



RESEARCH

Clinical and treatment outcomes, prognostic factors, and survival in pediatric acute leukemia

Pediyatrik akut lösemide klinik ve tedavi sonuçları, prognostik faktörler ve sağkalım

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Abstract

Purpose: The aim of this study was to evaluate overall survival and treatment-related mortality in children with acute leukemia treated in a middle-income healthcare setting and to test the hypothesis that early treatment response and sex independently predict survival outcomes.

Materials and Methods: We retrospectively analyzed 105 pediatric patients diagnosed with acute leukemia between February 2021 and May 2023 at the Health Sciences University, Adana City Training and Research Hospital, Turkey. Data were obtained from institutional electronic medical records. Overall and event-free survival were estimated using the Kaplan–Meier method and compared using the log-rank test.

Results: The median age was 9 years. Acute lymphoblastic leukemia was diagnosed in 91 patients, acute myeloid leukemia in 13, and mixed-phenotype acute leukemia in one. The overall survival rate was 62.6%. Survival was higher in girls than in boys (80% vs. 48%). Patients with a favorable day-8 steroid response demonstrated substantially higher survival than poor responders (83% vs. 35%). In multivariate analysis, early steroid response was independently associated with a marked reduction in mortality risk.

Conclusion: In this single-center cohort from a middle-income country, female sex and early steroid response were associated with improved survival in pediatric acute leukemia. However, treatment-related mortality remained substantial, underscoring the need to strengthen supportive care, infection control, and access to modern risk-stratified monitoring. Incorporation of early response assessment and molecular follow-up into routine clinical practice may further improve outcomes, although the lack of minimal residual disease data limited more refined prognostic stratification.

Keywords: Pediatric acute leukemia; survival; prognosis; early treatment response; treatment-related mortality.

Öz

Amaç: Bu çalışmanın amacı, Sağlık Bilimleri Üniversitesi Adana Şehir Eğitim ve Araştırma Hastanesi'nde akut lösemi tanısı alan pediyatrik hastalarda sağkalım sonuçlarını ve tedaviye bağlı mortalite oranlarını değerlendirmektir.

Gereç ve Yöntem: Şubat 2021 ile Mayıs 2023 tarihleri arasında akut lösemi tanısı konulan 105 pediyatrik hastanın verileri retrospektif olarak incelendi. Veriler hastane elektronik tıbbi kayıt sisteminden elde edildi. Sağkalım analizi Kaplan–Meier yöntemiyle yapıldı; gruplar arasındaki farklar log-rank testi ile karşılaştırıldı.

Bulgular: Çalışmaya alınan 105 çocuğun (ortalca yaş: 9 yıl) 91'inde akut lenfoblastik lösemi (ALL), 13'ünde akut myeloid lösemi (AML) ve 1 hastada karışık fenotipli akut lösemi (MPAL) saptandı. Genel sağkalım oranı %62,6 idi. Kız hastalarda sağkalım oranı erkeklere göre anlamlı derecede yüksekti (%80'e karşı %48). Sekizinci günde steroid yanıtı iyi olan hastalarda sağkalım belirgin şekilde daha yüksekti (%83'e karşı %35). Çok değişkenli analizde erken steroid yanıtı, mortalite riskini yaklaşık %90 oranında azaltan bağımsız bir sağkalım belirleyicisi olarak bulundu.

Sonuç: Kız cinsiyet ve erken steroid yanıtı, pediyatrik akut lösemide daha iyi sağkalım ile ilişkili bulundu. Genel sağkalım oranı orta düzeyde olsa da, tedaviye bağlı mortalite oranı yüksek seyretmiştir. Bu durum, destek tedavilerinin güçlendirilmesi, enfeksiyon kontrol önlemlerinin iyileştirilmesi ve sosyoekonomik eşitsizliklerin azaltılması gerekliliğini ortaya koymaktadır. Cinsiyete özgü risk sınıflandırması, erken tedavi yanıtı ve moleküler izlemin bireyselleştirilmiş tedavi protokollerine entegre edilmesi, uzun dönem sağkalımı artırabilir. Bununla birlikte, minimal rezidüel hastalık (MRD) verilerinin olmaması, ayrıntılı prognostik değerlendirmeyi sınırlamaktadır.

Anahtar kelimeler: Pediyatrik akut lösemi; sağkalım; prognoz; klinik sonuçlar; tedaviye bağlı mortalite.

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INTRODUCTION

Acute leukemia is the most common malignancy of childhood and arises from the uncontrolled proliferation of immature hematopoietic cells. It is primarily classified as acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) according to lineage of origin. ALL accounts for approximately one-third of all pediatric cancers, whereas AML constitutes most of the remaining cases^{1,2}. Without effective treatment, acute leukemia is universally fatal; however, modern multi-agent chemotherapy and risk-adapted protocols have increased cure rates to more than 80% in high-income countries³.

Despite these advances, treatment-related mortality (TRM) remains a major obstacle to further improving survival. TRM ranges from approximately 2–5% in ALL to 5–20% in AML and is largely driven by severe infections, organ toxicity, and therapy-associated complications⁴. These preventable causes of death highlight the continued importance of robust supportive care systems, early recognition of sepsis, and individualized treatment strategies, particularly during intensive phases of therapy⁵.

Over the past decade, immunophenotypic, cytogenetic, and molecular profiling has transformed pediatric leukemia classification and prognostication. The integration of minimal residual disease (MRD) assessment and molecular risk stratification into contemporary treatment protocols such as the updated WHO 2022 classification and recent BFM and COG guidelines has enabled more precise tailoring of therapy and improved outcomes in resource-rich settings^{6,7,8-10}. However, the clinical benefits of these innovations are unevenly distributed.

In many middle-income countries, limited access to molecular diagnostics, inconsistent supportive care infrastructure, and socioeconomic barriers continue to compromise treatment delivery and survival. Refugee populations and socially disadvantaged groups are particularly vulnerable to delayed diagnosis, treatment interruptions, and infection-related complications. As a result, survival rates reported from high-income countries may not accurately reflect outcomes in real-world clinical environments where modern risk-stratified therapy is only partially implemented^{14,22}.

Data on survival, treatment-related mortality, and prognostic factors from such settings remain limited. In particular, the relative impact of early treatment response, sex, and conventional risk stratification on survival in middle-income healthcare systems has not been well defined^{7,9,13}. Clarifying these relationships is essential for identifying modifiable risk factors and for guiding pragmatic improvements in supportive care and treatment adaptation.

Therefore, this study aimed to evaluate overall and event-free survival and treatment-related mortality in pediatric patients with acute leukemia treated at a tertiary referral center serving both local and refugee populations in southern Turkey. We hypothesized that early steroid response and patient sex would independently predict survival outcomes in this middle-income setting.

MATERIALS AND METHODS

Sample

This retrospective, single-center cohort study included pediatric patients aged 1 month to 18 years who were evaluated for acute leukemia at the Department of Pediatric Hematology and Oncology, Health Sciences University, Adana City Training and Research Hospital, between February 28, 2021, and May 28, 2023. During the study period, 124 consecutive patients were screened for eligibility. Nineteen patients were excluded because of referral to another center before completion of induction therapy ($n = 11$) or incomplete clinical documentation ($n = 8$). The final analytical cohort consisted of 105 patients.

Clinical and laboratory data were extracted from institutional electronic medical records by two independent pediatric hematologists and cross-checked for accuracy.

Inclusion criteria were: (1) confirmed diagnosis of acute leukemia based on morphological, immunophenotypic, and cytogenetic evaluation; (2) initiation and continuation of treatment at our institution; and (3) availability of complete baseline and follow-up data. Exclusion criteria included transfer to another hospital before completion of induction therapy or missing key outcome data.

Procedure

The study was approved by the Clinical Research Ethics Committee of the Health Sciences University, Adana City Training and Research Hospital (Approval No: 2284; December 1, 2022) and conducted in accordance with the Declaration of Helsinki.

Collected variables included age, sex, leukemia subtype (ALL or AML), immunophenotype, cytogenetic abnormalities, BFM-based risk group (standard, intermediate, or high risk), early steroid response on day 8, occurrence of treatment-related complications, relapse, and survival status.

Treatment protocols and supportive care

Children with ALL were treated according to the ALL–Berlin–Frankfurt–Münster (BFM) 2009 protocol, and patients with AML were treated using the AML–BFM 2012 protocol. Supportive care was provided by a multidisciplinary pediatric oncology team and included antibacterial, antifungal, and antiviral prophylaxis when indicated; transfusion support for anemia and thrombocytopenia; nutritional support; and prompt management of febrile neutropenia and organ toxicities in accordance with international pediatric oncology guidelines.

Outcome definitions

Overall survival (OS) was defined as the time from diagnosis to death from any cause or last follow-up. Event-free survival (EFS) was defined as the time from diagnosis to relapse, treatment failure, death, or last follow-up in patients without events.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics. Categorical variables were compared using the chi-square or Fisher's exact test, and continuous variables using the Student's t test or Mann–Whitney U test, as appropriate. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Variables associated with overall survival in univariate analysis ($p < 0.10$) or considered clinically relevant (age, sex, leukemia subtype, risk group, and early steroid response) were entered into a multivariate Cox proportional hazards regression model to identify independent predictors of mortality.

A two-sided p value < 0.05 was considered statistically significant. A post hoc power analysis demonstrated a statistical power of 0.82 at $\alpha = 0.05$, indicating adequate sample size to detect medium effect sizes.

RESULTS

A total of 105 pediatric patients with acute leukemia were retrospectively analyzed between February 2021 and May 2023. The median age at diagnosis was 9 years (range, 1 month–18 years), and 58 patients (55.2%) were male.

According to the final diagnostic classification, 84 patients (80.0%) were diagnosed with acute lymphoblastic leukemia (ALL) and 21 (20.0%) with acute myeloid leukemia (AML) (Table 1). Among patients with ALL, 86.6% had B-cell lineage and 13.4% had T-cell lineage. Based on Berlin–Frankfurt–Münster (BFM) risk stratification, 37.1% of patients were classified as high risk.

Cytogenetic data were available in 23 patients (21.9%). Among these, recurrent chromosomal abnormalities were identified in a minority of cases, with t(8;21) being the most frequently observed abnormality.

During follow-up, relapse occurred in 21 patients (20.0%). At the last follow-up, 40 patients (38.1%) were in complete remission, 22 (21.0%) had active disease, 31 (29.5%) had died, and 12 (11.4%) were lost to follow-up. Of the recorded deaths, 42% were attributable to treatment-related causes, including severe infections, drug toxicity, and other therapy-related complications (Table 2)

Survival outcomes

Overall survival for the entire cohort was 62.6%, and the five-year event-free survival was 60.5%, reflecting outcomes that are substantially lower than those reported from high-income countries but consistent with results from other middle-income settings. Female patients demonstrated significantly superior overall and event-free survival compared with males (80% vs. 48% for OS and 77% vs. 47% for EFS), a pattern that has been described in several pediatric leukemia cohorts and may reflect sex-related differences in treatment tolerance and pharmacokinetics (Figure 1).

Table 1. Baseline demographic and clinical characteristics of the patients (n = 105)

Variable	Total (n = 105)	ALL (n = 84)	AML (n = 21)	p value
Age (years), mean \pm SD	6.7 \pm 4.1	6.3 \pm 3.8	8.2 \pm 4.9	0.162
Gender (Male/Female)	58 / 47	45 / 39	13 / 8	0.049*
Refugee status, n (%)	18 (17.1)	15 (17.8)	3 (14.3)	0.726
Socioeconomic status (low), n (%)	62 (59.0)	50 (59.5)	12 (57.1)	0.845
Risk group (high), n (%)	39 (37.1)	31 (36.9)	8 (38.1)	0.912
Cytogenetic abnormality, n (%)	23 (21.9)	19 (22.6)	4 (19.0)	0.732
Steroid poor response, n (%)	12 (11.4)	10 (11.9)	2 (9.5)	0.788

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; SD, standard deviation; n, number; %, percentage. p-value < 0.05 was considered statistically significant.

Table 2. Treatment-related complications and outcomes

Variable	ALL (n = 84)	AML (n = 21)	Total (n = 105)	p value
Febrile neutropenia, n (%)	54 (64.3)	16 (76.2)	70 (66.7)	0.278
Sepsis, n (%)	27 (32.1)	10 (47.6)	37 (35.2)	0.186
Organ dysfunction, n (%)	24 (28.6)	8 (38.1)	32 (30.5)	0.423
Treatment-related mortality (TRM), n (%)	7 (8.3)	5 (23.8)	12 (11.4)	0.042*
Overall survival, mean \pm SE (months)	48.7 \pm 3.9	32.5 \pm 5.2	—	0.017*
Event-free survival, mean \pm SE (months)	46.8 \pm 4.2	29.3 \pm 5.0	—	0.021*

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; TRM, treatment-related mortality; SE, standard error; n, number; %, percentage. p < 0.05 is statistically significant.

No significant difference in overall survival was observed between patients with ALL and AML, likely reflecting the relatively high burden of treatment-related mortality in both groups. Within the ALL subgroup, however, marked survival heterogeneity was evident: patients with B-cell lineage had nearly double the survival of those with T-cell disease (67% vs. 35%), consistent with the well-established adverse prognosis of T-cell ALL. Survival also declined progressively across BFM risk groups, from 85% in standard-risk patients to 38% in high-risk patients, underscoring the continued clinical relevance of conventional risk stratification even in the absence of routine molecular monitoring.

Early treatment response was one of the strongest discriminators of outcome. Patients with a favorable day-8 steroid response achieved markedly higher overall and event-free survival than poor responders (83% vs. 35% and 79% vs. 37%, respectively). This

finding aligns with BFM and St. Jude studies demonstrating that early steroid sensitivity reflects leukemic cell chemosensitivity and predicts long-term remission. In settings where minimal residual disease testing is limited, early steroid response therefore remains a practical and powerful tool for risk stratification.

Multivariate Cox proportional hazards regression analysis demonstrated that the overall model was statistically significant ($\chi^2 = 11.99$, $df = 4$, $p = 0.017$) (Table 3). Male sex was independently associated with an increased risk of mortality (HR = 1.72, 95% CI: 1.08–3.24, $p = 0.043$). High-risk disease according to BFM classification was also a significant predictor of death (HR = 2.41, 95% CI: 1.24–4.68, $p = 0.017$). Patients with a poor early steroid response had nearly a three-fold higher mortality risk compared with favorable responders (HR = 2.92, 95% CI: 1.36–6.44, $p = 0.008$). In addition, treatment-related mortality was strongly associated with worse survival (HR = 3.21, 95% CI: 1.65–7.38, $p = 0.003$).

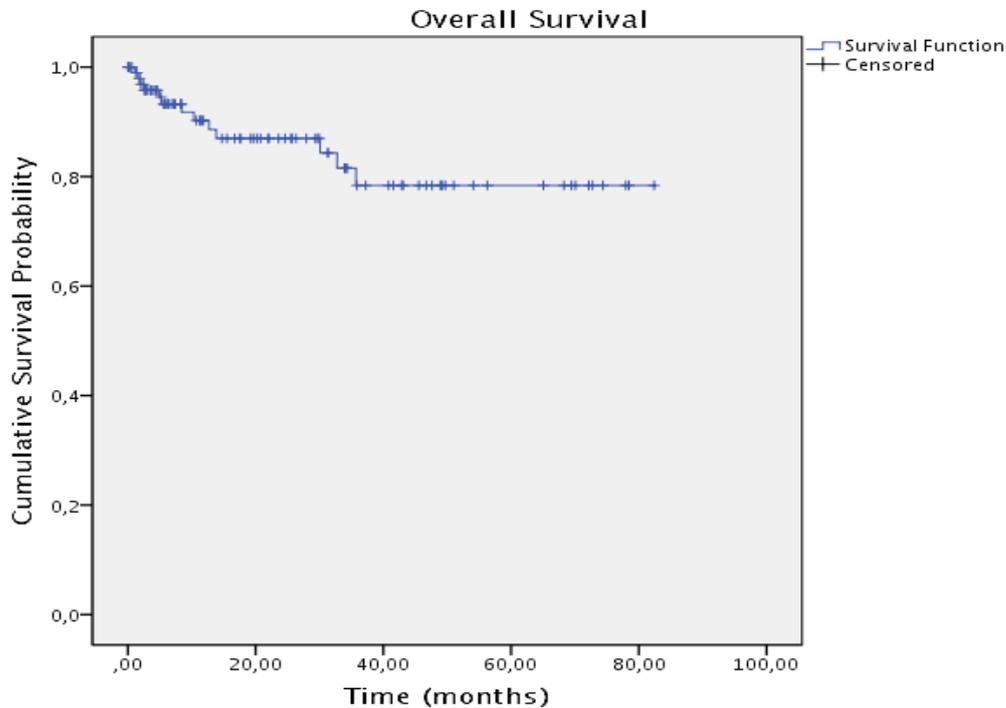


Figure 1. Kaplan–Meier survival curve demonstrating overall survival of patients with acute leukemia (n = 105). The 5-year overall survival rate was 79.8%.

Table 3. Multivariate Cox regression analysis of factors affecting overall survival

Variable	HR (95% CI)	p value
Male gender	1.72 (1.08–3.24)	0.043*
High-risk group	2.41 (1.24–4.68)	0.017*
Poor steroid response	2.92 (1.36–6.44)	0.008*
TRM	3.21 (1.65–7.38)	0.003*

HR, hazard ratio; CI, confidence interval; TRM, treatment-related mortality; p < 0.05 is statistically significant.

DISCUSSION

Leukemias constitute the most common childhood malignancies, accounting for approximately 30–35% of all pediatric cancers. Acute lymphoblastic leukemia (ALL) is the predominant subtype, with an incidence of approximately 4 per 100,000 children under 15 years of age in high-income countries¹². Advances in multi-agent chemotherapy, central nervous system (CNS) prophylaxis, and risk-adapted treatment strategies have led to remission rates exceeding 80% in many settings¹³. Nevertheless, prognosis remains strongly influenced by baseline clinical characteristics,

cytogenetic risk profiles, and particularly early treatment response, which has emerged as one of the most robust predictors of outcome¹⁴.

In the present cohort, high-risk patients constituted 43% of the study population and exhibited significantly lower survival rates, consistent with previous reports^{13,16}. This observation corresponded with established high-risk biological and clinical features, including elevated leukocyte counts, T-cell phenotype, and suboptimal early steroid response. Early treatment response, reflected by day-8 steroid sensitivity, was strongly associated with survival

outcomes, in agreement with findings reported by Stary et al. and Hazar et al.^{7,9}. These results further emphasize the critical role of early response metrics in refining contemporary risk stratification models and guiding individualized treatment intensity¹⁷.

Cytogenetic analysis was available for nearly half of the cohort, and the detected abnormalities, such as t(8;21), were aligned with established prognostic classifications^{19,20}. The limited availability of cytogenetic data likely reflects infrastructural and resource constraints typical of middle-income regions. In this context, broader integration of molecular diagnostics, including minimal residual disease (MRD)-based risk reassessment, remains essential to improve risk allocation and optimize therapeutic strategies.

Relapse occurred in 20% of patients, slightly exceeding relapse rates reported in several regional and international cohorts^{9,14,22}. The overall survival (OS) rate of 62.6% was comparable to outcomes reported from other resource-limited settings¹⁴. Treatment-related mortality (TRM) accounted for nearly 30% of all deaths, with infections and treatment-associated toxicities identified as the leading contributors. These findings highlight the urgent need to strengthen critical clinical processes, including standardized febrile neutropenia management protocols, early sepsis recognition and rapid response pathways, pediatric antimicrobial stewardship programs, infection-prevention bundles tailored for immunocompromised patients, and enhanced monitoring during high-risk treatment phases. Such structured and system-centered interventions may substantially reduce preventable mortality in vulnerable pediatric oncology populations¹⁸.

Female patients demonstrated significantly higher OS compared with males (80% vs. 48%). Although sex-based survival differences have been variably reported in the literature^{7,21,27}, the inconsistency across studies suggests that such findings should be interpreted cautiously. Therefore, the sex-related survival advantage observed in our cohort should be considered hypothesis-generating rather than indicative of a definitive biological mechanism. Larger multi-institutional studies incorporating pharmacogenetic and endocrine factors may help elucidate the underlying determinants of these differences.

Consistent with existing evidence, T-cell ALL was associated with inferior outcomes compared with B-cell ALL^{1,2}. The markedly lower survival observed in T-cell lineage cases underscores the necessity for intensified supportive care strategies and timely identification of high-risk treatment-related complications in this subgroup. Taken together, our findings indicate that female sex and favorable early steroid response represent significant prognostic indicators of improved survival in pediatric acute leukemia. Early identification of poor responders should prompt timely treatment intensification and close clinical monitoring. Moreover, addressing infection-related mortality and expanding equitable access to molecular diagnostic tools remain critical priorities for optimizing long-term outcomes and advancing therapeutic equity across healthcare systems.

In conclusion, our results demonstrate that early steroid response and sex-related differences are key determinants of survival in pediatric acute leukemia, reinforcing the central role of early treatment response in contemporary risk stratification. The observed burden of treatment-related mortality, particularly due to infections, indicates that improvements in supportive care are as critical as advances in antileukemic therapy. Future large-scale, prospective studies integrating MRD-based risk assessment, genomic profiling, and health system-level factors are essential to clarify the biological and structural determinants of outcome variability. Addressing these dimensions may not only optimize individualized treatment strategies but also contribute to achieving more equitable and sustainable improvements in pediatric leukemia survival worldwide.

This study has several limitations. First, its retrospective, single-center design limits the generalizability of the findings and may not fully reflect variations in clinical practice across different institutions. Second, the absence of minimal residual disease (MRD) monitoring which is a key component of contemporary leukemia risk stratification represents the most significant limitation and restricted the ability to perform more precise prognostic classification. Third, although socioeconomic status and refugee status were recorded during routine clinical evaluations, these variables were not included in the statistical analyses; therefore, potential confounding effects related to treatment adherence, infection risk, and supportive

care access could not be accounted for. Fourth, the loss-to-follow-up rate of 11.4% may have introduced attrition bias if these patients differed systematically from those who completed follow-up. Additionally, the modest sample size limited the robustness of subgroup analyses and reduced the precision of effect estimates. Nevertheless, the post hoc power analysis (0.82 at $\alpha = 0.05$) indicated that the study had adequate statistical power to detect medium effect sizes for the primary survival outcomes.

Our results underscore the importance of early steroid response and risk-based treatment adaptation in pediatric leukemia management. Strengthening infection prevention, ensuring nutritional and psychosocial support, and early intervention for high-risk patients may reduce treatment-related mortality. Moreover, implementing MRD-based monitoring and expanding access to molecular diagnostic tools in national protocols are crucial steps toward improving survival and equity in middle-income healthcare systems.

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