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Retrospective analysis of demographic and clinical characteristics and treatment outcomes of pediatric acute lymphoblastic leukemia patients

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Abstract

Aim: This study aimed to compare treatment outcomes (mortality and relapse) between two pediatric acute lymphoblastic leukemia (ALL) protocols (TR-ALL BFM 2000 vs ALL-IC-BFM 2009) and to describe the demographic, clinical, and laboratory characteristics of patients treated at a single center (2010–2015).

Methods: We retrospectively reviewed the medical records of 121 children (<18 years) diagnosed with ALL and treated with either TR-ALL BFM 2000 or ALL-IC-BFM 2009. Baseline characteristics, risk group, immunophenotype, protocol, relapse status, and survival status were recorded. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate ($p < 0.05$).

Results: The cohort was 53.7% male, with a mean age at diagnosis of 7.55 ± 3.89 years. B-cell ALL accounted for 78.5% and T-cell ALL for 21.5%. The overall mortality rate was 11.6% (14/121), and relapse occurred in 5.8% (7/121) of patients. Mortality differed by risk group (SRG 6.5%, IRG 7.3%, HRG 23.5%; $p = 0.036$). Relapse was higher in T-cell ALL than in B-cell ALL (23.1% vs 1.1%; $p = 0.001$). Compared with ALL-IC-BFM 2009, TR-ALL BFM 2000 was associated with higher mortality (19.2% vs 5.8%; $p = 0.022$) and relapse (11.5% vs 1.4%; $p = 0.019$).

Conclusion: In this single-center retrospective cohort study, the high-risk group was associated with higher mortality, and the T-cell immunophenotype was associated with higher relapse. Patients treated with ALL-IC-BFM 2009 had lower crude mortality and relapse rates than those treated with TR-ALL BFM 2000; however, these protocol comparisons should be interpreted cautiously, given potential confounding and limited event numbers.

Keywords: Acute lymphoblastic leukemia, pediatric, treatment protocol, mortality, relapse, prognostic factors

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood, accounting for approximately 25–30% of all pediatric cancers (1). Thanks to advances in multi-agent chemotherapy protocols and improvements in supportive care over the past 40 years, 5-year survival rates in pediatric ALL have approached 90% (2, 3). However, relapse remains one of the major obstacles to treatment, and survival after relapse remains considerably lower than that achieved after first-line therapy (4).

ALL is a heterogeneous disease, and its prognosis is influenced by many factors, including age at diagnosis, white blood cell count, immunophenotype, cytogenetic abnormalities, and early response to treatment (5). Identifying these prognostic factors allows patients to be assigned to the correct risk groups and enables the application of treatment protocols with varying intensities, thereby reducing toxicity and increasing survival (6).

Recent epidemiological studies have shown that the burden of ALL is not uniformly distributed across populations. A global analysis of children aged 0–5 years demonstrated marked variation in prevalence, mortality, and disability burden across regions and socio-demographic settings, with persistent disadvantages in low-resource areas despite overall progress in outcomes (7). In addition, geographic and demographic analyses based on Global Burden of Disease 2021 data highlighted differences in leukemia burden according to sex, age, geographic location, and modifiable risk profiles, emphasizing the importance of interpreting institutional series within their broader epidemiologic context (8). Socioeconomic determinants may also affect treatment access and delivery, as population-based SEER data have shown that chemotherapy utilization in ALL varies according to age, income, education, marital status, and insurance coverage (9).

Clinical presentation of ALL is highly variable, and the disease may follow either a rapidly progressive or a more insidious course. In most children, the initial manifestations are related to bone marrow failure or extramedullary infiltration and include nonspecific symptoms such as fatigue, pallor, fever, bone pain, and loss of appetite, along with physical findings such as lymphadenopathy, hepatomegaly, and splenomegaly. Because these findings may mimic common pediatric conditions, careful evaluation of demographic, clinical, and laboratory features remains important for early diagnosis, accurate risk stratification, and appropriate treatment planning in routine practice (6, 9).

In this context, real-world data from single-center cohorts remain valuable, particularly in regions where referral patterns, healthcare access, and supportive-care conditions may differ from those reported in large multicenter trials. Therefore, the present study aimed to compare treatment outcomes between the TR-ALL BFM 2000 and ALL-IC-BFM 2009 protocols and to describe the demographic, clinical, and laboratory characteristics of children with ALL treated at a tertiary center between 2010 and 2015.

This retrospective study primarily aimed to compare treatment outcomes (mortality and relapse) between the TR-ALL BFM 2000 and ALL-IC-BFM 2009 protocols in pediatric patients with ALL treated at the Dicle University Children's Hospital (2010–2015). The secondary objective was to describe baseline demographic, clinical, and laboratory characteristics and to explore their univariable associations with outcomes.

Materials and Methods

Ethics committee approval for this study was obtained from the Dicle University Local Ethics Committee, in accordance with the World Medical Association Declaration of Helsinki (Date: 12 January 2017, Approval No: 2017/09).

Study design and setting

This retrospective cohort study included 121 children (<18 years) diagnosed with ALL and treated at the Hematology and Oncology Outpatient Clinic of Dicle University Faculty of Medicine Children's Hospital between January 2010 and December 2015.

Data collection

Medical records were reviewed to extract age at diagnosis, sex, place of residence (urban/rural), presenting symptoms, and physical examination findings (lymphadenopathy, hepatomegaly, and splenomegaly). Baseline complete blood count values at diagnosis (white blood cell count, hemoglobin, platelet count), immunophenotype (B-ALL/T-ALL), cytogenetics t(9;22), t(4;11) when available), risk group (standard, intermediate, high), treatment protocol (TR-ALL BFM 2000 or ALL-IC-BFM 2009), hematopoietic stem cell transplantation status, relapse status, and vital status were recorded.

Outcomes

Mortality was defined as death from any cause during follow-up. Relapse was defined as any documented bone marrow or extramedullary recurrence after achieving remission. Variables such as residence and presenting symptoms were summarized descriptively and were not modeled as prognostic factors, consistent with the primary endpoint of protocol comparison.

Statistical analysis

Analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as the mean ± standard deviation, and

categorical variables are presented as numbers (percentages). Baseline demographic, clinical, laboratory, and disease characteristics were compared between the TR-ALL BFM 2000 and ALL-IC-BFM 2009 groups at the 95% confidence level. Categorical comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. Because the number of events was limited (14 deaths and seven relapses) and precise time-to-event data were not consistently available, multivariable regression models and survival (Kaplan–Meier) analyses were not performed; outcomes are reported as crude proportions. A two-sided p-value <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

The baseline demographic and clinical characteristics at diagnosis are summarized in Table 1. The mean age at diagnosis was 7.55 ± 3.89 years, and 53.7% of patients were male.

Laboratory findings and disease characteristics

Laboratory and disease characteristics are shown in Table 2. Overall, 78.5% of the patients had B-ALL, and 21.5% had T-ALL. The risk group distribution was as follows: standard risk (SRG), 38.0%; intermediate risk (IRG), 33.9 %; and high risk (HRG), 28.1 %. Cytogenetic abnormalities, t(9;22) and t(4;11), were detected in 3.3% and 0.8% of the patients, respectively (Table 2).

Treatment and outcomes

Treatment protocols and outcomes are summarized in Table 3. ALL-IC-BFM 2009 was administered to 69 patients (57.0%), and TR-ALL BFM 2000 was administered to 52 (43.0%). Hematopoietic stem cell transplantation was performed in five patients (4.1%). Relapse occurred in seven patients (5.8%), and 14 patients (11.6%) died during the follow-up.

Analysis of prognostic factors

In univariable analyses (Table 3), mortality differed by risk group (SRG 6.5%, IRG 7.3%, HRG 23.5%; p = 0.036) and by treatment protocol (TR-ALL BFM 2000 19.2% vs ALL-IC-BFM 2009 5.8%; p = 0.022). Relapse was more frequent in T-cell ALL than in B-cell ALL (23.1% vs 1.1%; p = 0.001) and was higher with TR-ALL BFM 2000 than with ALL-IC-BFM 2009 (11.5% vs 1.4%; p = 0.019). Other baseline comparisons, including sex and baseline blood count categories, were not statistically significant (p > 0.05).

A graphical illustration of the study is shown in Figure 1. It was enhanced with the assistance of Google NotebookLM Pro (Google LLC, San Francisco, CA, USA).

Table 1. Baseline demographic and clinical characteristics at diagnosis (N=121).

Characteristic	Value
Age at diagnosis, years	7.55 ± 3.89 (Mean ± SD)
Age 1-6 years	85 (70.2%)
Sex, male	65 (53.7%)
Sex, female	56 (46.3%)
Residence, urban	63 (52.1%)
Residence, rural	58 (47.9%)
Presenting symptom: fatigue	100 (82.6%)
Presenting symptom: loss of appetite	94 (77.7%)
Presenting symptom: pallor	91 (75.2%)
Presenting symptom: fever	82 (67.8%)
Physical finding: lymphadenopathy	80 (66.1%)
Physical finding: splenomegaly	64 (52.9%)
Physical finding: hepatomegaly	61 (50.4%)

No statistically significant baseline differences were found between the TR-ALL BFM 2000 and ALL-IC-BFM 2009 groups (all p > 0.05, 95% confidence level).

Table 1 summarizes the baseline demographic and clinical characteristics of the 121 pediatric ALL patients at diagnosis. The mean age was 7.55 ± 3.89 years, 70.2% were aged 1–6 years, and there was a slight male predominance; fatigue, loss of appetite, pallor, and fever were the most common presenting symptoms, while lymphadenopathy, splenomegaly, and hepatomegaly were the main physical findings.

Table 2. Laboratory and disease characteristics at diagnosis (N=121).

Characteristic	Value
WBC <20,000/mm³	79 (65.3%)
Hemoglobin >7 g/dL	86 (71.1%)
Platelets ≤100,000/mm³	82 (67.8%)
Immunophenotype: B-ALL	95 (78.5%)
Immunophenotype: T-ALL	26 (21.5%)
Risk group: SRG	46 (38.0%)
Risk group: IRG	41 (33.9%)
Risk group: HRG	34 (28.1%)
Cytogenetics: t(9;22)	4 (3.3%)
Cytogenetics: t(4;11)	1 (0.8%)

No statistically significant baseline differences were found between the TR-ALL BFM 2000 and ALL-IC-BFM 2009 groups (all $p > 0.05$, 95% confidence level).

Table 2 presents the laboratory and disease characteristics of the patients at diagnosis. B-ALL was the predominant immunophenotype (78.5%), most patients had WBC <20,000/mm^3, hemoglobin >7 g/dL, and platelet counts ≤100,000/mm^3, and the risk groups were distributed across standard-, intermediate-, and high-risk categories, while cytogenetic abnormalities t(9;22) and t(4;11) were rare.

Table 3. Treatment, outcomes, and univariable associations with mortality and relapse.

Factor / Outcome	Category	n/N (%)	p-value
Overall treatment and outcomes			
Treatment protocol	TR-ALL BFM 2000	52/121 (43.0%)	
Treatment protocol	ALL-IC-BFM 2009	69/121 (57.0%)	
HSCT performed	Yes	5/121 (4.1%)	
Mortality (overall)	Deaths	14/121 (11.6%)	
Relapse (overall)	Relapse	7/121 (5.8%)	
Univariable associations with mortality			
Risk group (mortality)			0.036
Risk group	SRG	3/46 (6.5%)	
Risk group	IRG	3/41 (7.3%)	
Risk group	HRG	8/34 (23.5%)	
Treatment protocol (mortality)			0.022
Treatment protocol	TR-ALL BFM 2000	10/52 (19.2%)	
Treatment protocol	ALL-IC-BFM 2009	4/69 (5.8%)	
Univariable associations with relapse			
Immunophenotype (relapse)			0.001
Immunophenotype	B-ALL	1/95 (1.1%)	
Immunophenotype	T-ALL	6/26 (23.1%)	
Treatment protocol (relapse)			0.019
Treatment protocol	TR-ALL BFM 2000	6/52 (11.5%)	
Treatment protocol	ALL-IC-BFM 2009	1/69 (1.4%)	

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-cell ALL; T-ALL, T-cell ALL; SRG, standard-risk group; IRG, intermediate-risk group; HRG, high-risk group; HSCT, hematopoietic stem cell transplantation. P-values are from chi-square tests; Fisher's exact test was used when the expected cell counts were <5.

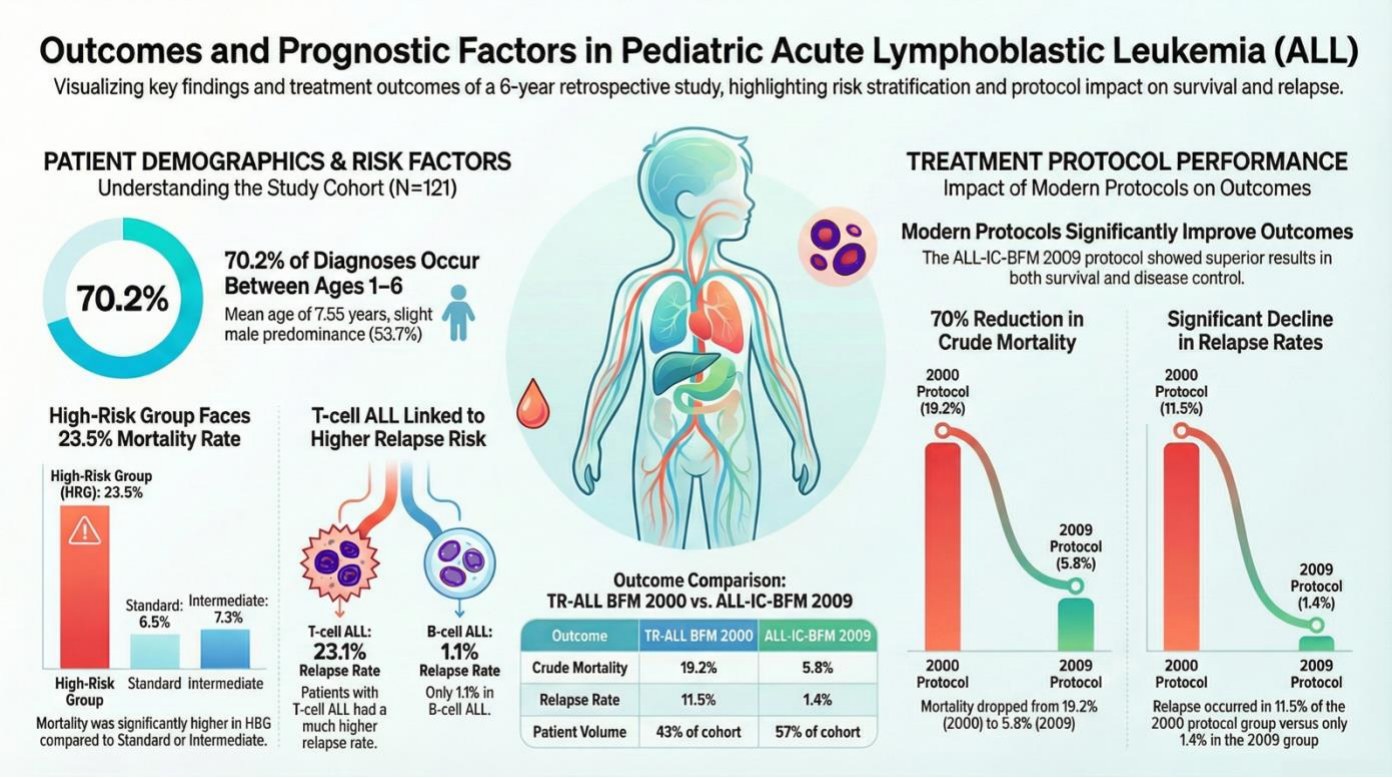

Figure 1. Graphical illustration of the study (Enhanced with the assistance of Google NotebookLM Pro).

Discussion

This retrospective study evaluated the demographic profile, clinical presentation, and treatment outcomes of children with ALL treated at a single tertiary center in Southeast Anatolia over a six-year period. The slight male predominance (53.7%) and peak incidence in the 1–6-year age group (70.2%) are consistent with prior reports (1, 10). Recent large-scale epidemiologic studies have also shown that the burden of ALL varies according to age, sex, geography, and socio-demographic setting, further supporting the importance of reporting single-center data from regions that are less represented in the literature (7-9).

The most common presenting symptoms in our cohort—fatigue, loss of appetite, pallor, and fever—and the frequent physical findings of lymphadenopathy, hepatomegaly, and splenomegaly reflect the classic manifestations of marrow failure and leukemic infiltration and are broadly comparable with previously published series (11, 12). The relatively high frequency of organomegaly in our cohort may reflect the clinical spectrum of patients referred to a tertiary center and possible differences in timing of diagnosis.

The B-ALL/T-ALL distribution (78.5%/21.5%) and the proportion of patients classified as high-risk (28.1%) were within the range reported in international cohorts (13, 14). The overall survival proportion in our cohort (88.4%) was slightly lower than the approximately 90% survival rate reported in contemporary cooperative trials (3,15), which may reflect differences in case mix, local supportive-care conditions, and the use of an older treatment protocol in a substantial proportion of patients.

In univariable analyses, mortality was higher in the HRG group than in the SRG/IRG groups (Table 3), which is consistent with the well-established prognostic importance of risk stratification in childhood ALL (6, 16, 17). Similarly, relapse was markedly more frequent in T-cell ALL than in B-cell ALL (Table 3), in keeping with prior studies describing the distinct biology, treatment response, and relapse profile of T-ALL (17).

Another relevant observation was that sex and baseline blood count categories were not significantly associated with mortality or relapse in the univariable analyses. Although leukocyte count, hemoglobin level, and platelet count are traditionally considered part of the prognostic framework of childhood ALL, the lack of statistically significant associations in the present cohort may be related to the limited number of outcome events and the relatively small sample size. In addition, the very low frequency of documented high-risk cytogenetic abnormalities and the small proportion of patients who underwent hematopoietic stem cell transplantation suggest that variations in outcome in this cohort were more strongly driven by risk-group classification, immunophenotype, and treatment-era differences than by these less frequent variables (11, 18, 19).

We also observed lower crude mortality and relapse rates in patients treated with ALL-IC-BFM 2009 compared with TR-ALL BFM 2000 (Table 3). Although this finding is

directionally consistent with ongoing protocol refinement (15, 20, 21), the comparison requires cautious interpretation because protocol assignment in this retrospective cohort was time-dependent rather than concurrent. Therefore, the apparent advantage observed with ALL-IC-BFM 2009 may reflect not only protocol-related differences, but also calendar-time improvements in supportive care, earlier recognition and management of treatment-related complications, broader transfusion support, more effective antibacterial and antifungal therapy, and advances in diagnostic and monitoring practices. This issue is particularly relevant in retrospective comparisons of sequential treatment eras and should temper any causal interpretation of protocol-specific outcome differences.

Finally, recent population-based studies suggest that age, geography, and socioeconomic context can influence both disease burden and treatment utilization in ALL. Although these variables were not modeled directly in the present study, the single-center nature of the cohort and the rural/urban distribution of the patients indicate that local healthcare-access patterns may also have contributed to the observed outcomes. Larger multicenter studies incorporating socioeconomic indicators, supportive-care variables, and time-to-event analyses would help clarify the relative contributions of disease biology, treatment protocol, and health-system factors (7, 9, 21).

Limitations

This study has some limitations that should be addressed. Its retrospective, single-center design is inherently susceptible to referral and documentation bias and thereby limits generalizability. The 2010–2015 window spans two protocol generations (TR-ALL BFM 2000 and ALL-IC-BFM 2009) as well as secular improvements in supportive care; therefore, residual confounding by calendar time and protocol adherence is likely. The small number of outcome events (14 deaths and seven relapses) limited statistical power and precluded reliable multivariate adjustment. Advanced cytogenetic/molecular testing and early MRD assessment were not uniformly available, constraining precise risk stratification and subgroup analyses. The follow-up duration was variable, and exact time-to-event data were not consistently recorded; therefore, outcomes were summarized as crude proportions rather than time-to-event endpoints. Prospective, multicenter studies with standardized MRD protocols, comprehensive cytogenetic panels, and time-to-event modeling are warranted.

Conclusion

In this single-center retrospective cohort study of pediatric ALL, baseline demographic and clinical characteristics were comparable with prior reports. High-risk classification was associated with higher mortality, and the T-cell immunophenotype was found to be associated with higher relapse. Patients treated with ALL-IC-BFM 2009 had lower crude mortality and relapse rates than those treated with TR-ALL BFM 2000; however, because of the retrospective design, time-dependent protocol allocation, and limited event numbers, these findings should be interpreted cautiously. Larger prospective, multicenter studies with standardized diagnostics and time-to-event analyses are needed to better define protocol-specific outcomes.

Disclosures

Acknowledgments: This study is based on the findings of our thesis titled “Evaluation of Demographic, Clinical, and Laboratory Findings of Patients with Acute Lymphoblastic Leukemia Followed in Our Clinic Between 2010 and 2015,” which was prepared in 2017 (Thesis number: 471425).

Ethical Approval: Ethics committee approval was obtained for this study from the Dicle University Local Ethics Committee, in accordance with the World Medical Association Declaration of Helsinki. (Date: 12 January 2017, Approval No:2017/09).

Use of AI-Assisted Technologies in Visualization: During the preparation of this manuscript, the author(s) utilized Google NotebookLM Pro to enhance Figure 1, the graphical representation of the study. The underlying data, context, and prompts input into the tool were solely provided by the authors and derived from the original research. The author(s) have rigorously reviewed and verified the enhanced visual for scientific accuracy and take full responsibility for the integrity of the final published figure.

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