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Bridging the Gap in Pediatric Relapsed Acute Lymphoblastic Leukemia Treatment: Insights and Outcomes From the ALL-IC REL 2016 Guidelines

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ABSTRACT

Background: The Acute Lymphoblastic Leukemia InterContinental (ALL-IC) Study Group exemplifies the potential of broad international collaboration. Patient outcomes have improved by standardizing therapeutic options and employing flow cytometry-based minimal residual disease (MRD) for treatment stratification. Nevertheless, relapse occurs in 10%–20% of cases, with survival rates falling short of benchmarks set by top-tier published studies.

Objectives: We aimed to unify treatment guidelines for children with first relapse of ALL across the ALL-IC network, analyze post-relapse outcomes, and report findings from an observational registry.

Methods: Patients were stratified as standard-risk (SR) or high-risk (HR) based on relapse features and genetics. HR criteria included T-cell immunophenotype, very early or early isolated bone marrow relapse, and relapse post-stem cell transplant (SCT). SR was assigned to all others. SCT was indicated in the whole HR group and in SR patients with poor responses (MRD $\geq$ 0.1% on Day 29).

Results: Among 370 patients (mean age 9 years; 33.2% female) diagnosed with first relapse between 2017 and 2021, 90.5% had received ALL-IC-Berlin-Frankfurt-Münster (BFM) 2009 treatment initially. Upon relapse, 46.8% were classified as SR and 53.2% as HR. Complete remission rates post-induction were 84% (SR) and 56% (HR). MRD < 0.1% was achieved by 53% (SR) and 29% (HR).

Abbreviations: AEs, adverse events; ALL-IC, Acute Lymphoblastic Leukemia InterContinental; BFM, Berlin-Frankfurt-Münster; CNS, central nervous system; EFS, event-free survival; EOI, end-of-induction; FD, family donor; HR, high-risk; ICU, intensive care unit; IntReALL, International Study for the Treatment of Childhood Relapsed ALL; MFD, matched family donor; MMFD, mismatched family donor; MMUD, mismatched unrelated donor; MRD, minimal residual disease; MSD, matched sibling donor; MUD, matched unrelated donor; OS, overall survival; SCT, stem cell transplantation; SR, standard-risk; StE, standard error; TBI, total body irradiation; UD, unrelated donor.

Marko Kavcic and Dániel J. Erdélyi contributed equally as co-first authors.

Five-year overall survival was 50.5% (74% SR, 32% HR). HR outcomes were hindered by disease progression, treatment toxicity, and posttransplant complications.

Conclusions: This inaugural ALL-IC REL Consortium report demonstrates promising SR outcomes, akin to the International Study for the Treatment of Childhood Relapsed ALL (IntReALL) findings, but highlights poor HR outcomes with standard chemotherapy. Novel therapeutic strategies are urgently needed in upcoming ALL-IC-BFM REL protocols.

1 | Introduction

Since its inception in 1975, the Berlin-Frankfurt-Münster (BFM) study group (SG) has profoundly reshaped the treatment protocols for Acute Lymphoblastic Leukemia (ALL) [1]. The BFM protocol emerged as a pivotal framework for both pediatric and adult treatment regimens, quickly becoming a bedrock for further advancements in ALL care and significantly improving patient outcomes globally [2–4].

As the International BFM SG entered the new millennium, it broadened the scope of its collaborative efforts with the formation of the ALL InterContinental (IC)-BFM consortium, bringing together experts from 15 countries across three continents [5]. This expansion facilitated greater access to high-caliber clinical trials in regions less represented in such research [6]. However, even with the advancements in primary ALL treatment evidenced by the 2002 and 2009 ALL-IC-BFM trials, relapsed ALL management has remained a significant challenge [5, 6]. This is highlighted by the inconsistent care standards revealed when participating centers were asked to report on relapsed cases following the ALL-IC-BFM 2002 study. Among those with documented protocols, there was a diversity, with more than 20 different treatment regimens reported. Moreover, the 5-year survival rate post-relapse varied widely across the SGs, exhibiting a range from 20% to 63% (unpublished data), underscoring the critical need for standardized approaches in relapsed ALL treatment [7].

In response to these challenges, the ALL-IC REL SG adopted a more accessible strategy, designed to encourage broader participation across its network. This led to the launch of an observational study for relapsed pediatric ALL, utilizing well-established drug combinations and avoiding the complexities of randomization in its initial phase. Such efforts are instrumental in driving forward the standardization of care and gathering data on treatment outcomes [7, 8].

This article navigates the intricate pathways of the proposed strategy, its implications for relapsed ALL patients, and the trajectory toward the standardization of treatment approaches on a global scale. It underlines the collaborative spirit that has driven progress in pediatric oncology and the potential to address pressing scientific inquiries through well-structured investigations [9].

2 | Methods

2.1 | Study Population

Data were prospectively collected from institutions in countries participating in the ALL-IC-BFM 2002 and 2009 clinical trials for primary ALL [5, 6]. ALL first relapses that occurred from November 2017 to December 2021 in patients ≤18 years of age were recruited for analyses.

2.2 | Treatment

The treatment guidelines were developed under the guidance of a steering committee consisting of leaders from ALL-IC-BFM institutions and the International Study for the Treatment of Childhood Relapsed ALL (IntReALL) SG and are detailed in the supplemental material. The guidelines employed stratification criteria and treatment elements derived from the IntReALL 2010 study, with a focus on diagnostic and therapeutic means accessible and standardized across the frontline ALL-IC-BFM study participating countries [10]. Patients were stratified into standard-risk (SR) or high-risk (HR) groups based on the immunophenotype of ALL, the relapse site, and the timing of relapse post-initial treatment, following the criteria outlined in the protocols provided as supplemental materials and as established in the IntReALL 2010 guidelines [11]. Certain genetic subgroups were classified to HR irrespective of other features, and these genetic stratifiers were extended in the September 2019 update version of the protocol—see Appendix 2 in both protocol versions provided as supplementary materials. However, routine testing of some of these genetic variations was very heterogenous among countries and may also not have been fully reported in the registry, hence the low proportion of certain genetic subgroups highlighted in Table 1.

2.3 | Minimal Residual Disease (MRD) Assessment

Treatment efficacy was assessed by measuring MRD using flow cytometry [12]. Centers adhered to a ≥6-color flow cytometry protocol for MRD detection, following an amendment to the ALL-IC-BFM 2009 Standard Operating Procedures by M.N. Dworzak and J. Kappelmayer. MRD was measured after the fourth week of induction therapy, where a level of 0.1% or higher indicated a suboptimal response. Patients in the SR group showing suboptimal responses were evaluated for allogeneic stem cell transplantation (SCT). MRD level after induction did not affect further treatment in the HR group, and all patients reaching complete morphological remission were eligible for an SCT after consolidation chemotherapy [10, 13–15].

2.4 | Statistical Methods

Event-free survival (EFS) and overall survival (OS) were estimated using the Kaplan–Meier method. The log-rank test

TABLE 1 | Demographic and clinical characteristics of children.

First presentation, frontline therapy	SR	HR
N (%)	173 (46.8)	197 (53.2)
Sex		
Boys	124 (71.6)	123 (62.4)
Girls	49 (28.3)	74 (37.6)
Age at primary diagnosis, years		
Median (range)	4.3 (0.2–14.6)	6.8 (0.3–16.8)
<10	154 (89)	132 (67)
>10	19 (11)	65 (33)
Primary treatment protocol		
ALL-IC 2009	154 (89)[a]	181 (91.9)[b]
Treatment arm in primary treatment protocol		
SR	40 (23.1)	9 (5.2)
IR	107 (61.8)	105 (53.3)
HR	21 (12.1)	78 (39.6)
CNS involvement at primary diagnosis (%)	7 (4)	17 (8.6)
Relapse		
Age at relapse (years)		
Median (range)	8 (3.3–17.6)	9 (1–17.99)
<10	118 (68.2)	110 (55.8)
>10	55 (31.8)	87 (44.2)
Immunophenotype		
B-precursor	171 (98.8)	153 (77.7)
T	2 (1.2)	43 (21.8)
MPAL	0 (0)	1 (0.5)
Genetic abnormalities at relapse		
Favorable prognosis		
Hyperdiploidy	9 (5.2)	6 (3)
ETV6::RUNX1	21 (12.1)	4 (2)
Unfavorable		
KMT2A rearranged	0	10 (5)
TCF3::PBX1	3 (1.7)	6 (3)
Hypodiploidy	0	4 (2)
BCR::ABL	0	13 (6.6)
Other	6 (3.5)[c]	16 (8.1)[d]
Unknown	134 (77.4)	138 (70.0)
Extramedullary disease at relapse		
CNS	36 (CNS2: 3, CNS3: 33) (20.8)	49 (CNS2: 11, CNS3: 38) (24.9)
Testis	42 (24.3)	10 (5)
Other	8 (maxilla, skin, femur, ovary, fatty tissue, pleura, lymph node, parotid gland, fatty tissue) (3.5)	6 (breast + BM, palate + right mammary gland + liver + spleen + kidneys, ileum + femur, mediastinum, lymph node, bilateral optic nerve) (3)
Time from first diagnosis to relapse, mean (SD), months	39 (19)	16.8 (14.4)
Time from first diagnosis to relapse		
Very early (<18)	0	120 (60.9)
Early (≥18 and ≤30)	39 (22.5)	63 (32)
Late (>30)	134 (77.5)	14 (7.1)

Abbreviations: ALL-IC, Acute Lymphoblastic Leukemia InterContinental; CNS, central nervous system; HR, high-risk; IR, intermediate risk; MPAL, mixed phenotype acute leukemia; SR, standard-risk.

[a]Other: 1 pt AEIOP BFM 2009, 6 pts ALL BFM 2002, 2 pts ALL-IC like, 1 pt ALL-BFM 2000, 2 pts NHL-BFM, 5 pts St Jude Total XV.

[b]Other: 5 pts ALL BFM 2002, 4 pts EsphALL, 1 pt I-BFM LBL, 1 pt Infant ALL, 3 pts Interfant, NHL BFM.

[c]Other: 1 pt del(19q), 1 pt p16 deletion, 1 pt RUNX tetrasomy, 1 pt trisomy 11, 1 pt trisomy 7, 1 pt del(9)(p21).

[d]Other: 1 pt ABF1-PDGFRB, 1 pt CDKN2A+ and MYC trisomy, 1 pt 90% CDKN2A gene deletion, 17. Chromosome monosomy, NGS: Tp53, NRAS, NT5C2, 1 pt PAX5del, ETV6del, EBF1del, 1 pt IKZF1 gene 1–8 exon losing ATF7IP-JAK2, 5 pts del(9p21), 1 pt in 20% of cells E2A gene sign was detected, 1 pt 3–4 RUNX1 sign, 1 pt NOTCH1 and NUP124/ABL1 fusion, 1 pt FLT3-ITD, 1 pt SIL-TAL1 fusion, 1 pt t(7:14)(p15;q32).

was used to compare different groups. EFS was defined by the occurrence of a second relapse, death, or secondary malignancy. Probabilities of EFS and OS were calculated from the time of relapse diagnosis to the events defined above or any cause of death, respectively. Patients lost to follow-up were censored at the last known contact.

3 | Results

3.1 | Total Cohort

Out of the initial 772 patients registered in the electronic registry, 457 were diagnosed with a relapse between November 2017 and December 2021. A total of 87 records were excluded from the final analyses as detailed in Figure 1. The remaining 370 patients comprised the final cohort for analysis. Table 1 delineates the demographics and clinical characteristics of these patients, stratified by their assigned risk group for relapse. These patients were

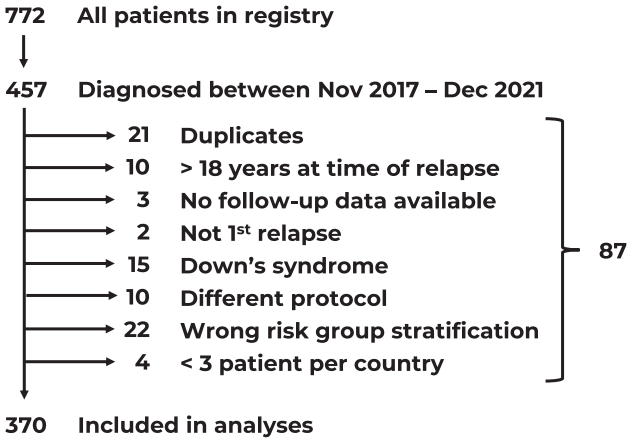


FIGURE 1 | Flowchart of patient selection.

treated across several countries [8] participating in the ALL-IC-BFM study. Not all full-member groups of the frontline ALL-IC trials participated in this project or filled the registry. On the other hand, some observer countries did participate. Argentina (only the GATLA group, $N = 111$), Bulgaria ($N = 13$), Chile ($N = 71$), Greece ($N = 7$), Hungary ($N = 25$), Romania ($N = 16$), Slovenia ($N = 7$), and Turkey ($N = 120$) registered cases, and hence contributed to the analyses being presented. The ALL-IC REL Guidelines have also been used in Armenia, Bosnia–Herzegovina, Croatia, Georgia, Lebanon, Montenegro, Russia, Serbia, and Ukraine to our knowledge, though these countries contributed with no or with less than three cases each to the registry.

Different protocol was defined as any different induction cycle used. Patients with later deviations from the protocol were not excluded.

3.2 | Outcomes: EFS, OS, MRD Remission, and Allogeneic Hematopoietic SCT Outcomes

Table 2 illustrates the outcomes concerning EFS, OS, MRD, remission, and post-allogeneic hematopoietic SCT. Events occurred in 34.1% (59 of 173) of SR patients and 72.6% (143 of 197) of HR patients. The Kaplan–Meier analysis estimated 5-year EFS and OS rates for the cohort at 44.3% and 50.5%, respectively, with Figures 2–4 depicting these outcomes segregated by risk stratification. In the full cohort, six patients who relapsed had been treated for infant ALL on frontline therapy. The only patient in the SR group was alive at last follow-up, whereas one of five HR patients survived.

3.3 | Stratification and Outcomes Based on MRD

After induction, 58.2% of SR patients achieved MRD levels <0.1%. These patients had a 5-year EFS of 63.8% ± 5.2%, which was only slightly higher than the 60.9% ± 6.1% seen in patients with MRD ≥ 0.1% ($p = 0.27$). A similar pattern was seen for OS: SR patients with MRD < 0.1% had a 5-year OS of 74.6% ± 4.8% versus 68.7% ± 5.8% for those with MRD ≥ 0.1% ($p = 0.27$) (Figure 3).

TABLE 2 | Event-free survival, overall survival, minimal residual disease remission, and allogeneic hematopoietic stem cell transplant outcomes.

	SR ($N = 173$)	HR ($N = 197$)
Primary end points		
Median follow-up of total cohort (years)	4.36 (IQR 2.79–5.54)	0.86 (IQR 0.37–3.62)
Median follow-up of patients alive at last follow-up (years)	4.97 (IQR 4.1–6)	4.3 (IQR 3.7–5.7)
5 years event-free survival (StE)	64.5 (±3.7)	26.9 (±3.2)
5 years Overall survival (StE)	74 (±3.5)	32 (±3.4)
Events (subsequent relapse or death)	59 (34.1)	143 (72.6)
EOI complete remission (M1)	137/162 (84.6)	107/175 (61.1)
EOI flow MRD < 0.1%	92/158 (58.2)	58/163 (35.6)
Event after achievement of complete remission	42/137 (30.7)	65/111 (58.6)
Event after EOI MRD < 0.1	32/92 (34.8)	34/58 (58.6)
Total second relapses	43 (24.9)	75 (38)
Death from any cause other than relapse	27/44 (61.4)	54/134 (40.3)
Second malignancy	0	0
Secondary end points		
Death from any cause	44 (25.4)	134 (68)
Death during induction	1 (2.3)	11 (8.2)
Death after EOI CR	36 (81.8)	60 (44.8)
Death after EOI MRD < 0.1%	24 (54.5)	32 (23.9)
Subset of patients who underwent allogeneic hematopoietic stem cell transplant in second complete remission	75 (43.4)	92 (46.7)
Time to transplant, median (range), months	7.2 (3.2–31.3)	5.3 (0.8–28)
Donor type		
MSD/MFD	23/5	24/5
MUD	29	35
MMFD/MMUD	6/1	16/1
FD/UD—unknown HLA typing	4/4	3/6
Conditioning: TBI based	51	54
Conditioning: Chemotherapy based	14	29

(Continues)

TABLE 2 | (Continued)

	SR ($N = 173$)	HR ($N = 197$)
Died after receiving a hematopoietic stem cell transplant	21/75 (28)	40/92 (43.5)
Transplant-related death	9	12
Died due to relapse/disease progression after SCT	6	19

Abbreviations: EOI, end-of-induction; FD, family donor; MFD, matched family donor; MMFD, mismatched family donor; MMUD, mismatched unrelated donor; MRD, minimal residual disease; MSD, matched sibling donor; MUD, matched unrelated donor; SCT, stem cell transplant; StE standard error; TBI, total body irradiation; UD, unrelated donor.

Despite recommendations for further chemotherapy, 20 patients with MRD < 0.1% underwent SCT. These standard-risk patients, who received SCT despite favorable MRD levels, had estimated 5-year EFS and OS rates of 54% ± 11.4% and 61.1% ± 11.9%, respectively ($p = 0.24$ and 0.17). Among these SR patients, seven deaths occurred—three were relapse-related, two were treatment-related, and two were attributable to the transplant. In the SR cohort with favorable MRD who did not undergo transplantation ($n = 72$), 15 deaths were recorded: nine were relapse-related, four were treatment-related, and two lacked a recorded cause. MRD data were available for 157 of 173 SR patients (91.3%).

In the HR cohort, 58 of 163 patients (35.6%) achieved MRD < 0.1% after induction therapy. Their 5-year EFS was 40.2% ± 6.5%, compared with 23.2% ± 4.2% in patients with higher MRD levels. HR patients who underwent SCT had estimated 5-year EFS and OS rates of 49.1% ± 5.3% and 54.6% ± 5.4%, respectively. In contrast, HR patients who did not receive SCT ($n = 105$) had poor outcomes: 5-year EFS was 7.2% ± 2.6% ($p < 0.001$) and OS 10.0% ± 3.0% ($p < 0.001$). Among these non-transplanted HR patients, 94 deaths were recorded: 62 were relapse-related, 30 were treatment-related, and 2 lacked a recorded cause (Figure 4).

A subgroup of 43 patients with T-cell immunophenotype was treated on the HR arm. MRD levels were measured in 33 of these patients, and 15 achieved end-of-induction MRD < 0.1%. Thirteen of the 15 underwent SCT, with estimated 5-year EFS and OS of 40.0% ± 12.6% and 43.8% ± 12.4%, respectively (Figure 5).

3.4 | MRD Dynamics and the Use of Immunotherapy

For patients with high initial MRD, subsets in both SR and HR groups achieved MRD levels of less than 0.1% following additional treatment. Specifically, of the 66 SR patients with end-of-induction (EOI) MRD greater than or equal to 0.1%, 29 attained MRD levels below 0.1% before the SC3 block. Similarly, among the 135 HR patients with high EOI MRD (>0.1%), 29 successfully reduced their MRD to below 0.1% prior to undergoing SCT.

Of the patients with high EOI MRD, 29 were treated with blinatumomab, and their survival outcomes varied by risk category as follows. In the SR group, 8 out of 11 patients survived the follow-up period. In contrast, in the HR group, 6 out of 18 patients survived. Inotuzumab was administered to six patients—five in the HR group and one in the SR group—with one HR patient surviving and being censored at the time of SCT. All 13 patients with Ph+ ALL in this cohort received a tyrosine kinase inhibitor (TKI) during relapse therapy and were assigned to the HR arm.

Overall, SCT was conducted in 43.4% of SR and 46.7% of HR patients. Among HR patients who did not proceed to transplant, the most common reasons included refractory or progressive disease ($N = 55$) and treatment-related mortality ($N = 20$). In a minority of cases, noncompliance or donor and logistical limitations ($N = 10$) were contributing factors, or the reason for not transplanting was not reported.

3.5 | Adverse Events (AEs)

AEs were systematically recorded from the start of therapy to SCT or the end of the final consolidation chemotherapy cycle (SC7) for the SR group. Table 3 compiles these events, revealing a range of AEs with varying frequencies and severities across the chemotherapy courses. Infections were the most common AEs, markedly affecting mortality, especially during the induction phase, with moderate-to-severe infections reported in 60% of the SR group and 79% of the HR group. The HR group also encountered a higher frequency of intensive care unit (ICU) admissions and severe AEs, underlining the increased management challenges associated with their treatment toxicity.

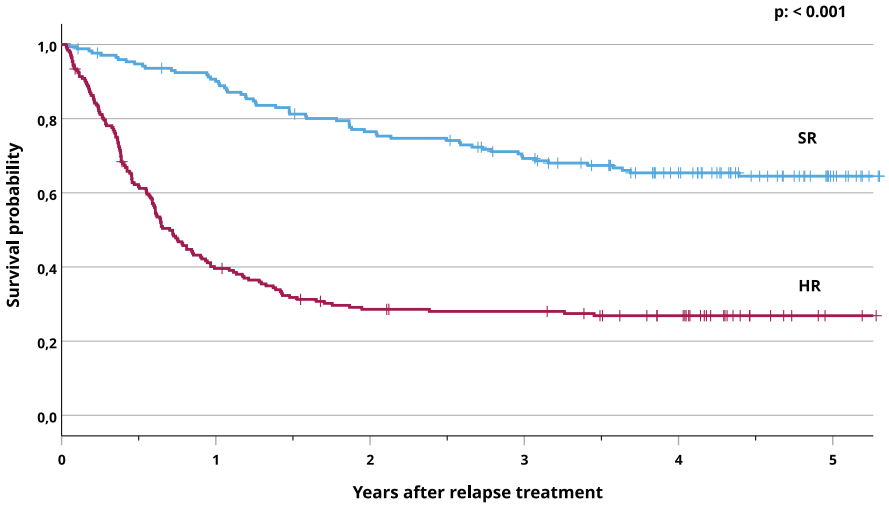
4 | Discussion

The prognosis for children with ALL has improved significantly, yet relapse remains a significant cause of mortality [9]. The ALL-IC-BFM consortium, through its international cooperative efforts, has enabled the recruitment of a sufficient number of patients to conduct meaningful clinical studies, a necessity given the disease's rarity [5, 6].

Our initiative aimed to standardize diagnostic and treatment guidelines for children with the first relapse of ALL, focusing on institutions not engaged in prospective randomized trials. This report represents the first consolidated outcome data from the consortium, highlighting the feasibility of intensive chemotherapy across participating middle-income countries.

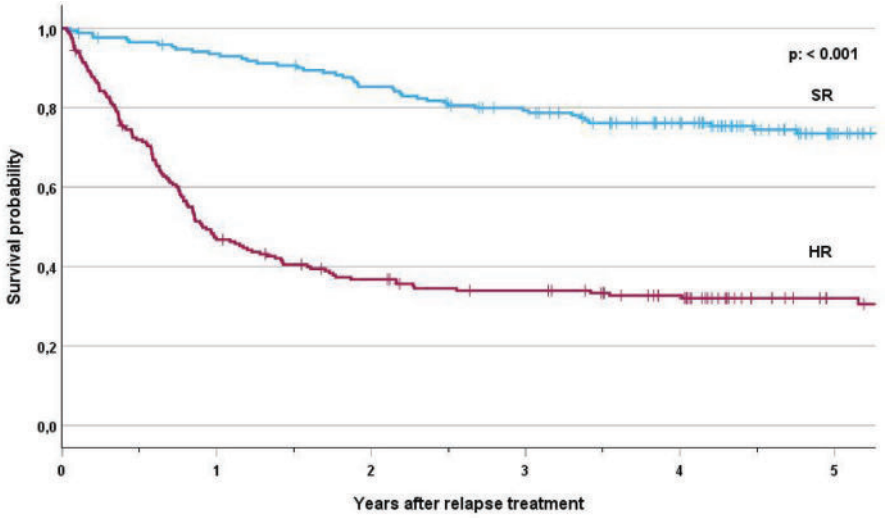
In the SR group, the observed toxicity was within acceptable limits, and the EFS and OS rates were comparable to contemporary control arms of clinical trials, signaling an encouraging trend [13], for example, with preliminary findings from the IntReALL SR 2010 cohort, reported in abstract form that demonstrated favorable outcomes with the ALL-REZ BFM 2002 regimen, particularly in patients with isolated central nervous system (CNS) relapse [16]. Given the relatively favorable prognosis and distinct biology of isolated extramedullary relapses, particularly in the SR group, this subgroup represents an important focus for future analysis, and a dedicated study in our expanded cohort is currently in preparation.

A. Event-free survival



	0 year	1 year	2 years	3 years	4 years	5 years
SR, N at risk	173	153	129	113	90	57
HR, N at risk	197	77	53	50	40	19

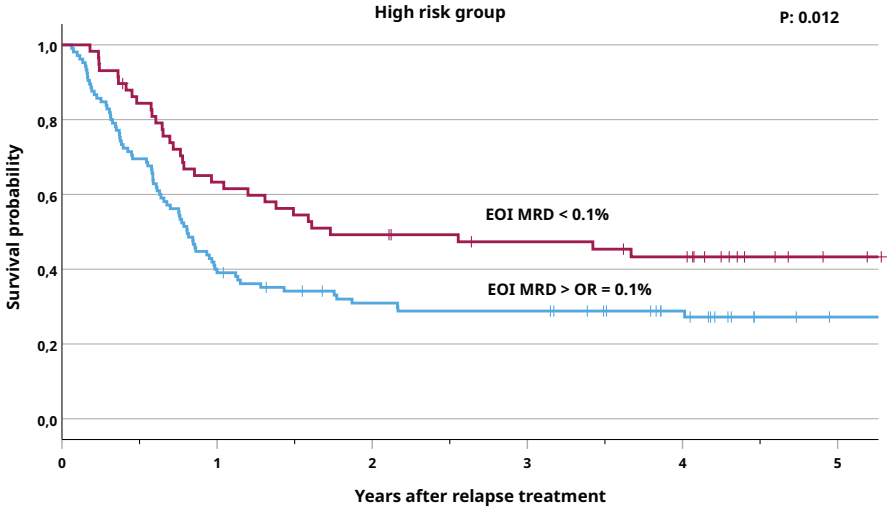
B. Overall survival



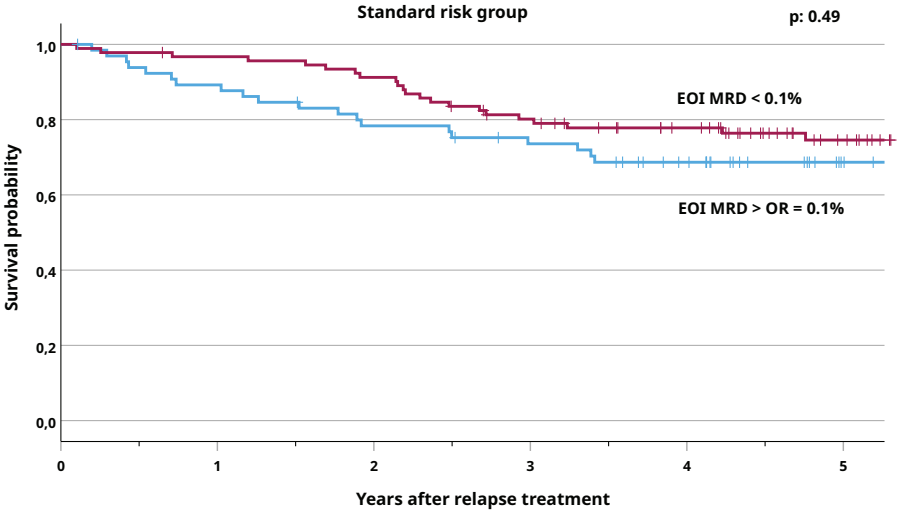
	0 year	1 year	2 years	3 years	4 years	5 years
SR, N at risk	173	159	144	129	106	64
HR, N at risk	197	91	68	59	46	22

FIGURE 2 | Event-free survival and overall survival by risk group. (A) Event-free survival. (B) Overall survival. HR, high-risk; SR, standard-risk.

HR patients presented with a less favorable prognosis, with OS probabilities below 30%. Despite various conventional cytotoxic drug combinations used in past trials, outcomes have not surpassed the 50% threshold, even with allogeneic SCT. The non-blinatumomab arm of the IntReALL 2010 HR study yielded a similar EFS to ours; however, it had better OS (49% at 4 years). Our results underscore the urgent need for integrating novel therapeutic agents alongside systemic therapy for HR patients, as evidenced by recent phase-3 studies highlighting the efficacy of blinatumomab [17, 18] and also implementing immunotherapies at further relapses.



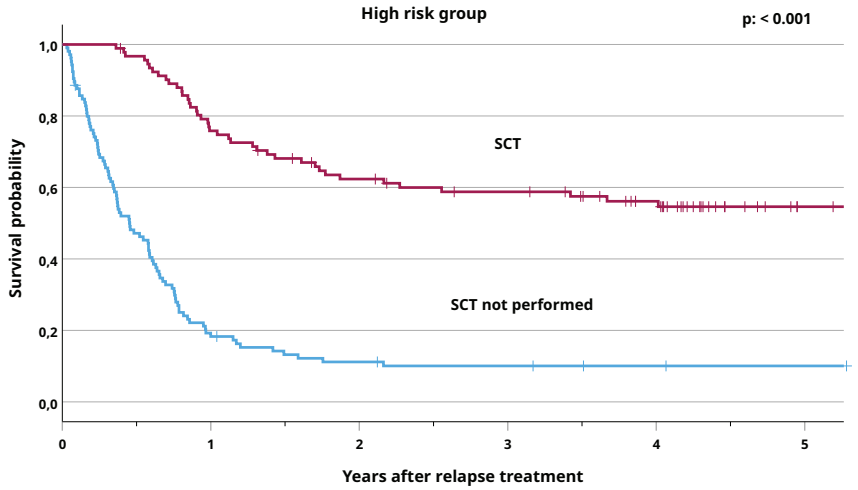
	0 year	1 year	2 years	3 years	4 years	5 years
EOI MRD < 0.1%, N at risk	58	36	28	24	21	10
EOI MRD > or = 0.1% , N at risk	105	41	29	27	18	7



	0 year	1 year	2 years	3 years	4 years	5 years
EOI MRD < 0.1%, N at risk	92	88	83	70	59	38
EOI MRD > or = 0.1%, N at risk	65	58	50	45	36	19

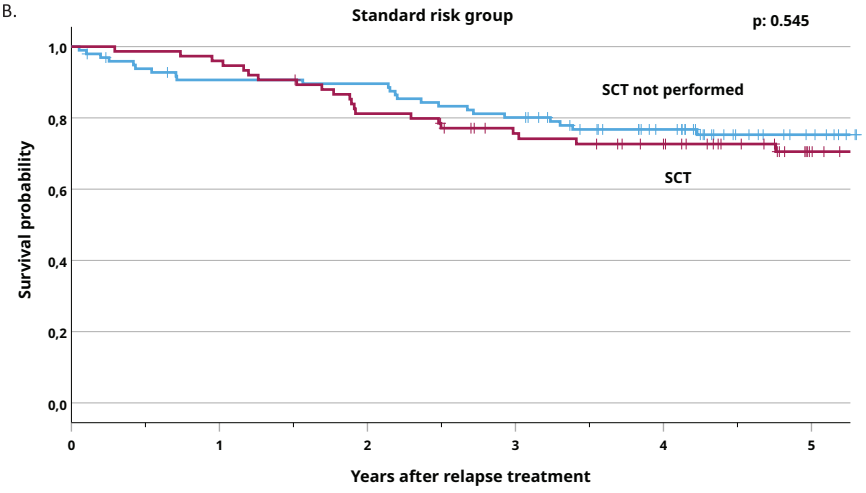
FIGURE 3 | Overall survival according to end-of-induction (EOI) flow MRD result. MRD, minimal residual disease.

A.



	0 year	1 year	2 years	3 years	4 years	5 years
SCT, N at risk	92	69	54	48	37	14
SCT not performed, N at risk	105	19	11	9	6	6

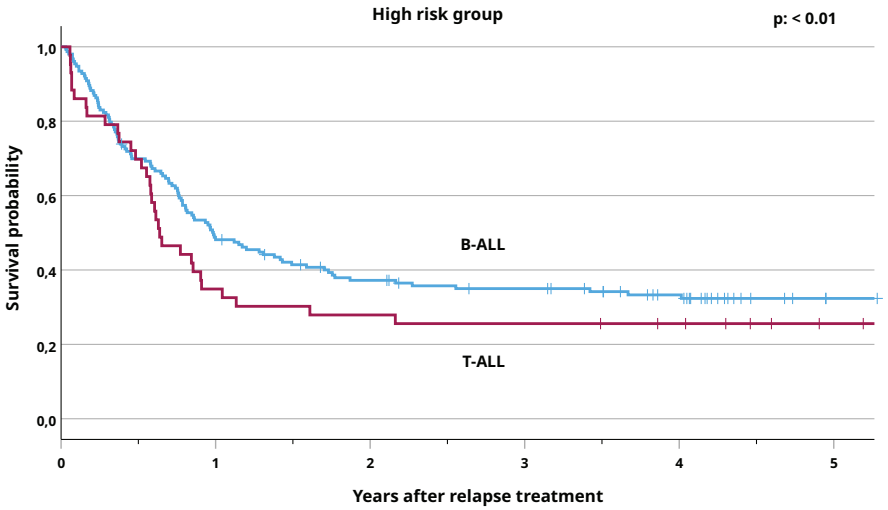
B.



	0 year	1 year	2 years	3 years	4 years	5 years
SCT, N at risk	75	72	60	51	44	26
SCT not performed, N at risk	98	86	85	76	59	37

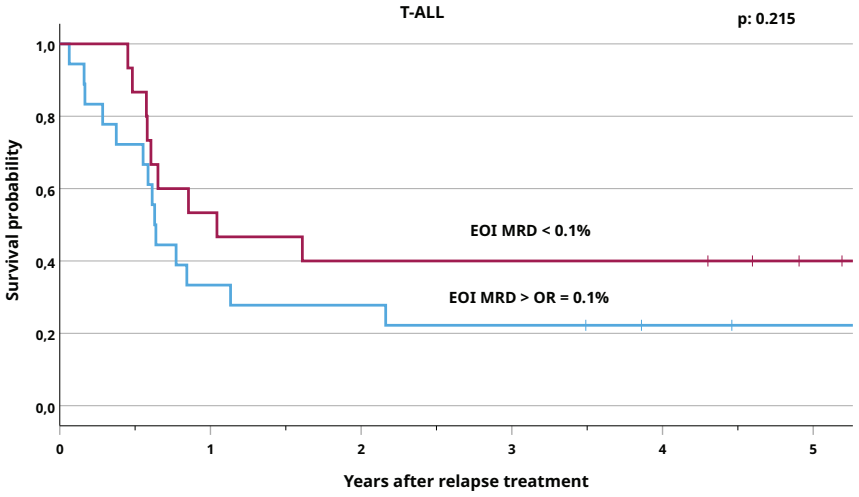
FIGURE 4 | Overall survival in (A) high-risk and (B) standard-risk patients with and without stem cell transplant (SCT).

A. Overall survival in high-risk patients stratified according to the immunophenotype



	0 year	1 year	2 years	3 years	4 years	5 years
B-ALL, N at risk	153	73	53	46	35	16
T-ALL, N at risk	43	15	12	11	9	4

B. Overall survival of patients with T-ALL according to end-of-induction (EOI) flow MRD result



	0 year	1 year	2 years	3 years	4 years	5 years
EOI MRD < 0.1%, N at risk	15	8	6	6	6	3
EOI MRD > or = 0.1%, N at risk	18	6	5	4	2	1

FIGURE 5 | (A) Overall survival in high-risk patients stratified according to the immunophenotype. (B) Overall survival of patients with T-ALL according to end-of-induction (EOI) flow MRD result. ALL, Acute Lymphoblastic Leukemia; MRD, minimal residual disease.

TABLE 3 | Frequency and severity of adverse events by chemotherapy course in standard-risk (SR) and high-risk (HR) groups.

	SR ($N = 162$)									HR ($N = 171$)				
Chemotherapy cycle	**SI**	**SC1**	**SC2**	**SC3**	**SC4**	**SC5**	**SC6**	**SC7**	**Total events**	**HI**	**HC1**	**HC2**	**HC3**	**Total events**
Toxicity data available	161	145	143	135	109	98	88	84	962	169	139	123	109	540
ICU admission	12	4	2	2	0	1	0	2	23	41	17	14	3	75
Infection														
Moderate: no organism isolated; on i.v. antibiotics	63	46	37	29	18	20	15	12	240	53	62	57	34	206
Severe (organism isolated)	24	9	4	8	7	7	3	3	65	52	31	19	16	118
Life-threatening with hypotension	9	1	1	0	0	2	0	0	13	19	5	10	2	36
Cause of death	2	0	0	2	0	0	0	0	4	11	5	5	0	21
Thrombosis	6	4	1	2	0	1	1	0	15	10	6	4	2	22
Pancreatitis	2	2	0	0	2	1	0	0	7	3	1	0	0	4
Steroid diabetes	11	5	2	6	3	3	2	5	37	7	0	3	0	10
Stomatitis	30	24	9	18	8	12	9	10	120	81	54	36	31	202
PNS/CNS toxicity > gr 2	2/5	3/8	1/5	5/4	8/3	2/4	3/2	1/2	25/33	9/12	5/7	5/6	3/4	22/29
Diarrhea (also at night, mild cramping)	4	2	2	5	1	0	3	1	18	24	11	11	4	50
Major protocol deviation due to AE reported	4	7	1	2	3	2	3	1	23	14	3	3	3	23

Abbreviations: AE, adverse event; CNS, central nervous system; HC, high-risk consolidation; HI, high-risk induction; ICU, intensive care unit; ICU, intensive care unit; PNS, peripheral nervous system; SC, standard-risk consolidation; SI, standard-risk Induction.

Flow cytometry has been instrumental in MRD quantification, aligning closely with molecular genetic approaches in prognostic value [13, 19]. For SR patients, achieving an EOI MRD of less than 0.1% correlated with satisfactory OS rates without SCT. Conversely, for those with an EOI MRD above 0.1%, successful SCT appeared to mitigate the suboptimal response to initial chemotherapy, echoing findings from Eckert et al. [10, 14]. Of note, SR patients with good EOI MRD transplanted against protocol advice tended to have poorer outcomes than patients treated with consolidation chemotherapy without SCT.

The HR group's challenges are underlined by their lower response rates to induction therapy and high relapse rates post-SCT. Notably, only a small fraction of HR patients with high initial EOI MRD levels achieved satisfactory reduction before SCT. This indicates that our current chemotherapy treatments might be insufficient, necessitating the inclusion of new therapeutic strategies for both SR and HR groups with high initial EOI MRD levels. The significant barrier here is the prohibitive cost of immunotherapy, which is not uniformly accessible across the consortium's participant countries.

Although our findings offer valuable insights into the treatment of relapsed ALL in children, there are inherent limitations to our approach that merit consideration. The variability in healthcare infrastructure and resources among the participating ALL-IC REL countries may affect diagnostic capabilities, the implementation of the standardized treatment guidelines, and subsequent outcome reporting [5, 6]. This variability could influence the generalizability of our results. Furthermore, the observational nature of our registry trial—without randomization and control groups—constrains our capacity to make causal inferences about the effectiveness of the treatment strategies. The reliance on flow cytometry for MRD stratification, albeit effective, may not be consistent across the consortium, potentially leading to variability in prognostic accuracy. Economic limitations within the consortium may have also hindered access to newer therapies, for example, haploidentical SCT or total body irradiation (TBI) or targeted therapies, disproportionately impacting the HR group's outcomes. These factors necessitate a careful interpretation of the results and substantiate the imperative for ongoing efforts to validate and enhance these benchmark outcomes.

Our comparative data lay the groundwork for benchmarking outcomes in children with primary ALL relapse in high-intermediate income countries. They corroborate prior findings on the poor prognosis associated with specific patient subsets and validate the feasibility of modern intensive chemotherapy across diverse medical infrastructures. As the field of precision medicine and immunotherapy evolves, we plan to refine our registry to accommodate various treatment pathways, enhancing our guidelines to continually improve patient outcomes globally.

Ethics Statement

Ethical approval for the study was obtained from the local medical research ethics committees.

Consent

Informed consent was secured from the patients or their guardians, in line with the prevailing local regulations.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File 1: pbc32063-sup-0001-SuppMat.pdf **Supporting File 2**: pbc32063-sup-0002-SuppMat.pdf