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# Treatment of infantile acute lymphoblastic leukemia, experience of a country with limited resources

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**Abstract:**

**BACKGROUND:** Infantile acute lymphoblastic leukemia (ALL) is associated with poor outcomes worldwide, particularly in low-resource settings. Despite advances in pediatric ALL therapy, survival rates for infants remain substantially lower than those observed in older children. Evaluating treatment outcomes over time may help identify factors associated with improved survival.

**OBJECTIVES:** To assess treatment outcomes and survival trends of infants with ALL treated at a single tertiary center in Iraq over three distinct treatment periods.

**MATERIALS AND METHODS:** This retrospective study included infants (<1 year old) diagnosed with ALL and treated at the Children's Welfare Teaching Hospital in Baghdad between January 2000 and December 2016. Patients were treated using adapted UKALL-97, UKALL-2003, and UKALL-2011 protocols, with a small subset receiving an infant-specific protocol. Patients were grouped by treatment period (2000–2005, 2006–2011, and 2012–2016). Overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan–Meier method and compared using the log-rank test.

**RESULTS:** Among 59 infants diagnosed with ALL, 11 (19%) refused treatment. Of the remaining 48 treated patients, 24 (50%) achieved complete remission, 4 (8%) were resistant to therapy, and 17 (35%) died during induction. Complete remission rates improved across treatment periods from 36% to 45% and 71%, respectively. Among responders, 6 (25%) relapsed, 10 died during subsequent therapy, and 5 were lost to follow-up. The 36-month OS and EFS for treated patients were 30.2% and 17%, respectively, with a nonsignificant trend toward improved EFS in the 2012–2016 cohort.

**CONCLUSION:** The outcomes of infantile ALL in this low-resource setting remain poor, characterized by high induction mortality and treatment abandonment. Although survival improved over time—particularly following the introduction of a steroid prephase and enhanced supportive care—overall prognosis remains unsatisfactory, underscoring the need for further therapeutic and supportive care improvements.

**Keywords:**

Infant, Iraq, leukemia

## Introduction

Acute lymphoblastic leukemia (ALL) in children treated with contemporary chemotherapy protocols has achieved cure rates exceeding 80% in high-income countries.[1-3] This success reflects advances in understanding and characterizing the immunobiology of ALL, the development of prognostic indicators, the optimized adaptation of chemotherapy regimens, and improvements in supportive care. In addition, a multidisciplinary approach to patient management, robust hospital infrastructure, and comprehensive psychosocial support for patients and



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their families are critical to further improving survival rates.[2,3]

ALL is the most common cancer among children in the United States, with approximately 6000 cases reported annually, about half of which occur in children and adolescents. It is also the leading cause of cancer-related death in individuals under 20 years of age.[4,5] Cure rates in children with ALL in India have not consistently exceeded 80%, as seen in developed nations.[5,6] Important contributing factors include socioeconomic constraints, disease biology, and management-related challenges, all of which result in poorer survival rates.[7,8]

Various studies from different countries have examined pediatric populations to identify factors associated with an increased incidence of ALL. Notably, age, race, ethnicity, genetic predisposition, and white blood cell (WBC) count have been shown to influence risk, with the United States reporting a marked peak incidence in childhood.[9] These factors can help predict outcomes, with older age and higher WBC counts associated with poorer prognosis. An age >10 years or a WBC count exceeding 50,000/mm$^3$ is defined as a high-risk group based on consensus guidelines.[10]

Fortunately, survival rates were substantially higher with the regimen described by Riehm *et al*., which includes induction and consolidation phases using eight drugs over an 8-week period. This regimen became the core of the Berlin–Frankfurt–Münster protocol due to its quality and effectiveness, achieving 5-year event-free survival (EFS) rates of up to 85% in the most recently reported data.[11,12]

In light of the above, the present study evaluates survival distributions after applying treatment protocols across three distinct time periods.

## Materials and Methods

This was a retrospective study of 59 participants diagnosed with ALL at <1 year of age, treated at the Children's Welfare Teaching Hospital, Baghdad, Iraq, between 2000 and 2016. Data collection and analysis were performed at the Pediatric Oncology Unit in Baghdad, and treatment outcomes were reported. Clinical data were obtained retrospectively from patients' medical records.

Data were analyzed using the Chi-square test and Fisher's exact test for univariate analysis, and the Kruskal–Wallis test for multivariate analysis. Survival distributions for overall survival (OS) and EFS were estimated using the Kaplan–Meier product-limit method. Subgroup analyses were performed for descriptive purposes. Differences in OS and EFS were assessed using the log–rank test in univariate analysis. All analyses were performed using SPSS software (version 23; IBM Corporation, Armonk, New York, USA), with $P < 0.05$ considered statistically significant.

Treatment consisted of adapted UKALL-97, UKALL-2003, and UKALL-2011 protocols, as well as a specific infant protocol for three patients. Since October 2008, a steroid prephase was introduced. Patients were divided into three cohorts according to treatment period (2000–2005, 2006–2011, and 2012–2016).

### Statistical analysis

Data were analyzed using SPSS (version 23; IBM Corporation, Armonk, New York, USA). Categorical variables were compared with the Chi-square or Fisher's exact test, and continuous data with the Kruskal–Wallis test. Survival outcomes (OS, EFS) were estimated using Kaplan–Meier curves and compared by log–rank test. A two-sided $P < 0.05$ was considered significant.

### Ethical considerations

This retrospective study was conducted in accordance with the ethical standards of the Institutional Review Board at the Children's Welfare Teaching Hospital, which approved the protocol before data collection. Given the retrospective design, the requirement for informed consent was waived; however, patient confidentiality and data anonymity were strictly maintained in line with the principles of the Declaration of Helsinki. The study protocol was approved under order number (1) on January 1, 2023.

## Results

Among all pediatric oncology cases registered at the facility over 17 years, 1635 children were diagnosed with ALL, of whom 59 (3.6%) were infants. Table 1 presents the demographic characteristics of these patients, categorized by year of diagnosis. There were

**Table 1: Demographic characteristics of patients enrolled in the study**

| Item | 2000–2005 (16) | 2006–2011 (23) | 2012–2016 (20) | *P* |
|---|---|---|---|---|
| Gender, *n* (%) | | | | |
| Male | 12 (75.0) | 12 (52.2) | 7 (35.0) | 0.058 |
| Female | 4 (25.0) | 11 (47.8) | 13 (65.0) | |
| Age group (months), *n* (%) | | | | |
| 1–5 | 9 (56.2) | 10 (43.5) | 10 (50.0) | 0.601 |
| 6–10 | 6 (37.5) | 12 (52.2) | 7 (35.0) | |
| 11–12 | 1 (6.2) | 1 (4.3) | 3 (15.0) | |
| Residence, *n* (%) | | | | |
| Baghdad | 4 (25.0) | 9 (39.1) | 11 (55.0) | 0.187 |
| Out of Baghdad | 12 (75.0) | 14 (60.9) | 9 (45.0) | |

no statistically significant differences between groups in terms of gender, age, or place of residence ($P > 0.05$). Age classification in months was presented to account for the narrow developmental range of infancy (<1 year). Subdividing patients into 1–5, 6–10, and 11–12 months allows for more precise comparison of outcomes, since even small differences in age during infancy may influence disease biology, treatment tolerance, and prognosis.

Table 2 compares the blood indices of patients across the three study periods, showing no statistically significant differences between groups. Taken together, the demographic characteristics [Table 1] and blood indices [Table 2] indicate no baseline differences likely to affect patient outcomes.

**Table 2: Age and blood indices of patients enrolled in the study**

| Item | 2000–2005, median (range) | 2006–2011, median (range) | 2012–2016, median (range) | *P* |
|---|---|---|---|---|
| Age (months) | 4.3 (1–11) | 6.0 (1–11.8) | 4.8 (1–11.9) | 0.967 |
| Hb (g/dl) | 6.70 (4–12.7) | 7.90 (2.7–12.8) | 6.50 (3–13.8) | 0.665 |
| WBC $\times 10^9$ | 101 (4.3–500) | 81.5 (7–448) | 195 (7.8–965) | 0.093 |
| Platelet $\times 10^9$ | 17 (10–120) | 25 (10–598) | 4 (6–218) | 0.309 |

WBC=White blood cell, Hb=Hemoglobin

**Table 3: Treatment protocol details for patients enrolled in the study**

| Item | 2000–2005, *n* (%) | 2006–2011, *n* (%) | 2012–2016, *n* (%) | *P* |
|---|---|---|---|---|
| Treatment protocol | | | | |
| UKALL 97 | 7 (43.8) | 1 (4.3) | 0 | 0.001 |
| UKALL 2003 | 6 (37.5) | 18 (78.3) | 5 (25) | |
| UKALL 2011 | 0 | 0 | 8 (40) | |
| Not treatment | 2 (12.5) | 3 (13) | 6 (30) | |
| Infant protocol | 1 (6.2) | 1 (4.3) | 1 (5) | |
| Prephase steroid | | | | |
| Yes | 0 | 10 (43.5) | 15 (75) | 0.001 |
| No | 16 (100) | 13 (56.5) | 5 (25) | |
| Prephase steroid response | | | | |
| Good response | 0 | 6 (26.1) | 9 (45) | 0.001 |
| Poor response | 0 | 2 (8.7) | 6 (30) | |
| Not evaluated | 16 (100) | 15 (65.2)* | 5 (25) | |
| Induction response | | | | |
| Complete remission | 5 (31.2) | 9 (39.1) | 10 (50) | 0.319 |
| Not responding | 0 | 2 (8.7) | 2 (10) | |
| Induction death | 7 (43.8) | 8 (34.8) | 2 (10) | |
| Lost | 4 (25) | 4 (17.4) | 6 (30) | |

*Include 2 received steroids and not evaluated and 13 did not receive steroids at all

Table 3 summarizes the treatment protocols used across the three groups, which were classified according to the period of diagnosis and treatment. Patients diagnosed between 2000 and 2005 were treated with the UKALL-97 protocol, whereas those diagnosed between 2006 and 2011 received the UKALL-2003 protocol. From 2012 to 2016, most patients were treated with the UKALL-2011 protocol.

A key distinction between these periods is that patients treated before 2006 did not receive a prednisolone prephase, which was introduced in 2006 and administered to subsequent patients. Consequently, prephase response could not be evaluated for those treated before 2006.

Table 4 presents the final status of patients included in the study. The cure rate improved to 71% during the 2012–2016 treatment period, compared with 36% in 2000–2005. The table also details the rate of death during induction chemotherapy and the number of patients who refused treatment.

Table 5, Figures 1 and 2 present the OS and EFS of the 59 patients studied over 3 years. The OS rate was 30.2%, with a median follow-up of 33 months, whereas the EFS rate among 47 evaluable patients was 17%, with a median follow-up of 30 months.

Figure 3 and Table 6 shows the 3-year OS of patients by treatment period. The highest survival rate was observed in patients treated during 2012–2016 (55.3%), compared with 13.6% for those treated during 2006–2011.

## Discussion

Diagnosing leukemia is challenging for clinical hematologists in low-income countries, and this difficulty is even greater in cases occurring in children under 1 year of age. The main obstacles include limited laboratory capabilities necessary for accurate diagnosis and reliance on traditional diagnostic methods.[13]

**Table 4: Treatment outcomes of patients enrolled in the study**

| Item | 2000–2005 (16) | 2006–2011 (23) | 2012–2016 (20) | Total (59) |
|---|---|---|---|---|
| Refused therapy | 2 | 3 | 6 | 11 |
| Treated | 14 | 20 | 14 | 48 |
| Complete remission, *n* (%) | 5/14 (36) | 9/20 (45) | 10/14 (71) | 24 (50) |
| No response | 0 | 2 | 2 | 4 |
| Induction death | 7 | 8 | 2 | 17 |
| Lost/unknown | 2 | 1 | 0 | 3 |

**Table 5: Overall and event-free survival of patients**

| Item | Months | Estimate (%) | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|
| Overall survival | 36 | 30.2 | 18.4 | 49.5 |
| Event-free survival | 36 | 17 | 9.1 | 32 |

CI=Confidence interval

**Table 6: Overall survival at 36 months by year of diagnosis**

| Year of diagnosis | Follow-up (months) | Survival rate (%) | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|
| 2000–2005 | 36 | 21.8 | 4.7 | 100 |
| 2006–2011 | 36 | 13.6 | 3.8 | 48.1 |
| 2012–2016 | 36 | 55.3 | 33.9 | 90.1 |

CI=Confidence interval

Given the lack of resources for diagnosing leukemia using advanced techniques, ALL was diagnosed with the available methods, primarily based on bone marrow morphology. The reliance on traditional diagnostic methods was reflected in the choice of treatment strategies. This study addresses the treatment of patients under 1 year of age who were diagnosed with leukemia and managed using different therapeutic approaches across distinct periods. Treatment protocols were selected in accordance with updates from international scientific references, with some modifications made to adapt to local resource availability and the level of supportive care services. These limitations often compelled physicians to avoid intensive regimens due to the inability to adequately manage treatment-related complications.[14,15]

When reviewing the experience of managing leukemia in low-income countries, the challenges observed are similar to those reported in the present study, although survival outcomes in some countries — such as Turkey and those in Latin America – have been better than those recorded here.[16,17]

The current study demonstrates an improvement in survival rates for children with ALL across the treatment periods examined, increasing sequentially from 36% to 45% and 71%. The lowest survival rate was recorded in patients treated between 2000 and 2005. This cannot be attributed solely to the treatment protocol used at that time, as several contributing factors likely played a role. During this period, Iraq was under United Nations sanctions, which led to shortages of essential chemotherapeutic agents, as well as the collapse of medical infrastructure and supportive care services.[14,18]

The relative improvement observed in the second study period may be attributed to Iraq's increased engagement with international collaborators, such as Italy, through telemedicine consultations, mutual

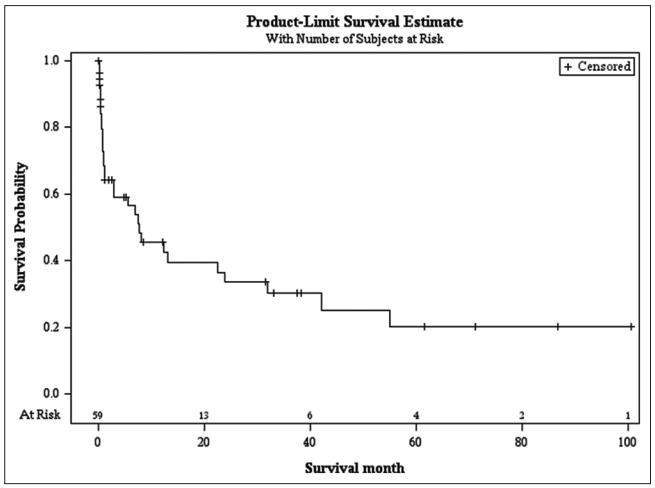


**Figure 1:** Three-year overall survival of patients

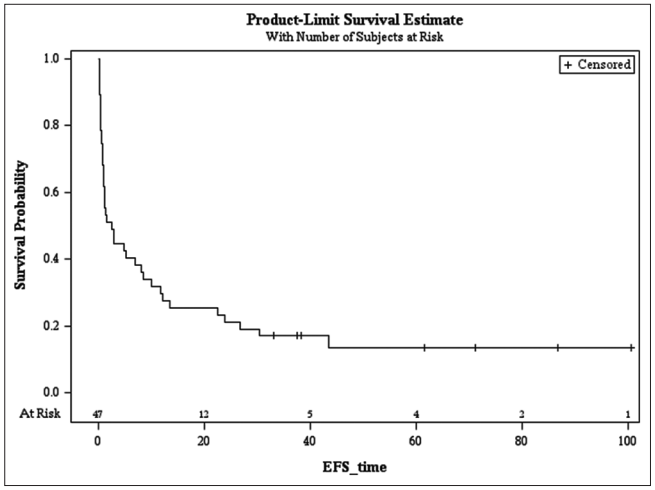


**Figure 2:** Three-year event-free survival of patients

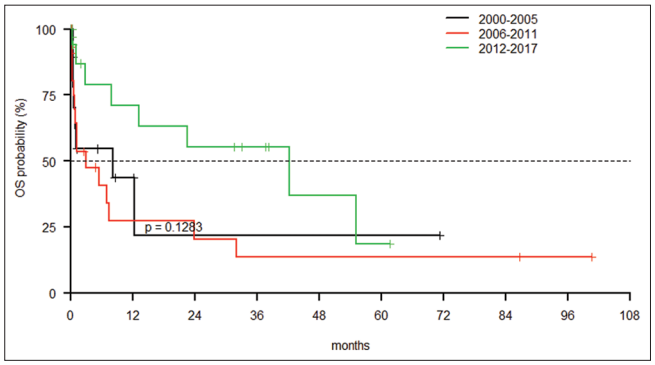


**Figure 3:** Overall survival of patients by treatment period

visits, and access to the experience of medical centers in high-income countries. These exchanges were reflected in better patient survival outcomes.[19,20] However, the survival rate during this time was still influenced by the challenging security and political environment, which created significant barriers for both oncologists and patients.[21]

In the third study period, the introduction of the prephase steroid protocol may have contributed to the marked improvement in survival rates.[22] Nonetheless, it was not the only factor; advancements in treatment approaches, improved diagnostic capabilities through collaboration with scientific research centers,[23] and enhanced supportive care services also played key roles. Despite these improvements, OS rates for infant ALL in this setting remain relatively low.[13]

## Conclusion

Although the introduction of the prephase steroid protocol improved survival rates for infants with ALL at the Children's Welfare Teaching Hospital in Baghdad, the cure rate remained low, with high mortality during the induction phase of chemotherapy and a substantial rate of treatment abandonment. While the cure rate increased to 50% during 2012–2016, the prognosis for this patient group remains poor.

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Nil.

### Conflicts of interest
There are no conflicts of interest.

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