JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1345525
J Contemp Med 2023;13(5):975-981

Original Article / Orijinal Araştırma

Outcomes of Low and Middle Income Children with Relapsed Acute Lymphoblastic Leukemia: Single-Center Experience

Nüks Eden Akut Lenfoblastik Lösemili Düşük ve Orta Gelirli Çocukların Sonuçları: Tek Merkez Deneyimi

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Abstract

Aim: Despite numerous advances in treating acute lymphoblastic leukemia (ALL) in children, relapse continues to be the leading cause of mortality. This study aimed to analyze patient characteristics and outcomes of children with relapsed ALL.

Material and Method: We retrospectively analyzed the records of patients aged 1–18 years old diagnosed with relapsed ALL between January 2004 and December 2018.

Results: 452 ALL patients were followed up in the study period and 55 patients relapsed. The relapse rate was 12.1%. Thirty-four (61.8%) of the relapsed patients were male. The median age was 7 years (1–17 years). Forty-six patients (83.6%) had precursor B-cell ALL and nine patients (16.3%) had T-cell ALL. The site of relapse was the bone marrow in 41 patients (74.5%), and extramedullary (central nervous system, testis, or soft tissue) in 11 patients (20%). The mean duration from the initial diagnosis to relapse was 32 months (min-max: 4 -108 months, SD±21.2) and 20 months (min-max: 7-38 months, SD± 11.1) in patients with B- cell ALL and T- cell ALL, respectively. The median follow-up time was 39.8 months (min-max: 3–198 months, SD±44.5) from the initial diagnosis. Thirty-seven patients (67.3%) died. The 5-year overall survival rate was 41.6%. Recurrent relapse and progressive disease were the most common causes of death. The mortality rate was significantly associated with immunophenotype, treatment response on days 8, 15, and 33 of initial diagnosis, the risk group at initial diagnosis, the site of relapse, and hematopoietic stem cell transplantation ($p<0.05$). Immunophenotype and the site of relapse were the independent variables associated with mortality.

Conclusion: Relapse affects a significant portion of patients with ALL. Survival rates are still poor in patients with relapsed ALL. Also, our findings that T-cell immunophenotype and the site of relapse (isolated bone marrow relapse) were independent risk factors for mortality suggest that more specialized treatment options are needed for patients with T-ALL and bone marrow relapse.

Keywords: Relapse, acute lymphoblastic leukemia, children

Öz

Amaç: Çocuklarda akut lenfoblastik löseminin (ALL) tedavisindeki sayısız ilerlemeye rağmen, nüks mortalitenin önde gelen nedeni olmaya devam etmektedir. Bu çalışma ile, nüks eden ALL' li çocuk hastaların özelliklerinin analiz edilmesi amaçlanmıştır.

Gereç ve Yöntem: Ocak 2004 ile Aralık 2018 tarihleri arasında nüks ALL tanısı alan 1-18 yaş arası hastaların kayıtlarını retrospektif olarak inceledik.

Bulgular: Çalışma döneminde 452 ALL hastası izlendi ve 55 hasta nüks ettiği görüldü. Nüks oranı %12.1 idi. Bu hastaların 34'ü (%61,8) erkekti. Medyan yaş 7 yıl (min-maks:1-17 yaş) idi. Kırk altı hastada (%83,6) öncül B-hücreli ALL ve dokuz hastada (%16,3) T-hücreli ALL vardı. Kırk bir hastada (%74,5) nüks yeri kemik iliği, 11 hastada (%20) ekstramedüller (merkezi sinir sistemi, testis veya yumuşak doku) idi. İlk tanıdan nükse kadar geçen ortalama süre B hücreli ALL'li hastalarda 32 ay (min-maks: 4 -108 ay, SD±21,2) ve T-hücre ALL' de 20 ay (min-maks: 7-38 ay, SD± 11,1) idi. Tanıdan itibaren ortanca takip süresi 39,8 aydı (min-maks: 3–198 ay, SD±44,5). Otuz yedi hasta (%67,3) öldü. 5 yıllık genel sağkalım oranı %41.6 idi. Tekrarlayan nüks ve ilerleyici hastalık en yaygın ölüm nedenleriydi. Mortalite oranı, immünofenotip, ilk tanının 8., 15. ve 33. günlerinde tedaviye yanıt, ilk tanı anındaki risk grubu, nüks bölgesi ve hematopoietik kök hücre nakli ile anlamlı şekilde ilişkiliydi ($p<0.05$). İmmünofenotip ve nüks bölgesi, mortalite ile ilişkili bağımsız değişkenlerdi.

Sonuç: Nüks, ALL hastalarının önemli bir bölümünü etkiler. Tekrarlayan ALL'li hastalarda hayatta kalma oranları hala düşüktür. Ayrıca, T-hücre immünofenotipi ve nüks bölgesi (izole kemik iliği nüksü) mortalite için bağımsız risk faktörleri olduğuna dair bulgularımız, T-ALL ve kemik iliği nüksü olan hastalar için daha özel tedavi seçeneklerine ihtiyaç olduğunu düşündürmektedir.

Anahtar Kelimeler: Nüks, akut lenfoblastik lösemi, çocuk

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Received *(Geliş Tarihi)*: 18.08.2023 **Accepted *(Kabul Tarihi)*:** 16.09.2023

INTRODUCTION

Recent advances in chemotherapy and hematopoietic stem cell transplantation (HSCT) protocols and supportive care have improved the survival rate of children with acute lymphoblastic leukemia to over 80–90% (ALL).[1,2] Despite this progress, relapse remains the main limiting issue for treatment success.[3] Relapse can occur due to the proliferation of drug-resistant clonal cells that could not be eliminated and/or another group of clonal cells with new genetic modifications.[4] Although the recurrence rate has been reduced to 15–25% with risk-based regimens, survival rates of relapsed ALL are still low.[1-7]

This study aimed to analyze the data on patient characteristics and outcomes in children with relapsed ALL.

MATERIAL AND METHOD

Ethical Consideration

The study was carried out with the permission of Ankara Pediatrics Hematology Oncology Training and Research Hospita Ethics Committee (Date: 30.07.2019, Decision No: 2019228). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data of patients aged 1–18 years who were followed up with the diagnosis of relapsed ALL at the pediatric hematology department of the University of Health Sciences Ankara Pediatric Hematology-Oncology Training and Research Hospital between January 2004 and December 2018 were analyzed retrospectively. Our hospital mostly serves children of lower or middle income families from all over Turkey. Patients with mature B-cell ALL, secondary ALL, and infant leukemia were excluded from the study. The demographic and clinical characteristics, treatment regimens, risk category at diagnosis, and treatment outcomes of the relapsed ALL patients were recorded.

Patients were divided into the standard risk group (SRG), intermediate risk group (IRG), and high risk group (HRG) according to their clinical, laboratory and genetic characteristics at the time of diagnosis in the BFM protocol.

Relapse was defined as the presence of a confirmed greater than 5% leukemic cell infiltration in the bone marrow or any other site in a patient who had previously achieved complete remission.[8] Isolated bone marrow relapse was defined as the presence of >25% lymphoblasts in the bone marrow with no leukemic involvement at any extramedullary site. Isolated extramedullary relapse was defined as extramedullary leukemic involvement with <5% blasts in the bone marrow.[8]

Patients were grouped into very early, early, and late relapse according to the first complete remission duration. Relapses occurring less than 18 months after initial diagnosis were defined as very early relapse; those occurring more than 18 months after initial diagnosis but less than six months after the completion of initial treatment were described as early relapse. Relapses appearing six months or later after the completion of initial treatment were defined as late relapses.[8]

Cytogenetic analysis, fluorescent in situ hybridization (FISH), and polymerase chain reaction (PCR) results of the patients were recorded. Genetic alterations at initial diagnosis were categorized as unfavorable (hypodiploidy (chromosomes ≤44), t (4;11) [MLL/AF4], t(9;22) BCR/ABL) and favorable (hyperdiploidy: chromosome number >50), t(12;21)).

REZ BFM 2002 (2003–2018) and ALL-IC REL 2016 (2018–present) protocols were given as first-line relapse therapy. The FLAG-IDA (fludarabine, cytarabine, idarubicine, G-CSF) treatment protocol was used as second-line therapy. Third-line salvage therapies were given to patients who did not go into remission or developed recurrent relapses. Patients with hematopoietic stem cell transplantation (HSCT) indication were transplanted.

Statistical Analysis

Continuous variables were tested for normality of distribution using the Kolmogorov–Smirnov test. Descriptive statistics are presented as mean ± standard deviation or frequency and percentage. Univariate comparisons of normally distributed variables were performed using an independent t-test and one-way ANOVA. Duncan's multiple comparison tests were then used to determine which groups differed. Categorical variables were analyzed with the chi-square test. In multivariate analysis, potential factors determined in previous studies were used to evaluate independent variables predicting survival using Cox regression analysis with the backward selection method. Model fit and proportional hazard assumptions were tested using residual (Schoenfeld and Martingale) analyses. Survival rates were calculated using Kaplan–Meier survival analysis. A univariate log-rank test was used to examine the effects of variables on survival. Bonferroni correction was used in comparisons of survival time between more than two groups. P values less than 0.05 were considered statistically significant in all analyses. IBM SPSS Statistics version 21.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Patient Characteristics

In the study period, 452 patients were diagnosed with ALL, and 55 of the patients (12.1%) relapsed. During the study period, patients were treated with the modified St Jude Total XIII (2004-2008; total number of patients: 82 and 17 patients relapsed), TR-ALL BFM 2000 (the modified BFM 95 protocol) (2009–2012; total number of patients: 136, relapsed patients: 9), and the ALL-IC BFM 2009 protocol (2013–2018; total number of patients: 234, relapsed patients: 27). There were 6 patients who relapsed after hematopoietic stem cell transplantation (HSCT).

Relapse rates of the modified St Jude Total XIII protocol (before 2008) and BFM protocols (after 2008) were 20.7% and 11.6%, respectively. The median age of the patients at relapse was 7 years (range; 1–17 years) and 34 patients (61.8%) were boys. Forty-six patients (83.6%) had B-cell ALL (B-ALL) and nine patients (16.3%) had T-cell ALL (T-ALL). The demographic and clinical characteristics of the patients are shown in **Table 1**. Twenty-nine B cell ALL patients (63%) had isolated bone marrow (BM) relapse, two (4.3%) had isolated central nervous system (CNS) relapse, three patients (6.5%) had isolated testis relapse, and one patient had localized soft tissue relapse (2%). The relapse site was isolated BM in 5 patients (55.5%), combined BM and CNS in 2 patients (22.2%), and isolated CNS in 2 patients (22.2%) with T cell ALL. No statistically significant difference was found between relapse sites according to the blastic cell type (p: 0.731).

Table 1. Patient Characteristics

	Patient (n)	%
Leukemia type		
B-ALL	46	83.6
T-ALL	9	16.4
Gender		
Male	34	61.8
Female	21	38.2
Age at diagnosis (years)		
Mean ± SD	7.8 ± 4.2	
Median (range)	7 (1-17)	
>1 to<6	19	34.5
≥6 to<18	36	65.5
Initial WBC count		
< 50x10^9/L	28	50.9
≥ 50x10^9/L	27	49.1
Initial risk group (patients receiving only the BFM protocol n:38)		
IRG	26	68.5
HRG	12	31.5
Time of Relapse		
Very early relapse	20	36.3
Early relapse	20	36.3
Late relapse	15	27.2
Relapse Site		
Isolated BM	34	61.8
Extramedullary	10	18.1
Combined	11	20.1
Genetic Abnormalities		
Favorable*	16	29
Unfavorable**	10	18.1
Karyotype Analysis		
Metaphase could not be obtained	11	20
Normal	35	63.6
Abnormal	9	16.4

*ETV6-RUNX1 or hyperdiploidy (>50chromosomes), **Hypodiploidy (<44chromosomes), MLL rearrangements, BCR-ABL1, B –ALL (precursor B cell acute lymphoblastic leukemia), T ALL (T cell acute lymphoblastic leukemia), IRG (intermediate risk group), HRG (high-risk group), BM (Bone marrow), WBC (white blood cell)

The duration between diagnosis and relapse was 28.7 months, (min-max: 2–184, SD: 21.7). 30.7±3.28 months (min-max: 4–184) in B-ALL and 18.6 ± 4.48 months (min-max: 2–38) in T-ALL patients. Relapse time in T-ALL was shorter than in B-ALL, but the difference was not statistically significant (p:0.122).

Twenty patients (36.4%) had a very early relapse, 20 patients (36.4%) had early relapse, and 15 patients (27.3) had late relapse. 15 patients (32.6%) had very early relapse, 16 patients (34.8%) had early relapse, and 15 patients (32.6) had late relapse in the B-ALL group. 5 patients (56%) had very early relapse and 4 patients (44%) had early relapse in the T-ALL group.

Karyotype analysis was normal in 35 patients (63.6%) and could not be determined in 11 patients (20%) (metaphase could not be obtained) at the initial diagnosis. By using polymerase chain reaction and/or fluorescent in situ hybridization methods, favorable genetic changes were detected in 16 patients (29%) and unfavorable genetic changes were detected in 10 patients (18.1%).

The duration of time to relapse was not associated with age, sex, or relapse site (p>0.05). When patients who received only the BFM protocol were evaluated, the mean time to recurrence was shorter in HRG patients at the time of diagnosis (p:0,023). Factors associated with time to relapse are shown in **Table 2**.

Tablo 2. Variables significantly associated with time to relapse

Variables	Time to Relapse	P Value
Diagnosis		
B –ALL	30.75±3.28	0.04
T –ALL	18.60±4.49	
Gender		
Male	26.70±2.59	0.371
Female	32.09±6.35	
Age		
1-6	32.47±5.59	0.357
≥6	26.80±3.31	
Initial Risk Group (Patients receiving only the BFM protocol n:38)		
IRG	28.32±3.44	0.023
HRG	18.01±4.10	
Genetic analysis		
Favorable*	30.15±6.81	0.972
Unfavorable**	29.21±3.58	
Cytogenetic analysis		
Metaphase could not be obtained	19.93±7.73	0.290
Normal	29.58±3.71	
Abnormal	34.74±4.69	
Relapse Site		
Isolated BM	26.51±3.40	
Combined	31.27±10.19	0.606
Isolated extramedullary	33.43±4.37	
WBC counts		
<50x 10^9/L	33.56±5.26	0.388
≥50x 10^9/L	22.88±2.63	
Day 8 (PGR) (Patients receiving only the BFM protocol n:38)		
Yes	24.53±2.60	0.002
No	12.72±5.12	
Day15 MRD (Patients receiving only the BFM protocol n:38)		
Negative	29.66±2.58	0.000
Positive	14.27±3.03	
Day 33 Remission (Patients receiving only the BFM protocol n:38)		
Yes	29.13±3.58	0.008
No	9.53±3.39	

*ETV6-RUNX1 and Hyperdiploid(>50chromosomes)
**Cytogenetic of poor prognosis; Hypodiploid(<44chromosomes), MLL rearrangements, BCR-ABL1 B –ALL(precursor B cellacutelymphoblasticleukemia), T ALL (T cellacutelymphoblasticleukemia),SRG (Standard risk group),IRG (intermediate risk group), HRG (high risk group), BM (Bone Marrow), PGR (prednisolonegoodresponse), MRD (Minimal ResidualDisease).

REZ BFM 2002 (2003–2018) and ALL-IC REL 2016 (2018–present) protocols were given as the first-line relapse therapy. The FLAG-IDA (fludarabine, cytarabine, idarubicine, G-CSF) treatment protocol was used as second-line therapy. Third-line salvage therapy was given to patients who did not go into remission or developed recurrent relapses. Details of relapse treatments are shown in **Figure 1**. HSCT was performed on 22 patients after relapse. Relapsed patients who had recurrent relapse (minimum-maximum:1-4) or resistant disease (n=10) received different salvage regimens such as clofarabine-based regimens (clofarabine, etoposide, cyclophosphamide or clofarabine, cyclophosphamide, etoposide, bortezomib), nelarabine for T-cell ALL or bortezomib-based regimens (bortezomib, vinorelbine, topotecan, thiotepa, dexamethasone). The third line treatment details are shown in **Figure 2**.

Thirty-seven (67.3%) patients died. The most common causes of death were progressive disease (30 patients, 81%) and infection (7 patients, 19%). The 5-year overall survival rate was 41.6%. The 1-, 3-, and 5-year overall survival (OS) rates of the relapsed patients with B-ALL were 86%, 68%, and 48%, respectively. The 1-, 3- and 5-year OS rates of the relapsed T-ALL patients were 64.5%, 27%, and 18%, respectively. A Log-rank test was performed to identify differences in survival according to diagnostic variables. There was a statistically significant difference in survival between B -ALL and T- ALL patients (X2=20.324, P <0.001). Kaplan Meier survival analyses are shown in **Figure 3**. The 5-year OS rates of the patients with very early, early, and late relapse were 22%, 46%, and 58%, respectively. The 5-year OS rates of the B-ALL patients with very early, early, and late relapse were 26.6%, 40.2%, and 72.4%, respectively. The 3-year OS rates of the T-ALL patients with very early and early relapse were 14.8% and 32%, respectively.

All patients who received salvage therapies died due to progressive disease or infection.

The mortality rate was significantly associated with immunophenotype, the risk group at initial diagnosis, the site of relapse, and post-relapse HSCT (p<0.05). Sex, age at diagnosis, and genetic profiles were not associated with mortality (p>0.05). The mean post-relapse survival was longer in the group with HSCT than in the group without HSCT (97.55 months and 45.50 months, respectively (X2=4.168, p=0.041).

After univariate survival analyses of variables associated with mortality were performed by log-rank test, those found to be significant were further examined by Cox regression analysis with the backward selection method (-2 Log Probability=228.176). Cox regression analysis is summarized in **Table 3**. T-ALL immunophenotype and isolated bone marrow relapse were determined as the independent variables affecting mortality.

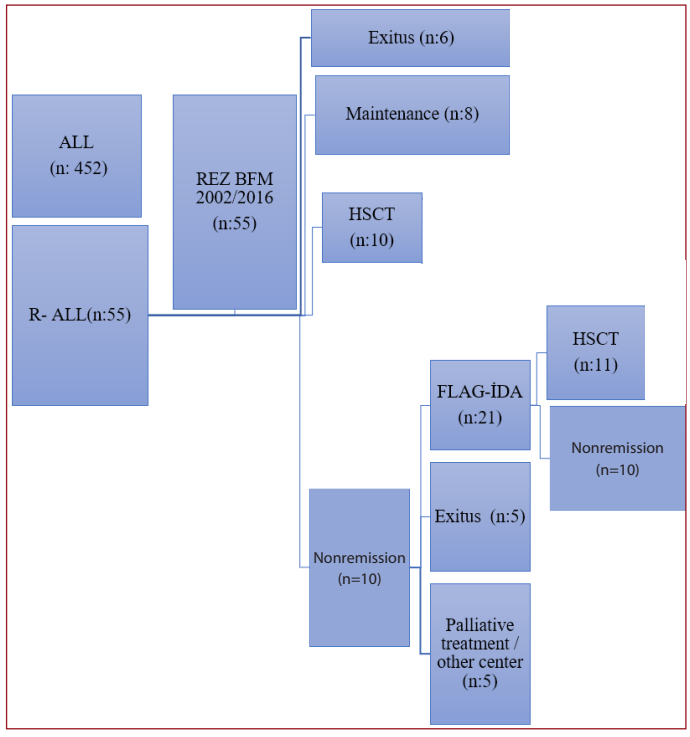

Figure 1. Details of treatments

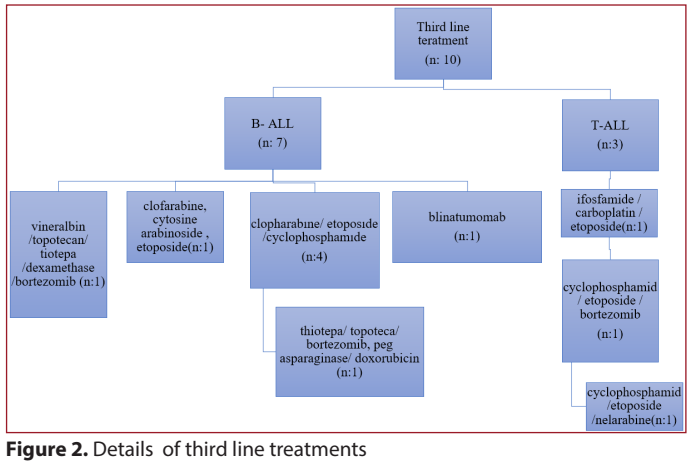

Figure 2. Details of third line treatments

Table 3: Coefficients of the best model obtained by Cox regression analysis

Variables	B	Wald	Sig.	Exp(B)	95.0% CI for Exp (B)	
					Lower	Upper
Immunophenotype (T cell ALL)	1.898	16.768	0.000	6.671	2.690	16.544
Relapse Sitea (Isolated BM)		4.459	0.108			
Relaps Site (Combined)	1.156	4.445	0.035	3.176	1.085	9.298
Relaps Site (Isolated extramedullary)	0.949	2.223	0.136	2.582	0.742	8.986

a Reference category, BM (Bone Marrow)

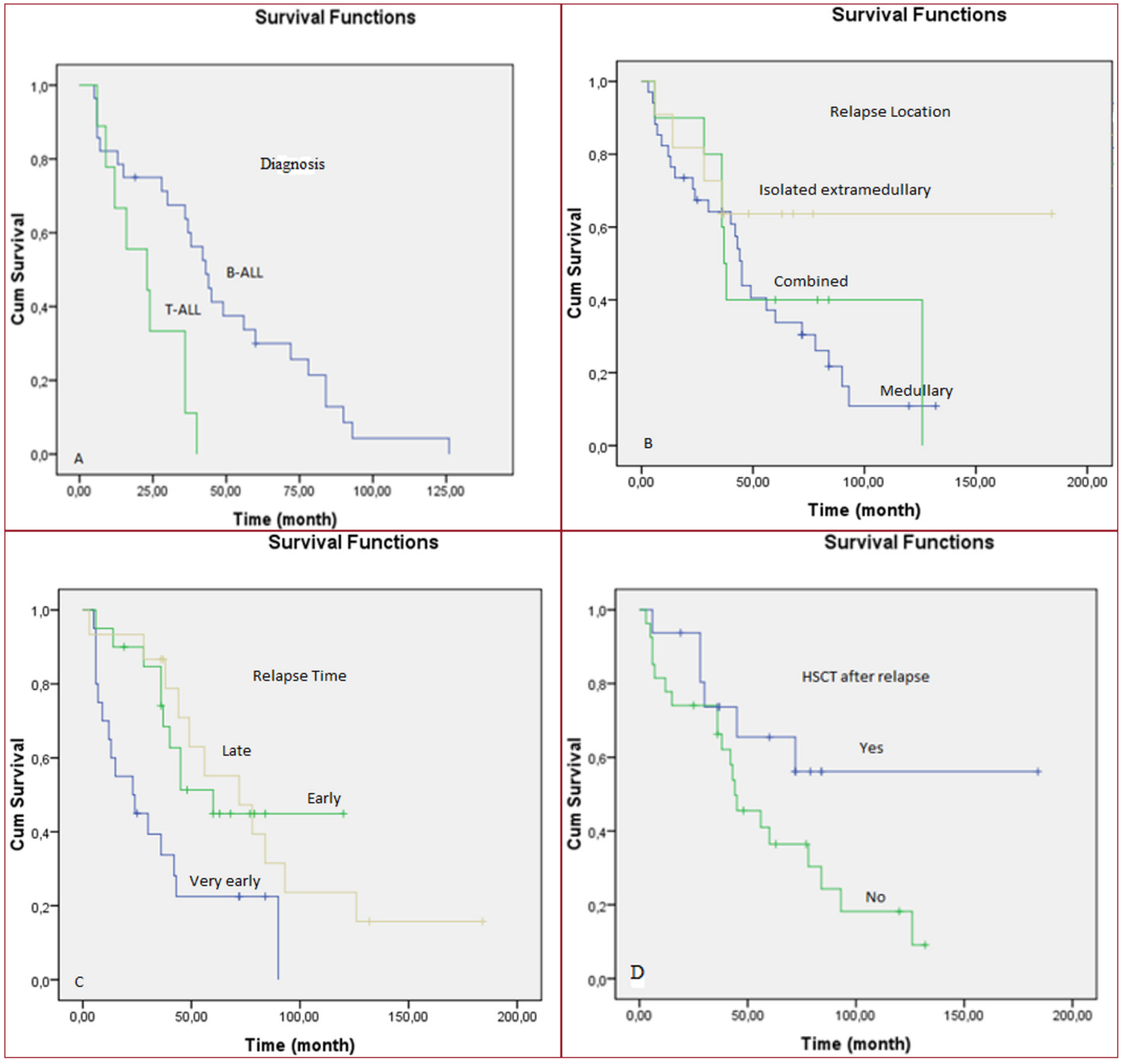

Figure 3. A; Overall survival according to diagnosis. B; Overall survival according to site of relaps.. C; Overall survival according to time of time of relaps. D; Overall survival according to HSCT treatment.

DISCUSSION

Relapse affects 15–25% of pediatric ALL patients and continues to be an important determinant of treatment success.[1-5] Relapse rates of the pediatric ALL have been reported as 15-35% in different studies. In the present study, the relapse rate was 12.1% compared to the aforementioned studies. Immunophenotype, the site of relapse, duration time of the first complete remission, the risk group at diagnosis, genetic abnormalities, and response to relapse treatment influence the prognosis in relapsed ALL patients.[12,13] Although the second remission rates vary between 71 and 93% in those patients, the short duration of the second remission causes long-term survival rates to decrease to 35.5–40%.[14,15] In our study, the 5-year OS rate was 41.6% in general and the T-ALL group showed a substantially lower survival rate compared to B-ALL; 18% and 48%, respectively. B cell ALL and T cell ALL patients have several differences in terms of clinical features, genetic characteristics, and sensitivity to chemotherapeutics. Patients with T-cell ALL are often older than patients with B-cell ALL. Furthermore, patients with B-cell ALL may have favorable genetic subtypes (e.g., ETV6–RUNX1 and hyperdiploidy) and

appropriate targeted therapies may be administered in some patients.[16] T-cell immunophenotype was a poor prognostic factor associated with a high initial white blood cell count.[17] In our study, the T-cell immunophenotype was independently associated with a high mortality rate. Therefore, the development and widespread use of T-ALL-specific treatment regimens are important for improving the outcomes of these patients.[18]

Bone marrow is the most common site of relapse in pediatric ALL patients.[1] Patients with isolated bone marrow relapse have been reported to have poorer survival outcomes than patients with extramedullary relapse.[7,12,17] Similarly, isolated bone marrow relapse was also most prevalent in our study, and patients with isolated bone marrow relapse had lower survival rates than those with CNS, testicular, and combined bone marrow relapse. Additionally, isolated bone marrow relapse was identified as an independent variable associated with mortality in our study.

In particular, unfavorable genetic risk factors have an important place in determining the risk grouping of the patient.[18] Conventional chromosomal analysis could not be performed in approximately 20% of patients due to failure to obtain metaphases. The fact that these patients had a shorter time to relapse than other patients suggests that genetic changes associated with poor prognosis may not have been detected. Most of the patients (66%) diagnosed with relapsed B-ALL were in the IRG at the time of diagnosis. We also suggest that in some patients genetic changes that play a key role in the risk assessment could not be detected. Therefore, new genetic methods such as next generation sequencing could be used to predict prognosis.

Philadelphia chromosome (Ph)-like ALL can be an example of a genetic change that we could not analyse during the study period. Philadelphia-like ALL is characterized by a gene expression profile similar to BCR-ABL1 positive, but the BCR-ABL1 oncogene is not detected.[19] The rate of Ph-like ALL among all ALL cases has been reported to be 12% in children and 21% in adolescents.[20] Detecting genetic changes that affect prognosis is of great importance in determining the appropriate risk group.[21] The impact of Ph-like ALL on outcomes could not be evaluated in our study. Comprehensive genomic studies will also enable molecular targeted therapies to be found, such as tyrosine kinase inhibitors.[22]

The duration of time to relapse has been described as the most important determinant of mortality.[7] Survival rates are particularly lower in patients with early bone marrow relapse.[14] Nguyen et al. reported 5-year OS rates after isolated bone marrow relapse as 11.5%, 18.4%, and 43.5% in patients with early, intermediate, and late relapse, respectively.[7] In our study, 5-year OS rates (very early, early, and late relapse were 22%, 46%, and 58%, respectively) were higher compared to that study. These results may indicate that time to relapse is still an important indicator of survival, as demonstrated in previous studies.

The ultimate treatment goal in relapsed ALL is to provide complete remission and to perform HSCT.[23] Studies comparing the outcomes of conventional chemotherapy and HSCT after complete remission in relapsed patients have yielded different results.[24,25] In particular, the utility of HSCT in late bone marrow relapse remains unclear.[26] In our study, relapsed patients who underwent HSCT had a better survival rate.

Until recently, treatment options were limited to intensive cytotoxic chemotherapy and allogeneic hematopoietic stem cell transplantation, whereas in recent years, therapeutic immunotherapeutic drugs for children with relapsing ALL have been investigated to a greater extent.[22] It has been reported that the use of blinatumomab, inotuzumab ozogamicin, and CAR-T cell treatments in relapsed patients improves survival rates.[22] We used these treatments in a small number of patients in the years that covered our study.

CONCLUSION

Relapse affects a significant portion of patients with ALL. Survival rates are still poor in patients with relapsed ALL. It is estimated that the risk groups of patients may change by comprehensive analysis of genetic risk factors at the time of diagnosis. Also, our findings that T-cell immunophenotype and the site of relapse were independent risk factors for mortality suggest that more specialized treatment options are needed for patients with T-ALL and bone marrow relapse.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Pediatrics Hematology Oncology Training and Research Hospita Ethics Committee (Date: 30.07.2019, Decision No: 2019228).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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