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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Supplementary data on methods

Minimal residual disease (MRD) was assessed by flow cytometry for patients with BCP-ALL and with PCR of clonal immune gene rearrangements for patients with T-ALL. If either method failed the alternative was used. With these combined methods only 0.14% of BCP [1] and 0.7% of T-ALL patients [2] had no MRD marker.

Statistical analyzes

Effect modification of risk group on age and sex was evaluated by conducting separate Cox regression analyzes for EFS and OS and competing-risks regression for relapse and death in CR1, for each risk group and by conducting Wald tests to identify any statistically significant interactions between risk group and age and sex, respectively. The robust sandwich estimator was used to calculate standard errors. The proportional hazard assumption was tested based on Schoenfeld residuals. Cumulative incidences were estimated based on Kaplan-Meier estimates and cause-specific hazard functions [3].

We analyzed treatment-related toxicity by describing frequencies of induction deaths (induction failure) and deaths in first complete remission (DCR1), as well as the 19 predefined toxicities registered in the trial database. The frequencies were compared separately by Chi-squared test between sexes, age groups, and risk groups. Logistic regression models, including age and sex, were performed for each of the treatment-related toxicities stratified by risk group. The results are presented as odds ratios (OR) with a 95% confidence interval. The 19 toxicities were separately analyzed by age using logistic regression adjusted for sex and the administered treatment arm. The OR were illustrated with a forest plot including only the predefined toxicities (11 of 19) with ≥50 observations to facilitate comparison with previous publication from the NOPHO ALL2008 trial [4].

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Supplementary Table S1 Frequencies of treatment-related toxicities by sex and age at diagnosis.

	Sex, N (%)			**Age at diagnosis in years, N (%)**			
	Male	**Female**	***p*-value**	**Age 1-9.9**	**Age 10-17.9**	**Age 18-45**	***p*-value**
Heart failure	8 (0.8)	5 (0.6)	0.783	8 (0.7)	4 (1.3)	1 (0.4)	0.374
Anaphylaxis	110 (11.2)	96 (12.2)	0.517	167 (14.1)	27 (8.8)	12 (4.3)	**<0.001**
Osteonecrosis	42 (4.3)	62 (7.9)	**0.001**	26 (2.2)	47 (15.4)	31 (11.2)	**<0.001**
Pancreatitis	73 (7.4)	63 (8.0)	0.655	76 (6.4)	32 (10.5)	28 (10.1)	**0.015**
Severe hyperlipidemia	75 (7.6)	59 (7.5)	0.910	82 (6.9)	35 (11.4)	17 (6.1)	**0.017**
Abdominal catastrophe	15 (1.5)	13 (1.6)	0.836	14 (1.2)	6 (2.0)	8 (2.9)	0.102
Liver dysfunction with encephalopathy	25 (2.5)	29 (3.7)	0.167	35 (2.9)	14 (4.6)	5 (1.8)	0.142
Veno-occlusive disease (VOD)	15 (1.5)	27 (3.4)	**0.009**	31 (2.6)	8 (2.6)	3 (1.1)	0.308
Dialysis/severe kidney dysfunction	26 (2.6)	14 (1.8)	0.261	14 (1.2)	16 (5.2)	10 (3.6)	**<0.001**
Hypertension (crisis)	6 (0.6)	12 (1.5)	0.092	14 (1.2)	4 (1.3)	0	0.182
CNS/catastrophic bleeding	20 (2.0)	15 (1.9)	0.844	16 (1.3)	7 (2.3)	12 (4.3)	**0.005**
Thrombosis	93 (9.5)	56 (7.1)	0.076	51 (4.3)	49 (16.0)	49 (17.7)	**<0.001**
PRES	28 (2.8)	37 (4.7)	**0.040**	44 (3.7)	15 (4.9)	6 (2.2)	0.213
Coma	12 (1.2)	11 (1.4)	0.746	14 (1.2)	6 (2.0)	3 (1.1)	0.527
Seizure	39 (4.0)	35 (4.4)	0.620	45 (3.8)	22 (7.2)	7 (2.5)	**0.010**
Peripheral paralysis	95 (9.7)	89 (11.3)	0.264	123 (10.4)	38 (12.4)	23 (8.3	0.266
PJP pneumonia	39 (4.0)	25 (3.2)	0.373	31 (2.6)	14 (4.6)	19 (6.9)	**0.002**
Invasive fungal infection	103 (10.5)	76 (9.6)	0.563	112 (9.4)	38 (12.4)	29 (10.5)	0.295
Intensive care	167 (17.0)	128 (16.2)	0.676	174 (14.6)	69 (22.5)	52 (18.8)	**0.002**

Supplementary Table S2. Frequencies of treatment-related toxicities by final treatment group. (1750 patients included in the analyzes since 21 patients could not be assigned a risk group.)

	Standard Risk **N (%)**	**Intermediate Risk** **N (%)**	**High Risk** **N (%)**	***p*-value**
Heart failure	4 (0.5)	5 (0.8)	4 (1.2)	0.43
Anaphylaxis	91 (11.5)	70 (11.0)	45 (13.9)	0.41
Osteonecrosis	43 (5.5)	47 (7.4)	14 (4.3)	0.12
Pancreatitis	60 (7.6)	54 (8.5)	21 (6.5)	0.54
Severe hyperlipidemia	63 (8.0)	64 (10.1)	7 (2.2)	**<0.001**
Abdominal catastrophe	9 (1.1)	8 (1.3)	8 (2.5)	0.21
Liver dysfunction with encephalopathy	25 (3.2)	19 (3.0)	8 (2.5)	0.82
Veno-occlusive disease (VOD)	24 (3.0)	16 (2.5)	2 (0.6)	0.054
Dialysis/severe kidney dysfunction	8 (1.0)	10 (1.6)	20 (6.2)	**<0.001**
Hypertension (crisis)	6 (0.8)	7 (1.1)	4 (1.2)	0.70
CNS/catastrophic bleeding	9 (1.1)	16 (2.5)	6 (1.9)	0.15
Thrombosis	57 (7.2)	59 (9.3)	32 (9.9)	0.23
PRES	19 (2.4)	32 (5.0)	14 (4.3)	**0.028**
Coma	6 (0.8)	9 (1.4)	6 (1.9)	0.26
Seizure	33 (4.2)	27 (4.2)	14 (4.3)	0.99
Peripheral paralysis	90 (11.4)	78 (12.3)	16 (4.9)	**0.001**
PJP pneumonia	19 (2.4)	26 (4.1)	19 (5.9)	**0.016**
Invasive fungal infection	48 (6.1)	56 (8.8)	71 (21.9)	**<0.001**
Intensive care	98 (12.4)	101 (15.9)	88 (27.2)	**<0.001**

Supplementary Table S3. Odds ratios (OR) for treatment-related toxicities stratified by risk group.

Risk group		Intensive care	Anaphylaxis	Osteonecrosis	Pancreatitis	Severe hyper-lipidemia	Thrombosis	PRES
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Standard	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	1.63 (0.92-2.91)	0.46 (0.19-1.08)	**8.91 (4.29-18.52)**	1.95 (0.96-3.94)	1.75 (0.87-3.52)	**4.39 (2.31-8.32)**	0.92 (0.21-4.09)
	Age 18-45 yrs	0.89 (0.37-2.14)	0.38 (0.12-1.24)	**8.63 (3.54-21.07)**	**2.77 (1.26-6.06)**	1.93 (0.83-4.53)	**4.24 (1.95-9.24)**	1.67 (0.37-7.58)
	Male	1	1	1	1	1	1	1
	Female	1.07 (0.70-1.64)	1.04 (0.67-1.62)	**3.84 (1.91-7.73)**	0.93 (0.54-1.59)	1.46 (0.87-2.45)	0.90 (0.51-1.58)	2.22 (0.86-5.72)
Inter-mediate	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	**1.78 (1.08-2.95)**	0.34 (0.15-0.78)	**8.06 (3.53-18.41)**	1.97 (0.98-3.95)	**1.89 (1.05-3.43)**	**3.12 (1.49-6.52)**	1.47 (0.65-3.33)
	Age 18-45 yrs	0.93 (0.51-1.70)	0.26 (0.10-0.66)	**8.71 (3.81-19.94)**	**2.48 (1.26-4.85)**	0.83 (0.38-1.78)	**7.24 (3.75-13.99)**	0.50 (0.15-1.71)
	Male	1	1	1	1	1	1	1
	Female	0.75 (0.49-1.16)	1.05 (0.63-1.73)	1.65 (0.89-3.07)	1.18 (0.67-2.07)	0.65 (0.38-1.11)	0.63 (0.35-1.13)	1.19 (0.58-2.43)
High	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	0.85 (0.46-1.59)	0.90 (0.44-1.84)	**4.82 (1.29-17.99**)	0.90 (0.32-2.51)	3.68 (0.66-20.65)	**9.28 (3.00-28.74)**	0.82 (0.24-2.79)
	Age 18-45 yrs	1.06 (0.60-1.89)	0.19 (0.06-0.55)	NA	0.37 (0.10-1.34)	0.75 (0.07-8.39)	**4.51 (1.39-14.68)**	0.17 (0.02-1.38)
	Male	1	1	1	1	1	1	1
	Female	1.21 (0.74-2.00)	1.14 (0.59-2.18)	1.84 (0.60-5.61)	1.62 (0.66-3.96)	1.17 (0.25-5.37)	1.18 (0.55-2.55)	2.61 (0.85-8.05)

Continued:

Risk group		Seizures	Peripheral paralysis	Invasive fungal infection	PJ pneumonia	Heart failure	Abdominal catastrophe	Liver DF with encephalopathy
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Standard	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	**2.48 (1.08-5.73)**	1.59 (0.86-2.91)	0.49 (0.15-1.61)	1.14 (0.25-5.17)	2.18 (0.22-21.21)	1.14 (0.14-9.59)	1.37 (0.46-4.10)
	Age 18-45 yrs	1.01 (0.23-4.41)	1.22 (0.53-2.80)	1.44 (0.54-3.83)	**5.31 (1.78-15.82)**	NA	4.10 (0.80-21.05)	0.57 (0.08-4.35)
	Male	1	1	1	1	1	1	1
	Female	1.36 (0.68-2.75)	1.37 (0.88-2.12)	1.07 (0.59-1.92)	1.57 (0.62-3.93)	0.41 (0.04-3.92)	1.70 (0.45-6.46)	1.35 (0.61-3.00)
Inter-mediate	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	1.88 (0.80-4.43)	1.55 (0.89-2.73)	1.55 (0.82-2.92)	2.42 (0.99-5.90)	0.77 (0.08-6.96)	3.14 (0.62-15.80)	**3.99 (1.41-11.28)**
	Age 18-45 yrs	0.64 (0.18-2.25)	0.80 (0.40-1.60)	0.57 (0.23-1.39)	1.39 (0.48-4.04)	NA	2.22 (0.37-13.49)	2.05 (0.59-7.17)
	Male	1	1	1	1	1	1	1
	Female	0.59 (0.26-1.33)	1.22 (0.76-1.97)	0.95 (0.55-1.65)	0.76 (0.34-1.72)	0.74 (0.12-4.47)	0.76 (0.18-3.23)	1.81 (0.71-4.61)
High	Age 1-9.9 yrs	1	1	1	1	1	1	1
	Age 10-17.9 yrs	1.38 (0.42-4.53)	0.35 (0.07-1.69)	0.84 (0.44-1.59)	0.71 (0.18-2.84)	3.71 (0.33-41.79)	0.58 (0.06-5.67)	0.59 (0.12-2.99)
	Age 18-45 yrs	0.46 (0.09-2.27)	0.74 (0.24-2.31)	0.62 (0.32-1.18)	1.86 (0.66-5.21)	1.56 (0.10-25.52)	1.99 (0.43-9.18)	NA
	Male	1	1	1	1	1	1	1
	Female	2.76 (0.90-8.50)	0.47 (0.15-1.49)	0.87 (0.51-1.51)	0.55 (0.19-1.57)	1.61 (0.22-11.71)	0.96 (0.22-4.13)	1.32 (0.32-5.46)

Continued:

Risk group		Veno-occlusive disease OR (95%CI)	Dialysis/severe kidney DF OR (95%CI)	Hypertensive crisis OR (95%CI)	CNS/catastrophic bleeding OR (95%CI)	Coma OR (95%CI)
Standard	Age 1-9.9 yrs	1	1	1	1	1
	Age 10-17.9 yrs	1.10 (0.32-3.80)	3.95 (0.92-16.93)	NA	2.59 (0.49-13.65)	3.34 (0.60-18.53)
	Age 18-45 yrs	1.34 (0.30-5.96)	NA	NA	3.95 (0.74-21.03)	NA
	Male	1	1	1	1	1
	Female	**2.59 (1.09-6.15)**	0.17 (0.02-1.43)	2.38 (0.43-13.06)	0.17 (0.02-1.34)	0.62 (0.11-3.40)
Inter-mediate	Age 1-9.9 yrs	1	1	1	1	1
	Age 10-17.9 yrs	1.14 (0.36-3.61)	**7.84 (1.50-41.03)**	1.31 (0.25-6.88)	0.80 (0.17-3.82)	1.09 (0.22-5.47)
	Age 18-45 yrs	NA	4.95 (0.81-30.08)	NA	2.65 (0.90-7.83)	0.57 (0.07-4.84)
	Male	1	1	1	1	1
	Female	2.57 (0.88-7.52)	0.57 (0.14-2.25)	1.54 (0.34-6.97)	1.23 (0.45-3.35)	1.46 (0.39-5.52)
High	Age 1-9.9 yrs	1	1	1	1	1
	Age 10-17.9 yrs	1.28 (0.08-20.97)	3.02 (0.95-9.60)	1.98 (0.27-14.55)	1.94 (0.27-14.19)	1.28 (0.21-7.87)
	Age 18-45 yrs	NA	2.16 (0.66-7.05)	NA	1.70 (0.23-12.48)	0.55 (0.06-5.42)
	Male	1	1	1	1	1
	Female	NA	1.09 (0.43-2.76)	4.39 (0.45-43.20)	3.26 (0.58-18.22)	3.00 (0.54-16.75)

CI=Confidence interval, yrs=years, PRES=Posterior reversible encephalopathy syndrome, PJP=Pneumocystis jiroveci pneumonia, DF=dysfunction, CNS=Central nervous system, NA=Not applicable.

Supplementary Table S4. Odds ratios (OR, 95% confidence interval) for all 19 predefined toxicities by age groups (adjusted for sex and treatment group).

Toxicity	**N (%)**	**OR (95% CI)**
Intensive care +/- assisted ventilation		
Age 1-9.9	174/1188 (14.6)	1
Age 10-17.9	69/306 (22.5)	**1.50 (1.08-2.07)**
Age 18-45	52/277 (18.8)	1.10 (0.77-1.58)
Anaphylaxis (CTCAE grade 4)		
Age 1-9.9	167/1188 (14.1)	1
Age 10-17.9	27/306 (8.8)	0.55 (0.35-0.85)
Age 18-45	12/277 (4.3)	0.25 (0.13-0.46)
Osteonecrosis (CTCAE grade 2-4)		
Age 1-9.9	26/1188 (2.2)	1
Age 10-17.9	47/306 (15.4)	**10.23 (6.11-17.13)**
Age 18-45	31/277 (11.2)	**8.07 (4.56-14.26)**
Pancreatitis (CTCAE grade 2-4)		
Age 1-9.9	76/1188 (6.4)	1
Age 10-17.9	32/306 (10.5)	**1.83 (1.17-2.85)**
Age 18-45	28/277 (10.1)	**1.84 (1.14-2.97)**
Severe hyperlipidemia (CTCAE grade 2-4)		
Age 1-9.9	82/1188 (6.9)	1
Age 10-17.9	35/306 (11.4)	**2.00 (1.30-3.07)**
Age 18-45	17/277 (6.1)	1.10 (0.63-1.92)
Thrombosis		
Age 1-9.9	51/1188 (4.3)	1
Age 10-17.9	49/306 (16.0)	**4.40 (2.87-6.73)**
Age 18-45	49/277 (17.7)	**5.05 (3.25-7.86)**
PRES (posterior reversible encephalopathy syndrome)		
Age 1-9.9	44/1188 (3.7)	1
Age 10-17.9	15/306 (4.9)	1.19 (0.65-2.21)
Age 18-45	6/277 (2.2)	0.49 (0.20-1.19)
Seizures (CTCAE grade 2-4)		
Age 1-9.9	45/1188 (3.8)	1
Age 10-17.9	22/306 (7.2)	**2.02 (1.17-3.46)**
Age 18-45	7/277 (2.5)	0.69 (0.30-1.58)
Peripheral paralysis		
Age 1-9.9	123/1188 (10.4)	1
Age 10-17.9	38/306 (12.4)	1.39 (0.93-2.07)
Age 18-45	23/277 (8.3)	0.96 (0.59-1.56)
Fungal infection		
Age 1-9.9	112/1188 (9.4)	1
Age 10-17.9	38/306 (12.4)	1.04 (0.69-1.57)
Age 18-45	29/277 (10.5)	0.75 (0.47-1.18)
Pneumocystis jirovecii pneumonia		
Age 1-9.9	31/1188 (2.6)	1

Age 10-17.9	14/306 (4.6)	1.65 (0.85-3.18)
Age 18-45	19/277 (6.9)	**2.50 (1.35-4.63)**
Heart failure		
Age 1-9.9	8/1188 (0.7)	1
Age 10-17.9	4/306 (1.3)	1.64 (0.47-5.70)
Age 18-45	1/277 (0.4)	0.42 (0.05-3.50)
Abdominal problems leading to laparotomy		
Age 1-9.9	14/1188 (1.2)	1
Age 10-17.9	6/306 (2.0)	1.55 (0.57-4.18)
Age 18-45	8/277 (2.9)	2.15 (0.84-5.49)
Liver dysfunction with encephalopathy		
Age 1-9.9	35/1188 (2.9)	1
Age 10-17.9	14/306 (4.6)	1.70 (0.89-3.24)
Age 18-45	5/277 (1.8)	0.67 (0.25-1.77)
Veno-occlusive disease (VOD)		
Age 1-9.9	31/1188 (2.6)	1
Age 10-17.9	8/306 (2.6)	1.24 (0.55-2.77)
Age 18-45	3/277 (1.1)	0.57 (0.17-1.94)
Dialysis/severe kidney dysfunction		
Age 1-9.9	14/1188 (1.2)	1
Age 10-17.9	16/306 (5.2)	**3.51 (1.65-7.48)**
Age 18-45	10/277 (3.6)	2.02 (0.85-4.80)
Hypertensive crisis		
Age 1-9.9	14/1188 (1.2)	1
Age 10-17.9	4/306 (1.3)	0.97 (0.31-3.08)
Age 18-45	0/277	
CNS/catastrophic bleeding		
Age 1-9.9	16/1188 (1.3)	1
Age 10-17.9	7/306 (2.3)	1.61 (0.64-4.04)
Age 18-45	12/277 (4.3)	**3.02 (1.35-6.74)**
Coma		
Age 1-9.9	14/1188 (1.2)	1
Age 10-17.9	6/306 (2.0)	1.43 (0.53-3.85)
Age 18-45	3/277 (1.1)	0.71 (0.20-2.59)

Supplementary Table S5. The hazard ratios (HR) or sub-distribution hazard ratios (SHR) and 95% confidence intervals (CI) for the studied outcomes in each risk group from Cox regression or competing-risks regression. Test results of interactions by age and sex for each outcome in risk groups are presented as well. (Patients without assigned risk group excluded, N=21).

	EFS (HR, 95% CI)		**Relapse** (SHR, 95% CI)		**Death in CR1** (SHR, 95% CI)		**OS** (HR, 95% CI)	
Standard risk								
Age <10 y	1		1		1		1	
Age 10-17.9 y	**2.40**	**(1.36-4.25)**	**2.83**	**(1.48-5.40)**	2.29	(0.45-11.60)	**4.42**	**(1.92-10.16)**
Age 18-45 y	**3.40**	**(1.86-6.24)**	**4.76**	**(2.45-9.23)**	1.76	(0.22-14.37)	**6.42**	**(2.68-15.38)**
Female	1		1		1		1	
Male	1.12	(0.71-1.77)	1.04	(0.61-1.76)	0.98	(0.26-3.68)	0.84	(0.41-1.70)
Intermediate risk								
Age <10 y	1		1		1		1	
Age 10-17.9 y	1.37	(0.81-2.32)	1.30	(0.72-2.33)	1.84	(0.54-6.28)	**3.01**	**(1.42-6.41)**
Age 18-45 y	**3.43**	**(2.26-5.22)**	**3.28**	**(2.06-5.22)**	**3.65**	**(1.30-10.23)**	**7.84**	**(4.11-14.96)**
Female	1		1		1		1	
Male	1.18	(0.80-1.72)	1.39	(0.91-2.14)	0.63	(0.25-1.57)	1.05	(0.62-1.78)
High risk								
Age <10 y	1		1		1		1	
Age 10-17.9 y	1.28	(0.80-2.04)	0.82	(0.43-1.59)	1.74	(0.82-3.68)	1.19	(0.71-2.01)
Age 18-45 y	**1.86**	**(1.22-2.84)**	**1.99**	**(1.20-3.29)**	1.20	(0.55-2.61)	**1.95**	**(1.25-3.05)**
Female	1		1		1		1	
Male	0.85	(0.59-1.23)	0.82	(0.52-1.31)	0.98	(0.52-1.87)	0.86	(0.58-1.28)
Interactions:								
*Sex*risk group*		*p*=0.38		*p*=0.22		*p*=0.77		*p*=0.69
*Age*risk group*		*p*=0.14		*p*=0.06		*p*=0.51		*p*=0.002

Supplementary Table S6. A separate analysis for the patients in the intermediate-risk group: The hazard ratios (HR) or sub-distribution hazard ratios (SHR) and 95% confidence intervals (CI) for the studied outcomes in multivariate Cox and competing-risks regression analysis adjusted by sex, age group, immunophenotype, WBC at diagnosis, and MRD at the end of induction.

	EFS		**Relapse***		**Death in CR1***		**OS**	
	HR	**95% CI**	**SHR**	**95% CI**	**SHR**	**95% CI**	**HR**	**95% CI**
Age <10 y	1		1		1		1	
Age 10-17.9 y	1.44	(0.85-2.44)	1.44	(0.80-2.59)	1.62	(0.49-5.40)	**2.93**	**(1.38-6.25)**
Age 18-45 y	**3.79**	**(2.47-5.81)**	**3.89**	**(2.44-6.20)**	**2.94**	**(0.95-9.07)**	**7.88**	**(4.07-15.26)**
Female	1		1		1		1	
Male	1.30	(0.88-1.91)	**1.55**	**(1.02-2.35)**	0.59	(0.20-1.72)	1.09	(0.62-1.89)
BCP	1		1		1		1	
T-cell	0.79	(0.43-1.46)	0.59	(0.28-1.21)	1.94	(0.51-7.32)	1.33	(0.60-2.91)
EOI-MRD								
<0.1%	1		1		1		1	
0.1-4.9%	**1.81**	**(1.13-2.90)**	**1.92**	**(1.16-3.20)**	1.01	(0.27-3.74)	1.71	(0.87-3.36)
WBC								
<100	1		1		1		1	
≥100	1.70	(0.93-3.12)	1.60	(0.79-3.27)	1.76	(0.54-5.73)	1.81	(0.83-3.99)

*Competing risks (death in CR1, SMN, relapse) were considered in the analyzes.

Supplementary Table S7. Probability of survival at 5 years after first relapse in total and by risk groups of primary treatment.

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (103)	0.65	±0.05	1	
	10-17.9 (43)	0.38	±0.08	1.81	1.09-2.98
	18-45 (77)	0.28	±0.05	2.67	1.74-4.11
Sex (N)	female (89)	0.47	±0.05	1	
	male (134)	0.47	±0.04	0.98	0.68-1.42
Time to relapse (N)	very early (58)	0.15	±0.05	1	
	early (48)	0.58	±0.07	0.34	0.20-0.59
	late (117)	0.58	±0.05	0.30	0.20-0.44

Survival at 5 years after relapse in standard risk group (pOS 0.70 ±0.06)

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (33)	0.84	±0.07	1	
	10-17.9 (13)	0.53	±0.14	3.73	1.26-11.06
	18-45 (12)	0.50	±0.14	4.08	1.30-12.75
Sex (N)	female (24)	0.62	±0.10	1	
	male (34)	0.75	±0.08	0.63	0.25-1.55
Time to relapse (N)	very early (8)	0.13	±0.12	1	
	early (14)	0.79	±0.11	0.16	0.05-0.52
	late (36)	0.80	±0.07	0.12	0.05-0.30

Survival at 5 years after relapse in intermediate risk group (pOS 0.56 ±0.06)

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (40)	0.82	±0.06	1	
	10-17.9 (16)	0.38	±0.13	3.47	1.30-9.26
	18-45 (33)	0.35	±0.09	4.89	1.95-12.26
Sex (N)	female (33)	0.60	±0.09	1	
	male (56)	0.53	±0.07	1.20	0.61-2.36
Time to relapse (N)	very early (14)	0.21	±0.11	1	
	early (22)	0.64	±0.10	0.35	0.14-0.86
	late (53)	0.61	±0.07	0.34	0.17-0.70

Survival at 5 years after relapse in high risk group (pOS 0.20 ±0.05)

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (29)	0.24	±0.08	1	
	10-17.9 (13)	0.31	±0.13	0.78	0.34-1.80
	18-45 (32)	0.13	±0.06	1.21	0.70-2.11
Sex (N)	female (31)	0.23	±0.08	1	
	male (43)	0.18	±0.06	1.14	0.67-1.92
Time to relapse (N)	very early (34)	0.15	±0.06	1	
	early (12)	0.25	±0.13	0.85	0.37-1.95
	late (28)	0.25	±0.08	0.64	0.37-1.11

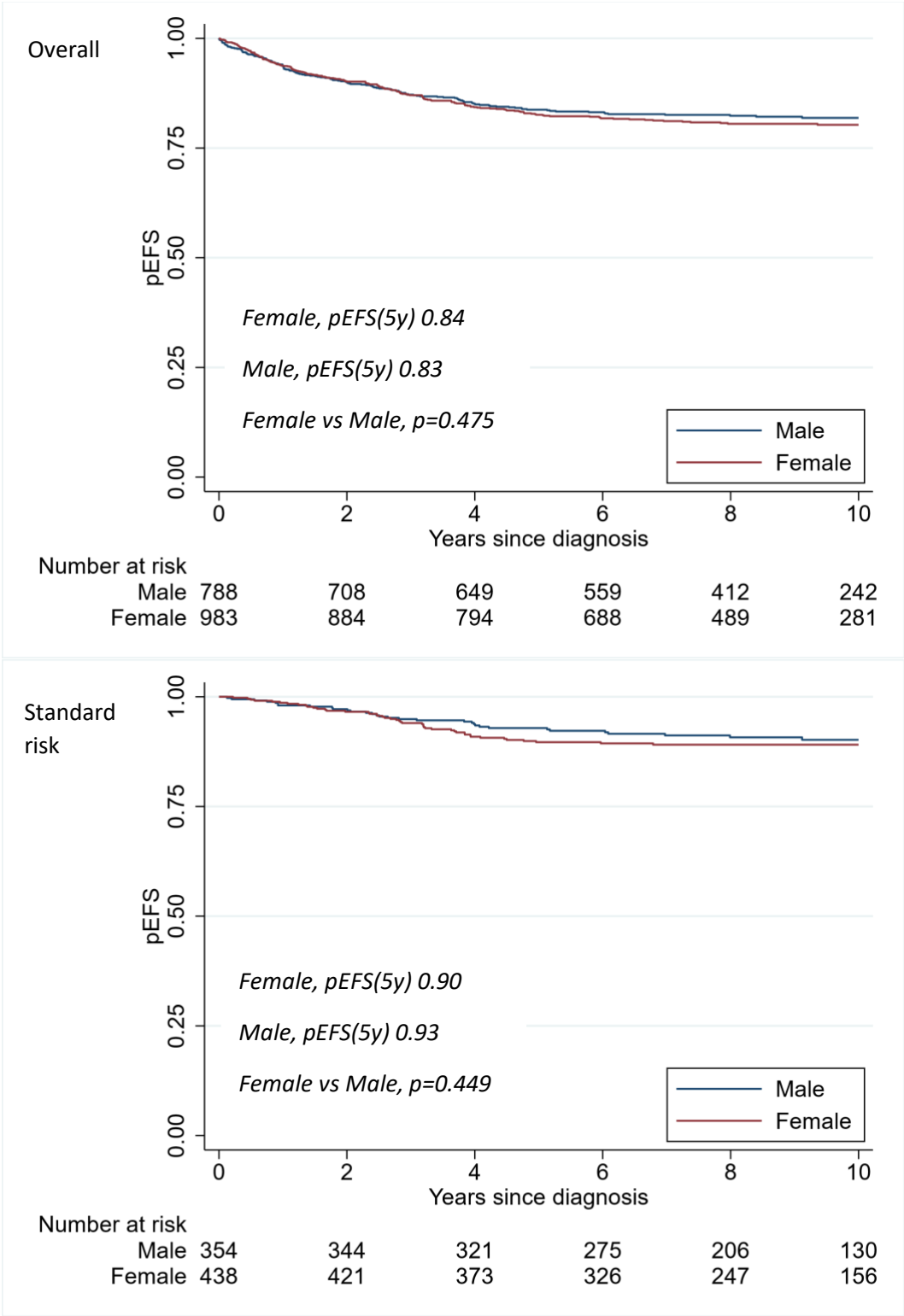
Survival at 5 years after relapse in high risk chemo group (pOS 0.20 ±0.06)

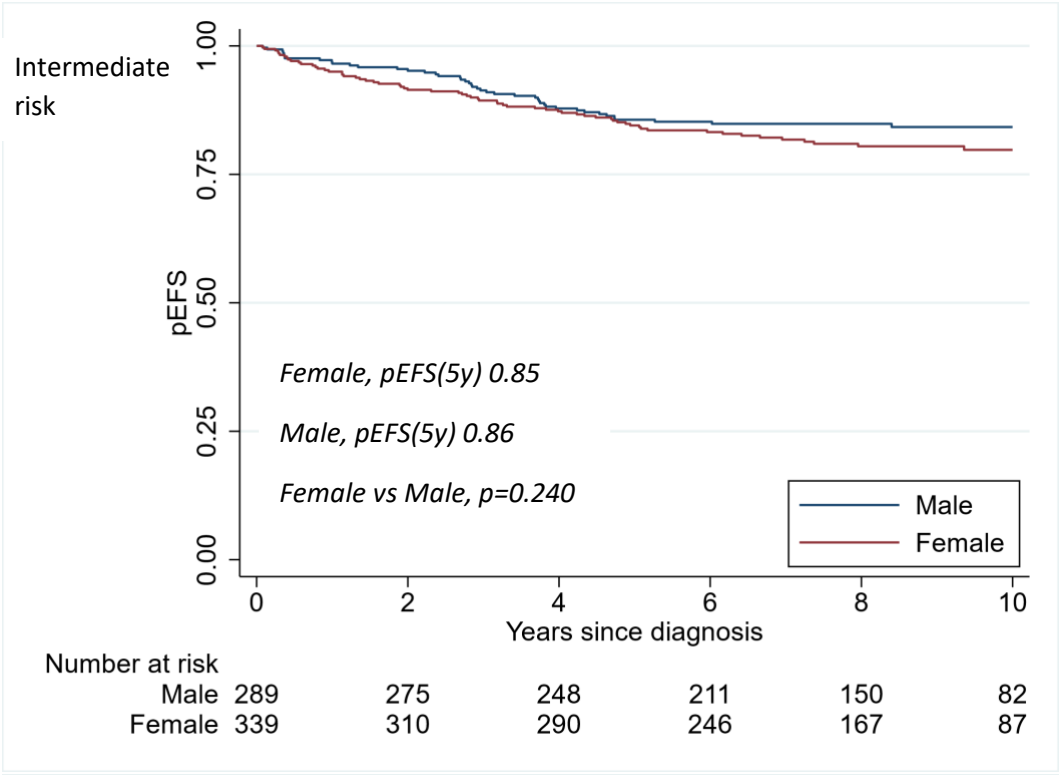
		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (23)	0.22	±0.09	1	
	10-17.9 (8)	0.38	±0.17	0.49	0.19-1.28
	18-45 (13)	.	.	1.32	0.65-2.69
Sex (N)	female (19)	0.21	±0.09	1	
	male (25)	0.20	±0.08	0.98	0.49-1.98
Time to relapse (N)	very early (24)	0.13	±0.07	1	
	early (10)	0.20	±0.13	0.89	0.39-2.07
	late (10)	0.40	±0.15	0.44	0.18-1.06

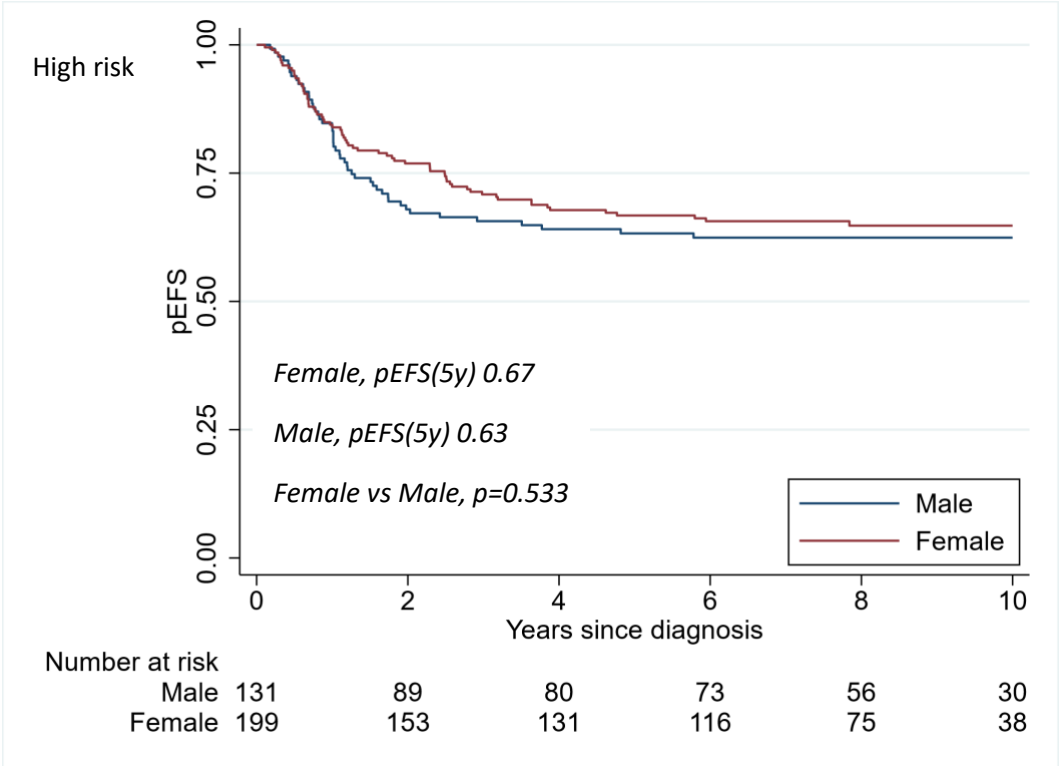
Survival at 5 years after relapse in high risk SCT-CR1 group (pOS 0.20 ±0.07)

		Survival (pOS)	SE	HR	95%CI
Age (N)	1-9.9 (6)	0.33	±0.19	1	
	10-17.9 (5)	0.20	±0.18	1.90	0.40-9.10
	18-45 (19)	0.16	±0.08	1.82	0.66-5.00
Sex (N)	female (12)	0.25	±0.13	1	
	male (18)	0.17	±0.09	1.38	0.63-3.05
Time to relapse (N)	very early (10)	0.20	±0.13	1	
	early (2)	0.50	±0.35	0.50	0.04-5.87
	late (18)	0.17	±0.09	0.94	0.39-2.22

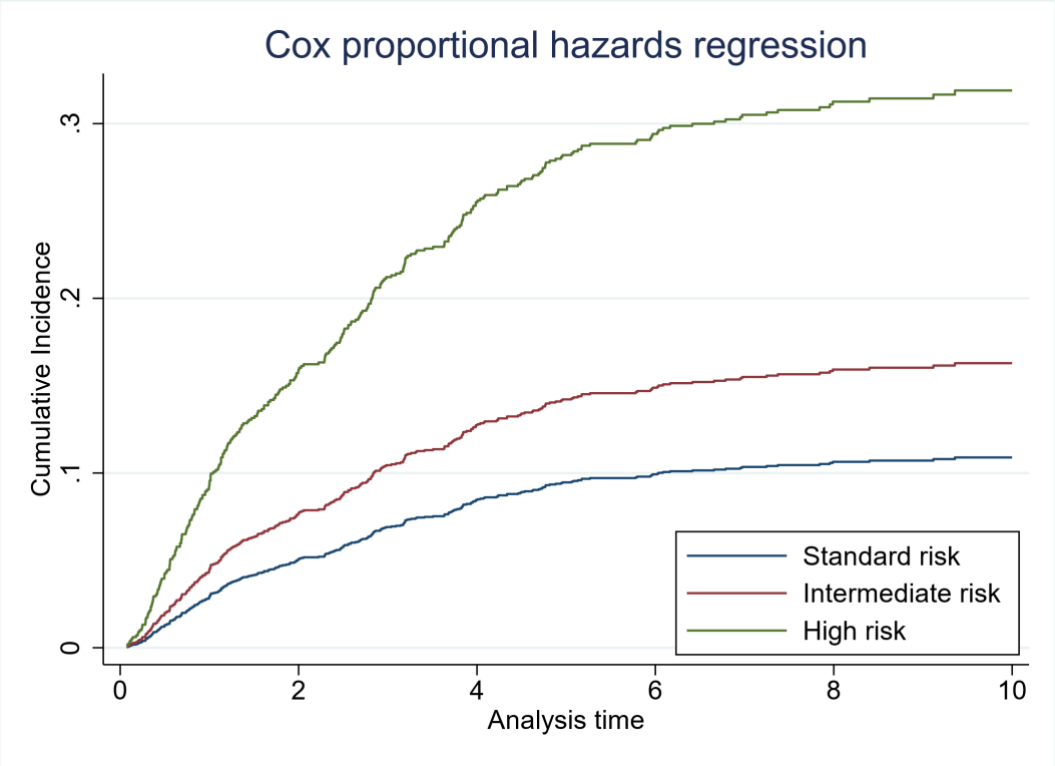
Supplementary Figure S1. Event-free survival (pEFS) at 5 years overall and in the final risk groups of the NOPHO ALL2008 trial by sex.



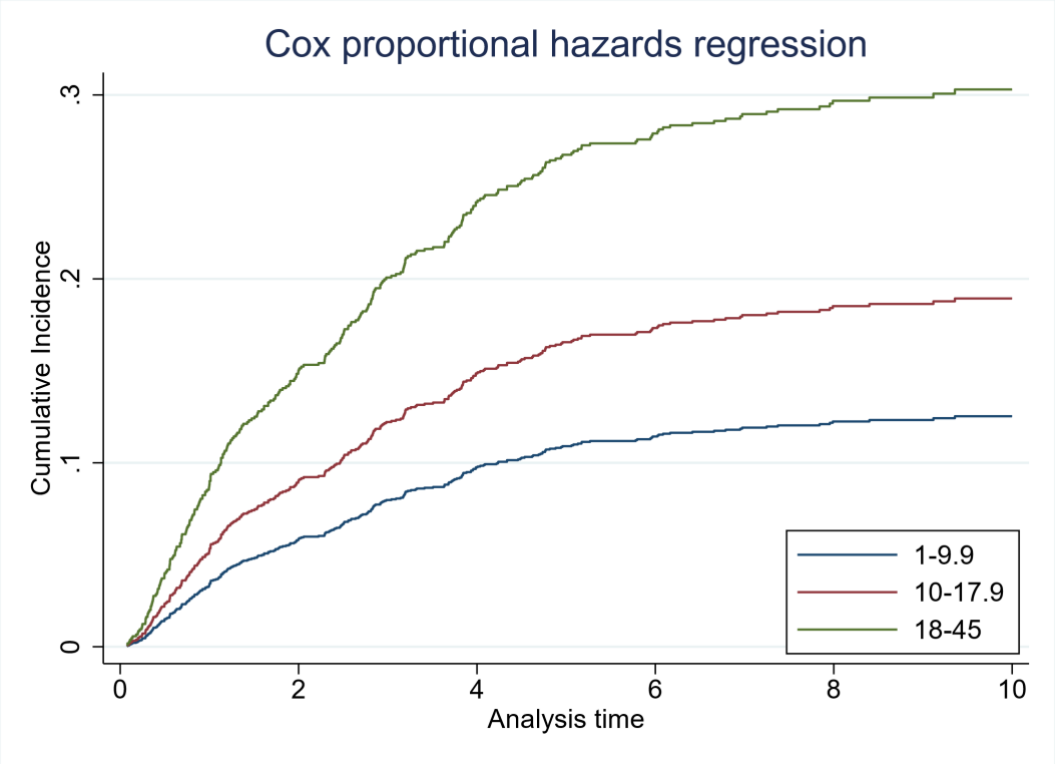

Intermediate risk
pEFS
1.00
0.75
0.50
0.25
0.00
Female, pEFS(5y) 0.85
Male, pEFS(5y) 0.86
Female vs Male, p=0.240
Male
Female
0
2
4
6
8
10
Years since diagnosis
Number at risk
Male 289 275 248 211 150 82
Female 339 310 290 246 167 87


High risk
pEFS
1.00
0.75
0.50
0.25
0.00
Female, pEFS(5y) 0.67
Male, pEFS(5y) 0.63
Female vs Male, p=0.533
Male
Female
0
2
4
6
8
10
Years since diagnosis
Number at risk
Male 131 89 80 73 56 30
Female 199 153 131 116 75 38

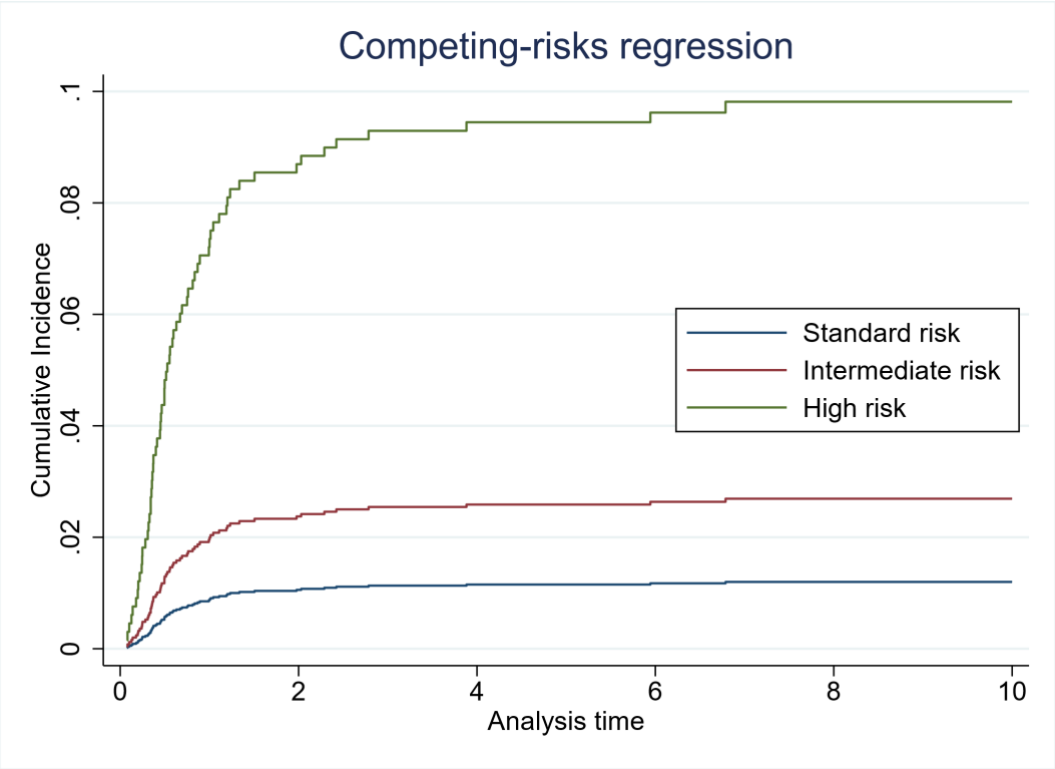
Supplementary Figure S2a. Predicted cumulative incidence of lower 5-year event-free survival in each risk group adjusted by sex and age group (patients without assigned risk group excluded, N=21).



Supplementary Figure S2b. Predicted cumulative incidence of lower 5-year event-free survival in each age group adjusted by sex and risk group (patients without assigned risk group excluded, N=21).



Supplementary Figure S2c. Predicted cumulative incidence of death in first complete remission (DCR1) in each risk group adjusted by sex and age group. Patients without assigned risk group excluded, N=21. Competing risks (relapse, second malignancy) taken into account.



Supplementary Figure S2d. Predicted cumulative incidence of relapse in each risk group adjusted by sex and age group. Patients without assigned risk group excluded, N=21. Competing risks (DCR1, second malignancy) taken into account.