Analysis of Factors Contributing to International Prognostic Index and Correlation Between High International Prognostic Index (IPI) and symptom duration in Lymphoma Patients

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ABSTRACT

INTRODUCTION: There are sparse publications in Non-Hodgkin's Lymphoma in Nepal. Risk profile as per International Prognostic Index at the time of presentation is largely unknown. Often diagnosis is delayed for various reasons which may impact the risk profile which is not present in published studies. This study was undertaken to address these issues.

METHOD: Newly diagnosed Non-Hodgkin's Lymphoma from May, 2016 presenting in Bir Hospital were taken for study. 33 patients meeting the criteria were taken for analysis. International Prognostic Index for each patient was worked out based upon their age, LDH level, Performance Status, involved extranodal sites and stage. Regression analysis was done to which factors were most sensitive to IPI. Duration at presentation was correlated with IPI.

RESULT: In this study 57.5% were male, 42.5% female. Median age was 58 years. Patients presented at median of 15 weeks from their first symptom. About 70% had pain and half reported B symptoms. Among 5 factors contributing to IPI, Raised LDH was seen in 24 (72%) cases, stage > 2 in 18 (55%), PS of >= 2 in 13 (39%), 12 (36%) were above 60 years and only 4 (12%) had more than one extra nodal sites involved. IPI grouping shows higher proportion of patients in low or low intermediate group (19, 57%) while in age adjusted risk grouping there were 18 or 54% of patients in high or high intermediate risk group. Correlation coefficient for B symptoms is -.005 and is non-significant.

CONCLUSION: Symptom duration was not correlated with IPI score. In this group IPI score is most sensitive to having >1 extra nodal sites involved and raised LDH. Further larger trials is desired to confirm or refute these findings.

KEY WORDS: IPI, Lymphoma

INTRODUCTION

Non Hodgkin's Lymphoma (NHL) is a common cancer. It is one of the top 10 cancers worldwide. In male it covers 2.9% of all cancer incidence worldwide with incidence rate of 6/100000/Year, and NHL related mortality for men is 3.1/100000/year. In female it covers 2.5% of all cancer incidence worldwide with incidence rate of 4.1/100000/Year, and NHL related mortality for women is 2/100000/year.[1] In Nepal there were total 213 new cases of NHL in the year 2012 covering 3% of all cancers. Male: Female ratio was 4.5/1.7. NHL was 4th common cancer in Nepal with burden of 4.5% of all cancer in male. While in female it was 13th common cancer and covering 1.7% of total cancer incidence.[2] As per SEER database (USA) lifetime risk of developing NHL is 2.1% for men and women. Outcome for NHL is continuously improving in last 2 decades. Currently 5 year survival rate is more than 70%.[3]

The long term outcome does not depend upon any single factor such as stage. International Prognostic Index (IPI) was devised back in 1993 to reliably prognosticate the outcome. It combines multiple factors and gives a score. 5-year survival rates were

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73%, 51%, 73% and 26% for low, low intermediate, high intermediate and high risk group respectively. High risk patients frequently develop resistance to therapy, early relapse and hence have poor survival.[4] More studies on IPI and survival outcomes in NHL followed validating IPI as strong predictor.[5] The current study intends to find out the proportion of patients presenting with high/low risk based upon respective IPI scores. The other objective of this study is to find out whether late presentation is also a factor leading upto poor IPI. Correlation between symptom duration and IPI will help to find actual relationship.

METHOD

Study proposal was submitted and permission taken from IRB (Institutional Review Board), NAMS. Newly diagnosed Non Hodgkin's Lymphoma patients from May, 2016 presenting in Bir Hospital were taken for study. 33 patients meeting the criteria were taken for analysis. Detailed history was taken, baseline evaluation of blood count, stage, histopathology and immunohistochemistry are taken and entered into database. International Prognostic Index for each patient was worked out based upon their age, LDH level, Performance Status, involved extranodal sites and Ann Arbor stage. A node considered bulky when maximum diameter is more than 10cm and mass measuring more than 1/3 of diameter of chest (on X-ray) is classified bulky. Regression analysis was done to which factors were most sensitive to IPI. Duration at presentation was correlated with IPI. Pearson's correlation was used for correlation studies. SPSS version 20 was used for data analysis.

IPI definition and classification

International Prognostic Index (IPI) is a set of clinical features that aid in predicting the prognosis of patients with non-Hodgkin's lymphoma. International prognostic Index (IPI) is worked out in reference to publication by The International Non Hodgkin's Lymphoma Prognostic Factors Project.[4] One point is assigned for each of the five these risk factors age greater than 60 years, stage III or IV disease, elevated serum LDH, ECOG performance status of 2, 3, or 4 and More than 1 extranodal site. The risk groups are defined as low risk (0-1 points), low-intermediate risk (2 points), high-intermediate risk (3 points), and high risk (4-5 points).

RESULT

Demographics and Baseline data

In the current study there were total 33 patients amongst which 19 (57.5%) were male and 14 (42.5%) were female. The age varied from 17 years to 80 years and median age was 58 years. Patients presented at median duration of 15 weeks but some presented as late as 1 year from their initial symptoms. About 70% complained of pain and about 70% had enlarging lymph nodes in their body as presenting symptoms. B symptoms were reported by slightly more than half of the patients (54.5%).

Median value for hemoglobin was 10.76 gm/dL. Staging evaluation revealed about a fifth (7 patients) had bulky disease. Most of the patients had advanced disease with stage III and stage IV comprising about 55%. There were 2 (6%) in stage I, 13 (about 40%) in stage II, 13 (about 40%) in stage III, and 5 (15%) in stage IV.

Table 1. Demographics and Baseline data

	Number	Percent
Sex		
Male	19	57.58%
Female	14	42.42%
Age (years)		
Range	17 - 80	
Median	58	
Symptom Duration (Week)		
Range	2 - 52	
Median	15	
Pain		
Pain present	23	69.70%
Pain absent	10	30.30%
Superficial Lymphadenopathy		
Sup LN present	23	69.70%
Sup LN absent	10	30.30%
B symptoms		
B symptoms present	18	54.55%
B symptoms absent	15	45.45%
Blood Counts		
Median WBC	6000/micL	
Median Platelet	207084/micL	
Median Hemoglobin	10.76gm/dL	
Stage		
Stage I	2	6.06%
Stage II	13	39.39%

Stage III	13	39.39%
Stage IV	5	15.15%
Bulky Disease		
Bulky Dis. present	7	21.21%
Bulky Dis. absent	26	78.79%

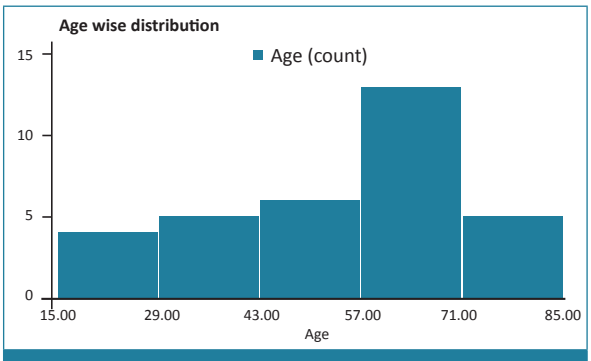

Figure 1. age distribution

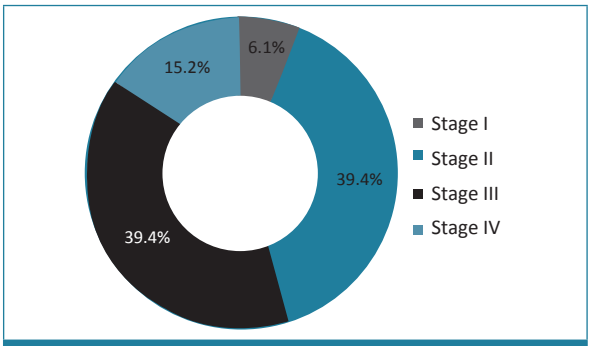

Fig 2. Stage wise distribution

More than half the patient had designated predominant site as superficial lymph nodal region (60%), followed by abdominal (15%) and mediastinal nodes (6%). Biopsy was performed in 63% of the patients, more than one third had only FNAC for histological evaluation. IHC reports were available for 17 (51%) of the patients and amongst these patients, CD20 was positive in 14 (82%) of cases and negative in 3 cases.

Table 2. Sites of involvement, histology and immunohistochemistry work up

Main Site of Involvement	Number	Percent
Neck/Axilla/Inguinal	20	60.61%
Abdominal Node/Mass	5	15.15%
Mediastinal	2	6.06%
Gastro-Intestinal (GI)	2	6.06%
Central Nervous System (CNS)	1	3.03%
Thyroid	1	3.03%
Tonsil	1	3.03%
Jaw/Bone	1	3.03%
Diagnostic Procedure		
Fine Needle Aspiration (FNA) done	22	66.67%
Biopsy	21	63.64%
FNA + Biopsy	10	30.30%
Histology		
DLBCL	15	45.45%
NHL	16	48.48%
MALT	1	3.03%
PCNSL	1	3.03%
Immunohistochemistry(IHC)		
IHC unavailable	16	48.48%
IHC Available	17	51.52%
CD 20 +/-		
CD 20+	14	82.35%
CD 20-	3	17.65%

Upon analyzing the 5 factors contributing to IPI it was observed that raised LDH was most frequently observed and seen in 24 (72%) cases, followed by higher stage i.e. stage > 2 was found among 18 (55%), Poor performance or PS of >= 2 was noted in 13 (39%), 12 (36%) were above 60 years of age and only few (4, 12%) had more than one extra nodal sites involved. Overall IPI score distribution is was IPI score 0: 6 (18%), IPI score 1: 5 (15%), IPI score 2: 8 (24%), IPI score 3: 9 (27%) and IPI score 4: 5 (15%). While there were no patients with IPI of 5.

Table 3. Factors contributing to IPI, IPI score and risk group analysis

Factors	Number	Percent
Age > 60	12	36.36%
Raised LDH	24	72.73%
Stage > 2	18	54.55%
PS >= 2	13	39.39%
EN Sites > 1	4	12.12%
IPI Score		
IPI Score 0	6	18.18%
IPI Score 1	5	15.15%
IPI Score 2	8	24.24%
IPI Score 3	9	27.27%
IPI Score 4	5	15.15%
IPI Score 5	0	0.00%
IPI Risk Group		
Low risk (0, 1)	11	33.33%
Low Intermediate (2)	8	24.24%
High Intermediate (3)	9	27.27%
High (4, 5)	5	15.15%

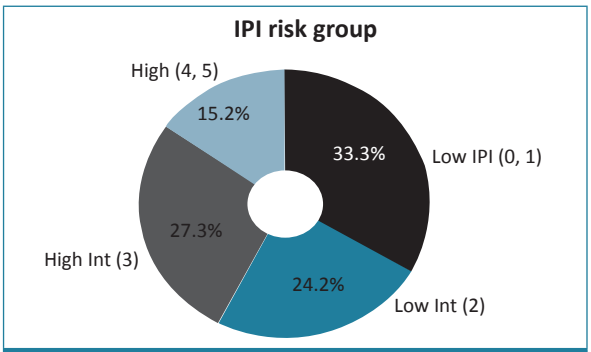

Fig 3. IPI Risk group

Regression analysis has R square and adjusted R square values of .903 and .885 respectively which implies almost all of the IPI score is explained by these 5 factors. Analysis of Variance (ANOVA) has p value < .0001 hence the results of model are significant. Coefficients for regression of these 5 factors are; extranodal sites >1: 1.34, LDH > UNL: 1.21, Performance Status: .465, stage: .42 and age: .016. Which means in this group IPI score is most sensitive to having >1 extra nodal sites involved and raised LDH, moderately sensitive to higher stage and poor performance status and least sensitive to age.

Correlation coefficient for B symptoms is -.005. Symptom duration is not correlated with IPI score and hence probability of falling into poor risk group with increasing presentation duration. This could mean symptom duration does not predict having higher IPI score. But small sample size, possible mix up of less aggressive NHL might be confounding factors.

Variable	IPI Score	Significance
Symptom Duration	-.005	.523
B Symptom	.639	<.0001

DISCUSSION

Worldwide there were estimated 385741 people diagnosed with NHL in the year 2012. Male to female ration worldwide is 1.3:1.[1] Median age at presentation for NHL is seventh decade life. [6, 7] Survival rates have consistently improved in developed countries and according SEER database 5-year survival rate is above 70%.[8] Studies from India report less favorable outcome for NHL. Overall survival at five years was 50%. They opined disparities in survivorship and outcomes, due to unaffordability and attitudes of the patients.[9] In the earliest trial on IPI the distribution of factors contributing IPI was reported as, patients over 60 years 41% and up to 60 year 59%.[4] Median age reported from this region tends to be lower. Dehghani et al. from Iran reported mean age of the patients was 48.48 (SD±18.55) years with range of 17-84 years.[10] Saraschandra Vallabhajosyula et al. analyzed 303 cases from India. Amongst these patients, 164 (66.1%) were male, and 84 (33.9%) female. The median age of our study population was 55.5 years.[11] Laurie H. Sehn reviewed 365 patients from Canada, they found median age at diagnosis to be 61 years (range, 16-90 years). In their study there were 61% male and 39% female.[12] In another study from India Sharma et al. 664 patients and in the study there were 57% male and 47% female. [13]

In the current study 19 (57.5%) were male and 14 (42.5%) were female. The median age was 58 years. Ratio of sex was close to worldwide ratio however median age was less than 60. Lower median age could mean lower age of presentation similar to above reports from this region but it could be due to small sample size.

Late presentation and poor outcome is well studied and it is particularly common in developing world.[14, 15] In a study from India by Gupta D et al from India in testicular lymphoma median duration of symptoms was 3.5 months (range 1-8 months).[16] In this study median duration of symptoms at presentation in this study was 15 weeks, and patients came as late as 1 year.

In the study by international lymphoma project B symptom was present among 41% of patients.[4] Study from Iran found B symptoms 36% of the study population.[10] In a study by Rohini Sharma et al. 53% of patients had B symptoms and in 47% B symptoms were absent. They found that inflammatory symptoms are independent predictors for myelosuppression from chemotherapy.[13] In study done by Vidyanagar et al. 31% presented with B-symptoms. [11] In this study B symptoms were reported by slightly more than half of the patients (54.5%) which is similar to study from India by Sharma et al. Anemia is frequently associated with NHL, Moullet et al studied Frequency of anemia in non-Hodgkin's lymphoma patients and they found 32% of the patients and it was an adverse prognostic factor (p < .0001).[16,17] Median hemoglobin in this study is below 11gm/dL and only 13 (40%) had hemoglobin more than 11gm/dL.

In a large epidemiologic study authors found substantial differences were found in the distribution of the major subtypes of NHL across geographic regions ($P < 0.0001$).[18] Diffuse large B-cell lymphoma represents approximately 30% of all lymphomas and is the most common subtype throughout the world.[18] However, DLBCL is often reported at much higher rate in many studies. In a study DLBCL was reported among 60%, followed by SLL (6.7%) and FL (6.7%).[10] One large study from India which included 2773 patients diffuse large B-cell lymphoma was the most common subtype (34% of all NHLs).[19] In another trial the most common histopathology was Diffuse Large B-Cell Lymphoma 37.6%. Additionally 11.2% were Mixed Small and Large Cell Diffuse Lymphoma. 28.2% patients did not have sub typing of NHL.[11] CNS lymphoma is rare. In a large review including 2514 patients with NHL, 106 patients (4.2%) developed CNS involvement during primary treatment.[20] In the present study histopathology examination reported 45% DLBCL, 48% as NHL. There was one case of CNS lymphoma. Despite availability of IHC there is a tendency to lump into NHL without specifying subtypes. DLBCL is probably over reported and Follicular and other indolent lymphomas likely underrepresented. CD20 was positive in most of cases (14, 82%) and negative in 3 cases.

The international NHL project had following stage distribution - Stage I disease in 8%, stage II in 27%, stage III in 21% and stage IV in 45%. More than 1 extranodal site among was found among 30% of cases. PS of 0 or 1 in 61%, PS 2 12%, PS 3 in 4%, PS 4 in 2% and in 27% of patients. Raised LDH was found in 40%, normal LDH in 37% and unknown 23%. Deghani et al reported percentage of patients in the stage 1, 2, 3, 4 were 6.5%, 27.1%, 18% and 21%, (rest reported as extranodal). (10) In study by Sharma et al. stagewise, there were 10.5%, 26.5%, 29.1% and 33.9% in stage 1, 2, 3, and 4 respectively. [13] In Another study from India Stage I and II Lymphomas were found in 34 patients (34%), 13 patients (13%) were of stage III and the remaining 53 patients (53%) were in Stage IV. Extra nodal presentation was found in 24 patients (24%) of the analyzable population of 100 patients.[11] Another study found extranodal sites 1 or more involved in 65% of cases. [10]

In the current investigation staging evaluation revealed about a fifth (7 patients) had bulky disease. Most of the patients had advanced disease with stage III and stage IV comprising about 55%. There were 2 (6%) in stage I, 13 (39%) in stage II, 13 (39%) in stage III, and 5 (15%) in stage IV. Proportion of patients in early and advanced disease were similar. But there is marked difference in percentage of patients in stage 4 which could be due to incomplete work up especially CT evaluation and Bone marrow examination in few patients.

In the current study it was observed that raised LDH was most frequently observed and seen in 24 (72%) cases, followed by higher stage (> 2) was found among 18 (55%) . IPI score of 2 and 3 had the highest frequency. IPI score of 3, 4 or 5 was seen in about 42% of the patients. In this study overall IPI score distribution is was IPI score 0: 6 (18%), IPI score 1: 5 (15%), IPI score 2: 8 (24%), IPI score 3: 9 (27%) and IPI score 4: 5 (15%). While there were no patients with IPI of 5. Overall there were 33% in low risk, low int 24%, high int 27% and high risk 15% of patients. Overall risk group for all patients in the study by prognostic factors study project was low (IPI 0,1) for 35%, low int (IPI 2) for 27%, high int (IPI 3) for 22% and high (IPI 4 or 5) 16%. [4] Another large study by J Hermans et al validating IPI had reported IPI risk group for the project as low 35%, low int 27%, high int 22% and high 16%.[5] Risk group distribution is similar to larger studies mentioned.

Coefficients for regression of these 5 factors are; extranodal sites >1: 1.34, LDH > UNL: 1.21, Performance Status: 0.465, stage: 0.42 and age: 0.016 (p value < .0001). Which implies in this group IPI score is most sensitive to having >1 extranodal sites involved and raised LDH, moderately sensitive to higher stage and poor performance status and least sensitive to age.

Symptom duration is not correlated with IPI score and hence probability of falling into poor risk group with increasing presentation duration. This could mean symptom duration does not predict having higher IPI score. It indicates inherent biology is probably is more important factor influencing IPI. But small sample size, possible mix up of less aggressive NHL might be confounding factors.

CONCLUSION

The findings suggesting late presentation does not necessarily lead to worse IPI. Large scale studies to prospectively evaluate outcome is desirable to better understand the dynamics of presentation, IPI score and outcomes.

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REFERENCE

1. GLOBOCAN Factsheet [Internet]. [cited 2016 Jun 1]. Available from: http://globocan.iarc.fr/old/factsheet.asp
2. Website [Internet]. [cited 2016 Jun 1]. Available from: http://globocan.iarc.fr/Subedi K. Facts from Cancer registry report 2012. Message to: Munesh R Lakhey Sept 8th 2014. [cited 2016 Jan 5] old/factsheet.asp
3. Non-Hodgkin Lymphoma - SEER Stat Fact Sheets [Internet]. [cited 2016 Jun 1]. Available from: http://seer.cancer.gov/statfacts/html/nhl.html
4. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med. 1993 Sep 30;329(14):987–94.
5. Hermans J, Krol AD, van Groningen K, Kluin PM, Kluin-Nelemans JC, Kramer MH, et al. International Prognostic Index for aggressive non-Hodgkin's lymphoma is valid for all malignancy grades. Blood. 1995 Aug 15;86(4):1460–3.
6. Non-Hodgkin lymphoma incidence statistics [Internet]. Cancer Research UK. 2015 [cited 2016 Aug 25]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/incidence
7. Hoffman R, Benz EJ Jr, Silberstein LE, Heslop H, Weitz J, Anastasi J. Hematology: Basic Principles and Practice, Expert Consult Premium Edition - Enhanced Online Features. Elsevier Health Sciences; 2012. 2384 p.
8. Non-Hodgkin Lymphoma - SEER Stat Fact Sheets [Internet]. [cited 2016 Aug 25]. Available from: http://seer.cancer.gov/statfacts/html/nhl.html
9. Vallabhajosyula S, Baijal G, Vadhiraja BM, Fernandes DJ, Vidyasagar MS. Non-Hodgkin's lymphoma: is India ready to incorporate recent advances in day to day practice? J Cancer Res Ther. 2010 Jan;6(1):36–40.
10. Dehghani M, Haddadi S, Vojdani R. Signs, Symptoms and Complications of Non-Hodgkin's Lymphoma According to Grade and Stage in South Iran. Asian Pac J Cancer Prev. 2015 Apr 29;16(8):3551–7.
11. Vidyasagar MS, Saraschandra V, Gunjan B, Vadhiraja BM, DonaldJ F. Non-Hodgkin s lymphoma: Is India ready to incorporate recent advances in day to day practice? J Cancer Res Ther. 2010;6(1):36.
12. Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007;109(5):1857–61.
13. Sharma R, Cunningham D, Smith P, Robertson G, Dent O, Clarke SJ. Inflammatory (B) symptoms are independent predictors of myelosuppression from chemotherapy in Non-Hodgkin Lymphoma (NHL) patients--analysis of data from a British National Lymphoma Investigation phase III trial comparing CHOP to PMitCEBO. BMC Cancer. 2009 May 18;9:153.
14. Madubogwu CO. Colorectal Cancer: Late Presentation and Outcome of Treatment. Afrimedic Journal. 2013;3(1):13–5.
15. Koong HN, Chan HS, Nambiar R, Soo KC, Ho J, Ng HS, et al. Gastric cancers in Singapore: Poor prognosis arising from late presentation. ANZ J Surg. 1996 Dec;66(12):813–5.
16. Gupta D, Sharma A, Raina V, Bakhshi S, Mohanti BK. Primary testicular non-Hodgkin lymphoma: a single institution experience from India. Indian J Cancer. 2009 Jan;46(1):46–9.
17. Moullet I, Salles G, Ketterer N, Dumontet C, Bouafia F, Neidhart-Berard EM, et al. Frequency and significance of anemia in non-Hodgkin's lymphoma patients. Ann Oncol. 1998 Oct;9(10):1109–15.
18. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. Ann Oncol. 1998 Jul;9(7):717–20.
19. Naresh KN, Srinivas V, Soman CS. Distribution of various subtypes of non-Hodgkin's lymphoma in India: A study of 2773 lymphomas using R.E.A.L. and WHO Classifications. Ann Oncol. 2000;11(suppl 1):S63–7.
20. Hollender A, Kvaloy S, Nome O, Skovlund E, Lote K, Holte H. Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model. Ann Oncol. 2002 Jul 1;13(7):1099–107.