopathy. **Conclusion:** The clinico-epidemiological pattern of Hodgkin's lymphoma in Pakistan manifested is similar to that observed in other developing countries, with male predominance, mixed cellularity as the commonest histological type, advanced stage at presentation and absence of bimodal age distribution.

**Key Words:** Hodgkin's lymphoma - epidemiology - Pakistan

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## Introduction

Hodgkin's lymphoma is a malignant lymphoma of unknown etiology that has been a leading example of curable cancer with an overall 5-year survival rate reaching more than eighty percent in developed countries (SEER, 2006). Clinico-epidemiological patterns of Hodgkin's lymphoma are of particular interest due to their variations among different populations according to geographic location, socio-economic class and immunologic status.

HL has bimodal age distribution and NS is the predominant histological type in developed countries (SEER, 2006; Hunger et al., 1994; Lee et al., 2005; Schellong et al., 1999), whereas many developing countries have reported a unimodal distribution with MC as the most common histological type (Correa et al., 1971; Riyat, 1992). A review of literature revealed very little published data focusing on epidemiology of HL in Pakistan. This paucity of information and absence of a national cancer registry system in Pakistan led us to conduct this study, to evaluate the clinico-epidemiological characteristics of HL in a cohort of 658 patients who presented to our institution over the years.

Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC) is a tertiary care cancer center, serving mainly the Punjab province which represents 56% of total population of Pakistan. Hodgkin's lymphoma is the seventh leading malignancy (3.8%) among all patients registered at this hospital and second commonest malignancy (13.70%) in age group  $\leq 18$  (CCCR of SKMCH & RC, 1994-2005).

## Subjects and Methods

This study was performed on all histopathologically proven cases of HL, who presented from Dec 1994 - June 2003 at SKMCH & RC. All the information pertaining to clinico-epidemiological features was collected through hospital based and disease specific registries, integrated into the Hospital Information System.

All patients were evaluated for their socio-economic status by hospital social services and finance department at the time of their presentation. After assessment they were placed in one of the three groups: A: Upper socio-economic class; B: Middle class; C: Lower socio-economic class.

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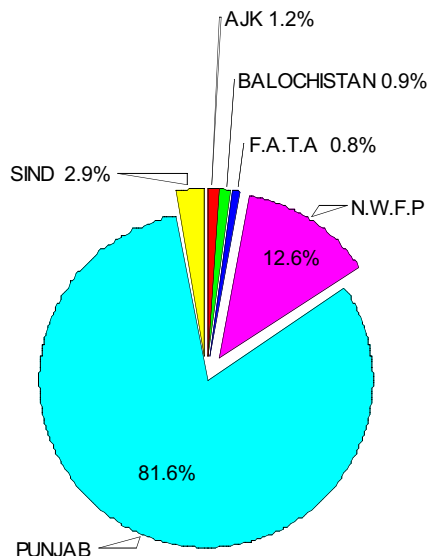
In order to study the influence of seasonal variation on onset of HL the month of presentation for all patients was recorded. For staging purposes Ann Arbor classification was used. According to this staging system Stages I-IV are further classified into A and B subclasses. Stage A stands for absence of B symptoms and stage B includes patients who suffer from any or all of the following symptoms; unexplained weight loss of > 10% of body weight in the months prior to diagnosis, drenching night sweats, or unexplained fever. Staging was based on the results of surgical biopsy, detailed history with particular attention to presence or absence of systemic symptoms, physical examination and results of the following studies: chest radiograph, CT neck, chest, abdomen and pelvis as well as bone marrow examination and cytology sampling of any effusion.

To ascertain the follow up trends among these patients, average follow up period (AFUP) was taken as the time duration between the date of registration at SKMCH & RC, and date of last visit to Oncology clinic. To calculate the AFUP only those patients (589) were included whose follow up period was for at least a month or more. Statistical Package for Social Sciences (SPSS) version 10.0 was used to run all the statistical analyses. Test of means was done using the one way analysis of variance (ANOVA). The local scientific review committee approved the study.

**Results**

*Geographical location:*

Due to its location in Lahore, SKMCH & RC caters to mostly the population from the province of Punjab, though it also gets referral from all other areas of Pakistan. Out of 658 Hodgkin’s lymphoma patients, 81.6% belonged to Punjab. The rest were from the North West Frontier Province (N.W.F.P.), Sindh, Azad Jammu and Kashmir (AJK), Balochistan and Federal Administered Tribal Areas (F.A.T.A.). (Figure 1)



**Figure 1. Geographic Distribution of Cases**

*Patient characteristics:*

There were 505 male patients as compared to 153 females. The male to female ratio was 3.3:1. Though there was variation in the male to female ratio in different age groups (Table 1), male predominance was observed in all ages. The age distribution studies revealed that the mean age at presentation was 23.8 years; median age was 19 years, and age range from 1 year to 85 years (Figure 2). Three hundred and twenty cases (48.6%) belonged to age group ≤18 years (Table 2). Only 7.3% of the cases were from the older age group i.e. 50 -85 years. There was no second peak observed in the age distribution curve (Figure 2).

Majority of the patients presented with lymphadenopathy

**Table 1. Male to Female Ratio in HL Patients According to Age Groups**

Age groups	Male	Female	Total	Male: Female
1-10	144	28	172	5.1:1
11-20	137	44	181	3.1:1
21-30	80	32	112	2.5:1
31-40	63	24	87	2.6:1
41-50	40	18	58	2.2:1
51-60	21	2	23	10.5:1
61-70	16	2	18	8:1
71-80	3	2	5	1.5:1
81-90	1	1	2	1:1

**Table 2. Patient Characteristics**

	Number	Percent
Sex: (n= 658)		
Male	505	76.7%
Female	153	23.3%
Age: (n= 658)		
≤ 18	320	48.6%
> 18	338	51.4%
Histological Types*: (n= 658)		
1. MC	420	63.8%
2. NS	131	19.9%
3. LP	48	7.3%
4. LD	8	1.2%
5. NOS	51	7.8%
Stage at Presentation: (n= 599)		
Stage I	62	10.4%
IA	49	8.2%
IB	13	2.2%
Stage II	217	36.2%
IIA	112	18.7%
IIB	105	17.5%
Stage III	206	34.4%
IIIA	65	10.9%
IIIB	141	23.5%
Stage IV	114	19.0%
IVA	24	4.0%
IVB	90	15.0%
Bone marrow involvement: (n= 521)		
Positive	82	15.7%
Negative	434	83.3%
Equivocal	5	0.95%

\* LD: Lymphocyte depleted, LP: Lymphocyte predominant, MS: Mixed cellularity, NS: Nodular sclerosis, NOS: Not otherwise specified.

**Table 3. Symptoms Reported by 658 Patients with Hodgkin's Lymphoma**

Symptoms at Presentation	Frequency	Percentage
Lymphadenopathy	580	88.1
Fever	391	59.6
Weight loss	221	33.6
Night sweats	176	26.7
Breathlessness	82	12.5
Gastrointestinal	64	9.7
Weakness and lethargy	33	5.0
Chest pain	6	0.9
Pruritis	5	0.8
Others	82	12.5

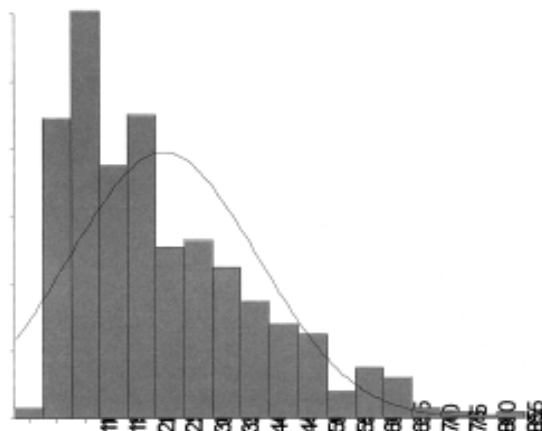
**Table 4. Sites Involved with Hodgkin's Lymphoma at Presentation**

Site Involved	Frequency	Percentage
Neck	534	81.2
Axilla	240	36.5
Mediastinal /Hilar	154	23.4
Inguinal	153	23.3
Spleen	90	13.7
Chest	66	10.0
Pelvis	53	8.1
Liver	25	3.8
Kidney	4	0.6
Other sites	39	5.9

**Table 5. Average Follow-up Period**

Socioeconomic Class	Mean (months)	Number patients	Range (months)	Standard deviation
Upper	21.2	191	1.00 to 124.90	23.54
Middle	32.6	59	1.00 to 86.80	25.40
Lower	40.3	339	1.30 to 189.80	27.01
Total	33.3	589	1.00 to 189.80	27.17

(Table 3). Other symptoms included a variety of complaints like pain in joints and bones, dysphagia, gum bleeding, hemoptysis, jaundice, diminished vision and features of superior vena cava syndrome. B symptoms were reported in fifty five percent (349) patients. The most common sites of involvement were neck (81.2%), axilla (36.5%) and

**Figure 2. Age Distribution Curve**

mediastinal/hilar lymph nodes (23.4%) (Table 4). Other sites involved at presentation included thyroid, paraspinal region, nasopharynx and tonsil.

#### *Histopathology:*

Mixed cellularity (MS) was the commonest subtype of HL that was reported in our patients. Nodular sclerosis (NS) was the second most common (19.9%), followed by lymphocyte predominant (LP) (7.3%) and lymphocyte depleted (LD) (1.2%). Some pathological reports (7.8%) were not specified (NOS) as any of these categories.

#### *Stage:*

For 599 patients results of staging work up were available. There was a preponderance of patients with stage III and IV disease (Table 2). Five hundred and twenty one patients underwent bone marrow examination. Out of these, eighty-two patients (15.74%) had bone marrow involvement (BMI). BMI was present in 34 out of 262 pediatric patients (12.98%) and 48 out of 259 adults (18.53%). As compared to 17.04% of males, 11.47% of females had BMI. BMI was present in 28.57% of LD cases, 16.6% in LP, 15.1% in MC, and 9.5% in NS.

#### *Seasonality:*

The highest number of cases were observed in the month of May i.e., 12% of all cases. This pattern was present in both genders, with 11.5% and 13.75% of cases presenting in the month of May in males and females respectively. Similar was the case when we observed the pediatric and adult age groups with 12.9% and 11.2% of cases presented in the month of May respectively.

#### *Socio-economic status:*

When we stratified the patients according to socio-economic class (SEC), 245(37.2%), 62(9.4%) and 351(53.3%) patients were from high, middle and low (SEC), respectively. MC was the most common histological type in all socioeconomic classes with nodular sclerosis being the second commonest type.

#### *Follow up:*

Average follow up period (AFUP) of 589 patients was 33.34 months, and ranged from 1.00 month to 189.80 months (Table 5). When we stratified the patients according to the socio-economic class, the AFUP between the three groups was significantly different ( $p < 0.001$ ). It was observed that low SEC patients had the highest AFUP of 40.32 months, followed by the middle SEC with AFUP of 32.59 months and high SEC patients had AFUP of 21.19 months. The difference between AFUP of high SEC and middle SEC ( $p = 0.008$ ) and also between that of high and low SEC ( $p < 0.001$ ) was significant.

## **Discussion**

Malignant lymphomas are among the most common

malignancies affecting the Pakistani population. HL comprises a substantial proportion of these tumors. Studies from Pakistan, regarding clinical and epidemiological patterns of this disease are scanty (Akram et al., 2001; Anwar et al., 1997). This is the largest study reported from Pakistan regarding the clinico-epidemiological characteristics of Hodgkin's lymphoma.

The MC was the most common type of HL type encountered in our patients. Previous studies from Pakistan and other developing countries have also reported MC as the most frequent histological subtype. (Siddiqui et al., 1999; Saleh et al., 1998; Ramadas et al., 1994; Riyat, 1991; Yahya et al., 1979). Although MC was the predominant pathology in all age groups of our patients, there were variations among percentage of cases of each histological subtype in these groups. MC was present in more than 80% of cases in age group more than fifty years. The NS reached its peak (28.6%) in age group of 21-30 years. Variation of histological subtypes in different age groups has been a subject of debate. Some authorities have proposed that it may be due to different etiologies of HL at different stages of life (Diehl et al., 1995; Mack et al., 1995).

In their landmark study of epidemiological patterns of HL, Correa and O' Conner described three patterns of the disease, that were related to economic development and urbanization of a geographical area. Pattern I has a preponderance of MC histological subtype and high incidence in male children. Pattern III is seen in developed (affluent societies) and characterized by predominance of NS and low incidence rates in children with a second peak in older age groups. Pattern II has intermediate features between types I and III. (Correa et al., 1971). Age distribution of HL in our patients showed that the 1 - 14 year age group was the largest group affected. The predominance of pediatric age group in Pakistan and other developing countries may be due to the fact that children from these regions are malnourished and less immunocompetent leading to high susceptibility to infections including EBV infection. As the development of HL and its biological behaviour may be influenced by the level of host immune response to EBV infection (Kandil et al., 2001).

Our observation that there was little evidence of a second peak in older age group is similar to the pattern observed in other developing countries (Al-Diab et al., 2003; Riyat, 1992; Yahya et al., 1979).

In HL patients, high male to female ratio has been observed consistently in various studies (Abrahamsen et al., 1997; Al-Diab et al., 2003; Dinshaw et al., 1985; SEER, 2006; Correa et al., 1971; Petridou et al., 2006; Hunger et al., 1994). We observed a male predominance in all of the histological subtypes of HL. This male preponderance was more striking in children under the age of 11 years and in the older age group. A number of explanations have been put forward to explain this male predominant pattern of Hodgkin's lymphoma. Correa P and colleagues suggested that females appeared to be less susceptible and more resistant than males to the initiating process and causative

factors of HL. In a study conducted by Pearce et al, significant negative correlation was found between sex ratios for childhood cancer registrations and gross domestic product (GDP). It was suggested that socio economic factors may underlie this high male to female sex distribution particularly in pediatric age groups due to limited access of girls to health facilities as compared to boys (Pearce et al., 2001). The indifferent behavior towards females' health care is also more marked in male dominant society of Pakistan. The excess of male patients in adult age group might be partly explained on the basis of hormonal factors (Cartwright et al., 2004).

Majority of the patients presented with lymph node enlargement. This is consistent with previous reports of HL (Lee et al., 2005; Riyat, 1992). Fever was the second most common symptom followed by weight loss. Unlike economically developed countries where majority of patients present with early stage (stage I and II) (Shankar et al., 1997), 53.4% patients at our center presented with advanced stage. This is comparable with figures of 53%, 51.4% and 64 % observed in India, Saudi Arabia and Kuwait, respectively (Ramadas et al 1994; Al-Diab et al 2003; Riyat, 1992). The number of patients who had BMI is less than previous reports from Pakistan (Butt et al., 2002). In literature percentage of BMI in HL shows a range from 3.3 % to 13 % (Doll et al., 1989; Gómez-Almaguer et al., 2002; Howell et al., 2002, Macintyre et al., 1987; Munker et al., 1995; Levis et al., 2004). A higher percentage of BMI in Pakistan may be explained on the basis that more than 50% patients present at late stages of disease in contrast to developed countries. This delay in seeking medical treatment is partly due to financial constraints and lack of wide spread diagnostic and referral facilities.

With regard to seasonality previous studies about the month of diagnosis of HL have suggested that the seasonal variation may influence the diagnosis of HL, with peak times in the months of February and March (Douglas et al., 1998; Chang et al., 2005). In our patients comparatively higher percentage of cases (12%) presented in the month of May and lower percentage of cases (6.2%) presented in the month of November and December. However in other months the range was from 7.3% to 10 % and we didn't see any particular pattern of seasonal variation in our patients. This may be partly explained by the fact that many of our patients present to us late in the course of their disease; therefore the date of presentation may not be a true reflection of the actual development or onset of disease.

Surprisingly, patients from the lower socio-economic group were more compliant with follow up after treatment and it was the affluent class who did not attend for their clinic appointments regularly. This may be due to confounding factors, as High SEC may later on seek treatment from oncology centers in Western countries. This may have led to early loss to follow up in these patients, in contrast to other classes of patients who were supported fully or partially by the hospital.

In summary, the results from this study indicate that the

clinico-epidemiological features of Hodgkin's lymphoma in Pakistan manifest the Type 1 pattern as described by Correa et al., with mixed cellularity as the most common histological type, male predominance and absence of bimodal age distribution. Majority patients have advanced stage and B symptoms at the time of presentation. Further studies on the role of secular trends, space time clustering and infectious agents would be instructive in understanding this complex but curable malignancy.

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