Prognostic factors of adult acute lymphoblastic leukemia and their impact on treatment outcome and long term survivals

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Abstract

Aim: To assess the prognostic factors of our adult ALL patients and their correlation to long term leukemia free (LFS) and overall (OS) survivals.

Patients and methods: Hundred and fifteen patients were included, they were stratified according to their prognostic factors into standard (SR), high (HR), and very high risk (VHR) groups.

Treatment plan:

Induction phase I: Vincristine, Doxorubicin, L-Asparaginase and prednisone with intrathecal MTX. Patients that attained CR were subjected to cranial irradiation and intrathecal MTX.

Phase II induction:Cyclophosphamide and Cytarabine.

Consolidation phase I: Vincristine, Doxorubicine and prednisone with Triple intrathecal.

Phase II consolidation: Cyclophosphamide, Cytarabine and Etoposide with triple intrathecal. **Maintenance therapy**: 6 mercaptopurine and methotrxate. For patients below 50 years with HR and VHR, one cycle of (HAM regimen) was added between induction and consolidation. VHR patients were referred to transplantation in CR1**.**

Results: The median age was 25 years. The study included 73 males and 42 females. Immunophenotypes were pro B (7%), CALL/Pre B (56.5%) and T phenotype (20.9%).The BCR-ABL and ALL1-AF4 fusion gene transcripts were positive in 15 and 4 of the precursor B cases respectively. Forty five patients were SR while 55 and 15 were HR and VHR respectively. CR was achieved in 76.5%. CR of the SR was 88.9% versus 70.9% and 60% for HR and VHR respectively. Median OS was 14 months. Survival at 60 months was 28.24 %, it was 34%, 21% and 20.7% for SR, HR and VHR respectively. There was significant survival difference between pro-B, Pre B /CALL and T phenotypes. Median time to progression was 16 months. At 60 months, 35.2% were still in remission. Time to progression was 44, 12 and 14 months for the SR, HR and VHR groups respectively, While it was 3, 17 and 16 months for Pro-B, pre-B/C-ALL, and T phenotypes respectively**.**

Conclusion: The CR, LFS and OS of the SR are satisfactory while those of the HR and VHR are still in need to be improved; whether we can achieve this by higher post remission chemotherapy, targeted therapy or stem cell transplantation remains to be investigated.

Introduction

ALL represents about 20% of adult leukemia. The median age in most registries varies between 25 and 35 years and 25% of patients are older than 15 years. ALL is diagnosed with an overall incidence of 1 to 1.5 per 100,000 population, but it has a bimodal age distribution: an early peak at around 4 to 5 years where the incidence may be as high as 4 to 5 per 100,000 population and a second gradual increase at around age 50 where it reaches up to 2 per 100,000 populations. (1, 2). For many years, adults with ALL have been treated with multi agent chemotherapy in the induction and post-remission settings. Most trials in adults were based loosely on regimens that were beneficial in children with high-risk disease, although at best, 40% of all adults with ALL achieved long-term disease-free survival, compared with 80% to 90% success rates in children with the same disease (3)

Despite improvements in the achievement of complete remission and progress in the supportive care of adults with acute lymphoblastic leukemia during the last decade, the majority of patients have eventually relapsed with overall survival of only 30-40%. However, the recent approach of adapting therapy according to biologic features appears to be resulting in significant progress for specific subsets of adults with acute lymphoblastic leukemia (4)

In the pre-imatinib era the prognosis for patients whose leukemic blast cells carry the BCR-ABL fusion created by t (9; 22) is poor with DFS rates of less than 10% with chemotherapy and 10% to 35% with allogeneic stem-cell transplantation. (5)

The aim of this study was to improve the leukemia-free survival of our adult ALL Cases through more intensified post remission therapy and to weigh benefits versus risks of stratifying the patients to treatment protocol according to their prognostic criteria. We are also reporting, for the first time, in this study the 5 years LFS and OS figures of our cases.

Patients and Methods

Hundred and fifteen patients were included in this study between December 1999 and March 2004; patients were followed up for OS and LFS till March 2009. The diagnosis of ALL was performed according to standard clinical, radiological and laboratory workup. At presentation, patients were subjected to complete blood count, bone marrow examination and cytochemistry and immunophenotyping.

BCR / ABL as well as ALL1/AF4 fusion gene transcripts detection by RT – PCR were tested in the precursor B phenotype group. Exclusion criteria included mature B phenotype and age > 60 years. Before the start of treatment blood electrolytes and chemistries were done to test for organ functions and CSF examination for possible CNS involvement at presentation. The patients were then classified into standard, high and very high risk groups. The criteria for risk stratifications are summarized in table (1). The patient was considered high risk when at least one unfavorable criterion was present and very high risk when BCR / ABL fusion gene transcripts were detected by RT – PCR.

The treatment plan was risk adjusted, SR versus HR and VHR groups and was modified according to patient's age. Table (2), Fig (1)

Treatment regimen for the standard risk patients consisted of:-

Prephase for patients with TLC > 25 x 109/L and/or organomegaly included: vincristine 2 mg Day 1 and prednisone 60 mg / m^2 P.O. Day 1 to Day 7.

Phase I Induction: Four drugs:

- Vincristine 1.4 mg/m^2 days 1, 8, 15, 22
- Daunorubicin 45 mg/m^2I.V. days 1, 8 , 15, 22
- L- Asparaginase: 5000 U/$m^2$30 minute infusion days 15 to 28.
- Prednisone: 60 mg/m^2 P.O. day 1 through 28.
- Intrathecal methotrexate 15 mg on day 1.

Patients who attained CR after phase I induction were subjected to CNS prophylaxis including cranial irradiation (24 Gy) and intrathecal methotrexate 15 mg twice weekly for four injections. Phase II induction:

Started when neutrophils count is ≥ 1500/L and platelet count is ≥ 100 x 109 / L and include:

- Cyclophosphamide 650 mg/m^2 I.V. short infusion on days 1, 14 and 28.
- Cytarabine 75 mg/m^2 short infusion four days a week for 4 weeks.

Phase I Consolidation :

- Vincristine: 2mg days 1, 8, 15, 22
- Adriamycin: 25 mg/m^2 days 1, 8, 15 and 22
- Prednisone: 60 mg/m^2 P.O. days 1 through 28 with gradual tapering.
- Triple intrathecal injection of: Methotrexate 15 mg, Cytarabine 40 mg and Dexamethazone 4 mg.

Phase II consolidation:

- Cyclophospamide 650 mg / m^2 short infusion day 1.
- Cytarabine 75 mg/m^2 short infusion days 3, 4, 5, 6 and days 9, 10, 11, 12 then cytarabine 100 mg/m^2 short infusion days 25, 26, 27 and 30.
- Vepesid 100 mg/m^2 short infusion days 25, 26, 27 and 30.
- Triple intrathecal injection

Maintenance therapy:

Given for two years with:

- 6 mercaptopurine 60 mg /m^2 P.O daily
- Methotrexate 20 mg/m^2 I.V weekly.

Blood picture should be checked on a weekly basis.

- Maintenance triple intrathecal injection was given every two months till the end of maintenance therapy

HR and VHR patients above age of 50 years were treated as the standard risk group while those below age of 50 years, one cycle of high dose cytarabine and mitoxantrone (HAM regimen) was added between induction and consolidation.

HR and VHR cases below age of 50 years with available donor for transplantation were referred to allogeneic transplantation in CR1.

Imatinib methylate therapy was not given in this study as the study was planned before its establishment as an essential drug in the treatment of the VHR patients. Informed consents were signed by all cases.

Statistical Analysis

Statistical Package for social sciences (SPSS) version 12 was used for data analysis. Kaplan Meier was used for estimating survival and Log rank for comparing curves. P is significant at ≤ 0.05.

Results

Between December 1999 and March 2004, 115 patients were included and followed up till March 2009. The median age was 25 years with a range of 16 to 60 years. Seventy three patients (63.5%) were males and 42(36.5%) were females. CNS disease at presentation was reported in 14 cases (12.2%).The patients' main clinical presentations are summarized in table (3).

The median TLC was 21 x 10^9 /L (Range 0.5 to 423) with TLC ≤30 x 10^9 in 58.3% of cases. The median HB level was 7.4 gm /dl (Range 2.2 to 13.4) with HB level ≤ 6 gm / dl in 38.3%. The median platelet count was 39.5 x 10^3 /L (Range 10 to 330). Platelet count ≤ 25 x 10^9 /L was encountered in 34.3%. The median bone marrow blasts was 88 % (Range 32 to 99%). The immunophenotyping results were pro B in 8cases (7%), CALL/Pre B in 65cases (56.5%), and T phenotype was reported in 24cases (20.9%), the immunophenotype was not available in18 cases (15.7%).The BCR-ABL fusion gene transcript was positive in 15 (20.5%) and ALL1-AF4 fusion genes transcripts was reported in 4 (5.47%) of the precursor B phenotype cases.

According to their prognostic factors, patients were stratified into SR group (n=45), HR group (n=55), and VHR group (n=15).The main reported toxicities of the induction phase are summarized in table (4)

Complete remission was achieved in 76.5% (n = 88). The CR rate was 88.9%, 70.9% and 60% for the SR, HR and VHR groups respectively (p=0.029).Only three cases, belonging to the very high risk group, were subjected to allogeneic transplantation as post-remission therapy.

The median survival for all patients was 14 months (95% CI, 9.2 to18.8), survival at 36 and 60 months was 30.12 % and 28.24 % respectively. Survival curve for all patients is shown in fig (2). For the SR group, the median OS was 21months, with 3 and 5-years OS of 42.56% and 34% respectively. For the HR group, the median OS was 8 months with 3 and 5 -years OS of 21%. While the median OS of the VHR group was 7 months with 3 and 5-years OS rate of 20.7%.There was significant difference in OS between patients with SR, HR and VHR (P=0.017) (Fig 3). There was also a statistically significant difference in OS between patients with pro-B, pre-B/C ALL, and T phenotype (p=0.0019) (Fig 4)

The median time to progression was 16 months (95% CI, 13.5to 18.5) (Fig5).The LFS at 3 and 5 years was 40.6% and 35.2% respectively. Time to progression was 44, 12 and 14months for the SR, HR and VHR groups respectively (p=0.047) (Fig6). Time to progression of patients with Pro-B, pre-B/C-ALL, and T phenotype was 3, 17 and 16 months respectively (p=0.0007) (Fig 7)

Discussion

This study was conducted on 115 adult ALL patients. The median age was 25 years (range16 to 60) in comparison to a median of 35(Range 15 to 65) in the

GMALL trial (6), and 33(Range 15 to 55) in the LALA-94 trial. (7). Age is probably the most important prognostic factor (3). Age of 35 years appears to be a clear prognostic cut off for adult ALL (8). OS continuously decreases with increasing age from 34-57% below 30 years to 15-17% above 50years (9, 10, 11&12). Although major improvement in survival was observed for patients less than 60 years, survival for patients aged 60 years or more remained unchanged at a level of around 10% (13). This group older than 60 years were treated with COAP regimen and were not included in this study. A male predominance was reported in our study with a male to female ratio of 1.74/1, which is nearly equal to the ratio of 1.82/1 reported in LALA-94(7) and documents the male predominance of ALL reported in our previous studies (14,15). Female gender is proposed to be one of the new clinical prognostic factors in recent analysis (16, 13). The median TLC at presentation in this study was 21 x 10^9/L (0.5 – 423) which is nearly equal to a median of 22.4 x 10^9/l (0.5-423x10^9/L) reported by our previous study (15). Presenting TLC ≥30 x 10^9/L for precursor-B cell and ≥100 x 10^9 /L for T cell ALL is of bad prognosis (8). In our study 41.7% of patients presented with a TLC ≥ 30 x 10^9 /L compared to 38% reported at the LALA-94 trial (7) .In GMALL studies TLC ≥30 x 10^9/L in precursor-B ALL (CALL/pre B) was considered the most deleterious prognostic factor with overall survival of 19-29% (6, 16), while in T –ALL the TLC was not a significant factor in multivariate analysis (6).High TLC may be associated with risk of complications during induction and higher risk of CNS relapse (16)

The immunophenotyping results in our study were pro B (7%), CALL/Pre B (56.5%), T phenotype was reported in 20.9%. these data are comparable to a precursor-B phenotype of 72% and a T phenotype of 26 % reported in the LALA-94 trial(7). Many groups confirmed the superior outcome of T cell compared to precursor-B cell phenotypes in adult ALL (6, 8&10). Pro B and/or t (4; 11) ALL is considered a poor prognostic subtype in many trials (16). In the GMALL, Pro B is considered an indication for SCT in CR1 (16) denoting its independent prognostic significance, a finding which is also documented in our study. CALL/Pre-B bears a large proportion of ph/BCR-ABL+ ALL and pre-B is associated with about 4% t (1; 19) (7, 16). According to the associated cytogenetic abnormalities Pre-B/CALL can be subdivided into high, very high or standard risk cases. The BCR-ABL fusion gene transcript was positive in 15 of our precursor B cases (20.5%) compared to 23% and 24 % Philadelphia positive in adult ALL reported by others(7,16). Ph+ ALL occurs in 20-30% of adult ALL with higher incidence in precursor B cases compared to 3-5% of children and it is generally associated with poor prognosis (5,13).The frequency of ALL1/AF4 fusion gene in the German series (17) is 6% which is comparable to 5.47% in ours. In our study 39% and 48% were allocated to the SR and HR groups, compared to 48% and 33% respectively in the GMALL studies (17)

Complete remission was achieved in 76.5% compared to 83% reported in GMALL trial (16) and 84% reported in LALA-94 trial (7). The CR rate of the large trials in adult ALL ranged between 74-93% with a mean of 83% (16). In the GMALL studies(16,17), the CR rate of the precursor-B lineage standard risk group was 88% compared to 87% in the T lineage standard risk which is comparable to the CR rate of 88.9% in our SR group. The CR rate of the HR and VHR groups in our study was 70.9 and 60 % respectively compared to 83 and 77% in the GMALL Trial (17). In our study the CR rate of the ph+ve group was 60% compared to 51% in the pre-imatinib era (18)

In our study the median OS for all patients was 14 months, survival at 36 and 60 months were 30.12 % and 28.24 % respectively. The median OS of the SR group was 21months, with 3 and 5years OS of 42.56% and 34% respectively. Median OS of the HR group was 8 months with 3 and 5-year OS of 21% while the median OS of the VHR group was 7 months with 3 and 5years OS rate of 20.7%. In the LALA-94 trial(7), the reported median OS was 23 months, Patients with *SR- ALL showed a* Median OS of 37.8 months, with 3 and 5-years OS of 50% and 44%respectively. The median OS of the high risk patients was 29 months with 3 and 5-year OS of 46% and 38% respectively. While the *Ph-positive group showed* a median OS of 15.7 months with 3 and 5years OS rate of 28%and 24% respectively.

In our cohort, median time to progression was 16 months. At 3 and 5 years, 40.6% and 35.2% of the patients, respectively, were still in remission. There was significant difference in time to progression between patients classified as SR, HR and VHR (p=0.047). In LALA-94 trial the median LFS was 17.5 months with 3 and 5-years event free survival of 37 and 30% respectively and the estimated 3-year LFS rate was 35% and 43% for T- and (non–Ph-positive) B-lineage ALL respectively, (7).The LFS in large trials ranged between 27-48 % (at 3-10 years) with a weighted mean of 36 %(16). Only three VHR cases were subjected to transplantation. The lack of strict transplantation is related to several causes including lack of donor, impaired organ function, lack of financial coverage or refusal.

Conclusions and future direction

Our risk adapted protocol applied in this study was tolerable with accepted morbidity and mortality. Studying the prognostic criteria and stratification of the patients accordingly is mandatory. The integration of new risk factors as MRD detection and molecular genetic studies of the patients is evolving. The CR rate and LFS of the SR group are accepted and comparable to other studies with similar intensity, while those of the HR and VHR are still in need to be improved. Intensification of the post-remission chemotherapy, targeted therapy and strict referral to SCT are now considered in our ongoing protocol.

References

1. Jemal A, Tiwari RC, Murray T, et al. Cancer Statistics. CA Cancer J Clin 2004; 54(1):8–29. [PMID: 14974761]

2. Ries LAG, Smith MA, Gurney JG, et al. eds. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. Bethesda, MD: National Cancer Institute; 1999

3. Pui, C-H, Evans WE.: Treatment of acute lymphoblastic leukemia. N Engl J Med. 2006; 354:166-178

4. Larson S, Stock W. Progress in the treatment of adults with acute lymphoblastic leukemia. Curr Opin Hematol. 2008;15(4):400-7.

5. Kantarjian HM, O'Brien S, Smith TL, et al. Resultsof treatment with hyper-CVAD, a dose-intensive regimen in adult acute lymphocytic leukemia. J Clin Oncol. 2000; 18:547-561.

6. Goekbuget N, Arnold R, Buechner T, et al. Intensification of induction and consolidation improves only subgroups of adult ALL: analysis of 1200 patients in GMALL study 05/93. Blood 2001; 98:802a.

7. Thomas X, Boiron JM, Huguet F, et al. Outcome of Treatment in Adults with Acute Lymphoblastic Leukemia: Analysis of the LALA-94 Trial. J Clin Oncol. 2004; 22(20): 4075-4086

8. Fielding A. The treatment of Adults with Acute Lymphoblastic Leukemia. Hematology (Am Soc Hematol Educ Program). 2008; 381-389.

9. Takeuchi J, Kyo T, Naito K, et al. Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and maintenance therapy for adult acute lymphoblastic leukemia: the JALSG-ALL93 study. Leukemia 2002; 16:1259-1266

10. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood. 2005;106: 3760-3767.

11. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow up results of Hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper- CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer. 2004; 101:2788-2801.

12. Annino L, Vegna ML, Camera A, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood. 2002;99:863-871

13. Pulte D, Gondos A and Brenner H. Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. Blood 2009; 113(7):1408- 1411.

14. Mahmoud H; Hamza R; Gad-Elmawla N;et al. The impact of an intinsified induction protocol on remission rate and duration in adult acute lymphoblastic leukemia patients. Egypt. J. Hematol. 1995; 20:225-36

15. AbdelHamid Th, Mahmoud H; Kamel A; et al. Risk Adapted chemotherapy for adult acute lymphoblastic leukemia. Egypt J. Hematol. 2005; 30(3):579-94

16. Nicola Gökbuget and Dieter Hoelzer. Treatment of Adult Acute Lymphoblastic Leukemia. Hematology (Am Soc Hematol Educ Program). 2006; 133-141.

17. Hoelzer D, Gökbuget N, Ottmann O ,et al. Acute Lymphoblastic Leukemia. Hematology (Am Soc Hematol Educ Program). 2002; 162-192.

18. Towatari M, Yanada M, Usui N, et al. Combination of intensive chemotherapy and imatinib can rapidly induce high-quality complete remission for a majority of patients with newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia. Blood. 2004;104:3507-3512.

Tables

Table 1: Criteria for risk stratification of adult ALL

	favorable	unfavorable
Age	**≤ 35 years**	**> 35 years**
WBC **B lineage** **T lineage**	 < 30 x 109/L < 100 x 109/L	 > 30 x 109/L > 100 x 109/L
Immunophenotyping	Thymic T (T-lin.CD1a+ve or CD4/CD8 co-expression and sCD3-ve)	Pro B (B-lin. CD 10 –ve) Early T (T-lin. CD 1a –ve, sCD 3-ve). Mature T (T-lin. CD1a –ve , s CD3 + ve)
Molecular genetics		T (9,22) BCR/ABL T(4,11) ALL1/AF4
Treatment response	CR ≤ 4 weeks	CR > 4 weeks

Table 2: Summary of the treatment plan and modification according to age in adult ALL

Risk	Age < 50 years	50-60 years	>60 years
Standard risk	Standard risk protocol	Standard risk protocol	COAP regimen
High risk and very high risk	High risk protocol + allogeneic transplantation (in presence of HLA identical donor)	Treat as standard risk group and no transplantation	COAP regimen

Table 3: Baseline clinical presentations of 115 adult ALL cases

Fever and infection	22
Bleeding manifestations	27
Generalized lymphadenopathy	66
Mediastinal lymphadenopathy	6
Hepatosplenomegaly	65
CNS disease	14
Pleural effusion	6
Pulmonary infiltrates	6
Bone lesions	5
Impaired organ functions: -Hepatic -Cardiac - Renal	 13 1 5

Table 4: Main reported toxicities of the induction phase in 115 adult ALL patients

Toxicity	Number
Fever and neutropenia	112 episodes
Mucositis	30
Diarrhea	12
Bleeding manifestations	9
Hepatic toxicity	21
Renal impairment	4
Diabetic keto-acidosis	2
Peripheral neuropathy	2

Figures

Fig 1: Risk-adapted treatment plan for adult ALL (other than mature B-ALL)

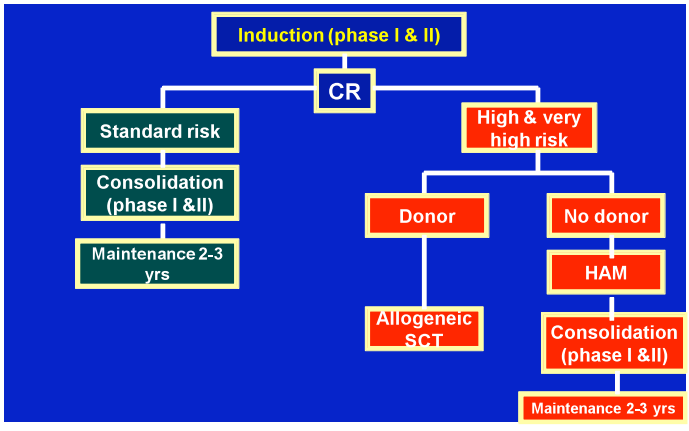

Fig 2: Overall survival of the whole group of ALL cases

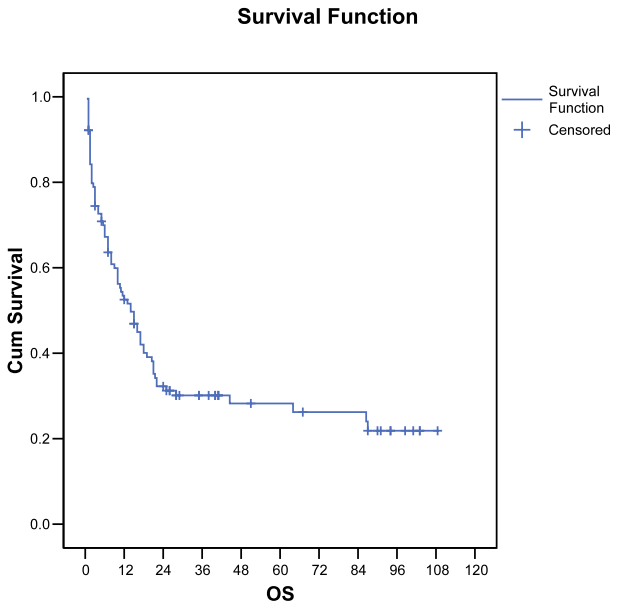

Fig 3: Overall survival according to risk groups

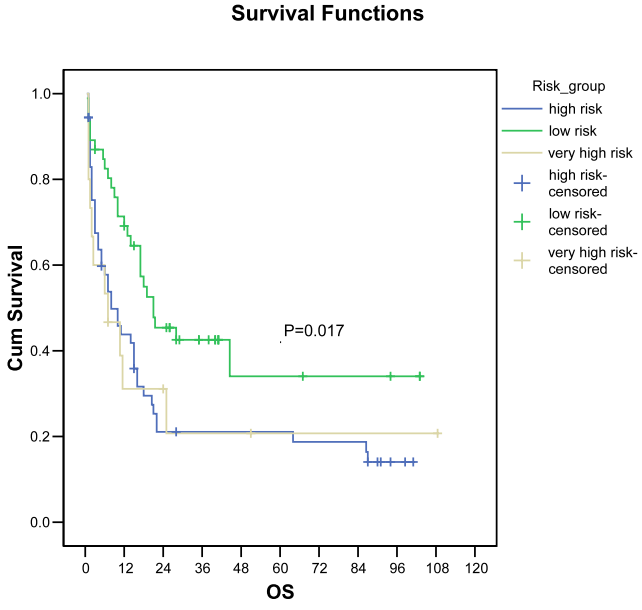

Fig 4: Overall survival according to immunophenotype

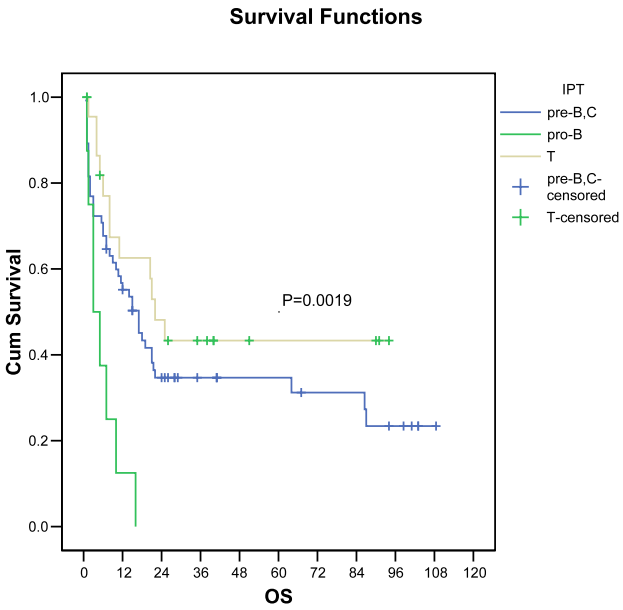

Fig 5: Disease free survival of the whole ALL group

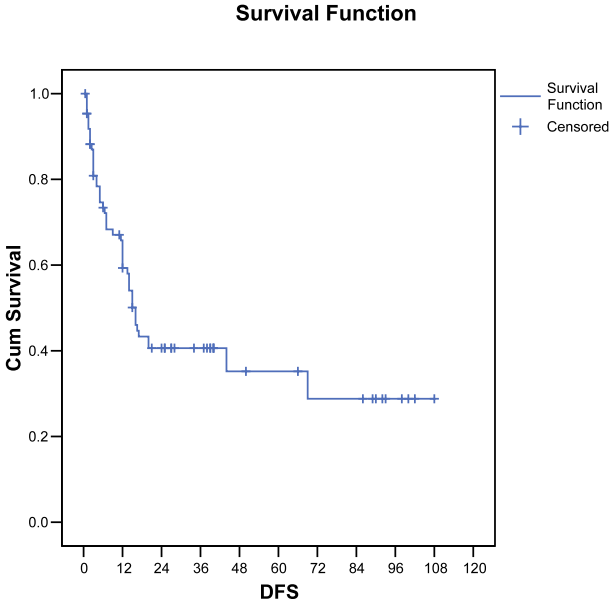

Fig 6: Disease free survival according to risk groups

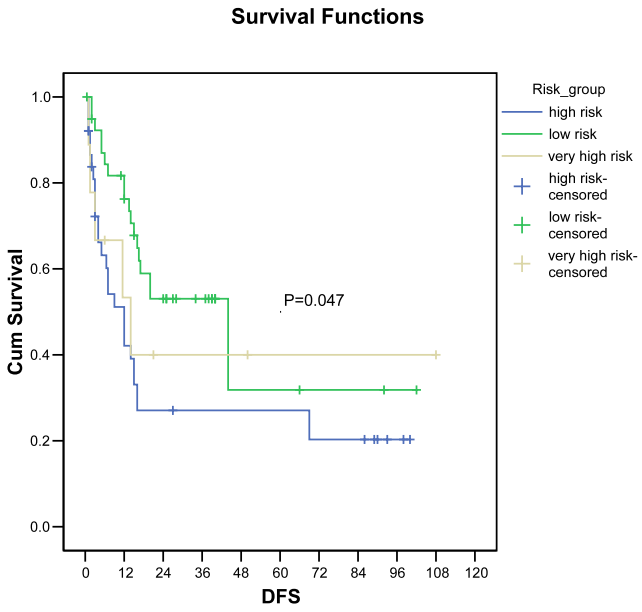

Fig 7: Disease free survival according to immunophenotype