ORIGINAL ARTICLE

Incidence and Outcome of Childhood Acute Leukemia in A Tertiary Care Hospital of Bangladesh Armed Forces

Kamrun Nahar[1], Shormin Ara Ferdousi[2], Ahmed Rashidul Hasan,[3]Afiqul Islam,[4]Azizul Islam[5]

Abstract

Background: *Worldwide cancer is the second leading cause of death in children under 15 years and acute leukemia is the most prevalent cancer among children.*

Objective: *The objective of the study was to analyze the incidence and overall outcome of childhood leukemia patients aged 0-12 years in Combined Military Hospital (CMH), Dhaka.*

Methods: *It was a retrospective cross-sectional study. Children below 12 years of age with confirmed diagnosis of leukemia and received treatment from the paediatric oncology unit of department of paediatrics of CMH, Dhaka were taken for this study. Data has been collected from Hospital based cancer registry records from 2011 to 2021. There present status has been collected from regular OPD or by phone calls.*

Results: *The commonest cancer was found Acute Leukemia (52%), among them Acute Lymphoblastic Leukemia (ALL) 83.15% and Acute Myeloid Leukemia (AML) 16.85%. Morphological (FAB classification) sub-divisions revealed ALL-L2 (31%) was the commonest group for ALL. In case of AML, AML-M3 (APML) was the commonest (27%). Immunophenotyping of cells revealed Pre-B ALL was the commonest. Cytogenetic analysis revealed ETV6-RUNX1 (21%), t(1;19) ((q23,p13) E2A/PBX1 (11%) were two most common genetic abnormalities found in ALL and t(15;17) (q22;q12) M3,M3v PML-RARA was the commonest cytogenetic abnormalities and (8;21) (q22;q22) RUNX1/RUNX1T1 for AML. In case of ALL overall survival was 54% and in case of AML 40%. About 10% of patients reported relapses.*

Conclusion*: Incidence of acute leukemia was the highest among all childhood cancer. At the end of the study, overall survival was 52% of cases, and relapses were seen in 10% of cases.*

Keywords: *Childhood leukemia, cytogenetics, demographic profile, immunophenotyping.*

DS (Child) HJ 2022;38(1):17-26
DOI: https://doi.org/10.3329/dshj.v38i1.66997

1. Classified Specialist in Paediatric Oncology, Department of Paediatrics, Combined Military Hospital, Dhaka.
2. Head of the Department, Pediatric Hemato-Oncology, Gonoshasthaya Samaj Vittik Medical College & Gonoshasthaya Nogor Hospital, Dhaka, Bangladesh.
3. Register, Department of Paediatric Gastroenterology, Hepatology and Nutrition, Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh.
4. Professor, Department of Paediatric Hematology and Oncology, Labaid Cancer Hospital & Super Speciality Center, Dhaka, Bangladesh.
5. Consultant Physician General, Bangladesh Armed Forces, Directorate General of Medical Services, Ministry of Defense, Dhaka, Bangladesh.

Correspondence to: Dr. Kamrun Nahar, Classified Specialist Paediatric Oncology, Combined Military Hospital, Dhaka. Cell: 01711220833, E-mail: drka_nahar2006@yahoo.com
Received: 2 January 2022; **Accepted**: 12 April, 2022

Introduction

Cancer is cruel and spares no age. A cancer diagnosis is upsetting at any age, but especially so when the patient is a child. Even countries like the United States estimated that for the year 2021 they would have about 10,500 newly diagnosed cases of childhood cancer and about 1,190 children are expected to die from the disease.[1,2] This incidence varies worldwide between 50 and 200 per million children[3], and ranked the leading cause of death.[1] The most common types of cancer seen in children are leukemia, followed by brain and other central nervous system (CNS) tumors, lymphomas, neuroblastoma, kidney tumors, and malignant bone tumors.[1] Childhood cancers are neglected in developing countries, even though approximately 84% of the cancer cases under 15 years old occur in low-income and middle-income countries (LMICs).[4] In Bangladesh, the incidence of paediatric cancer is alarming and most of these patients die without a correct diagnosis and adequate medical treatment.[5] It is now one of the major causes of mortality and morbidity among non-communicable diseases in Bangladesh.[6] The overall incidence of childhood cancer in Bangladesh is largely unknown, due to population-based cancer registries are still unavailable.[7,8] It is estimated around 13,000 new cases per year,[9] but fewer than 500 children receive hospital based treatment annually.[10] 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.[11] The proportion of childhood cancers is expected to be high because of the young population structure, at present about 30% (47.4 million) of the population is under 15 years of age.[10]

Leukemia is the most common type, accounting for about 25-30% of total cancer in children less than 15 years of age.[12] It accounts for 27% of childhood cancers in the United States,[13] 30% in France[14] and Ireland,[15] 33% in Germany,[16] 35% in Shanghai, China[17], and 76% in Chennai, India.[18] Acute leukemia (cancer of blood cells) represents a clonal expansion and arrest at a specific stage of normal myeloid or lymphoid hematopoiesis. They constitute 97% of all childhood leukemia. It consists of two main types - acute lymphoblastic leukemia (ALL), accounting for 75%, and acute myeloid leukemia (AML) is about 20%. It can occur at all ages, from birth to adulthood, but the peak incidence is between 2 and 6 years of age. Improvements in treatment have led to remarkable gains in survival, estimated at 79% at 5 years.[12] The outcome is poorer for acute myeloid leukemia (AML) than for acute lymphoblastic leukemia (ALL), with a 5-year survival rate of 41%. Risk factors of childhood leukemia are barely known, highly probable of the interaction of environmental and genetic factors.[19]

In Bangladesh, the overall cancer burden including adolescent and childhood cancer is largely unknown due to the nonexistence of population-based cancer registries.[6-8] The objective of the study was to analyze the incidence and overall outcome of childhood leukemia patients aged 0-12 years in Combined Military Hospital (CMH), Dhaka, Bangladesh.

Materials and Methods

This retrospective cross-sectional study was conducted in the Paediatric Oncology Unit of the Department of Paediatric in Combined Military Hospital (CMH), Dhaka, Bangladesh. We here enrolled all the diagnosed cases of childhood leukemia below 12 years of age from 2011 to 2021 from our hospital-based cancer registry and analyzed them. The data were collected after obtaining informed consent from parents. The data were then put on computer software MS office Excel datasheet and 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 because our department is designated for the 0 to 12 years age group. Here inclusion criteria were a) all newly diagnosed acute leukemia patients b) age completed 12 years And exclusion criteria were a) age above 12 years and b) patient having a relapse.

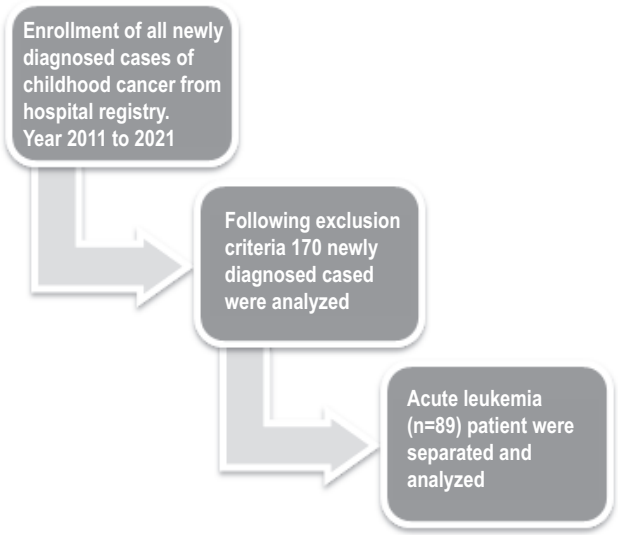

Fig.-1 *Scheme review of data analysis*

Results

During this study period of 11 years, a total of 170 newly diagnosed childhood cancer patients came to the Pediatric Oncology unit. Among these enrolled patients, haemopoietic cancer 102 (60%) and solid tumor 68 (40%) [Fig.-2]. Disease distribution analysis showed most common cancer was childhood leukemia 52.4%, and lymphoma was 7.65%. Other common cancers were CNS tumors, Neuroblastoma, Liver tumors, Renal tumors, etc. The present analysis provides a gist of the incidence of our main childhood cancer, leukemia.

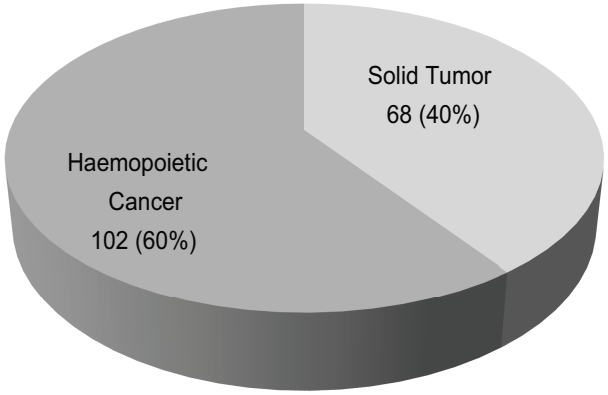

Fig.-2 *Distribution of Childhood Cancer (N=170)*

Distribution of childhood cancer showed that haemopoietic cancer was found in102(60%), and solid tumor in 68(40%) cases (Fig.-2).

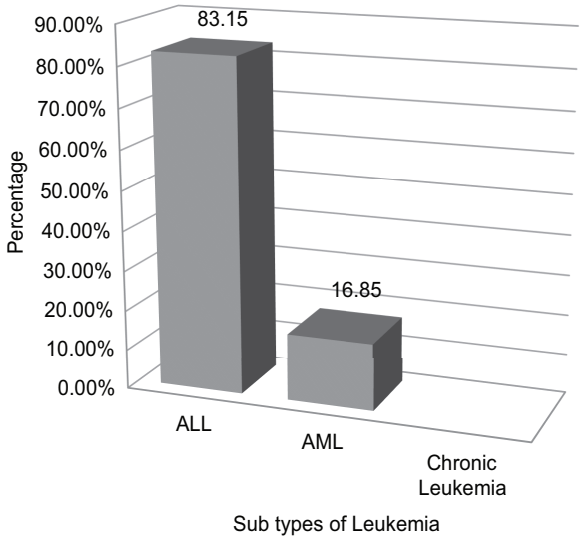

Fig.-3 *Distribution of Childhood Leukemia (n=89)*

Among all leukemia patients, ALL were 83.15%, AML 16.85%, and no patient was diagnosed with chronic leukemia (Fig.-3).

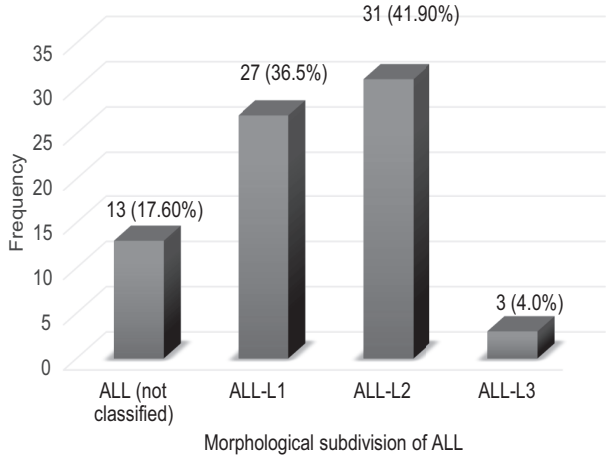

Fig.-4 *Distribution of ALL (n=74) based on French-American-British (FAB) morphological classification*

In Fig.-4 further sub-division of the 74 ALL patients were done according to their morphological findings based on French-American-British (FAB) classification. Here, L1 was 36.5%, L2 was 41.9% (most common) and L3 was 4%. Rest 17.6% were not classified.

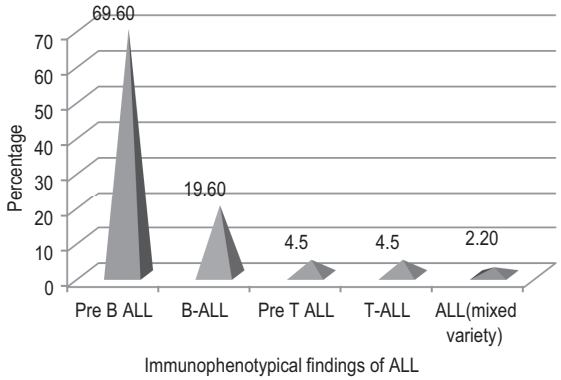

Fig.-5 *Distribution of Immunophenotyping (IPT) analysis of ALL (n=46)*

Immunophenotyping (IPT) findings of ALL (n=46) showed that Pre-B-ALL was the most common presentation (69.60%) (Fig.-5).

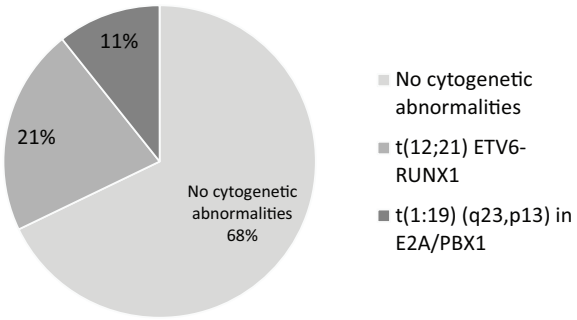

Fig.-6 *Cytogenetic Abnormalities in ALL (n=28)*

Cytogenetic analysis reported in 28 ALL patients showed majority of the patient (68%) had no genetic abnormalities. Most common abnormalities found ETV6-RUNX1 fusion genet(12;21) (p13q22). t(12;21), [TEL-AML], were positive in 21%patients. Abnormalities of t(1:19) (q23, p13) in E2A/PBX1 gene were present in 11% of patients of ALL having B-Cell (Fig.-6).

Next we evaluated 15 patients who were diagnosed with AML, accounting for 16.85% of our acute Leukemia cases.

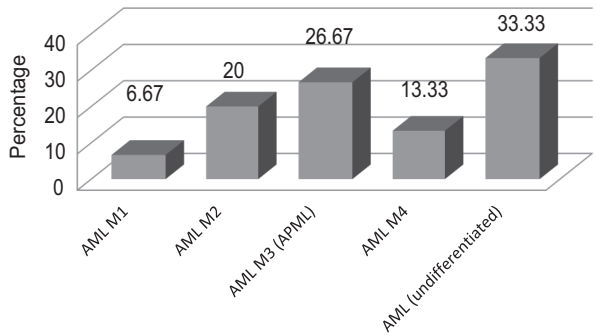

Fig.-7 *Distribution of AML based on FAB classification*

Distribution of AML patients according to FAB classification showed M1 (6.67%), M2 (20%), M3 (26.67%), M4 (13.33%), and 33.33% patients were not categorized in any group. IPT was done in 53% of cases; of them, APML alone was 50% & other myeloid groups of cells were represented in rest 50% of patients (Fig.-7).

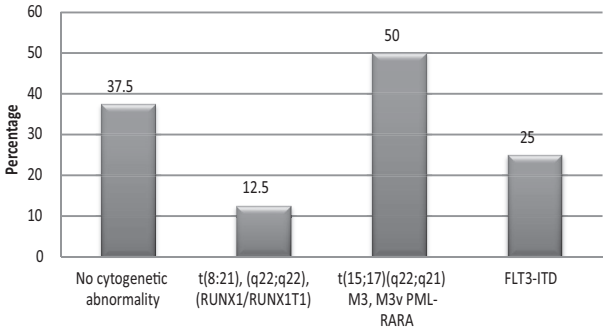

Fig.-8 *Cytogenetic analyses of AML (n=8)*

Cytogenetic analyses of AML showed, 37.5% had no abnormalities. About 50% had t(15;17)(q22;q12) PML-RARA gene fusion, FLT3-ITD mutation or point mutations in 25% and 12.5% had t(8:21), (q22;q22), (RUNX1/RUNX1T1) was positive (Fig.-8).

Table I
Gender and age distribution of Acute Leukemia with histological subtypes (N=89)

Age & Gender	Acute leukemia (n=89)		ALL (n=74)		AML (n=15)	
	Number	Percentage	Number	Percentage	Number	Percentage
Gender						
Male	49	55	43	58	6	40
Female	40	45	31	42	9	60
M: F	1.23:1		1.4:1		0.66:1	
Age Group						
0-4 years	44	49.44	40	54.05	4	26.67
5-9 years	35	39.32	25	33.78	10	66.67
>10 years	10	11.24	9	12.16	1	6.67

Table-I showed demographic characteristics of all studied cases. Gender distribution analysis revealed in case of ALL, males were predominance (58%) and in case of AML, females were predominance (60%). In general their age distribution revealed '0-4 years age group' was most common group. Median age was 5.7 years. But in separate analyses ALL found more in '0-4 years age group' (54%) whereas in case of AML, most common group was '5-9 years age group' accounting 66.7%.

Table II
Distribution of Infantile Leukemia

Leukemia	Number	Percentage
Infantile AML	1	1.12
Infantile ALL	4	4.50
Acute Leukemia more than 1 year of age	84	94.38

Here in Table-II, infantile acute leukemia (Leukemia diagnosed below 1 year of age) were found in 5.6% of all leukemia cases. Of them, 4.5% of patients were suffering from ALL and 1.12% patients had AML.

Table III
Distribution of Acute leukemia with Down syndrome (DS)

Disease	Number	Percentage
AML with DS	1	1.12
ALL with DS	1	1.12
Acute leukemia not associated with DS	87	97.76

Table III showed among all acute leukemia patients 2 had Down syndrome. Of them ALL 1.12%, and AML 1.12%.

Table-IV revealed among the 89 patients with acute leukemia, 91% of patients started receiving treatment. About 4.5% of patients refused to do it. Other 4.5% of patients presented with advanced disease and had an early death. On the day of last follow-up (10th Jan 2022), about 51.7% of patients are alive and 41.55%of patients has been expired. About 10% of patients reported relapse and 6.75% were lost to follow-up. In case of ALL, 90% of patients started treatment, but 5% of patients refused treatment, and 5% of patients experienced an early death. Overall survival of ALL 54%. Among AML 100% of patients started treatment, but only 40% of patients survived. Overall mortality is 39% in ALL, and 53.3% in AML.

Table IV
Treatment status of Childhood Acute Leukemia

Treatment status	Acute Leukemia (n=89)		ALL (n=74)		AML (n=15)	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Rx received	81	91.0	66	89.19	15	100
Refused treatment	4	4.5	4	5.4	0	0
Early death	4	4.5	4	5.4	0	0
Alive	46	51.70	40	54	6	40
Relapse	9	10.11	8	10.81	1	6.66
Expired	37	41.55	29	39.2	8	53.33
Lost to follow up	6	6.75	5	6.8	1	6.66

Discussion

Every year new cases of childhood cancer exceed 2 million globally and the majority of them (>80%) belong to the developing world.[20,21]In developing countries every year childhood cancer happens to be increased by 30%.[22] The situation of our country's children with cancer is similar to other developing countries.[23] Still now no national population-based childhood cancer registry is available for us.[24,25] According to World Child Cancer Report 2005, Bangladesh has some 1.3 to 1.5 million childhood cancer patients.[23,26] Available scenario in nearby countries like Pakistan incidence is 100 per million and in India, it is 64 per million in <15 years of age.[27,28] In India, cancer is the 8th most common cause of death among children between 5 and 14 years of age, covering 2.9%.[29] In 2010, the national pediatric cancer death rate was 39 for children aged 0 to 14 years.[30]

Over the last 11 years, 170 newly diagnosed childhood cancer patients admitted to CMH Dhaka. Ferdousi et al[31] reported, that per month around 5000-5500 visits happen in child OPD of CMH Dhaka. Per year average of 17 malignant cases came to the paediatric oncology unit. The overall incidence rate is about 3.6 per ten thousand per year, among them ALL 8 patients per year (1.7 per ten thousand per year), CNS tumors 1.4 patients per year (0.29 per ten thousand per year) and other solid tumors were 6.6 patients/year (1.4 per ten thousand per year).[31] Over time, childhood and adolescent cancer incidence has increased mostly due to improved referring knowledge. GLOBOCAN 2018 reported worldwide leukemia (32.5%) appears to be the most common cancer in children aged 0-14 years. The highest incidence was recorded in Asia (62.6%).[32] The next common cancer was CNS tumor and Lymphoma. Over one-year (2012) BSMMU found 68% Acute leukemia cases (ALL 58%, AML 10%).[26] In this study in the pediatric oncology unit we observed, the incidence of Acute leukemia was 89 (52.4%) patients. Of them, ALL were 83.15% and AML 16.85% and no patient was diagnosed with chronic leukemia. This result is similar to the findings of Ferdousi et al[31] Jabeen et al[33] reported childhood cancer was 4.4% of total cancers cases in the National Institute of Cancer Research & Hospital (NICRH), among them most common was lymphoma (24.2%), and leukemia (14.3%). Khasru et al[23] also found similar results. The distribution is similar to other developed countries. It made up about a third of paediatric cancers in Australia,[34] 27% of paediatric cancers in the United States,[13] 30% in France[14] and, in Ireland,[15] 33% in Germany,[16] 35% in Shanghai, China[17] and Chennai, India.[18] Studies have shown that in Eastern Mediterranean countries, prevalence of leukemia is around 30-50% of all childhood cancers.[35-38] Gender distributions revealed males in predominance (55%) and females 45% with a ratio of 1.23:1. These results are quite similar to the results from BSMMU[26] and NICRH.[33] We also found, in case of ALL, males were in predominance (58%), and in case of AML, females were predominance (60%). But Hossain et al[39] reported AML was male predominance. Age distribution analysis showed, in case of acute leukemia, 0-4 years age group was 49.44%, 5-9 years age group was 39.32%, and >10 years age group was 11.24%. Median age was at 4.6 years. The commonest group for ALL was 0-4 years covering 54%. Then 5-9 years was 34% and >10 years was 12%. In case of AML, most common group was 5-9 years accounting for 66.7%, next 0-4 years was 26.7%, and >10 years was 6.7%.

Hossain et al[24] report stated the mean age of leukemia in South Asian countries (Bangladesh, India, and Pakistan) was higher (6-7 years) than those of Western countries (between 0 to 4 years). In their study they found, Leukemia was mostly diagnosed in children aged 5-9 years (41%), ALL was common in 5-9 years group whereas AML was found more commonly in children aged 10-14 years (45%). Jabeen et al[33] reported majority of childhood leukemia belonged to 10-14 years (37.7%), followed by 5-9 years (31.4%) and 0-4 years (30.9%). American cancer society reported ALL is most common in early childhood, peaking between 2 and 5 years of age. AML tends to be more spread out across the childhood years, but it's slightly more common during the first 2 years of life and the teenage years.[40] In our study, the incidence of children below 1 year of age having acute leukemia (Infantile leukemia) was 5.6%, of them 4.5% ALL and 1.1% AML. Infants account for approximately 2-5% of all children with ALL.[12]

French American British classification (FAB) classifications of ALL & AML were made based on morphological findings of the leukemic cell. ALL were divided into 3 types; L1, L2 &L3. In our study, L2 was the most common variety (41.90%), L1-36.5%, and L3- 4%. Rest 17.6% of patients were not morphologically classified. Madhumathi et al[41]

reported B-ALL between 72.9%-91%. Pakistani studies also found similar results; B-ALL in 78.5-87%[42,43] and T-ALL 13-23%.[44,45]About 2.2% of patients had a mixed variety of ALL. Cytogenetic analyses were done in 28 ALL patients and found majority of patients (68%) had no genetic abnormalities. This aberration is known to predict a favorable prognosis with high remission rates and long median survival.[46,47] Most common ETV6-RUNX1 fusion gene t(12;21) (p13q22) [TEL-AML], were positive in 21%patients. About 11% patients presented with t(1:19) (q23,p13) in E2A/PBX1 gene. ETV6-RUNX1 fusion gene t(12;21) (p13q22) previously referred to as TEL-AML1 considered the most common translocation in childhood ALL, with a prevalence of 20-25%.[48] It is seen in B-ALL &associated with an excellent prognosis.[12] FAB classified AML based on morphology and in our study, we found M1-6.67%, M2-20%, M3-26.67%, M4-13.33%, and rest 33.33% patients were not categorized into any group. Immunophenotyping was done in 8 patients, who had a high number of CD33, CD15, CD64, and other myeloid groups of cell surface markers. Of them, APML was 50%. Cytogenetic analyses were done in 8 AML patients and 37.5% had no abnormalities. The t(15;17)(q22;q21) fuses RARA gene on chromosome 17q21 to PML gene on chromosome 15q22.[49] This mutation is present in 25-40% of children with APML which is similar to our study result,[50] we found it in 50% cases. FLT3-ITD mutation or point mutations were also identified in 25% of all cases. The reciprocal translocation t(8;21)(q22;q22) between 8 & 21 chromosomes results in AML1/ETO (RUNX1/CBFA2T1) fusion gene is considered to have the highest incidence in childhood AML (12%), mostly AML-M2.[51-53] In our study we found it one patient (12.5%). A report published that kFLT3-ITD or point mutations have been identified in 15-30% of pediatric AML patients. This mutation indicates a poorer prognosis.[12] Several other cytogenetic abnormalities have been suggested by multiple studies like Inv(16)(p13;q22), MLL rearrangements, Aberration of 7q,5. We did not observe these abnormalities in this study may be due to the small sample size.

This analysis revealed among the 89 patients with acute leukemia, 91% of patients started receiving treatment. About 4.5% of patients presented with advanced disease and had an early death. The other 4.5% of patients refused to do it. Refusal or abandonment is mostly due to considering malignancy is a grave disease, taboo & other personal reasons, and seeking treatment from abroad. Our results are similar to Ferdousi et al.[31] BSMMU also found that 43% of their study population refused and 11% abandoned treatment midway. Financial inability is the main reason for this refusal.[26] In acute leukemia patient's overall survival was found at about 51.7% of patients and expired in about41.55% of patients. About 10% of patients reported relapse and 6.75% are lost to follow-up. In case of ALL, 90% of patients started treatment, but 5% of patients refused treatment, and 5% of patients had an early death. Among them, alive 54% of patients, and 39% of patients expired. Among AML 100% patient started treatment& 80% completed treatment. But until a recent follow-up, only 40% survived and were on regular follow-up. About 53% of patients expired and 13.33% lost for follow-up. Death occurs mainly due to advanced disease at diagnosis, disease progress, sepsis, myelosuppression, and others. American Cancer Society estimates that improved' treatment made higher overall survival, in case of ALL was 90% & AML was 64%.[21] Only one patient had relapsed and started relapse treatment protocol but failed to survive. The relapse rate is expected and comparable to available data from neighboring countries.[41,42]

Ross et. al[54] studies suggested a down syndrome child is at higher risk for developing leukemia, nearly a 20-fold rise than other individuals.[55] ACCO said AML is much more common in Down syndrome children than in ALL, especially below 5 years of age.[55] In our study we had 2 Down syndrome patients suffering from Acute leukemia, one ALL and one AML both were below 5 years of age.

Conclusion

This study found that Acute Leukemia was the most common childhood cancer. The most common age group was 0-4 years. Infantile leukemia was found in 5.6% of cases. Morphologically FAB L-2 & Immunophenotypically Pre-B-ALL was the commonest ALL. In case of AML, both morphologically & immunophenotypically AML-M3 (APML) was the most common. Cytogenetic analyses revealed most children presented with no cytogenetic abnormalities. About 91% of patients started receiving treatment and refusal rate is only 4.5% which is mostly due to considering malignancy as a grave disease, taboo & others. Overall survival was 51.7% of cases and expired in 41.6% of cases, and

6.7% of cases were lost to follow-up. About 10% of patients reported relapses.

Recommendation

As many common childhood malignancies are curable there is a need to have a dedicated pediatric cancer registry for assessing the magnitude of the problem in our country.

Conflicts of interest

Conflict of interest relevant to this article was not reported.

References

1. National Cancer Institute. Childhood Cancers. Available from: https://www.cancer.gov/types/childhood-cancers [accessed March 2022]
2. Siegel Lamellar KD, Fuchs HE, Jemal A. Cancer Statistics. *CA: A Cancer Journal for Clinicians* 2021;**71**:7-33.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008.*Int J Cancer* 2010; **127**: 2893-917.
4. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li CK, et al. Paediatric cancer in low-income and middle-income countries. *Lancet Oncol* 2013;**14**:e104-16.
5. MOHFW. National cancer control strategy and Pan of action 2009-2015. Bangladesh: Directorate General of Health Services, Ministry of Health and Family Welfare; 2008.
6. Hussain S, Zaman M. National Cancer Control Strategy and Plan of Action 2009-15. Available from: https://dghs.gov.bd/bn/licts_file/images/Strategy/2009_NationalCancerControlStrategy 2009-15.pdf [cited 29 March 2022].
7. Hossain MS, Ferdous S, Karim-Kos HE. Breast cancer in South Asia: a Bangladeshi perspective. *Cancer Epidemiol* 2014;**38**:465-70.
8. Hossain MS, Iqbal MS, Khan MA, Rabbani MG, Khatun H, Munira S, et al. Diagnosed hematological malignancies in Bangladesh - a retrospective analysis of over 5000 cases from 10 specialized hospitals. *BMC Cancer* 2014;**14:**438.
9. The Daily Star. Cancer affects 13,000 children in Bangladesh every year: experts. Feb 24, 2018. Available from: https://www.thedailystar.net/health/paediatricians-at-an-international-conference-says-cancer-affects-13000-children-in-bangladesh-every-year-experts-1539418 [cited 8 Feb 2022].
10. Rahman S, Otim M, Almarzouqi A, Rahman S. Setting Priorities in Childhood Cancer in Low-Income Countries Using Nominal Group Technique: Experience from an International Childhood Cancer Forum Exercise in Bangladesh. *Asian Pacific Journal of Cancer Prevention* 2019;**20**:97-103.
11. World child cancer. Country profile: Bangladesh. UK, 2022. [Internet] last updated Nov 2020. Available from: https://worldchildcancer.org/bangladesh/#:~:text=It's%20estimated%20that%20 around% 209%2C000,these% 20children%20ever%20access% 20it [cited 22 Feb, 2022].
12. Carroll WL, Bhatla T. Acute lymphoblastic leukemia. In: Lanzkowsky P, Lipton J, Fish JD, editors. Lanzkowsky's Manual of Pediatric Hematology and Oncology. 6th ed. USA: Elsevier;2016:367-410.
13. Linabery AM, Ross JA. Trends in childhood cancer incidence in the US (1992–2004). Cancer: Interdisciplinary. *Int J Am Cancer Soc* 2008;**112**:416-32.
14. Desandes E, Clavel J, Berger C, Bernard JL, Blouin P, de Lumley L, et al. Cancer incidence among children in France,1990-1999. *Pediatr Blood Cancer* 2004; **43**:749-57.
15. Stack M, Walsh PM, Comber H, Ryan CA, O'Lorcain P. Childhood cancer in Ireland: A Population-based Study. *Arch Dis Child* 2007;**92**:890-97.
16. Spix C, Eletr D, Blettner M, KaatschP.Temporal trends in the incidence rate of childhood cancer in Germany 1987-2004. *Int J Cancer* 2008;**122**:1859-67.
17. Bao PP, Zheng Y, Gu K, Wang CF, Wu CX, Jin F, et al. Trends in childhood cancer incidence and mortality in urban Shanghai, 1973-2005. *Pediatr Blood Cancer* 2010;**54**:1009-13.
18. Swaminathan R, Rama R, Shanta V. Childhood cancers in Chennai, India, 1990-2001: incidence and survival. *Int J Cancer* 2008;**122**:2607-11.
19. Wiemels J. Perspectives on the causes of childhood leukemia. *ChemBiol Interact* 2012;**59**:196.
20. Arora RS, Eden T, Kapoor G. Epidemiology of childhood cancer in India. *Indian J Cancer* 2009;**46**:264e73.
21. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA: A Cancer Journal for Clinicians* 2014;**64**:83-103.
22. Rodriguez-Galindo C, Friedrich P, Morrissey L, Frazier L. Global challenges in pediatric oncology. *Current Opinion in Pediatrics* 2013;**25**:3-15.

23. Khasru AA. Childhood Cancer: A Situation Analysis and Challenges, Bangladesh Perspective. *BJCH* 2018;**41**:140-42.

24. Hossain M, Begum M, Mian M, Ferdous S, Kabir S, Sarker H, et al. Epidemiology of childhood and adolescent cancer in Bangladesh, 2001-2014. *BMC Cancer* 2016;**16:**104.

25. Kamrul Hasan. Childhood cancer treatment remains inadequate. Dhaka Tribune [Internet]. 16 Feb 2017. Available from: https://www.dhakatribune.com/bangladesh/2017/02/16/childhood-cancer-treatment-remains-inadequate [cited 30 Dec 2021].

26. Islam A, Eden T. Brief report on pediatric oncology in Bangladesh. *South Asian J Cancer* 2013;**2:**105-06.

27. Howard SC, Metzger ML, Wilimas JA, Quintana Y, Pui CH, Robison LL, Ribeiro RC. Childhood cancer epidemiology in low-income countries. *Cancer* 2008;**112**:461-72.

28. World Bank. Indicator for childhood cancer. 2020. Available from: http://data.worldbank.org/indicator/SH.DYN.MORT [Accessed 14 Jan 2022]

29. Registrar General of India. Summary Report on Causes of Death: 2001 2003 in India. New Delhi, India: Office of the registrar general and ministry of home affairs; [cited on Oct 2021] Available from: http://www.cghr.org/wordpress/wp-content/uploads/Causes_of_death_2001-03.pdf.

30. Gupta S, Morris S, Suraweera W, Aleksandrowicz L, Dikshit R, Jha P. Childhood Cancer Mortality in India: Direct Estimates From a Nationally Representative Survey of Childhood Deaths. *Journal of Global Oncology* 2016;**2**:403-11.

31. Ferdousi S, Nahar K, Moslem MM, Elahi EQ, Islam A. Incidence and outcome of childhood cancer in Bangladesh armed forces. *Bangladesh Armed forces Med J* 2021;**54**:19-27.

32. Global Cancer Data: GLOBOCAN 2018. IARC; Geneva, Switzerland. updated12 Sep 2018. [Last accessed Dec 2022]. Available from: https://www.uicc.org/news/global-cancer-data-globocan-2018#:~:text=What%20is%20GLOBOCAN%3F,for%20all% 20cancer %20sites%20 combined

33. Jabeen S, Haque M, Islam MJ. Profile of Paediatric Malignancies: A Five Year Study. *J Dhaka Med Coll* 2010;**19**:33-38.

34. Baade P, Youlden D, Valery P, Hassall T, Ward L, Green A, et al. Trends in the incidence of childhood cancer in Australia, 1983-2006. *British Journal of Cancer* 2010;**102**:620-26.

35. Ba-Saddik IA. Childhood cancer in Aden, Yemen. *CancEpidemiol* 2013;**37**:803e6.

36. Mousavi SM, Pourfeizi A, Dastgiri S. Childhood cancer in Iran. *J PediatrHematolOncol* 2010;**32**: 376e82.

37. Abuidris DO,Ahmed ME, Elgaili EM, Arora RS. Childhood cancer in Sudan: 1999-2007. *Trop Doct* 2008;**38**:208-10.

38. Al-Sheyyab M, Bateiha A, Kayed SE, Hajjawi B. The incidence of childhood cancer in Jordan: A population-based study. *Ann Saudi Med 2003*;**23**:260-63.

39. Hossain MJ, Xie L. Sex disparity in childhood and young adult acute myeloid leukemia (AML) survival: Evidence from US population data. *Cancer Epidemiol* 2015;**39**:892-900.

40. Bethesda, MD: National Cancer Institute. Key Statistics for Childhood Leukemia. Available from: https://www.cancer.org/cancer/leukemia-in-children/about/key-statistics.html [cited Jan 2022]

41. Madhumathi DS, Prasannakumari, JayadevaNaik, Appaji L, Arunakumari B, V LD. Optimised panel for characterisation of pediatric ALL in a tertiary cancer centre from a developing country: Initial experience with literature review. *Int J Human Pathol Res* 2015;**1**:1-10.

42. Fadoo Z, Nisar I, Yousuf F, Lakhani LS, Ashraf S, Imam U, et al. Clinical features and induction outcome of childhood acute lymphoblastic leukemia in a lower/middle income population: A multi-institutional report from Pakistan. *Pediatric Blood Cancer* 2015;**62**:1700-1708.

43. Iqbal Z. Molecular Genetic Studies on 167 Pediatric ALL Patients from Different Areas of Pakistan Confirm a Low Frequency of the Favorable Prognosis Fusion Oncogene TEL-AML1. *Asian Pacific J Cancer Prevent* 2014;**15**:1.

44. Tipu HN, Muhammad MB, Altaf C, Noman M, Malik HS. The spectrum of acute leukemias and aberrant markers expression based on flow cytometry in a tertiary care center. *Pak Armed Forces Med J* 2018;**68**:450-54.

45. Khan S, Mir A, Khattak B, Rehman A, Zeb A. Childhood Leukemias in Khyber Pakhtunkhwa and Afghan Children Visiting to Hayatabad Medical Complex Hospital. *Arch Can Res* 2017;**5**:149.

46. rózek K, Heinonen K, Bloomfield CD. Clinical importance of cytogenetics in acute myeloid leukemia. *Best Pract Res Clin Haematol* 2001;**14**:19-47.

47. Nucifora G, Rowley JD. The AML1 and ETO genes in acute myeloid leukemia with a t(8;21). *Leuk Lymphoma* 1994;**14**:353-62.

48. Lazic J, Tosic N, Dokmanovic L, Krstovski N, Rodic P, Pavlovic S, Janic D. Clinical features of most common fusion genes in childhood acute lymphoblastic leukemia. *Med Oncol* 2010;**27**:449-53

49. deThé H, Chomienne C, Lanotte M, Degos L, Dejean A. The t(15;17) translocation of acute promyelocytic leukemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. *Nature* 1990;**347**:558-61.

50. Kim M, Lee SA, Park HI, Oh EJ, Park CW, Lim J, et al. Two distinct clonal populations in acute promyelocytic leukemia, one involving chromosome 17 and the other involving an isochromosome 17. *Cancer Genet Cytogenet* 2010;**197**:185-88.

51. Gamerdinger U, Teigler-Schlegel A, Pils S, Bruch J, Viehmann S, Keller M, et al. Cryptic chromosomal aberrations leading to an AML1/ETO rearrangement are frequently caused by small insertions. *Genes Chromosomes Cancer* 2003;**36:**261-72.

52. Nucifora G, Rowley JD. The AML1 and ETO genes in acute myeloid leukemia with a t(8;21). *Leuk Lymphoma* 1994;**14**:353-62.

53. Burjanivova T, Madzo J, Muzikova K, Meyer C, Schneider B, Votava F, et al. Prenatal origin of childhood AML occurs less frequently than in childhood ALL. *BMC Cancer* 2006;**6**:100-7.

54. Ross JA, Spector LG, Robison LL, Olshan AF. Epidemiology of leukemia in children with Down syndrome. *Pediatr Blood Cancer* 2005;**44**:8-12.

55. Margolin J, Rabin KR, Steuber CP, Poplack, DG. Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG, editors. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:518- 565.