Journal of High Institute of Public Health 2021;51(1):39-46.

Original Article

Pattern and Survival of Childhood Malignancies: A 10-Year Retrospective Study

Ayat F. Manzour [1 ¥], Sara M. Makkeyah [2], Mahmoud M. Shawiesh [3], Iman A. Ragab [2]

[1] Department of Community, Environmental and Occupational Medicine, Faculty of Medicine, Ain Shams University, Egypt
[2] Department of Pediatrics, Faculty of Medicine, Ain Shams University, Egypt
[3] Department of Pediatrics, Houtat Beni Tamim General Hospital, Riyadh, Saudi Arabia

Abstract

Background: Hematopoietic neoplasms constitute more than 40% of malignancies in children and represent a wide range of disorders, including acute leukemias and lymphomas. Childhood cancer is curable if diagnosed early, and the survival has improved dramatically over the last 20 years due to aggressive combined modality management.

Objective: To estimate the proportion of hematologic malignancies, identify patient characteristics, and calculate the overall and event-free survival of childhood malignancies at the Pediatric Oncology Clinic, Ain Shams University Hospital.

Methods: A total of 220 patients with acute lymphoblastic leukemia (ALL), 42 patients with acute myeloid leukemia (AML), 65 patients with non-Hodgkin lymphoma (NHL), and 29 patients with Hodgkin's lymphoma (HL), registered at the Pediatric Oncology Clinic, Ain Shams University Children's Hospital from January 2005 through December 2014, were included in the study. A checklist adapted from patients' files contents was filled, and overall survival (OS) and event-free survival (EFS) were studied.

Results: The most common type of hematologic malignancies among children was ALL (61.8%). Regarding patients with ALL, the mean age at diagnosis was 6.1 ± 3.9 years, and the male : female ratio was 1.2:1. The 10-year OS was 85.3%, and the 10-year EFS was 80.4%. In the AML group, the OS was 78.8%, and the EFS was 74.4%. The OS and EFS of the patients with NHL were 89.1% and 84.6%, respectively. The 10-year OS and EFS for patients with HL were 88.9% and 75.9%, respectively.

Conclusion: The survival rates of ALL, AML, and NHL approach universal estimates. The survival rates of patients with HL was lower than international rates, which mandates the application of response-based therapy. The high survival rates of patients with AML was attributed to the definition of risk groups, which led to a more risk-adapted treatment.

Keywords: Hematologic malignancy, survival, pediatric, oncology, acute lymphoblastic leukemia

Available on line at:
jhiphalexu.journals.ekb.eg

Print ISSN: 2357-0601
Online ISSN: 2357-061X

¥*Correspondence*:
Email:
ayatfaroukm@med.asu.edu.eg

Suggested Citations: Manzour AF, Makkeyah SM, Shawiesh MM, Ragab IA. Pattern and survival of childhood malignancies: A 10-year retrospective study. JHIPH. 2021;51(1):39-46.

INTRODUCTION

Cancer is the second most common cause of death in children in developed countries. However, the probability of cure is increasing due to highly specific diagnostic procedures and the introduction and continuous improvement of multimodal treatment strategies.(1)

A study by the South Egypt Cancer institute demonstrated that 2831 pediatric cases were diagnosed with cancer over a 13-years period. Pediatric malignant tumors comprise11.2% of all malignancies, and in this study, hematological malignancies represented 50.7% of all pediatric malignancies. Leukemias, myeloproliferative diseases, and myelodysplastic diseases accounted for 33.4% of all tumors in the Pediatric Oncology Department. Acute lymphoblastic leukemia (ALL) is the most common hematological malignancy, and accounts for 29.3% of total malignancies among patients admitted to the department, and 87.8% of total leukemias.(2)

Acute leukemias account for approximately 40% of childhood cancers; of which, ALL comprises approximately 70%–80% and acute myeloid leukemia (AML) comprised approximately 10%–15%. The cure rates of ALL in developed countries are as high as 79%–86% using intensive protocols.(3) The incidence rate of

childhood AML has been estimated to be approximately 5–7 cases per million people per year.[4]

Lymphomas are the third most common group of cancers in children and adolescents after leukemias and brain tumors, accounting for 10%–15% of newly diagnosed cancers. Hodgkin lymphoma (HL) comprises 40% of all childhood lymphomas, and occurs in 5–7 per 100,000 population. The incidence rate is highest in late childhood and early adulthood (15–35 years), and is considered rare under 5 years of age.[5]

Although HL is considered a highly curative neoplasm, conventional chemotherapy alone or combined with radiotherapy fails to produce remission in approximately one-third of patients. However, treatment with second-line chemotherapy produces low remission rates, with disease-free survival in 0% to 10% of patients with primary progressive HL. Moreover, salvage radiotherapy is an effective treatment for localized relapsed HL.[6]

Non-Hodgkin lymphoma (NHL) accounts for approximately 7% of cancers in children. It occurs most commonly in the second decade of life, and occurs less frequently in children younger than 3 years of age. With current treatments, approximately 80% of children and adolescents with NHL will survive at least 5 years.[7]

Patients with ALL between the ages of 1 and 9 years old, with an initial white blood cell (WBC) count < 50,000/mm^3 have a 4-year event-free survival (EFS) of 80%, while patients < 1 year of age and > 10 years of age have a worse prognosis.[8]

Hospital registries are the only available source to assess patterns of malignancies in the community, and few papers have examined the survival of pediatric patients with hematologic malignancies. To the best of our knowledge, no previous studies have identified the pattern and survival of hematologic malignancies in Ain Shams Pediatrics Hospital. This study explored the pattern of hematologic malignancies over a 10-years period, and identified the socio-demographic and clinico-pathological factors, as well as the survival of all types of hematologic malignancies. We aimed to estimate the proportion of hematologic malignancies, to identify patient characteristics, and calculate the overall survival (OS) and EFS of these malignancies at the Pediatric Oncology Clinic, Ain Shams University Hospital.

METHODS

A retrospective record review was conducted including all available oncology files in the Pediatric Oncology Clinic (838 files), Ain Shams University, Pediatrics Hospital from January 2005 until December 2014. Three hundred fifty-six hematologic malignancy cases were detected, among which, there were 220 (61.8%) patients with ALL, 42 (11.8%) with AML, 65 (18.3%) with NHL, and 29 (8.1%) patients with HL. The patients ranged in age from 1 to 16 years old.

The collected data from patients' files included demographic data, initial presentation, initial diagnostic investigations (complete blood count, immune-phenotyping, cytogenetics, LDH), and staging, in addition to dates of diagnosis, death, relapse, and loss to follow-up. OS is defined as the percentage of patients who have not died from a specific disease in a defined period of time. The time period usually begins at time of diagnosis or at the start of treatment and ends at time of death.[9] EFS was defined as the length of time after primary treatment of a cancer that the patient remains free of certain complications or events that the treatment was intended to prevent or delay; these events may include relapse or death.[10]

Diagnosis of different malignancies was based on the following:

I- Acute Lymphoblastic Leukemia (ALL)
Diagnosis of ALL was based on morphologic, biochemical, and immune-phenotypic (IPT) features of leukemic cells.[11]

II- Acute Myeloid Leukemia (AML)
Diagnosis of AML and its subtypes was established according to the (French-American-British morphology) classification, as well as IPT and cytogenetics.[12]

III- Non-Hodgkin lymphoma
NHL was diagnosed and classified according to histopathological examination and immune-phenotypic features into lymphoblastic lymphoma, mature B-NHL and anaplastic large cell lymphoma.[13]

IV- Hodgkin lymphoma
Available diagnoses in patients' records was based on the "Cancer Staging Manual," as well as classification and staging.[14]

Statistical analysis

Data were coded, entered, processed, and analyzed using Statistical Package for Social Science version 20.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Survival (overall/event free) analysis was performed using Kaplan–Meier survival tests. Cox proportional hazards model was performed to evaluate the effect of several factors on patients' survival. *p*-values ≤ 0.05 were considered significant.

Ethical considerations

The study conformed to the international ethics guidelines and that of Declaration of Helsinki (2013). Ethical approval was obtained from the Faculty of Medicine, Ain Shams University, Egypt.

RESULTS

There were fluctuations in the proportions of hematologic malignancies over the study period. During 2005, slightly less than half (47%; 95% CI = 35.3–53.9) of pediatric

patients were diagnosed with a hematologic malignancy. The lowest recorded proportion was during 2010 (33.3%, 95% CI = 17– 41.5), and the highest (54.4%; 95% CI = 35.6–62.7) was during 2008 (Table 1).

Table 1: Proportion of hematologic malignancies by year of occurrence among attendants at the Pediatric Oncology Department

Year	No. of pediatric malignancies	No. of hematologic malignancies	Proportion (%)	95% CI (%)* Lower bound-upper bound
2005	117	55	47.0	35.3–53.9
2006	119	41	34.5	24.4–42
2007	88	34	38.6	25.3–46.1
2008	57	31	54.4	35.6–62.7
2009	55	29	52.7	33.7–61.2
2010	57	19	33.3	17–41.5
2011	75	35	46.7	35.8–57.9
2012	95	46	48.4	35–55.8
2013	83	32	38.6	24.8–46.2
2014	92	34	37.0	27.1–47.7
Total	838	356	42.5	39.1–45.8

*(CI) Confidence interval of a proportion = P ± (Zα*SEM)

The most common hematologic malignancy was consistently ALL over the study period. The least common was HL, with zero occurrence in 2006 and 2009 (Figure 1). Patients with HL were significantly older than patients with ALL, AML or NHL ($p < 0.0001$), while there were no significant differences with regard to sex. Presenting with fever was significantly lower in both NHL and HL groups ($p < 0.0001$), while anemia was significantly more common in patients with AML and HL. Lymphadenopathy presentation was significantly prominent in lymphoma of both types ($p < 0.0001$).

Hepatosplenomegaly was significantly more common in patients with AML and NHL, with zero presence in HL ($p = 0.038$). No statistically significant differences were found regarding OS or EFS survival (Table 2). Neither the overall nor event-free survival differed significantly between all types of hematologic malignancies (Table 2, Figure 2).

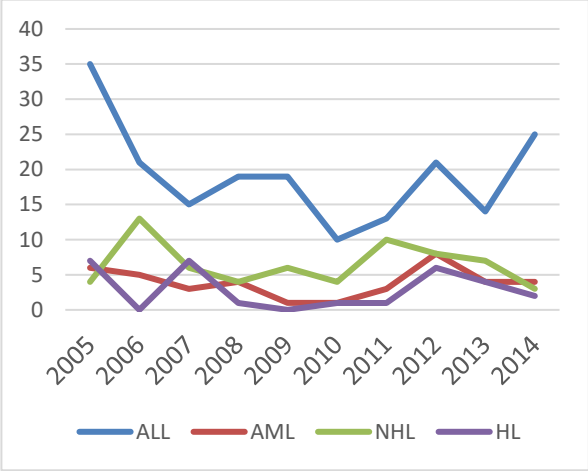

Figure 1: Relative frequencies of hematologic malignancies (ALL, AML, NHL, HL) during the 10-year study period

Table 2: Demographic, clinico-pathological characteristics, and survival of patients with hematologic malignancies

Variable	ALL (n = 220) No. (%)	AML (n = 42) No. (%)	NHL (n = 65) No. (%)	HL (n = 29) No. (%)	*p*-value
Age (years)					
Mean ± SD	6 ± 3.9	6.9 ± 4.5	6 ± 3	9 ± 4	< 0.0001*
Range	1–16	1–15	2–14.3	3–16	
Sex					
Male	120 (54.5)	26 (66.7)	48 (73.8)	19 (65.5)	0.067
Female	100 (45.5)	13 (33.3)	17 (26.2)	10 (34.5)	
Male:female ratio	1.2:1	2:1	2:1	2:1	
Clinical presentation#					
Fever	108 (49.0)	21(50.0)	16 (24.6)	11(37.9)	< 0.0001*
Anemia	189 (85.9)	38 (90.5)	56 (86.2)	27 (93.1)	0.004*
Bleeding	8 (3.6)	5 (11.9)	1 (1.5)	1 (3.4)	0.055
Lymphadenopathy	19 (8.6)	6 (14.3)	27 (41.5)	25 (86.2)	< 0.0001*
Hepatosplenomegaly	65 (29.5)	5 (11.9)	25 (38.5)	0 (0)	0.038*
CNS involvement	3 (1.4)	0 (0)	4 (6.2)	0 (0)	0.067
Survival (10-year)					
OS	188 (85.4)	33 (78.6)	58 (89.2)	26 (89.6)	0.32
EFS	177 (80.5)	31 (73.8)	55 (84.6)	22 (75.8)	0.55

*p-value < 0.05 (significant). #Some patients had more than one presenting symptom.

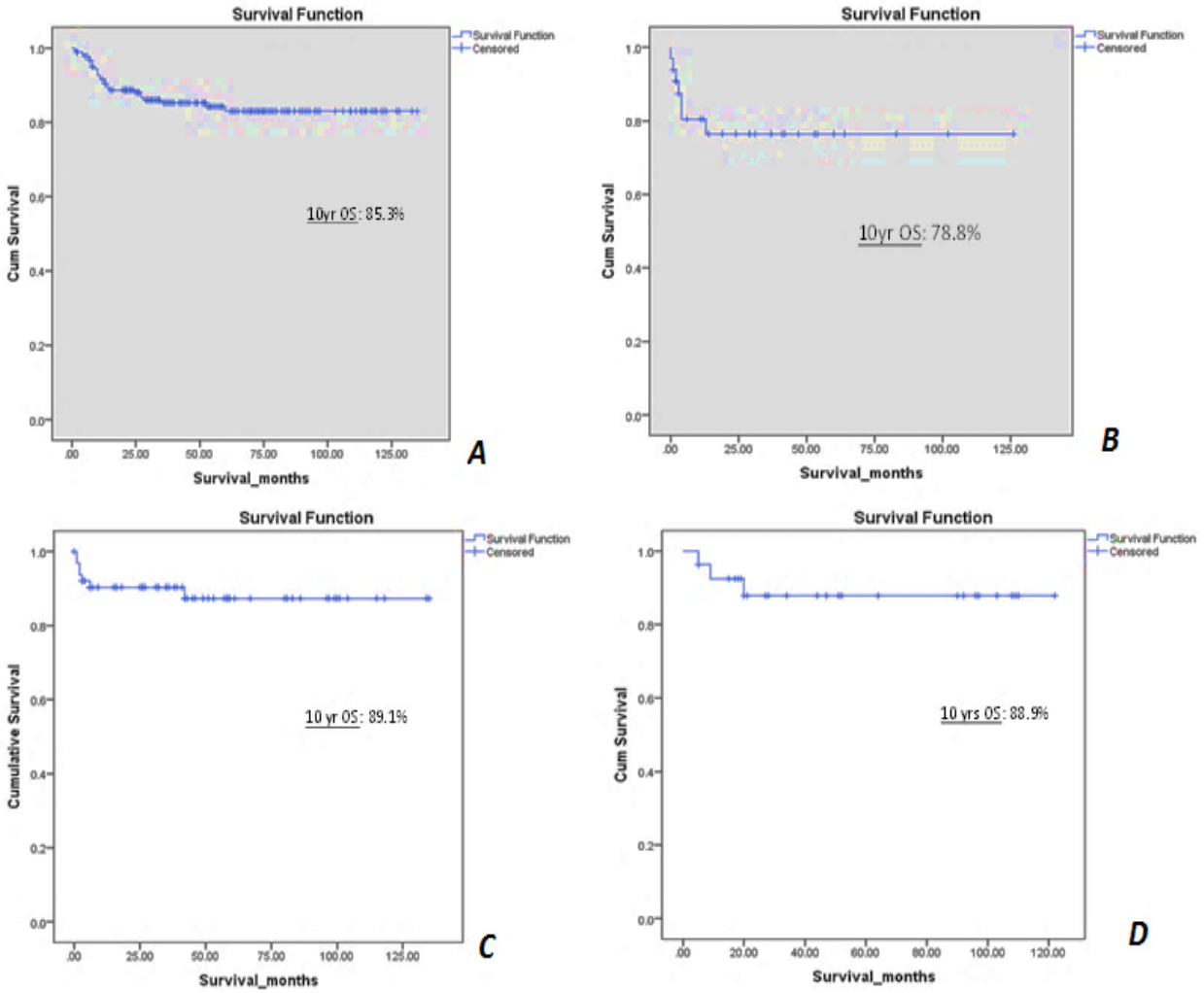

Figure 2: Kaplan–Meier graphs showing overall survival of patients with ALL (A), AML (B), NHL (C), and HL (D)

Investigating ALL in detail revealed that most patients had a precursor-B (84.6%). Unfortunately, data regarding cytogenetics were lacking in almost half of the included files. The majority of patients were anemic with Hb concentration < 10 g/dl. Almost 47% were treated with standard risk protocol of therapy. At day 14 after start of chemotherapy, the majority of patients had < 5% blasts in their bone marrow aspirate (Table 3).

Table 4 shows that the most common immune-phenotyping was M1-M2. The cytogenetics of 38.1% of the available files were normal. The mean initial WBC count was 52.4 ± 88.8, while the mean initial Hb was 7.1 ± 2.2.

Testing immune-phenotyping of NHL showed that the majority (75.4%) were of B-NHL type. The most common site of initial involvement was the abdomen. Most of the patients with NHL (64.6%) presented at stage 3 (Table 5).

Most patients with HL presented with cervical masses (65.6%), and 41.4% were at stage 2 at time of presentation. Approximately 20% of cases were non-responders after 2 cycles of chemotherapy (Table 6).

By studying the effect of different factors on the outcome of patients with ALL, it was found that the standard risk protocol of therapy and younger age at presentation (1–4 years and 5–9 years) independently and significantly contributed to improved survival of patients (p = 0.021, 0.038, and 0.004 respectively) (Table 7).

Table 3: Clinical, laboratory, and assigned protocol of therapy for patients with acute lymphoblastic leukemia

ALL patients (n = 220)	No. (%)
IPT (NA in 21 [9.6%])	
Pre-B	169 (76.8)
T-ALL	30 (13.6)
Cytogenetics (NA in 105 [47.7%])	
Normal	91 (41.4)
Trisomy 21 (down)	3 (1.4)
Others*	21 (9.5)
Initial WBC counts (x 10^3 cells/µl)	
Mean ± SD	35.8 ± 68.9
> 50	38 (17.3)
≤ 50	182 (82.7)
Initial Hb (g/dL)	
Mean ± SD	6.9 ± 2.3
≥ 10	18 (8.2)
< 10	202 (91.8)
Protocol of therapy (NA in 10 [5%])	
Standard risk	103 (46.8)
High risk standard arm	52 (23.6)
High risk augmented arm	54 (24.5)
Single vs double DI (NA in 9 [4.5%])	
Single	93 (42.3)
Double	117 (53.2)
D14 BMA	
M1 (< 5% blasts)	170 (77.3)
M2 (5%–25% blasts)	18 (8.2)
M3 (> 25% blasts)	4 (1.8)

WBC: White blood cell, Hb: Hemoglobin, IPT: Immune-phenotyping
*Others, including trisomy 4, trisomy 22, trisomy 8, t (9:11), 54 xy (hyperdiploidy), and t (8:21).
DI: Delayed intensification, NA: Not available, BMA: Bone marrow aspiration.

Table 4: Clinical and laboratory characteristics of the studied patients with acute myeloid leukemia

AML patients (n = 42)	No. (%)
IPT	
M0-M1	3 (7.1)
M1-M2	16 (38.1)
M3	3 (7.1)
M4–M5	11 (26.2)
M7	9 (21.4)
Cytogenetics (NA in 14.3%)	
Normal	16 (38.1)
Trisomy 21 (DS)*	6 (14.3)
Others#	14 (33.3)
Initial BM blasts (NA in 11.9%)	
≤ 5%	32 (76.2)
> 5%	5 (11.9)
Initial WBCs count (x10^3 cells/µl)	
Mean ± SD	52.4 ± 88.8
Range	(2.0–485.0)
Initial Hb (g/dL)	
Mean ± SD	7.1 ± 2.2
Range	(3.2–13.5)

WBC: White blood cell, Hb: Hemoglobin, BM: Bone marrow, IPT: Immune-phenotyping, DS: Down syndrome.
#Others, including t (10;11), trisomy 8, t (1;7), t (15;17), and t (8;21).

Table 5: Clinical and laboratory characteristics of patients with non-Hodgkin lymphoma

NHL patients (n = 65)	No. (%)
IPT	
B-NHL	49 (75.4)
LL	14 (21.5)
ALCL	2 (3.1)
Site of initial involvement	
Abdominal	42 (64.6)
Mediastinal	8 (12.3)
Nasopharyngeal	4 (6.2)
Cervical	6 (9.2)
Maxillary	2 (3.1)
Others#	3 (4.6)
LDH at diagnosis (U/L)	
< 500	17 (26.2)
500–1000	34 (52.3)
> 1000	14 (21.5)
Stage	
II	9 (13.8)
III	42 (64.6)
IV	14 (21.5)
Initial WBC count (x10^3 cells/µl)	
Mean ± SD	14.6 ± 29.5
Range	(0.2–200)
Initial Hb (g/dL)	
Mean ± SD	9.6 ± 1.9
Range	(3.8–12.9)

WBC: White blood cell, Hb: Hemoglobin, LDH: Lactate dehydrogenase, IPT: Immune-phenotyping, BMT: Bone marrow transplantation.
#Others are spinal, scrotal, and eye mass

Table 6: Clinical and laboratory characteristics of patients with Hodgkin lymphoma

HL patients (n=29)	No. (%)
Site of initial involvement	
Cervical	19 (65.5)
Abdominal	5 (17.2)
Mediastinal	5 (17.2)
Stage	
I	2 (6.9)
II	12 (41.4)
III	10 (34.5)
IV	5 (17.2)
Risk	
Low	4 (13.8)
Intermediate	13 (44.8)
High	12 (41.4)
Initial WBC count (x 10^3 cells/µl)	
Mean ± SD	11.6 ± 9.7
Range	1.8–38.6
Initial Hb (g/dL)	
Mean ± SD	6.5 ± 1.9
Range	5.7–12.6
LDH at diagnosis (U/L)	
Mean ± SD	736 ± 513
Range	276–2948
Response after 2 cycles of chemotherapy	
Complete response	10 (34.5)
Partial response	13 (44.8)
No response	6 (20.7)

WBC: White blood cell, Hb: Hemoglobin, LDH: Lactate dehydrogenase.

Table 7: Cox proportional hazard model studying effect of different factors on the survival of patients with acute lymphoblastic leukemia

	B	SE	*p*-value	Risk ratio	95% CI for risk ratio	
					Lower	Upper
Sex	-0.637	0.408	0.119	0.529	0.238	1.177
Age groups						
1–4 years	–1.108	0.535	0.038*	0.330	0.116	0.942
5–9 years	–1.793	0.627	0.004*	0.167	0.049	0.569
10–15 years	–0.913	0.624	0.143	0.401	0.118	1.364
Protocol of therapy						
Standard risk	–1.351	0.585	0.021*	0.259	0.082	0.815
High risk standard	–0.288	0.497	0.562	0.750	0.283	1.985
WBC count*	0.759	0.539	.159	2.136	0.743	6.139
Diagnosis subtypes	0.853	0.491	.082	2.347	0.897	6.140

*WBC count was categorized into < 50 and > 50 (x 10^3) *(Jeha & Pui 2009)*.[8]

DISCUSSION

The international comparison of cancer frequency and incidence rate varies due to variability in the diagnosis and classification, as well as the differential access to medical care and incomplete registration of the cases.[15] Good quality population level statistics on the occurrence of cancer at a young age have been more difficult to obtain than in adults.[16]

The total 10-year rate of hematologic malignancies was 41.8%, which is close to the 13-year incidence rate study performed in Upper Egypt based on data from the South Egypt Cancer Institute [2]. The mentioned study found that pediatric leukemias accounted for 33.4% of all tumors in the pediatric oncology department, while lymphomas represented 17.3%. Another 10-year incidence rate study in India revealed that leukemias and lymphomas accounted for 40% of all pediatric tumors.[15]

A 3-year study performed in Myanmar, Asia revealed that hematologic malignancies represented 62.2% of all pediatric malignancies,[17] which is higher than our results. This difference may be attributed to differences in genetic profiles and environmental exposures.

The current study showed that ALL was the most common hematologic malignancy (61.8%), which is consistent with the findings of many previous studies.[2,18] However, the frequency is different in Sub-Saharan Africa, where lymphoma constitutes 40% of childhood cancer and leukemia 6.3%.[19]

Regarding the most common presenting symptoms, fever was the most common presentation in leukemia ($p < 0.0001$), while lymphadenopathy was more common in HL (< 0.0001). Clarke et al., 2016[20] illustrated in their systematic review that fever is one of the most common presentations of acute leukemia (53%), which was also concurred by Pahloosye et al. [21] (fever was found in 59% of ALL cases) in 2011.

The survival of patients with ALL was comparable to that of reports from other developing countries that adopted the same therapy protocol for ALL, in that the estimated 5-year OS and EFS in Jordan were 89% and 80%, respectively.[22] However, in a prospective study on leukemia survival in Iran, the 5-year AML and ALL survival rates were 58% and 43%, respectively.[23] This inconsistency might be due to differences in medical care, the time of discovering illness and starting management, as well as biological and cultural factors. The relatively high survival rates of AML in our study could be partly due to improvement in supportive care and defining risk groups, which led to a more risk-adapted treatment. Early presentation and early management are other possible causes of high survival rates.

The 10-year OS of NHL in our study was 89.1% and that of EFS was 84.6%, which is comparable to the results of other studies. Pedrosa et al., 2007[24] found that the 2-year OS was 80% (after omitting deaths on early admission). In the first national AIEOP trial, the EFS was 89.4% and OS was 81.6%,[25] while Sherief et al., 2015 [26] found that the EFS at 5 years was 85.1%.

Modern combination chemotherapy and radiotherapy have increased the long-term survival for patients with HL to more than 80% in recent decades. The results have shown considerable improvement even in developing countries. The main challenge today is finding a balance between maximizing cure and minimizing the toxic effects. The 10-year survival of HL was 88.9% in our study, which agrees with literature.[27] however, our outcome is slightly lower than that stated by Kelly, 2015[28] in their review article, in which the OS of pediatric HL patients was said to reach up to 98%.

Regarding immune-phenotyping of examined hematologic cancers, it was found that majority of ALL were of B-lineage (84.6%) which is similar to the observations of Zhang et al., 2019,[29] who found that 81.4% were B-cell ALL. The patients with AML mainly had M1-M2 type (38.1%), followed by M4-M5 type (26.2%) which is similar to the findings of Noronha et al., 2011, who found that the most common types of AML were M4 followed by M1 (33.4% and 22.2%, respectively).[30] Moreover, B-NHL was found in 75.4% of pediatric patients, which is similar to the findings of Sheikhpour et al., 2017, who found the same subtype in the

majority of their studied group (87%).[31] HL sub-classification was not mentioned in the patient files, and as such, was considered as incomplete data.

Although each type of hematopoietic malignancy is formed of different disease entities, and within each type, further genetic subtypes and risk classes impact outcome, we aimed to study the wider outcome of hematopoietic neoplasms in our area with limited health resources.

Regarding factors affecting ALL survival, we found that standard risk protocol of treatment and younger age significantly improved the survival outcome of those patients. Reliance on risk based stratification is considered one of the hallmarks of treatment of childhood ALL. Patients with favorable features can be treated with less toxic regimens, whereas more aggressive regimens are reserved for those with higher-risk disease.[32] This result is similar to what was stated by (Jeha & Pui 2009), [8] who showed that patients age 1–9 years, with an initial WBC count of < 50,000/mm^3 (standard risk), have a 4-year EFS of 80%, while patients < 1 year of age and > 10 years of age have a worse prognosis.

CONCLUSION AND RECOMMENDATIONS

Survival analysis of hematopoietic neoplasm was approaching international figures in ALL and NHL, but remained lower in HL. Response-based treatment adaptation and sparing toxicity by reduction of radiotherapy and tailoring of chemotherapy are mandated to improve the survival of patients with HL. Moreover, improvements in hospital filing systems regarding availability and completeness of available records are of utmost importance.

Study limitations

Retrospective data recording from hard records should be interpreted cautiously due to the presence of missing data. Small numbers in hematologic malignancies other than ALL prevented the prediction of survival by the Cox hazard model. Larger numbers are needed for prediction.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

FUNDING

No funding sources

REFERENCES

1. Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev. 2010; 36(4): 277-85.
2. Ali AM, Sayed HA, Sayed DM, Mikhail NN. Pattern of pediatric tumors at pediatrics department in South Egypt cancer institute: thirteen years report. J Pediatr Child Nutr. 2016;(2) 100-12.
3. Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin Oncol. 2010; 29(5): 551-65.
4. Golub TR, Arceci RJ. Acute myelogenous leukemia. In: Pizzo PA, Poplack DG eds. Principles and practice of pediatric oncology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006: 1780 p.
5. Schwartz CL. The management of Hodgkin's disease in the young child. Curr Opin Pediatr. 2003;15(1):10-6.
6. Engert A, Schiller P, Josting A, Herrmann R, Koch P, Sieber M, et. al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's lymphoma study group. J Clin Oncol. 2003; 21(19): 3601-8.
7. Gore L, Trippett TM. Emerging non-transplant-based strategies in treating pediatric Non-Hodgkin's lymphoma. Curr Hematol Malig Rep. 2010; 5(4): 177-84.
8. Jeha S, Pui CH. Risk-adapted treatment of pediatric acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2009; 23(5): 973-90, v.
9. National cancer institute, Survival rate, Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/survival-rate, [Accessed 2 August 2019].
10. National cancer institute, Survival rate, Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/event-free-survival, [Accessed 2 August 2019].
11. Seibel NL, Steinherz PG, Sather HN, Nachman JB, Delaat C, Ettinger LJ, et. al. Early post-induction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the children's oncology group. Blood. 2008;111(5): 2548-55.
12. Mckenna RW. Multifaceted approach to the diagnosis and classification of acute leukemias. Clinical Chemistry.2000;46(8):1252–59.
13. Perkins SL, Morris SW. Biology and pathology of pediatric Non-Hodgkin lymphoma. In: Weinstein HJ, Hudson MM, Link MP eds. Pediatric lymphomas. Berlin, Heidelberg: Pediatric Oncology. Springer; 2007. p91-140. Doi.org/10.1007/978-3-540-68753-5_6.
14. Edge SB, Byrd DR, Carducci MA, Compton CC. The American Joint Committee on Cancer: the 7th Edition of the AJCC cancer staging manual and the future of TNM. New York, NY: Springer; 2009:599–628.
15. Kusumakumary P, Jacob R, Jothirmayi R, Nair MK. Profile of pediatric malignancies: A ten year study. Indian Pediatr. 2000;37(11):1234-8.
16. Jabeen S, Haque M, Islam MJ, Talukder MH. Profile of pediatric malignancies: A five year study. J Dhaka Med Coll. 2010; (19) 33-8.
17. Mon SW, Khaing AA, Win H, Hnin TM, Thu YM, Thwin T et al. Profile of pediatrics malignancies in Yangon children hospital: a three year study. Journal of Global Oncology 2. 2016. 2(3). DOI: 10.1200/JGO.2016.004838
18. Prajapati Z, Kokani MJ, Gonsai RN. Clinico-epidemiological profile of hematological malignancies in pediatric age group in Ahmedabad. Asian J Oncol. 2017;3:54-8.
19. Couitchere L, N'da G, Aholi JM, N'doumy M, Azagoh R, Oulai S. Childhood cancer: epidemiology in the pediatric oncology department of a university hospital center in Abidjan, Ivory Coast. Med Sante Trop. 2019;29(1):97-101.
20. Clarke RT, Van den Bruel A, Bankhead C, Mitchell CD, Phillips B, Thompson MJ. Clinical presentation of childhood leukemia: A systematic review and meta-analysis. Arch Dis Child. 2016;101(10):894-901.
21. Pahloosye A, Hashemi A, Mirmohammadi SJ, Atefi A. Presenting clinical and laboratory data of childhood acute lymphoblastic leukemia. J Ped Hematol Oncol. 2011;1(3):71-7.
22. Halalsheh H, Abuirmeileh N, Rihani R, Bazzeh F, Zaru L, Madanat F. Outcome of childhood acute lymphoblastic leukemia in Jordan. Pediatr Blood Cancer. 2011;57(3): 385-91.

23. Parvareh M, Khanjani N, Farahmandinia Z, Nouri B. The survival of childhood leukemia and its related factors in Kerman, Iran. Iran J Health Sci. 2015;3(4):24-32.
24. Pedrosa MF, Pedrosa F, Lins MM, Pontes Neto NT, Falbo GH. Non-Hodgkin's lymphoma in childhood: Clinical and epidemiological characteristics and survival analysis at a single center in Northeast Brazil. J Pediatr (Rio J). 2007;83(6):547-54.
25. Pillon M, Di Tullio MT, Garaventa A, Cesaro S, Putti MC, Favre C, et al. Long term results of the first Italian association of pediatric hematology and oncology protocol for the treatment of pediatric B-cell Non-Hodgkin lymphoma (AIEOP LNH92). Cancer. 2004;101(2): 385-94.
26. Sherief LM, Elsafy UR, Abdelkhalek ER, Kamal NM, Youssef DM, Elbehedy R. Disease patterns of pediatric Non-Hodgkin lymphoma: A study from a developing area in Egypt. Mol Clin Oncol. 2015;3(1);139-44.
27. Weinstein HJ, Hudson MM, Link MP (eds). Pediatric lymphomas. Berlin, Heidelberg: Springer; 2007.
28. Kelly KM. Lymphoma in children and adolescents: improving the therapeutic index. Blood. 2015;126(22): 2452-58.
29. Zhang HH, Wang HS, Qian XW, Fan CQ, Li J, Miao H et al. Genetic variants and clinical significance of pediatric acute lymphoblastic leukemia. Ann Transl Med. 2019;7(14):296 Doi.org/10.21037/atm.2019.04.80
30. Noronha EP, Marinho HT, Thomaz EB, Silva CA, Veras GL, Oliveira RA. Immunophenotypic characterization of acute leukemia at a public oncology reference center in Maranhão, northeastern Brazil. Sao Paulo Med J. 2011;129(6):392-401.
31. Sheikhpour R, Pourhosseini F, Neamatzadeh H, Karimi R. Immunophenotype evaluation of Non-Hodgkin's lymphomas. Med J Islam Repub Iran. 2017 (23 Dec);31:121 Doi.org/10.14196/mjiri.31.121.
32. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. Pediatr Clin North Am. 2015;62(1):61-73.