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Outcome of Hodgkin lymphoma among children in Bangladesh Shishu hospital, Dhaka, Bangladesh

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Abstract
Background: Staging has an important for the prognosis of Hodgkin lymphoma (HL) and choosing the best treatment protocol. This study was designed to evaluate the features of HL and estimate the survival rate in patients got admitted to Bangladesh Shishu Hospital & Institute (BSH&I) for diagnosis and treatment.
Methods: Total 40 patients <18 years of age diagnosed with HL at BSH&I from January 2018 to 2024 were enrolled. Staging, demographic findings, treatment protocols and outcomes were studied and analyzed for possible correlation between various parameters.
Results: In our study, the mean age of patients was 9.9 years (SD±3.8), and included 60% (n 18) male and 40% (n 12) female patients. Fifty percent of patients were treated with ABVD protocol and 50% with BEACOPP protocol. There was a significant association between coughing as a symptom and high stage of the disease (p 0.042). The 5-year event-free survival (EFS) and overall survival (OS) rate for patients in low-risk group were better than intermediate and high-risk group.
Conclusion: Treatment modalities based on staging is important for improving outcomes in HL. In the limited settings, ABVD and other treatment protocols supplemented with BMT in relapsed cases is associated with good outcomes.

Keywords: Hodgkin lymphoma, event-free survival (EFS), overall survival (OS), BEACOPP, ABVD

1. Introduction
Hodgkin Lymphoma (HL) is a type of neoplasm which occurs across different age groups including childhood, adolescence and young adulthood and old age [1, 2]. According to World Health Organization (WHO), the incidence of HL in children aged 0 to 18 is the 4th in ranking of all common childhood cancers of Asia. During year 2018, according to the estimated number of HL crude rate in Bangladesh for 0 to 18 years of age patients, the incidence, prevalence and mortality per 100,000 children were 0.69 (male: 0.86 and female: 051),1.8 (male: 2.1 and female: 1.4) and 0.06 (male: 0.07 and female: 0.06), respectively [3, 4]. Additionally, the overall survival (OS) rate has improved dramatically over the past decades for HL [5]. Although long term follows up of patients with HL show >90% survival, there are late effects seen because of treatment such as cardiopulmonary disturbances and second malignancies [6, 7, 8]. In spite of high OS in patients with HL, the current treatment strategies aim to improve the EFS and the late effects. The risk ratios for death from HL is overtaken by the risk of other causes of death [9]. The 5-year relative survival rate (aged 0 to 18 years) in the United States improved approximately from 70% in 1975 to just over 88% in 2006 [10]. Furthermore, the one-year and chemotherapy and radiotherapy can five-year survival rates for all patients of any age diagnosed with HL are 92 and 86 percent respectively [11]. Fortunately, the treatment of HL is usually effective and many patients are successfully cured [12-14]. The combination of increase the survival from HL (age range of 20 to 84 years) by more than 80% [15], although such treatment depends on the stage of the disease and pathology of the HL [16]. Bangladesh Shishu Hospital is the biggest children Hospital for Pediatric Cancer Treatment and Research Center in Bangladesh. It provides support children with cancer, provide free therapeutic and diagnostic services throughout the Bangladesh. The aim of designing this study was to evaluate HL (in patients younger than 18 years of age) according to their age, treatment plan, and contributing risk factors. Also, survival and outcomes in enrolled patients had been considered by this study too.

2. Materials and Methods

2.1. Population

This prospective observational study was conducted on 40 individuals younger than 18 years' old who were diagnosed with HL in Bangladesh Shishu Hospital & Institute (BSH &I) from January 2018 to December 2024. The study excluded those patients who refused treatment after the diagnosis. The study was approved by the ethical review board of Bangladesh Shishu Hospital & Institute and was performed in accordance with the revised Helsinki Declaration.

2.2. Data collection

A designed questionnaire according to the aims of the study had been validated by ethical review l committee. This unique questionnaire included demographic information such as sex, age, consanguinity etc. Also, specialized and pathologic information including Type of cancer, stage of the disease, bone marrow transplantation (BMT), laboratory tests, radiotherapy, treatment protocols, etc. were collected from patient and relative in Pediatric Hematology & Oncology departments of Dhaka Shishu Hospital.

2.3. Treatment modalities

Chemotherapy protocols that had been administrated for considered patients are as below:

BEACOPP- This regimen administered as 4,6 and 8 cycles for low risk, intermediate risk and high-risk patients respectively.

Drugs are- Bleomycin day 1

- Etoposide day 1-3
- Adriamycin day 1
- Cyclophosphamide day 1
- Vinblastine day 1
- Prednisolone day 1-14
- Procarbazine day 1-7
- Repeat every 21 days

ABVD regimen consisted of

- Adriamycin day 1 & day 15
- Bleomycin day 1 & day 15
- Vinblastine day 1 & day 15
- Decarbazine day 1 & day 15
- Repeat every 28 days

The ABVD regimen administered 4,6 and 8 cycles for low risk, intermediate risk and high-risk patients respectively. At the time of diagnosis all of the patients with HL, evaluated by PET-scan. Following chemotherapy regimens, the response assessment to chemotherapy had been considered by PET-scan after completion of chemotherapy cycles. Computed Tomography (CT) scan according to the tumor location was another choice if PET-scan was not accessible. Decision making about radiotherapy eligibility had been done by PET-scan or CT-scan (based on tumor location). PET-scan could metabolically and morphologically evaluate the residue. If there was report of residue after completion of chemotherapy, then the patient had eligibility of radiotherapy modality. The external radiotherapy had been locally done based on the tumor location.

Patients who conferred with relapse, had been administered by chemotherapy regimen. Then tumor markers of the patient had been checked for remission. If there was not any report of residue by PET-scan and also if there were negative tumor markers, then the patient had eligibility of autologous Bone Marrow Transplantation (BMT) with conditioning regimen. Patients who relapsed were given salvage chemotherapy with ICE regimen.

2.4. Statistical analysis

Statistical analysis was performed using Mann-Whitney, Spearman correlation co efficient, Kaplan-Meier, Log Rank, Cox regression via SPSS-27.0. The p-value less than 0.05 were considered statistically significant.

3. Results

Demographic data and treatment protocol of 40 cases of HL (M/F: 1.2/1.0) were analyzed. The mean age ±SD was 10.2 ±3.5 years. The clinical stage of disease was determined as which are shown in Table 1. For treatment process, 50.4% (n ¼57) were under radiotherapy, 58% (n ¼69) of patients were treated by ABVD protocol, 38.7% (n ¼46) of patients were treated by Hybrid protocol and 3.3% (n ¼4) of patients were treated by other routine protocols. In 34.5% (n ¼41) of all cases, relapses were seen, among whom, 61% (n ¼25) were treated by ABVD protocol and 34.1% (n ¼14) were treated by Hybrid protocol and 26.8% (n ¼11) administered by external radiotherapy. Results showed that 34.1% (n ¼14) and 65.9% (n ¼27) of patients had early and late relapse respectively. Patients who had recurrence less than 6 months after diagnosis categorized as early relapse. Late relapse group consisted of patients who had relapse more than 6 months after the diagnosis. Out of enrolled patients 26.1% (n ¼31) had BMT. BMT was done in 71% (n ¼22) and 25.8% (n ¼8) of cases after the first and second relapse respectively. One child had BMT and never conferred with relapse. He had been cured and is alive without any complication. In general, eight patients died, four of them were during treatment by ABVD protocol, three of them were during treatment by Hybrid protocol, and one patient was treating by other protocols who died because of bleeding. Other 7 patients died out of MPCTRC in their residential cities.

Table 1: Distribution of characteristics of patients with Hodgkin Lymphoma in MAHAK Children Hospital, Tehran, Iran.

Characteristics		Number	Percent
Gender	Male	22	55
	Female	18	45
Age	< 5 years	05	12.5
	5 yr to 9.9 yrs	18	45
	10 yr to 14.9 yr	12	30
	>15 yr	05	12.5
Stage at diagnosis	IA or IB	08	20

	IIA or IIB		15	37.5
	IIIA or IIIB		10	25
	IVA or IVB		07	17.5
Immuno histochemistry marker	CD 15	+ve	30	75
		-ve	10	25
	CD 20	+ve	10	25
		-ve	30	75
	CD 30	+ve	25	62.5
		-ve	15	37.5
Radiation	Given		20	50
	Not given		20	50
Relapse	yes		06	15
	no		34	85
Treatment protocol	BEACOPP		20	50
	ABVD		20	50

This table shows majority patients (n=30) are within 5 to 15 years.

Table 2: Distribution of symptoms according stage of disease in Hodgkin Lymphoma patients.

Symptoms		Stages								P value
		IA or IB		IIA or IIB		IIIA or IIIB		IVA or IVB		
		N	%	N	%	N	%	N	%	
Fever	+	8	20	15	37.5	20	50	25	62.5	0.689
	-	32	80	25	62.5	20	50	15	37.5	
Cough	+	0	0	5	12.5	10	25	8	20	0.042
	_	40	100	35	87.5	30	75	32	80	
Night sweat	+	5	12.5	10	25	15	37.5	15	37.5	0.607
	_	35	87.5	30	75	25	62.5	25	62.5	
Weight loss	+	4	10	20	50	10	25	15	37.5	0.474
	_	36	90	20	50	30	75	25	62.5	
Bone pain	+	2	5	0	0	0	0	3	7.5	0.0540
	_	38	95	40	100	40	100	37	92.5	
Pruritus	+	0	0	4	10	2	5	2	5	0.632
	_	40	100	36	90	38	95	38	95	
Dyspnoea	+	2	5	2	5	3	7.5	2	5	0.490
	_	38	95	38	95	37	92.5	38	95	
BM involvement	+	0	0	0	0	0	0	5	12.5	0.709
	_	40	100	40	100	40	100	35	87.5	

3.1. Association of HL symptoms with stage of the disease

There was no significant association between the stage and any of the symptoms, including fever, night sweats, bone pain, weight loss, and pruritus, and dyspnea. However, coughing had a significant relationship with the stage of the disease (p ¼0.044) (Table 2). Out of 10 patients who had cough as a symptom, five children had mediastinal mass and one case had pulmonary involvement.

3.2. Correlation of laboratory parameters with stage of the disease

The correlation between stage of the disease and laboratory parameters was only statistically significant in four of 18 parameters. Furthermore, there was a direct and significant correlation between the stage of the disease and Erythrocyte Sedimentation Rate (ESR; r ¼0.299, p ¼0.005), Ferritin (r ¼0.287, p ¼0.015) and Prothrombin Time (PT; r ¼0.247, p ¼0.019). There was also a significant and indirect relationship between the stage of the disease and Hgb (r ¼0. 0.254, p ¼0.008). Cut off hemoglobin level was 14.0e17.5 g/dL for males and 12.2e14.0 g/dL for females.

3.3. Treatment protocol

Limited stages (or low risk) include stage I and II and advanced stage (or high risk) includes stage III and IV. Fig. 1 shows the treatment plan for HL with different stages in this study. During the treatment of HL, 41 patients experienced relapse, 31 of whom were underwent BMT. Approximately all of the BMT-cases (97%) except one of them were successfully cured and got their recuperation, which means that BMT could be an effective treatment for relapse HL (Table 1).

Table 3: Overall Survival and Event-free Survival rate based on treatment protocol and risk of disease

Overall Survival						Event-free Survival			
Risk group	Regimen	3 years	5 years	7 years	P value	3 years	5 years	7 years	P value
Low risk	BEACOPP	95.7%	95.7%	95.7	0.05	88.4	85.3	76.4	0.049
	ABVD	100%	100%	100%		84.3	78.4	71.5	
Intermediate risk	BEACOPP	90.2	90.2	90.2	0.049	78.2	65.4	60.1	0.452
	ABVD	97.3	87.6	87.6		76.5	64.5	59.7	
High risk	BEACOPP	92.3	92.3	92.3	0.044	71.4	61.6	55.6	0.480
	ABVD	96.4	86.7	86.7		68.3	57.3	48.3	

3.4. Overall survival rate
The overall survival (OS) rate, 3-years, 5-years and 7-years were better in case of ABVD receiving group in all risk group then BEACOPP receiving group (Table 3).

3.5. Event-free survival rate
The event-free survival rate, 3-years, 5-years and 7-years were better in case of BEACOPP receiving group then ABVD receiving group (Table 3).

4. Discussion
From year 2018 to 2024, approximately 1200 children were registered with cancer diagnoses in DSH &I, and 40 of them were diagnosed with HL. HL is usually more prevalent at younger ages, and the average age of patients in the countries with a young population is expected to be relatively lower [11, 17]. In our study, the mean age of patients was 9.9. According to a systematic review study, incidence rates of HL varies geographically, which seems to be the lowest among Asian population [17]. According to the latest WHO reports, India is the first Asian country for high incidence of childhood HL [18, 19], while Bangladesh ranks as the 12th. In this regard according to international agency for research on cancer by World Health Organization (WHO), mortality due HL in Iran (0.07) is very low in comparison with other Asian countries (0.10) [20]. In addition, in our study, 40 of 1200 children diagnosed with cancer had HL, which is almost similar to the HL incidence reported by the GLOBOCAN. Due to poor data collection system and lack of diagnosis methods such as PET scan in the past, we failed to have access to accurate HL staging system, but this problem has been solved recently with the advent of these vital systems [11, 15]. In our study, like several other studies, more than half of patients were at stages I or II [2, 21]. A 2017-published article illustrates that the incidence of disease increases directly with high stages of HL [2]. In other studies, symptoms such as fatigue, fever and lymphadenopathy are very common in children with HL, which was similar to what we obtained in this study [11, 22]. Additionally, as a great number of our patients were diagnosed with mediastinal masses which are related to higher HL stages, coughing has shown a significant relationship with the stage of disease. In a retrospective cohort study of 469 newly diagnosed HL patients, cough has been reported significant among patients [23]. In most of studies, BMT is suggested as a treatment of cancer relapse, and can reduce the likeliness of further relapses and also mortality [14, 24]. Adult studies have shown that ABVD is effective for limited (5- year OS 96%e98%) [25-27] and advanced stages (5-year OS 84%e90%) of disease [28, 29]. In our study, low risk group patient having better OS and EFS in compared to high risk group. The ABVD protocol having better long-term result then BEACOPP protocol.

5. Conclusion
Treatment modalities based on staging is important for improving outcomes in HL. Treatment with ABVD protocol having better outcome in low-risk group in comparison to BEACOPP protocol.

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