Acute Lymphoblastic Leukaemia in children: A single centre experience

Mousa Qatawneh MD*,Tania Ogeilat MD**. Moath Altarwneh MD*, Asim Momani MD**,Maher Mustafa MD*, Majd Odtallah MD*

ABSTRACT

Objective: To analyse the frequencies of clinical and laboratory risk factors and cytogenetic abnormalities in Jordanian children with acute lymphoblastic leukaemia and their response to therapy.

Methods: We conducted a retrospective analysis of 116 paediatric acute lymphoblastic leukaemia cases diagnosed and treated in Queen Rania Hospital for Children between January 2015 and December 2019. Children were diagnosed by bone marrow aspirate microscopic examination and flow cytometry. Cytogenetic anomalies were detected using fluorescence *in situ* hybridisation. Descriptive analysis was given for the age, gender, acute lymphoblastic leukaemia immune phenotype, cytogenetic anomalies, initial white cell count, and initial response to chemotherapy. These variables were correlated in frequencies with each other and with response to treatment in order to detect high risk groups and characteristic patterns.

Results: The ages ranged from 3 months to 14 years with a peak age group of 1-4 years and almost equal gender distribution. B-cell acute lymphoblastic leukaemia was diagnosed in 104 (89.7%) cases, while 12 (10.3%) were of T-cell lineage. CD10 negativity was detected in 10 cases (9.6%), high white cell count in 18 (15.5%), t(12;21) in 15 (14.4%), t(9;22) in 4 (3.8%) and 11q23 rearrangement in 3 infants (2.9%). A poorer response to therapy and higher mortality was detected in T-cell subtype, infancy, older age, high white cell count, presence of t(9;22) and 11q23 rearrangement, and slow responders to initial chemotherapy.

Conclusion: Identifying adverse prognostic factors of the most common paediatric leukaemia allows for tailoring chemotherapy protocols, closer monitoring of high risk groups to improve treatment outcomes.

Key words: Acute lymphoblastic leukaemia, ALL, cytogenetics, t(9;22), 11q23.

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Introduction

Acute lymphoblastic leukaemia (ALL) is a clonal neoplasm of the blood and bone marrow (BM) arising from an uninhibited proliferation of lymphoblasts, which are the immature precursor cells of B or T lymphocytes (1).

From the Department of:
* Queen Rania Children Hospital
** Princess Iman Research and Laboratory Sciences Center, King Hussein Medical Center
Correspondence should be addressed to:
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It is the most common childhood leukaemia and accounts for 25% of all malignancies in children (2,3). The incidence is estimated at 3.4 per 100,000 people in the United States and the majority of cases are of the B-ALL type (4,5). Long-term survival increased over the past decade to exceed 80% in developed countries. Although lower rates are observed in developing countries, prognosis is improving with recent advances and better access to health care (6-9).

Certain clinical, immunophenotypic and cytogenetic features influence the response of ALL to treatment, and their evaluation aids the risk stratification of patients. High risk features include age <1 year or ≥10 years, male gender, CNS involvement, initial white blood count ≥50× 10^9/ L for B-ALL and ≥100× 10^9/L for T-ALL, T-cell lineage, BCR–ABL positive, and MLL rearrangements among others (10,11).

This study analysed the above-mentioned features in children diagnosed with and treated for ALL at Queen Rania Hospital for Children (QRH) in correlation with their response to chemotherapy in order to identify higher-risk ALL patients and administer the proper chemotherapy protocols.

Methods

Prior approval of the ethics committee was acquired at the Royal Medical Services in March 2021.

This retrospective study included 116 patients under 14 years of age who were diagnosed with ALL between January 2015 and December 2019. Over this period, the average follow up time for patients was 3 years.

Children from different geographical areas in Jordan were referred to QRH for further evaluation, diagnosis, treatment and follow up. A diagnosis of ALL was made when 20% or more lymphoblasts were observed upon microscopic examination of BM smears and confirmed by immunophenotyping using the Becton Dickinson fluorescence activated cell sorter Canto II, See **figure 1.** BM specimens were also tested by fluorescence *in situ* hybridisation for three specific anomalies: t(12;21), also known as the ETV6-RUNX1 rearrangement, t(9;22) which is known as the Philadelphia chromosome or BCR-ABL1 fusion gene, and the MLL gene rearrangements (11q23).

All of our study patients received chemotherapy at QRH and their remission statuses were assessed at the following points: after induction chemotherapy, after completing consolidation treatment, and at any point where there is clinical or laboratory suspicion of disease relapses. Remission is defined as the morphologic evidence of less than 5% blasts in the BM (12).

Electronic medical records were retrospectively reviewed to collect the following data: age, gender, immunophenotypic subtype, and WBC at the time of diagnosis, Cytogenetic study results were collected form the department's records. Data were analysed using Microsoft Excel Spreadsheet Software 2010 and descriptive analysis using frequencies was applied to the variables of this study.

Exclusion criteria were age above 14 years, patients who were not diagnosed or did not receive their treatment in QRH, acute leukaemia of myeloid lineage, lymphoblastic lymphomas without BM involvement, as well as high risk syndromes including Down syndrome, Fanconi anaemia, neurofibromatosis, ataxia telangiectasia, and Bloom and Li-Fraumeni syndromes.

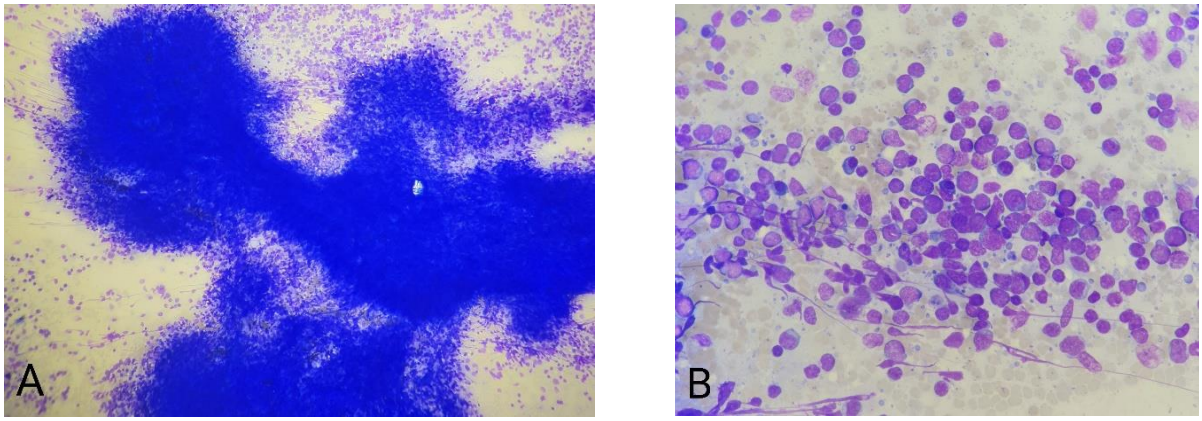

Figure 1 : Precursor B-cell acute lymphoblastic leukaemia.
A Hypercellular bone marrow aspirate due to infiltration by blasts.
B Lymphoblasts show a high nuclear:cytoplasmic ratio with homogenous nuclear chromatin.

Results

Our study included 116 ALL patients whose ages ranged between 3 months and 14 years. The characteristics of ALL children in Jordan, including their gender, age, ALL type, CD10 expression, initial WBC and cytogenetic anomalies are shown in **Table I**.

Age distribution: The vast majority (74.1%) were aged between 1 and 9 years, with a peak age group of 1–4 years. Infantile leukaemia (leukaemia in infants up to 1 year of age) comprised 4.3% and children older than 10 years comprised 21.6%. All infantile leukaemia cases were of the B-ALL type, and 80% were CD10 negative, with MLL rearrangements detected exclusively in this age group. A significant association (p <.05) was found between infantile age group and high WBC, MLL rearrangements, and CD10 negativity with X^2 values of 8.0, 61.2, and 29.9, respectively. Infancy per se had a significant correlation with mortality (X^2 =5.5, p < .05). The average ages were older in T-ALL cases, followed by CD10 positive B-ALL and CD10 negative B-ALL with an average of 7.9, 5.9 and 4.8 years, respectively.

Gender distribution: There was an almost equal distribution among the two genders with 61 males comprising 52.6% of ALL cases, and 55 females comprising the remaining 47.4%. Of note, we found a 2:1 female predominance in infants. On the other hand, the T-ALL subtype was seen twice as frequently among males.

B-ALL was the most common type of paediatric leukaemia comprising 89.7%, of which 93.3% had a CD10-positive phenotype. T-ALL cases constituted 10.3% of the total sample.

Table II shows patient characteristics and treatment responses in relation to their ALL subtype. CD10 negativity showed a significant correlation with mortality (X^2=4.1, $p < .05$).

The initial WBC at presentation was highest in CD10 negative B-ALL followed by T-ALL and CD10 positive B-ALL, averaging 61.3 x10^6/µL, 32.1 x10^6/µL and 20.0x10^6/µL, respectively. No patients with T-ALL had leukopenia (WBC less than 4x10^6/µL). WBC exceeding 50 x10^6/µL was detected in 16 out of 104 B-ALL cases. A high WBC count showed a significant correlation with relapse rates (X^2=4.2, $p < .05$).

Cytogenetic results of 104 B-ALL patients revealed t(12;21) in 15 cases (14.4%) as the most frequent chromosomal anomaly. In this group, the average age was 4.9 years with a 100% CD10 positivity. All had successful induction and their overall survival was 100%.

Next in frequency was t(9;22) in 4 cases (3.8%). Their average age was 8.5 years and all were CD10-positive. Two failed remission induction (50%), one relapsed after bone marrow transplant and died, and another relapsed and achieved remission again. The presence of this transaction carried a significant risk for disease relapse (X^2=6.8, $p < .05$).

MLL rearrangement was found in 3 infants, which constituted 2.9% of the total study subjects and 60% of infantile leukaemia. The average age in this group was 8 months and all were CD10-negative. The average WBC was 131.3 x10^9/L. The youngest of these three was 4 months old, had the highest WBC count of 196x10^9/L, and died during induction. MLL correlation with mortality was significant (X^2=4.3, $p < .05$).

A total of six cases failed induction chemotherapy (5.2%). Two had t(9;22) and one had 11q23 rearrangements. Of these 6 cases, 3 relapsed (50%) and one died. Failure of remission induction is a significant risk factor associated with subsequent relapses and higher mortality (X^2=13.6 and 22.9, respectively).

Table I: Characteristics of Jordanian children with ALL.

Patient characteristic	Number	Percentage	Patient characteristic	Number	Percentage
Age (years)			**Initial white cell count (x10^9/L)**		
			<4	**23**	**19.8**
0-4 (0-1)	**47 (6)**	**40.5 (5.2)**	**4-10**	**44**	**37.9**
5-9	**44**	**37.9**	**11-50**	**31**	**26.7**
10-14	**25**	**21.6**	**>50**	**18**	**15.5**
Gender			**Response to induction chemotherapy**		
Male	**61**	**52.6**	**Remission**	**110**	**94.8**
Female	**55**	**47.4**	**Non-Remission**	**6**	**5.2**
Subtype			**Cytogenetic anomalies (in B-ALL cases)**		
B-ALL	**104**	**89.7**	**t(12;21)**	**15**	**14.4**
T-ALL	**12**	**10.3**	**t(9;22)**	**4**	**3.9**
			11q23	**3**	**2.9**
			Negative	**83**	**79.8**
CD10 (in B-ALL cases)					
Positive	**94**	**90.4**	**Negative**	**10**	**9.6**

ALL: acute lymphoblastic leukaemia.

Table II: Distribution of risk factors and treatment responses in relation to the immunophenotype.

Patient characteristic	CD10 positive B-ALL	CD10 negative B-ALL	T-ALL
Number of cases	94	10	12
Average age (years)	5.9	4.8	7.9
Infantile leukaemia No. (%)	2 (2.1%)	4 (40%)	0
Male: Female	1:1	1:1	2:1
Average WBC ($x10^9$/L)	20.0	61.3	32.1
Cytogenetic anomalies No. (%)	t(12;21): 15 (16%) t (9:22): 4 (4.3%)	11q23: 2 (20%)	
Remission Induction Success No. (%)	91 (96.8%)	7 (70%) success	12 (100%)
Disease relapse No. (%)	9 (9.6%)	2 (20%)	2 (16.7%)
Mortalities No. (%)	4 (4.3%)	2 (20%)	2 (16.7%)

ALL: acute lymphoblastic leukaemia. WBC: White blood cells.

Events and treatment results:

A 5-year event-free and overall survival rate could be calculated for a subset of our study subjects who were diagnosed in 2015 and 2016. Rates were 81.8% and 86.4%, respectively.

Disease relapses were detected in 13 cases (11.2%). One or more risk factors were present with the following frequencies: two had the T-ALL subtype, two had CD10-negative B-ALL, three were of the older age group, four had high WBC, two were positive for t(9;22) and three failed remission induction. A statistically significant correlation was determined with high WBC, t(9;22), and failure of induction.

The mortality rate was 6.9% (8 of 116), 16.7% in T-ALL, and 5.8% in B-ALL. Among B-ALL cases, mortality was 4.3% in CD10-positive and 20% in CD10-negative phenotypes. Induction mortality occurred in one patient (0.9%). These mortalities were associated with the following risk factors: two had T-ALL, two were CD10-negative, one of whom was an infant with MLL rearrangement and died during induction, two were from the older age group, two had high WBC, one had t(9;22) and three failed remission induction. Among these, age < 1 year, CD10 negativity, MLL rearrangement, and failure of remission induction were statistically significant. **Table III** details relapse and mortality rates among suggested risk groups in comparison with the overall rates.

Risk factors	Total No.	Disease Relapses	Percentage	Mortalities	Percentage
Age < 1 year	5	0	0	1	20%
Age ≥ 10 year	25	4	16%	3	12%
Subtype					
CD10 -ve B-ALL	10	2	20%	3	30%
T-ALL	12	2	16.7%	2	16.7%
WBC> 50 x10^9/L	18	4	22.2%	2	11.1%
Failed induction	6	4	66.7%	3	50%
T(9;22)	4	2	50%	1	25%
MLL	3	0	0	1	33.3%
Total sample	116	14	12.1%	8	6.9%

Table III: Treatment results among suggested risk groups.

ALL: acute lymphoblastic leukaemia. WBC: White blood cells.

Discussion

The 5-year event-free survival rate for paediatric ALL exceeds 80% in developed countries (13). Our ALL patients in Jordan had a comparable rate of 82% as well as superior treatment outcomes compared to many developing countries such as Egypt, Mexico and India where the three-year overall survival is close to 60% (10,14,15). Better outcomes are due to improved health care access as well as our risk-directed treatment protocols that avoid under- and over-treatment.

ALL patients at QRH undergo the St. Jude total XV chemotherapy protocol, which consists of three phases and lasts for 36 months for males and 30 months for females regardless of their risk stratification.

The five-week induction phase includes the following agents: dexamethasone, vincristine, doxorubicin, L-asparaginase, cyclophosphamide, cytarabine and 6-mercaptopurin, in addition to triple intrathecal therapy. High risk protocol includes 9 doses of L-asparaginase instead of 6 doses given for lower risk ALL. High risk patients with CNS involvement also receive intrathecal chemotherapy twice weekly until two subsequent blast-free fluid specimens are obtained.

The consolidation phase is composed of 8 weeks in which 4 doses of high-dose methotrexate are given with the continuation of 6-Mercaptopurine, in addition to 4 intrathecal chemotherapy sessions. High risk ALL patients receive 5 grams/m² of methotrexate while the low risk ALL patients receive 2.5 grams/m².

The continuation phase continues over 27 months for female patients and 33 months for males, during which a combination of the previously mentioned agents is given. High risk patients receive more doses of doxorubicin and L-asparaginase, on the other hand, high risk patients receive 2 doses of 5 grams/m² methotrexate instead of 3 doses of 2.5 grams/m² given in standard risk patients.

Many factors play a role in the prognosis of ALL in children. Age is one of the prognostic factors and most studies showed a good prognosis for the age group (1–9 years), and poorer prognosis in infants and older children (3). The majority (73.3%) of our study subjects were of a favourable age. The average age and the peak age group did not differ from the international collaborative study by the Middle East Childhood Cancer Alliance, and other Western studies (16-18). It was also comparable to the averages of 5.5 and 6.3 years reported in Iran and Brazil, respectively (19,20).

In this study, infants exhibited a characteristic presenting pattern of high initial WBC (96.1 $x10^9$/L on average), CD10 negativity (in 80%) as well as the presence of 11q23 rearrangement (in 60%).

The T-cell subtype, which accounts for 10–15% of paediatric ALL cases, is considered a higher-risk paediatric leukaemia than B-ALL (21,23). It comprised 10.3% of our subjects, which was close to the Brazilian but less than the Middle East study (16,20).

Its poor prognosis may in part be due to the frequent adverse prognostic factors associated with this subtype, such as the older age and WBC counts than B-ALL cases observed in our study. The literature estimates the survival of high-risk relapse children at 30% (23). Our study had two relapsed T-ALL cases, and they both died.

The most common chromosomal translocation in paediatric B-ALL is the favourable t(12;21) occurring in 25% of cases (24). In our study, it was also the most frequent. We recognised 15 cases (14.4%) which is lower than in Western populations but similar to the Middle East region (13,22). Their average age was 4.9 years and all were CD10-positive. All had successful induction and their overall survival was 100%. These outcomes were consistent with its favourable prognostic value. However, the outcome may be modified by overlapping adverse prognostic factors. For example, one case exhibiting this translocation had disease relapse which was explained by the presence of hyperleukocytosis, which is defined as WBC above 100 $x10^9$/L, at presentation.

Unfavourable translocations in B-ALL include t(9;22) and translocations involving the MLL gene (25). Halalsheh et al. detected t(9;22) in 7.4% of Jordanian children with ALL (25). In our study, we detected t(9;22) in 4 cases (3.8%) and an 11q23 rearrangement in 3 infants (2.9%) which was closer to the frequencies in Western studies (3% and 5%, respectively) (27). In our study, t(9;22) was positive in older children than in the t(12;21) group (average 8.5 years) and showed poorer outcomes, with 50% relapse and 25% mortality rates.

MLL rearrangement is found in 3–5% of children and 61–80% of infants with ALL and is characterised by its rapid onset, hyperleukocytosis and poor prognosis (28). Similarly, it was found in 2.9% of all children and 60% of infants in our study and was recognised in 3 infants presenting with a typical clinical picture of sudden onset hyperleukocytosis with an average WBC of 131.3 $x10^9$/L and a CD10-negative phenotype. The youngest patient in the study sample was a 4 month-old baby who had MLL rearrangement and the highest WBC count of 196 $x10^9$/L, and she died during remission induction.

The initial WBC count is another ALL prognostic factor. The published literature established high WBC at presentation as a poor prognostic factor of ALL (29). The average WBC in our patients was highest in the CD10-negative phenotype, especially in the MLL group discussed previously. T-cell phenotypes also shared a higher average WBC. WBC exceeding 50 $x10^9$/L was detected in 16 cases who suffered higher relapses and mortalities.

Limitations of this study included the difficulty in collecting data due to its retrospective nature, the absence of patients' computerised records in earlier years, as well as the loss of contact with a few patients due to the remoteness of their residence. Other prognostic factors could not be included in this study. For example, data regarding CNS involvement was incomplete. A known number of 85 out of the total 104 B-ALL patients had no CNS involvement at the time of diagnosis. Another two cases were found to have CNS involvement in association with other risk factors, one with t(9;22) another with high WBC count. DNA index, minimal residual disease, and other chromosomal translocations were not performed at our centre. Another limitation was the short follow up period for patients which had an average of three years, meaning that the long-term survival analysis was rendered beyond the scope of the study.

Conclusion

ALL is the most common paediatric malignancy, and despite improvements in management and care access, there remains a possibility of disease relapse for some patients. Therefore, it is of great importance to determine prognostic factors in newly diagnosed ALL cases to tailor risk-directed therapy. Further studies are recommended to confirm the long-term prognostic value of these characteristics with the addition of prognostic factors that were not included in this study.

Abbreviations

ALL: Acute lymphoblastic leukaemia
BM: Bone marrow
QRH: Queen Rania Hospital for Children
WBC: White Blood Cell Count

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