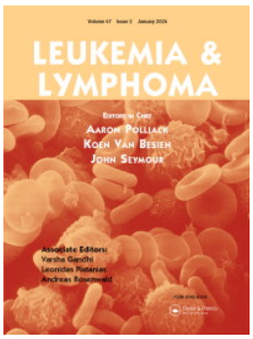

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: www.tandfonline.com/journals/ilal20

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To cite this article: Volkan Hazar, Monika Makiya, Koray Yalçın, Juan Tadecilla Cadiu, Federico Manni, Andrea Reyes Barragan, Sophia Polychronopoulou, Anca Colita, Boryana Avramova, Marko Kavcic, Mirella Ampatzidou, Letitia Elena Radu, Tanya Hristova, Tomaz Prelog, Bence Höbör, Roula Farah, Janez Jazbec & Daniel Janos Erdelyi (2026) Prognostic factors and survival outcomes of first CNS relapse in childhood acute lymphoblastic leukemia: results from the ALL-IC REL 2016 study, Leukemia & Lymphoma, 67:2, 416-423, DOI: 10.1080/10428194.2025.2598861

To link to this article: https://doi.org/10.1080/10428194.2025.2598861

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LEUKEMIA & LYMPHOMA
2026, VOL. 67, NO. 2, 416–423
https://doi.org/10.1080/10428194.2025.2598861

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Prognostic factors and survival outcomes of first CNS relapse in childhood acute lymphoblastic leukemia: results from the ALL-IC REL 2016 study

Volkan Hazar[a], Monika Makiya[b], Koray Yalçın[c], Juan Tadecilla Cadiu[d], Federico Manni[e], Andrea Reyes Barragan[d], Sophia Polychronopoulou[f], Anca Colita[g], Boryana Avramova[h], Marko Kavcic[i], Mirella Ampatzidou[f], Letitia Elena Radu[g], Tanya Hristova[h], Tomaz Prelog[i], Bence Höbör[j], Roula Farah[k], Janez Jazbec[i] and Daniel Janos Erdelyi[j]

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is among the most curable pediatric cancers, yet relapse involving the central nervous system (CNS) remains a major therapeutic obstacle. In this prospective cohort, 97 children (aged 1.1–18.2 years) experiencing their first CNS relapse were enrolled in the ALL-IC REL study. Relapses were classified as isolated CNS (i-CNS, $n=43$) or combined CNS (c-CNS, $n=54$), and patients received treatment through standard- or high-risk regimens, encompassing chemotherapy, cranial irradiation, and allogeneic stem cell transplantation. The estimated 2-year event-free survival was 40.0%, and overall survival 49.4%, closely matching outcomes reported internationally. Survival rates were comparable across i-CNS and c-CNS relapses, while induction failure occurred more frequently in c-CNS. Multivariable analysis identified female sex, T-cell phenotype, and very early relapse as independent predictors of poor prognosis. These results underscore the critical necessity for risk-adapted therapy techniques and the incorporation of innovative medicines into forthcoming procedures.

ARTICLE HISTORY
Received 24 September 2025
Revised 19 November 2025
Accepted 30 November 2025

KEYWORDS
Childhood acute lymphoblastic leukemia; central nervous system relapse; prognostic factors; survival; hematopoietic stem cell transplantation

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and is characterized as a systemic neoplasm with a marked propensity for central nervous system (CNS) involvement at relapse following initial remission [1,2]. Advances in frontline therapeutic regimens have made ALL one of the most curable childhood cancers, with current overall survival (OS) rates exceeding 85% [3–6]. Even with modern chemotherapy protocols, the relapse rate remains 10-20% [7]. When relapse occurs, the CNS is involved in approximately 20–40% of cases. This can present as isolated CNS (i-CNS) relapse or combined systemic and CNS (c-CNS) relapse. Treating CNS relapse is challenging, as outcomes depend on several factors: timing of relapse, whether it's isolated or combined, the biological and molecular characteristics of the leukemia, and response to reinduction therapy [8–10].

In the early 2000s, the International BFM Study Group established the ALL IC-BFM consortium, uniting experts from 15 countries across three continents. This step was particularly significant as it enabled the inclusion of patients from regions that had historically been underrepresented in high-quality clinical trials. While major progress has been made in frontline ALL treatment, as shown in the ALL IC-BFM 2002 and 2009 studies [11,12], relapsed ALL remained a significant challenge. The ALL IC-BFM 2002 trial revealed heterogeneity in relapse management, with over 20 distinct protocols across centers and 5-year post-relapse survival rates ranging from 20% to 63% (unpublished data), emphasizing the urgent need for standardized therapeutic approaches [13]. To address this, the ALL-IC Relapsed Study Group adopted a practical and inclusive approach designed to encourage broad participation across its network. This led to the launch of an

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/10428194.2025.2598861.
This article has been corrected with minor changes. These changes do not impact the academic content of the article.
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observational study on relapsed pediatric ALL, using standard drug combinations without randomization. This effort marks an important step toward aligning treatment practices and building robust outcome data to better guide relapse management in the future.

Outcome results of the 2017–2021 full 1st relapse patient cohort have been published [accepted at Pediatric Blood and Cancer]. In the present study, we provide a prospective cohort analysis focusing specifically on patients with CNS relapse treated according to the standard-of-care recommendations delineated in the ALL-IC REL protocols.

Materials and methods

Patients

This analysis included all patients diagnosed with childhood ALL who experienced a first CNS relapse at age <18.5 years between December 2016 and November 2023, were treated according to the ALL-IC REL 2016 guideline, and were registered in the REDCap electronic database. Ethical approval was obtained from all participants and/or their legal guardians, in accordance with local regulations. Patients with first non-CNS relapses and isolated bone marrow relapses were analyzed as comparators.

Definitions

An i-CNS relapse was defined as ≥5 white blood cells (WBC)/μL in cerebrospinal fluid (CSF) with cytospin-confirmed blasts, or a biopsy-proven CNS recurrence without morphologic bone marrow involvement; bone marrow minimal residual disease (MRD) positivity did not exclude i-CNS classification. A c-CNS relapse was defined as CNS involvement accompanied by ≥5% blasts in the bone marrow aspirate. Isolated bone marrow relapse was defined as ≥25% blasts in the bone marrow without CNS or testicular disease. Second complete remission (CR2) was defined as <5% blasts in bone marrow, absence of CSF blasts, and resolution of extramedullary involvement at the end of induction. Failure to meet these criteria constituted induction failure. Relapse timing was classified as very early (<18 months from initial diagnosis), early (18–36 months), or late (≥36 months).

Minimal residual disease

For patients with c-CNS relapse, MRD was assessed at the end of induction from bone marrow aspirates using flow cytometry (FC-MRD), as previously described [14]. An end-of-induction MRD <0.1% (10^{-3}) was considered a good response, while MRD ≥0.1% indicated a poor response. Cytogenetic testing was conducted at local laboratories and not centrally reviewed.

Treatment

The therapeutic protocol is publicly available at semmelweis.hu/tuzoltoklinika/en/researches/all-ic/. According to protocol design, all very early relapses [precursor B (pB)- and T-cell) were classified as high-risk (HR). Early and late pre-B CNS relapses, whether isolated or combined, were assigned to the standard-risk (SR) arm. Among T-cell relapses, early and late i-CNS relapses were treated in the SR arm, while c-CNS relapses were managed in the HR arm (Table 1S). Patients with BCR::ABL1, TCF3::PBX1, TCF3::HLF, iAMP21, KMT2A rearrangements, hypodiploidy (<44 chromosomes), or NT5C2/TP53 mutations were treated in the HR group. All HR patients proceeded to allogeneic hematopoietic stem cell transplantation (HSCT) following chemotherapy. While the patients who relapsed with BCR::ABL1 were treated in the HR arm, the tyrosine kinase inhibitor was also given. In the SR group, patients with MRD ≥0.1% at end of induction were also referred for HSCT (Figure 1S). Additional HSCT indications in the SR arm were explicitly specified in the guideline (Table 2S). Conditioning regimens for HSCT were at the discretion of treating centers. Patients ineligible for HSCT after intensive chemotherapy received cranial and upper cervical (C1–C3) irradiation at a dose of 18 Gy. Protocol discontinuation was recommended for SR patients not achieving hematologic remission (≥M2 marrow) after cycle SC3 or HR patients with ≥M2 marrow after cycle HC2. In such cases, treatment decisions including early-phase clinical trial enrollment, continuation of protocol, alternative therapies (e.g. clofarabine-, fludarabine-based regimens, or CAR-T cell therapy), or palliative care were made by the treating center.

Statistical analysis

This cohort included patients with CNS relapse treated under the ALL-IC REL 2016 protocol. Event-free survival (EFS) was defined as the interval from study registration to induction failure (≥5% marrow blasts or persistent CSF blasts at end of induction), second relapse, death, or secondary malignancy. OS was measured from the time of first relapse until death or the last follow-up. Survival analyses were conducted using Kaplan–Meier estimates, and differences between groups were assessed with log-rank tests, Cox proportional hazards regression was performed for multivariable analysis of OS, adjusting for

predefined covariates: age (<10 vs. ≥10 years), sex, immunophenotype (pB- vs. T-cell), time to relapse (very early, early, late), type of CNS relapse (isolated vs. combined), CSF blast count (<50 vs. ≥50/μL), and induction failure. Because induction failure was already defined as a EFS event, it was excluded as a covariate in EFS modeling. All variables with a p value <0.200 in the univariate analysis were subsequently entered into the multivariate model for further evaluation. Hazard ratios (HR) with 95% confidence intervals (CI) were reported; HR >1 indicated worse outcome. Statistical analyses were conducted using SPSS version 18.0 (SPSS Inc.) and XLSTAT version 2017.2. All tests were two-sided, with statistical significance defined as $p < 0.05$.

Results

Among 491 relapse cases recorded in the REDCap database and treated under the ALL-IC REL 2016 guideline, 313 had isolated bone marrow relapse. This was followed by 87 isolated extramedullary relapses (39 in the CNS, 35 in the testis, 9 in other extramedullary sites, and 4 affecting both CNS and testis) and 91 combined relapses (54 BM+CNS, 33 BM+testis, and 4 BM+other). Of those with CNS involvement, 43 cases were classified as i-CNS relapse and 54 as c-CNS relapse. For statistical purposes, four patients with concurrent CNS and testis relapse were categorized within the i-CNS group. Data review revealed treatment allocation discrepancies: two patients meeting HR criteria were treated in the SR arm, whereas seven patients fulfilling SR criteria were treated in the HR arm. These patients were analyzed in the group in which they were treated.

For survivors of all relapses, the median follow-up duration was 59.6 months (range, 1.0–111.5). The estimated 2-year EFS and OS rates were 43.3% (95% CI, 38.9–47.7; Figure 2S) and 57.1% (95% CI, 52.7–61.6; Figure 3S), respectively. Subsequent analyses focused on the CNS relapse cohort ($n = 97$). No statistically significant differences were observed between groups with respect to age, immunophenotype, risk category, time to relapse, prior hematopoietic stem cell transplantation (HSCT), or time from diagnosis to relapse. However, CNS relapses, particularly i-CNS, were more frequent in male patients ($p = 0.008$), while induction failure was significantly higher in c-CNS compared with i-CNS relapse ($p = 0.008$; Table 1).

Within the CNS relapse cohort, over a median follow-up of 57.8 months (range, 1.4–111.5) among survivors, there were 21 induction failures, 36 s relapses (10 post-HSCT), and 56 deaths (Table 2). Cytogenetic analysis of CNS relapses revealed ETV6::RUNX1 in 5 patients, KMT2A rearrangements in 4 patients, and BCR::ABL1, TCF3::PBX1, IGH::CCND1, and iAMP21 in one patient each. Among patients with CNS relapse, the 2-year EFS and OS rates were estimated to be 40.0% (95% CI, 30.1–49.8) and 49.4% (95% CI, 39.2–59.6), respectively. The estimated 2-year EFS rates for i-CNS and c-CNS relapses were 41.9% (95% CI, 27.1–56.6) and 38.6% (95% CI, 25.5–51.6), respectively ($p > 0.05$; Figure 1). The corresponding 2-year OS rates were 53.1% (95% CI, 38.1–68.1) for i-CNS and 46.6% (95% CI, 33.0–60.2) for c-CNS relapses ($p > 0.05$; Figure 2). When patients were stratified by relapse timing (very early, early, or late), significant differences in EFS or OS were found for either i-CNS or c-CNS cases. Table 3 provides an overview of the 2-year EFS and OS outcomes, as well as the univariate and multivariate hazard ratios (HRs) for factors linked to survival. In univariate analyses, EFS was influenced by sex, immunophenotype, and time to relapse, while OS was associated with sex (borderline), immunophenotype, time to relapse, and induction failure. Male sex, pB immunophenotype, and late relapse at the time of relapse were associated with more favorable

Table 1. Characteristics of patients with iCNS and cCNS relapses.

	i-CNS relapse *n*: 43	c-CNS relapse *n*: 54	*p* value	CNS relapse (total) *n*: 97
Age (years)			n.s	
<10	29 (67.4)	38 (70.4)		67 (69.1)
≥10	14 (32.6)	16 (29.6)		30 (30.9)
Sex			0.008	
Female	9 (20.9)	24 (44.4)		33 (34.0)
Male	34 (79.1)	30 (55.6)		64 (66.0)
Country			0.048	
Argentina	13	24		37
Türkiye	19	12		31
Chile	1	9		10
Greece	3	2		5
Romania	4	1		5
Bulgaria	2	2		4
Slovenia	1	3		4
Hungary	0	1		1
Immunophenotype			n.s	
pB-cell	34 (79.1)	44 (81.5)		78 (80.4)
T-cell	9 (20.9)	10 (18.5)		19 (19.6)
Relapse type			n.s	
Very early	17 (39.5)	20 (37.0)		37 (38.1)
Early	18 (41.9)	16 (29.6)		34 (35.0)
Late	8 (18.6)	18 (33.4)		26 (26.9)
Risk group			n.s	
SR	22 (51.2)	23 (42.6)		45 (46.4)
HR	21 (48.8)	31 (57.4)		52 (53.6)
Induction failure	4 (9.3)	17 (31.5)	0.008	21 (21.6)
HSCT			n.s	
Yes	16 (37.2)	19 (35.2)		35 (36.1)
No	27 (62.8)	35 (64.8)		62 (63.9)
Time from diagnosis to relapse (months)	20.1 (3.1–155.9)	25.4 (3.1–87.0)	n.s	21.2 (3.1–155.9)
Median FU-time (months) (min-max) for alive patients	58.2 (12.8–107.7)	58.0 (1.4–111.5)	n.s	58.2 (1.4–111.5)

pB, precursor B; SR, standard risk; HR, high risk; HSCT, hematopoietic stem cell transplantation; CNS, central nervous system.

Table 2. Treatment flow diagram.

iCNS relapses		cCNS relapses		CNS relapses (all)	
Induction (n:43)		*Induction (n: 54)*		*Induction (n: 97)*	
Event Induction failure *n*: 4 Induction death *n*: 2		Event Induction failure *n*: 17 Induction death *n*: 4		Event Induction failure *n*: 21 Induction death *n*: 6	
Consolidation/Salvage (*n*: 41)		Consolidation/Salvage (*n*: 50)		Consolidation/Salvage (*n*: 91)	
Event Progressive disease *n*: 1 • Ex (1) TRM *n*: 3 Relapse *n*:10 • Ex (10)		Event Progressive disease *n*: 4 • Ex (4) TRM *n*: 3 Relapse *n*:16 • Ex (14)		Event Progressive disease *n*: 5 • Ex (5) TRM *n*: 6 Relapse *n*:26 • Ex (24)	
HSCT time (*n*: 27)		HSCT time (*n*: 29)		HSCT time (*n*: 56)	
Chemotherapy Radiotherapy (*n*: 11)	HSCT (*n*: 16)	Chemotherapy Radiotherapy (*n*: 10)	HSCT (*n*: 19)	Chemotherapy Radiotherapy (*n*: 21)	HSCT (*n*: 35)
Event -	Event Relapse *n*: 6 • Ex (5) TRM *n*: 4	Event –	Event Relapse *n*: 4 • Ex (4) TRM *n*: 2	Event –	Event Relapse *n*: 10 • Ex (9) TRM *n*: 6
Alive *n*: 11	Alive *n*: 7	Alive *n*: 10	Alive *n*: 13	Alive *n*: 21	Alive *n*: 20

HSCT, hematopoietic stem cell transplantation; TRM, treatment related mortality; CNS, central nervous system; iCNS, isolated CNS; cCNS, combined CNS.

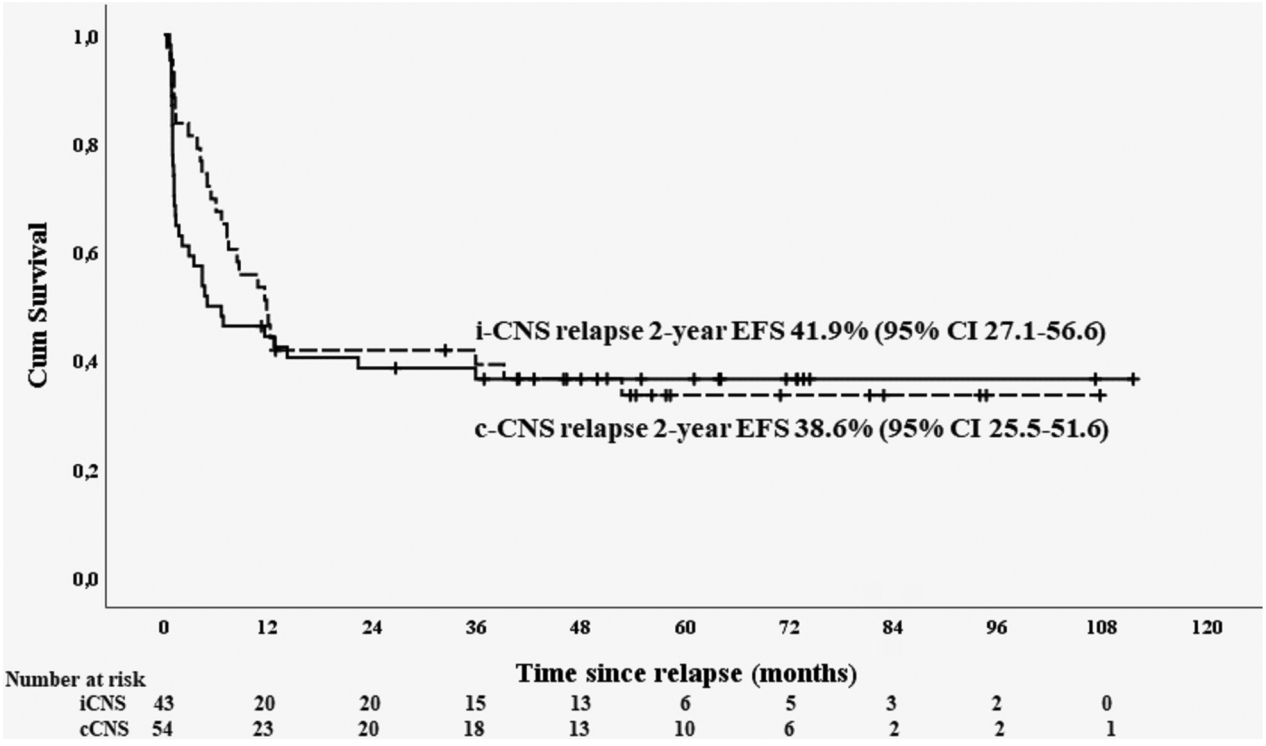

Figure 1. The estimated EFS according to CNS involvement. CNS, central nervous system; EFS, event-free survival.

outcomes. Given the observation of poorer prognosis among female patients, the potential effect of study center was explored. When cases from Argentina and Türkiye, which constituted the majority of the cohort, were sequentially excluded, the adverse prognostic impact of female sex persisted. When cases from Argentina were excluded, the 2-year EFS and OS rates were 31.8% (95% CI 12.3–51.3) and 40.9% (95% CI 20.2–61.6) in females, compared with 46.6% (95% CI 30.5–62.7) and 59.3% (95% CI 43.2–75.4) in males ($p > 0.05$ for both comparisons). Upon exclusion of cases from Türkiye, the 2-year EFS and OS rates were 21.7% (95% CI 4.8–38.6) and 21.7% (95% CI 4.8–38.6) in females, versus 43.5% (95% CI 28.3–58.7) and 59.0% (95% CI 43.8–74.2) in males ($p = 0.014$ and 0.033, respectively). In countries other than Argentina and Türkiye, which had more participants in the study, the results were worse in the female gender, but no statistical

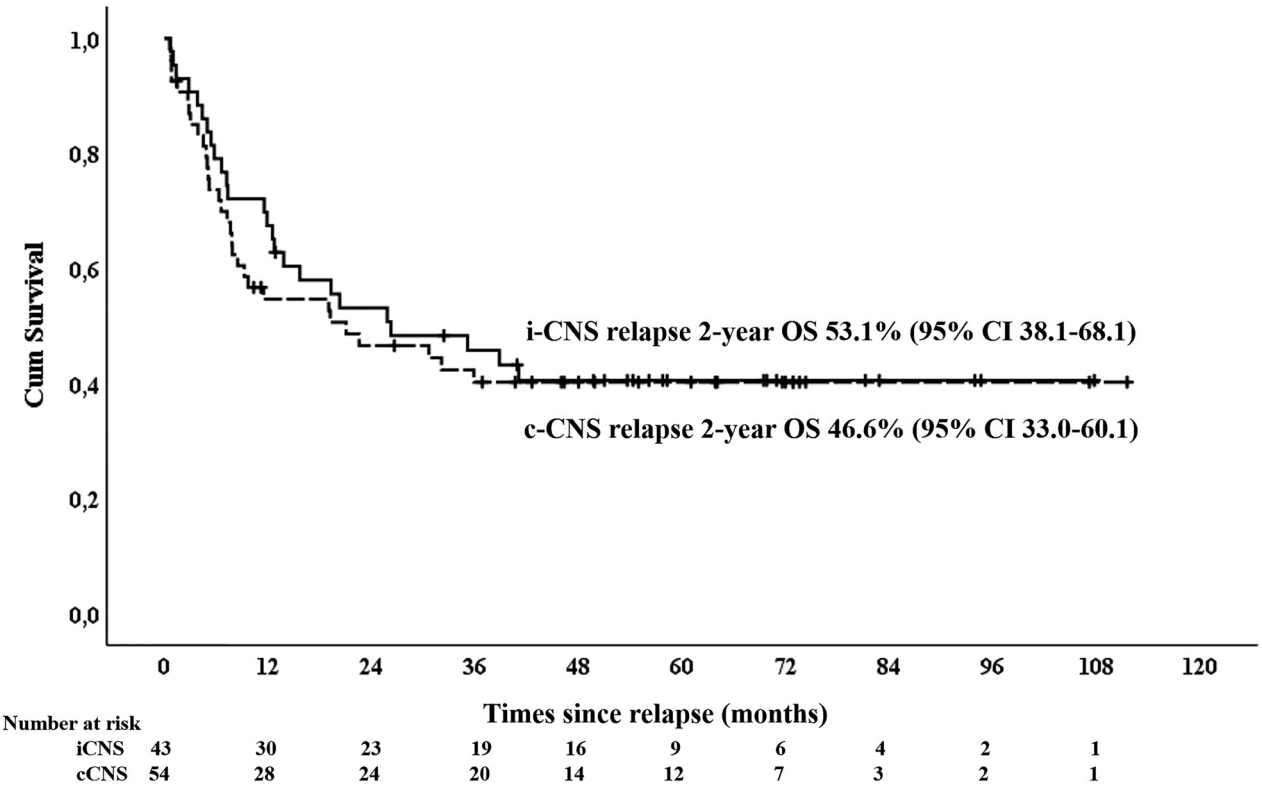

Figure 2. The estimated OS according to CNS involvement. CNS, central nervous system; OS, overall survival.

Table 3. Univariate and multivariate analysis associated with PFS and OS for patients with CNS relapse.

	Event free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	2-year EFS (95% CI)	*p*	HR (95% CI)	*p*	2-year OS (95% CI)	*p*	HR (95% CI)	*p*
Age (years)		0.639				0.474		
<10 (*n*: 67)	39.9 (28.1–51.71)		–	–	49.0% (36.9–61.0)		–	–
≥10 (*n*: 30)	40.0 (22.5–57.5)				50.5% (31.8–69.1)			
Sex		0.033		0.014		0.050		0.027
Male (*n*: 64)	46.5 (34.2–58.8)		1		58.1% (45.7-70.4)		1	
Female (*n*: 33)	27.3 (12.1–42.5)		1.96 (1.15–3.35)		38.3% (17.2–49.4)		1.95 (1.0–3.52)	
Immunophenotype		<0.001		0.392		<0.001		0.007
pB cell (*n*: 78)	47.1 (36.0–58.5)		1		59.1% (48.0–70.2)		1	
T-cell (*n*: 19)	10.5 (0.00–24.3)		1.32 (0.70–2.52)		10.5% (0.0–24.3)		2.51 (1.29–4.8)	
Relapse type		<0.001		<0.001		<0.001		0.003
Late (*n*: 26)	65.2 (46.7–83.6)		1		68.8% (50.8–86.8)		1	
Early (*n*: 34)	52.9 (36.2–69.7)		1.24 (0.57–2.71)	0.59	67.7% (51.9–83.4)		1.01 (0.44–2.33)	0.97
Very early (*n*: 37)	10.8 (0.81–20.8)		4.34 (2.00–9.45)	<0.001	17.9% (5.1–30.8)		3.05 (1.31–7.11)	0.010
CNS involvement		0.539				0.404		
iCNS (*n*: 43)	41.7 (27.1–56.6)		–	–	53.1% (38.1–68.1)		–	–
cCNS (*n*: 54)	38.6 (25.5–51.6)				46.6% (33.0–60.2)			
CNS blast count (/μL)		0.118		0.179		0.076		0.172
<50 (*n*: 29)	51.7 (33.5–69.9)		1.514 (0.83–2.77)		60.7% (42.6–78.8)		1.56 (0.82–2.94)	
≥50 (*n*: 68)	34.8 (23.5–46.1)				44.5% (32.6–56.4)			
Induction failure*						0.009		0.258
No (*n*: 76)	–	–	–	–	56.2% (44.9–67.4)		1	
Yes (*n*: 21)					22.5% (3.5–41.5)		1.46 (0.76–2.79)	

*Induction failure was not accepted as a pre-specified prognostic covariate for EFS.
EFS, event-free survival; CI, confidence intervals; HR, Hazard ratios; OS, overall survival; CNS, central nervous system; iCNS, isolated CNS; cCNS, combined CNS.

difference was found. The 2-year EFS and OS rates were 25.0% (95% CI 0.6–49.4) and 25.0% (95% CI 0.6–49.4) in females, versus 64.7% (95% CI 42.0–87.4) and 38.1% (95% CI 13.9–62.3) in males ($p=0.116$ and 0.229, respectively).

Patients with i-CNS relapse showed a tendency toward improved survival compared to those with c-CNS relapse, although the difference did not reach statistical significance.

Discussion

In this prospective cohort of children with ALL who experienced a first CNS relapse and were treated under the ALL-IC REL 2016 protocol, the estimated 2-year EFS and OS were 40% and 49%, respectively. These outcomes are broadly consistent with recent international series, which report 2-year EFS rates of ~40–45% and OS rates of ~50–55% after a first CNS relapse [15]. Within the CNS relapse subgroup ($n=97$), no significant survival differences were observed between isolated and combined relapses, although induction failure occurred more frequently in combined cases. Multivariable analyses identified sex, immunophenotype, and relapse timing as independent prognostic factors. Interestingly, and in contrast to most previous reports that associate male sex with inferior outcomes [15,16], female sex in our cohort was linked to a significantly worse EFS and OS. In addition, pB immunophenotype, and late relapse were associated with favorable prognosis, consistent with prior reports on relapse biology [17,18].

The most striking and unexpected finding was the prognostic role of sex. While most published studies have consistently reported male sex as an adverse factor in both frontline and relapsed ALL [15,16], our cohort demonstrated the opposite pattern: female patients had significantly worse outcomes for both EFS and OS. This discrepancy may reflect biological differences in leukemic cells, or pharmacogenomic variability in treatment response. Given that CNS relapses were more frequent in males overall, yet survival was superior in this group, further investigation is warranted to elucidate potential sex-specific interactions with treatment intensity, CNS-directed therapy, or toxicity.

As expected, immunophenotype strongly influenced outcome: patients with pB-cell ALL had markedly better survival than those with T-cell ALL. This finding is consistent with prior international studies demonstrating that T-cell immunophenotype is associated with higher rates of treatment failure and post-relapse mortality [15,18]. The poor prognosis of T-cell relapses, particularly in the context of CNS involvement, likely reflects greater chemotherapy resistance, higher frequency of early relapse, and limited sensitivity to conventional CNS-directed regimens. These findings highlight the urgent need to investigate novel targeted therapies or immunotherapies for T-cell ALL relapse.

Relapse timing was one of the most powerful prognostic indicators: children with late CNS relapse achieved 2-year OS rates approaching 70%, whereas those with very early relapse had survival rates below 20%. This mirrors prior observations that very early relapses represent biologically aggressive disease with intrinsic resistance to standard therapy [10,17]. In contrast, late relapses are generally considered to reflect a less aggressive disease biology, often displaying greater chemosensitivity and responsiveness to salvage regimens, with correspondingly higher chances of achieving durable remission after hematopoietic stem cell transplantation. Our findings therefore reaffirm relapse timing as a critical determinant of outcome and an indispensable element of contemporary risk stratification in ALL.

Although induction failure was a strong adverse predictor of post-relapse OS in univariate analysis, its prognostic impact was attenuated and lost statistical significance after adjustment for patient- and disease-related characteristics.

Several limitations should be acknowledged. First, its observational design and the center-to-center variation in treatment allocation, including instances of risk misclassification, may have introduced bias into survival estimates. Second, the relatively small number of patients in certain subgroups, particularly those with T-cell immunophenotype or high CSF blast burden, limited the statistical power and widened confidence intervals. Third, cytogenetic and molecular data were generated locally without central review, which may have introduced variability in how cases were classified. In particular, the observation that female sex was associated with inferior survival should be interpreted with caution. The relatively small number of female patients in our cohort, together with potential center-level treatment variations and unmeasured confounders, may have contributed to this finding. Larger datasets and collaborative analyses will be needed to confirm or refute this association.

Conclusion

Our prospective analysis of CNS relapse in childhood ALL under the ALL-IC REL 2016 protocol demonstrates survival outcomes consistent with international reports, while also providing new prognostic insights. As expected, immunophenotype, and relapse timing significant predictors. However, the association of female sex with poorer outcomes was unexpected and novel, challenging current assumptions. Future collaborative studies are essential to confirm this observation and clarify the underlying mechanisms. Taken together, our results emphasize the need for refined risk-adapted strategies, integration of biological markers, and the advancement of innovative therapies to improve outcomes for children facing relapsed CNS ALL.

Acknowledgments

The authors gratefully acknowledge the centers listed below for contributing patient data to this study.
Türkiye: University of Health Sciences Bilkent City Hospital, Pediatric Hematology & Oncology, Ankara; Uludağ University Faculty of Medicine, Pediatric Hematology & Oncology, Bursa; Göztepe Medical Park Hospital, Pediatric Hematology & Oncology, İstanbul; Akdeniz University Faculty of Medicine, Pediatric Hematology & Oncology, Antalya; Kocaeli University, Pediatric Hematology & Oncology, Kocaeli; Dr.Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Pediatric Hematology & Oncology, İzmir; University of Health Sciences Çam and Sakura Educational and Research Hospital, Pediatric Hematology & Oncology, İstanbul; Marmara University Faculty of Medicine, Pediatric Hematology & Oncology, İstanbul; Osmangazi University Faculty of Medicine, Pediatric Hematology & Oncology, Eskişehir; Ege University Faculty of Medicine, Pediatric Hematology & Oncology, İzmir; Bahçelievler Medical Park Hospital, Pediatric Hematology & Oncology, İstanbul; Atatürk University Faculty of Medicine, Pediatric Hematology & Oncology, Erzurum; Koç American Hospital, Pediatric Hematology & Oncology, İstanbul; Konya Meram University Faculty of Medicine, Pediatric Hematology & Oncology, Konya; University of Health Sciences Etlik City Hospital, Pediatric Hematology & Oncology, Ankara; Yeditepe University Faculty of Medicine, Pediatric Hematology & Oncology, İstanbul;University of Health Sciences Ümraniye Educational and Research Hospital, Pediatric Hematology & Oncology, İstanbul; Sakarya University Faculty of Medicine, Pediatric Hematology & Oncology, Sakarya; Antalya Medical Park Hospital, Pediatric Hematology & Oncology, İstanbul; Van Yüzüncü Yıl University Faculty of Medicine, Pediatric Hematology & Oncology, Van; On Dokuz Mayıs University Faculty of Medicine, Pediatric Hematology & Oncology, Samsun; İstanbul Medipol University Faculty of Medicine, Pediatric Hematology & Oncology, İstanbul; Yeni Yüz Yıl Gazi Osman Paşa University Faculty of Medicine, Pediatric Hematology & Oncology, İstanbul; Adana Acıbadem Hospital Pediatric Hematoloji Unit, Adana; Cerrahpaşa University Faculty of Medicine, Pediatric Hematology & Oncology, İstanbul; VKV American Hospital, İstanbul; Istanbul University Oncology Institute Pediatric Hematology & Oncology, İstanbul.
Argentina: Hospital Italiano de Buenos Aires, Buenos Aires; Hospital de Niños de santiago del Estero, Santiago del Estero; Hospital de Niños sor María Ludovica, La Plata, Buenos Aires; Hospital de Niños Ricardo Gurierrez, Buenos Aires; Hospital de Niños de Rosario, Santa Fe; Hospital San Roque, Entre Rios; Clinica San Lucas, Neuquen; Hospital Rawson, San Juan; Hospital Privado de Cordoba, Cordoba; Hospital de Niños de Cordoba, Cordoba; Hospital de Niños de Bahia Blanca, Buenos Aires; Hospital Austral, Buenos Aires; Hospital de Niños Comodoro Rivadavia, Chubut; Instituto del diagnostic, Buenos Aires; Hospital de Niños de Santa Fe, Santa Fe; Hospital Alassia de Santa Fe, Santa Fe; Hospital Nacional Alejandro Posadas, Buenos Aires; Hospital Italiano de San Justo, Buenos Aires; Hospital Noti, Mendoza; Clinica del Salvador, Cordoba.
Chile: Hospital Roberto del Rio, Santiago; Hospital Luis Calvo Mackena, Santigo; Hospital San Borja Arriaran, Santiago; Hospital Exequiel Gonzalez Cortez, Santiago; Hospital Sotero del Rio, Santiago; Hospital San Juan de Dios, Santiago; Hospital Guillermo Grant Benavente, Concepcion; Hospital regional de Valdivia, Valdivia; Hospital Regional de Temuco, Temuco; Hospital Regional de Talca, Talca; Hospital Gustavo Fricke, Viña del Mar; Hospital Regional de Antofagasta, Antofagasta.
Greece: Department of Pediatric Hematology & Oncology (TAO), "Aghia Sophia" Children's Hospital, Athens; Division of Pediatric Hematology-Oncology, First Department of Pediatrics, National and Kapodistrian University of Athens, "Aghia Sophia" Children's Hospital, Athens; Oncology Department, "P. and A. Kyriakou" Children's Hospital, Athens; Pediatric Oncology Department, Mitera Hospital, Athens; Bone Marrow Transplantation Unit, "Aghia Sophia" Children's Hospital, Athens; Department of Pediatrics, School of Medicine, University of Thessaloniki, University General Hospital AHEPA, Thessaloniki; Pediatric Oncology Department, Hippokration Hospital, Thessaloniki; Department of Pediatrics, School of Medicine Department of Pediatric Hematology-Oncology & Autologous Stem Cell Transplantation Unit, University Hospital of Heraklion (PAGNI), Crete.
Hungary: Debrecen University, Pediatric Hematology & Oncology, Debrecen; Heim Pál Hospital, Pediatric Hematology & Oncology Unit, Budapest; Semmelweis University, Pediatric Hematology & Oncology, Budapest; Pécs University, Pediatric Hematology & Oncology, Pécs; BAZ County Hospital, Miskolc; Szeged University, Pediatric Hematology & Oncology, Szeged; DPC Hospital, Budapest.
Slovenia: UMC Ljubljana, Ljubljana
Romania: Fundeni Clinical Institu

Authors' contributions

VH was responsible for the conceptualization and design of the work, and the analysis of data and writing of the manuscript. BH and KY were responsible for data acquisition. MM, JTC, FM, AC, BA, MA, TH provided data. ARB, SP, MK, LER, TP, RF, JJ, DJE were involved in the interpretation and critical revision of the work. All authors have reviewed and approved the final version for submission.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The authors reported there is no funding associated with the work featured in this article.

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