RESEARCH ARTICLE

Relapses in children with acute lymphoblastic leukaemia excluding L 3: a retrospective descriptive study from a single centre in Baghdad.

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ABSTRACT

Introduction: Acute lymphoblastic leukaemia is the most common childhood cancer, and relapse is the main reason for treatment failure in childhood acute lymphoblastic leukaemia.

Objective: to measure the relapse rate, factors affecting it and its outcomes among children with acute lymphoblastic leukaemia treated at the Child's Central Teaching Hospital in Baghdad from 1st January 2013 to 1st March 2020.

Methods: A retrospective study was conducted at the hemato-oncology ward in the Child's Central Teaching Hospital in Baghdad 2022. We reviewed the records of children diagnosed with and treated for acute lymphoblastic leukaemia except L3 at our centre during the studied period. We measured the relapse rate and studied the association between the development of relapse with some demo, clinical, haematological, and treatment parameters.

Results: Of 521 cases with acute lymphoblastic leukaemia, 68 (13.05%) patients relapsed. The male gender, T cell leukaemia and patients treated with modified UKALL 2011 were significant risk factors for relapse with p values (0.007, 0.00013, 0.000092), respectively. The relapse was very early in 35 patients (51.4%), early in 22 (32.3%), and late in 11 (16.17%), with bone marrow being the most common site of relapse in 34 (50%). WBC count of more than 50x109/L and using modified UKALL 2011 protocol for treatment were correlated with very early relapse, with p values of 0.0059 and 0.006, respectively. Of all relapsed patients, 5 (7.3 %) died before starting treatment, 16 (25.3 %) died during treatment, and 47 (69.1 %) got into a second remission. The overall survival over three years was 44.5%, with no difference between male and female gender. In correlation with other risk factors, overall survival for relapsed patients was significantly lower for T-cell leukaemia, with a p-value of 0.04.

Conclusion: Relapse is not uncommon in children with Acute lymphoblastic leukaemia. Male gender, T cell type and using modified UKALL 2011 protocol are associated with a high relapse rate. Overall survival of the relapse patient still poor with T cell leukaemia had a lower survival duration than type B cell.

Key words: acute lymphoblastic leukaemia, pediatric oncology, relapses, Iraq.

INTRODUCTION

Acute lymphocytic leukaemia (ALL) is one of the most common malignancies in children, accounting for about one-third of all childhood cancers, with a survival rate of about 90%. [1,2] Outcomes were worse in low- and middle-income countries than in high-income countries. [3] Childhood ALL is more common among those aged 3-4 years, in Caucasians than in African Americans (1.8:1 in the United States), and slightly more common in boys than girls.[4]

ALL are broadly classified as B-ALL or T-ALL based on immunophenotyping, with B-ALL comprising approximately 85% of cases.

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However, this percentage can differ depending on age at diagnosis, race, or ethnicity.[5] Acute lymphoblastic leukaemia represents a clonal expansion arrest at a specific stage of normal lymphoid hematopoiesis and is divided into precursor B-lymphoblastic leukaemia and precursor T-lymphoblastic leukaemia.[6]

The clinical manifestations of ALL vary and are generally nonspecific. Early signs and symptoms are often of anaemia, such as irritability, anorexia, weakness, and pallor; fever and infection may occur due to neutropenia; and bleeding, which may result from thrombocytopenia. Infiltration of various organs by leukaemic cells can lead to additional clinical symptoms, including hepatomegaly, splenomegaly, lymphadenopathy, and even central nervous system (CNS) symptoms.[7] At initial diagnosis, 30-50% of children with ALL may present with a palpable liver or spleen measuring 4 cm below the rib margin.[8] Organ infiltration may cause lymphadenopathy, hepatosplenomegaly, testicular enlargement, or CNS disorders such as cranial neuropathy, headache, seizures, and increased intracranial pressure.

The major cause of treatment failure is relapse, reported in 15-20 % of patients, resulting in a long-term overall survival (OS) rate of approximately 36%.[9] Most relapses in ALL occur in the bone marrow (BM) alone or combined, mainly with the central nervous system (CNS) or testes.[10] Survival can be predicted by sites involved at relapse, length of first complete remission, time from diagnosis to relapse, and immunophenotype of relapsed ALL.[11] Relapse in the bone marrow is reported in 15-20 % of patients with ALL, and it is the most serious, especially if it occurs during or shortly after completion of therapy. Intensive chemotherapy with agents not previously used in the patient, followed by allogeneic stem cell transplantation, can result in long-term survival for some patients with bone marrow relapse.[12]

The current study aims to measure the relapse rate, its associated factors, and outcomes among children with acute lymphoblastic leukaemia who attended the Child's Central Teaching Hospital in Baghdad from 2013 to 2020.

METHODS:

Setting and study design: A retrospective descriptive study was conducted from 1st March 2020 to 1st March 2022 on records of children under 15 years who were diagnosed with and treated for ALL at the haemato-oncology unit of Child's Central Teaching Hospital in Baghdad between 1st January 2013 and 1st March 2020.

Ethical approval: The proposal for the study was approved by the ethical committee of the Iraqi Council for Medical Specializations. Before data collection, the researcher obtained consent to utilise records from the administration of Child's Central Teaching Hospital.

Definition of the cases, inclusion and exclusion criteria: All records of children diagnosed with and treated for ALL at our centre between 1st January 2013 and 1st March 2020 were included in this study, which was 600 patients. We excluded seventy-nine patients; nine of them died very early before starting the induction phase of treatment, and seventy were referred to or starting treatment at other centres. Patients with ALL type L3 were excluded from this study because it was treated as a case of non-Hodgkins lymphoma.

Procedure and outcomes: Patients' data were retrieved from the records, encompassing age, gender, the outcome of the induction period and time of relapse, investigations at the time of relapse, therapy, and relapse outcome. At our centre, the initial diagnosis of ALL was conducted by an experienced haematologist based on the morphological classification of blast cells on bone marrow aspiration, following the French-American-British (FAB) classification. Immunophenotyping was unavailable in Iraq from 2013 to 2016. Consequently, 294 of all included patients were diagnosed using flow cytometry. It is worth noting that cytogenetic studies are unavailable in Iraq. The initial laboratory workup of patients with ALL included complete blood count and

blood film analysis, renal function tests, serum electrolytes, serum uric acid, liver function tests, screening for hepatitis, chest x-ray, and echocardiography. Computerised tomography and MRI scans were only performed when clinically indicated.

We classified the patients at the initial diagnosis into the standard risk group, defined as aged between 1 and< 10 years, with an initial WBC count of less than 50,000 X 10^9/L and the high-risk group, defined as age less than one or more than ten years with WBC count more than 50,000 X 10^9/L or T-cell leukaemia.[13]

The diagnosis of patients with T-cell leukaemia depended on either flow cytometry or clinical features in the form of mediastinal widening associated with older age, high WBC count, lymphadenopathy, and hepatosplenomegaly.

The treatment protocols of ALL used in our centre during the study were modified from the United Kingdom Acute Lymphoblastic Leukaemia (UKALL) protocols. Patients with precursor B-cell ALL (306 patients) were treated with UKALL 2003, modified by increasing the number of intrathecal doses during induction therapy. Patients with T-cell leukaemia were treated with NHL/BFM 95 protocol before 1st October 2017 (22 patients) and with modified MRC ALL 2011 after 1st October 2017 (193 patients). MRC was modified by increasing the number of intrathecal doses during the induction period and decreasing the dose of methotrexate from 5 g/m^2 to 2 g/m^2.[6]

The treatment protocols for relapsed patients were modified from MRC-UKALL-R3. Clofarabine was unavailable, and patients were treated by intermediate R3 protocol to adapt to the local limitations of supportive measures and the shortage of some chemotherapeutic agents. Infantile leukaemia was treated as a high-risk group with UKALL-group B protocol. CNS involvement in the presentation was treated according to age and WBC count. Cytogenetic study and minimal residual disease (MRD) were not available in the country at the time of the study. BM aspiration was done on days eight and fifteen after the start of induction, and according to the results, we shifted to another protocol.

Definition of relapse: An isolated bone marrow (BM) relapse was diagnosed when 25% of lymphoblasts were found in the BM without evidence of leukaemia at extramedullary sites. Isolated extramedullary relapses were diagnosed when patients exhibited clinically overt extramedullary manifestations of leukaemia with less than 5% marrow infiltration. CNS relapse was diagnosed in patients with a positive cytomorphology and WBC count of more than 5/μL or clinical signs of CNS leukaemia, such as facial nerve palsy or brain/eye involvement. Testicular relapse was diagnosed through clinical and ultrasound examination, and involvement of any other extramedullary site was confirmed histologically. In this study, only one patient presented with a late relapse of cervical lymph node was diagnosed by a biopsy, which revealed T lymphoblastic lymphoma with blast cells comprising less than 1% in the BM.

Complete remission was defined as the absence of leukaemic blasts in peripheral blood and CSF, less than 5% blasts on bone marrow aspirate, hematopoietic regeneration, and the absence of extramedullary (localised) disease. Induction failure was defined as the failure to achieve remission after one month of therapy. Abandonment of treatment was defined as care termination by the parent/caregiver or if more than four weeks had passed with a no-show/non-attendance for scheduled therapy by the patient. Overall survival is defined as the time from the date of diagnosis and/or start of treatment to the date of death.

Time of relapse: Based on time factor, relapses were categorised as follows:

- *Very early*: within 18 months of diagnosis, while on chemotherapy
- *Early*: occurred after 18 months of diagnosis and within six months of treatment completion
- *Late*: relapse documented more than six months after completion of therapy

Table 1 | Comparison between non-relapsed patients and relapsed with demographic data

	Total (%)	Non-relapsed (%)	relapsed (%)	P value
Total	521	453 (100)	68 (100)	
Gender:				0.007
Male	274 (52.6)	228 (83.2)	46 (16.8)	
Female	247 (47.4)	225 (91.1)	22 (8.9)	
Age (year)				0.15
< 1	25 (4.8)	20 (80)	5 (20)	
1 – <10	427 (81.5)	377 (88.30)	50 (11.70)	
≥ 10	69 (13.25)	56 (81.2)	13 (18.8)	
Clinical examination				0.9
Organomegaly	454 (87.14)	401 (88.5)	53 (11.67)	
Lymphadenopathy	324 (62.18)	287 (88.58)	37 (11.41)	

Statistical analysis: Patient data were processed using the SPSS version 20 statistical package. Qualitative data are shown as frequency and percentage, and quantitative data are shown as mean± standard deviation and median. The chi-square test was used for comparative analysis. Life-table estimates were calculated using the Kaplan-Meier method. Patients without adverse events were censored at the date of the last reported contact. The differences between curves were tested for statistical significance using the log-rank test. The p-value is significant at 0.05.

RESULTS

From 1st January 2013 to 1st March 2020, 521 patients were diagnosed with ALL; 274 (52.6%) were males, and 247 (47.4%) were females. The total patients who relapsed were 68 (13%); 46 (16.8%) were males, and 22(8.9%) were females, with a male-to-female ratio of 2:1. The range of ages of patients with ALL was between 2 months and 15 years. Of all patients with ALL, 25 (4.8 %) patients were less than one year, 5 (20%) of them relapsed; 427 (81.5%) patients were between 1 and < 10, 50 (11.70%) of them relapsed; and 69 (13.25 %) patients were ten years and above, 13 (18.8%) of them relapsed. Table 1 compares age, gender, organomegaly and lymphadenopathy of patients with ALL who relapsed to non-relapsed, with p-values of 0.007, 0.15, and 0.9, respectively.

Table 2 presents the laboratory data of patients. An initial haemoglobin level of 5 g/dl and less was observed in 74 (89.2%) non-relapsed patients and 9 (10.8%) relapsed patients. Conversely, haemoglobin levels exceeding 10 g/dl were recorded in 78 (82.9%) non-relapsed patients, compared to 16 (17.1%) relapsed patients. A total white blood cell (WBC) count of less than $50x10^9$/L was noted

Table 2 | Laboratory data of all patients with acute lymphoblastic leukaemia, non-relapsed and relapsed patients

	Total	Non–relapsed (%)	Relapsed (%)	P value
Total	521	453 (100)	68 (100)	
Hb g/dl				0.41
≤ 5	83(15.93)	74 (89.2)	9(10.8)	
>5 <10	344 (66.02)	301(87.5)	43(12.5)	
>10	94(18.04)	78 (82.9)	16(17.1)	
WBC count				0.74
< 50 x109/L	384(73.7)	335(87.3)	49(12.7)	
≥ 50 x109/L	137 (26.29)	118(86.13)	19(13.87)	
Mediastinal widening	46 (8.82)	37(80.4)	9(19.6)	0.8
FAP classification				0.7
L1	343 (65.83)	301(87.8)	42(12.2)	
L2	173 (33.2)	148(85.5)	25(14.5)	
Undifferentiated leukemia	5 (0.95)	4(80)	1(20)	
Types of leukaemia				0.00013
B-cell	467 (89.63)	415(88.8)	52(11.13)	
T-cell	54 (10.36)	38(70.4)	16(29.6)	

Table 3 | Risk group, treatment protocols, bone marrow status during induction and initial CNS involvement in non-relapsed and relapsed patients with ALL.

Character	Total	Non-relapsed No. (%)	Relapsed No. (%)	P value
	521	453(100)	68 (100)	
Risk Status				0.0015
Standard risk	299 (57.3)	272 (90.96)	27 (9.04)	
High risk	222 (42.6)	181 (81.55)	41 (18.5)	
Treatment Protocols				0.000092
UKALL 2003	306 (58.7)	281 (91.85)	25 (8.15)	
UKALL2011	193 (37,1)	157 (81.4)	36 (18.7)	
NHL/BFM 95	22 (4.2)	15 (86.2)	7 (10.2)	
Initial CNS disease	(521)			0.0036
Negative	505 (97)	442(87.5)	63 (12.47)	
Positive	16 (3)	10 (62.5)	6(37.5)	

in 335 (87.3%) non-relapsed patients and 49 (12.7%) relapsed patients. Conversely, a WBC count of 50x10^9/L and above was found in 118 (86.13%) non-relapsed patients and 19 13.87%) relapsed patients, yielding a p-value of 0.74. All haematological indices in Table 2 exhibited statistically non-significant associations in relapsed and non-relapsed patients, except for the type of leukaemia, where relapse was more common in B-cell than in T-cell leukaemia, with a p-value of 0.00013.

Table 3 shows that 299 (57.3) patients were in the standard-risk group and 222 (42.6%) were in high risk; 27 (9.04 %) of the standard-risk patients relapsed, compared to 41 (18.5) of high-risk. This difference was statistically significant, with a p-value of 0.0015. Three hundred and six (58.7%) patients were treated according to the modified UKALL 2003 protocol; 25(8.15%) patients relapsed. One hundred and ninety-three (37.1%) patients were treated according to modified UKALL 2011; 36 (18.7%) patients relapsed. Twenty-two (4.2%) patients with T cell leukaemia were treated according to NHL BFM95 protocol; seven of them (10.2%) relapsed. Initial CSF examinations were positive in 16 patients (3.0 %), and 6 (37.5 %) relapsed. Table 3 shows that risk group, protocol of treatment used and CNS involvement had a statistically significant association in relapsed and non-relapsed patients with ALL, with p-values of 0.0015, 0.000092, 0.0036, respectively.

Of the 68 patients who relapsed, 35 (51.4%) did so very early, 22 (32.3%) early, and 11(16.17%) late.

The site of relapse was divided as follows: isolated bone marrow relapse occurred in 34 patients (50%), isolated extramedullary CNS in 22 patients (32.3%), isolated extramedullary local site (lymph nodes) in 1 patient (1.4%), and combined relapses in 11 patients (16.17%). See Table 4.

Table 5 correlates the time of relapse with gender, age, WBC count, risk group, and the treatment protocol. Only WBC counts, and the treatment protocol demonstrated statistically significant associations, with p-values of 0.0059 and 0.006, respectively.

The flow chart in Figure 1 shows the details

Table 4 | Time and Site of relapse of 68 patients

	Number	%
All ALL patients	521	
Relapsed	68	13.1
Non-relapsed	453	86.9
Time of relapse		
Very early	35	51.4
early	22	32.2
late	11	16.1
Site of relapsed		
Isolated BM	34	50
Combined	11	16.17
Extramedullary CNS	22	32.3
Extramedullary local site (lymph node)	1	1.4

Table 5 | Correlation between time of relapse and other variable

		Very early No. (%)	Early No. (%)	Late No. (%)	P value
	Total	35	22	11	
Gender					0.5
Male	46	23 (50)	14 (30.4)	9 (19.6)	
Female	22	12 (54.5)	8 (36.4)	2 (9.1)	
Age (years)					0.6
1 – <10	51	27 (53)	15 (29.4)	9 (17.6)	
≥ 10	17	8 (47.1)	7 (41.1)	2 (11.8)	
WBC count					0.0059
< 50 x109/L	45	17 (37.7)	18 (40)	10 (22.3)	
≥ 50 x109/L	23	18 (78.3)	4 (17.4)	1 (4.3)	
Risk group					0.06
Standard risk	25	9 (13.2) 36	9 (13.2) 36	7 (10.2) 28	
High risk	43	26 (60.5)	13 (30.2)	4 (9.3)	
Protocol type					0.006
UKALL 2003	25	7 (28)	11 (44)	7 (28)	
UKALL2011	36	26 (72.2)	8 (22.2)	2 (5.6)	
NHL/BFM 95	7	2 (28.6)	3 (42.8)	2 (28.6)	

of the outcomes of the relapsed patients. Five (7.3 %) died before starting treatment, 16 (25.3%) died during induction, and 47 69.1% got into second remission.

Figures 2 shows the Kaplan-Meier curves showing the overall survival of relapsed children with ALL plotted againt duration in days. Figure 3 shows the affect of gender on overall survival; 48% for males and 30% for females with a p-value of 0.5. On the other hand, Figure 4 shows The effect of type of Lukaemia on overall survival; 46 % for B-ALL and for 30 % for T cell type, with a p value of 0.04 .

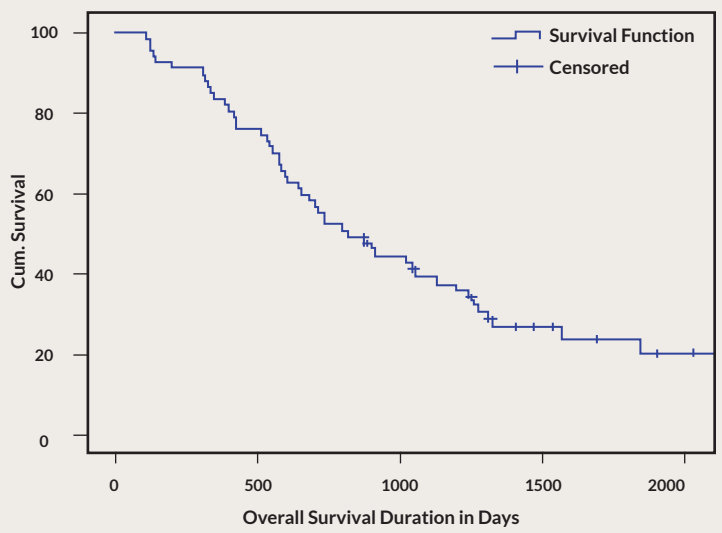
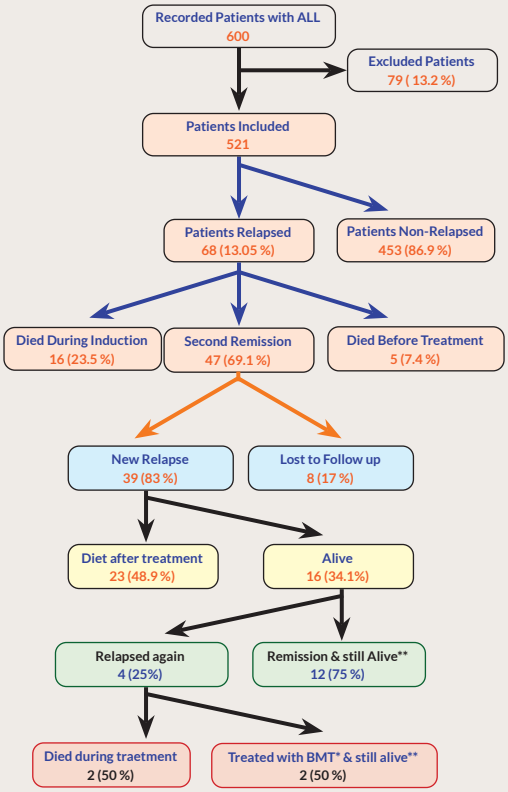


Figure 2 | Three years Overall survival of relapsed patient with ALL.

DISCUSSION

ALL relapses represent a catastrophic event, leading to diminished survival and serving as the primary cause of treatment failure.[14] In our study, relapse was identified in 68 (13%) patients with ALL, a result which is comparable to that reported by a study in Turkey.[15] In our series, 46 children who relapsed were males, and 22 were females, with a male:female ratio of 2.09:1. In an unpublished study conducted in Iraq, Al-Safaar has also shown that males are more commonly relapsed than females, 1.2:1. [16] Similarly, a study from 3 Central American countries showed a male:female ratio of about 1.6:1.[14] WBC count did not significantly affect the relapse rate in our study, with a p-value of 0.178, similar to what Abdelmabood et al.[17] found in their research.

In our study, we found that 63 (12.47 %) of negative CNS involvement relapsed compared



* BMT: Bone marrow transplantation, ** Alive till the 1st March 2022

Figure 1 | Flow chart of the outcome of relapsed patients with ALL.

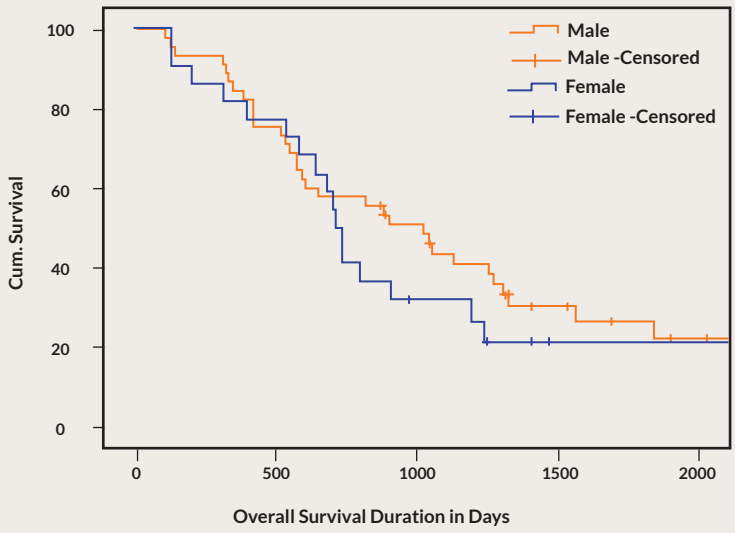


Figure 3 | Overall Survival of the relapsed patients with ALL according to gender.

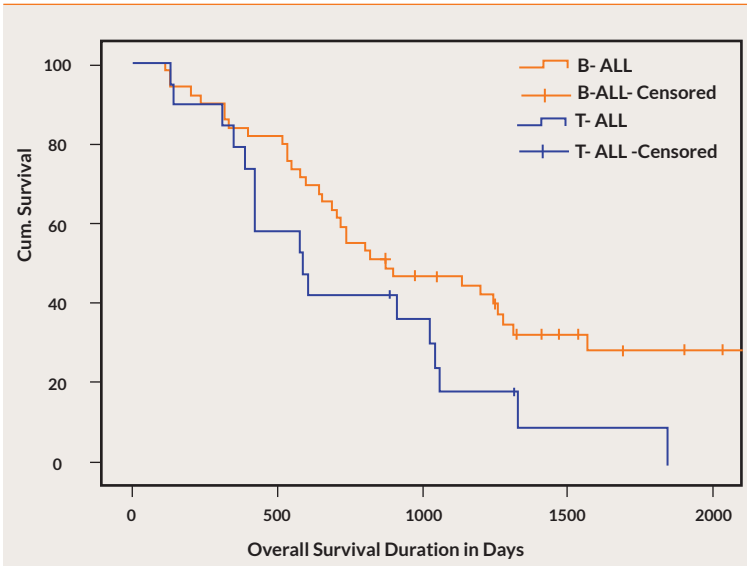


Figure 4 | Overall Survival of the relapsed patients with ALL according to the type of lukaemia.

to 6(37.5%) in those who had positive CNS involvement, with a p-value of 0.0036. This percentage is much less than that stated by Al-Shujairy et al.,[18] who found that 70 % of patients with ALL who have CNS involvement relapsed.

T-cell leukaemia was associated with relapse significantly, with a p-value of 0.00013. This association agrees with what Oskarsson et al. found in Nordic society;[19] however, Abdelmabood[17] found this relation statistically insignificant. Similarly, we found that children in the high-risk group were statistically associated with relapse consistent with that reported by Abdelmabood.[17] and this is supported by the fact that the high-risk group had a high incidence of relapse in many works of literature.

We identified that 51.4 % of all relapses occur very early. This percentage is relatively higher than the 46.3 % reported by Abdelmabood [17] and the 33 % reported by Al-Safaar [16] but falls slightly below that of Jaime-Perez et al., 56.3%.[14] Early relapse was identified in 32.2% of our patients, consistent with the findings reported by Abdelmabood et al.[17] (31.7%) and Al-Safaar et al.[16] (33%), yet surpassing the rate documented by Jaime-Perez et al.[14] (26.4%). Late relapse was found in 16.1% of our series, approximately matching that of Jaime-Perez et al.[14] but lower than that reported by Abdelmabood et al., 22% [17] and in the Al-Safaar et al. 34 %[16] studies.

Regarding the type of relapse, isolated bone marrow (BM) relapse accounted for 50%, which is similar to Ghali, 51.8%,[20] but lower than Abdelmabood, 53.7%,[17] and slightly higher than Al-Safaar, 47%.[16]

We found that isolated CNS relapse in 32.3% of our patients, representing around 4% of the total patients, which is lower than that reported by Al-Shujairy et al.[18] in a study conducted in our centre in 2007, where CNS relapse, isolated or combined, was 23.1%. This decrease in the percentage of CNS relapse can be attributed to the use of a high dose of methotrexate in the UKALL 2011 protocol and increased doses of intrathecal therapy. Our rate of CNS relapse is similar to Abdelmabood, 31.7%,[17] and lower than Al-Safaar, 35%).[16] We observed a combined relapse in 16.17% of cases, similar to Jaime-Perez's 17.2%,[14] but higher than Ghali's 12.7%,[20] and Abdelmabood's 12.2%. [17] We found a lymph node involvement in only one patient, representing 1.4 %. Similarly, Abdelmabood [17] reported lymph node involvement in only one patient, representing 2.7% of his sample. Isolated testicular relapse was not observed in this study and was only presented in combined relapse cases, which differs from the findings of Kulkarni et al.,[21] where testicular relapse occurred in 7.4% of cases. This discrepancy may reflect changes in chemotherapy regimens and their impact on reducing the percentage of relapse.

Our study found a statistically significant association between the time for relapse and WBC count and the type of protocol used, where the modified UKALL 2011 protocol showed more association for early relapse. Al-Safaar[16] found a similar association with WBC count. The association of types of treatment at the time of relapse may be due to the modification of the UKALL 2011 protocol rather than the characteristics of the original UKALL 2011 protocol.

The correlation between the time of relapse and risk factors revealed a statistically significant association between the time of relapse and WBC count, with a p-value of 0.0059, similar to findings reported by Al-Safaar et al.[16] Additionally, a correlation was observed with the type of protocol used, where the modified UKALL 2011 protocol showed a risk factor for early relapse. This may be attributed to modifications in the protocol rather than reflecting the characteristics of the original UKALL 2011 protocol.

Our study's three-year overall survival (OS) rate was 48 % for males and 30 % for females. The rates are higher than the 25 % and 20 % reported by Al-Safaar.[16] The overall survival in our series correlated significantly with the type of leukaemia, in contrast to Abdelmabood's findings,[17] where the p-value was 0.19

CONCLUSION

Relapse is not uncommon in children with Acute lymphoblastic leukaemia who were treated at the Child's Central Teaching Hospital from January 2013 to March 2020. Male gender, T cell type and using modified UKALL 2011 protocol are associated with a high relapse rate. Most of the relapses occurred very early. Overall survival of the relapse patient still poor with T cell leukaemia had a lower survival duration than type B cell.

REFERENCES

1. Inaba H, Greaves M and Mullighan CG. Acute lymphoblastic leukemia. *Lancet* 2013; 381:1943-55.
2. HungerSP and Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med* 2015; 373(16):1541-52.
3. Marjerrison S, Antillon F, Fu L, Martinez R, Vasquez R, Bonilla M, Howard SC, Sung L. Outcome of children treated for relapsed acute lymphoblastic leukemia in Central America. *Cancer*. 2013 Mar 15;119(6):1277-83. doi: 10.1002/cncr.27846. Epub 2012 Nov 16. PMID: 23165914.
4. Scheurer ME, Lupo PJ, Schüz J, Spector LG, Wiemels JL, Aplenc R et al. An overview of disparities in childhood cancer: report on the Inaugural Symposium on Childhood Cancer Health Disparities, Houston, Texas, 2016. *Pediatric hematology and oncology*. 2018 Feb 17;35(2):95-110.
5. Inaba H, Pui CH. Advances in the Diagnosis and Treatment of Pediatric Acute Lymphoblastic Leukemia. *J Clin Med*. 2021 Apr 29;10(9):1926. doi: 10.3390/jcm10091926. PMID: 33946897; PMCID: PMC8124693.
6. Pillai PM and Carroll WL. Chapter 18 - Acute Lymphoblastic Leukemia. In: Editor(s): Philip Lanzkowsky, Jeffrey M. Lipton, Jonathan D. Fish. Lanzkowsky's Manual of Pediatric Hematology and Oncology. 7th edition, Elsevier Inc., 2021.
7. Roganovic J. Acute lymphoblastic leukemia in children. In:

Guenova M, editor. Leukemia. London: InTech Open; 2013. p39–74.

8. Gutierrez A, Silverman LB. Acute Lymphoblastic Leukemia. In Nathan and Oski's Hematology and Oncology of Infancy and Childhood E-Book. Elsevier Health Sciences, 2015 (50):p2000-41.
9. Saarinen-Pihkala UM, Parto K, Riikonen P, et al. RALLE pilot: response-guided therapy for marrow relapse in acute lymphoblastic leukemia in children. J *Pediatr Hematol Oncol*. 2012;34:263–70.
10. Malempati S, Gaynon PS, Sather H, et al. Outcome after relapse among children with standard-risk acute lymphoblastic: Children's Oncology Group study CCG-1952. *J Clin Oncol*. 2007;25:5800–7.
11. Locatelli F, Schrappe M, Bernardo ME, et al. How I treat relapsed childhood acute lymphoblastic leukemia. *Blood*. 2012;120:2807–2816.
12. Friehling E, Ritchey AK, Tubergen DG, Bleyer A. Acute Lymphoblastic Leukemia. In Nelson Text book of Pediatrics . Elsevier Health Sciences, 2020 (522.1):10413-27.
13. Margolin JF, Rabin KR, Steuber CP, Poplack DG. Acute Lymphoblastic Leukemia. In: Principles and Practice of Pediatric Oncology, 7th ed, Pizzo PA, Poplack DG (Eds), Lippincott-Raven, Philadelphia 2016;19:1016-114.
14. Jaime-Pérez JC, Pinzón-Uresti MA, Jiménez-Castillo RA, Colunga-Pedraza JE, González-Llano Ó, Gómez-Almaguer D. Relapse of childhood acute lymphoblastic leukemia and outcomes at a reference center in Latin America: organomegaly at diagnosis is a significant clinical predictor. *Hematology*. 2018 Jan;23(1):1-9. **doi: 10.1080/10245332.2017.1333294. Epub 2017 Jun 3. PMID: 28580844.**
15. Guzelkucuk Z, Arman Bilir Ö, Ok Bozkaya, Kaçar D, Isik M, Gürlek Gökçebay D, Özbek NY, Yaralı HN. Outcomes of Low and Middle Income Children with Relapsed Acute Lymphoblastic Leukemia: Single-Center Experience. *J Contemp Med*. September 2023;13(5):975-981. **doi:10.16899/jcm.1345525**
16. Al-Safaar H; Al-Badri SA. Outcome of relapse in acute lymphoblastic leukemia in children , Experience of a single institute. A thesis was submitted to the Arab Board for Health Specialization in Pediatrics, 2020 (the study is unpublished).
17. Abdelmabood S, Fouda AE, Boujettif F, Mansour A. Treatment outcomes of children with acute lymphoblastic leukemia in a middle-income developing country: high mortalities, early relapses, and poor survival. *Journal de Pediatria* (Versao em Portugues), 2020; 96(1):108-16.
18. Al-Shujairi, T A, Al-Nassir I, Abass AA, Al-Shaibani MR, Al-Janabi AN, Allawi AA. Central Nervous System Relapse in acute Lymphoblastic Leukemia: Prognostic Factors and the Outcome. *Iraqi Postgraduate Medical Journal*, 2008;7(4):339-346.
19. Oskarsson T, Söderhäll S, Arvidson J, Forestier E, Frandsen TL, Hellebostad M, Lähteenmäki P, Jónsson ÓG, Myrberg IH, Heyman M, Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL Relapse Working Group. Treatment related mortality in relapsed childhood acute lymphoblastic leukemia. *Pediatric Blood & Cancer*. 2018 Apr;65(4):e26909.
20. Ghali, H H. Effectiveness of modified UKALL protocols in children with acute lymphoblastic leukemia; An experience of Children Welfare Teaching Hospital. *Mustansiriya Med J* 2014;13(2): 53-60.
21. Kulkarni KP, Terhan A, Bansal D. Testicular relapse in childhood acute lymphoblastic leukemia: the challenges and lessons. *Indian journal of cancer* 2010;47(2): 134-8.

Abbreviations list: Acute lymphocytic leukaemia (ALL), Bone marrow (BM), Central nervous system (CNS), French-American-British (FAB), Magnetic Resonance Imaging (MRI), Minimal residual disease (MRD), Non-Hodgkin lymphoma Berlin–Frankfurt–Münster-95 (NHL/BFM 95), Overall survival (OS), The Statistical Package for Social Sciences (SPSS), United Kingdom Acute Lymphoblastic Leukemia (UKALL), White Blood Cell (WBC),

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