# Anemia and survival in childhood acute lymphoblastic leukemia

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## ABSTRACT

### Background
Several studies have demonstrated that patients with childhood acute lymphoblastic leukemia presenting with mild anemia at diagnosis have an increased risk of poor outcome compared to patients with more severe anemia. However, it has not been reported whether there is any correlation between degree of anemia and leukemia subtype.

### Design and Methods
In a cohort of 1162 patients with childhood acute lymphoblastic leukemia we analyzed whether there was a correlation between degree of anemia and leukemia subtype. We also studied the association between degree of anemia and event-free survival within the subtypes.

### Results
Hemoglobin levels at diagnosis were distributed in a non-random pattern. The degree of anemia was significantly different for three distinct groups of patients compared to the remaining patients (mean hemoglobin; T-cell leukemia: 106 g/L versus 76 g/L (precursor B-cell acute lymphoblastic leukemia); within precursor B-cell ALL: *TEL-AML1* positive: 68 g/L versus 79 g/L; *BCR-ABL* positive: 93 g/L versus 76 g/L; each $p<0.05$). Furthermore, in contrast to the entire study group, patients with T-cell leukemia, *TEL-AML1*$^+$, and *BCR-ABL*$^+$ precursor B-cell leukemia had a more favorable prognosis if presenting with a higher hemoglobin level (≥80 g/L).

### Conclusions
These observations indicate that the formerly reported direct correlation between severity of anemia and survival in childhood acute lymphoblastic leukemia mainly reflects differences in the degree of anemia between distinct biological subgroups with different treatment outcomes. On the other hand, the inverse relationship between severity of anemia and survival found within specific subgroups suggests that very low hemoglobin levels at diagnosis are associated with more advanced disease in these subgroups.

Key words: childhood acute lymphoblastic leukemia, anemia, myeloid suppression, *TEL-AML1*.

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## Introduction

Anemia is common in patients with newly diagnosed childhood acute lymphoblastic leukemia (ALL). Several studies have demonstrated a correlation between degree of anemia and survival.[1-4] Evidence suggests that patients presenting with higher hemoglobin (Hb) levels at diagnosis have an increased risk of poor outcome compared to patients with lower Hb levels. However, in multivariate models, Hb was not identified as an independent risk factor.[3,4] Despite the fact that Hb is not applicable for risk stratification in clinical trials, the relationship between anemia and prognosis might hold some important biological information that warrants further investigation.

The pathomechanism of anemia in childhood ALL is not completely understood. Anemia in children with cancer is associated with decreased erythropoietic activity but not with inadequate erythropoietin production, leading to the assumption that anemia in patients with leukemia mainly results from suppression of normal hematopoiesis in the bone marrow by infiltrating blasts.[5,6]

To further understand the pathophysiology of anemia in childhood ALL, it is important to consider the heterogeneity of diseases in these patients, including immunological subgroups (precursor B-cell ALL versus T-cell leukemia) and cytogenetic subgroups (e.g. *TEL-AML1*, *E2A-PBX1*, *BCR-ABL*, hyperdiploid karyotype with >50 chromosomes, and *MLL* gene rearrangements).

The differences in clinical features at presentation between patients with T-cell leukemia and precursor B-cell ALL are well recognized and include higher Hb levels in patients with T-cell leukemia.[7-9] However, the prognostic influence of the initial Hb level in T-cell leukemia is controversial. In some studies, a higher Hb level was associated with a worse prognosis.[10,11] In other series, there was no association, or even an opposite association.[12,13] The Hb level at diagnosis is apparently not suitable for application in risk stratification strategies in current clinical trials.[14]

Precursor B-cell ALL is a heterogeneous disease comprising several distinct biological subtypes that are associated with different outcomes. Patients with t(1;19) leading to a *E2A-PBX1* gene fusion, hyperdiploidy involving more than 50 chromosomes, or *TEL-AML1* gene fusion have a favorable outcome, whereas those with t(4;11) leading to a *MLL-AF4* gene fusion and a t(9;22) leading to a *BCR-ABL* gene fusion have a dismal prognosis.[15] Despite the accurate analysis of the incidence and clinical relevance of these subtypes, it has not been reported whether there is any relationship between cytogenetic subtypes and degree of anemia.[16-21]

In the present study, we evaluated whether there is a correlation between degree of anemia and leukemia subtype. Furthermore, we studied the association between degree of anemia and event-free survival (EFS) within these subtypes of leukemia.

## Design and Methods

The present study utilized initial diagnostic characteristics of patients with ALL enrolled in the multicenter ALL-BFM 95 trial of the Berlin-Frankfurt-Munster (BFM) study group between April 1995 and June 2000 who underwent screening for fusion genes (*TEL-AML1, BCR-ABL, MLL-AF4*).[22] Differences in the distribution of parameters between subgroups of patients were examined using the $\chi^2$ or Fisher´s exact test. Survival probabilities were calculated using the Kaplan and Meier method with differences compared by the log-rank test; standard error were calculated according to Greenwood.[23-25] The probability of EFS (pEFS) was calculated from the date of diagnosis to the first event (death from any cause, tumor progression/relapse or non-response, or second malignancy) or to the date of last follow-up. The prognostic impact of anemia on treatment outcome was analyzed together with other known prognostic factors using Cox regression analysis.[26] Statistical analyses were performed using the SAS program (SAS-PC, version 9.1, Cary, NC: SAS Institute Inc.). The patients' follow-up data were updated as of October 2005.

## Results

Initially, we analyzed the Hb levels and the relation between anemia and survival in the entire group of patients. Based on 1162 peripheral blood samples, the mean Hb level at diagnosis was 80 g/L (standard deviation 27 g/L) (Table 1). Patients who presented with higher Hb levels at diagnosis (Hb ≥80 g/L) had an increased risk of poor outcome compared to patients with lower Hb levels (Hb <80 g/L) (pEFS: 0.76 versus 0.8, log-rank $p$=0.05).

To characterize the distribution of anemia in the heterogeneous group of patients with childhood ALL, the Hb levels were analyzed according to immunophenotypic and cytogenetic subtypes of ALL (Table 1).

**Table 1. Hemoglobin levels (in g/L) according to the immunological and cytogenetic subtypes of childhood acute lymphoblastic leukemia.**

| | *n* | *Hb, mean* | *Hb, s.d.* | *Hb, median* | *Hb, range* | *p-value* |
|---|---|---|---|---|---|---|
| All types of ALL | 1162 | 80 | 27 | 77 | 19-167 | |
| T-cell leukemia | 138 | 106 | 28 | 108 | 30-167 | <0.001 |
| Precursor B ALL* | 981 | 76 | 25 | 74 | 19-163 | |
| *TEL-AML1* positive | 241 | 68 | 20 | 66 | 19-163 | <0.001 |
| *TEL-AML1* negative | 740 | 79 | 26 | 78 | 25-156 | |
| DNA index ≥1.16 | 157 | 76 | 22 | 77 | 31-138 | 0.91 |
| DNA index <1.16 | 612 | 77 | 26 | 74 | 25-163 | |
| *BCR-ABL* positive | 23 | 93 | 31 | 86 | 34-156 | 0.01 |
| *BCR-ABL* negative | 946 | 76 | 25 | 74 | 19-163 | |
| *MLL-AF4* positive | 11 | 75 | 33 | 72 | 30-129 | 0.52 |
| *MLL-AF4* negative | 633 | 81 | 28 | 80 | 19-167 | |

**E2A-PBX1 positive precursor B-ALL were not analyzed separately.*

Patients with T-cell leukemia (n=138) presented with significantly higher Hb levels at diagnosis than patients with precursor B-cell ALL (n=981) (mean Hb level, 106 g/L versus 76 g/L; $p<0.001$). Within the group of patients with T-cell leukemia, an inverse relation between Hb level and hyperleukocytosis (leukocytes $\geq 100\times10^9$/L) was found (Table 2A). There was no association between degree of anemia and age among patients with T-cell leukemia (Table 2B).

Within the heterogeneous group of precursor B-cell ALL, the lowest mean Hb level was associated with *TEL-AML1*$^+$ leukemia (n=241) (mean Hb level 68 g/L). The mean Hb level was 75 g/L in *MLL-AF4*$^+$ leukemia (n=11), 76 g/L in hyperdiploid karyotype leukemia (n=157), and 93 g/L in *BCR-ABL*$^+$ leukemia (n=23). Considering only precursor B-cell ALL, the observed Hb levels were significantly different ($p<0.05$) for both the *TEL-AML1*$^+$ and *BCR-ABL*$^+$ subgroups compared to the remaining precursor B-cell ALL group (Table 1). Again, the association between anemia and hyperleukocytosis, and the influence of age, was evaluated for these two subgroups. As for T-cell leukemia, an inverse relation was found between Hb level and hyperleukocytosis (leukocytes $\geq 100\times10^9$/L) which was, however, only statistically significant in the *TEL-AML1*$^+$ subgroup (Table 2A). Furthermore, younger age (<10 years) was associated with lower Hb levels at diagnosis in both groups (Table 2B).

Patients enrolled in the ALL-BFM 95 trial did not undergo screening for the *E2A-PBX1* gene fusion. Therefore, anemia could not be analyzed separately in this subgroup of patients.

The second aim of this retrospective study was to evaluate whether there is an association between Hb level and prognosis within the subgroups. Due to a limited number of patients in the *MLL-AF4* group, this evaluation could only be performed for T-cell leukemia, *TEL-AML1*$^+$, *BCR-ABL*$^+$, and hyperdiploid karyotype precursor B-cell ALL.

Among children with T-cell leukemia, the Hb level at diagnosis was significantly associated with EFS. Patients presenting with lower Hb levels at diagnosis had an increased risk of poor outcome compared to patients with higher Hb level [(pEFS: 0.77 (Hb ≥80 g/L, n=114) versus 0.54 (Hb <80 g/L, n=24), $p=0.03$, and 0.82 (Hb ≥110 g/L, n=67) versus 0.65 (Hb <110 g/L, n=71), $p=0.03$)] (Figures 1 and 2). There was a trend for a similar difference in the *TEL-AML1*$^+$ subgroup. Again, an advantage was observed for patients with higher Hb level as compared to those with lower Hb levels [(pEFS: 0.97 (Hb ≥80 g/L, n=66) versus 0.89 (Hb <80 g/L, n=175), log-rank $p=0.12$, 6-year pEFS $p=0.01$)]. In addition, there was a significant association between anemia and EFS within the *BCR-ABL*$^+$ subgroup. Treatment failed in all patients who were diagnosed with *BCR-ABL* rearrangement in combination with lower Hb level at diagnosis [(pEFS: 0.35 (Hb ≥80 g/L, n=17) versus 0 (Hb <80 g/L, n=8), $p=0.02$)]. No substantial association was found between Hb level and prognosis for hyperdiploid karyotype leukemias [(pEFS: 0.85 (Hb ≥80 g/L, n=74) versus 0.88 (Hb <80 g/L, n=86), log-rank$p=0.52$, 6-year pEFS $p=0.51$)].

**Table 2. Hemoglobin levels (in g/L) according to initial leukocyte count (A) and age (B).**

| *Leukocytes [×10⁹/L]* | *<100* | | *≥100* | | *p-value* |
|---|---|---|---|---|---|
| | *n* | *Hb, mean* | *n* | *Hb, mean* | |
| **A** | | | | | |
| T-cell leukemia | 75 | 112 | 63 | 99 | 0.004 |
| *TEL-AML1* positive* | 231 | 68 | 10 | 50 | 0.002 |
| *BCR-ABL* positive* | 18 | 96 | 7 | 86 | 0.54 |

| *Age [years]* | *<10* | | *≥10* | | *p-value* |
|---|---|---|---|---|---|
| | *n* | *Hb, mean* | *n* | *Hb, mean* | |
| **B** | | | | | |
| T-cell leukemia | 81 | 103 | 57 | 110 | 0.14 |
| TEL-AML1 positive* | 220 | 66 | 21 | 79 | 0.02 |
| BCR-ABL positive* | 17 | 83 | 8 | 114 | 0.05 |

**Precursor B acute lymphoblastic leukemia.*

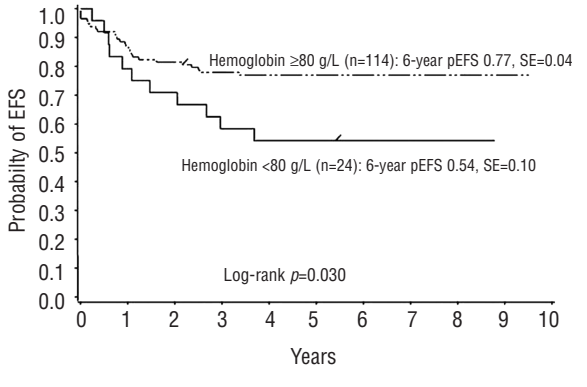


**Figure 1. Kaplan-Meier estimate of event-free survival of 138 children with T-cell leukemia according to the hemoglobin level at diagnosis. The cut-off hemoglobin level of 80 g/L is the mean value of the entire study group.**

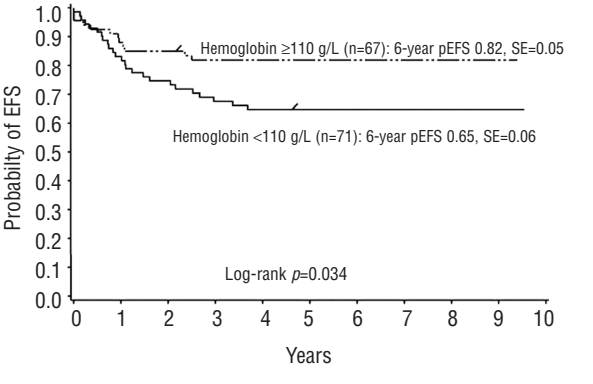


**Figure 2. Kaplan-Meier estimate of event-free survival of 138 children with T-cell leukemia according to hemoglobin level at diagnosis. The cut-off hemoglobin level of 110 g/L is the mean value within the group of patients with T-cell leukemias.**

To further evaluate the prognostic impact of Hb in T-lineage and *TEL-AML1*$^+$ *ALL*, Cox models were applied including factors such as Hb level (≥80 g/L) and leukocyte count (≥100×10$^9$/L) at diagnosis, age (≥10 years), and prednisone response (the presence of ≥1,000 blasts per microliter of peripheral blood at day 8 was defined as a prednisone poor response). Due to the limited number of patients, no Cox model was constructed for the *BCR-ABL* group. In T-cell leukemia, only a prednisone poor response was an independent prognostic factor (RR=5.74, 95%CI 2.62–11.44, $p$<0.001). All data including those for Hb, leukocytes, and age are presented in Table 3A. Applying the Cox model to the *TEL-AML1* subgroup, no independent risk factor could be identified (Table 3B). Thus, when adjusted for other risk factors, Hb is not an independent risk factor.

## Discussion

Anemia is a consistent hematologic finding at the diagnosis of childhood ALL. Here, we confirm the results of former studies in which a relationship between degree of anemia and outcome was observed. Severe anemia at diagnosis (Hb <80 g/L) was again associated with a better EFS than that in patients with only mild anemia (Hb ≥80g/L). However, the observed difference was only moderate and did not take into consideration the heterogeneity of childhood ALL.

Until now, no studies evaluated a possible correlation between degree of anemia and leukemia subtype. Our study demonstrates that Hb levels at diagnosis are distributed in a non-random pattern in childhood ALL. As expected, patients with T-cell leukemia presented with significanty higher Hb levels at diagnosis than did patients with precursor B-cell ALL. Although the basis for this difference is not well understood, it is likely that biological regulation of bone marrow infiltration, cell clone proliferation, and circulating peripheral blasts substantially differentiate T-cell leukemia from precursor B-cell ALL. In addition to the difference in the Hb level between T-lineage ALL and precursor B-cell leukemias, we also found a statistically significant difference in Hb level between both *BCR-ABL*$^+$ and *TEL-AML1*$^+$ ALL and precursor B-cell ALL without these fusions. Several studies have analyzed the clinical and biological features in ALL patients carrying the translocation t(12;21) leading to the *TEL-AML1* gene fusion.[27-38] None of those studies reported a low Hb level to be associated with *TEL-AML1*. One study addressed this issue, but failed to demonstrate a correlation between Hb and *TEL-AML1*, probably due to the limited number of patients analyzed (11/51 patients *TEL-AML1*$^+$).[39] However, a possible association between lower Hb levels at diagnosis and the *TEL-AML1* subtype were observed for the first time recently by a group from China.[40] The analysis of 95 pediatric ALL patients including 20 *TEL-AML1*$^+$ cases revealed a significantly lower Hb level in the *TEL-AML1*$^+$ patients than in the other patients (61 g/L versus 76 g/L; $p$=0.003). Their findings have now been confirmed by our data. We add significant information having evaluated a much larger group of patients and having conducted a comprehensive subgroup analysis.

Our data strongly suggest that there is a correlation between leukemia subtype and the degree of anemia indicating distinct mechanisms in the formation of erythropoietic insufficiency. Lower Hb levels (Hb <80 g/L) were more often diagnosed in leukemia subtypes associated with a favorable outcome (*TEL-AML1*$^+$, hyperdiploid karyotype). In contrast, more aggressive leukemia subtypes (T-cell leukemia and BCR-ABL$^+$ precursor B-cell leukemia) were associated with higher Hb levels (Hb ≥80 g/L).[22] We suppose that the correlation between degree of anemia and survival is due to the correlation between degree of anemia and the distinct biological subgroups that are associated with different outcomes.

Evaluating the *TEL-AML1*$^+$ subgroup, anemia was more pronounced among younger patients (<10 years). There was a trend for a similar difference in the *BCR-ABL*$^+$ subgroup. It is possible that lower baseline Hb levels in the younger population before developing leukemia might contribute to this finding; however, an additional impact of other biological factors cannot be excluded. Patients carrying the *TEL-AML1* translocation are overrepresented in the younger age group (<10 years). We think it is rather unlikely that lower baseline Hb levels before developing leukemia exclusively contributes to the strong association of *TEL-AML1* and severe anemia (Hb <80 g/L). This assumption is based upon the observation that the mean Hb level was lower in the *TEL-AML1* subgroup than in the other subgroups in older patients (>10 years).

As regards the predictive power of Hb level in subgroups, the literature data on the prognostic influence of Hb in T-cell leukemia are controversial.[10-13] Based on our data, higher Hb levels in this group of patients were clearly associated with better outcome compared to lower Hb levels. We observed a similar trend in the *TEL-*

**Table 3. Cox regression analysis in T-cell leukemia (A) and TEL-AML1 positive precursor B acute lymphoblastic leukemia (B): Risk ratios and 95% confidence interval.**

| *Risk factors*[a] | *RR*[b] | *LL* | *UL* | *p* |
|---|---|---|---|---|
| **A** | | | | |
| Moderate/mild anemia | 0.71 | 0.34 | 1.48 | 0.36 |
| Hyperleukocytosis | 1.36 | 0.67 | 2.75 | 0.40 |
| Older age | 1.96 | 0.98 | 3.93 | 0.06 |
| Prednisone poor response | 5.47 | 2.62 | 11.44 | <0.001 |
| *Risk factors*[a] | *RR*[b] | *LL* | *UL* | *p* |
| **B** | | | | |
| Moderate/mild anemia | 0.45 | 0.13 | 1.57 | 0.21 |
| Hyperleukocytosis | 0.36 | 0.03 | 3.99 | 0.40 |
| Older age | 0.76 | 0.10 | 5.85 | 0.79 |
| Prednisone poor response | 4.88 | 0.88 | 27.17 | 0.07 |

*RR: risk ratios; LL: lower limit; UL: upper limit. [a]definition of risk factors: moderate/mild anemia (Hb ≥80 g/L), hyperleukocytosis (leukocyte count ≥100×10$^9$/L), older age (≥10 years), prednisone poor response (the presence of ≥1,000 blasts/μL peripheral blood at day 8 of treatment). [b]RR related to the first event after diagnosis (death from any cause, tumor progression/relapse or non-response, or second malignancy)*

*AML1*$^+$ subgroup. Due to an unusual late relapse, there was no overall significance in this group using the log-rank test, however, EFS at 6 years was significantly different between the two groups. Despite a limited number of patients (n=25), estimation of EFS revealed striking differences within the subgroup of *BCR-ABL*$^+$ precursor B-cell leukemia. Again, a low Hb level at diagnosis was an adverse prognostic marker. Despite the reported (univariate) association between anemia and EFS within the mentioned subgroups, the Hb level at diagnosis was not an independent risk factor and, therefore, of negligible value for risk assignment. The predictive power of treatment response was much stronger than that of the initial Hb level.

To summarize, initial degree of anemia in childhood ALL is non-randomly distributed. Moreover, in contrast to the group of patients considered as a whole, patients with T-cell leukemia, *TEL-AML1*$^+$, and *BCR-ABL*$^+$ precursor B-cell leukemia have a more favorable prognosis if presenting with higher Hb levels. Given that it was observed in several series that a higher Hb level is associated with poorer outcome, it was assumed that this reflects conditions with a high proliferation rate of an aggressive leukemic cell clone (*shorter history in fast disease*).[41,42] Based on our data, this hypothesis is not sustainable for (at least) the three ALL subtypes mentioned above. This is further supported by the observation that hyperleukocytosis was associated with lower Hb levels. We suggest that lower Hb levels or severe anemia at diagnosis might correspond to conditions of advanced disease. It is possible that patients presenting with higher Hb levels or mild anemia are detected at an early stage of disease, and are, therefore, more susceptible to chemotherapeutic interventions.

## Authorship and Disclosures

OT: prepared the study, collected data, and wrote the manuscript; MS: designed the study, and contributed to the analysis and interpretation of the data and to writing the manuscript; GC, WDL: collected and analyzed data; SL: collected data and contributed to writing manuscript; BWS: analyzed and interpreted data and contributed to writing manuscript; MZ: analyzed data and performed the statistical analyses; MS: collected, analyzed and interpreted the data, designed the study and wrote manuscript; FKN: collected and interpreted data, designed the study and wrote the manuscript.

The authors reported no potential conflicts of interest.

## References


1. Santana VM, Dodge RK, Crist WM, Rivera GK, Look AT, Behm FG, et al. Presenting features and treatment outcome of adolescents with acute lymphoblastic leukemia. Leukemia 1990;4:87-90.
2. Reiter A, Schrappe M, Ludwig WD, Hiddemann W, Sauter S, Henze G, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. Blood 1994;84:3122-33.
3. Donadieu J, Auclerc MF, Baruchel A, Leblanc T, Landman-Parker J, Perel Y, et al. Critical study of prognostic factors in childhood acute lymphoblastic leukaemia: differences in outcome are poorly explained by the most significant prognostic variables. Fralle group. French Acute Lymphoblastic Leukaemia study group. Br J Haematol 1998;102:729-39.
4. Hann I, Vora A, Harrison G, Harrison C, Eden O, Hill F, et al. Determinants of outcome after intensified therapy of childhood lymphoblastic leukaemia: results from Medical Research Council United Kingdom acute lymphoblastic leukaemia XI protocol. UK Medical Research Council's Working Party on Childhood Leukaemia. Br J Haematol 2001;113:103-14.
5. Dowd MD, Morgan ER, Langman CB, Murphy S. Serum erythropoietin levels in children with leukemia. Med Pediatr Oncol 1997;28:259-67.
6. Corazza F, Beguin Y, Bergmann P, André M, Ferster A, Devalck C, et al. Anemia in children with cancer is associated with decreased erythropoietic activity and not with inadequate erythropoietin production. Blood 1998;92:1793-8.
7. Greaves MF, Janossy G, Peto J, Kay H. Immunologically defined subclasses of acute lymphoblastic leukaemia in children: their relationship to presentation features and prognosis. Br J Haematol 1981;48:179-97.
8. Pullen DJ, Boyett JM, Crist WM, Falletta JM, Roper M, Dowell B, et al. Pediatric Oncology Group utilization of immunologic markers in the designation of acute lymphocytic leukemia subgroups: influence on treatment response. Ann N Y Acad Sci 1984;428:26-48.
9. Pui CH, Behm FG, Crist WM. Clinical and biologic relevance of immunologic marker studies in childhood acute lymphoblastic leukemia. Blood 1993;82:343-62.
10. Shuster JJ, Falletta JM, Pullen DJ, Crist WM, Humphrey GB, Dowell BL, et al. Prognostic factors in childhood T-cell acute lymphoblastic leukemia: a Pediatric Oncology Group study. Blood 1990;75:166-73.
11. Steinherz PG, Siegel SE, Bleyer WA, Kersey J, Chard R Jr, Coccia P, et al. Lymphomatous presentation of childhood acute lymphoblastic leukemia. A subgroup at high risk of early treatment failure. Cancer 1991;68:751-8.
12. Pui CH, Behm FG, Singh B, Schell MJ, Williams DL, Rivera GK, et al. Heterogeneity of presenting features and their relation to treatment outcome in 120 children with T-cell acute lymphoblastic leukemia. Blood 1990;75:174-9.
13. Advani S, Pai S, Venzon D, Adde M, Kurkure PK, Nair CN, et al. Acute lymphoblastic leukemia in India: an analysis of prognostic factors using a single treatment regimen. Ann Oncol 1999;10:167-76.
14. Pullen J, Shuster JJ, Link M, Borowitz M, Amylon M, Carroll AJ, et al. Significance of commonly used prognostic factors differs for children with T cell acute lymphocytic leukemia (ALL), as compared to those with B-precursor ALL. A Pediatric Oncology Group (POG) study. Leukemia 1999;13:1696-707.
15. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med 2004;350:1535-48.
16. Schrappe M, Reiter A, Ludwig WD, Harbott J, Zimmermann M, Hiddemann W, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German-Austrian-Swiss ALL-BFM Study Group. Blood 2000;95:3310-22.
17. Gaynon PS, Trigg ME, Heerema NA, Sensel MG, Sather HN, Hammond GD, et al. Children's Cancer Group trials in childhood acute lymphoblastic leukemia: 1983-1995. Leukemia 2000;14:2223-33.
18. Harms DO, Janka-Schaub GE. Cooperative study group for childhood acute lymphoblastic leukemia (COALL): long-term follow-up of trials 82, 85, 89 and 92. Leukemia 2000;14:2234-9.
19. Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood 2001;97:1211-8.
20. Gustafsson G, Schmiegelow K,

Forestier E, Clausen N, Glomstein A, Jonmundsson G, et al. Improving outcome through two decades in childhood ALL in the Nordic countries: the impact of high-dose methotrexate in the reduction of CNS irradiation. Nordic Society of Pediatric Haematology and Oncology (NOPHO). Leukemia 2000;14:2267-75.
21. Pui CH, Sandlund JT, Pei D, Rivera GK, Howard SC, Ribeiro RC, et al. Results of therapy for acute lymphoblastic leukemia in black and white children. JAMA 2003;290: 2001-7.
22. Möricke A, Reiter A, Zimmermann M, Gadner H, Stanulla M, Dördelmann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. German-Austrian-Swiss ALL-BFM Study Group. Blood 2008;111:4477-89.
23. Kaplan EI, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
24. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163-70.
25. Kalbfleisch EL, Prentice RL. The Statistical Analysis of Failure Time Data. New York, NY: John Wiley 1980. p. 163-88.
26. Cox DR. Regression models and life tables. J R Stat Soc 1972;34:187-220.
27. Shurtleff SA, Buijs A, Behm FG, Rubnitz JE, Raimondi SC, Hancock ML, et al. TEL/AML1 fusion resulting from a cryptic t(12;21) is the most common genetic lesion in pediatric ALL and defines a subgroup of patients with an excellent prognosis. Leukemia 1995;9:1985-9.
28. McLean TW, Ringold S, Neuberg D, Stegmaier K, Tantravahi R, Ritz J, et al. TEL/AML-1 dimerizes and is associated with a favorable outcome in childhood acute lymphoblastic leukemia. Blood 1996;88:4252-8.
29. Liang DC, Chou TB, Chen JS, Shurtleff SA, Rubnitz JE, Downing JR, et al. High incidence of TEL/AML1 fusion resulting from a cryptic t(12;21) in childhood B-lineage acute lymphoblastic leukemia in Taiwan. Leukemia 1996;10:991-3.
30. Borkhardt A, Cazzaniga G, Viehmann S, Valsecchi MG, Ludwig WD, Burci L, et al. Incidence and clinical relevance of TEL/AML1 fusion genes in children with acute lymphoblastic leukemia enrolled in the German and Italian multicenter therapy trials. Associazione Italiana Ematologia Oncologia Pediatrica and the Berlin-Frankfurt-Munster Study Group. Blood 1997;90:571-7.
31. Rubnitz JE, Downing JR, Pui CH, Shurtleff SA, Raimondi SC, Evans WE, et al. TEL gene rearrangement in acute lymphoblastic leukemia: a new genetic marker with prognostic significance. J Clin Oncol 1997;15: 1150-7.
32. Takahashi Y, Horibe K, Kiyoi H, Miyashita Y, Fukuda M, Mori H, et al. Prognostic significance of TEL/AML1 fusion transcript in childhood B-precursor acute lymphoblastic leukemia. J Pediatr Hematol Oncol 1998;20:190-5.
33. Maloney K, McGavran L, Murphy J, Odom L, Stork L, Wei Q, et al. TEL-AML1 fusion identifies a subset of children with standard risk acute lymphoblastic leukemia who have an excellent prognosis when treated with therapy that includes a single delayed intensification. Leukemia 1999;13:1708-12.
34. Jamil A, Theil KS, Kahwash S, Ruymann FB, Klopfenstein KJ. TEL/AML-1 fusion gene. Its frequency and prognostic significance in childhood acute lymphoblastic leukemia. Cancer Genet Cytogenet 2000;122:73-8.
35. Tsang KS, Li CK, Chik KW, Shing MM, Tsoi WC, Ng MH, et al. TEL/AML1 rearrangement and the prognostic significance in childhood acute lymphoblastic leukemia in Hong Kong. Am J Hematol 2001;68: 91-8.
36. Ozbek U, Sirma S, Agaoglu L, Yuksel L, Anak S, Yildiz I, et al. Prognostic significance of the TEL-AML1 fusion gene in pediatric acute lymphoblastic leukemia in Turkey. J Pediatr Hematol Oncol 2003; 25:204-8.
37. Stams WA, den Boer ML, Beverloo HB, Meijerink JP, van Wering ER, Janka-Schaub GE, et al. Expression levels of TEL, AML1, and the fusion products TEL-AML1 and AML1-TEL versus drug sensitivity and clinical outcome in t(12;21)-positive pediatric acute lymphoblastic leukemia. Clin Cancer Res 2005;11:2974-80.
38. Loh ML, Goldwasser MA, Silverman LB, Poon WM, Vattikuti S, Cardoso A, et al. Prospective analysis of TEL/AML1-positive patients treated on Dana-Farber Cancer Institute Consortium Protocol 95-01. Blood 2006;107:4508-13.
39. Lin D, Liu SH, Zhu XF, Bo LJ, Li CW, Chen YM, et al. [Study of the childhood acute lymphoblastic leukemia with t(12;21)]. Zhonghua Xue Ye Xue Za Zhi 2004;25:17-21.
40. Guo X, Li Q, Zhu YP, Zhou CY, Gao J, Li XH, et al. [Comparative study on clinical features between TEL-AML1 positive and negative childhood acute lymphoblastic leukemia]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2007;24:560-3.
41. Hirt A, Leibundgut K, Luthy AR, von der Weid N, Wagner HP. Cell birth and death in childhood acute lymphoblastic leukaemia: how fast does the neoplastic cell clone expand? Br J Haematol 1997;98:999-1001.
42. Kanerva J, Saarinen-Pihkala UM, Niini T, Riikonen P, Möttönen M, Mäkipernaa A, et al. Favorable outcome in 20-year follow-up of children with very-low-risk ALL and minimal standard therapy, with special reference to TEL-AML1 fusion. Pediatr Blood Cancer 2004;42:30-5.