Research Article
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Incidence and treatment outcome of childhood lymphomas in a tertiary care hospital of a developed country: a study in Combined Military Hospital Bangladesh

Abstract

Background: Over the years incidence of childhood cancer has been increasing. Being the third most common childhood malignancy, Lymphoma also achieved improved survival and reduced mortality along with other cancer in children & adolescents.

Objective: The objective of the study was to analyze the incidence and overall outcome of childhood lymphoma patients aged 0-12 years who attended Combined Military Hospital (CMH), Dhaka, a tertiary level hospital in Bangladesh.

Methodology: It was a retrospective cross-sectional study. All the children up to 12 years with a confirmed diagnosis of Lymphoma who received treatment from the Paediatric Oncology Unit of the Department of Pediatrics CMH, Dhaka were taken for analysis. Their data has been collected from hospital-based cancer registry records from 2016 to 2021. Their present status has been collected by phone call. Data has been collected and put on datasheet of MS-Exel 2019 and were analyzed using SPSS –VR 25, MS-Exel 2019.

Results: Over the study period, childhood lymphomas were found one of the commonest cancer, with an incidence of 10%. Of them Hodgkin Lymphoma (HL, 41%), and Non-Hodgkin Lymphoma (NHL, 59%). For both, the most common age group was '5 to 9 years age', females were predominance for HL & males were predominance in NHL. Histopathological analysis revealed the mixed cellularity variety of classical HL was the commonest; 71% of all HL. In case of NHL, 60% had Burkitt Lymphoma [BL] & 40% had Lymphoblastic Lymphoma [LL]. Immunohistochemistry of tumor masses revealed BL patients had B-Cell and all LL patients had T-cell. About 100% of patients agreed to start treatment and achieved remission but later on, 23.5% of them experienced a relapse. Overall survival was 76.5%. In case of HL 100% of patients survived, and 14% of them had relapsed. In case of NHL, 60% of patients survived [67% of BL & 50% of LL] and relapse was found in 30% of cases. Overall mortality rate was 23.5%, and all belonging to NHL represent 40% of all NHL patients.

Conclusion: With current therapeutic & supportive regimens childhood lymphoma patients have excellent improvement. Even being a developed country, 100% of patients achieved remission and only 23.5% had relapsed. Overall survival was 76.5%, in case of HL 100%, and NHL 60%. Mortality rate was only 23.5%, all belonging to NHL.

Keywords: Childhood Lymphoma, NHL, HL, overall survival, relapse

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Kamrun Nahar,[1] Ahmed Rashidul Hasan,[2] Shormin Ara Ferdousi,[3] Md Azizul Islam,[4] Afiqul Islam,[5] Chowdhury Yakub Jamal[6]

[1]Pediatric Hematology and Oncology, Associate Professor, Pediatric Oncology, Combined Military Hospital, Rangpur, Bangladesh
[2]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh
[3]Child Specialist and Fellow Pediatric Oncology Combined Military Hospital, Dhaka, Bangladesh
[4]Consultant Physician General, Bangladesh Armed Forces, Directorate General of Medical Services, Ministry of Defense, Dhaka, Bangladesh
[5]Pediatric Hematology and Oncology, Professor, Dept. of Pediatric Hematology and Oncology, Bangabandhu sheikh mujib medical university (BSMMU), Dhaka, Bangladesh
[6]Dept. of Pediatric Hematology and Oncology, Bangabandhu sheikh mujib medical university (BSMMU), Dhaka, Bangladesh

Correspondence: Kamrun Nahar MBBS, FCPS (Pediatric Hematology and Oncology), Classified Specialist Pediatric Oncology, Combined Military Hospital, Rangpur, Bangladesh, Tel 8801711220833, Email drka_nahar2006@yahoo.com

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Introduction

Cancer is cruel and spares no age. Worldwide, every 3 minutes a child is diagnosed with cancer.[1] Even countries like the United States estimated that for the year 2021 they would have about 10,500 new diagnosed cases of childhood cancer and about 1,190 children are expected to die from the disease [children from birth to 14 years of age group].[2,3] This incidence varies worldwide between 50 and 200 per million children.[4] With the advantage of modern advanced treatment approach death rates for this age group have declined by 70% from 1970 to 2016.[1] But still, it remains the leading cause of death in children,[2] globally causing around 90,000 deaths per year.[1] The most common types of cancer seen in children are Leukemia, followed by Brain and other central nervous systems (CNS) tumors, Lymphomas, Neuroblastoma, Renal tumors, Liver tumors, and malignant bone tumors.[2,3] WHO reported approximately 84% of childhood cancer cases under 15 years old belong in low-income and middle-income countries (LMICs).[5] In Bangladesh, the incidence rate is also alarmingly high. Here it became one of the major causes of mortality and morbidity among the non-communicable diseases.[6] Overall incidences are estimated to be 13,000 cases per year,[7] but fewer than 500 children received treatment.[8] World child cancer estimated that every year around 9,000 to 12,000 children get cancer in Bangladesh but only one-third receive a proper diagnosis and treatment.[9] Most of them die without correct diagnosis and adequate medical treatment.[5]

Lymphoma (cancers of the lymphatic system), is the 3rd most common malignant tumor in children and adolescents in precedence of leukemia and CNS tumor;[2,10,11] its prevalence is 7% of childhood cancers.[10–12] Two types of lymphomas are found - Hodgkin's disease (Hodgkin lymphoma; HL) makes up 6%[13] and Non-Hodgkin's lymphoma (NHL) represents 6-8%[11] of cancer in children under 14.[12–16] In 2021 in the US, an estimated 945 new cases of lymphoma are

expected to be diagnosed in children and adolescents younger than 15 years, accounts approximately for 9% of all cancers expected to be diagnosed in this age group.[16] The UK estimated it at 10%.[17] In children younger than 15 years, the age-adjusted incidence rate for NHL (1.1 per 100,000) is higher than for HL (0.6 per 100,000).[12,16,18] HL prevalence with bimodal age incidence curve with one peak at 15-35 years of age and the other above 50 years of age; incidence is highest among 15 to 19 years old.[13] Median age of NHL presentation is 10 years and incidence increases with age[12,15] and rare to have cases under 3 years of age, quite unlikely in infants.[12] Both HL & NHL are male predominance, and incidence in white children are more common than in African Americans.[13,15] Childhood HL is one of the few pediatric malignancies that share aspects of its biology and natural history with adult cancer.[13] They usually have two pathological subtypes:[19,20] Classical HL and Nodular lymphocyte-predominant HL. This classical variety again has four subtypes; Nodular-sclerosing HL (80%), Mixed-cellularity HL (20%), Lymphocyte-rich HL, Lymphocyte-depleted HL.[21] Characteristic multinucleated giant cells (Hodgkin and Reed-Sternberg [HRS] cells) or large mononuclear cell variants are concentrated in the cancerous lymph node.[13] NHL comprises a heterogeneous group of lymphoid neoplasm. The vast majority (70%)[22] of childhood NHL are high-grade tumors with aggressive clinical behavior.[10,23,24] Unlike adults, mostly they are typically extra-nodal, with early widespread dissemination to bone marrow and CNS.[25] The distribution of subtypes according to WHO Classification of Tumors of Haematopoetic and Lymphoid Tissues is significantly different in children and adults.[26] In children, Lymphoblastic lymphoma (LBL/LL) 23%, Burkitt lymphoma (BL) 60%, and anaplastic large-cell lymphoma (ALCL) 17% are predominate,[24] while the proportion of diffuse large B-cell lymphoma (DLBCL) increases with increasing age.[27] The typical features exhibit significant differences in terms of their molecular and cellular biology and clinical features, which may be crucial for determining therapeutic strategies.[27] The five-year relative survival rate has risen to 99% for HL,[18] and 85-95% for NHL.[16] Different lymphoma required different treatment strategies based on their biological characteristics.[27] Relapse still occurs and is the principal cause of treatment failure.[28]

Despite the high cure rates in developed countries, the success is not mirrored in resource-poor countries. Being a limited resource country, we also have poor reported cases and inferior survival. Currently, we do not have any population-based cancer registries in Bangladesh. For this, the overall incidence of childhood cancer is largely unknown. This study looks into the prevalence of childhood lymphoma and its outcome in Combined Military Hospital, Dhaka.

Materials and method

This retrospective cross-sectional study was conducted in the Paediatric Oncology Unit of the Department Paediatric in Combined Military Hospital (CMH), Dhaka, Bangladesh. We here enrolled all the diagnosed confirmed cases of childhood lymphoma cases below 12 years of age from 2016 to 2021 and observed them for analysis. The data were collected after obtaining informed written consent from parents. The results were analyzed using computer software (Microsoft Excel 2019 & SPSS version 25). It is to be mentioned that, paediatric dataset included data from the paediatric cancer registries collecting data in children below 15 years but here in our study we collected data for children who have completed 12 years of age because our department is designated for 0 to 12 years age group. All patients had undergone pre-treatment evaluation including a complete history and physical examination, investigations including imaging, and cytospin analyses of malignant effusions. Histopathological findings were taken as for diagnostic including immunohistochemistry for some cases. Then we provide specific & supportive management to all the patients following a multidisciplinary approach to risk-adapted protocol-based treatment therapy. Their overall treatment status was analyzed. Inclusion criteria set for the patients were a. Children up to 12 years b. New confirmed cases suffering from Lymphoma c. Patient completed treatment d. patient treated only in Department Pediatric in Combined Military Hospital. Exclusion criteria set for this patients were a. Children aged more than 12 years b. Patient refused or abandoned treatment d. patient partially treated in other hospital.

Results

During this study period, a total of 170 newly diagnosed childhood cancer patients came to Pediatric oncology unit. Disease distribution among these enrolled patients was haemopoietic cancer 102 (60%) and solid tumor 68 (40%). Out of them, the most common cancer was childhood leukemia (52.4%), CNS tumor (12%) and lymphoma was 10% of patients. Other common cancers were Neuroblastoma, Liver tumor, Renal tumor, etc. The present analysis was done with childhood lymphoma patients.

The distribution of childhood cancer showed in figure 1, here haemopoietic cancer 60% and solid tumor 40%. Among our study population, 17 out of 170 childhood cancer patients were diagnosed with Lymphoma, with a prevalence of 10%. Following inclusion & exclusion criteria all 17 patients were selected for analysis. Here figure 2 showed that out of 17 patients, 10 (58.8%) were suffering from NHL and 7(41.2%) had HL.

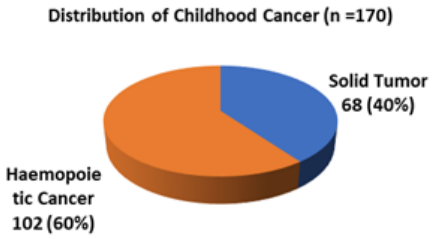

Figure 1 Distribution of Childhood Cancer (n=170).

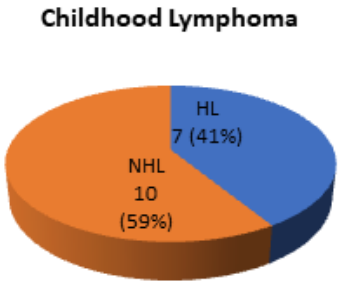

Figure 2 Distribution of Childhood Lymphoma (n=17).

Table 1 showed among all patients with childhood lymphoma, 53% were male and 47% were female. Males were predominant, with a male-female ratio of 1.13:1. In case of HL, male 43%, female 57% & M: F 1:1.3. In NHL, male 60%, female 40% & M:F 1.5:1

Their age group distribution showed, among all lymphoma cases '5-9 years' age group consists of the highest incidence, 47% patients followed by '0-4 years' [29.4%] & '>10 years age' group [23.6%]. When only HL patients were analyzed, the most prominent group found '5-9 years age group' consisting of 43%. Rest two groups had

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28.5% patients in each. In NHL patients, the most prominent group was patients in '5-9 years' group, consisting of 50%. Patients of '0-4 years age' is 30% and '>10 years' age group was 20%.

Lymphomas were diagnosed mainly by histopathology of tumor masses. Table 2 showed the histopathological analyses of enlarged lymph nodes or masses of all patients. In case of HL, 71% had mixed cellularity variety of classical HL, 14% had Nodular lymphocyte predominant HL (NLPHL), and 14% of patients' histopathological subdivisions were not ruled out. In case of NHL, 60% had BL & 40% had LL.

About 8 patients did immunohistochemistry of tumor tissue, here table 3 showed among them, 50% had mature B-cell considering BL and 50% had T-cell suggestive LL.

Here in Table 4, their overall treatment status was analyzed. We found that about 100% of patients received treatment. No patient refused or abandoned, but we lost one patient (HL) for follow-up. Overall survival was 76.5% and relapse was found in 23.5% of patients. In case of HL 100% of patients survived, and 14% of them had relapsed. In case of NHL, 60% of patients survived [67% of BL & 50% of LL] and relapse was found in 30% of NHL cases. Overall mortality was 23.5%, all belonging to NHL representing 40% of all NHL patients.

Relapse was seen in 4 [23.5%] patients. Of them 1 had HL [14.3% of HL] and 3 had NHL [30% of NHL]. The relapsed HL patient continuing his treatment with relapse protocol. Among these relapsed cases of NHL, 2 had T-cell and one had B-cell variety of NHL. They failed to survive due to disease progression.

Here table 5 showed among 10 NHL patients, 6 were BL & 4 were LL patients. All patients received treatment and achieved remission. Among BL patients, 17% had relapses, 33.33% of patients expired, and the rest 67% alive. Among LL patients, 50% had a relapse, expired 50%, and the rest 50% of patients were alive until the last follow-up.

Here Figure 3 showed that overall survival was 13 (76.5%) patients out of 17, with HL 7 [100%], and with NHL 6 [60%]. About 4 [23.5%] patients expired; all were suffering from NHL. In case of NHL, 60% of patients were alive and 40% expired.

Table 1 Demography and survival status of Childhood Lymphoma

Trait		Childhood Lymphoma (n=17)		HL (n=7)		NHL (n=10)	
		Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Gender							
	Male	9	52.94%	3	42.86%	6	60%
	Female	8	47.06%	4	57.14%	4	40%
	Male: Female	1.13:1		1:1.3		1.5:1	
Age							
	0-4 yrs	5	29.40%	2	28.57%	3	30%
	5-9 yrs	8	47.05%	3	42.86%	5	50%
	>10 yrs	4	23.55%	2	28.57%	2	20%

Table 2 Histopathological findings of Childhood Lymphoma

Disease – HL	Frequency (n=7)	Percentage	Disease – NHL	Frequency (n=10)	Percentage
HL (not defined)	1	14.30%	Burkitt Lymphoma	6	60%
Mixed cellularity HL	5	71.40%	Lymphoblastic Lymphoma	4	40%
NLPHL	1	14.30%			

Table 3 Immunohistochemistry findings of NHL (n=8)

Disease – NHL	Frequency (n=8)	Percentage
NHL– B cell	4	50%
NHL – T cell	4	50%

Table 4 Treatment status of Childhood Lymphoma

Trait	Childhood Lymphoma (n=17)		HL (n=7)		NHL (n=10)	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Rx received	17	100.00%	7	100%	10	100%
Relapse	4	23.5%	1 (on Rx)	14.3%	3 (1 B-cell, 2 T- cell)	30%
Expired	4	23.5%	0	-	4 (3 relapsed cases, 1 due to disease progress)	40%
Lost to follow up (FU)	1	5.88%	1	14.3%	0	0
Alive	13	76.5%	7	100%	6 regular fu	60%

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Table 5 Treatment status of Childhood NHL

Trait	NHL (n=10)		Burkitt Lymphoma (BL) (n=6)		Lymphoblastic lymphoma (LL) (n=4)	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Rx received	10	100%	6	100%	4	100%
Remission achieved	10	100%	6	100%	4	100%
Relapse	3	30%	1	16.67%	2	50%
Expired	4	40%	2 (1 relapse, 1 due to disease progress)	33.33%	2 (relapsed)	50%
Lost to follow up (FU)	0	0	1	16.67%	-	-
Alive	6	60%	4	66.67%	2	50%

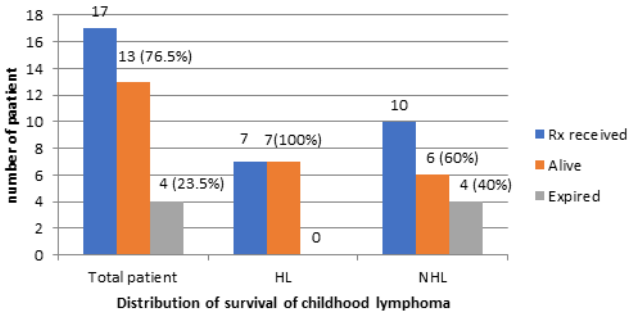

Figure 3 Survival status of Childhood Lymphoma (n=17).

Discussion

Every year new cases of childhood cancer exceed 2 million globally and a majority of them (>80%) belong to the developing world.[29,30] In developing countries every year childhood cancer happens to be increases by 30%.[31] The situation of our country's children with cancer is similar to other developing countries.[32] Still now no national population-based childhood cancer registry is available for us.[33,34] According to World Child Cancer Report 2005, Bangladesh has some 1.3 to 1.5 million childhood cancer patients.[31,35] Over time, childhood and adolescent cancer incidence has increased in CMH Dhaka too. Ferdousi et al. reported per year average of 17 malignant cases came to the pediatric oncology unit of CMH Dhaka. The overall incidence rate is about 3.6 per ten thousand per year.[36] This increasing rate of childhood cancer might be due to improved reporting of cases in recent years. GLOBOCAN 2018 reported worldwide that childhood lymphoma appears to be one of the most common cancers in children aged 0-14 years.[37] BSMMU reported NHL were 11% & HL was 3% of children with cancer in their one-year study.[35] With this study in our pediatric oncology unit we observed that 17 out of 170 childhood cancer patients were diagnosed with Lymphoma, prevalence was 10%. Of them, 7 (41%) were suffering from HL, and 10 (59%) were from NHL. This result is similar to the findings of Ferdousi et al.[36] Jabeen S et al reported childhood cancer was 4.4% of total cancers cases in National Institute of Cancer Research & Hospital (NICRH), among them Lymphomas were the most prevalent malignancies, accounting for 24.2%.[38] Khasru et al.[32] and studies from some other developed countries found lymphoma with 8-15% prevalence.[33,38-41] Jabeen S et al. & Hossain MS et al.[33] also found NHL in higher proportion (70%) comparison to HL. In the USA, lymphoma was reported as the 3rd most common cancer in CH prevalence of HL accounts for 6%[13] & NHL 7%.[15] In the UK, 11% children had lymphoma; HL 45% & NHL 55%.[42]

In our study, gender-wise distribution showed male was predominance (53%) over female (47%) with a ratio of 1.13:1. In case of HL, male 43%, female 57% & M: F 1:1.3. In NHL, male 60%, female 40% & M:F 1.5:1. Asthana et. al found a ratio of female to male cases for lymphoma ranged from 1:1.0 to 1:4.1.[43] Huang MS et al said incidence of NHL were 2-3 times higher in male children in comparison to female.[12] Jabeen S et al,[40] NCI & ASCO also reported similar.[15,18] Friedman said overall there is a slight female predominance in children younger than 20 years having HL which is similar to our study result.[44] but NCI reported HL is a male predominance.[13] In our study, age group distribution showed, in case of all lymphoma cases '5-9 years age' group consists highest 47%, followed by '0-4 years' [29.4%] & '>10 years age' group [23.6%]. When only HL patients were analyzed, the most prominent age group found '5-9 years age' consisting of 43%. Rest two groups had 28.6% patients in each. In case of NHL patients, the most prominent group was patients in '5-9 years age' group, consisting of 50%. Patients of '0-4 years age' is 30% and '>10 years' age group was 20%. These gender and age distributions were quite similar to studies done in India & Pakistan.[29,45] Hossain MS et al reported that 80% of lymphoma cases were diagnosed in children aged between 5 to 14 years with a median age of 7 years and the age distribution was similar for NHL and HL.[33] In the UK boys suffer both types of lymphomas twice than girls.[42,46] There HL predominantly affects older children, with 2/3rd in 10-14 year age group and no cases in infants.[42] Jabeen S et al. found the frequency of HL was higher in the 10-14 years age group.[38] NHL affects all ages but is very rare among infants; incidence increases with a peak age of 4 years.[46] In developing countries, there is a much higher incidence rate in childhood but in the US highest incidence is seen in adolescents aged above 15 years.[47] Younger the age group higher the chance of male predominance.[13,48]

Lymphomas were diagnosed mainly by histopathology of tumor masses. The hallmark of HL is a variable number of characteristic multinucleated giant cells (HRS cells) or large mononuclear cell variants (lymphocytic and histiocytic cells).[49] Almost all cases of HL arise from germinal center B cells.[50] They are two histologic variants of HL: [44]

I. Classical HL includes the Nodular Sclerosis classical HL [74%], mixed cellularity HL (MCHL) [16%], lymphocyte-depleted and lymphocyte-rich classical HL subtypes.

II. Nodular lymphocyte-predominant HL [NLPHL] (5-10%), with a higher frequency in under 10 years aged children.[21]

In our study, among HL cases, 71% had MC variety classical HL, 14% had NLPHL, and in 14% of cases, histopathology was not differentiated. NCI reported, that in young childhood HL, nodular sclerosing was 40-45%, mixed cellularity 30-45%, and NLPHL 8-10%.[13] Immunophenotypically, HRS cells almost always express CD30, CD15 (70%), and CD20 (6-10%) & do not express B-cell antigens [e.g., CD45, CD19, and CD79A].[51-52] Incidence and subsites distribution of NHL vary throughout the world. Based

on immunophenotype, molecular biology, and clinical response to treatment, most NHL cases occurring in childhood and adolescence fall into three categories: a) Mature B-cell NHL e.g i. Burkitt lymphoma/ leukemia (19%), ii. Diffuse large B-cell lymphoma (DLBL), and iii. Primary mediastinal B-cell lymphoma (PMBL); DLBL & PMBL together consists of 22% b) Lymphoblastic lymphoma – both T & B-LL comprise about 20% c) Anaplastic large cell lymphoma (10%).[15] Our study found that among NHL patients, 60% had BL & 40% had LL. In the US, BL/leukemia accounts for 40% of childhood NHL.[23,24] Immunohistochemistry done in 8 NHL patients, 50% found having B-Cell [mature B lymphoblasts, enzyme terminal deoxynucleotidyl transferase (TdT) negative, express surface immunoglobulin (sIg), CD10, CD19, CD79a, CD22] considering BL and all 4 LL patients had T-cell NHL [T lymphoblasts (TdT, CD2, CD3, CD7, CD4, CD8 positive)], 50% cases.[23,24]

Treatment plans for childhood lymphoma were decided by a multidisciplinary team of cancer specialists based on the histologic subtype of the disease. Their overall treatment status was analyzed and found, that 100% of our childhood lymphoma patients received treatment. No patient refused or abandoned. Over the years dramatic improvements in survival have been achieved for children and adolescents with cancer.[53] Overall survival rate raised to 98% for HL[47] and 90% for NHL in children under 15 years.[23,24] American Cancer Society estimates, in case of HL overall survival was 97% & for NHL was 85%.[18] A study in India found survival was lower to 20% for HL and NHL compared to other developed countries.[40] In our study, the overall survival was 76.5%; 100% of HL & 60% of NHL patients survived. A study done in Cameroon found 5-year overall survival rate for HL was 74% and 51% for NHL which is similar to our result.[54] Here in this study relapses were seen in 4 cases which belongs to 23.5% of all lymphoma cases; of them 1 had HL [14%] and 3 had NHL[30% of NHL]. The relapsed HL patient is still alive and corresponds to 14.3% of HL, which is similar to Friedmann et al.'s study.[55] In case of NHL, 3 [30% of NHL] patients experienced relapse and 100% of them failed to survive due to disease progression. Two had T-cell variety and one had B-cell variety of NHL. NCI reported survival rate of recurrent or refractory aggressive mature B-cell NHL was 10-50%, mostly 20%.[56,57] and for recurrent or refractory LL survival was10-40%.[56,58,59]

Over the years childhood cancer mortality has been declining. In our study, overall mortality was 23.5%, and all of them belong to the NHL variety which constitutes 40% of all NHL. Ketchen D also found a similar result for NHL.[54] There was no mortality for HL which is also supported by NCI's report.[47]

Conclusion

This study found the prevalence of childhood lymphoma is 10%, among them NHL was 59% & HL was 41%. For both, the most common age group was '5 to 9 years age', females were predominance for HL & males were predominance in NHL. Mixed cellularity varieties of HL were most commonly found (71.4%). In case of NHL, 60% were Burkitt Lymphoma & 40% were Lymphoblastic lymphoma. About 100% of patients received treatment; overall survival was 76.5% and relapse was found in 23.5% of patients. In case of HL 100% of patients survived, and 14% of them had relapsed. In case of NHL, 50% of patients survived [67% of BL & 50% of LL] and relapse was found in 30% of NHL cases. Overall mortality was 23.5%, all belonging to NHL representing 50% of all NHL patients.

Recommendation

Even with the limited facilities childhood malignancies are now having a high curable rate. With the help of dedicated pediatric cancer registry assessing the magnitude of the problem in our country would be clear which will benefit us for future progress.

Conflicts of interest

Conflict of interest relevant to this article was not reported.

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