APPLICABILITY OF INTERNATIONAL PROGNOSTIC INDEX IN NON HODGKIN'S LYMPHOMA IN PAKISTAN

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Background: Aggressive non Hodgkin's Lymphomas (NHL) are common in Southeast Asia, Middle East and Africa. Data on survival with relation to prognostic factors is scarce. The primary objective of the study was to evaluate the applicability of International Prognostic Index (IPI) to predict overall survival (OS) and disease free survival (DFS) in developing countries. **Methods:** Two hundred and nineteen patients of NHL consecutively presenting to the Department of Oncology, Jinnah Hospital Lahore between August 1998 to July 2000 were analyzed. All patients underwent initial staging according to Ann Arbor staging system. The patients were categorized by five independent risk factors: patient age, disease stage, serum lactate dehydrogenase (LDH) levels, performance status, and number of extranodal sites involved. Patients were divided into three risk categories Low (0 or one risk factors), Intermediate (2 risk factors) and High (3 or more risk factors). **Results:** According to IPI low risk category comprised of 15%, intermediate 21% and high 64% of patients, Overall survival (OS) for 2 years and 5 years (n=197) was (69%), (51%), (32%) and (64%), (46%), (13%) respectively (p=0.0008). Disease free survival (DFS) for 2 years and five years (n=197) was (66%), (43%), (34%) and (66%), (43%), (18%) respectively. Age adjusted (≤ 60) DFS for 2 and 5 years (n=164) was (70%), (45%), (40%) and (63%), (45%) (19%)respectively. OS for 2 and 5 years (n=164) was (71%), (52%), (34%) and (64%), (46%),(11%) respectively (p=0.0013). **Conclusions:** The IPI accurately predicted survival in our population. Modification of treatment protocols according to specific risk groups will be beneficial to the developing countries with limited resources.

Key Words: Developing Countries, International Prognostic Index, Survival, Non Hodgkin's Lymphoma

Introduction

Non Hodgkins Lymphoma (NHL) are a diverse group of neoplasms both in their natural history and in their response to treatment. They rank fifth in cancer incidence in United States, and are increasing at a rate of almost 7% per year.[1] Available epidemiological data from various parts of Asia indicate marked geographical variation in the incidence, histopathologic and clinical behavior of NHL.[2-5] NHL appears to be more common in developing countries[6,7] where a combination of environmental, infectious and genetic factors affect the development of these disorders. In Northern Pakistan[8] NHL is the most common cancer in males while it is the sixth most common cancer in females.

The International Prognostic Index (IPI)[9] has been specifically developed by the International Lymphoma Task Force to predict outcome in patients with aggressive non-Hodgkin's lymphoma based on pretreatment clinical features which include age, disease stage, performance status, LDH, number of extra nodal sites. However data on the applicability of IPI on DFS and OS from developing countries is scarce.

It has been suggested that socioeconomic status is an important prognostic factor for survival differences in third world countries[10]. No information is available correlating socio economic status(SES) with survival in patients with NHL.

MATERIAL AND METHODS

We conducted a data base analysis on two hundred and nineteen patients with aggressive non-Hodgkin's lymphoma treated with doxorubicin based chemotherapy presenting to our Department from August 1998 to July 2000 to determine the applicability of the IPI. The patients were classified into three different prognostic groups. Treatment outcomes were analyzed and OS and DFS were calculated. Correlation of SES and overall survival were done.

Staging Workup

All patients underwent an initial staging workup according to the Ann Arbor System. This included a complete hematological, renal and hepatic profile, serum lactic dehydrogenase (LDH), and uric acid. Serological HIV testing was performed at the time of diagnosis. Radiological investigations included chest X Rays, abdominal and pelvic ultrasounds, and CT/MRI scans. In case of gastrointestinal symptoms upper GI series with small bowel follow through or barium enema were carried out. Bilateral bone marrow aspirates and biopsies were done on all patients. Histopathologic diagnosis was made on the basis of International Working Formulation. SES was determined by economic characteristics.

 Annual Income of household (US$<1000=Low, US$>1000=High)[11]

Chemotherapy protocols

All patients received doxorubicin based chemotherapeutic regimens, which included <u>CHOP</u> (Cytophosphamide 750 mg/m^2 IV day 1, Doxorubicin 50 mg/m^2 IV day 1, Vincristine 1.4 mg/m^2 IV day 1 , Prednisone 100 mg/d PO days 1-5). Radiotherapy was given for bulky disease (>10 cm).

Response criteria

Response categories are defined by the standardized response criteria for NHL[12].Complete remission is defined as the disappearance of all clinical evidence of active tumor for a minimum of four weeks. Partial remission is a decrease of more than 50 percent in the sum of the products of the maximal perpendicular diameters of the measured lesions, lasting at least four weeks. Disease progression is indicated by the appearance of new lesions or by a 25 percent increase in the size of preexisting lesions.

International Prognostic Index

All patients were evaluated for pretreatment clinical features predictive for disease-free and overall survival. These included age, PS, LDH, stage, and number of extranodal disease sites. A patient's relative risk of death was calculated by adding the number of adverse prognostic factors present at diagnosis. Three groups of patients with similar relative risk, low (zero to one adverse factor), intermediate (two adverse factors), high risk (three to five adverse factors) were identified.

For patients under 60 years, the age-adjusted index was applied based on stage, PS and LDH.

Statistical Analysis

All the data entry and statistical analysis was done using Microsoft Access, Excel (office 2000 version) and SPSS (version 10.1.0) database software.

Overall survival and disease free survival were estimated with Kaplan and Meier method. Log rank statistical significance was applied to overall survival in different risk groups.

RESULTS

Clinicopathological characteristics and socioecono-mic status of these patients are given in Table 1. Median age of our patients was 42 years. Male female ratio was 2.26:1. Majority of our patients belonged to Stage III and IV(76%). Primary extranodal involvement was present in 32% of cases. Bone marrow was the most common extranodal site involved. Other extranodal sites were CNS (07%), gastrointestinal tract (19%),abnormal LDH was present in (65.3%). %). No patient tested HIV positive on initial investigations. Mean duration of symptoms before diagnosis was 6.8 months.78% of patients belonged to poor socio-economic status.

Table 1: Characteristics of 219 patients presenting with Aggressive NHL.

Characteristics	No.	(%)
Sex		
Male	152	70
Female	67	30
Age		
≤60 yr	170	78
≥60yr	49	22
Ann Arbor Stage		
I	15	07
II	36	17
III	40	18
IV	128	58
Presentation		
Nodal	150	68
Extranodal	69	32
Symptoms		
Fever	135	62
Weight loss	122	56
G. I symptoms	59	27
Lymphomatous involvement		
Spleen	103	47
Bone Marrow	102	47
Liver	50	23
Gastroinestinal tract	41	19

|		
CNS	16	07
Others(lung, bones, kidney etc)	58	27
LDH		
1, Normal	45	20)
2, Abnormal	143	65)
9, Not known	31	14)
Extra nodal involvement		
1 site	71	32
2 or > 2 sites	121	55
Performance Status		
0-1(fully active, ambulatory)	93	42
2,3,4 (50%,>50% and completely bed ridden)	119	54
9 Not known	7	03
Social status		
1, High	41	22
2, Low	142	78

Table 2: Out come According to Risk Group Defined by the International Prognostic Index and the Age-Adjusted International Index

Risk Group	No. of Risk Factor	No. of Patients %	Complete Response Rate %	Disease free Survival		Overall Survival	
				2 yr Rate %	5 yr Rate %	2 yr Rate %	5 yr Rate %
International Index, all patients (n=197)							
Low	0 0r 1	15	72	66	66	69	64
Intermediate	2	21	55	43	43	51	46
High	3 to 4	64	38	34	18	32	13
Age Adjusted Index, Patients 60 yrs (n=164)							
Low	0 0r 1	16	76	70	63	71	64
Intermediate	2	24	60	45	45	52	46
High	3 to 5	60	44	40	19	34	11

DFS

High _____ ,

_.._.._.._.._.._ *Intermediate*

Low -----------

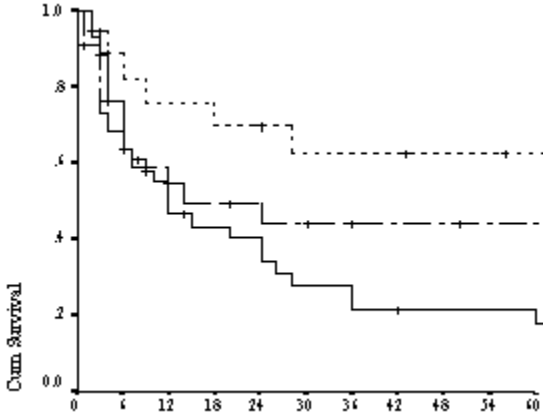**Figure 1: Kaplan Meier curve for disease free survival of all ages according to risk group defined by IPI(n=91)**
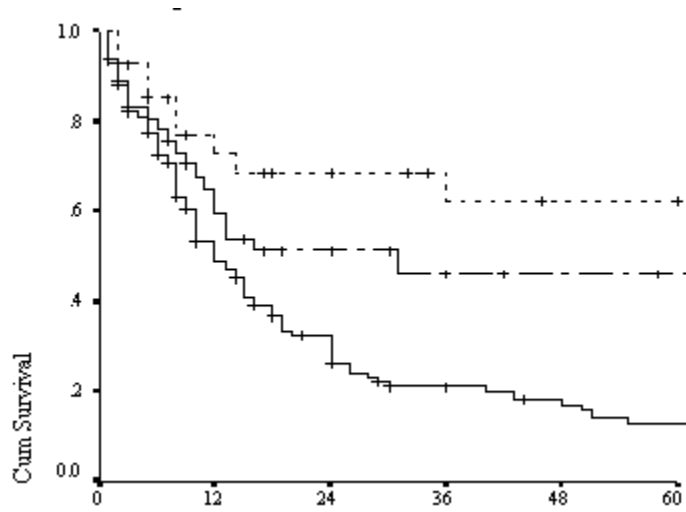
Overall Survival

High _____

_.._.._.._.._.._ *Intermediate*

Low -----------

Log rank Statistical significance for IPI grades is p= .0008

Figure 2: Kaplan Meier curve for Overall Survival patients of all ages according to risk group defined by the IPI(n=197)
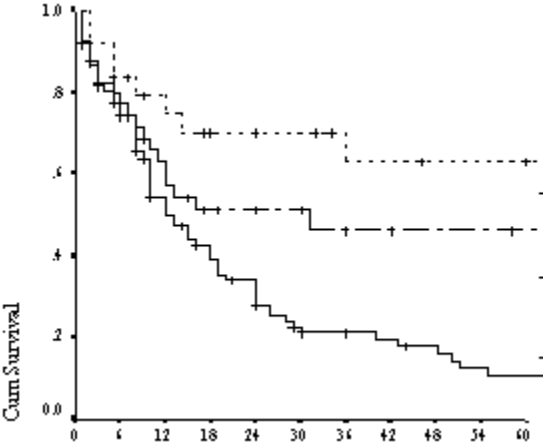

Disease Free Survival

High _____

_._._._._._Intermediate

Low -----------

Figure 3: Kaplan Meier curve for disease free survival among younger patients (≤ 60 yrs) according to risk group defined by the Age Adjusted IPI(n=87)
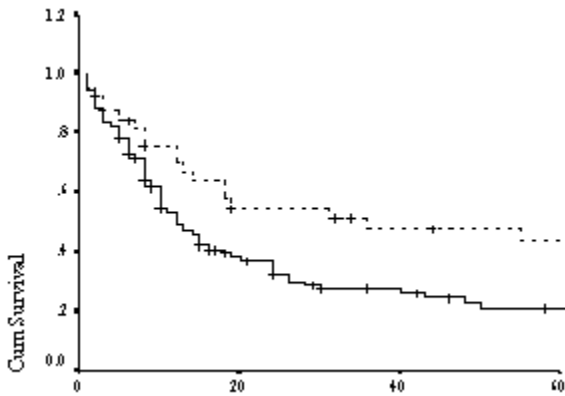
OS of all patients according to SES

High　　　　　＿＿＿＿＿

＿·＿·＿·＿·＿·＿Intermediate

Low　　　　　-----------

Log rank statistical significance for IPI grade is p= .0013

Figure 4:Kaplan Meier curve for overall survival among younger patients (≤ 60 yrs) according to risk group defined by the Age Adjusted IPI(n=164)

Overall Survival of all patients according to SES

High ＿＿＿＿＿

Low-----------

Log rank test and significance p= 0.009

Figure 5: Kaplan Meier curve for overall survival of all patients according to socioeconomic status.

Overall Survival according to International Prognostic Index:

One hundred and ninety seven patients could be assessed for overall survival of all ages. Twenty-two patients were lost to follow up. The predicted two and five-year survivals of the three risk groups, low (no

or one risk factors), intermediate (two risk factor) and high (three or more risk factors) were 69%, 51%, 32% and 64%, 46%, and 13% respectively (Table 2 and figure 2). The survival difference is significant in different risk groups stratified according to IPI (p=0.0008)

Disease Free Survival

Complete response was achieved in 46% of the patients. Complete response rates according to low, intermediate and high groups among all patients were 72, 55 and 38% (table2). The two and five year disease free survival among these patients were (66%), (43%),(34%) and (66%),(43%),(18%) as shown in (table 2,figure 1).

In age adjusted group (≤ 60) complete response obtained according to defined risk groups were 76.6% and 40% as depicted in table 2. The two and five year DFS among these patients were (70%),(45%),(40%) and (63%), (45%) (19%) respectively. (table 2, figure 3)

Accurate assessment of survival in patients ≥ 60 yrs could not be done due to small sample size (n=33).

DISCUSSION

A number of studies have been identified risk factors that carry independent prognostic significance thereby identifying patients requiring different therapeutic approaches.[13-18] The IPI has now become a standard prognostic factor model for aggressive lymphomas with doxorubicin containing regimens in Europe and North America[19,20].

In contrast little information is available from developing countries where advanced disease, B symptoms and aggressive lymphomas are more frequent.[21-23] Disease free survival and overall survival data is also limited with majority of patients being lost to follow up[24]. Modifications of the IPI have been made by researchers from developing countries. Chinese investigators have divided their patient population into three risk groups low, intermediate and high[25,26]. Mok et al further found that the IPI was applicable to their patient population despite high numbers of primary extra nodal lymphomas[27]. Investigators from Brazil[28] have also condensed the four categories of IPI into two groups of low and high risk due to missing data, which is a frequently encountered problem in developing countries.

Clinico-pathological analysis of our patients revealed data similar to other developing countries. Seventy-five percent of our patients were below 60 years. Poor performance status, advanced disease and extranodal involvement ≥2 were present in more than 50%. We divided the patients in two groups, one group for all ages and second for patients who are 60 years or less. The sample size for patients over 60 years (n=33) was too small to accurately predict survival (n=33). We classified our patients into three risk groups Low (0,1), intermediate(2) and high (3 to 5).

Two and five year's disease free and overall survival of all patients as seen in Figure 1&2 are accurately predictive of DFS and OS according to risk groups. Our results are inferior due to multiple factors including poverty, illiteracy, malnutrition and repeated infections[9]. Lack of trained personnel and tertiary care cancer centers do not allow easy access to patients as a result an average patient has to travel a few hundred kilometers before he can undergo cancer treatment. Our patients do not appreciate the concept of dose density and intensity and average treatment delay of one week or more is quite

frequent. Other contributory factors include co-morbid conditions like hepatitis[29] and malnutrition[30-32] which cause further delays in treatment. These problems are common to all developing countries[6,21,27].

Log rank analysis done on OS were significant for all ages p=0.0008 and for age less than 60 years where p=0.0013, thus confirming the accuracy of predicting prognosis by applying IPI on our patient population.   Our results are superior to that reported from Brazil where overall survival rates were only 44% and 17% in low and high risk groups. Our overall five year survival for intermediate and high risk groups (46 and 13%) respectively is also superior to the results reported by Yong et al (21.6 and 7.4%)[25].

In our series we found SES was an important predictor for survival. Patients belonging to high socioeconomic status had superior outcome as compared to low socioeconomic group. Log rank analysis for two socioeconomic group difference is *p*= 0.009 similar to observations made by investigators from India and Brazil[10,32]. We are unable to compare SES and survival outcomes for each IPI subgroup due to small sample size.

In conclusion the clinical model of IPI accurately identified specific patients risk groups in our patient population. New biological and immunological variables are now substituting for clinical surrogate features in the prognostic factors model for NHL. However in developing countries with technical and financial constraints[33] the International Prognostic Index will continue to help us in identifying specific risk groups and help us in modifying our treatment approaches accordingly.

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