Low platelet counts after induction therapy for childhood acute lymphoblastic leukemia are strongly associated with poor early response to treatment as measured by minimal residual disease and are prognostic for treatment outcome

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Online Supplementary Table S1. Number of patients with childhood acute lymphoblastic leukemia per quartile of blood cell counts during induction treatment (treatment days 8 and 15) and after induction treatment (treatment day 33).

	Day 8	Day 15	Day 33
Hemoglobin (g/L); patients per quartile			
Quartile 1	63	54	64
Quartile 2	58	70	65
Quartile 3	57	64	63
Quartile 4	78	63	57
Platelet count ($x10^9$/L); patients per quartile			
Quartile 1	61	61	62
Quartile 2	66	64	64
Quartile 3	65	63	61
Quartile 4	64	63	62
Absolute neutrophil count ($x10^9$/L)[a]; patients per quartile			
Quartile 1	62	57	55
Quartile 2	61	57	58
Quartile 3	62	58	57
Quartile 4	61	57	57
Absolute lymphocyte count ($x10^9$/L)[a]; patients per quartile			
Quartile 1	62	54	57
Quartile 2	60	60	57
Quartile 3	63	58	57
Quartile 4	61	57	56
Absolute monocyte count ($x10^9$/L)[a]; patients per quartile			
Quartile 1	64	57	57
Quartile 2	62	58	54
Quartile 3	56	57	61
Quartile 4	57	57	55

[a]*calculated from white blood cell counts and differential blood cell count percentages.*

Online Supplementary Table S2. Characteristics of 475 pediatric patients with acute lymphoblastic leukemia from the replication cohort in comparison to 256 patients from the initial cohort treated at Hannover Medical School from 1990 to 2005.

	Replication cohort n (%)	Initial cohort n (%)	P[f]
Gender			
male	259 (54.5)	135 (52.7)	
female	216 (45.5)	121 (47.3)	0.643
Age at diagnosis (years)			
<1	-	5 (2.0)	
1-<6	263 (55.4)	162 (63.3)	
6-<10	99 (20.8)	54 (21.1)	
≥10	113 (23.8)	35 (13.7)	0.001
Presenting WBC[a] ($x10^9$/L)			
<20	306 (64.4)	172 (67.2)	
20-<100	119 (25.1)	56 (21.9)	
≥100	50 (10.5)	28 (10.9)	0.630
Immunophenotype			
B	404 (85.1)	223 (87.1)	
T	69 (14.5)	28 (10.9)	0.197
unknown	2 (0.4)	5 (2.0)	
DNA index[b]			
<1.16	295 (62.1)	164 (64.1)	
≥1.16	60 (12.6)	35 (13.7)	0.837
unknown	120 (25.3)	57 (22.3)	
TEL/AML1[c]			
positive	123 (25.9)	27 (10.5)	
negative	320 (67.4)	103 (40.2)	0.111
unknown	32 (6.7)	126 (49.2)	
BCR/ABL			
positive	7 (1.5)	3 (1.2)	
negative	459 (96.6)	208 (81.2)	0.936
unknown	9 (1.9)	45 (17.6)	
MLL/AF4[c]			
positive	1 (0.2)	1 (0.4)	
negative	441 (92.8)	109 (42.6)	0.286
unknown	33 (7.0)	146 (57.0)	
Prednisone response[d]			
good	426 (89.7)	227 (88.7)	
poor	47 (9.9)	23 (9.0)	0.750
unknown	2 (0.4)	6 (2.3)	
Risk group[e]			
standard	198 (41.7)	80 (31.2)	
intermediate	202 (42.5)	144 (56.2)	
high	75 (15.8)	32 (12.5)	0.002

[a]WBC: white blood cell count; [b]ratio of DNA content of leukemic G_0/G_1 cells to normal diploid lymphocytes; [c]obligate screening for TEL/AML1 *fusion transcripts only in ALL-BFM 2000 and for* MLL/AF4 *only in ALL-BFM 95 and 2000; [d]good: <1000 leukemic blood blasts/μL on treatment day 8; poor: ≥1000/μL; [e]for different risk group stratification criteria see* Design and Methods *section, minimal residual disease-based stratification leading to an increase in standard risk patients was only performed in ALL-BFM 2000; [f]P Fisher's exact test for all 2x2 comparisons, all others* χ^2.

Online Supplementary Table S3. Univariate hazard ratios of an event: comparison of platelet counts in quartile 1 on treatment day 33 to established prognostic factors in the validation cohort.

	Hazard ratio	95% confidence interval	*P*
Platelets in quartile 1 on day 33[a,b]	2.28	1.46 - 3.56	<0.001
Female sex[c]	0.87	0.75 - 1.01	0.070
T-cell immunophenotype[d]	1.37	1.12 - 1.66	0.002
White blood cell count ≥100x10^9/L at diagnosis[e]	2.52	2.11 - 3.02	<0.001
Prednisone poor-response[f]	2.40	1.98 - 2.91	<0.001
BCR/ABL1 positivity[g]	3.47	2.49 - 4.84	<0.001
DNA-PCR MRD standard-risk[h]	0.27	0.21 - 0.34	<0.001
DNA-PCR MRD high-risk[i]	4.21	3.46 - 5.13	<0.001

[a]in comparison to platelet counts > quartile 1; [b]hazard ratio of platelets in quartile 1 on day 33 in the initial cohort was 2.89, 95% confidence interval 1.62-5.15; [c]in comparison to male sex; [d]in comparison to precursor B-cell immunophenotype; [e]in comparison to white blood cell count <100,000/μL at diagnosis; [f]in comparison to prednisone good-response (see Introduction *for explanation); [g]in comparison to* BCR/ABL1 *negativity; [h]in comparison to DNA-PCR MRD intermediate- and high-risk; [i]in comparison to DNA-PCR MRD standard- and intermediate-risk.*

Online Supplementary Table S4. Frequency of blood product transfusion during induction treatment in 256 patients with childhood acute lymphoblastic leukemia[a].

	Treatment week 1	Treatment week 2	Treatment week 3	Treatment week 4	Treatment week 5
Platelets					
Number of patients transfused (%)	103 (40.2)	67 (26.2)	33 (12.9)	16 (6.2)	13 (5.1)
Median number of transfusions in transfused patients (range)	4 (1-28)	2 (1-13)	2 (1-16)	1.5 (1-8)	2 (1-10)

[a]median time to end of induction (treatment day 33): 33 days (range 30 to 84 days).

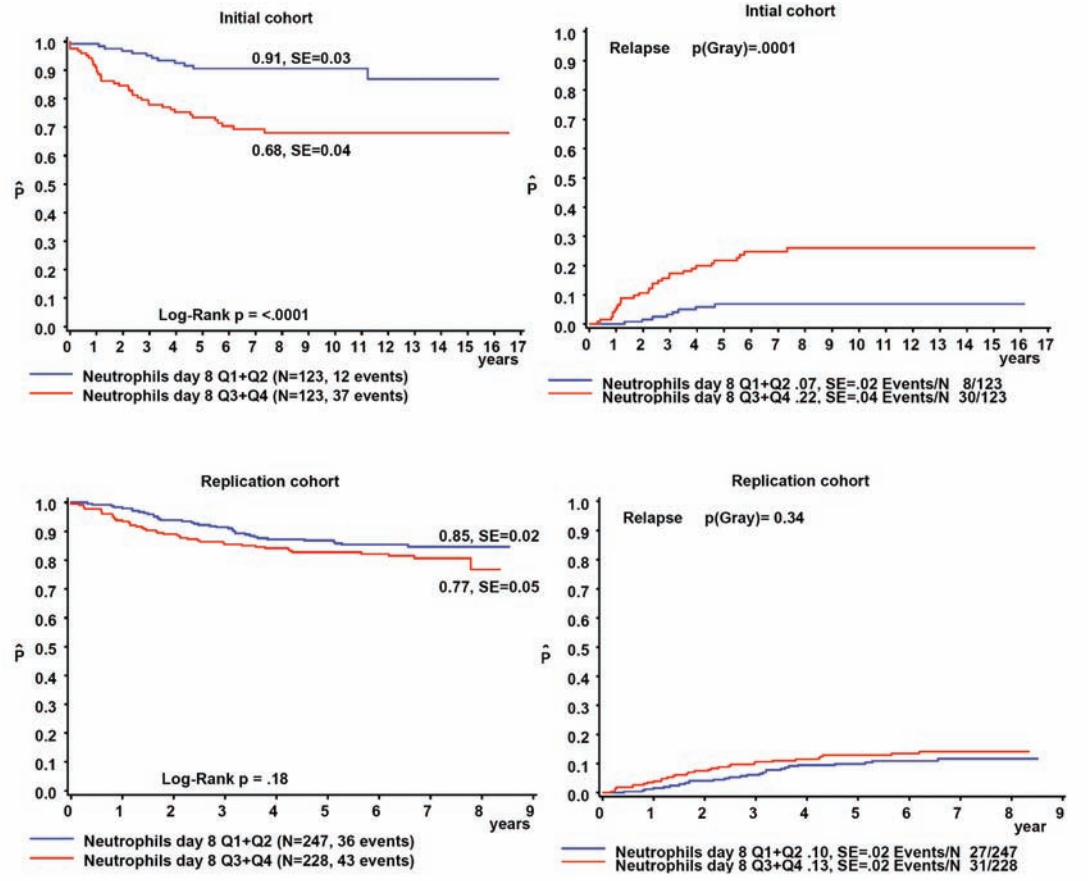

Figure 1. Neutrophil counts on day 8 categorized according to the median. Kaplan-Meier estimates of event-free survival at 8 years and cumulative incidences of relapse in the two cohorts.