# Overview and outcome of Hodgkin's Lymphoma: Experience of a single developing country's oncology centre

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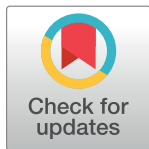
Abstract

Hodgkin's Lymphoma (HL) reveals variable epidemiological and clinico-pathological features in different geographical locations. In this retrospective study, we aimed to assess the epidemiological and clinic-pathological features, and outcome of HL patients treated at one hemato-oncology centre in Erbil, northern Iraq. Medical records of 103 HL patients treated over more than six years were reviewed. Treatment outcome was evaluated by measuring the 5-year overall and progression-free survival rates. The median age of patients was 23 years, children up to 17 years constituted 31.1%, and male to female ratio was 1:1.05. The majority (96.1%) of patients presented with lymphadenopathy. Nodular sclerosis subtype was the mostly encountered histologic type (48.5%); about half of the patients (49.5%) had stage II disease. Relapse occurred in 20 patients; the 5-year overall survival for children was better (89%) compared to adult patients (79%). The associated risk features found to have adverse effects on the survival, however, only high LDH level and presence of B-symptoms at presentation showed significant correlation. The epidemiological and clinical characteristics of HL in our locality followed the pattern in the western world. The 5-year overall and progression-free survivals were far below the international rates, a matter which may necessitate a revision to HL treatment strategy at our centre.

Introduction

Hodgkin Lymphoma (HL) is an uncommon tumour, although it is one of the more frequent malignancies in young people. Its annual incidence is 2–3 per 100,000 in Europe and the USA; though it accounts for 5–6% of all childhood cancer. There are variations in the epidemiologic and clinico-pathological characteristics of HL in relation to geography and socioeconomic status. In the industrialised countries, HL has a bimodal incidence with the main peak in young adults of 15–35 years and the second one occurring after the age of 50. On the other hand, the disease appears more in young children in the developing countries. Males are affected more

often than females in all subtypes; however, the nodular sclerosing type occurs slightly more often in young females [1,2].

HL is considered as one of the malignant diseases that respond well to treatment. With continuing clinical trials and combination therapy over the last 30 years, survival rates have been continuously raised. The improvement in patients' survival is mainly remarkable in the paediatric age and low risk groups [3–6]. Fortunately, the success story of HL is not restricted to the developed world; promising rates of survival have been reported from many developing areas [7–11]. Reducing short and long-term toxicity with maintaining excellent cure rates has become the principal objective of the recent trials in the developed part of the world [12,13]. This attempt may be difficult in our setting where patients, as well as physicians, often choose certainty of cure over the risk of late effect.

In our centres, and like the case in some other centres in the developing world, HL patients are principally treated with extensive cycles of ABVD (Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine) chemotherapy. There are increased reports of promising survival rates of HL (80–95%) in the last two decades [14–16]. However, there is lack of outcome data about HL patients who have been treated at our centre. Therefore, we deemed necessary to review and study our records to assess the quality of care and the effectiveness of the treatment protocols applied at our centre. Hence, this study aimed to describe the demographic and clinico-pathological aspects of patients with HL, assess the 5-year overall (OS) and progression-free survival (PFS) rates of paediatric and adult patients, and evaluate the effect of the associated unfavourable risk factors on patients' survival.

Patients and methods

This retrospective study was carried out at Nanakali Hemato-Oncology Teaching Centre in Erbil. Nanakali Centre is a 100-bed public hospital that receives paediatric and adult patients with benign and malignant haematology diseases and solid tumours. Monthly, an average of 120 new and/or follow up cases are admitted and treated for free at this centre.

Records of 103 patients (32 children/adolescents, 71 adults) with HL who were registered and treated at Nanakali Centre from May 2010 to December 2016 were reviewed. Eighteen patients were excluded from this analysis; eight have escaped the follow up and ten have chosen to be treated outside the country after they were diagnosed. The included patients were fully anonymised before accessing their files and the study was approved by the ethical committee of the Hawler Medical University. Demographic data, presenting symptoms, examination findings, mainly number and size of nodal and extranodal regions, routine laboratory and histopathology results, treatment plan, and treatment outcome were retrieved from patients' records. The diagnosis of HL was made based on routine histopathologic and immunophenotypic studies done at the histopathology referral lab in Rizgary Teaching Hospital, Erbil. Cases were histologically classified according to the WHO classification [17]. At diagnosis, all patients had chest radiography, abdominal ultrasonography, as well as computed tomography (CT) scans of neck, chest, and abdomen. Some patients (24/103) were evaluated by fluorodeoxyglucose-positron emission tomography (FDG-PET) scan. FDG-PET was available for a limited number of patients who could afford it outside Iraq. Bone marrow aspiration and biopsy were performed for all patients. Clinical staging followed the Ann Arbor classification [18] and was decided upon by the hemato-oncology committee at Nanakali Centre based on the clinical and radiological findings as well as the results of laboratory investigations. Bulky disease was defined as lymph node (LN) mass ≥10cm diameter or mediastinal mass exceeding one-third of the maximum mediastinal width on an upright posteroanterior chest radiograph. Patients with stages I and II-A

were considered as early stages and those with stages II-B, III, and IV were considered as advanced stages of the disease.

Treatment protocol

HL patients were treated only with ABVD chemotherapy. Involved field radiotherapy (dose range: 25-30Gy, over 12–15 days) was used only for adult patients with bulky disease. A varying number of ABVD cycles were used according to the stage of disease and/or presence of associated risk features.

Children and adolescents

Patients with localised disease (stage I and II-A) were treated with four cycles ABVD. Patients with stage II-B and III diseases were treated with six cycles ABVD. Patients with stage IV disease were treated with eight cycles ABVD. Patients with the relapsed disease were treated with four cycles COPP-ABV (cyclophosphamide, vincristine, prednisolone, procarbazine, doxorubicin, bleomycin, vinblastine) protocol.

Adults

Patients with localised disease (stage I and II-A) were treated with four cycles ABVD. Patients with stage II disease who had B-symptoms and/or one or more of the following unfavourable features at presentation: mediastinal mass >10cm, extranodal disease, and involvement of >3 nodal sites were given six cycles ABVD therapy. Patients with advanced clinical stage (stage III and IV) were treated with eight cycles ABVD.

The treatment was started with administering two to three cycles of ABVD chemotherapy, and then patients were re-examined to evaluate the response. Response to therapy was evaluated depending on clinical judgment and CT scan (or FDG-PET in some) results. Good responders, defined as diminished clinical symptoms and tumour size regression to >50% of its initial size, continued to complete their chemotherapy plan as per their clinical stages. Refractory cases with poor response, defined as persistence of clinical symptoms and/or minimal reduction of the initial tumour size, were switched to 4-cycle ICE (Ifosfamide, Carboplatin, Etoposide) or DHAP (Dexamethasone, high-dose Cytarabine, Cisplatin) chemotherapy protocols. Cases with the relapsed disease were treated with 4-cycle ICE or DHAP protocols as well.

The treatment outcome was evaluated by measuring the 5-year OS and PFS rates. The associated risk features that could be relevant to survival and that were evaluated in relation to the prognosis included age, gender, histologic type, site of the disease, stage, the presence of B-symptoms, ESR, and serum LDH level.

Statistical analysis

The data were analysed using the statistical package for the social sciences (version 19). The estimates of OS and PFS were calculated using the life table method. Kaplan–Meier method and the log–rank test were used to estimate the differences in OS and PFS among the patients. A P value of ≤0.05 was considered statistically significant for all statistical tests. All the variables mentioned above were included as covariates in the multivariate analysis using Cox regression model. Hazard ratios and the corresponding 95% confidence intervals (CI) were constructed in models adjusted for all listed covariates of interest.

Results

During the period between May 2010 and December 2016, 103 patients with HL were diagnosed, admitted, and treated at Nanakali Hemato-oncology Teaching Centre in Erbil. The age of diagnosis ranged from 3 to 83 years with a median of 23 years; children between 3 and 17 years constituted 31.1% (32 cases). Fifty patients (48.5%) were male; male to female ratio was 1:1.05. Among children, 17 patients (53%) were male and 15 (47%) were female.

In the current cohort, the majority (n = 99, 96.1%) of the patients presented with lymphadenopathy. The most common nodal sites involved were cervical and mediastinal (n = 73, 70.9% and n = 10, 9.7%, respectively). Four patients had an extranodal disease at presentation, two of which with pulmonary involvement. B-symptoms were encountered in 61 patients. Concerning the histologic types of the disease, nodular sclerosis (NS) was observed to be the predominant type, affecting 50 patients (48.5%), followed by mixed cellularity (MC) in 47 patients (45.6%). All patients were staged using the Ann Arbor staging system. Seventy patients (68%) had localised disease (stage I/II) and 33 others (32%) had by definition Ann Arbor stage III/IV disease (Table 1).

The mean period of following up the patients was 24.4 months. A total of 99 patients achieved remission and are still alive, while four patients (3.88%) had died. Of patients who achieved remission, 20 patients (19.4%) had a relapse, were treated, and are still alive. The majority of relapses (18/20) occurred within the first 24 months of diagnosis.

The 5-year overall survival (OS) and progression free survival (PFS) rates of our study were 79% and 60%, respectively (Fig 1A and 1B). The effect of the associated clinical and pathological risk features of the disease on the OS and PFS rates were elaborated by univariable and multivariable analysis. Univariable analysis showed that none of the associated risk features had any significant correlation with the 5-year OS; though, the 5-year PFS showed significant association with both high serum LDH level and presence of B-symptoms at time of presentation (P-values = 0.001 and 0.03 respectively) (Fig 2A–2D; Table 2). On multivariate analysis, only high LDH level revealed a significant association with the 5-year PFS (hazard ratio = 3.655, 95.0% CI 1.58–8.43) (Table 3).

Discussion

In the current retrospective study, we have described the clinical and pathological characteristics as well as the treatment outcome of 103 patients with HL who have been treated at Nanakali Hemato-oncology Centre in Iraqi Kurdistan. Children and adolescents constituted less than one-third (32 patients, 31.1%) of the studied patients. Male to female ratio was 1:1.05; this is contrary to many reports which showed male predominance in HL mainly in low socioeconomic communities [19,20].

The WHO classifies HL into the classical HL (~95% of cases) and the NLP HL (~5% of cases); the former includes the histology subtypes NS, MC, LR, and LD; whereas NLP HL is regarded as a distinctive type compared with classical HL [21]. The majority of our patients (n = 100, 97%) had the classical HL with NS subtype being the most common (48.5%), followed by MC subtype (45.6%). The overall age, sex, and histological distribution of our HL cases is more approximate to the pattern in the western countries and is fairly different to the usual picture in the developing world, where the MC type is reported to be the predominant type, particularly in males [8,11,22,23]. Many studies in Europe have reported NS as the most predominant subtype regardless of age [20,24–26]. Interestingly, a recent study from the nearby city of Mosul, northern Iraq, reported 78.6% NS histology type HL [27]. These findings may indicate that the etiological role of Epstein-Bar virus (EBV) infection in the pathogenesis

Table 1. Demographic and clinico-pathological characteristics of patients with HL.

Characteristic		N (= 103)	%
Age (yrs)	0–17	32	31.1
	18+	71	68.9
Gender	Male	50	48.5
	Female	53	51.5
Histologic type	NLP	3	2.9
	NS	50	48.5
	MC	47	45.6
	LR	1	1
	LD	2	1.9
Primary site	Peripheral LNs	81	78.6
	Deep LNs/ Internal organs	22	21.4
Stage	I	19	18.5
	II	51	49.5
	III	27	26.2
	IV	6	5.8
B-symptoms	Yes	61	59.2
	No	42	40.8
ESR (mm/hr)	≤50	53	51.5
	>50	50	48.5
Serum LDH (IU/L)	<500	69	67
	≥500	34	33
Treatment	4 ABVD cycles	26	25.2
	4 ABVD cycles + R	9	8.7
	6 ABVD cycles	50	48.5
	6 ABVD cycles + R	8	7.8
	8 ABVD cycles	7	6.8
	8 ABVD cycles + R	3	2.9
Outcome	Complete remission	79	76.7
	Relapse	20	19.4
	Death	4	3.9

R: Involved field radiotherapy (for bulky disease); NLP: Nodular lymphocyte predominant; NS: Nodular sclerosis; MC: Mixed cellularity; LR: Lymphocyte-rich; LD: Lymphocyte-depletion

ABVD: Doxorubicin, Bleomycin, Vinblastine, Dacarbazine

https://doi.org/10.1371/journal.pone.0195629.t001

of HL, which is well established in the developing and poor socioeconomic communities, is not of that extent in our geographical location [28–30].

More than two-thirds of our patients (70 patients, 68%) had early stage disease (stage I and II) at the diagnosis with stage II clinical stage being the most frequently encountered (51 patients, 49.5%). Similarly, the Surveillance, Epidemiology, and End Results program (SEER), which analysed data of 21,734 HL in the United States, reported figures of 19%, 49%, 19%, and 13% for clinical stages I, II, III, and IV, respectively [31]. Other studies from Europe have reported similar figures [7,32]. In contrary, at least more than half of HL patients in developing countries are diagnosed with advanced stage disease [9,10,33,34].

The survival figures of the current cohort are relatively low. The 5-year OS rate was 79%, which is considerably lower in comparison to the survival figures of many regions, including the developing countries [35]. In the current study, the OS in children and adolescents was
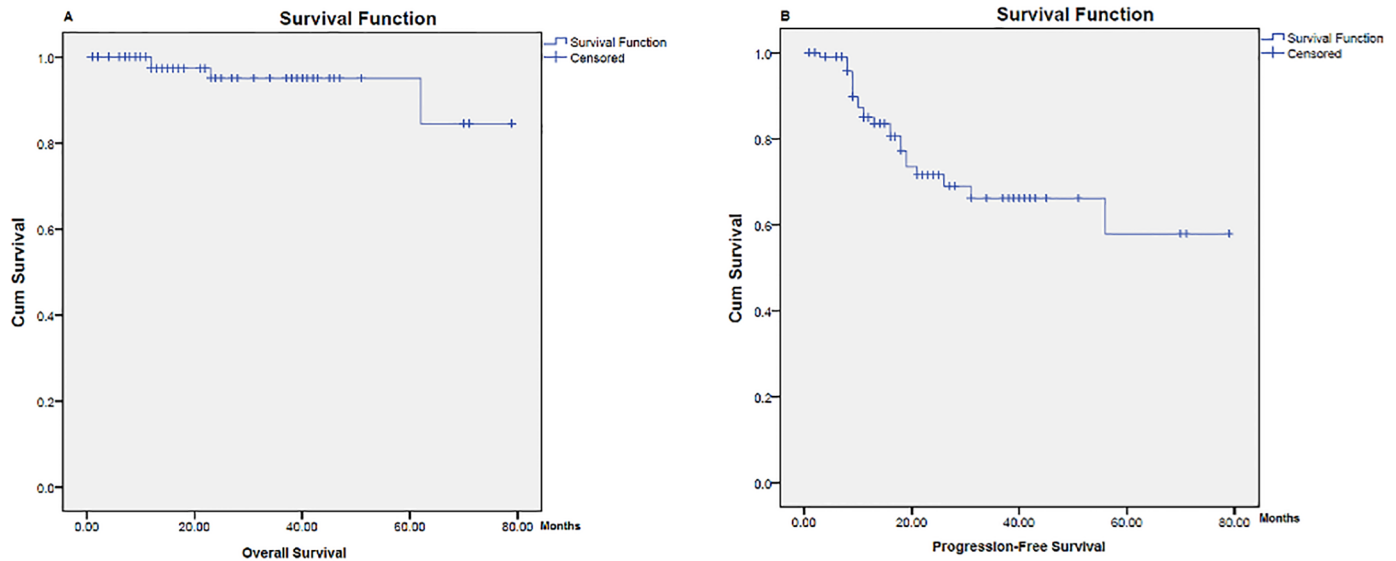
Fig 1. Five-year overall and progression-free survival rates of Hodgkin Lymphoma patients. (A) Five-year Overall Survival Rate. (B) Five-year Progression Survival Rate.

89%; which is slightly lower than the international rates [8,11,26,36]. Though, the results were discouraging in adults with the 5-year OS of 70%. A recent analysis of adult HL patients in Saudi Arabia has reported an OS of 91% [10]. Many factors have possibly contributed to the low survival of our HL patients. Firstly, the modality of the treatment used in our centre. The option of using a single modality therapy for treating HL by some oncology centres in the developing world [11], including ours, is not only because of unavailability or poor radiotherapy services. However, it is also because this modality has been considered by the NCCN guidelines as an alternative treatment option [37]. Taking into consideration the current survival results, oncologists and care providers in our facility should consider the use of alternative treatment options, possibly the combined chemo-radio treatment modality. In the ESMO clinical recommendation, consolidation radiotherapy is part of the treatment of patients with HL even in the early stages [38,39]. A systematic review analysis concluded that using combined chemo-radiotherapy improves tumour control and OS in the patients with HL, mainly in those with early stage disease [40].

Secondly, the interrupted therapy that some HL patients had received during their treatment course. Not all patients had regularly received the theoretical dosage of drugs because of unavailability of different drug items at the different times, which is regarded a week point in this analysis. Thirdly, the relatively short follow up period. The average follow up period in this study was 24 months; survival figures could have been more promising with longer follow up. Fourthly, the lack of effective salvage therapy. None of our HL patients had received brentuximab or had autologous bone marrow transplantation as they are not yet affordable in Iraq. Recent studies have shown that employing salvage therapy is highly effective for refractory or relapsed HL and improves patients' survival [41].

In the current cohort, we investigated the relationship of a number of disease risk features and patients' clinical characteristics such as age, gender, B-symptoms, advanced clinical stage, deep LNs, ESR >50 mm/hr, and LDH >500 IU/L to the 5-year OS and PFS rates. Generally, the associated risk features showed adverse correlation with the OS and PFS rates. However, only B-symptoms and high LDH revealed a significant correlation with the 5-year PFS rate.
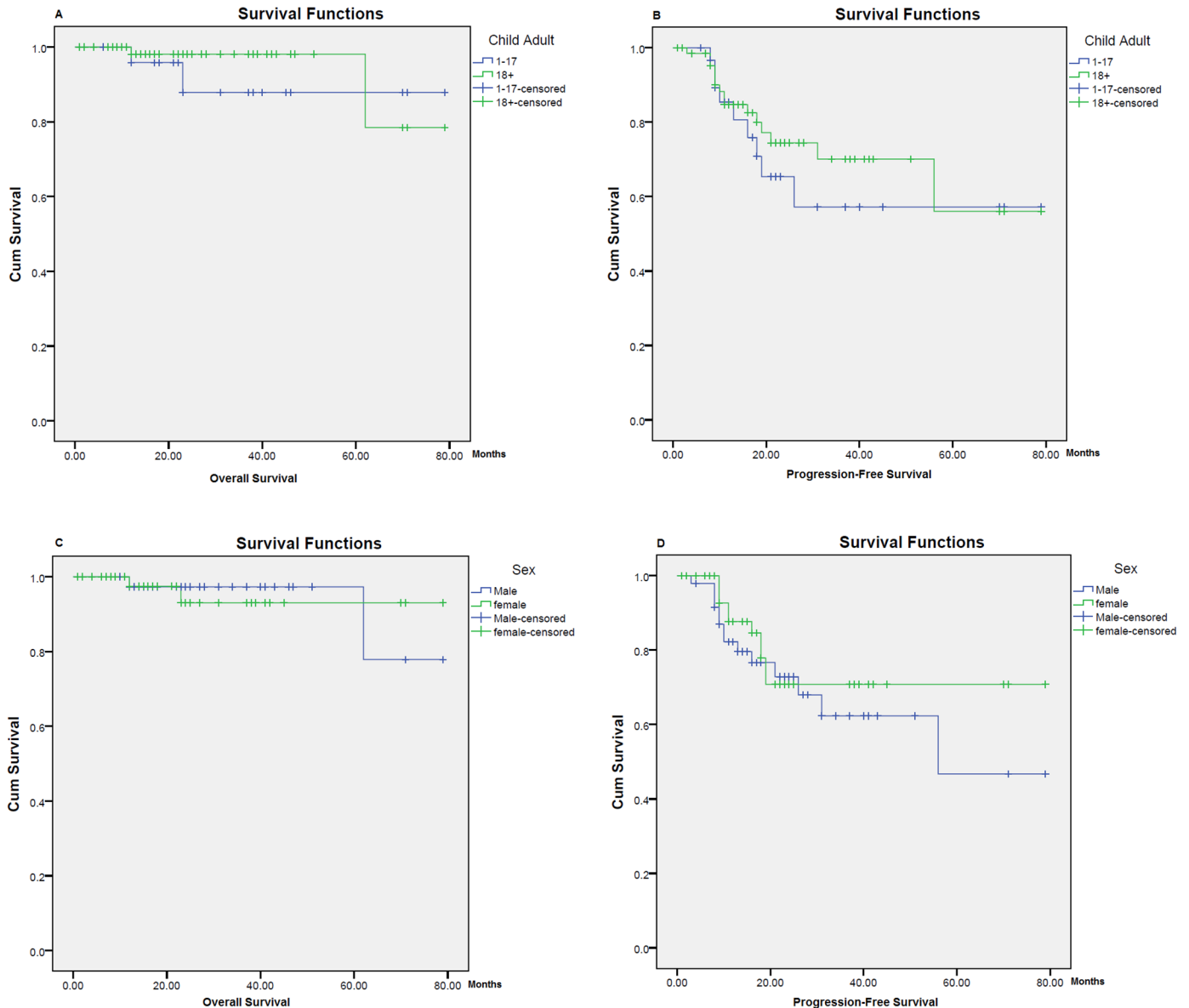
Fig 2. Five-year overall and progression-free survival rates in relation to age and gender. (A) Five-year Overall Survival Rate in Relation to Age. (B) Five-year Progression Survival Rate in Relation to Age. (C) Five-year Overall Survival Rate in Relation to Gender. (D) Five-year Progression Survival Rate in Relation to Gender.

https://doi.org/10.1371/journal.pone.0195629.g002

The absence of significant correlation between the survival and clinical stage of the disease is possibly due to the relatively short follow up period. Significant adverse correlation of the associated risk features with the survival had been reported by some studies but not by others [7,42–44].

In conclusion, the clinical and pathological characteristics of our HL patients followed the western developed pattern. Relapse was recorded in 20% of patients and death occurred in about 4%. The 5-year overall and progression-free survivals were far lower than the international rates, although the gap of difference was less in the paediatric age group. The associated risk features of the disease had a negative impact on survival rates; however, the associations did not reach statistically significant levels except for LDH.

Table 2. Association between overall survival and progression-free survival rates and the associated risk features.

Characteristics	Five-year OS		Five-year PFS	
	Rate (%)	P	Rate (%)	P
Gender				
Male	69	0.996	49	0.380
Female	93		72	
Age				
0–17	89	0.496	56	0.526
18+	70		59	
Primary site				
Peripheral	95	0.149	69	0.271
Deep	45		41	
B-Symptoms				
Yes	61	0.42	15	0.03
No	42		5	
Stage				
I, II	95	0.672	66	0.825
III, IV	68		57	
ESR (mm/hr)				
≤50	96	0.634	59	0.197
>50	77		63	
LDH level (U/L)				
<500	95	0.327	78	0.001
≥500	47		26	

https://doi.org/10.1371/journal.pone.0195629.t002

Table 3. Multivariate analysis of risk features for overall and progression-free survival rates.

	OS				PFS			
	Sig.	Hazard ratio	95.0% CI for Hazard ratio		Sig.	Hazard ratio	95.0% CI for Hazard ratio	
			Lower	Upper			Lower	Upper
Sex (Female)	0.767	0.712	0.076	6.711	0.360	0.663	0.275	1.599
Age (Adult)	0.232	0.208	0.016	2.731	0.204	0.554	0.223	1.378
Stage (III & IV)	0.770	0.653	0.038	11.344	0.206	0.528	0.196	1.421
Site (internal)	0.184	5.429	0.447	66.010	0.387	1.544	0.577	4.130
LDH (≥500)	0.373	2.691	0.305	23.762	0.002	3.655	1.584	8.435
ESR (>50)	0.639	1.748	0.169	18.042	0.204	0.590	0.261	1.332
B-symptoms (Yes)	0.747	1.691	0.070	41.096	0.135	2.296	0.773	6.824

https://doi.org/10.1371/journal.pone.0195629.t003

Supporting information

S1 File. Hodgkin's Lymphoma data file.
(XLSX)

Acknowledgments

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References

1. Thomas R, Re D, Zander T, Wolf J, Diehl V. Epidemiology and etiology of Hodgkin's lymphoma. Ann Oncol. 2002; 13: 147–152. PMID: 12401681

2. Salati M, Cesaretti M, Macchia M, El Mistiri M, Federico M. Epidemiological overview of Hodgkin lymphoma across the mediterranean basin. Mediterr J Hematol Infect Dis. 2014; 6.

3. Trehan A, Singla S, Marwaha RK, Bansal D, Srinivasan R. Hodgkin lymphoma in children: experience in a tertiary care centre in India. J Pediat Hematol Onc. 2013; 35: 174–179.

4. Fadoo Z, Belgaumi A, Alam M, Azam I, Naqvi A. Pediatric lymphoma: a 10-year experience at a tertiary care hospital in Pakistan. J Pediat Hematol Onc. 2010; 32: e14–e18.

5. Büyükpamukçu M, Varan A, Akyüz C, Atahan L, Ozyar E, Kale G, et al. The treatment of childhood Hodgkin lymphoma: improved survival in a developing country. Acta Oncol. 2009; 48: 44–51. https://doi.org/10.1080/02841860802310991 PMID: 18777215

6. Kapoor G, Advani SH, Dinshaw K, Muckaden MA, Soman CS, Saikia TK, et al. Treatment results of Hodgkin's disease in Indian children. Pediatr Hematol Oncol. 1995; 12: 559–569. PMID: 8589001

7. Büyükkapu-Bay S, Çorapçıoğlu F, Aksu G, Anık Y, Demir H, Erçin C. Prognostic factors and treatment results of pediatric Hodgkin's lymphoma: A single center experience. Turk J Pediatr. 2015; 57.

8. Sherief LM, Elsafy UR, Abdelkhalek ER, Kamal NM, Elbehedy R, Hassan TH, et al. Hodgkin lymphoma in childhood: clinicopathological features and therapy outcome at 2 centers from a developing country. Medicine. 2015; 94.

9. Avagyan A, Danielyan S, Voskanyan A, Sargsyan L, Hakobyan L, Zohrabyan D, et al. Treating Adults with Hodgkin Lymphoma in the Developing World: a Hospital-Based Cohort Study from Armenia. Asian Pac J Cancer Prev. 2016; 17: 101–104.

10. Shafi RG, Al-Mansour MM, Kanfar SS, Al Hashmi H, Alsaeed A, Al-Foheidi M, et al. Hodgkin Lymphoma Outcome: A Retrospective Study from 3 Tertiary Centers in Saudi Arabia. Oncol Res Treat. 2017; 40: 288–292. https://doi.org/10.1159/000460819 PMID: 28380488

11. Jain S, Kapoor G, Bajpai R. ABVD-Based Therapy for Hodgkin Lymphoma in Children and Adolescents: Lessons Learnt in a Tertiary Care Oncology Center in a Developing Country. Pediatr Blood Cancer. 2016; 63: 1024–1030. https://doi.org/10.1002/pbc.25935 PMID: 26855007

12. Horwich A, Specht L, Ashley S. Survival analysis of patients with clinical stages I or II Hodgkin's disease who have relapsed after initial treatment with radiotherapy alone. Eur J Cancer. 1997; 33: 848–853. PMID: 9291804

13. Jachimowicz RD, Engert A. The challenging aspects of managing adolescents and young adults with Hodgkin's lymphoma. Acta Haematol. 2014; 132: 274–278. https://doi.org/10.1159/000360205 PMID: 25228552

14. Brepoels L, Stroobants S, Verhoef G. PET and PET/CT for response evaluation in lymphoma: current practice and developments. Leuk Lymphoma. 2007; 48: 270–282. https://doi.org/10.1080/10428190601078118 PMID: 17325886

15. Geller SA, Taylor CR. Thomas Hodgkin: the "man" and "his disease": humani nihil a se alienum putabit (nothing human was foreign to him). Virchows Arch. 2013; 463: 353–365. https://doi.org/10.1007/s00428-013-1442-0 PMID: 23887583

16. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014; 64: 252–271. https://doi.org/10.3322/caac.21235 PMID: 24890451

17. Swerdlow S, Campo E, Harris N, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues 4th Ed. 2008.

18. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. Cancer Res. 1971; 31: 1860–1861. PMID: 5121694

19. Stefan DC, Stones D. How much does it cost to treat children with Hodgkin lymphoma in Africa? Leuk Lymphoma. 2009; 50: 196–199. https://doi.org/10.1080/10428190802663205 PMID: 19197725

20. Friedmann AM, Hudson MM, Weinstein HJ, Donaldson SS, Kun L, Tarbell NJ, et al. Treatment of unfavorable childhood Hodgkin's disease with VEPA and low-dose, involved-field radiation. J Clin Oncol. 2002; 20: 3088–3094. https://doi.org/10.1200/JCO.2002.03.051 PMID: 12118022

21. Feldman AL, Pittaluga S, Jaffe ES. Classification and histopathology of the lymphomas. In The lymphomas. Elsevier Inc. 2006.

22. Laskar S, Gupta T, Vimal S, Muckaden MA, Saikia TK, Pai SK, et al. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? J Clin Oncol. 2004; 22: 62–68. https://doi.org/10.1200/JCO.2004.01.021 PMID: 14657226

23. Baez F, Ocampo E, Conter V, Flores A, Gutierrez T, Malta A. Treatment of childhood Hodgkin's disease with COPP or COPP-ABV (hybrid) without radiotherapy in Nicaragua. Ann Oncol. 1997; 8: 247–250. PMID: 9137793

24. Engel M, Essop M, Close P, Hartley P, Pallesen G, Sinclair-Smith C. Improved prognosis of Epstein-Barr virus associated childhood Hodgkin's lymphoma: study of 47 South African cases. J Clin Pathol. 2000; 53: 182–186. https://doi.org/10.1136/jcp.53.3.182 PMID: 10823135

25. Noordijk EM, Carde P, Dupouy N, Hagenbeek A, Krol AD, Kluin-Nelemans JC, et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol. 2006; 24: 3128–3135. https://doi.org/10.1200/JCO.2005.05.2746 PMID: 16754934

26. Pourtsidis A, Doganis D, Baka M, Bouhoutsou D, Varvoutsi M, Synodinou M, et al. Differences between younger and older patients with childhood Hodgkin lymphoma. Pediatr Hematol Oncol. 2013; 30: 532–536. https://doi.org/10.3109/08880018.2013.823471 PMID: 23941743

27. Fadhil MS, Al-Nueimy WM, Lazim AF. Hodgkin's lymphoma. Saudi Med J. 2014; 35: 448–453.

28. Hjalgrim H, Askling J, Rostgaard K, Hamilton-Dutoit S, Frisch M, Zhang JS, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. N Engl J Med. 2003; 349: 1324–1332. https://doi.org/10.1056/NEJMoa023141 PMID: 14523140

29. Küppers R, Schmitz R, Distler V, Renné C, Bräuninger A, Hansmann ML. Pathogenesis of Hodgkin's lymphoma. Eur J Haematol. 2005; 75: 26–33.

30. Glaser SL, Lin RJ, Stewart SL, Jarrett RF, Brousset P, Pallesen G, et al. Epstein-Barr virus-associated Hodgkin's disease: Epidemiologic characteristics in international data. Int J Cancer. 1997; 70: 375–382. PMID: 9033642

31. Bazzeh F, Rihani R, Howard S, Sultan I. Comparing adult and pediatric Hodgkin lymphoma in the Surveillance, Epidemiology and End Results Program, 1988–2005: an analysis of 21 734 cases. Leuk Lymphoma. 2010; 51: 2198–2207. https://doi.org/10.3109/10428194.2010.525724 PMID: 21054151

32. Miltényi Z, Simon Z, Páyer E, Váróczy L, Gergely L, Jóna A, et al. Changing patterns in the clinical pathological features of hodgkin lymphoma: a report from debrecen, hungary. ISRN Hematol. 2011.

33. Arya LS, Dinand V, Thavaraj V, Bakhshi S, Dawar R, Rath GK, et al. Hodgkin's disease in Indian children: Outcome with chemotherapy alone. Pediatr Blood Cancer. 2006; 46: 26–34. https://doi.org/10.1002/pbc.20157 PMID: 16161019

34. Cerci JJ, Pracchia LF, Linardi CC, Pitella FA, Delbeke D, Izaki M, et al. 18F-FDG PET after 2 cycles of ABVD predicts event-free survival in early and advanced Hodgkin lymphoma. J Nucl Med. 2010; 51: 1337–1343. https://doi.org/10.2967/jnumed.109.073197 PMID: 20720036

35. Yeole B, Advani S, Sunny L. Epidemiological features of childhood cancers in greater Mumbai. Indian Pediatr. 2001; 38: 1270–1277. PMID: 11721067

36. Uysal KM, Çentingozr R, Gunes D, Demiral A, Özer E, Çakmakci H, et al. Clinical characteristics and therapy outcome of pediatric Hodgkin's lymphoma-a single centre experience from the west part of Turkey. Turk J Cancer. 2007; 37: 98–108.

37. NCCN clinical practice guidelines in oncology. Hodgkin's Disease/Lymphoma V2.2009. www.nccn.org.

38. Engert A, Eichenauer D, Dreyling M, Group EGW. Hodgkin's lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009; 20: iv108-iv109.39.

39. Eichenauer D, Engert A, André M, Federico M, Illidge T, Hutchings M, et al. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25: iii70–iii75. https://doi.org/10.1093/annonc/mdu181 PMID: 25185243

40. Herbst C, Rehan FA, Brillant C, Bohlius J, Skoetz N, Schulz H, et al. Combined modality treatment improves tumor control and overall survival in patients with early stage Hodgkin's lymphoma: a systematic review. Haematologica. 2010; 95: 494–500. https://doi.org/10.3324/haematol.2009.015644 PMID: 19951972

41. Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2016; 128(12): 1562–1566. https://doi.org/10.1182/blood-2016-02-699850 PMID: 27432875

42. Shamoon RP, Polus RK. Serum Lactic Dehydrogenase (LDH) Activity in Lymphomas: Prognostic Significance and Relationship to Presentation, Stage and Histologic Type. Zanco J. Med. Sci. 2010; 14 (special issue 1), 85–89.

43. Englund A, Glimelius I, Rostgaard K, Smedby KE, Eloranta S, Molin D, et al. Hodgkin lymphoma in children, adolescents and young adults—a comparative study of clinical presentation and treatment outcome. Acta Oncol. 2017 "in press".

44. Smith RS, Chen Q, Hudson MM, Link MP, Kun L, Weinstein H, et al. Prognostic factors for children with Hodgkin's disease treated with combined-modality therapy. J Clin Oncol. 2003; 21: 2026–2033. https://doi.org/10.1200/JCO.2003.07.124 PMID: 12743158