Indian J Hematol Blood Transfus (2024) 40:237–245
https://doi.org/10.1007/s12288-023-01692-9

ORIGINAL ARTICLE

Prognostic Factors and Outcomes of Early-Stage Hodgkin's Lymphoma: Multi-Institutional Data From South India

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Received: 3 May 2023 / Accepted: 10 August 2023 / Published online: 30 August 2023

Abstract Early-stage Hodgkin's lymphoma (ESHL) is highly curable, usually with a combination of chemotherapy and radiation. Real-world data may show differences in survival and prognostic factors when compared to clinical trials. There is limited published literature on ESHL from India. The data on the baseline characters, treatment, and outcomes of patients with ESHL (stage IA, IB, and IIA) were obtained from five institutions' medical records and entered in a common database. Event-free survival (EFS) and overall survival (OS) were estimated using the Kaplan Meier method, and cox-regression analysis was used to identify prognostic factors. There were 258 patients [median age was 37 (18–75) years; [males:160 (62%); stage I: 41%; B symptoms: 17 (6%); bulky disease:19 (15%)] treated between 2000 and 2020 who were evaluable. The common chemotherapies used were ABVD [N = 180 (70%)], COPP-ABVD hybrid [N = 52 (21%)], and COPP [N = 14 (5%)]. Median number of cycles were 4 (2–8) and 93 (47%) received radiation at end of treatment. After a median follow-up of 60 months, the 5 years EFS was 87% and OS was 92%. On multivariate analysis, the following factors adversely affected the EFS: Male gender [hazard ratio (HR) = 2.23, $P = 0.02$] and Hemoglobin < 10.5g/dL [hazard ration (HR) = 2.20, $P = 0.02$], and the following adversely affected the OS: Hemoglobin < 10.5g/dL [hazard ratio (HR) = 4.05, $P = 0.001$], Male gender [hazard ratio (HR) = 3.59, $P = 0.004$], Stage 2 [hazard ratio (HR) = 2.65, $P = 0.002$] and ECOG PS (2–3) [hazard ratio (HR) = 3.35, $P = 0.01$]. Using the hemoglobin, stage and gender a 3-item prognostic score could identify patients with very good outcomes (score 0; 5 years OS:100%) and poor outcomes (score 3; 5 years OS; 49%). This is one of the first multi-center real-world data exclusively focusing on ESHL from India. Though the survival of the entire population was good, there are subsets of patients who have poor outcomes, which may be identified using simple parameters. These parameters need validation in a larger dataset.

Keywords Early stage Hodgkin's Lymphoma · Survival, Prognostic factors · Chemotherapy · Radiation · India

Introduction

Early-stage Hodgkin's Lymphoma (ESHL) is a highly curable cancer with excellent long-term survival [1]. Survival outcomes and treatment strategies differ among early favorable and unfavorable subgroups [2]. Presence of factors such as elevated ESR, extensive mediastinal involvement, extranodal sites, and multiple nodal sites determine "unfavorable" groups of ESHL as defined by the German Hodgkin Study Group (GHSG), the European Organization for Research and

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12288-023-01692-9.

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Treatment of Cancer (EORTC), and the National Comprehensive Cancer Network (NCCN) [3]. These factors were originally defined in the era of radiotherapy. The influence of traditionally factors in the modern era of combined modality treatment (CMT) might be blunted [1].

Much of the published data on ESHL comes from clinical trials where there is the possibility of selection bias. Reports of real-world outcomes of ESHL are lesser due to various reasons [4]. Data on the real-world outcomes of ESHL is scarce, especially from developing countries. At present, guidelines indicate that very limited chemotherapy (2 cycles ABVD and IFRT) is possible in selected subsets of ESHL. However, there would be a small but significant proportion of patients with ESHL who fail therapy in real-world practice. It is essential to identify these patients to tailor the treatment in a better way. In our study, we have combined data from five different Institutions in South India to analyse factors affecting outcomes. We attempted to create a prognostic score that could identify a distinct group of ESHL with poor outcomes.

Methods

Data Sources

Data was collected from medical records of adult patients (≥ 18 years) with ESHL who started treatment between Jan 2000 till Dec 2020 from five different centers in South India. The data was collected in a common pre-structured proforma. Each Institution was responsible for obtaining approval from Ethics Committees for the collection of data. For this study, ESHL was defined as stage I (single lymph node region or single extra lymphatic organ) with or without "B" symptoms and stage 2 (involved two or more lymph node regions or contiguous extra lymphatic organs on the same side of the diaphragm) without "B" symptoms. "B" symptoms were defined as unexplained fever (> 38 deg. C), night sweats, and weight loss of > 10% within six months of diagnosis. As most of the centers treated stage IIB as advanced HL (AHL), this group was excluded from the definition of ESHL for this analysis. Bulky disease was defined as any nodal or extra-nodal mass > 10 cm in longest diameter. Lymph node involvement was determined by physical examination and Imaging (contrast-enhanced CT (CECT) or positron emission tomography CT (PET-CT, after 2007).

Treatment was with ABVD (doxorubicin, vinblastine, bleomycin, and dacarbazine) or hybrid regimen (with COPP- cyclophosphamide, vincristine, procarbazine, and prednisolone) for 2–8 cycles with or without radiotherapy. The decision to use radiation and the number of cycles of chemotherapy was physician-specific and often individualized. The exact reason for giving or withholding radiation in an individual patient was not available from the records. Patients who received more than six cycles usually had a partial response after six cycles (in the pre-PET era, when complete response couldn't be accurately determined). End of therapy response was evaluated using CECT (N = 162) or PET-CT (N = 96) as per the availability. There was no independent verification of the scans done for this study. Most centers had used the older WHO response criteria especially in patients who had CECT scans (any LN mass < 1.5 cm was considered as CR) and the International Working Group (IWG) response criteria were used to record end of treatment response (Deauville score 3 or less considered as complete metabolic response, or uptake values lower than mediastinum was considered as CR) in those who underwent PET-CT [5, 6].

Though individual centers provided data from different periods, it was ensured that the data for a particular period contributed by a center would be complete and capture all patients treated in that period. Estimation of survival was stratified by the different time periods, dichotomising the year of diagnosis into two groups (2000–2015) and (2015–2020). This cutoff was chosen as PET CT was widely available and accessible from 2015. Analysis of treatment group was stratified by use of radiotherapy to assess the influence of omitting RT on EFS and OS. Whether a more significant number of cycles negates the effect of RT was evaluated.

Analysis

The normality of data for continuous variables was checked using the Kolmogorov Smirnov test. Continuous variables were summarized as the mean ± standard deviation or median (Inter-quartile range), and categorical data were expressed as frequency and percentages. Event-free survival (EFS) was defined as the time from initiation of treatment for ESHL until the date of the first event (relapse, refractory, progression, or death due to any cause) or until the date of last follow up. Overall survival (OS) was defined as the period from the initiation of treatment for ESHL until death due to any cause or until the last follow-up date. The Kaplan-Maier method was used to estimate survival (EFS and OS), and the log-rank test was used to identify the prognostic factors. Continuous variables were dichotomized for further analysis. The cox-proportional hazard model was used to understand the impact of baseline characters on survival. Significant variables were further tested by multivariate cox-regression analysis. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 19.0 (SPSS Inc., Chicago, IL, USA). All values were two-sided, and a value of $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of the Study Patients

Data of 264 patients with ESHL was collected from the five centers. Of these, six patients were excluded (1 had relapsed disease at presentation, 1 received only palliative intent radiation due to severe co-morbidities, and four defaulted before the start of treatment). Thus, the data of 258 patients who underwent curative-intent treatment was analyzed. The median age at presentation was 37 (18–75) years [males: 160 (62%), stage I: 41%]. (Table 1) Few patients had B symptoms (6%, N = 17) and bulky disease (15%, N = 39).

Treatment and Outcomes

The most common chemotherapy protocol used was ABVD in 180 (70%) patients. Others received either COPP-ABVD hybrid: 52 (21%) or COPP: 14 (5%). At the end of therapy, 219/258 patients had responded [overall response rate (ORR): 95%]. In 205 (94%), there were complete responses and partial responses in 14 patients (6%). After a median follow-up (reverse KM method) of 55 months (range: 0.4–232.4 months), 56 patients had events, and 34 had died. The median follow in the time period 2000–2014 was 89.1 months (range: 0.5–232.4 months) and in the time period 2015–2020 was 34.6 months (range: 0.43–79.9 months). The median EFS and OS had not been reached. The estimated actuarial EFS was 87% and OS 92% at five years (Supplementary Fig. 1a and b).

Factors Affecting Survival

On univariate analysis, the following factors adversely affected the EFS: Hemoglobin (≤ 10.5) [hazard ratio (HR) = 2.19, $P = 0.006$], Male gender [hazard ratio (HR) = 1.45, $P = 0.04$], ECOG PS (2–3) [hazard ratio (HR) = 2.68, $P = 0.01$], and stage 2 [hazard ratio (HR) = 1.79, $P = 0.04$] disease (Table 2). For multivariate analysis, all these factors and albumin (P value 0.05 on univariate analysis) were incorporated into the analysis (Table 3, Fig. 1). On multivariate analysis for EFS, the following factors were significant: Male gender [hazard ratio (HR) = 2.23, $P = 0.02$] and Hemoglobin < 10.5g/dL [hazard ration (HR) = 2.20, $P = 0.02$]. Factors adversely affecting OS on univariate analysis were: Male gender [hazard ratio (HR) = 1.12, $P = 0.04$], Hemoglobin < 10.5 [hazard ratio (HR) = 2.96, $P = 0.002$], ECOG PS (2–3) [hazard ratio (HR) = 4.09, $P = 0.002$], and Stage 2 [hazard ratio (HR) = 2.10, $P = 0.004$]. The same factors predicted OS on multivariate analysis [Haemoglobin < 10.5g/dL [hazard ratio (HR) = 4.05, $P = 0.001$], Male gender [hazard ratio (HR) = 3.59, $P = 0.004$], Stage 2 [hazard ratio (HR) = 2.65,

Table 1 Baseline characteristics and treatment (N = 258)

Parameters	N (%)
Age at diagnosis, years, median (range)	37 (18–75)
Age ≤ 45	177 (18–45)
Age > 45	81 (46–75)
Gender	
Male, n (%)	160 (62)
Female, n (%)	98 (38)
Performance status (ECOG)	
0,1	245 (95)
2,3[a]	13 (5)
Stage	
Stage I	106 (41)
Stage II	152 (59)
Hb, g/dl, median (range)[b]	12.5 (10.8–14)
≥ 10.5 g/dl	203 (78)
< 10.5 g/dl	51 (22)
ESR, median (range)[b]	35 (15–52)
≥ 50	46 (18)
< 50	138 (82)
LDH, median (range)[b]	472 (323–643)
Elevated	107 (41)
Not elevated	66 (59)
Albumin, median (range)[b]	4 (3.6–4.5)
≥ 4	84 (32)
< 4	100 (68)
B symptoms	17 (6)
Bulky disease (> 10cm)	39 (15)
Chemotherapy	
ABVD	180 (70)
ABVD-COPP hybrid	52 (21)
COPP	14 (5)
Others	12 (4)
Number of cycles of chemotherapy (median, range)	6 (1–8)
< 4	117
> 4	141
Radiotherapy	93 (37)
RT in patients with ≤ 4 cycles chemotherapy	50
RT in patients with > 4 cycles	43
Year of diagnosis	
2000–2014	154 (60)
2015–2020	104 (40)
PET-CT done for staging	
Yes	95 (36)
No	163 (64)

[a]9/13 had ECOG 2 and 4 had ECOG 3. All 4 patients with ECOG 3 had stage IIB disease

[b]Numbers do not add to 258 as some values were missing

Table 2 Univariate analysis of prognostic factors

Variable	N	EFS (%) 5 yrs	95% CI	Hazard ratio	*P*	OS (%) (5 yrs)	95% CI	Hazard ratio	*P*
Age									
≥45	57	71	0.65–2.20	1.20	0.5	80	0.75–3.37	1.59	0.21
<45	201	77		1		86		1	
Gender									
Male	160	73	1.19–2.54	1.45	0.04	82	1.08–3.53	1.12	0.04
Female	98	80		1		90		1	
ECOG PS									
0,1	245	77	1.15–6.27	1	0.01	86	1.57 –10.63	1	0.002
2,3[a]	13	48		2.68		56		4.09	
Stage									
1	106	82	1.01–3.17	1	0.04	90	1.11–4.51	1	0.04
2	152	77		1.79		81		2.10	
Bulky disease[d]									
≥10cm	39	71	0.55–2.33	1.14	0.71	85	0.44–2.99	1.15	0.76
<10cm	218	76		1		85		1	
Hemoglobin[b]									
≥10.5 g/dl	203	80	1.22–3.1	1	0.006	92	1.43–6.13	1	0.002
<10.5 g/dl	51	61		2.19		72		2.96	
Total WBC									
≥15,000	18	58	101–4.98	2.25	0.06	85	0.46–5.05	1.53	0.47
<15,000	237	77		1		86		1	
Lymphocyte %[b]									
≥8	236	76	0.21–3.6	1	0.85	86	0.25–2.23	1	0.90
<8	10	59		0.87		88		0.75	
Albumin[b]									
≥4	84	83	0.99–3.55	1	0.05	88	0.61–2.98	1	0.45
<4	100	65		1.87		80		1.35	
LDH[b]									
Elevated	107	73	0.75–3.22	1.55	0.22	84	0.76–6.79	2.28	0.12
Not elevated	66	85		1		93		1	
Radiotherapy[b]									
Yes	93	78	0.41–1.29	1	0.27	85	0.39–1.69	1	0.58
No	159	75		0.72		85		0.81	
ESR									
≥50	46	80	0.53–2.30	1.15	0.76	86	0.25–2.23	0.75	0.45
<50	138	78		1		90		1	
Year of diagnosis									
2015–2020	104	81%	0.79–2.55	1	0.23	91%	0.69–3.5	1	0.28
2000–2014	154	73%		1.4		83%		1.5	
Imaging by PET CT									
Yes	95	77%	0.62–1.9	1	0.73	91%	0.77–4.2	1	0.16
No	163	75%		1.1		83%		1.8	

ECOGPS Eastern cooperative oncology group performance status, *EFS* event free survival, *ESR* erythrocyte sedimentation ratio, *LDH* lactate dehydrogenase, *OS* overall survival

[a]9/13 had ECOG 2 and 4 had ECOG 3. All 4 patients with ECOG 3 had stage IIB disease

[b]Numbers do not add to 258 as values were not available in some patients

Table 3 Multivariate analysis of factors affecting survival

Event-free survival				Overall survival			
Variable	HR	95% CI	*P* value	Variable	HR	95% CI	*P* value
Stage				Stage			
1	1	0.90 – 3.52	0.09	1	1	1.12 – 6.27	0.02
2	1.78			2	2.65		
ECOG				ECOG			
0–1	1	0.61 – 5.04	0.29	0–1	1	1.23 – 9.12	0.01
≥2	1.75			≥2	3.35		
Hemoglobin				Hemoglobin			
> 10.5	1	1.09 – 4.50	0.02	> 10.5	1	1.78 – 9.24	0.001
< 10.5	2.21			< 10.5	4.05		
Gender			0.02	Gender			0.004
Female	1	1.14 – 4.92		Female	1	1.50 – 8.59	
Male	2.37			Male	3.59		
Albumin							
≥4	1	0.92–3.53	0.08				
< 4	1.81						

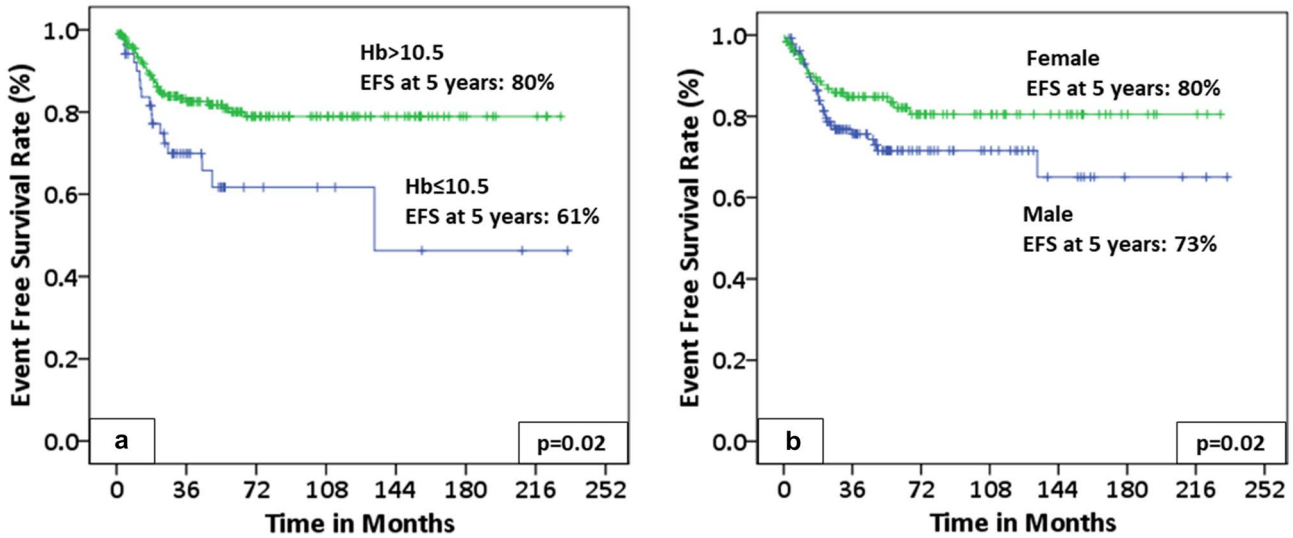

Fig. 1 Prognostic factors affecting Event Free Survival: Impact of hemoglobin (**1a**) and gender (**1b**) on event-free survival of patients with early-stage HL

P = 0.002] and ECOG PS (2–3) [hazard ratio (HR) = 3.35, *P* = 0.01] (Table 3, Fig. 2). The use of end therapy radiation did not have an effect on PFS (Table 2). When we looked at the effect of radiation only on those who underwent PET CT evaluation (N = 95, of which 36 received RT and 57 did not receive RT), again there was no difference in survival. The 5 years EFS among PET-staged patients with and without radiation was 82% and 74% respectively (*P* = 0.2). We looked at the impact of radiation on ABVD treated patients (N = 180; received RT = 120, no RT = 60) and did not find an impact of radiation on PFS or OS (5 year OS 92% vs 88%, *P* = 0.135).

Prognostic Score and Prediction of Survival

Four factors predicted the OS, of which ECOG PS was not considered for the development of a prognostic score as the number of patients with poor performance status (≥2) was less[N = 13(5%)] (Table 3). Thus, three factors [hemoglobin > 10.5 vs < 10.5; Stage II vs. I and gender (male vs female)] were included to form a simple prognostic score. Each adverse prognostic factor was given a score of 1, and the total score ranged from 0 to 3. The patients could be demarcated into four prognostic groups (Fig. 3a and b). The patients with the lowest score of 0 had a 5 years survival was

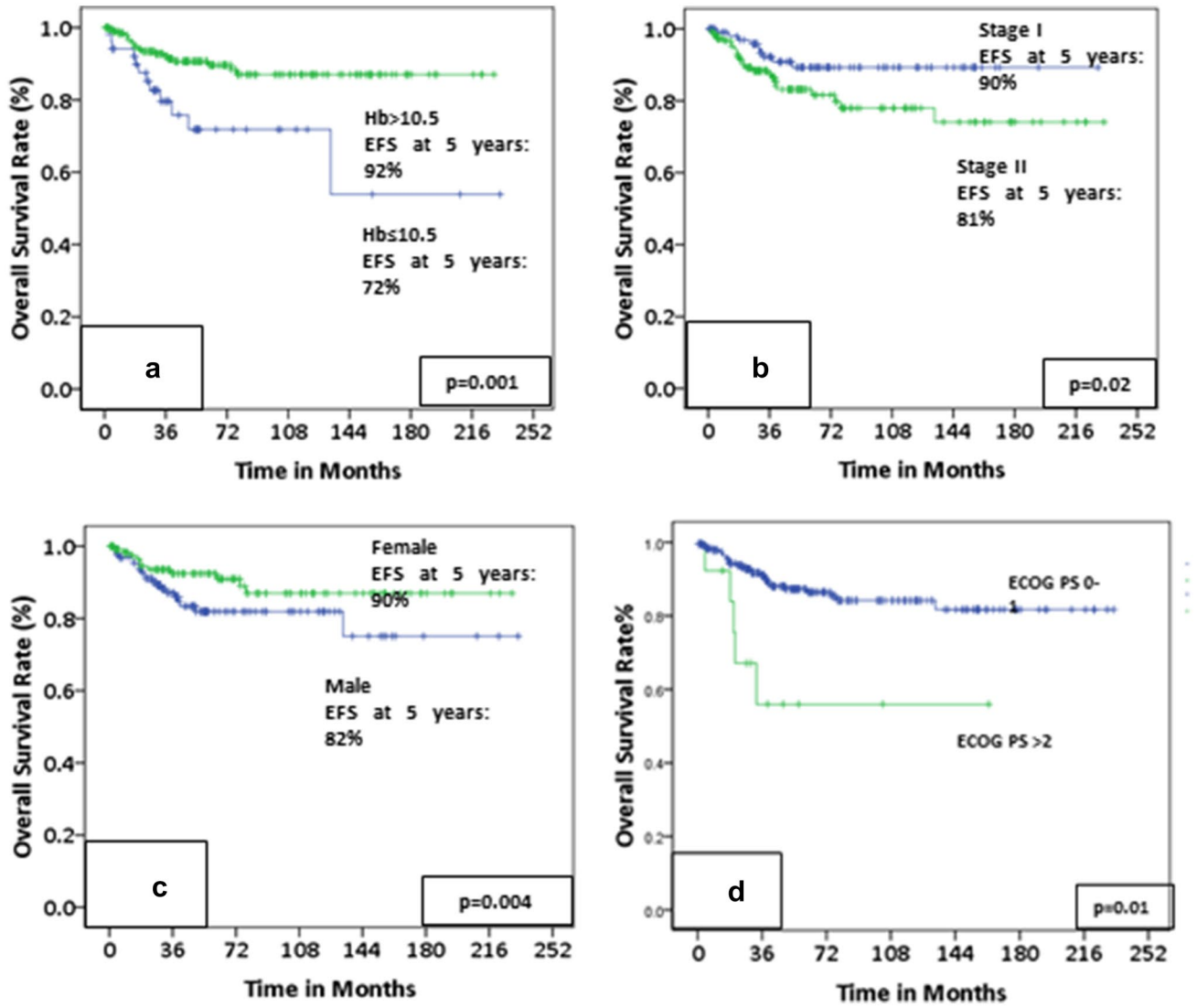

Fig. 2 Prognostic factors affecting Overall Survival: Impact of hemoglobin (**2a**), stage (**2b**), gender (**2c**) and performance status (**2d**) on the overall survival of early-stage HL

91%, while those with a score of 3 had a survival of 49%. Thus, this score can identify a population of ESHL with inferior outcomes.

Discussion

One of the challenges while treating ESHL is identifying the small proportion of patients who don't do well with current combined modality therapy. From a multi-institutional database of ESHL from India, we identified a simple prognostic score that could predict EFS and OS. The composite score with three factors includes hemoglobin, gender, and stage. The presence of all three factors could identify a subset of patients with a 5 years EFS and OS of 46% and 49%, respectively. Even among those with only 2 of the three unfavourable factors, the 5 years EFS was only 68%. Though the stage is a well-known factor in predicting outcomes, male sex and hemoglobin are not usually identified as prognostic in ESHL (though well-established in AHL) [7]. The usual prognostic factors in ESHL are ESR, nodal burden, and age. We did not identify a prognostic relevance for age. The data regarding ESR and the nodal burden was unavailable for most patients in a retrospective dataset. The factors identified in our model are almost always available in all patients undergoing treatment and make it a more convenient score for further evaluation.

Hemoglobin is one among seven factors in the International Prognostic Scoring System (IPSS) used in advanced Hodgkin's lymphoma (AHL) [7, 8]. In this study, we used

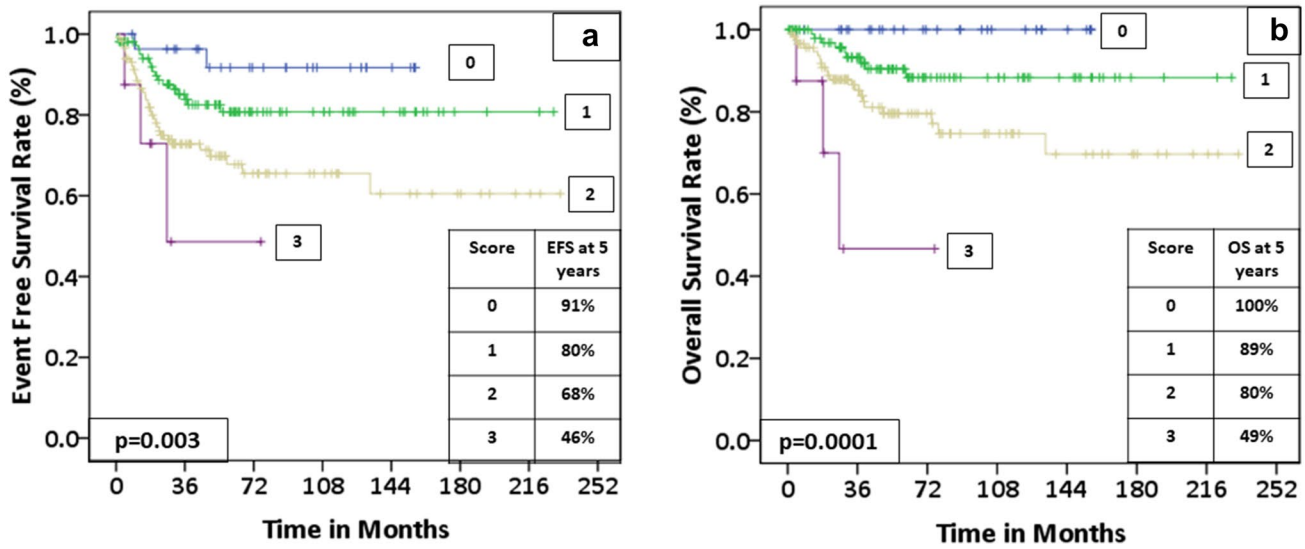

Fig. 3 Impact of the prognostic score on the outcomes of patients with ESHL: There were 3 factors which were included in the prognostic scoring system (Male gender, stage II disease and Hemoglobin < 10.5g/dL) and each of these was given 1 point and the final score for each patient was added up

a similar cut-off of 10.5 g/dL as has been used by the IPSS. Low hemoglobin in advanced-stage HL is due to an inflammatory cytokine milieu, possibly leading to "anemia of chronic disease"-like situation [7, 9]. In addition, there may be patients with marrow involvement by the lymphoma. In ESHL, there is no marrow involvement; hence the low hemoglobin might be due to inflammatory cytokines, which can reduce erythropoiesis by reducing erythropoietin production. Anemia is prevalent in the Indian population, and recent surveys have shown that about half the population will be anemic [10]. Anemia is particularly common in women, especially due to iron deficiency. Various studies have shown poor clinical outcomes in cancer patients with low hemoglobin and more aggressive behaviour of cancer cells due to tumor hypoxia [9]. Low hemoglobin also compromises response to chemotherapy and radiation. Incorporating hemoglobin with other known prognostic factors like stage and male sex yielded a robust prognostic score with high discriminative ability.

Combined modality has been established as the standard treatment for ESHL, even in the PET-CT era [11] [12]. This has been suggested by recent real-world data also [13]. However, in our study, addition radiation was not statistically significant in improving outcomes. This variation could be due to the increased number of chemotherapy cycles used by some of the centers, and also because of the smaller sample size in the study. Additionally, it is possible that PET positive residual disease was selected for additional radiation. This may have selected patients with good outcomes in chemotherapy-alone groups.

Gender has a prognostic influence on advanced Hodgkin's lymphoma, as evidenced by Hasenclever Index [7]. The effect on early HL is less well-defined. Males with HL have a poorer outcome than females. The mechanism of the prognostic impact of gender can be explained in two ways, the effect on Hodgkin lymphoma development and the implications for treatment response. A higher proportion of male patients are diagnosed with HL, especially the elderly; consequently, males have more often unfavorable disease characteristics [14]. The influence of female sex hormones leads to differences in pharmacokinetics. 17β-estradiol decreases the spontaneous production of interleukin 6 (IL6) by mononuclear cells, resulting in lower serum IL6 levels. Low IL6 levels are associated with a complete response to chemotherapy, providing a protective effect in females in contrast to males, who probably lack this mechanism. The impact of gender is not limited to HL; females fare better than their male counterparts in DLBCL, FL, and a few solid tumors [15].

The utility of such a prognostic score, once validated, would be immense. In AHL, PET-guided therapy has emerged as standard because of the solid predictive ability of the interim PET CT scans [16]. In ESHL, trials of PET-guided adapted therapy omitting radiation have failed to show non-inferiority of eliminating radiation based on PET-findings [11] [12]. Hence the need for robust prognostic scores to guide treatment. It is also possible that these predictive scores need to be tailored to different populations. This might identify the right patient for de-escalation of chemotherapy and omission of RT, which would help reduce treatment duration and future morbidity. There may

be differences in therapy between centers. This allows comparison of outcomes based on these variations. We did not find any difference in the outcomes (Table1). The limitation of this retrospective analysis is the missing information on the number of lymph nodal sites and ESR from many records. Long-term toxicity data is currently not available to comment on the effect of more than four cycles of chemotherapy and radiation. However, no second cancers were reported among these patients till last follow up. The currently available prognostic scoring systems like German Hodgkin Study Group (GHSG) and European Organization for Research and Treatment of Cancer (EORTC) include number of nodal sites as one of the prognostic factors. However, this data was not available/ was not reliable in the records of many of the centers [17]. Another important data which could not be obtained from records was the reason for the use of radiation in some patients. It is possible that high-risk patients were selected for radiation thus negating the survival benefits of combine modality treatment. Despite these limitations, this study is unique because it identifies a score against a poor prognostic subset of ESHL. Moreover, this is the most extensive series of ESHL from India involving multiple institutions and reflecting the real-world outcome data (Supplementary Table S1). Since this is a relatively small study with limited analysis, future studies need to prospectively validate and test the utility of the prognostic score in ESHL.

ECOG PS: Eastern Cooperative Oncology Group Performance Status.

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