

Sex-based disparities in outcome in pediatric acute lymphoblastic leukemia: a Children's Oncology Group report

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BACKGROUND: Boys with acute lymphoblastic leukemia (ALL) have historically experienced inferior survival compared to girls. This study determined whether sex-based disparities persist with contemporary therapy and whether patterns of treatment failure vary by sex. **METHODS:** Patients 1 to 30.99 years old were enrolled on frontline Children's Oncology Group trials between 2004 and 2014. Boys received an additional year of maintenance therapy. Sex-based differences in the distribution of various prognosticators, event-free survival (EFS) and overall survival (OS), and subcategories of relapse by site were explored. **RESULTS:** A total of 8202 (54.4% male) B-cell ALL (B-ALL) and 1562 (74.3% male) T-cell ALL (T-ALL) patients were included. There was no sex-based difference in central nervous system (CNS) status. Boys experienced inferior 5-year EFS and OS (EFS, $84.6\% \pm 0.5\%$ vs $86.0\% \pm 0.6\%$, $P = .009$; OS, $91.3\% \pm 0.4\%$ vs $92.5\% \pm 0.4\%$, $P = .02$). This was attributable to boys with B-ALL, who experienced inferior EFS (hazard ratio [HR], 1.2; 95% confidence interval [95% CI], 1.1-1.3; $P = .004$) and OS (HR, 1.2; 95% CI, 1.0-1.4; $P = .046$) after adjustment for prognosticators. Inferior B-ALL outcomes in boys were attributable to more relapses (5-year cumulative incidence $11.2\% \pm 0.5\%$ vs $9.6\% \pm 0.5\%$; $P = .001$), particularly involving the CNS ($4.2\% \pm 0.3\%$ vs $2.5\% \pm 0.3\%$; $P < .0001$). There was no difference in isolated bone marrow relapses ($5.4\% \pm 0.4\%$ vs $6.2\% \pm 0.4\%$; $P = .49$). There were no sex-based differences in EFS or OS in T-ALL. **CONCLUSIONS:** Sex-based disparities in ALL persist, attributable to increased CNS relapses in boys with B-ALL. Studies of potential mechanisms are warranted. Improved strategies to identify and modify treatment for patients at highest risk of CNS relapse may have particular benefit for boys. *Cancer* 2022;0:1-8. © 2022 American Cancer Society.

KEYWORDS: acute lymphoblastic leukemia, childhood, disparities, sex, survival.

INTRODUCTION

Cure rates for children and adolescents with acute lymphoblastic leukemia (ALL) have dramatically increased over the last decades, with further improvements in outcomes seen even in the most recent time periods.^{1,2} Sex-based differences in ALL outcomes have been observed since the advent of curative therapy, with inferior survival among boys noted even in the 1960s and 1970s.²⁻⁸ Past studies have attributed this increased risk at least partially to a greater prevalence of adverse disease prognosticators in boys.

Modern ALL therapy now uses complex risk stratification systems that incorporate factors such as cytogenetics and sophisticated measures of early response.^{1,9} Therapy is intensified for patients known to be at higher risk of relapse. Whether sex-based disparities persist in the context of modern therapy is unknown. Our primary objective was therefore to determine whether ALL outcomes differed between boys and girls after adjustment for various prognosticators. Our

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secondary objective was to identify any sex-based difference in patterns of treatment failure, including types of relapse and death in remission.

MATERIALS AND METHODS

Study Patients

Between 2004 and 2014, children, adolescents, and young adults 1 to 30 years old with newly diagnosed ALL were enrolled onto one of several Children's Oncology Group (COG) clinical trials. After enrollment on a common classification protocol, patients enrolled on AALL0331 (National Cancer Institute [NCI] standard-risk [SR] B-cell lymphoblastic leukemia [B-ALL], >1 year old and <10 years old and initial white blood cell count [WBC] <50,000/ μ L; 2005-2010), AALL0232 (NCI high-risk [HR] B-ALL, 10 to 30 years old or initial WBC $\geq$ 50,000/ μ L and any age; 2004-2011), or AALL0434 (T-cell lymphoblastic leukemia [T-ALL], 1 to 30 years old; 2007-2014). With the exception of those with Down syndrome and infants diagnosed <1 year of age, all other patients enrolled in 1 of these 3 clinical trials were included in this study. Two pilot studies of novel asparaginase agents or dosing were not included (AALL07P4 and AALL08P1). All studies were approved by the NCI, the pediatric central institutional review board, and/or by the institutional review board of each participating center. Participating patients and/or a parent or guardian provided informed consent. Details of each clinical trial, including chemotherapy regimens, randomized treatment interventions, and outcomes, have been previously published (AALL0331-NCT00103285, AALL0232-NCT00075725, and AALL0434-NCT00408005).¹⁰⁻¹³

Induction therapy with either 3 (AALL0331) or 4 (AALL0232 and AALL0434) drugs was followed by post-induction therapy, the intensity of which was dependent on risk stratification. The final phase of therapy, termed "maintenance," comprised a prolonged period of antimetabolite-based treatment with pulses of 1 dose of vincristine and 5 days of corticosteroid administered every 4 weeks. The duration of maintenance therapy was sex-dependent, with boys receiving an additional year. Indications for cranial radiation differed by study. All patients with central nervous system (CNS) 3 status at diagnosis ($\geq$ 5 WBCs/ μ L plus blasts with/without $\geq$ 10 red blood cells [RBCs]/ μ L or clinical signs of CNS disease) received 18 Gy of radiation. Among patients with NCI HR B-ALL, those with slow early response, *KMT2A* (*MLL*) rearrangements, and some patients pretreated with steroids received prophylactic cranial radiation (12 Gy).

Among patients with T-ALL, those with any of the following features received 12 Gy prophylactic cranial radiation: NCI HR disease, CNS2 status (<5 WBCs/ μ L and blasts with/without $\geq$ 10 RBCs/ μ L or $\geq$ 5 WBCs/ μ L plus blasts, with WBCs $\geq$ 5 times the number of RBCs), slow early response ($\geq$ 5% blasts by morphology on the day 15 bone marrow), or end of induction minimal residual disease (MRD) $\geq$ 0.1%.

Outcomes

Our primary outcomes were event-free survival (EFS) and overall survival (OS). EFS was defined as time from study enrollment to first event (induction death, failure to attain complete remission, relapse, remission death, or the development of a second malignant neoplasm) or last follow-up. OS was defined as the time from study enrollment to death from any cause or date of last follow-up if alive. Secondary outcomes included relapse, both overall and by site of relapse, induction death, death in remission (defined as any death while in complete remission), and second malignant neoplasms. Bone marrow involvement at relapse was determined through local morphology.

Covariates

Our key predictor of interest was biological sex. Additional covariates included age at diagnosis, presenting WBC, lineage (B-ALL vs T-ALL), CNS status (CNS1 [no blasts] vs CNS2 vs CNS3), and end of induction MRD. Cytogenetics in B-ALL were categorized as favorable (*ETV6-RUNX1* fusion or simultaneous trisomies of chromosomes 4, 10, and 17) versus unfavorable (hypodiploidy with modal chromosome number <44 and/or DNA index <0.81, intrachromosomal amplification of chromosome 21 [*iAMP21*], *KMT2A* rearrangements, or *BCR-ABL1* fusion)¹⁴⁻¹⁶ versus neutral (all others).

Analyses

Differences in the distribution of covariates between boys versus girls were examined using χ^2 tests or t tests as appropriate. Survival rates were estimated using the Kaplan-Meier method with standard errors of Peto et al.^{17,18} Survival curves were compared using the log-rank test. Cox proportional hazards models were used for multivariable analyses of EFS and OS. The cumulative incidence function approach was used to determine the risk of relapse (with death considered a competing event) overall and by sex, which was compared using Gray's test.¹⁹ Median time to relapse was compared by sex using t tests. Statistical significance was defined as $P < .05$. All analyses were performed using SAS software version 9.4

TABLE 1. Characteristics of Study Cohort, Stratified by Sex and Lineage

	B-Lineage ALL		<i>P</i>	T-Lineage ALL		<i>P</i>
	Boys, No. (%), (N = 4463)	Girls, No. (%), (N = 3739)		Boys, No. (%), (N = 1161)	Girls, No. (%), (N = 401)	
Age at diagnosis, y			<.0001			.04
<10	3311 (74.2)	2855 (76.4)		602 (51.8)	237 (59.1)	
10-16	767 (17.2)	671 (17.9)		385 (33.2)	112 (27.9)	
≥16	385 (8.6)	213 (5.7)		174 (15.0)	52 (13.0)	
WBC at presentation ($\times 10^9/L$)			.98			.06
<50	3739 (83.8)	3133 (83.8)		473 (40.7)	185 (46.1)	
≥50	722 (16.2)	604 (16.2)		688 (59.3)	216 (53.9)	
CNS status			.72			.45
CNS1	3924 (88.1)	3306 (88.5)		839 (72.5)	295 (74.0)	
CNS2	461 (10.3)	379 (10.1)		236 (20.4)	71 (17.8)	
CNS3	71 (1.6)	52 (1.4)		83 (7.2)	33 (8.3)	
Cytogenetics			.05			
Favorable	1842 (41.3)	1553 (41.5)		—	—	—
Neutral	2320 (52.0)	1982 (53.0)		—	—	—
Unfavorable	301 (6.7)	204 (5.5)		—	—	—
End of induction BM MRD			.04			.46
<0.01%	3268 (76.1)	2791 (78.1)		659 (58.9)	221 (56.8)	
≥0.01%	1026 (23.9)	784 (21.9)		459 (41.1)	168 (43.2)	
Cranial radiation			.15			.01
Yes	339 (7.6)	253 (6.8)		791 (68.1)	246 (61.3)	
No	4124 (92.4)	3486 (93.2)		370 (31.9)	155 (38.7)	

Abbreviations: B, B-cell; BM, bone marrow; CNS, central nervous system; MRD, minimal residual disease; N, number; T, T-cell; WBC, white blood cells.

(SAS Institute, Cary, North Carolina). All graphics were generated using R (<http://www.R-project.org>, version 2.13.1).

RESULTS

The study cohort comprised of 9764 children, adolescents, and young adults with ALL, 5624 (57.6%) of whom were male. Characteristics of the cohort are shown in Table 1. Boys were more likely to have T-ALL than girls (20.7% vs 9.7%; $P < .0001$). Among both patients with B-ALL and T-ALL, boys were older than girls at presentation (Table 1). Among patients with B-ALL, the median WBC did not differ by sex (boys, $9.5 \times 10^9/L$; [interquartile range [IQR] 4.1-29] vs 8.9; IQR, 3.9-29; $P = .16$). Among T-ALL patients, boys had a higher median WBC ($79 \times 10^9/L$; IQR 21-230 vs 59; IQR, 16-203; $P = .04$). CNS status did not differ by sex. For example, among patients with B-ALL, 10.3% of boys versus 10.1% of girls presented with CNS2 disease, whereas 1.6% versus 1.4% presented with CNS3 disease ($P = .72$). Boys with B-ALL were more likely to have unfavorable cytogenetics than girls. This was due to small but statistically significant increases in the prevalence of specific cytogenetic lesions, including hypodiploidy and *BCR-ABL1* (Supporting Table 1). Among B-ALL patients, boys were more likely to have end induction MRD $\geq 0.01\%$ than were girls (23.9% vs 21.9%; $P = .04$). Among T-ALL patients, there was no difference in rates of end of induction MRD

$\geq 0.01\%$ by sex. There was no difference in the proportion of children receiving cranial radiation among boys versus girls with B-ALL (7.6% vs 6.8%; $P = .15$). Boys with T-ALL were, however, more likely to receive cranial radiation (68.1% vs 61.3%; $P = .01$), compared to girls.

Study cohort outcomes are seen in Table 2. Among the entire cohort, including patients with both B- and T-ALL, boys experienced inferior 5-year EFS and OS as compared to girls (EFS, $84.6\% \pm 0.5\%$ vs $86.0\% \pm 0.6\%$; $P = .009$; OS, $91.3\% \pm 0.4\%$ vs $92.5\% \pm 0.4\%$; $P = .02$). This was predominantly attributable to patients with B-ALL (EFS, $84.6\% \pm 0.6\%$ in boys vs $86.4\% \pm 0.6\%$ in girls; $P = .003$; OS, $91.7\% \pm 0.4\%$ vs $92.8\% \pm 0.5\%$; $P = .047$) (Fig. 1). This disparity remained when adjusting for other covariates (Table 3). Boys experienced an approximately 20% increased hazard of an event (adjusted hazard ratio [aHR], 1.2; 95% CI, 1.1-1.3; $P = .004$) and of death (aHR, 1.2; 95% CI, 1.0-1.4; $P = .046$). No such sex-based disparity was seen among T-ALL patients (Fig. 1; Tables 2 and 4). The increased risk seen in B-ALL boys was due to an increased risk of relapse (5-year cumulative incidence [CI], $11.2\% \pm 0.5\%$ vs $9.6\% \pm 0.5\%$; $P = .001$). This in turn was mainly attributable to an increase in relapses involving the CNS (5-year CI, $4.2\% \pm 0.3\%$ vs $2.5\% \pm 0.3\%$; $P < .0001$). Boys were at increased risk of both isolated CNS relapses and

TABLE 2. Study Cohort 5-Year Outcomes by Sex, Stratified by Leukemia Lineage (B vs T)

	B-Lineage ALL			T-Lineage ALL		
	Boys (%)	Girls (%)	<i>P</i>	Boys (%)	Girls (%)	<i>P</i>
Event-free survival	84.6 ± 0.6 ^a	86.4 ± 0.6 ^a	.003 ^a	84.2 ± 1.1	82.7 ± 2.0	0.24
Overall survival	91.7 ± 0.4 ^a	92.8 ± 0.5 ^a	.047 ^a	89.5 ± 1.0	89.7 ± 1.6	0.95
Relapse	11.2 ± 0.5 ^a	9.6 ± 0.5 ^a	.001 ^a	9.2 ± 0.9	9.5 ± 1.5	0.83
Isolated BM relapse	5.4 ± 0.4	6.2 ± 0.4	.49	3.4 ± 0.5	3.1 ± 0.9	0.74
Relapse involving the CNS	4.2 ± 0.3 ^a	2.5 ± 0.3 ^a	<.0001 ^a	4.1 ± 0.6	3.8 ± 1.0	0.64
Isolated CNS relapse	3.0 ± 0.3 ^a	1.8 ± 0.2 ^a	.0001 ^a	2.7 ± 0.5	2.6 ± 0.8	0.85
Combined CNS and BM relapse	1.2 ± 0.2 ^a	0.8 ± 0.2 ^a	.032 ^a	1.4 ± 0.4	1.3 ± 0.6	0.59
Testicular relapse	0.7 ± 0.1	—	—	0.0	—	—
Death in remission	0.7 ± 0.1	0.7 ± 0.1	.995	0.9 ± 0.3	0.8 ± 0.4	0.84
Second malignant neoplasm	0.5 ± 0.1	0.6 ± 0.1	.75	1.0 ± 0.3	0.5 ± 0.4	0.56

Abbreviations: B, B-cell; BM, bone marrow; CNS, central nervous system; T, T-cell.

^aValues represent *P* < .05.

combined CNS and bone marrow relapses (Table 2). By contrast, there was no difference in the cumulative incidence of isolated BM relapses (5-year CI, 5.4% ± 0.4% vs 6.2% ± 0.4%; *P* = .49). The median time to CNS relapse was later in boys versus girls (2.5 years, IQR 1.7-3.7 years vs 2.1 years, IQR 1.6-2.8 years; *P* = .049). Characteristics of patients with B-ALL who suffered relapses involving the CNS are shown in Supporting Table 2. Again, no sex-based differences were seen in T-ALL patients, either in overall relapse or in relapse by site.

There was no difference in the rate of induction death either among patients with B-ALL (boys, 33/4463 [0.7%] vs girls, 40/3739 [1.1%]; *P* = .11) or with T-ALL (boys, 5/1161 (0.4%) vs girls, 2/401 (0.5%); *P* = 1.00). There was no difference in the cumulative incidence of either death in remission or second malignant neoplasms among children with either B-ALL or T-ALL (Table 2).

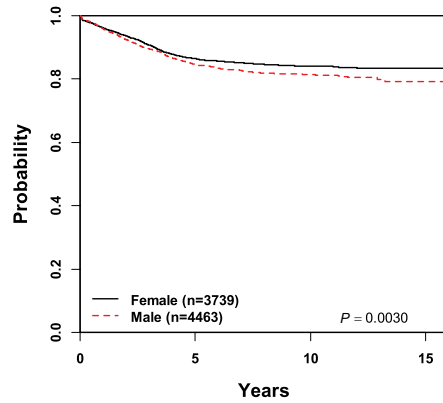
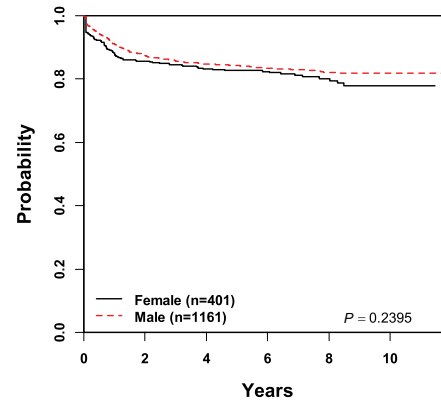
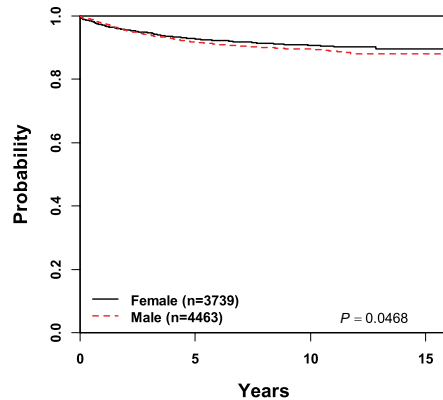
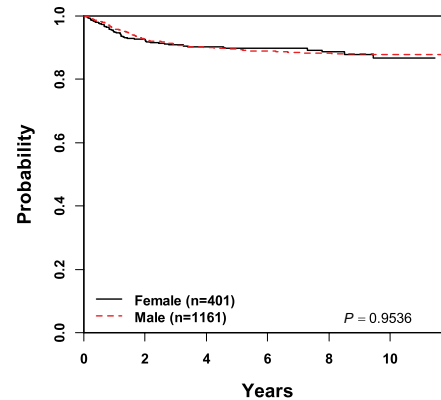
DISCUSSION

Among this group of almost 10,000 children, adolescents, and young adults with ALL diagnosed between 2004 and 2014, boys continued to have inferior EFS and OS as compared to girls. The sex-based outcome disparities were restricted to those with B-ALL and were not seen among patients with T-ALL. B-ALL outcome disparities were attributable to higher rates among boys of relapses involving the CNS. Neither isolated bone marrow relapses, induction deaths, deaths in remission, nor second malignant neoplasms varied by sex.

Inferior outcomes among boys have been noted for decades and have been at least partially attributable to imbalances in various prognosticators.²⁻⁸ Early on, Baumer et al³ described differences in age at diagnosis, with

boys presenting at older ages, whereas multiple groups noted the higher incidence of T-ALL among boys versus girls.^{5,7,8} Whether these imbalances fully account for this disparity has been less clear. Using a cohort of 2055 children treated on St. Jude Children's Research Hospital (SJCRH) ALL trials between 1962 and 1994, Pui et al⁵ found that stratification by variables such as immunophenotype and cytogenetics abrogated sex-based disparities. Interestingly, among this cohort, disparities were also restricted to children with B-ALL and not T-ALL, mirroring our findings. In contrast, using population-based registry-derived cohorts, Holmes et al⁸ found that adjustment for immunophenotype and age did not impact upon mortality disparities, with boys continuing to experience a 15% higher risk of death. In our earlier report of over 20,000 children, adolescents, and young adults treated on COG trials between 1990 and 2005, sex was a significant prognostic factor in multivariable analysis with girls having a 15% to 20% lower risk of death than boys.² Among more contemporary protocols, sex-based disparities have not been seen, although these cohorts were generally of smaller sample size than that of the current study and thus may not have been adequately powered to detect smaller differences.²⁰⁻²² In our current cohort of almost 10,000 patients, male sex retained independent adverse prognostic impact even after adjustment for modern risk classification variables that showed small but significant differences according to sex (eg, adverse cytogenetics and end induction MRD in B-ALL). Indeed, male sex was associated with similar magnitudes of increased risk both in univariate and multivariable analyses.

Few contemporaneous studies have examined these disparities in further detail by, for example, studying specific causes of treatment failure. Older cohorts treated in Children's Cancer Study Group (CCG) or SJCRH trials noted an increased risk of bone marrow

A Event-free survival of B-lineage ALL**B** Event-free survival of T-lineage ALL**C** Overall survival of B-lineage ALL**D** Overall survival of T-lineage ALL**Figure 1.** Event-free and overall survival of the study cohort by sex.

relapses among boys but no excess risk of CNS relapses, in direct contrast to our findings.^{4,5} Strategies to prevent CNS relapse in childhood ALL have evolved dramatically, moving from the addition of prophylactic radiation to replacing radiation with increased use of chemotherapeutic agents that reach the CNS, including intensive, prolonged intrathecal chemotherapy. The impact of different CNS strategies may well differ by sex. The introduction of prophylactic radiation on CCG trials in the 1970s was shown to have more benefit among boys versus girls.⁴ Similarly, the elimination of cranial irradiation among standard risk patients on the Dana-Farber Cancer Institute (DFCI) 87-01 trial resulted in a substantial increase in CNS relapses among boys but not among girls.²³ Historically, prophylactic cranial radiation has been administered more frequently to patients with T-ALL versus B-ALL²⁴; this may partially

explain the lack of sex-based disparities among children with T-ALL seen in our cohort because approximately 90% of the AALL0434 patients received cranial irradiation.¹³ As rates of cranial radiation decrease further in T-ALL, continued monitoring of sex-based disparities is warranted, although the addition of newer additional CNS-directed therapies such as nelarabine may mitigate this impact.¹³ Analyses of this subpopulation of patients treated on protocols that have entirely eliminated radiation would also be of use.²²

Although mechanisms underlying sex-based differences in CNS relapse rates are unclear, several hypotheses are possible. First, the strength and permeability of the blood-brain barrier has been shown to vary between sexes, which may impact CNS penetration of chemotherapeutic agents, the probability of CNS leukemia involvement at levels below that detectable by

TABLE 3. Univariate and Multivariable Predictors of Event-Free and Overall Survival Among Patients With B-ALL

	Event-Free Survival				Overall Survival			
	Univariate		Multivariable		Univariate		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis, y								
<10	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥10	2.7 (2.4-2.9)	<.0001	1.7 (1.5-1.9)	<.0001	4.1 (3.6-4.8)	<.0001	2.5 (2.2-3.0)	<.0001
Sex								
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.2 (1.1-1.3)	.003	1.2 (1.1-1.3)	.004	1.2 (1.0-1.3)	.047	1.2 (1.0-1.4)	.046
WBC at presentation (×10 ⁹ /L)								
<50	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥50	2.1 (1.9-2.4)	<.0001	1.6 (1.4-1.8)	<.0001	2.3 (2.0-2.7)	<.0001	1.5 (1.3-1.8)	<.0001
CNS status								
CNS1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
CNS2	1.8 (1.5-2.0)	<.001	1.4 (1.2-1.6)	<.0001	1.9 (1.6-2.3)	<.0001	1.4 (1.1-1.7)	.002
CNS3	1.7 (1.1-2.5)	.008	0.9 (0.6-1.5)	0.82	2.2 (1.4-3.4)	.0006	1.0 (0.6-1.8)	.91
Cytogenetics								
Favorable	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Neutral	2.8 (2.5-3.3)	<.0001	2.1 (1.8-2.5)	<.0001	4.1 (3.3-5.1)	<.0001	2.9 (2.3-3.8)	<.0001
Unfavorable	6.9 (5.7-8.2)	<.0001	3.6 (2.9-4.5)	<.0001	11.8 (9.3-15.2)	<.0001	5.8 (4.3-7.9)	<.0001
End of induction BM MRD								
<0.01%	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥0.01%	3.7 (3.3-4.1)	<.0001	2.9 (2.5-3.2)	<.0001	4.3 (3.7-5.0)	<.0001	2.9 (2.5-3.4)	<.0001

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; BM, bone marrow; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; MRD, minimal residual disease; WBC, white blood cells.

TABLE 4. Univariate and Multivariable Predictors of Event-Free and Overall Survival Among Patients With T-ALL

	Event-Free Survival				Overall Survival			
	Univariate		Multivariable		Univariate		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis, y								
<10	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥10	1.0 (0.8-1.3)	.85	1.0 (0.8-1.3)	.86	1.4 (1.1-1.9)	.01	1.4 (1.0-1.9)	.04
Sex								
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.2 (0.9-1.5)	.24	0.9 (0.7-1.1)	.29	1.0 (1.4-0.7)	.95	1.1 (0.7-1.5)	.73
WBC at presentation (×10 ⁹ /L)								
<50	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥50	1.5 (1.1-1.9)	.003	1.5 (1.2-2.0)	.003	1.7 (1.2-2.3)	.001	1.9 (1.3-2.7)	.0004
CNS status								
CNS1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
CNS2	1.2 (0.9-1.6)	.35	1.1 (0.8-1.5)	.71	1.1 (0.75-1.6)	.63	0.9 (0.6-1.4)	.72
CNS3	2.0 (1.4-2.9)	.0002	1.9 (1.3-2.9)	.0008	1.7 (1.1-2.8)	.02	1.5 (0.9-2.5)	.14
End of induction BM MRD								
<0.01%	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥0.01%	2.4 (1.9-3.1)	<.0001	2.5 (2.0-3.2)	<.0001	2.3 (1.7-3.1)	<.0001	2.4 (1.7-3.3)	<.0001

Abbreviations: BM, bone marrow; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; MRD, minimal residual disease; T-ALL, T-cell acute lymphoblastic leukemia; WBC, white blood cells.

conventional techniques, or both.²⁵ Second, although not a consistent finding, clearance of glucocorticoids has been found to be higher among males versus females.^{26,27} This may explain both higher rates of relapse and lower rates of osteonecrosis among the former.²⁸

Third, the dosing of intrathecal chemotherapy is based on age-dependent volumes of cerebrospinal fluid (CSF), and not body surface area, because CSF volume increases at a more rapid rate than body surface and reaches near adult values after 3 years of age.²⁹

Age-related dosing has thus been associated with increased therapeutic effect and reduced neurotoxicity.³⁰ Sex-based differences in CSF volume, however, have not been rigorously evaluated, although recent studies have suggested that adult females may have lower CSF volumes.³¹ Lower CSF volumes among girls as compared to age-matched boys would result in higher concentrations of intrathecal chemotherapy among the former. Finally, boys in our cohort received an extra year of maintenance therapy as compared to girls, including 4 extra intrathecal treatments. Although presymptomatic detection of CNS relapse may therefore be more likely in boys versus girls during that year, the median time to CNS relapse was longer among boys, indicating that our finding is not artifactual and instead reflects a true increase in risk.

Perhaps the most important remaining question is how the demonstrated sex-based outcome disparities can be abolished. Previous attempts to improve the outcomes of boys, including surveillance testicular biopsies, have not been successful. Longer treatment durations for boys have also been unsuccessful in eliminating sex-based outcome disparities. For example, an additional year of maintenance for boys in the ALL-BFM 95 study did not improve outcomes compared to historical controls; in both cohorts, boys experienced slightly inferior outcomes to girls.³² Overall, the rationale for continuing to expose boys to longer durations of therapy is weak.⁶ High overall cure rates represent an additional challenge in addressing small absolute differences in outcomes between sexes. For example, although the incidence of CNS relapse in boys was 70% higher than that in girls, intensification of CNS therapy in the former through cranial radiation, extra intrathecal chemotherapy, or high-dose methotrexate would result in the unnecessary exposure of large number of boys to additional treatment with consequent late effects for the possibility of preventing a comparably small number of relapses. Given this, 2 other strategies are possible. Should sex-based differences in CSF volume be identified, sex-based intrathecal chemotherapy dosing may be warranted and effective. Second, improvements in the ability to predict CNS relapse, regardless of sex, may be of particular benefit to boys. Recently, several groups have demonstrated that detection of low levels of CNS leukemia at initial diagnosis through techniques such as flow cytometry and next-generation sequencing may better identify patients at highest risk for subsequent CNS relapse, and thus targets for therapy intensification.³³⁻³⁵ These more sensitive techniques may well identify a larger number of boys at risk than girls.

Strengths of our study include its large sample size, uniform treatment, and the availability of detailed information on prognosticators, including centrally reviewed cytogenetics and centrally determined MRD. Several limitations also merit note. Although our multivariable models accounted for imbalance in prognosticators between sexes, we cannot rule out a degree of residual confounding. In addition, although modern therapy of newly diagnosed childhood ALL remains mainly unchanged from that received by the study cohort, novel immunotherapies have been incorporated into the treatment of relapsed disease.³⁶⁻³⁸ As the role of immunotherapy in first-line therapy is investigated,³⁹ continued monitoring of sex-based disparities is justified.

In conclusion, despite increases in overall cure rates, boys with ALL continue to experience small but significant decreases in outcome as compared to girls. This disparity is not accounted for by imbalances in risk factors and is attributable to higher rates of CNS relapse among boys with B-ALL despite an additional year of maintenance therapy. Continued monitoring of sex-based disparities is warranted as fewer children undergo prophylactic cranial irradiation and as immunotherapies are incorporated into treatment regimens. Improved strategies to identify patients at highest risk of CNS relapse may have particular benefit for boys.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Sumit Gupta: Conceptualization, methodology development, and writing—original draft. **David T. Teachey:** Conceptualization and methodology development. **Elizabeth A. Raetz:** Conceptualization and methodology development. **Mignon L. Loh:** Conceptualization and methodology development. **Stephen P. Hunger:** Conceptualization and methodology

development. **Meenakshi Devidas:** Conceptualization and methodology development. **Zhiguo Chen:** Conducted the formal analyses. All authors contributed to the interpretation of the results and the review and editing of the manuscript.

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