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Article

Causes of Death in Childhood Acute Lymphoblastic Leukemia: A Single-Center Experience

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Abstract: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Excellent overall survival rate of about 90% are the result of improvements in risk stratification and risk-adapted therapy, intensive chemotherapy regimens, hematopoietic stem cell transplantation and supportive care. *Background and Objectives:* The aim of this study is to review the epidemiology, prognostic factors, and causes of death of pediatric ALL in a tertiary center. *Materials and Methods:* A retrospective study was conducted at the Croatian Referral Center for Pediatric Hematology and Oncology, University Hospital Centre Zagreb, including 302 children (0–18 years) diagnosed with ALL between January 2001 and December 2015, accounting for about 70% of national cases. *Results:* Two hundred fifty-one children survived (5-year overall survival 83%). Relapse occurred in 13.6% of patients. Relapse rates were higher for B-cells precursor ALL than for T-cell ALL (14.3% vs. 10.4%), and no patient with relapsed T-cell ALL survived. Main causes of death were refractory/relapsed disease (43% of patients), followed by infections (35%) and GVHD (8%). The most frequent causes of infectious death were *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. The most critical treatment periods were induction and reinduction phases, especially de-escalation of corticosteroids. The time of relapse and risk group were independent factors in predicting the outcome. *Conclusions:* Our study confirmed that relapse and infections are major causes of mortality in children with ALL. To improve the outcome, we should encourage participation in collaborative international trials, improvement of supportive care and implementation of new treatment modalities.

Keywords: leukemia; children; death; prognostic factors; relapse; infection

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy accounting for one-fourth of all pediatric cancers. ALL arises from the proliferation of hematopoietic cells leading to disruption of normal marrow function and marrow failure [1]. The survival rate of pediatric ALL has improved significantly with risk stratification based on biologic features of leukemic cells and response to the treatment, therapy modifications based on patients' pharmacodynamics and pharmacogenomics, and better supportive care [2]. These advances have improved the survival rate from less than 10% in the 1960s to about 90% nowadays [3]. The most common cause of treatment failure and death in pediatric ALL depends on the country's development. According to studies [4–9], relapse is a common cause of treatment failure in high-income countries (8–19%), and post-relapse survival remains unsatisfactory (3-year overall survival (OS) 29.7% to 38.1% depending on the site of relapse) [10]. On the contrary, in low-income countries [11] infections remain a common cause of death (43.2%), while relapse is responsible for death in 27% of cases. Other causes of death have not been frequently reported.

The aim of this study is to investigate causes of death in pediatric ALL patients in a single center, and to identify risk factors and their impact on clinical outcome.

2. Materials and Methods

2.1. Study Design

A retrospective study was carried out at the Division of Hematology and Oncology, Department of Pediatrics, University Hospital Centre Zagreb, during the time period from 1st of January 2001 to 31st of December 2015. The Division is the Croatian Referral Center for Pediatric Hematology and Oncology, where about 70% of all children with ALL are treated.

2.2. Participants and Data Collection

The study included 302 children aged 0-18 newly diagnosed with ALL. Exclusion criteria were previous treatment and secondary ALL. Epidemiological and clinical data were obtained from patient records. Demographic information included gender, date of birth, age at diagnosis and therapy start date. Other collected data included ALL immunophenotype and risk group. Due to unavailable information on bone marrow cytogenetics, it was excluded from statistical analysis. Furthermore, molecular genetics and minimal residual disease were routinely incorporated in 2009, and these two parameters were excluded from statistical analysis as well.

Data about the time and site of relapse, treatment protocol, date of last follow-up/date of death, and causes of death were also collected. The majority of patients had initially been treated according to ALL-BFM 95, ALL-IC-BFM 2002 and ALL-IC-BFM 2009 protocols and classified into risk groups (standard risk – SR, intermediate risk – IR, high risk – HR), while infants had been treated according to Interfant protocol. Philadelphia chromosome–positive (Ph+) ALL positive patients were treated with hematopoietic stem cell transplantation (HSCT).

2.3. Statistical Analysis

Collected data were incorporated into a previously constructed database in Microsoft Excel 2010 and processed in Stata/MP 13. Basic statistics (descriptive statistics) were performed using Excel data analysis. The results were interpreted at a significance level of $p < 0.05$. Kaplan–Meier curve was used to analyze the survival rates. Univariate and multivariate analyses (Efron method) by Cox proportional hazard model were performed with 95% confidence intervals (CIs) in order to identify statistically significant prognostic factors of survival.

3. Results

The median age of patients was 5 years (range 9 months to 17 years). Female patients had a lower median age at diagnosis (4 years) compared to male patients (5 years). Five-year event-free survival (EFS) was 80%, while 5-year OS was 83%. Characteristics of patients with ALL and differences in epidemiology between newly diagnosed and relapsed patients are shown in Table 1.

Table 1. Characteristics of patients with acute lymphoblastic leukemia.

	Number of patients (%)	5-year EFS (%)	5-year OS (%)	Number of relapsed patients	Percentage of relapsed patients in relation to overall number at the diagnosis (%)	5-year OS of relapsed patients (%)
Patients	302 (100%)	80%	83%	41	14%	22%
GENDER						
Male	178 (59%)	77%	81%	30	17%	23%
Female	124 (41%)	85%	86%	11	9%	18%
AGE GROUPS						
Infants	8 (3%)	50%	50%	4	50%	0%
1 - 4 y.	165 (55%)	85%	88%	16	10%	31%
5 - 9 y.	66 (22%)	77%	83%	11	17%	36%
10 - 17 y.	63 (21%)	73%	73%	10	16%	0%
IMMUNOPHENOTYPE						
common	181 (60%)	82%	86%	22	12%	27%
pre B	63 (21%)	73%	78%	12	19%	25%
pro B	5 (1%)	60%	60%	2	40%	0%
T	53 (18%)	83%	83%	5	10%	0%
RISK GROUPS						
SR	69 (23%)	87%	96%	4	6%	25%
IR	154 (51%)	85%	89%	16	10%	44%
HR	79 (26%)	53%	63%	21	27%	5%

Abbreviations: SR – standard risk, IR – intermediate risk, HR – high risk, EFS – event-free survival, OS – overall survival.

Relapse occurred in 41 patients (13.6%) with no statistically significant difference in relapse rate according to gender, although girls had better OS than boys (86% vs 81%). Characteristics of ALL patients who experienced relapse are shown in Table 2.

Table 2. - Characteristics of patients with relapsed acute lymphoblastic leukemia.

	Number	Percentage	Survival	5-year OS (%)
Relapsed patients	41	14% (in relation to entire cohort)	9	22%
TIME OF RELAPSE				
Very early	18	44%	0	0%
Early	10	24%	1	10%
Late	13	32%	8	62%
SITE OF RELAPSE				
Bone marrow	27	66%	6	22%

Isolated CNS	1	2%	1	100%
Bone marrow + CNS	13	32%	2	15%
TREATMENT				
Chemotherapy	22	54%	3	14%
Chemotherapy + HSCT	19	46%	6	32%

Abbreviations: CNS – central nervous system, HSCT – hematopoietic stem cell transplantation.

The relapse rate was higher in B-ALL (14.5%) than in T-ALL (10%). Five-year OS of patients without relapse (251 patients) was 93%, while 5-year OS of patients who experienced relapse was 22%; there was a statistically significant difference between these groups (Table 3).

The median time from diagnosis to relapse was 20 months (for SR patients 52 months, for IR patients 12 months, and for HR patients 8 months), while the median post-relapse survival time was 9 months. Figure 1 shows 5-year OS of relapsed patients according to the time of relapse.

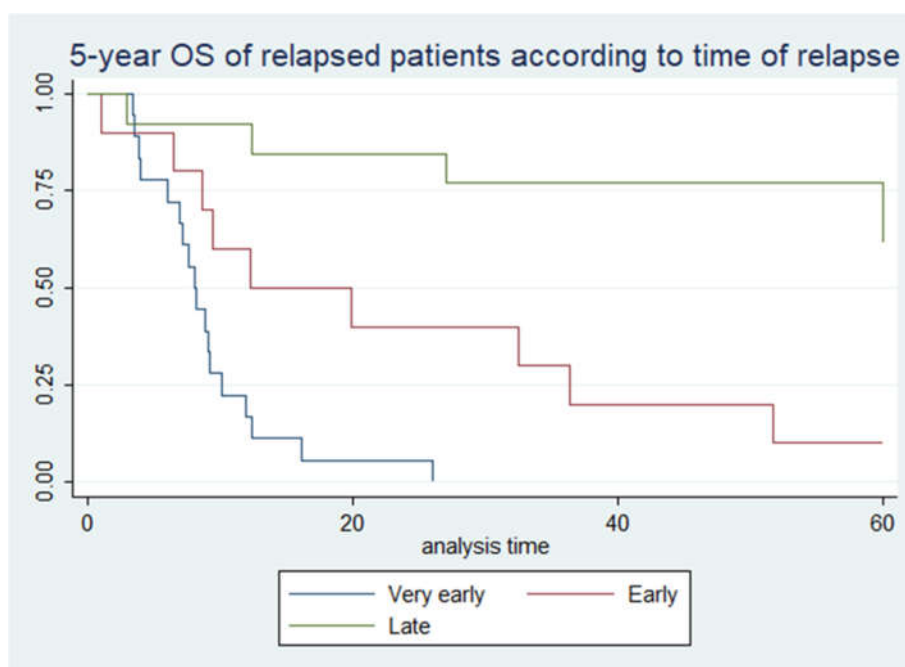


Figure 1. Kaplan-Meier curve according to time of relapse

We recorded 51 total deaths with a cumulative incidence of 16,9 %. Nineteen patients (37%) died without relapse and 32 patients died (63%) after relapse. The main cause of death was refractory/relapsed disease (43%) followed by infections (35%), graft-versus-host disease (GVHD, 8%), hemorrhage (6%), liver failure (4%), discontinued treatment (2%) and unknown cause (2% of patients). The most critical periods in non-relapsed patients were induction (8 patients, 42%) and reinduction phase of the treatment (9 patients, 48%), while only 1 patient died during intensification and 1 patient after HSCT.

Causes of death for non-relapsed and for relapsed patients are shown in Figures 2 and 3.

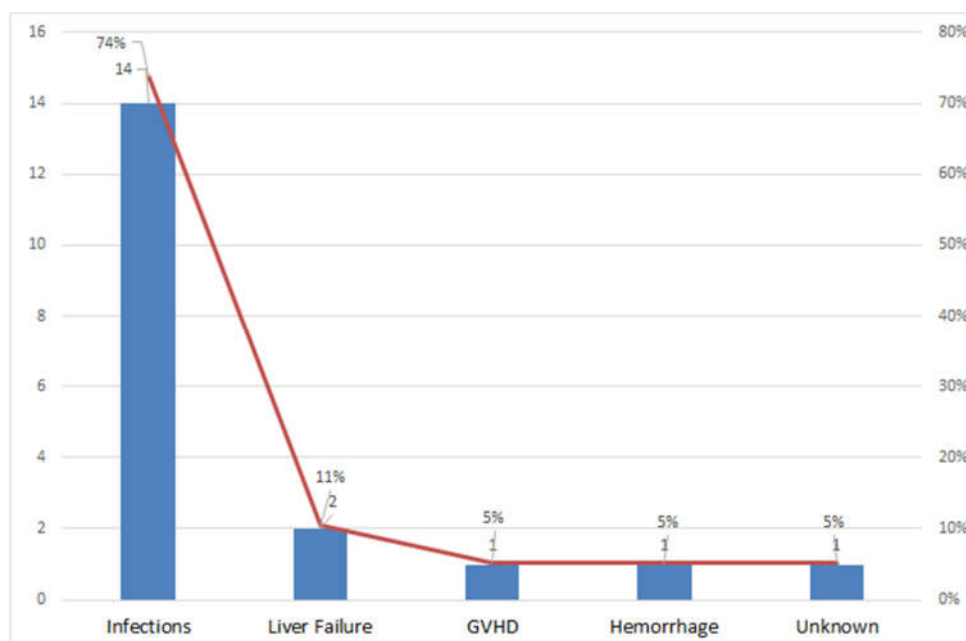


Figure 2. Causes of death in non-relapsed patients.

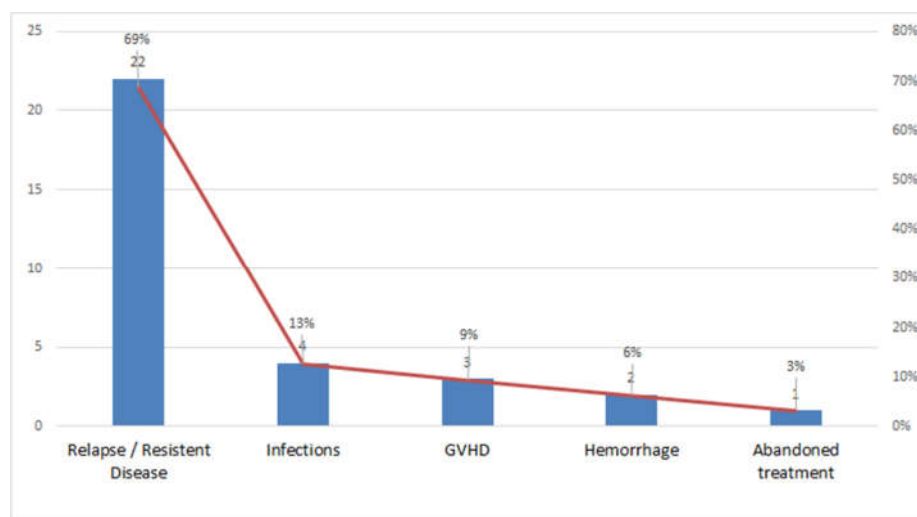


Figure 3. Causes of death in relapsed patients.

Regarding infections, the most common isolated microorganisms were *Pseudomonas aeruginosa* (7 patients – 5 non-relapsed and 2 relapsed), *Aspergillus fumigatus* (6 patients - 5 non-relapsed and 1 relapsed) and *Fusarium spp.* (2 patients – 1 non-relapsed and 1 relapsed).

The risks of death are shown in Table 3 and Table 4.

Table 3. Hazard risk of mortality associated with prognostic factors in pediatric ALL patient.

Analysis	Univariate HR	p	Multivariate HR	p
	INITIAL DIAGNOSIS			
Relapse				
No	1,00	Reference	1,00	Reference
Yes	15,78 (8,76-28,43)	<0,05	13,24 (6,92-25,37)	<0,05

Sex				
Male	1,00	Reference	1,00	Reference
Female	0,66 (0,37-1,2)	0,17	1,02 (0,54-1,91)	0,96
Age groups				
Infants	1,00	Reference	1,00	Reference
1y-4y	0,19 (0,06-0,55)	0,002	1,07 (0,33-3,54)	0,9
5y-9y	0,24 (0,08-0,77)	0,016	0,66 (0,19-2,3)	0,52
10y-17y	0,43 (0,14-1,28)	0,128	1,03 (0,33-3,27)	0,95
Immunophenotype				
common	1,00	Reference	1,00	Reference
pre B	1,72 (0,89-3,31)	0,104	1,41 (0,72-2,77)	0,32
pro B	3,6 (0,85-15,22)	0,082	1,48 (0,32-6,73)	0,61
T ALL	1,3 (0,61-2,78)	0,502	1,75 (0,77-3,98)	0,18
Risk group				
SR	1,00	Reference	1,00	Reference
IR	2,51 (0,73-8,64)	0,142	2,18 (0,61-7,75)	0,23
HR	11,76 (3,59-38,5)	<0,05	6,85 (1,87-24,9)	<0,05

Abbreviations: SR – standard risk, IR – intermediate risk, HR – high risk.

Table 4. Hazard risk of mortality associated with prognostic factors in relapsed pediatric ALL patient.

Analysis	Univariate HR	p	Multivariate HR	p
AFTER RELAPSE				
Sex				
male	1,00	Reference	1,00	Reference
female	1,02 (0,47-2,2)	0,95	1,06 (0,44-2,57)	0,897
Age groups				
infants	1,00	Reference	1,00	Reference
1y-4y	0,14 (0,04-0,5)	<0,05	0,36 (0,05-2,78)	0,33
5y-9y	0,14 (0,03-0,52)	<0,05	0,81 (0,14-4,69)	0,81
10y-17y	0,29 (0,08-1,03)	0,055	0,72 (0,14-3,59)	0,69
Immunophenotype				
common	1,00	Reference	1,00	Reference
pre B	1,96 (0,87-4,4)	0,102	2,16 (0,66-7,1)	0,21
pro B	23,56 (3,74-148,2)	<0,05	7,17 (0,76-67,76)	0,086
T ALL	9,1 (2,77-29,9)	<0,05	2,87 (0,49-16,84)	0,24
Risk group				
Standard risk	1,00	Reference	1,00	Reference
Intermediate risk	0,95 (0,26-3,5)	0,94	3,08 (0,44-21,69)	0,26
High risk	3,57 (1,04-12,27)	0,043	14,18 (1,2-167,4)	0,035
Time of relapse				
very early	1,00	Reference	1,00	Reference

early	0,1 (0,03-0,32)	<0,05	0,22 (0,03-1,55)	0,129
late	0,02 (0,004-0,08)	<0,05	0,008 (0,001-0,06)	<0,05
Site of relapse				
Bone marrow	1,00	Reference	1,00	Reference
Isolated CNS	/	/	/	/
Bone marrow + CNS	1,05 (0,5-2,2)	0,9	2,27 (0,6-8,4)	0,22
Chemo/HSCT				
Chemotherapy + HSCT	1,00	Reference	1,00	Reference
Chemotherapy	1,01 (0,5-2,02)	0,982	1,54 (0,64-3,74)	0,34

Abbreviations: CNS = central nervous system; HSCT = hematopoietic stem cell transplantation.

4. Discussion

Five-year OS of children with ALL in our study was 83%. In larger studies, Jeha (St Jude Total Therapy XVI protocol) [12] and Pieters (DCOG 10) [13] reported 5-year OS excellent rates of 94.1% and 92%, respectively. On the other side, 10-year EFS in the study of Keizo [14] was 77% for patients recruited from 1997 to 2002 without significant difference between risk groups – EFS rates for SR, IR, HR and very HR groups were 79.3%, 72.5%, 71.7% and 66.3%, respectively. Similar results were reported by Hao [15] with 10-year OS of 69%, confirming that survival rates are related to the resources of the country. Of note, our study, unlike several other studies, includes patients without exclusion of HR cases, such as Ph+ALL or infants

Long-term survival of infants remains unsatisfactory despite many efforts for improvement with intensified chemotherapy and immunotherapy. Hossain et al. [16] reported the lowest survival rate (50%) in infants, compared to age groups 1–4, 5–9, 10–14, and 15–19 years (82%, 75%, 57%, and 32%, respectively). The survival rate is also inversely proportional to age in our cohort except for infants, but in our study multivariate regression analysis had no statistical significance. To mention, univariate regression analysis showed age groups as significant predictors of outcome, but this was not documented in multivariate analysis. Relapse rates in our patients were highest in infants (50%) and lowest in children 1-4 years (10%).

Immunophenotype is an important component in the diagnostic evaluation of patients with ALL. Many studies [17,18] reported a higher relative risk of death in patients with T-cell ALL. Our results closely match for B-cell and T-cell ALL (survival rates 83,3% and 82%, respectively). We observed higher relapse rates for B-cell ALL than for T-cell ALL (14,3% and 10%, respectively), but there were no survivors in the cohort of patients with T-cell ALL who experienced a relapse. Pro-B ALL remains infrequent, but with the worst outcome. In the study of Rheingold and colleagues [19], relapse rates were similar for B- and T-cell ALL (12% and 11%), and the prognosis was better for patients with relapsed B-ALL (52±1%) than for T-ALL (33±3%) and infant ALL (19±4%), with greater variability in OS by the site in T-ALL vs. B-ALL. In multivariable analysis, their results were equal to ours showing that a shorter time to relapse was associated with the worse outcome with addition to the site of relapse, age <1 or >10 years at diagnosis, initial WBC > 100 × 10¹²/L and T-cell phenotype as statistically significant unfavorable prognostic factors. The small sample size in our study makes the conclusion about variability in OS by the site of relapse unreliable.

Risk-adapted therapy is one of the main contributors to the forceful improvement of survival in children with ALL. The OS for SR patients in our study was 96% with only 6% of relapsed patients, which is comparable to the results of Maloney et al. [20], with 6-year OS for children with SR ALL enrolled in AALL0331 exceeding 95%.

As reported in other studies [8,21], treatment-related mortality, mainly accounted by infections, primarily occurred in induction protocols. In our study, deaths were slightly more reported in the reinduction protocol (9 deaths in reinduction, 8 deaths in induction). Furthermore, we want to emphasize the tapering of corticosteroids as the critical period for susceptibility to infection. Inaba et

al. [20] noted that poor neutrophil surge after dexamethasone pulses during continuation, which can reflect the poor bone marrow reserve, was associated with infections.

Nakagawa et al. [22] reported that fatal infections mostly occurred during the third week of induction therapy. They suggested close monitoring, stringent infection control, and immediate administration of appropriate antibiotics through hospitalization as an approach to reducing the rate of infection-related induction deaths. Our patients were hospitalized throughout the entire induction phase, and during reinduction, they were discharged between therapies if their general condition and laboratory findings were acceptable. We checked up patients regularly in outpatient setting and they were admitted at the slightest suspicion of infection or deterioration. Microbiological specimens (stool, urine, oropharynx, nasopharynx, armpit, groin) were collected routinely at least once a week.

The most common isolated microorganisms as the cause of sepsis and death in our study were *Pseudomonas aeruginosa* followed by *Aspergillus fumigatus* and *Fusarium spp.* Also, Nakagawa [22] reported *Pseudomonas aeruginosa* as the most common cause of sepsis and death (32%), followed by *Bacillus spp.* (27%), while other microorganisms (*Enterobacter cloacae*, *Candida albicans*, *Aspergillus*, *Candida tropicalis* and *Chickenpox*) were rare causes of death. Ruijters and colleagues [23] reported that the most common fungal cause was *Candida*, followed by *Aspergillus*.

Due to the growing incidence of invasive fungal infections (IFI), many studies [24–27] focused on preventive strategies and reported the importance of environmental factors. Building constructions, tobacco, pets, potted plants, gardening, and rooms without HEPA filtration might increase the risk of IFI. Short-term laminar airflow use may reduce risk of aspergillosis, but its long-term use is inadequate.

In this study, relapse occurred in 51 patients (13.6%) which is higher than in UKALL2003 trial (relapse risk 8.8%) [4] and DFCI 05-001 trial (relapse risk 8.9%), but slightly lower in comparison with the study of Tuong et al [28] (relapse risk 16.7%). Most of our patients (43.9%) had a very early relapse with a dismal prognosis, while early and late relapses were associated with better, still poor prognosis (10% and 62%, respectively). The time of relapse was an independent unfavorable prognostic factor which is comparable with Egyptian study [29], reporting that ‘very early’ relapses had significantly lower 5-year OS (15.8%), compared to ‘early’ and ‘late’ relapses, (46.2% and 66.7% respectively), without significance in multivariate Cox regression analysis. Kelly et al. [30] reported that EFS was significantly higher in patients with a longer duration of the first complete remission regardless of whether the threshold was made at 24 months ($p < 0,05$) or 36 months ($p < 0,05$), which is in agreement with our results. Furthermore, their study showed no significant difference between disease-free survival (DFS) at 8 years for patients treated with chemotherapy alone ($45.3\% \pm 11.2\%$) and chemotherapy followed by SCT ($50\% \pm 9.1\%$).

Regardless of better results reported in some studies after relapse [10], extremely aggressive treatment for ALL relapse is often associated with substantial late sequelae. Therefore, improved strategies to prevent relapse are needed for the subset of HR patients. Pui et al. [18] reported that patients with NCI HR B-ALL or T- ALL had an inferior outcome, even with undetectable minimal residual disease (MRD) on day 46, with the cumulative risk of relapse of 12.7% and 15.5%, respectively.

Consequently, our goal is to reach better results comparable to highly developed centers using standardized treatment protocols for relapse and better supportive care. Further studies are needed to focus on molecular therapies and cellular immunotherapy to achieve better survival, reduce treatment-related mortality, and improve the quality of life in childhood cancer survivors.

5. Conclusions

This study showed a 5-year OS rate of 83% and a relapse rate of 13.6% in children with ALL. Infants and very early relapse had the poorest prognosis. Treatment-related mortality was primarily driven by infections, with a notable number occurring during reinduction. Despite limited resources, our results are comparable to those reported by more developed centers, demonstrating the effectiveness of consistent treatment protocols and comprehensive care. Future efforts should focus

on reducing relapse rates and treatment-related mortality through optimized therapy and enhanced supportive measures.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used “Conceptualization, M.J., J.R. and E.B.; methodology, M.J.; software, L.L. and M.J.; validation, J.R. and E.B.; formal analysis, M.J., M.P., L.M., S.D.B., Z.S., T.M., D.T., L.L., J.R. and E.B.; investigation, M.J. and J.R.; resources, M.J., M.P., L.M., S.D.B., Z.S., T.M., D.T., J.R. and E.B.; data curation, M.J., M.P., L.M., S.D.B., Z.S., T.M., D.T., L.L., J.R. and E.B.; writing—original draft preparation, M.J. and J.R.; writing—review and editing, M.J., M.P., L.M., S.D.B., Z.S., T.M., D.T., J.R. and E.B.; visualization, M.J. and E.B.; supervision, J.R. and E.B.; All authors have read and agreed to the published version of the manuscript.”

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Informed Consent Statement: Informed consent was obtained from all children and their parents or legal guardians before taking part in the study. Written consent was also received from them to allow us to publish the results of this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy reasons.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ALL	Acute lymphoblastic leukemia
OS	Overall survival
HSCT	Hematopoietic stem cell transplantation
CI	Confidence interval
EFS	Event free survival
IFI	Invasive fungal infection

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