Impact of age and sex on survival outcomes in patients aged 1-45 years with acute lymphoblastic leukemia treated according to the stratification used in the NOPHO ALL2008 trial

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Abstract

Age and sex have historically been associated with differences in the survival of patients with acute lymphoblastic leukemia (ALL). The NOPHO ALL2008 trial included patients aged 1-45 years with *BCR*::*ABL1*-negative B-precursor and T-cell ALL, but neither sex nor age was integrated into risk group allocation. Among 1,771 trial patients stratified into protocol-appropriate risk groups, we estimated the impact of age and sex on survival (even after relapse) and toxicities prospectively registered at 3-month intervals. In multivariate Cox regression analysis adjusted by sex, age group, and risk group, age but not sex was an independent risk factor for reduced 5-year event-free survival (EFS): hazard ratio=1.57 (95% confidence interval: 1.15-2.14) for patients 10-17.9 years, and 2.70 (95% confidence interval: 2.03-3.58) for patients 18-45 years, compared to patients <10 years old at diagnosis. The overall 5-year pEFS was 0.83. For standard-risk patients (B-lineage, white cell count <100x10^9/L, no risk genetics, minimal residual disease day 29 <0.1%), an inferior 5-year EFS was observed among patients 18-45 years (pEFS 0.78, *P*<0.001) and 10-17.9 years (pEFS 0.86, *P*=0.002) compared to patients <10 years at diagnosis (pEFS 0.93). For the intermediate-risk and high-risk groups, EFS was worse for patients 18-

45 years compared to patients <10 years: pEFS 0.69 *versus* 0.89 (*P*<0.001) and pEFS 0.55 *versus* 0.71 (*P*=0.005), respectively. Osteonecrosis and veno-occlusive disease were associated with female sex in the standard-risk group, and age ≥10 years was associated with osteonecrosis, thrombosis, and pancreatitis in sex- and treatment-group-adjusted analyses. In conclusion, this study indicates that risk-grouping and/or treatment-intensity criteria should differ across age groups and that age-adapted strategies to mitigate toxicities are needed.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in children and adolescents: the overall survival of these patients is now above 90% with the best contemporary treatments.[1,2] The dramatic improvements in outcome since the 1970s are mostly attributed to the evolution of multiagent chemotherapy and risk-adapted treatment strategies that include cytogenetic mapping and minimal residual disease (MRD) monitoring.[3] ALL is a rare type of cancer among adolescents and young adults, and outcome for these patients has lagged behind that of children despite intensified chemotherapy and frequent use of allogeneic hematopoietic stem cell transplantation (HSCT).[4-6] After the year 2000, publications on improved survival of adolescent and young adult ALL patients treated with pediatric-type regimens started to emerge.[7,8]

The inferior prognosis of ALL in adolescents and young adults compared to that in children can be partly explained by age-related variations in the molecular subtypes of ALL and immunophenotypes. *ETV6*::*RUNX1* and high-hyperdiploidy are common in young children, while T-cell leukemia, *ABL*-class fusions, and *KMT2A* rearrangements become more frequent with older age.[7,9,10] Toxicities, on the other hand, remain a major challenge, not least in those who undergo allogeneic HSCT,[11] and some studies report 10-30% treatment-related mortality among adolescents and young adults undergoing transplantation.[12]

Contemporary, risk-based pediatric ALL treatment uses baseline risk factors such as age, white blood cell count (WBC), immunophenotype, extramedullary involvement, genetic alterations as well as treatment response by detection of MRD to tailor the treatment intensity.[13] The ultimate goal is to balance the treatment intensity to induce and maintain long-term remission and minimize the risk of serious acute and long-term side effects.

In the NOPHO ALL2008 trial, therapy was primarily guided by genetics and MRD as the most profound changes compared to previous treatment,[14,15] and patients could be included up to the age of 45 years. In this study, prospectively registered data were used to analyze the effect of sex and age on survival and non-fatal toxicities in patients stratified and treated according to the NOPHO ALL2008 protocol for non-infant and *BCR*::*ABL1*-negative B-cell precursor (BCP) and T-cell ALL.

Methods

Patients

For the analyses in this study, we included all patients aged 1-45 years at diagnosis having BCP or T-cell ALL in Denmark, Estonia, Finland, Iceland, Lithuania, Norway, and Sweden from July 1, 2008 to March 1, 2016, while the NOPHO ALL2008 trial was open for randomizations. Patients were followed up until June 30, 2023. Figure 1 shows the detailed inclusion criteria.

The characteristics of the 1,771 patients included and their primary events are presented in Table 1 by sex and age group (1-9.9, 10-17.9, and 18-45 years at diagnosis). Central nervous system (CNS) leukemia (=CNS3; ≥10^6 cells/L with

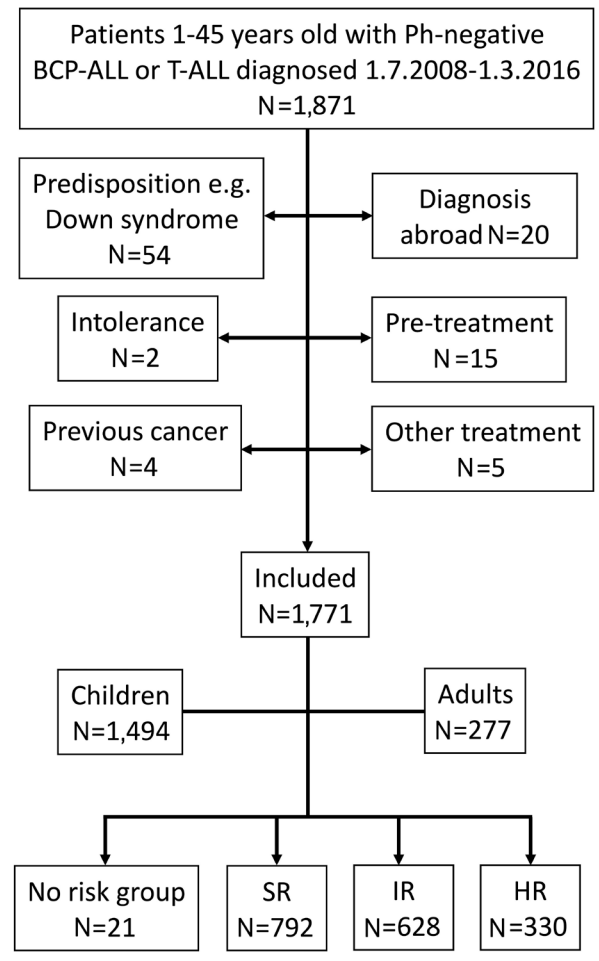


Figure 1. CONSORT diagram of the acute lymphoblastic leukemia patients aged 1-45 years at diagnosis. Patients with *BCR*::*ABL1*-positive or multiple-lineage acute lymphoblastic leukemia, Down syndrome, previous cancer, diagnosis outside a NOPHO country, pre-treatment beyond 1 week, intolerance to leukemia medication, or insufficient registration were excluded from the current analyses. Ph: Philadelphia chromosome; BCP-ALL: B-cell precursor acute lymphoblastic leukemia; T-ALL: T-cell acute lymphoblastic leukemia; N: number; SR: standard risk; IR: intermediate risk; HR: high risk.

Table 1. Description of the patients included in the study, by sex and age at diagnosis.

Characteristics	Total	Sex			Age at diagnosis in years			
		Female	Male	*P*	1-9.9	10-17.9	18-45	*P*
Total N	1,771	-	-	-	-	-	-	-
Median follow-up in years	8.3	-	-	-	9.0	7.3	6.6	-
Age at diagnosis, N (%)				0.006				-
1-9 years	1,188 (67.1)	559 (70.9)	629 (64.0)		-	-	-	
10-17 years	306 (17.3)	125 (15.9)	181 (18.4)		-	-	-	
18-45 years	277 (15.6)	104 (13.2)	173 (17.6)		-	-	-	
Sex, N (%)				<0.001				0.006
Female	788 (44.5)	-	-		559 (47.1)	125 (40.8)	104 (37.5)	
Male	983 (55.5)	-	-		629 (52.9)	181 (59.2)	173 (62.5)	
WBC at diagnosis, N (%)				0.21				0.10
<100x10^9/L	1,535 (86.7)	692 (87.8)	843 (85.8)		1,044 (87.9)	257 (84.0)	234 (84.5)	
≥100x10^9/L	236 (13.3)	96 (12.2)	140 (14.2)		144 (12.1)	49 (16.0)	43 (15.5)	
Immunophenotype, N (%)				<0.001				<0.001
BCP	1,493 (84.3)	707 (89.7)	786 (80.0)		1,071 (90.2)	228 (74.5)	194 (70.0)	
T-ALL	278 (15.7)	81 (10.3)	197 (20.0)		117 (9.8)	78 (25.5)	83 (30.0)	
Cytogenetics,* N (%)				<0.001				<0.001
Low risk	790 (44.6)	382 (48.5)	408 (41.5)		698 (58.8)	66 (21.6)	26 (9.4)	
Intermediate risk	117 (6.6)	62 (7.9)	55 (5.6)		75 (6.3)	26 (8.5)	16 (5.8)	
High risk	82 (4.6)	43 (5.5)	39 (4.0)		45 (3.8)	16 (5.2)	21 (7.6)	
Other	439 (24.8)	192 (24.4)	247 (25.1)		225 (18.9)	111 (36.3)	103 (37.2)	
Missing	65 (3.7)	28 (3.6)	37 (3.8)		28 (2.4)	9 (2.9)	28 (10.1)	
T-cell patients	278 (15.7)	81 (10.3)	197 (20.0)		117 (9.8)	78 (25.5)	83 (30.0)	
MRD day 29 (EOI), N (%)				0.001				<0.001
≥25%	22 (1.2)	3 (0.4)	19 (1.9)		9 (0.8)	9 (2.9)	4 (1.4)	
≥5% <25%	70 (4.0)	35 (4.4)	35 (3.6)		24 (2.0)	17 (5.6)	29 (10.5)	
≥0.1% <5%	431 (24.4)	197 (25.0)	234 (23.8)		265 (22.3)	82 (26.8)	84 (30.3)	
<0.1%	552 (31.1)	249 (31.6)	303 (30.8)		399 (33.6)	83 (27.1)	70 (25.3)	
Negative <0.1%	626 35.4)	277 (35.2)	349 (35.5)		460 (38.7)	102 (33.3)	64 (23.1)	
No sample	4 (0.2)	3 (0.4)	1 (0.1)		3 (0.3)	0	1 (0.4)	
No marker	6 (0.3)	3 (0.4)	3 (0.3)		2 (0.2)	1 (0.3)	3 (1.1)	
Death before day 29	17 (1.0)	12 (1.5)	5 (0.5)		11 (0.9)	3 (1.0)	3 (1.1)	
Day 15 >25%	43 (2.4)	9 (1.1)	34 (3.5)		15 (1.3)	9 (2.9)	19 (6.9)	
CNS status, N (%)				0.16				0.131
CNS1	1,549 (87.5)	677 (85.9)	872 (88.7)		1,027 (86.4)	267 (87.3)	255 (92.1)	
CNS2	148 (8.4)	73 (9.3)	75 (7.6)		110 (9.3)	22 (7.2)	16 (5.8)	
CNS3	72 (4.1)	36 (4.6)	36 (3.7)		50 (4.2)	16 (5.2)	6 (2.2)	
Missing	2 (0.1)	2 (0.3)	0 (0)		1 (0.1)	1 (0.3)	0 (0)	
Final risk group,** N (%)				0.049				<0.001
Standard risk	792 (44.7)	354 (44.9)	438 (44.6)		636 (53.5)	94 (30.7)	62 (22.4)	
Intermediate risk	628 (35.5)	289 (36.7)	339 (34.5)		389 (35.5)	127 (41.5)	112 (40.4)	
High risk	330 (18.6)	131 (16.6)	199 (20.2)		149 (12.5)	81 (26.5)	100 (36.1)	
No risk group	21 (1.2)	14 (1.8)	7 (0.7)		14 (1.2)	4 (1.3)	3 (1.1)	
HSCT in CR1, N (%)				0.074				<0.001
Yes	125 (7.1)	46 (5.8)	79 (8.0)		45 (3.8)	34 (11.1)	46 (16.6)	
No	1,646 (92.9)	742 (94.2)	904 (92.0)		1,143 (96.2)	272 (88.9)	231 (83.4)	
Primary events, N (%)				0.24				<0.001
CR1	1,447 (81.7)	650 (82.5)	797 (81.1)		1,036 (87.2)	237 (77.5)	174 (62.8)	
Induction failure	18 (1.0)	12 (1.5)	6 (0.6)		12 (1.0)	3 (1.0)	3 (1.1)	
DCR1	65 (3.7)	29 (3.7)	36 (3.7)		27 (2.3)	19 (6.2)	19 (6.9)	
SMN	15 (0.8)	6 (0.8)	9 (0.9)		10 (0.8)	4 (1.3)	1 (0.4)	
Relapse	226 (12.8)	91 (11.5)	135 (13.7)		103 (8.7)	43 (14.1)	80 (28.9)	

*Only including BCP ALL patients. Low-risk genetics includes high-hyperdiploidy and t(12;21); intermediate-risk genetics includes t(1;19), iAMP21 and dic(9;20); high-risk genetics includes *KMT2A*-rearrangement and hypodiploidy. **Intention-to-treat. Six male patients had testicular involvement at diagnosis (3 BCP ALL, 3 T-ALL). WBC: white blood cell count; BCP: B-cell precursor; T-ALL: T-cell acute lymphoblastic leukemia; MRD: minimal residual disease; EOI: end of induction; CNS: central nervous system; HSCT: hematopoietic stem cell transplantation; CR1: first complete remission; DCR1: death in first complete remission; SMN: second malignant neoplasm.

blasts; or clinical involvement by cranial nerve palsy or a leukemic mass on CNS or eye imaging) was detected at diagnosis in 72 patients (4.1%). Testicular involvement was reported in six (0.6%) male patients. Twenty-one patients were not assigned to any risk group because of death during induction (N=18) or severe infection-driven major treatment modifications (N=3). In total, 125 patients underwent HSCT in their first complete remission (CR1). The median follow-up time of survivors was 8.3 years; 9.0 years among patients 1-9.9 years at diagnosis, 7.3 years among patients 10-17.9 years at diagnosis, and 6.6 years among patients 18-45 years at diagnosis.

Risk assessment

The details of the NOPHO ALL2008 trial design and treatment strategy have been described in previous publications.[15,16] All patients received a three-drug induction and intrathecal therapy. Patients with T-cell immunophenotype or WBC ≥100x10^9/L (except patients with *ETV6*::*RUNX1*) received dexamethasone while all other patients received prednisolone. At the end of induction (EOI), patients were assigned to the standard-risk, intermediate-risk, or high-risk arms of the trial. However, patients initially treated with dexamethasone with MRD ≥25% on day 15 shifted to high-risk therapy already from that day. Stratifying genetic alterations in NOPHO ALL2008 were *KMT2A*-rearrangements and modal chromosome number <45 (stratified as high risk) as well as *TCF3*::*PBX1*, iAMP21, and dic(9;20) (not eligible for standard-risk therapy). After excluding stratifying genetic findings, BCP patients with WBC <100x10^9/L, no CNS3, and day 29 MRD <0.1% were stratified as standard risk, while T-cell and BCP patients with WBC ≥100x10^9/L and MRD <0.1% were stratified as intermediate risk. Furthermore, patients with EOI MRD ≥0.1% but <5% were stratified as intermediate risk (after prednisolone induction) or high risk (after dexamethasone induction). All patients with MRD ≥5% at EOI were allocated to high-risk treatment. HSCT was indicated for any patient with MRD ≥5% at EOI, high-risk patients with MRD ≥5% after block A1 or ≥0.1% after block B1, or standard- and intermediate-risk patients with MRD ≥0.1% at day 79.

Statistical analyses

Differences between sexes and age groups in the distribution of individual parameters were analyzed using the χ^2 test for categorical variables. The Kaplan-Meier method was used to estimate the probability of event-free survival (pEFS) and overall survival (pOS) rates, and differences were compared with the two-sided log-rank test. Cox regression was used for analyzing crude and adjusted hazard ratios (HR) with 95% confidence intervals (95% CI) of the major outcomes, EFS and OS, while competing-risks regression was used to analyze crude and adjusted subdistribution hazard ratios (SHR) of relapse and death in first complete remission (DCR1) where the competing events were relapse, DCR1 and second malignant neoplasm. For the adjusted analyses, the final risk group (standard, intermediate, high), age (1-9.9, 10-17.9, 18-45 years), and sex were included in the models as explanatory factors; the results are presented as cumulative incidence rates. In all analyses involving the trial's final risk groups, the 21 patients without an assigned risk group were excluded. Further details of the statistical methods are provided in the *Online Supplementary Data*.

The above analyses were conducted using STATA 16.1 (StataCorp, College Station, TX, USA). Cumulative incidences of single adverse outcomes and relapse types were compared between age groups and sexes using the Gray test.[17] Competing events were defined as induction failure, DCR1, relapse (including specific relapse types), and second malignant neoplasm. Relapse types were defined in two ways: (i) isolated bone marrow, isolated extramedullary, or combined, and (ii) CNS-involving *versus* non-CNS-involving. The function 'cuminc' in package 'cmprsk' in R version 4.1.1 (R Statistical Software v4.1.1; R Core Team 2021) was used.[18,19]

Ethical statement

Written informed consent was obtained from each participant or each participant's guardian and human investigations were performed in accordance with the Helsinki Declaration, after approval by the National Medicines Agencies (Eudract n. 2008-003235-20), and relevant ethical committees. The trial is registered at *www.clinicaltrials.gov* (NCT00819351).

Results

Baseline and response characteristics

All age groups in the study cohort included a higher proportion of male than female patients (*P*=0.006) (Table 1). The distribution of WBC at diagnosis, CNS status, indication for allogeneic HSCT in CR1, and primary events was similar between male and female patients (Table 1). However, T-cell immunophenotype (*P*<0.001), stratification to high-risk group (*P*=0.049), and poor EOI MRD response (*P*=0.001) were more frequent among males (Table 1).

The proportion of patients with T-ALL was higher (*P*<0.001) in the two older age groups (25.5%, 30.0%) compared to the youngest age group (9.8%). There was an age difference in genetic subgroups (*P*<0.001), e.g. low-risk genetics (high-hyperdiploidy, *ETV6*::*RUNX1*) were more common in patients 1-9.9 years of age (58.8%, 21.6%, 9.4%). Furthermore, the EOI MRD was lower (*P*<0.001) for patients <10 years at diagnosis. This translated into a higher proportion of older patients allocated to intermediate- and high-risk therapy as well as more having an indication for HSCT in CR1 (Table 1).

Of the included study patients, 1,699 (97.1%) achieved CR1 (MRD <5%) after induction (N=1,609) or the first blocks of high-risk treatment (after high-risk block A1 [including patients shifted directly to block therapy day 15; N=85], after high-risk block B1 [N=1] or after high-risk block C1

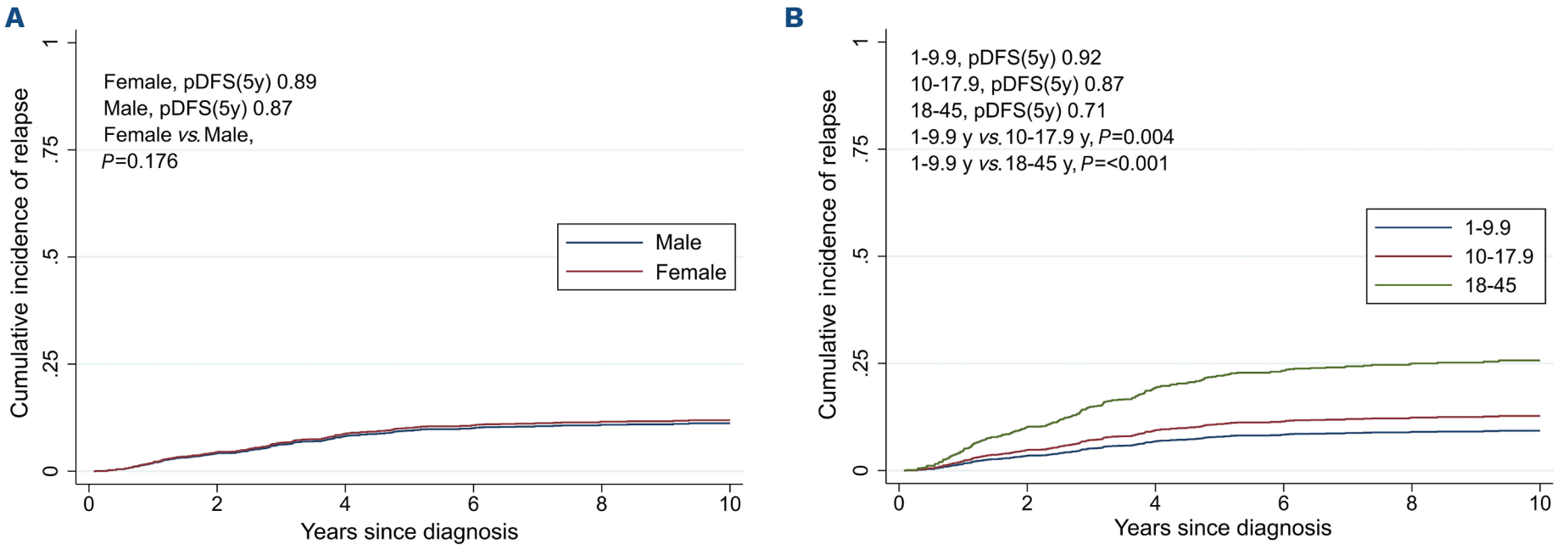


Figure 2. Cumulative incidence of relapse in the NOPHO ALL2008 trial. (A) The cumulative incidence of relapse is presented by sex. (B) The cumulative incidence of relapse is presented by age group. The panels also illustrate the timing of the relapses. pDFS: probability of disease-free survival; y: years.

Table 2. Description of the types of relapses in total and by immunophenotype.

Relapse characteristics	Sex			Age at diagnosis in years			
	Female N (%)	Male N (%)	*P*	1-9.9 N (%)	10-17.9 N (%)	18-45 N (%)	*P*
Relapse type (total)			0.16				<0.001
Isolated BM	63 (69.2)	74 (54.8)		59 (56.7)	27 (62.8)	51 (63.8)	
Combined	14 (15.4)	28 (20.7)		25 (24.0)	6 (14.0)	11 (13.7)	
Isolated EM*	14 (15.4)	32 (23.7)		18 (17.5)	10 (23.3)	18 (22.2)	
Missing	-	1 (1.0)		1 (1.0)	0 (0.0)	0 (0.0)	
Relapse type (total)			0.51				<0.001
CNS-involving	22 (24.2)	39 (28.9)		35 (33.7)	15 (34.9)	12 (14.8)	
Non-CNS	69 (75.8)	95 (70.4)		67 (65.0)	28 (65.1)	68 (85.0)	
Missing	-	1 (0.7)		1 (1.0)	0 (0.0)	0 (0.0)	
BCP relapse	80 (87.9)	103 (76.3)	-	84 (81.6)	37 (86.0)	62 (77.5)	-
BCP relapse type			0.66				0.73
Isolated BM	53 (66.3)	61 (59.2)		49 (58.3)	23 (62.2)	42 (67.7)	
Combined	13 (16.3)	19 (18.4)		18 (21.4)	5 (13.5)	9 (14.5)	
Isolated EM	14 (17.5)	22 (21.4)		16 (19.0)	9 (24.3)	11 (17.7)	
Missing	0 (0.0)	1 (1.0)		1 (1.2)	0 (0.0)	0 (0.0)	
BCP relapse type			0.67				0.007
CNS-involving	21 (26.3)	26 (25.2)		28 (33.3)	13 (35.1)	6 (9.7)	
Non-CNS	59 (73.8)	76 (73.8)		55 (65.5)	24 (64.9)	56 (90.3)	
Missing	0 (0.0)	1 (1.0)		1 (1.2)	0 (0.0)	0 (0.0)	
T-cell relapse	11 (12.1)	32 (23.7)	-	19 (18.4)	6 (14.0)	18 (22.5)	-
T-cell relapse type			0.014				0.18
Isolated BM	10 (91.0)	13 (41.0)		10 (53.0)	4 (67.0)	9 (50.0)	
Combined	1 (9.0)	9 (28.0)		7 (37.0)	1 (17.0)	2 (11.0)	
Isolated EM	0 (0.0)	10 (31.0)		2 (11.0)	1 (17.0)	7 (39.0)	
T-cell relapse type			0.054				0.99
CNS-involving	1 (9.0)	13 (41.0)		6 (32.0)	2 (33.0)	6 (33.0)	
Non-CNS	10 (91.0)	19 (59.0)		13 (68.0)	4 (67.0)	12 (67.0)	

*Twelve testicular relapses (11 BCP, 1 T-cell), 34 isolated CNS relapses. BM: bone marrow; EM: extramedullary; CNS: central nervous system; BCP: B-cell precursor acute lymphoblastic leukemia; T-cell: T-cell acute lymphoblastic leukemia.

[N=4]). The continuous remission rate (CR1) at the end of follow-up was 81.7% for the whole cohort (Table 1). After a median follow-up of 8.3 years, 226 relapses (5-year cumulative risk: 12.2% [10.7-13.9%]) had occurred: 135 among males (5-year cumulative risk: 13.1% [11.1-15.5%]) and 91 among females (5-year cumulative risk: 11.1% [9.0-13.6%]). The 5-year cumulative risk of relapse was highest (28.7%) among patients 18-45 years at diagnosis (Figure 2). Twelve patients had testicular involvement at relapse (median time to relapse: 34 months, range 24-59), none of whom had had overt testicular involvement at primary diagnosis. The relapse patterns differed from each other by age groups and immunophenotypes (Table 2). The 5-year cumulative risk of second malignant neoplasm (overall 0.9%) did not differ between sex or age groups.

When the frequencies of primary events were analyzed in each final risk group, there were no significant differences in the cumulative incidence of relapse between sexes (*P*=0.176), but age group was significantly associated with risk of relapse (<10 *vs*. 10-17.9 years, *P*<0.004; <10 *vs*. 18-45 years, *P*<0.001) (Table 3, Figure 2A, B).

Toxicity

A slightly higher (*P*=0.06) proportion of females (N=12; 1.5%) than males (N=6; 0.6%) suffered death during induction (Table 1), which was not significant when the analysis was stratified by type of induction glucocorticosteroid (0.9% [prednisolone] *vs*. 4.4% [dexamethasone] for females, and 0.4% *vs*. 1.3% for males, respectively; *P*=0.08).

Concerning the 19 predefined toxicities in the NOPHO ALL2008 trial,[16] females had significantly more osteonecrosis (*P*=0.001), veno-occlusive disease (*P*=0.009), and posterior reversible encephalopathy syndrome (*P*=0.040) than males (*Online Supplementary Table S1*). The frequencies of toxicities by age group are presented in *Online Supplementary Table S1* and by risk group in *Online Supplementary Table S2*. When stratified by risk group (*Online Supplementary Table S3*), females had increased odds ratios for osteonecrosis and veno-occlusive disease only in the standard-risk group. Odds ratios for thrombosis were significantly increased in all risk groups for patients ≥10 years, and for osteonecrosis in all risk groups for adolescents and in standard- and intermediate-risk groups for adults (*Online Supplementary Table S3*). Adolescents had an elevated odds ratio for seizures in the standard-risk group and in the intermediate-risk group for severe hyperlipidemia and severe kidney dysfunction. Adults had elevated odds for *Pneumocystis jiroveci* pneumonia in the standard-risk group and for pancreatitis in the standard- and intermediate-risk groups. Figure 3 illustrates the sex and risk-group adjusted odds ratio by age group for the 11 toxicities with ≥50 observations. *Online Supplementary Table S4* shows the adjusted results for all 19 toxicities.

Event-free survival

The 5-year EFS was 0.83±0.01 for the whole cohort 0.91±0.01 for patients stratified as standard risk, 0.85±0.01 for those stratified as intermediate risk, and 0.66±0.03 for high-risk

Table 3. Frequencies of all primary events by sex and age group in each final risk group (patients without assigned risk group excluded, N=21).

Primary events	Sex			Age at diagnosis			
	Male N (%)	Female N (%)	*P*	1-9 years N (%)	10 -17 years N (%)	18-45 years N (%)	*P*
Total	983[a]	788[b]	-	1,188[c]	306[d]	277[e]	-
Standard risk	438	354	0.79	636	94	62	<0.001
CR1	392 (89.5)	322 (91.0)		588 (92.5)	78 (83.0)	48 (77.4)	
DCR1	5 (1.1)	4 (1.1)		6 (0.9)	2 (2.1)	1 (1.6)	
Relapse	34 (7.8)	25 (7.1)		33 (5.2)	13 (13.8)	13 (21.0)	
SMN	7 (1.6)	3 (0.8)		9 (1.4)	1 (1.1)	0 (0.0)	
Intermediate risk	339	289	0.18	389	127	112	<0.001
CR1	275 (81.1)	245 (84.8)		341 (87.7)	107 (84.3)	72 (64.3)	
DCR1	8 (2.4)	10 (3.5)		7 (1.8)	4 (3.1)	7 (6.3)	
Relapse	56 (16.5)	33 (11.4)		40 (10.3)	16 (12.6)	33 (29.5)	
SMN	0 (0.0)	1 (0.3)		1 (0.3)	0 (0.0)	0 (0.0)	
High risk	199	131	0.93	149	81	100	0.005
CR1	130 (65.3)	82 (62.6)		106 (71.1)	52 (64.2)	54 (54.0)	
DCR1	23 (11.6)	15 (11.5)		14 (9.4)	13 (16.0)	11 (11.0)	
Relapse	44 (22.1)	32 (24.4)		29 (19.5)	13 (16.0)	34 (34.0)	
SMN	2 (1.0)	2 (1.5)		0 (0.0)	3 (3.7)	1 (1.0)	

[a]Seven males and [b]14 females could not be assigned a risk group. [c]Fourteen patients <10 years old at diagnosis, [d]four patients 10-17.9 years old, and [e]three patients aged 18-45 years could not be assigned a risk group. CR1: first complete remission; DCR1: death in first complete remission; SMN: second malignant neoplasm.

patients (0.64±0.03 for those given only chemotherapy, 0.67±0.04 for those given HSCT). We did not observe a sex difference in the EFS (*P*=0.48) for the whole cohort or within any risk group (*Online Supplementary Figure S1*).

When analyzing the 5-year EFS by age, patients 1-9.9 years at diagnosis had a significantly better outcome than those 10-17.9 years (HR=1.54 [95% CI: 1.15-2.07], *P*<0.001) or 18-45 years (HR=2.70 [95% CI: 2.03-3.58], *P*<0.001) (Figure 4). This difference was most pronounced for patients stratified as standard risk in whom a statistically significant difference was observed between patients 1-9.9 years and each older age group, but for patients stratified as intermediate risk and high risk, we only observed a significant difference between patients 18-45 years and the youngest age groups (Figure 4).

When the 5-year EFS was analyzed in Cox regression models, there were no significant interactions between the final risk group and sex or age (*Online Supplementary Table S5*).

The hazard ratios and 95% confidence intervals for EFS in multivariate Cox regression analyses adjusted by sex, age group, and risk group are presented in Table 4. Results are also illustrated as cumulative incidence curves for events by age group and risk group in *Online Supplementary Figure S2A*, *B*. When we estimated the EFS for the high-risk patients separately and stratified by HSCT status, the lower EFS in the oldest age group was only significant for patients who had an indication for HSCT in CR1 (age 18-45 compared to 1-9.9 years; HR=3.94, 95% CI: 1.78-8.75) (Figure 4).

When the risk of DCR1 was analyzed in competing-risks regression models, there were no significant interactions between the final risk group and sex or age (*Online Supplementary Table S5*). The SHR for DCR1 was significantly higher for patients 18-45 years in the intermediate-risk group, 3.65 (95% CI: 1.30-10.23), compared to age 1-9.9 years, but in the adjusted multivariable regression analysis, the SHR for DCR1 reached significance only in patients 10-17.9

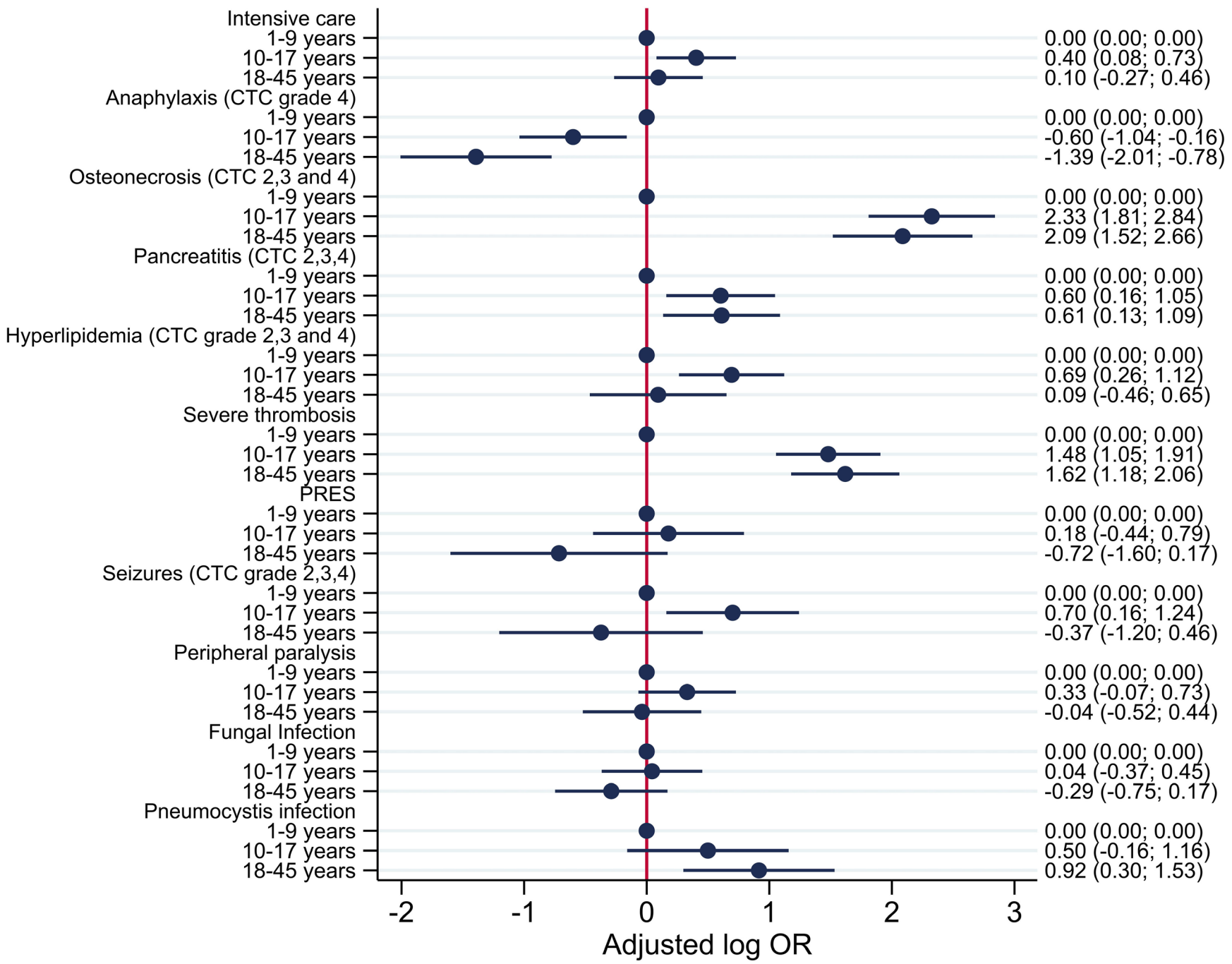
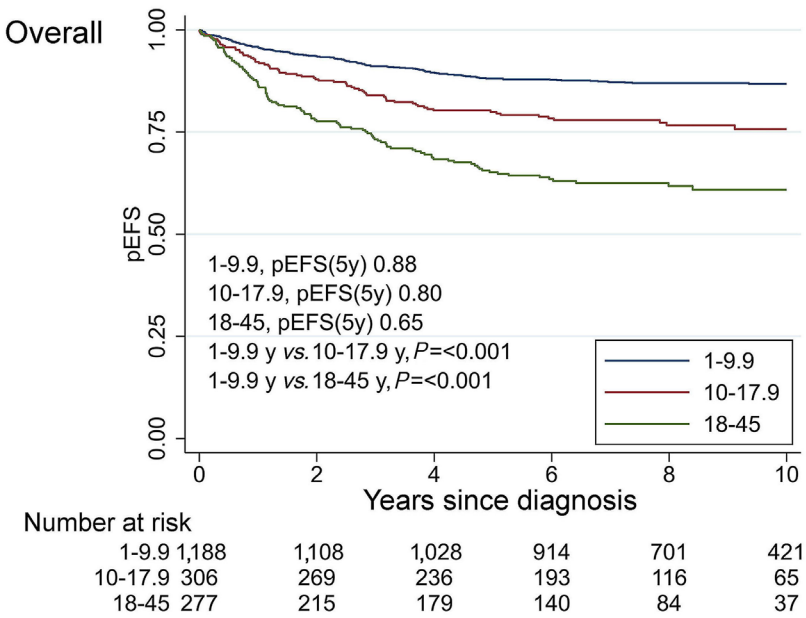


Figure 3. Toxicities. The adjusted (by sex and final treatment group) log odds ratios with 95% confidence intervals for the 11 most common toxicities of the NOPHO ALL2008 trial presented by age groups. Anaphylaxis: anaphylactic reaction to asparaginase; CTC: Common Terminology Criteria for Adverse Events; PRES: posterior reversible encephalopathy syndrome; OR: odds ratio.

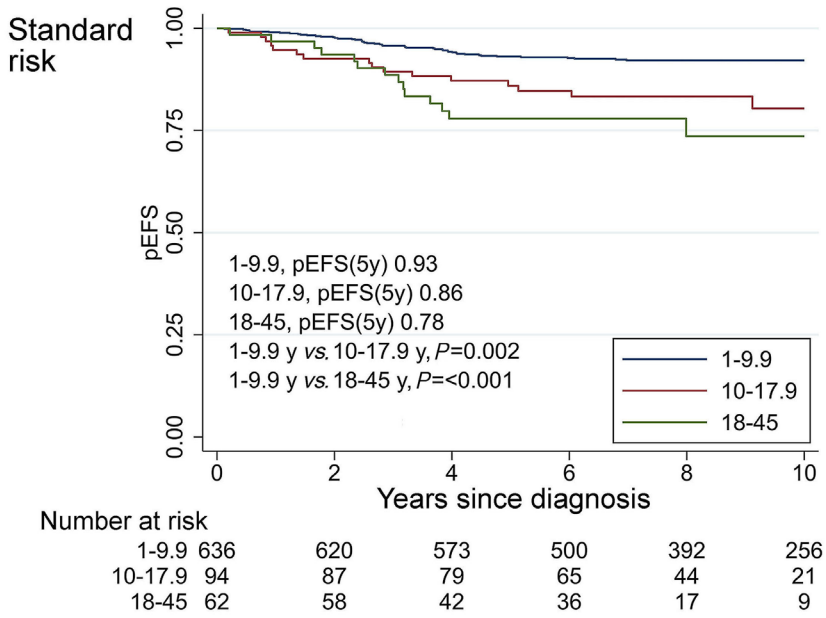
A



Number at risk

1-9.9	1,188	1,108	1,028	914	701	421
10-17.9	306	269	236	193	116	65
18-45	277	215	179	140	84	37

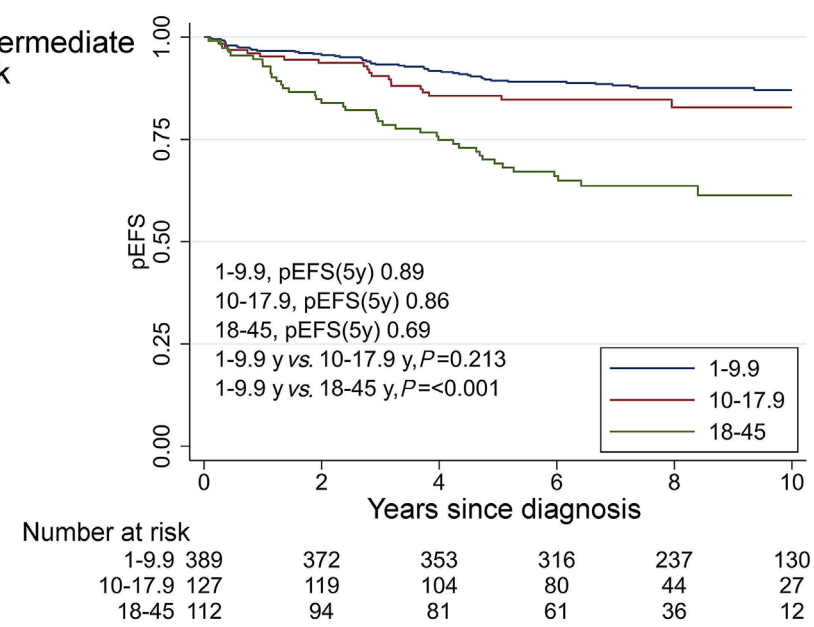
B



Number at risk

1-9.9	636	620	573	500	392	256
10-17.9	94	87	79	65	44	21
18-45	62	58	42	36	17	9

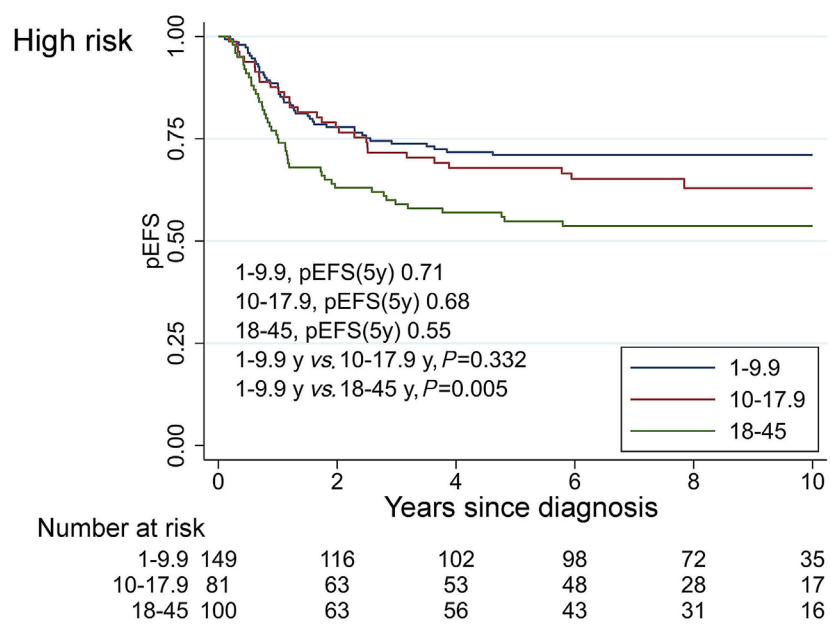
C



Number at risk

1-9.9	389	372	353	316	237	130
10-17.9	127	119	104	80	44	27
18-45	112	94	81	61	36	12

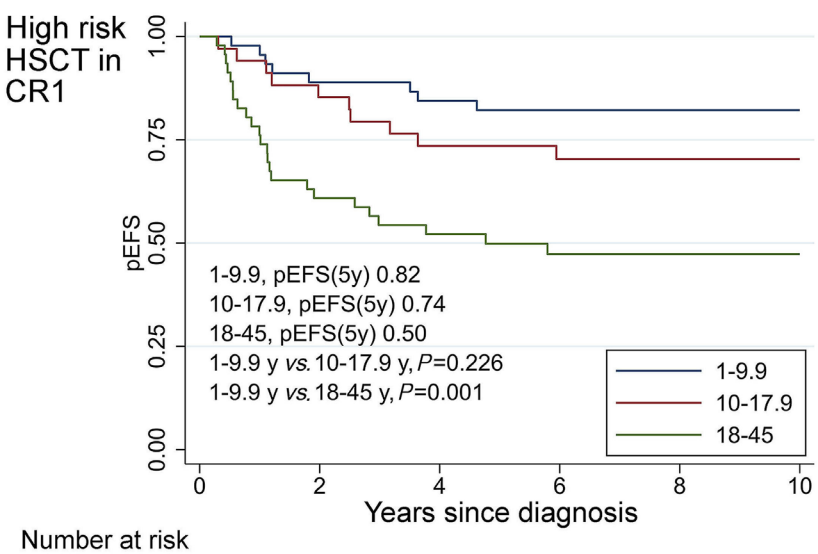
D



Number at risk

1-9.9	149	116	102	98	72	35
10-17.9	81	63	53	48	28	17
18-45	100	63	56	43	31	16

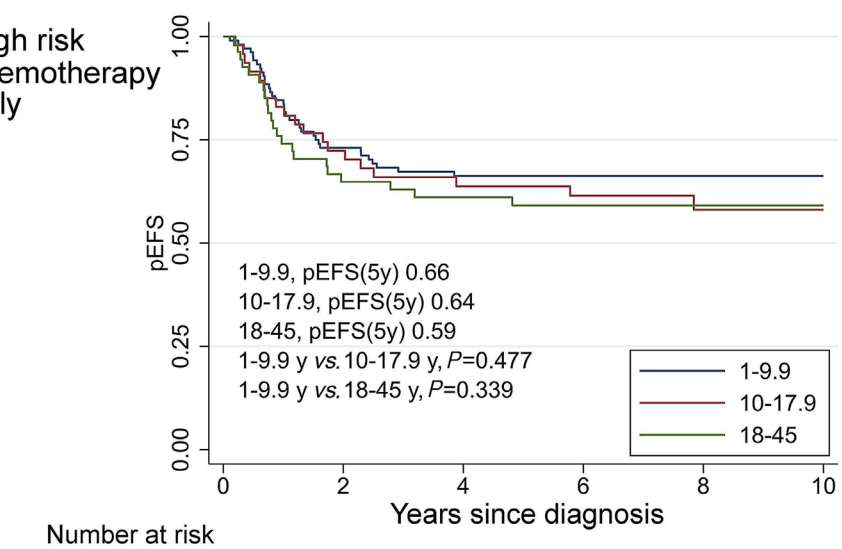
E



Number at risk

1-9.9	45	40	37	36	25	13
10-17.9	34	29	24	22	11	7
18-45	46	28	24	19	13	7

F



Number at risk

1-9.9	104	76	65	62	47	22
10-17.9	47	34	29	26	17	10
18-45	54	35	32	24	18	9

Figure 4. Event-free survival at 5 years in the NOPHO ALL2008 trial presented by age group. (A) The overall probability of event-free survival (pEFS) in the NOPHO ALL2008 trial at 5 years is presented by age group. (B) the pEFS of the standard-risk group at 5 years is presented by age group. (C) The pEFS of the intermediate-risk group at 5 years is presented by age group. (D) The pEFS of the high-risk group at 5 years is presented by age group. (E) The pEFS at 5 years of the high-risk group treated with hematopoietic stem cell transplantation in first complete remission is presented by age group. (F) The pEFS at 5 years of the high-risk group treated with chemotherapy only is presented by age group. y: years; HSCT: hematopoietic stem-cell transplantation; CR1: first complete remission.

years old (Table 4). *Online Supplementary Figure S2C* illustrates the cumulative incidence of DCR1 for the adjusted model by risk group. These curves showed that the effect on DCR1 was more pronounced in high-risk patients than in the other groups. The adjusted SHR for DCR1 was also analyzed within the final risk groups; the intermediate-risk group had a SHR of 2.26 (95% CI: 1.01-5.05) and the high-risk group a SHR of 8.56 (95% CI: 3.98-18.41) when compared with the standard-risk group.

Concerning the risk of relapse, there was no significant interaction between the final risk group and sex, but a trend (P=0.06) was found between age and the final risk group (*Online Supplementary Table S5*). This trend of interaction was explained by patients aged 10-17.9 years treated in the standard-risk group having a significantly elevated hazard ratio of 2.83 (95% CI: 1.48-5.40) compared to the patients <10 years old (P=0.002), which was not the case for intermediate-risk (P=0.213) or high-risk patients (P=0.332). Patients aged 18-45-year-old had a significantly elevated risk of relapse in all treatment groups. In the adjusted multivariable regression analysis, both the intermediate- and high-risk groups compared to the standard-risk group as well as the 18- to 45-year-old group compared to the younger groups had significantly increased risks of relapse (Table 4). These results are illustrated in *Online Supplementary Figure S2D* as cumulative incidences for the three risk groups separately, where all three groups had an increasing incidence over time, with the high-risk group having the highest incidence rates.

Overall survival

The 5-year OS for the whole cohort was 0.89±0.01. The 5-year OS estimates by final risk group were 0.96±0.01 for standard-risk patients, 0.92±0.01 for intermediate-risk patients, and 0.70±0.02 for high-risk patients (0.68±0.03 for those given only chemotherapy, 0.74±0.04 for those given HSCT). The OS for males and females was similar (P=0.475). When analyzing the 5-year OS by age groups, patients 1-9.9 years at diagnosis had a better outcome (0.94±0.01) than those 10-17.9 years (0.86±0.02) (P=0.001) or 18-45 years (0.73±0.02) (P<0.001).

An interaction between age and risk group was found regarding the risk of lower OS (*Online Supplementary Table S5*). This interaction was explained by patients aged 10-17.9 years at diagnosis treated as standard risk (HR=4.42 [95% CI: 1.92-10.16]) or intermediate risk (HR=3.01 [95% CI: 1.42-6.41]) having statistically significantly lower OS compared to patients aged 1-9.9 years at diagnosis, but not if they were allocated to high-risk therapy (HR=1.19 [95% CI: 0.71-2.01]). The hazard ratios and 95% confidence intervals for OS in multivariate Cox regression analyses adjusted by sex, age group, and risk group are presented in Table 4. In addition, the sex and age-adjusted hazard ratios were estimated for high-risk patients and stratified by HSCT status. This analysis showed that age group had a significant effect on OS impairment (age 10-17.9, HR=1.93, [95% CI: 0.67-5.53]; age 18-45 years, HR=4.33 [95% CI: 1.76-10.67]) only in the HSCT group as respective hazard ratios in the high-risk chemotherapy group were 1.08 (95% CI: 0.59-1.99) for age 10-17.9 years and 1.43 (95% CI: 0.82-2.51) for age 18-45 years compared with the group of patients aged 1-9.9 years.

In a subanalysis in which we only included patients stratified as intermediate risk and made further adjustments for immunophenotype, WBC count, and EOI MRD, patients ≥10 years at diagnosis had worse OS than patients 1-9.9 years, and adult patients had worse EFS and OS as well as higher risks of relapse and DCR1 compared to children 1-9.9 years old (*Online Supplementary Table S6*).

Survival after first relapse

For the whole relapse cohort, the 5-year pOS was 0.47±0.03.

Table 4. The hazard ratios or sub-distribution hazard ratio and 95% confidence intervals for the studied outcomes in multivariate Cox and competing-risks regression analysis adjusted by sex, age group, and risk group (patients without assigned risk group excluded, N=21).

Risk group	EFS		Relapse*		Death in CR1*		OS	
	HR	95% CI	SHR	95% CI	SHR	95% CI	HR	95% CI
Standard risk	1	-	1	-	1	-	1	-
Intermediate risk	1.54	(1.15-2.07)	1.63	(1.17-2.29)	2.26	(1.01-5.05)	1.77	(1.14-2.75)
High risk	3.33	(2.44-4.56)	2.52	(1.72-3.69)	8.56	(3.98-18.41)	5.92	(3.82-9.17)
Age <10 years	1	-	1	-	1	-	1	-
Age 10-17.9 years	1.57	(1.15-2.14)	1.40	(0.95-2.05)	1.90	(1.04-3.45)	2.04	(1.36-3.06)
Age 18-45 years	2.70	(2.03-3.58)	3.04	(2.19-4.21)	1.75	(0.94-3.25)	3.67	(2.54-5.31)
Female	1	-	1	-	1	-	1	-
Male	1.02	(0.81-1.29)	1.07	(0.81-1.41)	0.87	(0.53-1.40)	0.91	(0.68-1.22)

*Competing risks (death in first complete remission, second malignant neoplasm, relapse) were considered in the analyses. EFS: event-free survival; CR1: first complete remission; OS: overall survival; HR: hazard ratio; 95% CI: 95% confidence interval; SHR: subdistribution hazard ratio.

We found significant differences in pOS between the age groups: 10-17.9 years (0.38±0.08; *P*=0.021) and 18-45 years (0.28±0.05; *P*<0.001) compared to that for patients 1-9.9 years at primary diagnosis (0.65±0.05) (*Online Supplementary Table S7*). The age-group associations among the relapse patients were very similar to those for primary treatment where patients ≥10 years old primarily stratified as standard or intermediate risk had worse pOS than patients 1-9.9 years old but not if stratified as high risk (chemotherapy only or HSCT in CR1). The OS was similar between the age groups 10-17.9 years and 18-45 years for the different primary risk groups (standard, intermediate, high). We did not observe differences in the pOS after the first relapse between females and males, in general, or by risk group. Patients who relapsed very early (<18 months after the primary diagnosis) had significantly poorer survival than the others overall, but time to relapse did not have a significant effect on survival in high-risk patients (*Online Supplementary Table S7*).

Discussion

The results from the NOPHO ALL2008 trial are among the best reported for younger adults with ALL, demonstrating that pediatric-inspired therapy is both feasible and effective for this age group.

In general, males are considered to have worse overall survival after childhood cancer than females.[20,21] This has been shown specifically for ALL[22,23] and in earlier Nordic studies[24,25] although not in the NOPHO-ALL2000 trial.[14] In a recent large study, the 5-year OS in childhood ALL was 85% in males compared to 88% in females (HR=1.24, 95% CI: 1.12-1.37).[21] Other studies have also reported worse survival for male patients with ALL[26,27] but without further information on, e.g., relapse rate or treatment-related mortality. To counter the effect of sex on survival, some ALL trials allocate males to longer maintenance therapy than that allocated to females.[28] In the NOPHO ALL2008 trial, we abandoned all non-CNS extramedullary involvement (testicular, mediastinal, liver, spleen enlargements) at diagnosis in the risk-group assignment. Testicular involvement at diagnosis was a rare finding and none of the affected males relapsed during follow-up. In addition, the incidence of testicular relapse did not differ from that in previous NOPHO trials.

Even though T-cell immunophenotype and poor MRD response, both of which are associated with inferior survival, were more common among males in the NOPHO ALL2008 trial, we did not find statistically significant sex differences in the 5-year pEFS or pOS. The results from the NOPHO ALL2008 trial therefore indicate that stratification of treatment by cytogenetics and MRD will provide similar survival probabilities for females and males.

Concerning severe toxicity, induction failures were slightly more common in females than in males. However, the higher proportion of males with relapse abolished the effect of females' higher susceptibility to toxicity on impaired EFS and OS. In previous NOPHO trials, females were twice as likely to experience treatment-related mortality than were males,[29] which confirms reports from the US Children's Oncology Group, in which female high-risk patients experienced significantly more treatment-related mortality,[30] and the MRC UKALL X trial, in which female sex was associated with infection-related deaths during induction therapy.[31] The underlying biological mechanisms for these sex differences are still poorly understood and warrant further study.

With regard to the frequency of non-fatal toxicities evaluated in the NOPHO ALL2008 trial, osteonecrosis, veno-occlusive disease, and posterior reversible encephalopathy syndrome were more common in female than male patients. However, when adjusted for age, we only found an increased risk of osteonecrosis and veno-occlusive disease among females stratified as standard risk. The adverse effect of female sex has not been a consistent finding in previous publications on osteonecrosis.[32,33] Furthermore, alternate-week dexamethasone administration during delayed intensification instead of continuous treatment has been reported to reduce the risk of osteonecrosis in all patient groups.[32] This strategy was also utilized in the NOPHO ALL08 trial, and the standard-risk group got the lowest cumulative dose of dexamethasone despite age. Thus, our finding confirms the independent effect of female sex on the risk of developing osteonecrosis. Concerning veno-occlusive disease, treatment with 6-thioguanine has been identified as a risk factor[34] and seems to be associated with *TPMT* heterozygosity,[35] but the effect of prolonged exposure to pegylated asparaginase during the maintenance phase for standard- and intermediate-risk patients is a novel finding from the NOPHO ALL2008 trial.[36] The association between female sex and the risk of veno-occlusive disease has, to our knowledge, not been described previously. However, the pattern of non-fatal toxicities differing by age (<10 *vs*. ≥10 years) when adjusting for sex and trial risk group (like osteonecrosis, thrombosis, and pancreatitis) warrants further attention. Osteonecrosis, in addition to higher age, has been stated to be associated with, e.g., hypertriglyceridemia, and host germline polymorphisms of genes encoding, e.g., proteins involved in thrombosis, fibrinolysis, and lipid homeostasis.[37] Hence, preemptive measures for older patients such as thromboprophylaxis[38] and lipid-lowering measures[39] might be worth testing in prospective clinical trials.

Since several studies have confirmed higher age to be a risk factor for lower EFS and OS,[1,14,28,40] age is commonly used as a stratifying factor for risk-group allocation in childhood ALL. In addition to adolescent and young adult patients being more likely to have subtypes of ALL associated with worse outcomes,[3,41] outcome differences could also reflect age-related differences in pharmacokinetics and treatment adherence.[42] Some favorable prognosis-related cytogenetic markers, such as the chromosomal rearrangement

ETV6::*RUNX1* and high-hyperdiploidy, peak at preschool age.[43] Similarly, older children and young adults have a higher proportion of T-cell immunophenotype, *ABL*-class fusions, as well as a higher frequency of prednisone-poor response, all factors associated with inferior outcomes.[41,44,45] Furthermore, adolescent patients, in particular, may have problems with treatment adherence as they are more independent in their daily lives compared to small children.[46] In young adults, age-dependent changes in body composition and drug distribution, co-medication, and hormonal changes may also influence treatment efficacy and toxicity.[47]

Following previous findings, T-cell immunophenotype, worse EOI MRD response, and high-risk cytogenetics were more common among the older patients in NOPHO ALL2008. Although age was not a stratifying factor in the NOPHO ALL2008 trial, our study shows that despite the risk-stratification strategy used in the trial, age ≥10 years is associated with worse EFS and OS compared to younger age, including a higher risk of relapse among adult patients. Furthermore, the interaction analyses (age*risk-group) for risk of relapse and pOS showed that the effect of age is still different in risk groups despite taking into account the known age-related factors (immunophenotype, cytogenetics, EOI-MRD) in patients' stratification.

An analysis of survival after relapsed childhood ALL primarily treated within NOPHO trials was published recently.[48] In our study analyzing the whole trial cohort, the 5-year OS after the first relapse was significantly worse for patients ≥10 years compared to those <10 years at primary diagnosis. This supports that age ≥10 years at diagnosis predicts worse outcome both for the primary disease and relapse. The age difference we found was seen in patients primarily stratified as standard risk and intermediate risk but not in those stratified as high risk. This effect of age could also explain the finding in interaction analysis of pOS for the adolescent age group for which the hazards of relapse or DCR1 were not significantly elevated. One of the underlying factors for the large outcome difference after the first relapse could be a selection of treatment-resistant leukemic clones after high-risk upfront treatment. No association of survival with time to relapse was found after primary high-risk treatment.

A limitation of this study is that it was not possible to analyze age-related factors such as differences in pharmacokinetics, treatment adherence, or effects of toxicity on possible changes in treatment.

In conclusion, treatment based on the NOPHO ALL2008 risk-stratification system abolished the previously reported sex differences in EFS and OS of patients aged 1-45 years with *BCR*::*ABL1*-negative BCP and T-cell ALL and demonstrated the benefits of pediatric-inspired therapy for young adults. However, despite most adolescents and young adults being stratified to higher-risk groups, the age differences observed in this study suggest that de-intensifying the treatment for some adolescents and young adults might be problematic. In upcoming trials, more extensive inclusion of genetic mapping, addressing age-related factors such as adherence to oral chemotherapy, possible toxicity-driven treatment adaptations, and differences in pharmacokinetics, as well as evaluating whether MRD cut-offs for risk groups should differ between age groups, could be of interest.

Disclosures

The authors have no conflicts of interest related to this research. LT has received a personal grant from Turku University Hospital, TYKS-Foundation. MH, as a Principle Investigator for the ALLTogether1-study, received institutional support (no personal reimbursement) for the study drug supply from Pfizer, Amgen, and Novalab and for laboratory analyses from Servier. GV has received honoraria from AstraZeneca for lectures on NF1 (2024). UW-K has received honoraria from Amgen (2022), Jazz Pharmaceuticals (2022) and Pfizer (2023). KS has received speaker's and/or advisory board honoraria from Illumina (2021), Jazz Pharmaceuticals (2021, 2023) and Servier (2021, 2023); has received speaker's fees from Amgen (2021) and Medscape (2021); has received educational grants from Servier (2021, 2023); has received a research grant from Novo Nordisk Foundation (2022); and owns stocks in Novo Nordisk. PML has received speaker's fees from Sobi (2021) and from Pfizer (2024).

Contributions

KS, PML, TO, MH, BL, KL, GV, OGJ, NT, LG, HH, KP, UW-K, PQ-P, UN-N, KV, and JA entered the data into the study database and planned the analyses. TO and JE analyzed the data. TLT, TO, MH, KS, and PML interpreted the data first and then BL, KL, GV, OGJ, NT, LG, HH, KP, UW-K, PQ-P, UN-N, KV, and JA also interpreted the data. TLT, TO, KS, PML, and JE wrote the first version of the article. MH, BL, KL, GV, OGJ, NT, LG, HH, KP, UW-K, PQ-P, UN-N, KV, and JA reviewed it. PML, KS, and MH supervised the study.

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Data-sharing statement

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

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